Recent clinical trials using cisplatin, carboplatin and their combination chemotherapy drugs (Review)

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Abstract. Cisplatin continues to play a central role in cancer chemotherapy in spite of its toxicity. It is used as first line chemotherapy against epithelial malignancies of lung, ovarian, bladder, testicular, head & neck, esophageal, gastric, colon and pancreatic but also as second and third line treatment against a number of metastatic malignancies including cancers of the breast, melanoma, prostate, mesothelioma, leiomyosarcomas, malignant gliomas and others. Cisplatin has become in 2001 the gold standard treatment against cervical cancer in combination with radiotherapy. This review summarizes the state of the art on clinical trials published mainly in 2002 using cisplatin and carboplatin in their combinations with other anticancer drugs. For most advanced cancers the response rate to chemotherapy is about 50% in first line treatments and about 15% in second or third line treatments; for example response rates of 25-50% have been observed for chemonaive patients with advanced non-small cell lung cancer treated with cisplatin or carboplatin in combination with gemcitabine or taxanes and in exceptional cases these rates are up to 80% with addition of radiotherapy. Response rates are very discouraging in second or third line chemotherapy treatments (7% to 25%). Despite an increase in response rate from the use of modern-day chemotherapy drugs, no major difference in long-term survival has been achieved. It is a high priority at the dawn of the new millennium to invent novel approaches for cancer treatment. It is hoped that a fraction of the numerous experimental drugs will show virtues in the anticancer arena especially combined with existing treatment regimens. Efforts should focus on diminution of side effects improving the quality of life of the patient. A preferential tumor targeting of chemotherapy treatments would bring a revolution in molecular medicine and would greatly advance cancer therapy in the upcoming years.

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Abbreviations: 5-FU, 5-fluorouracil; AUC, area-under-the-concentration-time-curve (mg/mL.min); CR, complete response; DLT, dose limiting toxicity; EOC, epithelial ovarian cancer; G-CSF, granulocyte colony stimulating factor; i.v., intravenous; MTD, maximum tolerated dose; NSCLC, nonsmall cell lung carcinoma; OR, overall response; ORR, overall response rate; OS, overall survival; PBL, peripheral blood lymphocyte; PFS, progression-free survival; PR, partial response; RD, recommended dose; SCLC, small cell lung carcinoma; SCCHN, squamous cell carcinoma of the head and neck; TNF-α, tumor necrosis factor-α

Key words: cisplatin, carboplatin, chemotherapy, radiotherapy, paclitaxel, docetaxel, gemcitabine, 5-FU, lung cancer, NSCLC, ovarian cancer, head & neck cancer, gastric cancer, colorectal cancer, pancreatic cancer, breast cancer, metastatic melanoma, prostate cancer, glioblastoma

Contents

1. Introduction

The introduction of cisplatin, and later of carboplatin, have been milestone achievements in molecular oncology (1). A number of additional platinum drugs are at the clinical level, a greater

number is being evaluated in cell cultures or animal models and even a higher number of platinum compounds have already been synthesized, tested and abandoned. Research in this field gives support to the legend that 1% of synthesized pharmaceutical drugs will make it successfully through preclinical evaluation and through the Phases I, II and III human clinical trials to a marketed drug as opposed to aircraft engineers that have a 99% chance of success that a new model designed will fly. The success of cisplatin lies in its ability to induce major damage in DNA resulting in bulky adducts as well as intra- and inter-strand crosslinks (2); the cell, then, needs to activate sophisticated DNA repair pathways for their elimination. Cisplatin adducts and crosslinks can arrest DNA synthesis by inhibition of DNA polymerase-catalyzed chain elongation at the replication fork. Tumor cells are almost the only proliferating cells in the adult. In addition to DNA and RNA, platinum drugs react with small molecules and proteins, upregulate the expression of transcription factors and signal apoptosis. Cisplatin induces oxidative stress and is an activator of stress-signaling pathways especially of the mitogen-activated protein (MAP) kinase cascades. Induction of apoptosis by cisplatin proceeds via activation or modulation of signaling pathways (3). Renal tubular apoptotic death induced by cisplatin is responsible for its renal toxicity (4); the ototoxicity arises from apoptosis in auditory sensory cells. Optic neuropathy arises from apoptosis in optic nerve cells (reviewed in ref. 5).

The major limitation in the clinical applications of cisplatin has been the development of cisplatin resistance by tumors. Mechanisms explaining cisplatin resistance include the reduction in cisplatin accumulation inside cancer cells because of barriers across the cell membrane, the faster repair of cisplatin adducts, the modulation of apoptotic pathways in various cells by up- or down-regulation in the expression of kinase and phosphatase genes by cisplatin, the upregulation in transcription factors (AP-1, UBF), the loss of p53 and other tumor suppressor protein functions and a higher concentration of glutathione and metallothioneins in some type of tumors. Platinum compounds under evaluation for their ability to overcome this resistance include BBR3464 (reviewed in refs.5, 6).

This article reviews the most recent clinical trials (published mainly during 2002) involving cisplatin (Platinol, Bristol, patents expired) and carboplatin (Paraplatin, Bristol). A number of terms are used to evaluate the outcome of a clinical trial such as partial or complete response rate and clinical benefit. “Partial response means shrinkage of all measurable lesions by over 50% whereas their complete disappearance is described as “complete response”. The “clinical benefit” is defined by the level of pain and the consumption of analgesics, the performance status of the patient, the stabilization or gain in body weight and a reduction in the volume of measurable lesions of less than 25%. This minor reduction (<25%) in tumors used to fall in an older classification under “minor response”. Chemotherapy treatment of adults uses the body surface area of the patient; it is calculated from the height of the patient in cm times the weight in Kg divided by 3,600; the square root of this number gives the surface area of the patient in m^2. Carboplatin treatment uses the AUC, area-under-the-concentration-time-curve (mg/mL.min) that is calculated using Calvert's formula, rather than the mg/m^2 dosing scheme. Induction chemotherapy refers to drugs given before radiotherapy as opposed to concurrent chemoradiotherapy. The term neo-adjuvant refers to preoperative chemotherapy.

2. Drugs used in combination with platinum

A number of drugs are being used in combination with platinum compounds. A short description of their mechanism of action follows to better understand the principle of combination chemotherapy.

Paclitaxel (Taxol, Bristol-Myers) was first isolated in 1971 from the bark of *Taxus brevifolia* and was approved in 1992 by the U.S. Food and Drug Administration for treatment of metastatic ovarian cancer and later for breast cancer. To date, more than 200 taxanes have been synthesized. Paclitaxel is dissolved in a mixture of ethanol and cremophor (PEGylated castor oil) which provokes severe hypersensitive immune responses and peripheral neuropathy. Paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes these by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel interacts with bcl-2 and promotes phosphorylation of bcl-2 and Raf-1, events that have been related to the accumulation of cells in G_2M. Paclitaxel significantly down-regulates IκB, thereby increasing the nuclear translocation of nuclear factor κB. Paclitaxel is being widely used against a range of human malignancies as a single agent (7) and in combination therapy (8). Especially intriguing are clinical studies using combinations of Paclitaxel with herceptin, a monoclonal antibody against HER2/neu (9) and ZD1839 (Iressa), an inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase (10). Paclitaxel in combination with a platinum agent is now accepted as the standard first-line treatment for ovarian cancer and produces improved survival (see Epithelial ovarian cancer).

One major problem with paclitaxel chemotherapy is the acquisition of clinical resistance, which causes chemotherapeutic failure leading to progressive disease. Potential mechanisms of taxane resistance include the overexpression of P-glycoprotein and/or mutations in tubulin, both of which may impair the ability of the drug to bind efficiently to its target. These factors have motivated a search for other natural products that target the microtubule and have superior or equivalent activity compared with paclitaxel but without the associated problems. Recently, several additional compounds that fulfill these criteria have been isolated from diverse natural sources (see Conclusions and Perspectives).

Docetaxel (Taxotere, Aventis) is a semi-synthetic anticancer agent derived from bacatin III of the needles of the European yew Taxus baccata. Docetaxel binds with a 2-fold higher affinity than paclitaxel and stabilizes tubulin polymers, has a broader activity than paclitaxel against human tumors and acts at the S-phase whereas paclitaxel acts at the G_2/M phases of the cell cycle (reviewed in ref. 11).

Gemcitabine (Gemzar, Eli Lily) was introduced in the mid 1990's in the US/Europe and has been available in Japan since 1999. Gemzar is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer and as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Myelosuppression

is the principal dose-limiting toxicity with gemcitabine therapy. The combination of gemcitabine and cisplatin is emerging as a popular regimen against pancreatic cancer (reviewed in ref. 12).

Doxorubicin (Rubex, Bristol-Myers Squibb) is a cytotoxic anthracycline antibiotic isolated from the fungus Streptomyces peucetius var. caesius. The mechanism of cytotoxicity by doxorubicin is exerted at several levels: (i) Doxorubicin damages DNA by intercalation of the anthracycline portion, (ii) induces metal ion chelation, (iii) generates free radicals, (iv) inhibits DNA topoisomerase II and this interaction leads to DNA cleavage as an important mechanism of doxorubicin cytocidal activity, and (v) interacts with cell membrane lipids. Cytotoxic activity is cell cycle phase-nonspecific. Highest concentrations have been observed in liver, spleen, kidney, heart, small intestine and lung after i.v. administration. Cardiotoxicity and severe myelosuppression are the most severe side effect of doxorubicin and other anthracyclines. Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. Anthracyclines and taxanes are among the most effective agents in the treatment of advanced breast cancer, refractory or non-responsive to endocrine manipulation (13).

The liposomal formulation of doxorubicin, known as Doxil or Caelyx, is at least as effective as topotecan in patients with ovarian cancer refractory or sensitive to first-line platinum-based chemotherapy giving response rates of 18 to 28%. It is also active as second line treatment in patients with metastatic breast cancer whereas in Kaposi's sarcoma Doxil monotherapy produced overall response rates ranging from 46 to 77% in randomized trials. It has also shown activity in multiple myeloma and aggressive non-Hodgkin's lymphomas. The most common adverse events associated with PEG-liposomal doxorubicin are myelosuppression, cardiotoxicity, palmar-plantar erythrodysaesthesia, stomatitis and nausea (reviewed in ref. 14).

Vinorelbine is a semisynthetic vinca alkaloid that binds to tubulin and inhibits tubulin assembly and microtubule formation. It has less activity than other vinca alkaloids against axonal microtubules and this may account for its reduced neurotoxicity in clinical use. The main adverse effect of vinorelbine monotherapy is myelosuppression. Adverse events associated with most antineoplastic agents, such as mild alopecia, nausea, vomiting mucositis, moderate neurotoxicity, and constipation were also reported for vinorelbine in clinical trials. A phase I study using vinorelbine and concurrent radiation (64 Gy) in previously untreated patients with inoperable locally advanced esophageal cancer has reached the maximal tolerated dose at 25 mg/m^2/week and the recommended dose was 20 mg/m^2/week; the dose-limiting toxicities were febrile neutropenia and infection. The addition of gemcitabine to vinorelbine increased the incidence of both hematological and nonhematological adverse events (reviewed in ref. 15).

Irinotecan (CPT-11, Camptosar), a topoisomerase I inhibitor, is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata*. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of single-strand breaks. After intravenous infusion of irinotecan, a mean terminal elimination plasma half-life of about 6 to 12 hours was observed.

5-Fluorouracil (5-FU), developed in 1957, is a fluorinated pyrimidine that is metabolized intracellularly to its active form, fluorodeoxyuridine monophosphate (FdUMP). The active form inhibits DNA synthesis by inhibiting the normal production of thymidine; 5-FU is S-phase-specific. Following oral administration 15% of the drug is excreted through urine within 6h. The half life is 10-20 min; 60-80% is excreted as respiratory CO_2 and 2-3% via the biliary system. It is used mainly against breast, colorectal, gastric and hepatic cancers and less frequently against bladder, cervical, endometrial, head & neck, NSCL, ovarian, pancreatic and prostate cancers. Following IV infusion, stomatitis and diarrhea occur most commonly. Diarrhea may be profuse and life threatening following administration of leucovorin with fluorouracil. Leukopenia is the usual dose-limiting toxicity after i.v. bolus administration (16-18).

Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. The mechanism of action is thought to involve cross-linking of tumor cell DNA. The unchanged drug has an elimination half-life of 3 to 12 hours. Continued use of cyclophosphamide is contraindicated in patients with severely depressed bone marrow function. Secondary malignancies have developed in some patients with cyclophosphamide such as urinary bladder, myeloproliferative, or lymphoproliferative malignancies. It is used against a broad range of malignancies such as advanced breast cancer (19).

Pemetrexed disodium (ALIMTA®, Eli Lilly) is an antimetabolite with multiple sites of action. Pemetrexed inhibits multiple folate-dependent enzymes involved in both purine and pyrimidine synthesis including thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and aminoimidazole carboxamide ribonucleotide formyltransferase. As a single agent it is active against a variety of solid tumors. Pemetrexed disodium has demonstrated promising clinical activity in a wide variety of solid tumors, including non-small cell lung, breast, mesothelioma, colorectal, pancreatic, gastric, bladder, cervix, and head and neck. One phase II trial demonstrated a 14.5% response rate for single-agent pemetrexed disodium in patients with previously untreated mesothelioma (20). As a single agent, pemetrexed exhibits a moderate toxicity profile at a dose of 500 mg/m^2 by 10-minute infusion once every 21 days. Myelosuppression is the dose-limiting toxicity. In a Phase II trial against NSCLC the response rate of pemetrexed monotherapy in platinum-pretreated patients was 4.5% and 14.1% in the non-platinum-pretreated patients (21).

Trastuzumab (Herceptin; Genentech) is a monoclonal humanized antibody directed against epidermal growth factor receptor (HER) 2 protein, which is overexpressed in a wide variety of human cancers, including 20-30% of human breast cancers. HER-2 plays an important role in oncogenic transformation, tumorigenesis and metastatic spread. Overexpression is associated with a poor prognosis and predicts a poor response to several treatment modalities. Approximately 15-20% of patients with HER-2-overexpressing tumours benefited from treatment with trastuzumab given as a single agent. In a phase II trial as second-line treatment in ovarian or primary peritoneal carcinoma patients with HER2 overexpressing tumors it gave an overall response rate of 7.3% (22).

3. Combinations and synergistic effects of chemotherapy drugs and other agents

Combination chemotherapy remains a cornerstone of most cancer treatment regimens as opposed to monotherapy. Among the numerous clinical regimens used in combination chemotherapy, synergy is particularly marked in combinations containing cisplatin. An important issue is to have a synergistic rather than a simple additive or antagonistic therapeutic effect with the combination treatment. The advantage using combinations of gemcitabine, topotecan, liposomal doxorubicin, and prolonged oral etoposide with platinum has been attributed to inhibition of DNA synthetic pathways involved in the repair of platinum-DNA adducts. Gemcitabine and cisplatin act synergistically, increase platinum-DNA adduct formation and induce concentration and combination dependent changes in ribonucleotide and deoxyribonucleotide pools in ovarian cancer cell lines (23).

Many drug combinations involving platinum complexes have been explored, but those with taxanes are particularly noteworthy. Paclitaxel in combination with a platinum agent is now accepted as a standard component of first-line treatment for ovarian cancer and produces improved survival (reviewed in ref. 24). Docetaxel was combined with 18 other agents to define both synergistic and antagonistic drug combinations in the prostate cancer cell lines DU145, LnCaP or PC3. Drugs which have been combined clinically to treat hormone-refractory prostate cancer, i.e. cisplatin, carboplatin or etoposide, were antagonistic when combined with docetaxel; thus, combinations of docetaxel with platinum or etoposide against pancreatic cancer was suggested to lead to subadditive effects in clinical treatments. On the contrary, docetaxel demonstrated cytotoxic additive effects or synergy with retinoic acid, cyclosporin A and vinorelbine in all three cell lines and this combination may offer an enhanced cytotoxic effect in the management of hormone-refractory prostate cancer. Docetaxel combined with either epirubicin or doxorubicin displayed cytotoxic synergistic effects in hormone-refractory DU 145 and PC 3 cell lines (25).

Important questions are how the various drugs may interact and how the pharmacokinetics of one drug might be affected by the administration of the other drugs. Also the maximum tolerated dose (MTD) of new experimental drugs is expected to be affected in a combination regimen. Cisplatin and carboplatin are often used in combination with etoposide. Neither cisplatin nor carboplatin coadministration affected significantly the pharmacokinetics of etoposide in a randomized cross-over clinical trial involving 15 patients. Thus, in this case, the interaction between etoposide and platinum drugs is small and the clinical impact is unlikely to be significant (26). Epirubicin-taxane combinations are highly active in treating metastatic breast cancer and do not appear to be associated with any pharmacokinetic interactions (reviewed in ref. 27).

The concentration of cisplatin is an important factor determining synergy in cell culture studies. Oligonucleotides that target telomerase had a synergistic effect at 1 μg/ml cisplatin and an additive effect at 5 μg/ml cisplatin in malignant glioma cell lines (28). The combination of 5-FU and cisplatin used against gastric cancer showed a synergism at the concentration range of cisplatin from 1.5 to 3 μM, whereas single treatment with cisplatin did not show significant antitumor effect at this concentration. This finding justifies low dose 5-FU and cisplatin combination chemotherapy. In addition this treatment activated a receptor signaling pathway mediated by Fas leading to direct activation of caspase 3 and apoptosis in addition to increased folate level by cisplatin and non-receptor signaling activation by 5-FU in gastric carcinoma cells (29). Also, the order of treatment with two drugs is an important factor for synergy. The combination of nedaplatin and irinotecan, a topoisomerase I inhibitor, showed synergistic interaction in cell cultures, by concurrent exposure to both drugs; on the other hand, sequential exposure to the two drugs led only to additivity (30).

Pemetrexed (Alimta) as single-agent against NSCLC in previously untreated patients resulted in a response rate of 20%. In combination with cisplatin the response rate was 40% (reviewed in 31). Interleukins potentiate chemotherapy drug cytotoxicity. For example, 5.0 U/ml IL-1α dramatically increased the sensitivity of osteosarcoma cells to etoposide, to doxorubicin but not to cisplatin or topotecan. The mechanism of this enhanced activity was independent of P-glycoprotein, drug-uptake, or effects on topoisomerase II (32). Cisplatin and IL-1 treatment induced a blockade at G1/S of the cell cycle, down-regulating c-myc gene and inducing p53-dependent apoptosis in ovarian carcinoma cells (33).

Antioxidant vitamins (vitamin C, d-α-tocopheryl succinate, 13-cis-retinoic acid, β-carotene) can enhance the growth-inhibitory effect of cisplatin and other chemotherapeutic agents. The concentrations of various plasma antioxidants including vitamin C and E, uric acid and ceruloplasmin were diminished significantly after cisplatin-combination chemotherapy and returned to baseline levels before the start of the next chemotherapy cycle. This was thought to have resulted from destruction of antioxidants by chemotherapy induced-oxidative stress as well as renal loss of water-soluble, small molecular weight antioxidants such as uric acid (34). Treatment with vitamin E might be capable of protecting noncancerous cells from the oxidative damage caused by cisplatin but it might also reduce the effects of cisplatin on cancerous cells. Cisplatin-induced chromosomal aberrations in bone marrow and spermatogonia were decreased in vitamin E pretreated mice, but significantly only with high doses of vitamin E of 300 mg/kg. However, vitamin E failed to protect from the transmission of cytogenetic toxic effects of cisplatin in the male germline of mouse and rather potentiated them to some extent (35). The utility of adding vitamins to a chemotherapy regimen containing cisplatin (or other drugs) is worth undertaking in clinical trials.

4. Non-small-cell lung cancer (NSCLC)

Lung cancer accounts for about 28% of all cancer-related deaths. Lung cancer is divided into two major types: NSCLC and small cell lung cancer (SCLC) depending on the microscopic appearance of cells. NSCLC grows and spreads more slowly than SCLC. NSCLC constitutes 80% of all lung cancer cases, and in 70% of patients, the disease is diagnosed when it is locally advanced or metastatic. In the year 2000 lung cancer accounted for 16.75% of all cancer cases among men and for 7.02% among women worldwide (Table 1). There are four

main types of NSCLC: (i) Adenocarcinoma is the most common type of lung cancer, accounting for 30-35% of all cases. Over the past 30 years, the frequency of adenocarcinomas has increased, while, squamous cell carcinomas have decreased. The majority of adenocarcinomas occur at the periphery of the lung, and, as a result are often asymptomatic until late in their course. (ii) Bronchioloalveolar carcinoma represents 2-6% of all lung cancers. Histologically, the tumors are well differentiated and tumor cells secrete mucin and surfactant apoprotein leading to excessive discharge of mucus from the air passages of the lungs. It usually spreads through the airways, but may also metastasize by lymphatic and hematogenous routes. Patients with extensive consolidation or multifocal disease have a poor prognosis. Bronchioloalveolar carcinoma can manifest as a single peripheral nodule or mass usually in the upper lung. This form of tumor has a better prognosis for surgical resection.(iii) Large cell carcinoma is a malignant epithelial tumor with large nuclei, prominent nucleoli, and abundant cytoplasm. These represent 10-20% of bronchogenic tumors. Tumors tend to grow rapidly, metastasize early, and are strongly associated with smoking. Giant cell carcinoma, a subdivision of large cell carcinoma, is particularly aggressive and carries a very poor prognosis. (iv) Squamous cell carcinoma begins in squamous cells lining the respiratory tracts. Unlike adenocarcinoma, it is strongly linked with a history of cigarette smoking. Its histogenesis may be related to chronic inflammation and injury of the bronchial epithelium, which leads to replacement of the normal ciliated columnar epithelium by a squamous epithelium.

New drugs such as gemcitabine, vinorelbine, and the taxanes have been combined with cisplatin and tested in several phase-II and phase-III clinical trials versus cisplatin alone and different cisplatin/new drug combinations. Overall, the data seem to confirm that, despite a possible increase in response rate, no major difference in long-term survival has been achieved. Early studies of neo-adjuvant (pre-operative) chemotherapy for resectable stage III patients have shown promising results. For patients with non-resectable NSCLC platinum-based doublets are now established as first-line treatment, either alone or in combination with radiotherapy. The use of vinorelbine, gemcitabine, paclitaxel and docetaxel in combination with cisplatin or carboplatin against NSCLC have increased by as much as 10% the overall survival at one year. The possibility of discriminating cisplatin resistance is particularly attractive in choosing between cisplatin and non-cisplatin combinations in the treatment of NSCLC. Drugs that are mostly ineffective when used as single agents, such as 5-fluorouracil (5-FU), have significant activity when combined with cisplatin in the treatment of patients with NSCLC (reviewed in refs. 36-43).

Platinum plus gemcitabine in NSCLC. Cisplatin plus gemcitabine is a less toxic and effective combination as a preoperative treatment in NSCLC patients and among the most widely used regimens in Europe for first-line treatment of NSCLC. Problems with cisplatin in this setting include significant nonhematologic toxicity and difficulty of use in outpatients. Carboplatin constitutes a reasonable alternative to cisplatin in this combination, since it shows synergy with gemcitabine in vitro, is easier to use in ambulatory patients, and has a better nonhematologic toxicity profile. Thus, the combination of gemcitabine (Gemzar) and carboplatin (Paraplatin), initially hampered by unacceptable platelet toxicity, has gained increasing acceptance against NSCLC. Studies of gemcitabine/carboplatin on a 28-day schedule (gemcitabine on days 1, 8, 15 and carboplatin on day 1) generally resulted in excessive thrombocytopenia. Use of a 21-day schedule (e.g. gemcitabine on days 1 and 8, carboplatin on day 1) is associated with reduced toxicity and comparable efficacy. Unlike taxane based regimens, there is no need for steroid premedication, and neurotoxicity and alopecia are absent in Gemzar plus carboplatin regimens (reviewed in refs. 36-44).

A dose-finding study established the maximum tolerated dose (MTD) of carboplatin as an area under the curve (AUC) 5 administered on day 1 in combination with gemcitabine at the dose of 1000 mg/m^2 on days 1 and 8 in a 21-day cycle (45).

A phase III was conducted comparing the combination of gemcitabine (1200 mg/m^2) on days 1 and 8 plus carboplatin at AUC of 5 mg/ml/min on day 1 versus gemcitabine at the same dose plus cisplatin at 80 mg/m^2 on day 1 every 21 days in chemotherapy-naive patients with stage IIIB/IV NSCLC; interim analysis indicated comparable response rates of 47% and 48% (46). A three-arm phase III randomized trial has studied the combination of gemcitabine with ifosfamide or with the cisplatin-carboplatin on 284 chemotherapy-naive patients with metastatic stage IV NSCLC. The CCI arm was cisplatin-carboplatin-ifosfamide, the IG arm was ifosfamide-gemcitabine and the CCG arm was cisplatin-carboplatin-gemcitabine. Cisplatin was given at 60 mg/m^2 on day 1, carboplatin at AUC of 3 mg.min/ml on day 1, ifosfamide at 4.5 g/m^2 on day 1 and gemcitabine at 1 g/m^2 on days 1, 8 and 15. Courses were repeated every 4 weeks. The objective response rate for the CCI arm was 23%, for IG was 25% and for CCG was 29%. The median survival times were CCI arm: 24 weeks; IG arm: 30 weeks and CCG arm: 34 weeks. Severe alopecia was less frequent in the CCG arm, and IG was associated with significantly more thrombopenia while the CCG arm was associated with more leucopenia. Thus, gemcitabine was associated with a better but not statistically significant observed survival compared with the classical first-generation cisplatin-containing regimens (47).

A randomized phase III trial from Romania on 198 chemonaive patients with advanced or metastatic NSCLC has used two arms: arm A (99 patients) was cisplatin at 70 mg/m^2 on day 1 plus vinblastine at 6 mg/m^2 on days 1 and 8 on a 21-day course. Arm B (99 patients) used gemcitabine 1000 mg/m^2 on days 1 and 8 plus carboplatin 300 mg/m^2 on day 1 on a 21-day course. In arm A, there were 15 partial responders (15%) compared with 3 complete responders (3%) and 24 partial responders (24%) in arm B. The mean survival was 7.9 months in arm A and 11.6 months in arm B. The two treatment regimens showed similar toxicity profiles but the one-year survival rates were 13% for cisplatin/vinblastine compared to 36% for gemcitabine/ carboplatin. Thus, the gemcitabine/ carboplatin combination is superior to cisplatin/vinblastine in this dosing scheme (48). Preliminary findings in a phase III trial of the Swedish Lung Cancer Study Group (332 patients with stage IIIB or IV NSCLC) comparing gemcitabine (1,250 mg/m^2 on days 1 and 8 every 21 days) versus same gemcitabine regimen plus carboplatin at an AUC of 5 mg/mL/min on day 1 for a maximum of six cycles showed that the gemcitabine/carboplatin

Table 1. Incidence of the various forms of cancer WW (2000).[a]

Cancer type	WW (%)		USA (%)		W/S/N Europe (%)		Japan (%)	
Cancer Incidence in 2000 (Males)								
Lung and Bronchus	901,746	(16.75)	107,618	(15.92)	176,844	(18.27)	47,672	(15.49)
Stomach	558,458	(10.37)	13,884	(2.05)	52,822	(5.46)	77,388	(25.14)
Prostate	542,990	(10.09)	193,205	(28.58)	153,376	(15.84)	13,853	(4.50)
Colon and Rectum	498,754	(9.27)	74,938	(11.09)	126,323	(13.05)	48,270	(15.68)
Liver and Intrahepatic Bile Duct	398,364	(7.40)	7,523	(1.11)	21,980	(2.27)	32,514	(10.56)
Esophagus	278,985	(5.18)	8,777	(1.30)	21,013	(2.17)	11,220	(3.65)
Urinary Bladder	259,771	(4.83)	43,687	(6.46)	72,940	(7.53)	10,683	(3.47)
Oral Cavity	169,524	(3.15)	10,998	(1.63)	29,202	(3.02)	4,147	(1.35)
Non-Hodgkin's Lymphoma	166,624	(3.10)	28,094	(4.16)	30,375	(3.14)	7,514	(2.44)
Leukemias	144,321	(2.68)	16,176	(2.39)	24,639	(2.55)	4,815	(1.56)
Larynx	142,168	(2.64)	9,422	(1.39)	26,425	(2.73)	3,631	(1.18)
Kidney and Renal Pelvis	118,255	(2.20)	19,477	(2.88)	31,631	(3.27)	6,422	(2.09)
Pancreas	115,697	(2.15)	14,932	(2.21)	22,712	(2.35)	11,081	(3.60)
Other pharynx	100,902	(1.87)	5,381	(0.80)	19,568	(2.02)	1,939	(0.63)
Brain Nervous system	100,446	(1.87)	10,307	(1.52)	17,875	(1.85)	1,973	(0.64)
Melanoma of the skin	64,177	(1.21)	22,463	(3.32)	16,853	(1.74)	393	(0.13)
Testis	49,302	(0.92)	5,923	(0.88)	13,489	(1.39)	792	(0.26)
Nasopharynx	45,976	(0.85)	1,058	(0.16)	2,065	(0.21)	476	(0.15)
Multiple myeloma	39,480	(0.73)	7,303	(1.08)	10,309	(1.06)	2,088	(0.68)
Hodgkin's Disease	38,222	(0.71)	3,421	(0.51)	6,047	(0.62)	313	(0.10)
Thyroid	33,454	(0.62)	4,785	(0.71)	3,701	(0.38)	1,315	(0.43)
Others	614,466	(11.41)	66,556	(9.85)	87,862	(9.08)	19,309	(6.27)
All sites but skin	5,317,905	(98.79)	653,465	(96.68)	951198	(98.26)	307,415	(99.87)
Total	5,383,082	(100.00)	675,928	(100.00)	968,051	(100.00)	307,808	(100.00)
Cancer Incidence in 2000 (Females)								
Breast	1,050,346	(21.86)	183,494	(29.77)	235,143	(27.92)	31,124	(14.71)
Cervix	470,606	(9.79)	13,230	(2.15)	29,447	(3.50)	11,681	(5.52)
Colon and Rectum	445,963	(9.28)	73,033	(11.85)	115,914	(13.76)	34,938	(16.51)
Lung and Bronchus	337,115	(7.02)	78,320	(12.71)	47,473	(5.64)	17,556	(8.30)
Stomach	317,883	(6.62)	8,594	(1.39)	35,180	(4.18)	37,906	(17.91)
Urinary Bladder	76,024	(1.58)	13,007	(2.11)	20,648	(2.45)	2,945	(1.39)
Ovary	192,379	(4.00)	21,217	(3.44)	37,321	(4.43)	6,590	(3.11)
Corpus Uteri	188,952	(3.93)	32,421	(5.26)	46,074	(5.47)	4,511	(2.13)
Non-Hodgkin's Lymphoma	120,804	(2.51)	23,448	(3.80)	25,700	(3.05)	5,348	(2.53)
Liver and Intrahepatic Bile Duct	165,972	(3.45)	4,042	(0.66)	9,987	(1.19)	12,002	(5.67)
Esophagus	133,342	(2.78)	3,299	(0.54)	6,690	(0.79)	2,319	(1.10)
Leukemias	112,755	(2.35)	11,997	(1.95)	19,653	(2.33)	3,357	(1.59)
Pancreas	100,670	(2.10)	15,380	(2.50)	21,906	(2.60)	8,620	(4.07)

Cancer type	WW (%)		USA (%)		W/S/N Europe (%)		Japan (%)	
Oral Cavity	97,148	(2.02)	7,823	(1.27)	8,855	(1.05)	2,220	(1.05)
Thyroid	89,349	(1.86)	10,537	(1.71)	12,368	(1.47)	5,272	(2.49)
Brain Nervous system	75,610	(1.57)	7,744	(1.26)	14,537	(1.73)	1,599	(0.76)
Kidney and Renal Pelvis	70,822	(1.47)	12,968	(2.10)	18,167	(2.16)	3,348	(1.58)
Melanoma of the skin	67,425	(1.40)	18,183	(2.95)	22,353	(2.65)	313	(0.15)
Hodgkin's Disease	23,936	(0.50)	3,093	(0.50)	5,192	(0.62)	183	(0.09)
Multiple myeloma	34,463	(0.72)	6,947	(1.13)	9,970	(1.18)	2,174	(1.03)
Other pharynx	22,076	(0.46)	1,539	(0.25)	2,890	(0.34)	286	(0.14)
Larynx	19,235	(0.40)	2,633	(0.43)	2,553	(0.30)	208	(0.10)
Nasopharynx	18,820	(0.39)	389	(0.06)	744	(0.09)	163	(0.08)
Others	573,376	(11.93)	63,022	(10.22)	93,480	(11.10)	16,972	(8.02)
All sites but skin	4,737,646	(98.60)	598,177	(97.05)	819,892	(97.35)	211,322	(99.85)
Total	4,805,071	(100.00)	616,360	(100.00)	842,245	(100.00)	211,635	(100.00)

[a] Data were taken from GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0 (http://www-dep.iarc.fr/globocan/globocan.html). W/S/N Europe is the addition of incidence data for the following countries: Western Europe: Austria, Belgium, France, Germany, Luxembourg, The Netherlands, Switzerland; Northern Europe: Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Norway, Sweden, United Kingdom, UK; Southern Europe: Albania, Bosnia Herzegovina, Croatia, Greece, Italy, FYROM, Malta, Portugal, Slovenia, Spain, Yugoslavia

combination produced a response rate of 30% compared to 12% in the gemcitabine arm (49).

Docetaxel and platinum in NSCLC. In chemotherapy-naive patients with NSCLC the response rates using docetaxel ranged from 19% to 54% with a median duration of survival ranging from 6.3 months to 11 months, and 1-year survival ranging from 21% to 71%. Docetaxel has been efficiently combined with cisplatin with an overall response rate (ORR) of 33%-46%, with carboplatin (ORR 30%-48%), with vinorelbine (ORR 20%-51%), and with gemcitabine (ORR 37%-47%) (reviewed in ref. 11).

In previously untreated patients with locally advanced or metastatic NSCLC combination of docetaxel and gemcitabine using a 3-week schedule gave response rates ranging from 25 to 50%, and median survival from 11 to 13 months. Preliminary data with weekly and bi-weekly schedules indicated maintained efficacy while reducing the risk of neutropenia. A randomized phase III trial has shown that the combination of docetaxel and gemcitabine is as active as docetaxel plus cisplatin, achieving a 1-year survival rate of 39%, with significantly less neutropenia and gastro-intestinal toxicity. The combination of docetaxel with vinorelbine in phase II studies gave average response rates of 40%, and in one study using a 2-week schedule the 1-year survival rate was 60%. In a randomized phase II trial, docetaxel plus irinotecan achieved comparable levels of activity, though with a different toxicity profile (more diarrhea but less nausea and vomiting) to docetaxel plus cisplatin. The combination of docetaxel with irinotecan and carboplatin has achieved a 1-year survival rate of 55% (reviewed in refs. 36-44).

In a phase II study carboplatin had a more favorable therapeutic index than cisplatin, particularly with regard to nonhematologic toxicities, and had proven activity in combination with docetaxel against non-small cell lung cancer. As a continuation of this study, a large, multinational, randomized phase III trial in USA, involving 1,220 patients with advanced and/or metastatic non-small cell lung cancer has compared three treatments: docetaxel plus cisplatin every 3 weeks; docetaxel plus carboplatin every 3 weeks; or a standard reference arm of vinorelbine on days 1, 8, 15, and 22 plus cisplatin on day 1 every 4 weeks. Preliminary results of the phase III trial showed that the overall survival among patients randomized to receive docetaxel plus cisplatin was significantly better than that among patients treated with vinorelbine/cisplatin and similar between the docetaxel plus carboplatin versus control arm (50).

Paclitaxel and platinum in NSCLC. Paclitaxel-based combination chemotherapy, particularly with carboplatin, has become a very popular combination in the US against advanced NSCLC; this therapy produces good palliation and prolongation of survival and is superior to the older cisplatin-based chemotherapy. A randomized phase III Hellenic trial on 509 patients has been completed comparing the activity and toxicity of paclitaxel 200 mg/m^2 and carboplatin (at an AUC of 6 on day 1) versus paclitaxel 200 mg/m^2 and gemcitabine 1,000 mg/m^2 on days 1 and 8 as first line treatment against advanced NSCLC. The median survival time was 10.4 months for paclitaxel + carboplatin compared to 9.8 months for paclitaxel + gemcitabine. The 1-year survival rates were 41.7% and 41.4%. The response rate for paclitaxel + carboplatin were 28.0% (2% complete response, 26% partial response) compared to 35.0% (5% CR, 30% PR) for paclitaxel + gemcitabine. It was concluded that either combination was equally active and well tolerated (51). Attenuated doses of paclitaxel (135 mg/m^2 i.v. for 3 h D1) and carboplatin (AUC=5, D1) every 3 weeks on 35 chemotherapy-naive patients over 65 years gave an objective

response rate of 40% with 14 partial responses (52). Second-line chemotherapy with paclitaxel improved survival and quality of life in patients with NSCLC who fail first-line platinum-based regimens. Patients with Stage IIIB/IV NSCLC who had received first-line carboplatin/paclitaxel were treated with low-dose weekly paclitaxel at 80 mg/m^2 at the time of disease progression. The trial involved 62 patients and their Karnofsky performance status was 90-100% in 31% of patients, 70-80% in 55% of patients, and 60% in 14% of patients. The toxicity profile was extremely favorable with the exception of neuropathy, a well-known side effect of paclitaxel. The median survival was 5.2 months, the 1-year survival rate was 20%, and the 2-year survival rate was 9% (53).

A Phase III randomized trial in Spain comparing paclitaxel/carboplatin with paclitaxel/cisplatin in 618 patients with advanced NSCLC has been completed. Paclitaxel was given at a dose of 200 mg/m^2 (3-h intravenous infusion) followed by either carboplatin at an AUC of 6 or cisplatin at a dose of 80 mg/m^2, repeated every 3 weeks. The response rate was 25% (70 of 279) in the paclitaxel/carboplatin arm and 28% (80 of 284) in the paclitaxel/cisplatin arm. For all randomized patients, median survival was 8.5 months in the paclitaxel/carboplatin arm and 9.8 months in the paclitaxel/cisplatin arm; the 1-year survival rates were 33% and 38%, respectively; the 2-year survival rates were 9% and 15%, respectively. Excluding neutropenia and thrombocytopenia, which were more frequent in the paclitaxel/carboplatin arm, and nausea/vomiting and nephrotoxicity, which were more frequent in the paclitaxel/cisplatin arm, the rate of severe toxicities were generally low and comparable between the two arms (54).

A randomized phase III Italian trial has compared gemcitabine + cisplatin or paclitaxel + carboplatin or vinorelbine + cisplatin on 612 chemotherapy-naive patients. Treatment schedules were: gemcitabine 1,250 mg/m^2 days 1 and 8 plus cisplatin 75 mg/m^2 day 2 every 21 days (GC arm), or paclitaxel 225 mg/m^2 (3-hour infusion) then carboplatin (AUC of 6 mg/mL.min), both on day 1 every 21 days (PCb arm), or vinorelbine 25 mg/m^2/wk for 12 weeks then every other week plus cisplatin 100 mg/m^2 day 1 every 28 days (VC arm). Overall response rates were about 30% for all three arms. There were no differences in overall survival, time to disease progression, or time to treatment failure. Median survivals for the GC, PCb, and VC groups were 9.8, 9.9, and 9.5 months. Neutropenia and nausea/vomiting were higher on the VC arm, thrombocytopenia on the GC arm, and alopecia and peripheral neurotoxicity were most common on the PCb arm (55).

Cisplatin (90 mg/m^2) and paclitaxel (175 mg/m^2) as second-line treatment in 36 patients with NSCLC who had previously undergone first-line therapy with cisplatin combined with cytotoxic drugs other than taxanes, administered once every 3 weeks with 2-6 courses per patient, gave a partial response in 40% of the patients and tolerable toxicity (56).

Radiotherapy and chemotherapy in NSCLC. Chemoradiation is important as part of the trimodality strategy including chemotherapy, radiotherapy, and surgery, which might become standard of care in the treatment of stage IIIa NSCLC. Preoperative chemotherapy is also a challenge in the treatment of NSCLC. Preliminary data from several phase II studies of chemotherapy in a preoperative setting or in combination with radiotherapy have confirmed its efficacy and good tolerability.

Chemoradiation is standard treatment for patients with unresectable locally advanced NSCLC. However, local and distant relapse rates remain high. It has been postulated that the addition of consolidation chemotherapy might further decrease the systemic relapse rate. An Australian clinical trial with three arms has compared combinations of radiotherapy and chemotherapy against NSCLC. In the first arm, 204 patients were randomized to receive conventional or accelerated radiotherapy with or without concomitant carboplatin. In the second, 15 patients were treated with concomitant cisplatin, etoposide, and radiotherapy in a single-arm study. In the third, 24 patients were treated with concomitant carboplatin, 5-fluorouracil, and radiotherapy in a dose-escalation study. The median survival for all patients was 1.4 years with an estimated 10% surviving 5 years. No significant difference was found in survival among the three arms (57). A phase II study in 25 patients with locally advanced, inoperable NSCLC used two cycles of 225 mg/m^2 paclitaxel and carboplatin at an AUC of 6 on days 1 and 22 administered prior to and following thoracic radiation. Radiation consisted of 60 Gy given over 6 weeks beginning on day 43. Twelve patients with non-progressive disease received two additional cycles of consolidation carboplatin and paclitaxel but developed grade 3 or 4 neutropenia without improvement in survival in comparison to other studies utilizing chemoradiation alone. The overall response rate was 52.1%, the median survival was 10.5 months, the 1- year survival was 45%, and the 2-year survival was 17% (58).

A Phase I/II clinical trial at the Lineberger Comprehensive Cancer Center involved 62 patients with Stage IIIA/IIIB inoperable NSCLC. This trial used two cycles of induction chemotherapy (drugs given before radiotherapy), of carboplatin at an AUC of 6 plus paclitaxel at 225 mg/m^2. This was followed by concurrent weekly carboplatin at an AUC of 2 plus paclitaxel at 45 mg/m^2 and high radiation therapy at doses escalated from 60 to 74 Gy. The median survival of 24 months, the 2-year survival rate of 50% and the 3-year survival rate of 38% obtained are encouraging. The survival was best predicted by whether the patient had finished radiotherapy, the performance status, disease stage, and postchemotherapy tumor volume (59). The combination of intrapleural and i.v. chemotherapy with cisplatin and gemcitabine followed by pulmonary irradiation and post-radiation chemotherapy with docetaxel in patients with NSCLC and malignant pleural effusion gave an overall response rate of 55% with 7% complete remission; there was 48% partial remission, 22% stable disease, and 22% progressive disease (60). In phase II and Phase III trials, docetaxel combined with radiation therapy resulted in response rates of up to 80%, with the most commonly used schedule being docetaxel at 20 to 30 mg/m^2 per week with concomitant radiation administered at fractions of 1.8 to 2.0 Gy, 5 days a week over 5 to 6 weeks. Also doses of docetaxel at 20 mg/m^2 per week combined with cisplatin at 25 mg/m^2 or carboplatin at an AUC of 2 with concomitant radiation appear to be well tolerated and active (reviewed in 61). Escalating doses of carboplatin (AUC 1.5 to 3) plus vinorelbine at 15 mg/m^2 with concomitant radiation therapy in daily fractions of 200 cGy over 5-7 weeks were used in a Phase I trial. This treatment was proposed as an alternative for

NSCLC patients not able to tolerate cisplatin-based therapy. Of the 36 patients 27 had stage II or III disease, and 9 had stage IV disease but required thoracic radiation for palliation. Of the 33 patients evaluable for response within the radiation field, 17 (52%) had complete or partial response, and 13 (39%) had stable disease (62). A dose-escalation study of weekly irinotecan and daily carboplatin with concurrent thoracic radiotherapy (60 Gy total in 30 fractions) for unresectable stage III NSCLLC has been completed. The dose-limiting toxicities were pneumonitis, esophagitis, thrombocytopenia and neutropenia. The objective response rate was 60.0%, the median survival time was 14.9 months, and the 1- and 2-year survival rates were 51.6% and 34.2%, respectively (63).

Other combinations containing platinum in NSCLC. The response rate was approximately 20% with the single-agent pemetrexed in NSCLC and approximately 40% in combination with cisplatin (reviewed in ref. 44). Pemetrexed (Alimta) in single-agent phase II studies in previously untreated NSCLC patients resulted in a response rate of 20%. Combination of Pemetrexed with cisplatin achieved response rates of 40%. As a second-line single agent in-patients with early progression after first-line treatment, the response rate was 9% (reviewed in ref. 31).

A Japanese Phase II study against NSCLC used irinotecan at 50 mg/m^2 administered as a 90-min intravenous infusion on days 1, 8, and 15 and carboplatin dosed to an AUC of 5 mgmin/ml, administered by 90-min infusion, after the irinotecan infusion on day 1. This cycle was repeated every 28 days and there were at least two cycles. The overall response rate of 25.0%, the median survival time was 10.2 months and the 1-year survival rate was 42.2% (64). A phase II study of weekly irinotecan (50 mg/m^2 intravenously on days 1, 8 and 15) and carboplatin (AUC = 2 mg/ml min, intravenously on days 1, 8, 15) for refractory or relapsed small-cell lung cancer gave a response rate of 31.0%, a median time to progression of 3.5 months and a median survival time of 6.1 months (65).

A phase II study used nedaplatin (80 mg/m^2, day 1) and vindesine (3 mg/m^2, days 1 and 8) every 3 to 4 weeks for the treatment of relapsed or refractory NSCLC on 48 patients who had previously received chemotherapy gave a median survival time of 43.6 weeks (66). A phase I trial using escalating doses of the oral platinum analogue JM216 with concomitant radiotherapy to the chest (200 cGy daily, 5 x/week) in patients with locoregionally advanced NSCLC or esophageal cancer has defined myelosuppression as the major DLT; the recommended phase II dose of JM216 with concurrent radiation therapy was 30 mg/m^2/d for 5 days (67). Paclitaxel and cisplatin combined with vinorelbine or gemcitabine as front-line chemotherapy in brain metastases from NSCLC seem to achieve responses similar to those for extracranial disease. The trial involved 26 chemotherapy-naive patients. The dosing schemes were paclitaxel (135 mg/m^2) on day 1, cisplatin (120 mg/m^2) on day 1, and either vinorelbine (30 mg/m^2) on days 1 and 15 or gemcitabine (800 mg/m^2) on days 1 and 8. Whole-brain irradiation was offered early in case of progression and later as consolidation treatment. An intracranial response was observed in 38% of the patients and the median overall survival was 21.4 weeks (68).

Triplet drug combinations in NSCLC. Three-drug regimens against NSCLC consisting of gemcitabine/carboplatin and a taxane have been evaluated both with concurrent and sequential administration of the drugs. A randomized Phase II trial involving 267 patients has been completed with four arms: paclitaxel, carboplatin, and gemcitabine (Arm A); paclitaxel, carboplatin, and vinorelbine (Arm B); paclitaxel and gemcitabine (Arm C); and gemcitabine and vinorelbine (Arm D). Response rates were in the range of 32 to 45% and there were no statistical differences between arms. The median progression free survival ranged from 4.9 to 6.6 months. The median survival ranged from 8.7 months to 10.7 months and the 1-year survival rate was 38-44%. The two-drug combinations without a platinum drug were less toxic than three-drug, platinum-based regimens (69).

A phase II study on 50 patients was aimed at evaluating the efficacy and tolerability of carboplatin, docetaxel plus irinotecan as second-line therapy to patients with locally advanced or metastatic NSCLC. This treatment gave four complete responses (8%), 24 (48%) partial responses whereas 8 patients (16%) achieved stable disease. The median survival was 14.8 months. The patients had a median Eastern Cooperative Oncology Group (ECOG) status 1 and received i.v. carboplatin at AUC of 2, docetaxel 20 mg/m^2 and irinotecan 60 mg/m^2 on days 1, 8 and 15, repeated every 5 weeks (70). Patients with inoperable advanced NSCLC (131 squamous cell, 123 adenocarcinomas, 53 undifferentiated non-small, 15 large cell, 3 adenosquamous, 3 bronchoalveolar and 8 unclassified) were treated with cisplatin / vindesine / epirubicin induction chemotherapy prior to surgery, radiotherapy, second-line chemotherapy or supportive treatment. The result of induction therapy gave 49% complete + partial responses for at least 8 weeks or a 67.6% total response rate with minor response included; thus, induction chemotherapy gave a reasonably high response rate in operable NSCLC patients and second-line radiotherapy treatment was not superior to second-line chemotherapy (71).

A Phase II multicenter single-arm study evaluated the efficacy and safety of irinotecan, paclitaxel, and carboplatin in advanced (Stage IIIB/IV) previously untreated NSCLC patients. The dosing was paclitaxel 175 mg/m^2 administered over 3 hours, followed by carboplatin at an AUC of 5 over 30 minutes and irinotecan at a starting dose level of 100 mg/m^2 over 90 minutes, all given on the first day and repeated every 21-days. Twelve of 38 evaluable patients had confirmed tumor responses (32%), while 21 of 38 patients (55%) had stable disease (including 12 patients [32%] with minor responses). The median survival was 12.5 months (72). A paclitaxel/carboplatin-based chemotherapy with 3 arms involving 321 NSCLC patients has been completed. Treatments involved paclitaxel/carboplatin, paclitaxel/carboplatin/gemcitabine, and paclitaxel/carboplatin/vinorelbine. After a median follow-up of 58 months, the median survival for the entire group of patients was 8.6 months, with actual 1-, 2-, and 3-year survival rates of 40%, 19%, and 7%, respectively. No statistically significant differences in survival were seen among the three regimens. It was concluded that paclitaxel/carboplatin-based regimens, in addition to prolonging median survival and improving 1-year survival, resulted in substantial improvements in the 2-year survival of patients when compared with supportive care or traditional cisplatin-based regimens. No advantages of the three-

drug regimens were observed compared with paclitaxel/carboplatin (73). A phase I study of carboplatin combined with irinotecan and docetaxel on a divided schedule with recombinant human granulocyte colony stimulating factor (rhG-CSF) support gave encouraging survival data (74).

Studies in elderly populations in NSCLC. More than 50% of NSCLC patients are diagnosed over the age of 65 and about 33% of all patients with NSCLC are over the age of 70. Chemotherapy in the elderly is an important issue because of the poor performance status of this group of patients. Elderly patients tolerate chemotherapy poorly because of impaired organ function and co-morbidities. For this reason, these patients are often not considered eligible for aggressive cisplatin-based chemotherapy, the standard medical treatment of advanced NSCLC. Combined chemo-radiotherapy in locally advanced disease increases toxicity and does not appear to impart a survival advantage compared to radiation therapy alone (75,76). The randomized Elderly Lung Cancer Vinorelbine Study Group (ELVIS) trial has shown that elderly patients treated with vinorelbine plus best supportive care (BSC) have significantly improved survival and quality of life when compared with patients treated with BSC alone; patients receiving vinorelbine monotherapy achieved an objective response rate of 19.7%. The main adverse effect of vinorelbine monotherapy in the elderly was myelosuppression. Furthermore, the clinical trials of the Multicenter Italian Lung Cancer in the Elderly Study (MILES) and of the Southern Italy Cooperative Oncology Group (SICOG) demonstrated that the combination of gemcitabine plus vinorelbine in this patient population did not further improve survival or quality of life compared to single chemotherapy with vinorelbine or gemcitabine; objective response rates for vinorelbine/gemcitabine combination therapy in these phase III trials were 20 and 22%, respectively. The addition of gemcitabine to vinorelbine increased the incidence of both hematological and nonhematological adverse events (15, 77,78). In a study using gemcitabine-cisplatin in advanced NSCLC in elderly patients the clinical benefit could be derived from the evaluation of eight parameters: PS, cough, dyspnea, pain and hemoptysis, weight loss, asthenia and anorexia (79).

5. Small-cell lung cancer (SCLC)

Small cell carcinoma accounts for approximately 20% of all lung cancers, is a tumor of neuroendocrine origin, very aggressive, metastasizing early and often. Smoking is a well-demonstrated etiologic factor. SCLC is more responsive to chemotherapy than NSCLC but overall survival remains poor even in limited disease. A combination of paclitaxel, etoposide and carboplatin is an often-used regimen against SCLC. In a Spanish study involving 95 patients with SCLC using etoposide 80 mg/m^2/day i.v. on days 1, 2 and 3, paclitaxel 175 mg/m^2 i.v. on day 3 and carboplatin at an area under the concentration time curve (AUC) of 6, i.v. on day 3, of a 3-week cycle, and repeated for up to 6 cycles gave an overall response (OR) rate of 74%. The percentage complete response was 49% in the group of patients with limited-stage disease versus 20% in extensive-stage disease patients (80). A German study against SCLC using paclitaxel (175 mg/m^2 1 h i.v. infusion) immediately followed by a 30 min infusion of carboplatin at an area under the concentration time curve (AUC) of 5 on day 1 and etoposide 50 mg orally twice daily given on days 2-8 and with for a maximum of 6 courses repeated every 21 days gave an overall response rate of 82.1% with 17.8% complete remissions and 64.3% partial remissions. The median survival for patients with limited disease was 20.5 months with a 1 year survival rate of 71.4% and a 3 year survival rate of 21.4%. On the contrary, the median survival of patients with extensive disease and without distant metastases was 11 months with a 1 year survival rate of 31.3% and a 3 year survival rate of 3.1% (81). 55 consecutive limited disease SCLC patients were treated with three 21-day cycles of cyclophosphamide, epiadriamycin and vincristine (CEV) as induction chemotherapy giving an objective response in 80% of the patients. These then received treatment intensification consisting of thoracic irradiation (twice-daily, 1.5 Gy per fraction, to a total dose of 45 Gy) and concomitant chemotherapy with carboplatin and etoposide plus recombinant granulocyte colony stimulating factor (G-CSF). The long-term results from this study are similar to the best reported in the literature: Of 44 patients submitted to intensification with thoracic irradiation plus chemotherapy, 32 (73%) had a complete and 12 (27%) a partial response. Median overall survival of all 55 patients was 17 months with actuarial survival probabilities of 2 and 5 years, 32 and 25%, respectively (82).

Intensive weekly chemotherapy plus thoracic irradiation was superior to standard chemotherapy in the treatment of extensive-stage SCLC. Patients were randomized to receive cisplatin, vincristine, doxorubicin, and etoposide (CODE) or alternating cyclophosphamide, doxorubicin, vincristine/etoposide and cisplatin (CAV/EP). The response rate with CODE was higher than that of CAV/EP, but progression-free and overall survival were not significantly improved (83). Recombinant human interleukin-3 (rhIL-3) shortened both the duration of chemotherapy-induced neutropenia and thrombocytopenia; concurrent administration of rhIL-3 and of a chemotherapy regimen for relapsed small cell lung cancer (vincristine, ifosfamide, mesna, and carboplatin on day 1 every four weeks) did not enhance myelotoxicity and improved bone marrow recovery (84).

The neuron-specific enolase (NSE) tumor marker levels in 130 patients suffering from SCLC during systemic therapy were found to be consistent with clinical findings based on imaging techniques but remained of doubtful utility in an individual patient (85).

6. Epithelial ovarian cancer (EOC)

EOC is the most common cause of death from gynecological cancers, affecting approximately 1 in 75 women in the developed world. It accounts for about 4% of all cancers in women in the United States, with over 23,000 cases diagnosed annually. In most cases (>75%), the disease is disseminated beyond the ovary at diagnosis. Ovarian cancer spreads early in the disease into the abdomen. At surgery, large pelvic tumor lesions are found together with multiple tumor lesions involving the omentum, bowel, and mesentery together with a diffuse peritoneal carcinomatosis and diaphragmatic involvement. Unfavorable prognostic factors include stage IV disease,

peritonitis carcinomatosis, or ascites at primary surgery. A multimodality approach with cytoreductive surgery and taxol platinum-based chemotherapy is the mainstay of treatment of advanced ovarian cancer. Randomized trials over the past 10 years have indicated the superiority of paclitaxel-based treatment and that carboplatin is equivalent to cisplatin, but better tolerated. After primary cytoreductive surgery, standard treatment for patients with stage III and IV disease is systemic combination chemotherapy consisting of six cycles of paclitaxel and carboplatin. Docetaxel may be a better option than paclitaxel, with reduced neurotoxicity and comparable efficacy. Overall treatment results remain unsatisfactory, since the median survival for these patients is 2-3 years. The worse prognosis of the patients with a suboptimal primary cytoreductive surgery can be improved by an interval cytoreductive surgery after platinum-containing induction chemotherapy; the 5-year survival of the surgery patients was 24% versus 13% for the no-surgery patients (reviewed in refs. 86-90).

Cisplatin or carboplatin are the most important drugs to be included in first-line regimens against EOC. Resistance to platinum chemotherapy is a major reason for treatment failure and poor prognosis. Despite improvements in median and overall survival using a combination of platinum and paclitaxel, long-term survival rates for patients with advanced EOC remain disappointing, and the development of more effective primary therapy remains a priority. Standard therapy for patients affected with advanced EOC is cytoreductive surgery followed by combination chemotherapy. However, although most patients obtain clinical complete or partial response, relapse is common and salvage chemotherapy is often needed. Several chemotherapy agents have demonstrated activity individually in patients with recurrent EOC including gemcitabine, topotecan, liposomal doxorubicin (Doxil/Caelyx), and prolonged oral etoposide; these drugs inhibit DNA synthesis required for repair of platinum-DNA adducts. However, efforts to develop multidrug combinations with platinum and paclitaxel have encountered substantial bone marrow toxicity. With international collaboration, the Gynecologic Oncology Group (GOG) has launched a five-arm trial (GOG-0182) that will compare these combinations against carboplatin-paclitaxel (reviewed in refs. 91,92). Ninety previously untreated patients with advanced epithelial ovarian cancer were randomized, after initial cytoreductive surgery, to receive 175 mg/m^2 paclitaxel as a 3-hour infusion with either carboplatin at an AUC of 7 (group A) or carboplatin at an AUC of 7 on courses 1, 3, and 5, alternating with cisplatin 75 mg/m^2 on courses 2, 4, and 6 (group B). A 52% and 39% complete response rate for groups A and B, respectively, with no statistically significant difference between the groups was observed and a median time to progression of 20.36 months for group A (93).

Platinum/Paclitaxel. Carboplatin is a safe and effective first-line treatment for women with advanced ovarian cancer as deduced from four large randomized trials of paclitaxel in combination with platinum against a platinum-based control treatment representing 3,588 patients. Very positive results favor the paclitaxel/cisplatin over the cyclophosphamide/cisplatin regimen (reviewed in ref. 94). A meta-analysis found that, compared with non-platinum-based regimens, platinum, alone or in combination with other agents, improved survival when used as first-line chemotherapy for ovarian cancer. In addition, a randomized trial of cisplatin plus paclitaxel versus carboplatin plus paclitaxel did not detect a significant difference in survival between these regimens. While hematologic adverse effects were more frequent with carboplatin than with cisplatin, nonhematologic adverse effects were less frequent with carboplatin. In two randomized trials, treatment with paclitaxel plus cisplatin resulted in improved survival compared with cyclophosphamide plus cisplatin. The combination of paclitaxel with cisplatin did not appear to increase the incidence of serious adverse effects (reviewed in ref. 95). A randomized phase I/II trial with weekly cisplatin at 70 mg/m^2 (days 1, 8, 15, 29, 36, 43) in combination with escalating doses of paclitaxel either 4-weekly or weekly was conducted in 49 patients with advanced ovarian cancer. Paclitaxel could be safely escalated to 225 mg/m^2 4-weekly or 100 mg/m^2 weekly, with fatigue as the major adverse event. The overall response rate was 94% in 17 evaluable chemotherapy-naive patients and 84% in 25 patients who received before platinum-based chemotherapy. The median overall survival was 41 months (chemotherapy-naive: 48 months, recurrent: 24 months) (96).

A Japanese study on 110 patients with epithelial ovarian cancer using carboplatin at a dose of AUC 5 and a dose escalation of paclitaxel at levels of 150, 175 and 200 mg/m^2 observed grade 4 neutropenia in four of six patients in the paclitaxel 200 mg/m^2 administration group. At the chosen 175 mg/m^2 dose of paclitaxel in this regimen the response rate was 66.7% and the median progression-free survival was 432 days (97). A study of carboplatin and paclitaxel on mean age 73 versus mean age 49 women showed statistically significant differences; for example older women received lower carboplatin dose and dose intensity, had a lower hemoglobin and serum albumin, and a higher performance status postoperatively (98). Changes in peripheral blood lymphocyte (PBL) subsets during topotecan-based chemotherapy in advanced ovarian cancer patients were examined by flow cytometric analysis. Patients were treated with a) topotecan in association with carboplatin and taxanes as first line chemotherapy, b) topotecan alone or c) topotecan in association with carboplatin both as second line of treatment after platinum. Before starting chemotherapy, the absolute number of lymphocytes and the CD2$^+$, CD3$^+$, CD4$^+$ subsets were significantly lower in pre-treated patients. Topotecan-based therapy did not have a negative impact on PBL in either chemotherapy-naive or in pretreated ovarian cancer patients (99). Paclitaxel, carboplatin and cyclophosphamide as a first-line treatment was well tolerated. Abdominal pain and hematological toxicities were minor, while neurotoxicity grade I/II was reported in only 20% and myalgia in 24% of patients; adverse effects were fully reversible. After treatment 13 of 18 (72%) of the patients had no evidence of disease (100).

Gemcitabine, paclitaxel, and platinum (carboplatin) have demonstrated a response rate of 100% in patients with relapsed ovarian cancer as first line treatment; the median time to progression was 10 months and the median survival was more than 27 months (reviewed in ref. 101). In a Phase II study, chemonaive patients with advanced (stage III and IV) epithelial ovarian cancer received gemcitabine 1,250 mg/m^2 on days 1 and 8 and cisplatin 100 mg/m^2 on day 1, every 3 weeks, up to eight cycles. Of the 41 patients evaluable for tumor response, 20 had a

partial response and nine had a complete response, for an overall clinical and pathologic response rate of 70.7%. Median overall survival for all 42 patients was 23.4 months and the median progression-free survival time was 10.4 months (102). An intensive chemotherapy regimen combined with G-CSF and stem cell support in France as first-line treatment on 15 patients with stage III-IV ovarian cancer, all of whom underwent laparotomy to maximize tumor debulking and second-look surgery, gave promising results. The first cycle consisted of cyclophosphamide i.v. at 6 g/m^2; second, third, fourth and fifth cycles were paclitaxel at 250 mg/m^2 and the sixth and seventh cycles were carboplatin at AUC 18. All patients had macroscopic complete responses and 10 patients had complete histologic response in a 48 month median follow-up. Twelve patients had further progression at a median of 27 months (range, 9 to 42); three patients had no evidence of disease progression (103).

There are methods to predict resistance to platinum chemotherapy in patients by culturing tumor specimens and determining the percentage cell inhibition in vitro in the presence of cisplatin or carboplatin. Such specimens are then classified as low, intermediate or extreme drug resistance. Ovarian cancer patients with extreme resistance to platinum (17 patients) had progression-free survival of 6 months and an estimated overall 5-year survival of 19% when treated with standard platinum-based regimens. On the contrary, the group of patients with low resistance to platinum (62 patients) had progression-free survival of 24 months and overall 5-year survival of 68% when treated with standard platinum-based regimens (104).

Docetaxel at 70 mg/m^2 and carboplatin (AUC of 5) were administered consecutively on day 1 of a 21-day cycle for five planned cycles in chemo-naive patients with epithelial ovarian cancer. 9 of 11 assessable patients responded to the regimen. The major toxicity with this regimen was neutropenia of grade 3 (27% or 7 out of 26 patients) and grade 4 (69% or 18/26) which was brief and reversible with G-CSF support. Nausea/emesis, fatigue, arthralgia/myalgias, and alopecia were the most common nonhematologic toxicities, in which no grade 3 or 4 toxicity was observed (105).

7. Early and advanced cervical cancer

Cancer of the cervix accounted for 9.79% of all cancer cases among women worldwide with almost half a million new cases in 2000 and is the second most frequent type of cancer after breast cancer; cervical cancer accounts for only 2.15% of all cancer cases among women in USA but for 5.52% of all cancer cases among women in Japan (Table I). Early cervical cancer includes a broad range of disease, from clinically undetectable microinvasive cancer to large, bulky tumors that replace the entire cervix. In the United States, patients with stromal invasion of less than 3 mm and no lymphvascular involvement (stage IA) are usually treated conservatively with simple hysterectomy whereas patients with invasion of more than 3 mm or lymphvascular space involvement are at risk for pelvic lymph node metastasis and are most often treated with radical hysterectomy and pelvic lymphadenectomy.

Radiation therapy is preferred for women who may not tolerate radical surgery with tumors larger than 4 cm in diameter. Recent data convincingly demonstrate that the combination of cisplatin-based chemotherapy and radiation therapy significantly improves overall survival rates in cervical cancer patients (reviewed in ref. 106), reduces the risk of death by 30-50% (107) and gives an overall survival advantage of 30% (108). The molecular mechanism lies in the induction of strand breaks by the ionizing radiation that adds to the DNA damage caused by the platinum crosslinks and posses a formidable task to the DNA repair machinery.

The best treatment for advanced cancer of the cervix is primary radiotherapy (both external beam and intracavitary) with concurrent, cisplatin-based chemotherapy (reviewed in 109). Cisplatin-based neoadjuvant chemotherapy before surgery appeared to be more promising because this treatment modality could increase the operability rate and reduce the incidence of positive nodes and other pathological risk factors. Recently, five prospective randomized trials compared concurrent cisplatin-based chemotherapy and irradiation versus hydroxyurea plus irradiation or irradiation alone. All showed a significant improvement in the outcome of patients treated with concurrent cisplatin-based chemoradiation (reviewed in 110). Based on these data, the National Cancer Institute released a Clinical Announcement stating that concurrent cisplatin-based chemoradiation should be the new standard of therapy for high-risk early stage and locally advanced cervical cancer.

A weekly carboplatin and docetaxel schedule in a Phase I trial for locally advanced primary and recurrent cervical cancer has used a dose-escalation of docetaxel of 25, 30 and 35 mg/m^2 accompanied by carboplatin at AUC 2, AUC 2.5, and AUC 3. Dose-limiting toxicities included WHO grade (G) 3 hematotoxicity, G4 mucositis, and G2 neurotoxicity. The MTD was reached at docetaxel 35 mg/m^2 and carboplatin AUC 2 mg/mL.min. The overall response rate was 65% in the entire group of evaluable patients and 77% in patients with primary locally advanced cervical cancer (111).

8. Testicular cancer and germ cell tumors

Testicular germ-cell cancer is relatively rare, affecting less than 6 men per 100,000; nevertheless, it is the most common cancer in men under 45 years. The two main types of tumors, seminomas and non-seminomas, respond to treatment differently. The standard treatment for stage I seminomas following orchidectomy is infradiaphragmatic lymph node irradiation with response rates approaching 100%, although surveillance is also a management option. The majority of early stage non-seminomas are cured by orchidectomy alone (reviewed in ref. 112). Testicular germ cell cancer is one of the very few cancers that are highly sensitive to and curable by cisplatin-based chemotherapy even in an advanced stage. Bleomycin, etoposide and cisplatin, (BEP), is the most widely used chemotherapeutic regimen for metastatic germ cell tumors. However, in a few cases resistance to cisplatin occurs and patients subsequently die from progressive disease. Cisplatin resistance was associated with substantially decreased apoptosis in vitro and in derived nude mice xenografts (113). The treatment of low-stage testis cancer (defined as clinical stage I or

low-volume clinical stage II disease) varies, depending on whether or not the orchiectomy specimen reveals seminoma or nonseminoma. Treatments for clinical stage I seminoma include radiotherapy to the retroperitoneum, surveillance, or two courses of carboplatin chemotherapy. For clinical stage II seminoma, therapeutic options include radiotherapy or cisplatin-based chemotherapy (reviewed in ref. 114).

Only 20-30% of patients with refractory or recurrent germ cell tumors (GCT) are cured by salvage chemotherapy. A controversial question in patients with poor prognosis germ-cell tumors and in patients with refractory or relapsed disease after cisplatin-based chemotherapy as the first-salvage attempt is whether or not to use conventional-dose or high-dose chemotherapy. As the majority of patients will suffer systemic relapses, chemotherapy is the mainstay of treatment (115). A randomized clinical trial on 124 patients compared the efficacy of a low-dose (80% of dose) regimen of cisplatin, doxorubicin and cyclophosphamide alternated with vinblastine and bleomycin (CISCA/VB) versus the original CISCA/VB regimen in patients with disseminated nonseminomatous germ-cell tumors (NSGCT) having a predicted favorable outcome according to the M.D. Anderson Cancer Center classification [testicular primary and human chorionic gonadotropin (hCG) serum level <50000 mIU/ml]. 53 of 65 patients (82%) on the original CISCA/VB regimen and 53 of 59 patients (90%) on the low-dose CISCA/VB regimen achieved a complete response to therapy. The 5-year overall survival rate was 93.7% and 94.1% in the original CISCA/VB arm and the low-dose CISCA/VB arm, respectively. In addition, the low-dose CISCA/VB regimen resulted in significantly less neutropenic fever, grade 4 thrombocytopenia and severe mucositis than the original CISCA/VB regimen (116).

A pilot study investigated the efficacy of salvage chemotherapy with irinotecan in combination with cisplatin (CDDP) or nedaplatin. The combination chemotherapy consisted of 100-150 mg/m^2 irinotecan on Days 1 and 15 or 200-300 mg/m^2 on Day 1 in combination with 20 mg/m^2 cisplatin on Days 1-5 or 100 mg/m^2 nedaplatin on Day 1 every 4 weeks. Among 18 patients the response rate was 50 % (two complete responses and seven partial responses) and a 5-year survival rate of approximately 53% (117).

First-line sequential high dose chemotherapy is under investigation in patients with "poor prognosis" metastatic germ cell tumors in order to improve survival. Despite the use of autologous peripheral blood stem cell transplantation and granulocyte colony stimulating factor chemotherapy dose intensification is associated with severe hematotoxicity including anemia, which may significantly affect quality of life and tolerability of chemotherapy. A total of 101 newly diagnosed patients with "poor prognosis" metastatic nonseminomatous germ cell tumors were treated with one cycle of standard VIP followed by three cycles of HD-VIP-chemotherapy (etoposide, ifosfamide, cisplatin) within a large phase I/II study. 97 patients had to receive red blood cell transfusions because of hematological toxicities (118).

9. Squamous cell carcinoma of the head and neck (SCCHN)

Head and neck cancer includes cancers of the oral cavity, pharynx, paranasal sinuses, nasal cavity, larynx, thyroid, and salivary glands. It may also include skin tumors of the face and neck and tumors of the cervical lymph nodes. Excluding superficial skin cancers and lymphomas of the head and neck it is conservatively estimated that about 66,000 persons are diagnosed with head and neck cancer annually in USA, which is about 6% of all cancers in men and 4.3% of all cancers in women (Table 1). Worldwide 771,009 H&N cancer cases were reported in 2000 among men (14.31% of all cancer cases) and 379,970 cases among women (7.91% of all cancer cases). The lower SCCHN incidence in women comes from the lower cigarette consumption in women compared to men; a synergistic effect for SCCHN has been noted between alcohol and tobacco most likely from an increased solubility of tobacco related carcinogens; approximately 75 to 80% of all patients with oral carcinoma are noted to consume alcohol. Other etiological factors include HPV 16 and 18 and Epstein-Barr virus infections, exposure to sunlight, poor oral hygiene, recurrent herpes type-I stomatitis, and environmental carcinogens. For example, people of Chinese origin seem to be at particular risk of developing nasopharyngeal cancer after infection with the Epstein-Barr virus. Most head and neck cancers are squamous cell carcinomas (over 90%); the remaining cancers include lymphoepitheliomas, spindle cell carcinomas, sarcomas, melanomas, lymphomas (most often diffuse non-Hodgkins lymphomas), verrucous cancers, and undifferentiated carcinomas.

Despite aggressive early therapy, resistant head and neck squamous-cell cancers (HNSCC) often recur, accompanied by distressing symptoms (119). Options for local control in relapse are limited: prior extensive surgery and radiation therapy raise the risk of unacceptable complications with additional similar interventions (120).

Three major modalities are currently employed in the treatment of SCCHN: surgery, radiation and chemotherapy. Over the last 10 years, overall survival rates for patients with head and neck cancers have improved as has quality of life. New standards of care have been defined for patients with nasopharyngeal cancer and for those with advanced unresectable disease (121). Cisplatin is among the most active single agents against squamous cell carcinoma of the head and neck (SCCHN), and it is still the reference drug in the induction chemotherapy setting, when used in combination with infusional 5-FU. However, dose-related toxicity has been one of the major limiting factors in cisplatin-based therapies, because high doses are required for obtaining a significant antitumor effect. The intensification chemotherapy regimens required for effective local-regional control are also highly toxic (122), particularly in debilitated late-stage patients who typically develop recurrent head and neck cancer (123,124).

Solid evidence shows that chemotherapy administered during the course of radiotherapy (concurrent chemoradiotherapy) increases both local tumor control and patient survival in a number of cancer sites, including head and neck cancer. Concurrent, but not induction chemoradiotherapy improved locoregional tumor control and survival benefit in head and neck carcinoma relative to radiotherapy alone (125).

A phase II trial against locally advanced head and neck cancer involved 123 previously untreated patients with locally advanced squamous carcinoma of the head and neck. They received 6 weeks of induction chemotherapy followed by concurrent high-dose radiation therapy and weekly chemotherapy. Induction chemotherapy included paclitaxel (200 mg/m^2, 1-hour i.v. infusion) on days 1 and 22, carboplatin (AUC 6.0 i.v.) on days 1 and 22, and 5-fluorouracil (225 mg/m^2 per day, 24-hour continuous i.v. infusion) on days 1-43. After 1 week without therapy, radiation therapy was administered to the primary site and the bilateral cervical lymph nodes using 1.8 Gy/day, 5 days weekly, to a total dose of 68.4 Gy. During radiation therapy, patients also received six weekly doses of paclitaxel (50 mg/m^2, 1-hour i.v. infusion) and carboplatin (AUC 1.0 i.v.). Seventy of 116 evaluable patients (60%) had a clinical complete response to treatment and the 2-and 3-year actuarial survivals were 66% and 51%, respectively (126). Thymidylate synthase is the target enzyme of both raltitrexed and 5-FU; however, the two drugs have distinct sites of action on the enzyme and the combination of the two agents may be synergistic. Patients not pretreated with chemo- or radiotherapy received 60 mg/m^2 cisplatin and 2.5 mg/m^2 raltitrexed on day 1 and 250 mg/m^2 LFA and 900 mg/m^2 5-FU on day 2. This treatment gave 10 CR (28%) and 19 partial responses (PR) (53%), for an overall response rate of 81% (127).

The combination of cisplatin and docetaxel have demonstrated activity in squamous cell carcinomas of the lung, esophagus and in recurrent metastatic head and neck cancer. Treatment using 75 mg/m^2 docetaxel (1-hour infusion) and 75 mg/m^2 cisplatin (90-min infusion) on day 1, repeated every three weeks for a maximum of 6 courses gave an overall response rate of 52.5% with 17.5% complete responses (128). A 53% response rate was obtained in a similar study (129).

A Phase II trial of vinorelbine, cisplatin and continuous infusion of 5-fluorouracil followed by hyperfractionated radiotherapy gave a response in 19 patients (76%) including three complete responses and 16 partial responses (130). Patients with Stage IVa/b HNSCC were treated with Stealth liposomal cisplatin (SPI-077) escalated from 20-200 mg/m2 in six dose levels, given intravenously twice two weeks apart, concurrent with radiation therapy (60-72 Gy in 6-7 weeks). Further dose escalation was stopped in the absence of dose-limiting toxicity to address the reformulation of the liposomally bound cisplatin (131).

A Phase II trial consisting of 3 cycles of induction chemotherapy with cisplatin, 5-FU, l-leucovorin and interferon alpha2b followed by 7 cycles of 5-FU, hydroxyurea and concomitant radiation for 5 days for a total radiation dose of 70 Gy in patients with advanced head and neck cancer has been completed. The toxicity of this regimen was significant and consisted mainly of mucositis and, to a lesser extent, neutropenia/thrombocytopenia. The patients who achieved complete response were 3 out of 19 (15.8%), those who achieved a partial response were 7/19 (36.8%) whereas the median progression-free survival was 10.5 months. Conservative surgical resection was reserved to patients with no optimal response and radical surgery was performed as salvage treatment. Overall, this sequential induction chemotherapy and chemoradiotherapy program had been found moderately active and significantly toxic and was not recommended for a phase III randomized study (132). The efficacy and toxicity of a combination regimen consisting of 13-cis retinoic acid under the brand name Accutane at 1 mg/kg/d orally for 14 days, carboplatin at AUC of 5 mg/ml.min, and paclitaxel at a dose escalation of 135, 155, 175, 195, 205, or 225 mg/m^2 i.v. on day 8 every 4 weeks for 6 cycles has been studied on patients with recurrent or metastatic squamous cell carcinomas (12 head and neck, 4 cervix, 1 esophagus, and 1 anus). The maximum tolerated dose (MTD) was 205 mg/m^2 paclitaxel. There was one complete response, three partial responses (all in cervical cancer), and 2 stable diseases. In spite of 21 grade III or IV toxicities among the 72 treatment cycles, including neutropenia, anemia, thrombocytopenia, elevated prothrombin, elevated alkaline phosphatase, weight loss, alopecia, and three deaths from aspiration pneumonia and septic shock this regimen was recommended for a Phase II trial (133).

Especially important with low toxicity to the patient appear to be local intratumoral treatments. A phase III placebo-controlled study in advanced head and neck cancer was published using intratumoral cisplatin/epinephrine gel (120). Patients received intratumoral cisplatin/epinephrine injectable gel or placebo (up to 6 weekly treatments over 8 weeks); 25% (14 out of 57) of tumors responded (16% complete regression, 9% partial regression), vs 3% (one out of 35, complete regression) with placebo. The most frequent adverse event was pain during injection and the next most frequent was local cytotoxic effects consistent with the gel's mode of action (120).

Tumor stage, node stage, p53 gene status, and bcl-2 expression were independent predictors of tumor response to platin-fluorouracil in patients with squamous-cell carcinomas of the head and neck (134). Topoisomerase IIα expression was significantly higher in tumors of low and moderate differentiation versus tumors of high differentiation (135). Future efforts may be directed in combinations of chemotherapy with gene therapy. Combination of cisplatin with nonviral IL-2 gene therapy resulted in significant antitumor effects while avoiding dose-limiting toxicity in a head and neck squamous cell cancer murine model; a clear synergistic interaction between cisplatin and IL-2 was observed (136).

Nasopharyngeal cancer. A Phase II trial for Stage III and IV resectable oral cavity, oropharyngeal, or hypopharyngeal squamous cell carcinoma has been completed. The treatment included preoperative radiotherapy with concurrent cisplatin, followed immediately with surgery and intraoperative radiotherapy, and completed with early postoperative weekly paclitaxel (beginning on day 6 after surgery), two additional cisplatin cycles, and concurrent once daily radiotherapy beginning on day 28 after surgery. This regimen gave a time at risk of 2.6 to 24.7 months and excellent disease control rates (137). 210 patients with nasopharyngeal carcinoma and with cervical nodal metastasis were recruited onto a randomized trial comparing induction chemotherapy followed by radiotherapy (CT + RT) and radiotherapy alone (RT) using a similar treatment protocol. Patients in the CT + RT arm received two to three cycles of cisplatin, 60 mg/m^2 day 1, + epirubicin, 110 mg/m^2 day 1, followed by radiotherapy. At the end of radiotherapy, 92% of patients in the CT + RT arm and 86% in the RT arm achieved complete response (CR) in the neck. Radical neck dissection successfully salvaged 41% of neck failures in the CT + RT arm

and 46% in the RT arm. It was concluded that induction chemotherapy does not seem to improve the regional control and survival in nasopharyngeal carcinoma patients with regional metastasis compared with radiotherapy alone and is not recommended as a routine treatment (138). More recently, continuous cisplatin (20 mg/m^2/day) plus 5-FU (400 mg/m^2/day) both administered as a 96h infusion during the weeks 1 and 5 of RT have shown a better 5-year overall survival rate than RT alone (72% versus 54%) for patients with advanced nasopharyngeal carcinoma (139**).**

Gemcitabine alone or with cisplatin is active among patients with metastatic or locally recurrent nasopharyngeal carcinoma. Patients either received 1000 mg/m^2 gemcitabine on days 1, 8, and 15 every 28 days as a single agent, or gemcitabine with cisplatin given on day 2 at 70 mg/m^2. In the gemcitabine group (18 patients) there were five (28%) partial responses (PR) and one (6%) complete response (CR), giving an overall response rate of 34%. In the gemcitabine + cisplatin group (14 patients) there were two (14%) CRs and seven PRs (50%), giving an overall response of 64% (140).

10. Esophageal cancer

Esophageal cancer is the 6th most frequent cancer in men world-wide (5.2% of all cancers 279,000 new cases in 2000) and the 11th most frequent cancer in women (2.8% of all cancers 133,000 new cases in 2000) (Table 1). Paclitaxel, docetaxel, irinotecan, gemcitabine, vinorelbine, cisplatin and carboplatin have their place in chemotherapy of esophageal cancer. In phase II evaluation of weekly irinotecan plus cisplatin, response rates have exceeded 30% in esophageal and gastric cancers (reviewed refs. 141,142). Of 106 consecutive patients with squamous cell carcinoma of the esophagus treated with cisplatin (100 mg/m^2 per day) on Day 1 and fluorouracil (1000 mg/m^2 per day) on Days 1-4 given for two cycles, with concomitant RT (30 Gy in 15 fractions) over 19 days, the overall survival rate was 22% at 5 years and 12% at 10 years (143). About half of the patients with advanced esophageal cancer achieved a partial or complete response with a median duration of 13 months treated with a fixed dose of cisplatin of 70 mg/m^2 on days 1, 8, 15, 29, 36 and 43 and escalating doses of paclitaxel up to 110 mg/m^2 in a Phase I study (144). A combination of paclitaxel 180 mg/m^2 with cisplatin mg/m^2 every 14 days in the treatment of advanced cancer of the esophagus or the gastro-esophageal junction gave a 4% complete response, 39% partial response, 43% stable disease and 14% progressive disease in a Phase II study with 51 patients (145**).** Irinotecan, mitomycin and cisplatin administered to outpatients with previously untreated inoperable gastro-esophageal cancer in a 28-day cycle gave an overall response rates of 42%, with a median survival of 9.5 months; in patients with pancreatic cancer, the overall response rate was 42% with a median survival of 8 months (146). A phase II study of a vinorelbine-cisplatin combination in metastatic esophageal squamous cell carcinoma gave a response rate of 37% with a median duration of response of 7.7 months (reviewed in ref. 147).

The standard radiation dose for patients treated with concurrent 5-FU and cisplatin chemotherapy is 50.4 Gy. A higher radiation dose (64.8 Gy) did not increase survival or local/regional control. The chemotherapy scheme was 1,000 mg/m^2 5-FU for 4 days and 75 mg/m^2 cisplatin bolus on day 1 (148). A phase I study using vinorelbine and concurrent radiation (64 Gy) in previously untreated patients with inoperable locally advanced esophageal cancer ineligible for cisplatin-5-FU-based chemoradiation gave a major objective tumor response at each dose level (reviewed in ref. 147).

One aim of treatment for advanced esophageal cancer is relief of dysphagia with minimal treatment-related morbidity. A multicenter phase II trial was set to evaluate the safety and efficacy of primary chemotherapy followed by chemoradiation for localized adenocarcinoma or squamous carcinoma of the esophagus. Chemotherapy comprised five 3-weekly cycles of cisplatin and protracted continuous infusion of 5-fluorouracil, with conformally planned radiotherapy commencing at the start of the fifth cycle. Response rates to chemotherapy and to the entire treatment program were 47%, the dysphagia score improved in 54% of patients and the median survival duration was 14.6 months with Grade III/IV toxicity occurring in 38% of patients (149). Weekly doses of cisplatin (35 mg/m^2, maximum 7 cycles) concurrent with 66 Gy/33 fractions external beam radiotherapy (EBRT) has been used against inoperable or metastatic squamous cell esophageal cancers; improvement in the swallowing status was seen in 84% with a median duration of dysphagia relief of 6 months and an overall survival of 9 months (150). Weekly endoscopic intratumoral injection of cisplatin/epinephrine gel on 24 patients has been used to relieve obstruction and improve swallowing (the gel is designed to minimize diffusion of active drug away from the tumor injection site). Eight patients felt that their ability to swallow improved (151).

Other treatments for advanced esophageal carcinoma include combination cisplatin, 5-fluorouracil and interferon-α (152), a combination of cisplatin and late course accelerated fractionation radiotherapy (153), continuous infusion carboplatin, 5-fluorouracil, and radiotherapy (154), CPT-11 plus cisplatin (155), concurrent chemoradiotherapy with a protracted infusion of 5-fluorouracil and cisplatin (156), combination of epirubicin, cisplatin, and protracted venous-infusion fluorouracil in previously untreated patients with advanced esophagogastric cancer (157) and 5-FU/cisplatin combination chemotherapy with a new schedule of hydroxyurea, leucovorin, 5-FU and cisplatin (158). A case of complete regression of esophageal cancer with concomitant liver metastasis was achieved by concurrent chemoradiation therapy (159). Vinorelbine 25 mg/m^2 on days 1 and 8 plus cisplatin 80 mg/m^2 on day 1, every 3 weeks gave a progression-free survival was 3.6 months and median survival of the whole group was 6.8 months. At cycle 2, 43% of the patients reported at least a moderate improvement in global health status and 25% experienced a large improvement (160). An experimental preclinical study uses Cisplatin-loaded microspheres on rat models of esophageal cancer (161).

Few results from preoperative adjuvant chemotherapy are controversial depending on the type of chemotherapy, on whether radiation was used, stage of the disease and other factors. For example, a continuous-infusion regimen with cisplatin and 5-FU as preoperative adjuvant chemotherapy had no added benefit in the overall survival in patients with locally advanced squamous esophageal cancer (162). The vast majority, however, of published studies demonstrates a

considerable benefit of neoadjuvant chemotherapy. For example, cisplatin, paclitaxel with concurrent external beam radiation followed by esophagectomy produced a rapid dysphagia relief with initial chemotherapy, had a high overall response rate, and acceptable toxicity levels (163). 5-FU, cisplatin and radiation to a total dose of 4,500 to 5,040 cGy in 180 cGy/fraction every day for preoperative locally advanced thoracic esophageal carcinoma was effective to achieve a high pathologic complete response rate in about 50% of the patients (164). The results of a combined approach using chemoradiation followed by esophagectomy appeared to be better than those reported with surgery alone. Chemoradiation consisted of 5-FU at 1,000 mg/m^2 for 4 days, cisplatin at 100 mg/m^2 on day 1 and radiotherapy at a total dose of 40 Gy in daily fractions of 2 Gy five times per week. Esophagectomy was planned 4 weeks after induction treatment. A complete histologically proven response was observed in 9 patients (23%) and a partial in 20 patients (51%), respectively. The 3-year overall survival rate was 40% (165).

11. Gastric cancer

Stomach cancer in 2000 accounted for 25% of all cancer cases among males in Japan but only for 2% of all cancer cases among males in USA, 5% in EU and 10% world-wide (Table 1). Advanced gastric carcinoma is incurable, and the median survival time of patients with advanced disease is only 6 to 9 months. The evolution of chemotherapy for gastric cancer has been mixed with excitement and disappointment. There is no standard treatment for gastric cancer although cisplatin, 5-FU, leucovorin, taxanes, irinotecan, methotrexate, doxorubicin, and mitomycin are the most commonly used drugs (reviewed in refs. 166-168). Two of the most popular regimens-ECF (epirubicin-cisplatin-5-FU) and PELF (cisplatin-epirubicin-5-FU-leucovorin), have been shown to be active, but each has limitations. 5-FU and/or cisplatin, demonstrate response rates in the 20% to 40% range, with median survivals between 6 and 12 months. Multiple single-agent chemotherapies have been shown to be only modestly effective in advanced disease, and the search for the best combination of therapy has been difficult. Phase II trials showed that single-agent docetaxel is an active agent in advanced gastric cancer, producing overall response rates (ORRs) of 17.5-24%. Docetaxel-cisplatin has yielded response rates similar to those achieved by ECF and PELF. Adding 5-FU to docetaxel-cisplatin has achieved an ORR of 52 versus 45% for docetaxel-cisplatin in a randomized phase II trial (169). Neoadjuvant chemotherapy has received increasing attention because it can increase the rate of complete tumor resections, reduce systemic metastases, and prolong survival in patients with advanced gastric cancer. Among patients with curatively resected disease, postoperative chemoradiotherapy also appears to improve overall survival significantly.

The systemic absorption of cisplatin during intraoperative hyperthermic peritoneal lavage in patients with locally advanced gastric cancer was studied by Kern et al (170); the patients were receiving 8000 ml of Ringer's solution containing 150 mg/m^2 cisplatin and 15 mg/m^2 mitomycin C for one hour at 43.5 degrees C.

A phase I study of weekly docetaxel, 24-hour infusion of high-dose fluorouracil/leucovorin and cisplatin in patients with advanced gastric cancer has been completed; cisplatin and leucovorin dosages were fixed throughout the study at 30 and 300 mg/m^2, the 5-FU dosage was initially fixed at 1,600 mg/m^2 while docetaxel was evaluated at weekly 1-hour infusion dosages of 30, 40 and 50 mg/m^2 to determine the MTD. The MTD of docetaxel was defined at 40 mg/m^2 with grade 4 febrile neutropenia as the dose-limiting event. Weekly 5-FU dosages of 1,600, 2,000 and 2,400 mg/m^2 were then evaluated after setting the docetaxel dosage at the MTD. The DLT for 5-FU was found at 2,400 mg/m^2 per week. This incurred grade 4 neutropenia such that the MTD of 5-FU was defined at 2,000 mg/m^2. Following a change in the cisplatin administration schedule to a 3-hour infusion after 5-FU/leucovorin infusion rather than a 24-hour infusion of cisplatin simultaneously with 5-FU/leucovorin immediately following docetaxel reduced some side effects. There were 2 (7.8%) complete and 14 (53.8%) partial responses (171).

A meta-analysis of 17 clinical trials comparing adjuvant chemotherapy versus control after curative resection for gastric cancer with a total of 3,118 patients, of whom 1,546 randomized to the treatment arms and 1,572 to the control arms showed a significant advantage in survival for adjuvant chemotherapy; this observation undoubtedly requires confirmation in large randomized controlled trials including cisplatin before adjuvant chemotherapy (172). A phase II clinical trial in patients with advanced gastric cancer using bimonthly cisplatin (25-50 mg/m^2) bolus for 12 weeks and weekly 24-h infusion of high-dose 5-fluorouracil (2,600 mg/m^2) and leucovorin (150 mg/m^2) showed 41% (7/17) partial response, 18% (3/17) stable disease and 41% (7/17) progressive disease (173). A Phase II study on 54 patients with metastatic or advanced gastric cancer and histologically confirmed adenocarcinoma was completed in France. Disease sites mainly included the lymph nodes (67%), stomach (65%), and liver (61%). The regimen was oxaliplatin 100 mg/m^2 and folinic acid 400 mg/m^2 (2-hour intravenous infusion) followed by 5-FU bolus 400 mg/m^2 (10-minute infusion) and then 5-FU 3,000 mg/m^2 (46-hour continuous infusion) every 14 days. Best responses in the 49 assessable patients were two complete responses and 20 partial responses, giving an overall best response rate of 44.9%. Median time to progression, and overall survival were 6.2 months, and 8.6 months, respectively (174). A combination chemotherapy against gastric cancer in a Japanese clinical trial used i.v. infusion of 5-FU (800 mg/m^2/day), dipyridamole (4 mg/kg/day), and i.v. infusion of cisplatin (20 mg/m^2/day) for 5 days repeated every 4 weeks. Twelve patients (43%) had a partial response, stable disease occurred in 13 patients (46%), progression in 3 patients (11%) and clinical benefit was observed in 20 patients (71%) (175). 54 patients with advanced gastric cancer were treated with 5-FU at 300 mg/m^2/day for 14 days and cisplatin at 15 mg/m^2/day for 2 days as preoperative chemotherapy (group A). These patients were compared to 31 patients without any preoperative chemotherapy (group B). The apoptotic index of tumor specimens in group A was significantly higher than that in group B. In group A there were more p53-positive than negative patients and Bcl-2 positive, and high apoptotic index patients had better prognosis (176). In a pharmacokinetic study in patients with advanced gastric cancer irinotecan (CPT-11) at a

dose of 60 mg/m^2, delivered by continuous infusion for 24 h on day 1 and by a 90-min infusion on day 15, was combined with cisplatin, daily administered at a dose of 10 mg/m^2 on days 1-3 and days 15-17 for 4 weeks. The AUC of SN-38, the active metabolite from CPT-11, was increased by 24-hour infusion when compared with the 90-min infusion, and there was no increase in toxicity (177). The efficacy and feasibility of a combination consisting of 5-FU (360 mg/m^2 on days 1 through 5 and days 8 through 12), MMC (13 mg/m^2 on day 1) and cisplatin (7 mg/m^2 on days 1 through 5 and days 8 through 12) in patients with non-resectable or recurrent gastric cancer gave an overall response rate (all partial) of 48.1% in 13 of 27 patients (178).

A randomized, controlled trial of 280 patients with advanced gastric cancer compared fluorouracil (FU) alone with FU plus cisplatin (FP) and with uracil and tegafur plus mitomycin (UFTM). Tegafur is the tetrahydrofuranyl-5-fluorouracil, an oral pro-drug that releases 5-FU continuously; uracil is added to inhibit degradation of the released 5-FU. The UFTM arm showed a significantly inferior survival with higher incidences of hematologic toxic effects than FU alone and the registration of UFTM was terminated. The overall response rates of the FU-alone, FP, and UFTM arms were 11%, 34%, and 9%, respectively. However, no differences in overall survival were observed between the FU-alone and FP arms; the median survival times and 1-year survival rates were 7.1 months and 28% with FU, 7.3 months and 29% with FP (18). A total of 363 patients from the Japan Clinical Oncology Group (JCOG) trials with gastric cancer were followed up to 5 years after chemotherapy. Of these, 226 patients had "unresectable" disease prior to chemotherapy and 22 (10%) survived longer than 2 years, whereas 8 (4%) had survived longer than 5 years. Chemotherapy regimens consisted of tegafur + mitomycin C (FTM), uracil-tegafur + mitomycin C (UFTM), 5'deoxy-flurorouridine + cisplatin (5'P), etoposide + doxorubicin + cisplatin (EAP), and 5-fluorouracil + cisplatin (FP) (179).

An adjuvant intraperitoneal chemotherapy in patients with stage II-III gastric cancer consisted of 60 mg/m^2 cisplatin, 12 mg/m^2 mitoxantrone, 600 mg/m^2 5-FU, and 60 mg/m^2 folinic acid in 2 L saline repeated every 4 weeks for a total 6 cycles. The major nonhematologic toxicity was grade I-III nausea and/or vomiting experienced by 27 patients (69.2%). Twenty-four (61.5%) patients reported abdominal discomfort. The cumulative 5-year disease-free survival and overall survival were 24.7% and 30.7%, respectively (180). 21 patients with unresectable or non-curative resectable gastric cancer received neoadjuvant chemotherapy, consisting of 5-fluorouracil, leucovorin, and cisplatin (FLP) with at least two cycles before surgery. Resection was performed in 18 (85.7%). There was no complete response, but 12 patients (57.1%) had a partial response. The response rate was 47.6% for the primary region, 64.7% for abdominal para-aortic lymph node metastasis, 40.0% for liver metastasis, and 11.1% for peritoneal dissemination. One-year survival of the 21 patients was 40.5%. The median survival time in the responders was 571 days, and that in non-responders was 199 days (181).

Because docetaxel and cisplatin are both active against gastric cancer and have different mechanisms of action, their combination has been tested against gastric cancer in search for clinically relevant additive or synergistic effects. The recommended doses for the phase II evaluation were determined to be 60 mg/m(2) of docetaxel and 80 mg/m(2) of cisplatin. Severe leukopenia and neutropenia were observed in 71.4% and 82.1% of the patients, respectively. The overall response rate at the recommended dose was 25.0% (7/28 patients), and the rate was 40% (6/15) for patients with liver metastases. The median survival time was 9.7 months and the 1-year survival rate was 39.3% (182). Thirty-four patients with biopsy-proven noncurative gastric cancer were treated with either of two neoadjuvant chemotherapies: FEMTXP (5-fluorouracil, epirubicin, methotrexate, cisplatin) or THP-FLPM (pirarubicin, 5-fluorouracil, leucovorin, cisplatin, mitomycin C). Eight of 33 patients (24.2%) showed partial response and 14 (42.4%) underwent salvage surgery, including 8 curative resections (183). A phase II study used 50 mg/m2 of irinotecan plus 30 mg/m2 of cisplatin, both administered intravenously 1 day a week for 4 consecutive weeks, followed by a 2-week recovery period. Nine patients (31%) achieved a partial response. Median time to disease progression was 7 weeks and median survival time was 5 months (155, 184). Neoadjuvant therapy can be used in downstaging locally advanced gastric cancer preoperatively. Neoadjuvant therapy consisted of two cycles of 75 mg/m^2 irinotecan with 25 mg/m^2 cisplatin weekly four times every 6 weeks. This was followed by resection with D2 lymph node dissection and two cycles of intraperitoneal chemotherapy with floxuridine and cisplatin. Nineteen patients underwent surgery. Surgical morbidity did not appear to increase after the neoadjuvant regimen. It was concluded that irinotecan-based neoadjuvant therapy downstages locally advanced gastric cancer (185).

12. Colorectal cancer

The mainstay of chemotherapy for colorectal cancer is 5-FU modulated by leucovorin, alone or in combination with oxaliplatin or irinotecan. A continuous maintenance of 5-FU concentration in blood is the optimal method in 5-FU administration; this has prompted the development of oral 5-FU derivatives in Japan (186) but their value has recently been challenged (18). Oxaliplatin and irinotecan are also indicated as first-line as well as second-line treatment of advanced colorectal cancer patients. The toxicity profiles of oxaliplatin and irinotecan are not overlapping, and both drugs have shown synergism with folinic acid-modulated 5-FU. The recommended dose of irinotecan/oxaliplatin in every-2-week and every-3-week schedules ranged from 150-200 mg/m^2 and 85 mg/m^2, respectively. In the weekly schedule, the recommended doses of irinotecan/oxaliplatin were 65 mg/m^2 and 60 mg/m^2 (187). Intraperitoneal cisplatin-based chemotherapy seems to be an attractive approach in the treatment of high-risk colorectal cancer and peritoneal carcinomatosis from colorectal origin providing high local drug concentration with limited systemic side effects (188). In a randomized phase II clinical trial 42 patients were randomized to receive cisplatin before 5-FU modulated with leucovorin and 41 patients to receive cisplatin given after 5-FU modulated with leucovorin; patients were chemotherapy-naive with metastatic colorectal cancer or pretreated only with a 5-FU-bolus-based chemotherapy. Antitumor activity was similar in the two arms and was very promising both in pretreated patients (response rate 29%) and in

chemotherapy-naive patients (response rate 56%, complete response 9%). These results did not suggest a sequence dependence of the synergism between cisplatin and 5-FU. However, they challenged the need of oxaliplatin to improve 5-FU/ leucovorin activity in advanced colorectal cancer (189).

Patients with locally advanced extraperitoneal cancer of the rectum were treated with preoperative chemoradiation. The PLAFUR-4 regimen for patients with cT3N0-2 or cT2N1-2 rectal carcinoma (42 patients) consisted of 50.4 Gy (1.8 Gy/fraction) plus 5-FU, 1 g/m^2/d on Days 1-4 and 29-32, continuous infusion, and cisplatin, 60 mg/m^2/d on Days 1 and 29. Surgery was performed 6-8 weeks after chemoradiation. Adjuvant chemotherapy (5-FU + l-folinic acid) was delivered to 26 patients in the FUMIR-T4 protocol group. The 5-year survival rate was 100% for cT2, 77% for cT3, and 62% for cT4 (190).

A Phase I study using a triplet regimen including oxaliplatin plus irinotecan on day 1, and 6S-folinic acid (LFA) plus 5-FU on day 2, every 2 weeks was completed in order to determine the dose-limiting toxicities (DLTs), the maximum tolerated doses (MTDs), and the recommended doses (RDs). Grade 4 neutropenia (30% of patients) and diarrhea were the major side effects. The recommended doses for this biweekly regimen were oxaliplatin 110 mg/m^2 plus irinotecan 175 mg/m^2 on day 1, and 6S-folinic acid 250 mg/m^2 plus 5-FU 800 mg/m^2 on day 2 every 2 weeks. This schedule appeared active in pretreated gastrointestinal malignancies, and was proposed for advanced colorectal carcinoma after failure of 5-FU-based adjuvant or palliative treatment. Two complete and nine partial responses were reported on 40 evaluable patients (27.5%) (191).

A multicenter phase II study using oxaliplatin 50 mg/m^2, 5-fluorouracil (5-FU) and leucovorin as second line treatment on 46 patients with metastatic colorectal cancer was completed. All drugs were administered on days 1 and 2, every 14 days. This treatment gave 1 complete response (2.2%) and 14 partial responses (30.4%), giving an overall response rate of 32.6%. The three drugs have been shown to have a synergistic activity in vitro. 22 patients had stable disease (47.8%) and 9 patients progressed (19.6%). After a median follow-up of 13 months, median time to progression was 6.4 months (192). Colorectal cancer patients were treated with a regimen of epirubicin, cisplatin and continuous-infusion of 5-FU; the response rate was 51%, the progression-free survival was over 8 months and the overall survival more than 11 months with tolerable toxicity (193). A combination of oxaliplatin (120 mg/m2 intravenously for 2 hours) on day 1, irinotecan (250 mg/m2 i.v. for 90 minutes) on day 1, and 5-FU (2600 mg/m2 plus leucovorin 500 mg/m2 i.v. in a 24-hour infusion) on day 1 and 15, every 4 weeks on 23 patients with advanced colorectal cancer gave an overall response rate of 69.2% (18 patients) including 3 complete remissions (11.5%). Four additional patients (15.3%) had stable disease, only 1 (3.8%) progressed and the median progression-free survival was 14 months (194).

Pemetrexed, a new-generation antifolate drug, has demonstrated a 15% to 17% response rate in metastatic colorectal cancer, similar to those of other single agents in previously untreated patients. The generally mild side effect profile of pemetrexed, especially with folate supplementation and dexamethasone premedication, and the synergy between pemetrexed and irinotecan or oxaliplatin frequently used in gastrointestinal cancers are encouraging in the treatment of colorectal, pancreatic, and gastric cancers (reviewed in ref. 166).

Primary squamous cell colorectal carcinomas are uncommon, and their characteristics are not well known. Clinical features and common diagnostic methods do not easily differentiate squamous cell colorectal carcinomas from adenocarcinomas. An elevated squamous cell carcinoma antigen (SCC Ag) is one diagnostic tool; SCC Ag is a tumor marker for squamous cell cancers of the lung, head and neck, uterine cervix, and esophagus. A review of the literature, includes only 60 previously published cases. This type of cancer can be treated with abdominoperineal resection followed by platinum-based adjuvant chemotherapy and radiation (195).

Liver metastases from colon or breast cancer tumors were treated with 80 mg cisplatin diluted in hypotonic 25 g/l glucose solution and given through a balloon-occluded hepatic artery; cisplatin diluted in this hypotonic solution was dramatically more cytotoxic than cisplatin diluted in normotonic 9 g/l NaCl. Side effects were transient increase of hepatic transaminases and clinical jaundice. Of the 9 patients treated, one achieved a partial response, 7 had stable disease (mean duration: 6 weeks) and one had progressive disease (196).

13. Pancreatic cancer

Adenocarcinoma of the pancreas remains one of the most difficult malignancies to treat. Its incidence has steadily increased over the past four decades and its prognosis is still poor. Pancreatic cancer accounts for 2.1% of all new cancer cases in women and 2.15% of all cancers in men in 2000 worldwide (Table 1). The introduction of gemcitabine (Gemzar; Eli Lilly), has made a small advancement in pancreatic cancer treatment but the results are still very discouraging. Gemcitabine, officially introduced in 1996 in USA and in 1998 in Europe, is currently considered as the standard first line chemotherapy against locally advanced or metastatic adenocarcinoma of the pancreas. The administration regimen is 1,000 mg/m^2 once a week (30 minutes i.v. infusion), for 7 weeks out of 8, then 3 weeks out of 4 in consecutive cycles.

Comparative analysis of multiple phase II studies performed with gemcitabine/cisplatin showed response rates in the range of 11% to 58% and median survival times of 7.4 to 10 months, whereas various gemcitabine/5-FU-based regimens achieved response rates of 4% to 25% and median survival times of 4.4 to 10.3 months (reviewed in ref. 197). The major toxicity reported to occur with the gemcitabine-cisplatin combination is myelosuppression, which is greater than that encountered with single-agent gemcitabine. However, episodes of neutropenic fever or spontaneous bleeding are reported to be very infrequent (reviewed in ref. 12). One complete and four partial responses have been observed for an overall response rate of 9% in a phase II study of weekly gemcitabine and cisplatin (198). A randomized Phase III trial was performed to determine whether the addition of cisplatin to gemcitabine compared with gemcitabine alone, was able to improve the time to disease progression and the clinical benefit rate in patients with advanced pancreatic adenocarcinoma. The tumor growth control rate (i.e., total number of patients who achieved complete

responses, partial responses, and stable disease) was 42.6% in gemcitabine alone versus 56.6% in gemcitabine plus cisplatin without significant difference in clinical benefit between the two arms (199). A multi-center randomized phase III clinical trial using gemcitabine or gemcitabine plus cisplatin for locally advanced or metastatic pancreatic cancer with 42 untreated patients has been completed in Beijing. The differences between the two arms were small and the partial response was 6.3% for gemcitabine versus 11% for gemcitabine plus cisplatin; these numbers show the low success rate in advanced pancreatic cancer even as first line chemotherapy (200).

Although the combination of gemcitabine with docetaxel has demonstrated activity, data showing a clear survival benefit are not yet available. It is also premature to evaluate the activity of combinations with irinotecan or oxaliplatin (reviewed in ref. 197). In patients with advanced pancreatic cancer, pemetrexed achieved a 6% response rate and a 28% one year survival rate, which is comparable to the single-agent gemcitabine (reviewed in ref. 166).

A phase II study of cisplatin plus 5-fluorouracil versus cisplatin plus 5-fluorouracil with interferon-α gave no response in the 5-FU/cisplatin arm and only 2 partial responses were achieved in the interferon-arm, lasting 27 and 32 weeks, respectively (201). A high-dose 5-fluorouracil (5-FU)+leucovorin and bi-weekly cisplatin gave an overall response rate of 33% and a median survival of 7.9 months (202). In a phase II trial, 5-FU plus cisplatin (FUP) yielded a 26.5% response rate and a 29% survival rate at 1 year (203). A randomized trial comparing 5-FU with 5-FU plus cisplatin in advanced pancreatic carcinoma gave a superior response rate in the 5-FU plus cisplatin. The survival rates at 6 months were 28% and 38% for the FU and FUP arms, respectively, and 1-year survival rates were 9% and 17% (203). S1, a newly developed oral fluoropyrimidine derivative gave response rates of 20%; when S1 was combined with weekly cisplatin response rates of 57% were achieved in patients with pancreatic cancer; CA19-9 serum concentration was reduced by more than 50% in a significant fraction of patients (204).

Cisplatin at 80 mg/m^2 bolus on days 2 and 22 with preoperative external beam radiotherapy (30Gy split course RT or 45 Gy) gave an overall median survival for the 19 study patients of 20 months (205). Combined radiochemotherapy (42.5 Gy) with 5-fluorouracil and cisplatin gave a median survival of 9 months and time to progression of 4.4 months **(**206**)**. Intraoperative hyperthermia combined with multischedule pre- and post-operative chemotherapy (5-FU, doxorubicin and cisplatin), bypass surgery plus sandostatin and radiotherapy (45 Gy, 25 fractions, 5 days a week) had a potential advantage in the treatment of inoperable pancreatic cancer (207). Chemoradiation with gemcitabine and cisplatin can be administered safely in pancreatic carcinoma as concluded from Phase I trial using a strict time-schedule (208). Systemic chemo-radiotherapy on 27 patients with locally advanced pancreatic adenocarcinoma has given relatively good results. The method used 5-FU (600 mg/m^2), given as a 22-hour infusion on days 1 to 5, and cisplatin (100 mg/m^2), given as a 90-minute infusion on day 2, repeated every 3 weeks. Radiotherapy was delivered using megavolt irradiation of 25-MV photons with a two- or four-field isocentric technique at a dose of 42.5 Gy. The clinical benefit response was 7/27 (26%). Median survival and time to progression were, respectively, 9 and 4.4 months (206). Patients with unresectable pancreatic cancer were treated with simultaneous preoperative radiation therapy (45 Gy) and chemotherapy involving cisplatin, 5-fluorouracil, paclitaxel or docetaxel and gemcitabine (209).

14. Urothelial (urinary bladder) cancer

Recent efforts to improve the outcome of patients with metastatic transitional cell carcinoma have focused on identifying new drugs with single agent activity and on their incorporation into platinum-based combination regimens (reviewed in 210). Phase II studies of single-agent docetaxel (Taxotere) yielded promising results in advanced or metastatic transitional cell carcinoma (TCC) of the urothelium; when combined with cisplatin in previously untreated patients, response rates of 52% to 60% have been achieved, with median overall survival of 8 to 13.6 months (reviewed in ef. 211). For example, a combination of 75 mg/m^2 docetaxel and 75 mg/m^2 cisplatin on day 1, repeated every 21 days, to a maximum of six cycles gave an overall response rate of 58% (212). Histological specimens of 23 patients with urothelial metastatic transitional-cell carcinoma who were treated with paclitaxel and carboplatin, were investigated for p53 and p21 proteins; 48% of patients were classified as p53-positive, whereas 57% were classified as p21-positive. Neither p53- nor p21-status were significantly correlated with overall response to chemotherapy, progression-free survival and overall survival (213).

The overall response rate for single-agent gemcitabine is 25% with a complete response rate of 9% (reviewed in ref. 214). Overall median survival was 13.2 months and estimated 4 year survival was 13% from phase II trials using gemcitabine plus cisplatin for advanced transitional cell cancer (215). Gemcitabine, cisplatin, and ifosfamide as weekly therapy has achieved an overall response rate of 40.8% (216).

Combinations of paclitaxel, cisplatin, and gemcitabine have high levels of activity with overall and complete response rates of 76% and 26%, respectively and combinations of paclitaxel, carboplatin, and gemcitabine have overall and complete response rates of 68% and 32%, respectively (reviewed in ref. 217). A phase I/II trial with paclitaxel, cisplatin, and gemcitabine was set to identify pretreatment characteristics that were prognostic for survival. The pretreatment characteristics analyzed were age, gender, ECOG (Eastern Cooperative Oncology Group) performance status, histopathology (pure transitional versus other), visceral (liver, lung, or bone) metastasis, number of sites of disease, lactate dehydrogenase, and hemoglobin. The factors that were associated with a worse survival were performance status > 0, presence of visceral metastasis, and more than one site of malignant disease. Median survival times (from 33 to 10 months) were greatly dependent on number of risk factors (218). Weekly chemotherapy with docetaxel, cisplatin, and gemcitabine in a Phase II study achieved 28.5% complete response and 37.1% partial response (219).

A combination chemotherapy with gemcitabine and ifosfamide as second-line treatment was an active salvage regimen for metastatic urothelial cancer (220). Gemcitabine plus epirubicin in patients with advanced urothelial carcinoma who are not eligible for platinum-based regimens gave 1-year

survival rate of 38%, a median PFS of 6.4 months and OS of 16.4 months; 56.7% of the patients achieved a complete response, and 16.7% achieved a partial symptomatic response (221).

Many patients with metastatic transitional-cell carcinoma (TCC) of the urothelial tract are not appropriate candidates for standard cisplatin-based combination, because of inadequate renal function, poor performance status and other comorbid medical conditions; treatment of this group of patients with carboplatin (AUC=5) on day 1, and vinblastine (4 mg/m^2) on days 1 and 8, repeated every 4 weeks as a palliative regimen achieved a 13% complete and 20% partial response. The median duration of response was 32 weeks and median overall survival for all patients was 26 weeks; grade IV granulocytopenia was the major toxicity and occurred in 26% of patients (222).

The methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) regimen has been the standard treatment in patients with locally advanced and metastatic urothelial cancer for the past 15 years; the combination of paclitaxel and cisplatin has yielded a pooled overall response rate of 61%, and a complete response rate of 20% (reviewed in ref. 223). A randomized Phase III trial has been completed comparing interferon α-2b + fluorouracil + cisplatin (FAP) with methotrexate + vinblastine + doxorubicin + cisplatin (MVAC). Although the overall survival was not significantly different, patients assigned to MVAC had a much better chance of responding to front-line therapy. The objective response rate for patients assigned to FAP was 42% compared to 59% in the MVAC arm (224).

15. Metastatic prostate cancer

Prostate cancer is the second leading cause of cancer deaths in American men. On average, an American man has about a 30 percent risk of having prostate cancer in his lifetime, but only about a 3 percent risk of dying of the disease. Surgery is a common treatment for early stage prostate cancer. Radiation therapy can be used instead of, or after surgery. For hormonal therapy, leuprolide, goserelin, and buserelin are luteinizing hormone-releasing hormone (LH-RH) agonists that prevent the testicles from producing testosterone. Flutamide and bicalutamide are antiandrogens. Ketoconazole and aminoglutethimide prevent the adrenal glands from making androgens. Estramustine phosphate has a synergistic activity with paclitaxel against hormone refractory prostate cancer.

Hormone refractory prostate cancer is being treated with chemotherapy such as carboplatin (225), cisplatin plus radiation (226), ketoconazole/doxorubicin alternating with vinblastine/estramustine (227), paclitaxel, estramustine, and oral etoposide (227), calcitriol (vitamin D receptor ligand) and docetaxel (228,229) or many other schemes. Patients with small-cell prostate carcinoma (SCPCa) have been treated with doxorubicin in combination with cisplatin and etoposide (229). A number of experimental drugs are also under evaluation against prostate cancer such as atrasentan (ABT-627), an endothelin-A receptor antagonist (231).

Carboplatin as single agent has demonstrated a 17% response rate against measurable hormone refractory prostate cancer. Microtubulin binding agents such as docetaxel have significant preclinical and clinical activity in the treatment of hormone-refractory prostate cancer. Cell culture studies have shown that docetaxel has cytotoxic additive effects or synergy with cis-retinoic acid, cyclosporin A and vinorelbine against hormone-refractory prostate cancer but cisplatin, carboplatin or etoposide, were antagonistic when combined with docetaxel and thus combinations of docetaxel with platinum or etoposide against pancreatic cancer may lead to subadditive effects in treatment (25).

A clinical study on 70 patients has evaluated the effects of 50 mg/m^2 cisplatin plus 148 MBq ^{89}Sr (arm A) versus ^{89}Sr alone (arm B) in the treatment of metastatic hormone-refractory prostate cancer addressing both pain palliation and cytostatic effects. Overall pain relief occurred in 91% of patients in arm A and 63% of patients in arm B. New painful sites on previously asymptomatic bone metastases appeared in 14% of patients in arm A and in 30% of patients in arm B. Median global survival after therapy was 9 months in arm A and 6 months in arm whereas transient and moderate hematologic toxicity was apparent in both arms without significant differences (226).

Hormone refractory prostate cancer has been treated with combination chemotherapy using 100 mg/m^2 i.v. paclitaxel weekly, 10 mg/kg estramustine phosphate orally daily and i.v. carboplatin to an area under the curve of 6 on day 1 of a 4-week cycle (median of 7 consecutive cycles). Major toxicities, which were temporary and reversible, included grade 3 or 4 anemia in 59.4% of patients, leukopenia in 37.5%, thrombocytopenia in 28.1% and neuropathy in 12.5%. Levels of prostate specific antigen (PSA) decreased by greater than 50% in 100% of patients and by greater than 90% in 56.7%. Partial response was obtained in 61.1% of measurable lesions. Consumption of medication for cancer induced pain was reduced in 89.5% of patients. Tumor volume reduction and/or antitumor therapeutic effects were exhibited in 81.0% of patients with positive biopsy. At a median follow-up of 48 weeks median time to progression was 48 weeks and median overall survival was 95 weeks (225). A Phase II clinical trial on 16 patients with hormone-refractory prostate cancer used dolastatin-10, a natural, cytotoxic peptide with microtubule-inhibitory and apoptotic effects at a dose of 400 μg/m^2 i.v. every 3 weeks. The major toxicities observed were grade 3 and 4 neutropenia in 8 patients and grade 3 neuropathy in 1 patient. Three patients demonstrated stable disease; 2 of these had bone disease, and 1 had nodal metastasis. All others had disease progression (232). Patients with small-cell prostate carcinoma (pure or mixed), were treated every 4 weeks with doxorubicin 50 mg/m^2 as a 24-hour i.v. infusion followed by etoposide 120 mg/m^2/d and cisplatin 25 mg/m^2/d i.v. on days 2 to 4 and gave 61% partial response rate (22 of 36 patients). Median time to progression was 5.8 months and overall survival time 10.5 months. However, the toxicity of this regimen was severe (grade 3 or 4 neutropenia 100%, thrombocytopenia 66%, mucositis 21%, and infection 68%) and 3 patients died of toxicity. Thus, the addition of doxorubicin to the etoposide/cisplatin regimen caused higher toxicity in this patient population and failed to improve outcome (230).

A number of innovative technologies against prostate cancer are at the preclinical stage such as those using ribozyme-mediated inhibition of PKCα highlighting the importance of PKCα inhibition as a potential therapeutic strategy to sensitize androgen-independent prostate cancer cells to platinum drugs (233). Farnesyl:protein transferase inhibitors enhance the growth

inhibitory effects of gamma-radiation, etoposide, doxorubicin, cisplatin, estramustine and the antihormone bicalutamide against hormone-dependent and hormone-independent prostate cancer cell lines deserving clinical evaluation (234). Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a member of the TNF family that preferentially kills tumor cells. A combination treatment with TRAIL and cisplatin, etoposide, or doxorubicin overcame the resistance of prostate cancer cells by triggering caspase activation and this could become a new therapeutic intervention to induce apoptosis in resistant cancer cells (235).

16. Metastatic breast cancer

About 17 of every 1,000 women at ages 60- to 64- are expected to develop breast cancer within 5 years in Western countries; 30–40% of all patients with breast cancer in Western countries develop advanced disease. In the year 2000 breast cancer accounted for 22% of all cancer cases among women worldwide, 30% in USA and 28% in Europe; it is by far the most frequent type of cancer (Table 1). A woman's risk of developing breast cancer depends on several factors (hormonal factors, current age, genetic predisposition, presence of atypical hyperplasia in the breast etc). Dietary factors have also a role; high amounts of folate in the diet may help prevent breast cancer. The vast majority of breast cancers originate in mammary epithelial cells that line the inside of the milk ducts. Primary therapy generally involves lumpectomy (removal of the primary breast tumor) and radiation therapy or modified radical mastectomy.

Approximately 5 to 10 percent of breast tumors are hereditary; the remaining cases are caused by genetic changes that occur during a woman's life (sporadic). Gene-expression profiling on DNA microarrays showing the activity of 6,000 genes from cDNAs can be used to differentiate between breast tumors that were caused by inherited genetic changes and those that were acquired. In a study (236) samples of tumors had been surgically removed from 22 breast cancer patients. Of the 15 women known to have hereditary breast cancer based on family history and other analyses 7 had mutations in BRCA1 and 8 had mutations in BRCA2.

Hormone Therapy. The hormone replacement therapy is estrogen or an estrogen/progesterone combination. Premenopausal breast cancer patients might undergo ovary removal to eliminate estrogen; treatment of patients possessing estrogen receptor-positive tumors with tamoxifen is an accepted alternative to ovarian removal. Tamoxifen (Nolvadex®, AstraZeneca), approved in 1998 by FDA to reduce the incidence of breast cancer in women at high risk of the disease, interferes with the activity of estrogens. Tamoxifen, like estrogen, appears to preserve bone strength, decreasing fractures of the hip, wrist, and spine. Raloxifene (Evista®, Eli Lilly), approved by the FDA in 1997 for the prevention of osteoporosis in postmenopausal women, also seems to reduce the incidence of breast cancer. Buserelin, commonly used for prostate cancer, combined with tamoxifen increased the average survival time of patients by almost a year and yielded an average survival time of 3.7 years, versus 2.9 years with tamoxifen alone or 2.5 years with buserelin alone. However, women treated with tamoxifen often develop high levels of estradiol. Buserelin suppresses ovarian production of estradiol, as it blocks testosterone in prostate cancer patients. The European Organization for the Research and Treatment (EORTC) tested the combination of tamoxifen/ buserelin in a phase III clinical trial that enrolled 161 patients in nine countries. Buserelin alone (6.6 mg) was implanted under the skin at 6-week intervals for the first 12 weeks, and then at 8-week intervals. Tamoxifen was given at 40 mg daily. In a 7.3-year follow up the combined therapy group had an overall 5-year survival rate of 34 percent, compared with 15 to 18 percent for the single-agent groups (237,238).

Targeting of Her-2/neu tyrosine kinase. Overexpression of the HER2/neu oncogene (also known as c-erbB2), a tyrosine kinase, is a frequent molecular event in multiple human cancers, including breast and ovarian cancer. Patients with cancer that overexpress HER2/neu are associated with unfavorable prognosis, shorter relapse time, and low survival rate. Herceptin (trastuzumab, Genentech, Inc., South San Francisco), approved by FDA, is a monoclonal antibody given intravenously for the treatment of metastatic breast cancer in HER2 positive tumors (see Drugs used in combination with platinum). Approximately 25 to 30% of breast cancers overexpress HER–2; these tumors grow faster and are more likely to recur. Patients whose tumors are strongly positive for HER–2 protein overexpression (a score of 3+ on the laboratory test) are more likely to benefit. Side effects of Herceptin treatment include fever and/or chills, pain, weakness, nausea, vomiting, diarrhea, headaches, difficulty breathing, rashes, allergic reactions, and may affect and damage the lungs and the heart leading to heart failure. Herceptin is also being studied in clinical trials for other types of cancers that overexpress the HER–2 protein, including osteosarcomas and cancers of the lung, pancreas, salivary gland, colon, prostate, endometrium and bladder. Preliminary results of a phase II study of gemcitabine 1200 mg/m^2 i.v. on days 1 and 8 every 21 days plus trastuzumab 4 mg/kg over 90 minutes, followed by 2 mg/kg infused over 30 minutes weekly in previously treated metastatic breast cancer with 2+ or 3+ tumor HER2 expression were reported on 38 patients. Twelve patients (32%) have had an objective partial response, with a median response duration of 8.6 months with no unexpected toxicities or grade 4 nonhematologic toxicities (239).

Taxane combinations in breast cancer. Advanced breast cancer chemotherapy is a challenge in part because anthracyclines and taxanes (paclitaxel, docetaxel) are now being used earlier in the course of the disease and patients with recurrence might already have been treated with these drugs having chemoresistant tumors. A single high-dose cycle of chemotherapy can produce response rates in excess of 50%. However, disease-free survival (DFS) is 15-20% at 5 years. The single most important predictor of prolonged DFS is achieving a complete response (CR). Increasing the proportion of patients who achieve a complete response may improve disease-free survival. 511 patients in 16 countries with advanced breast cancer treated with a combination of capecitabine (Xeloda Tablets, Roche, a fluoropyrimidine carbamate) and docetaxel survived for an average of 14.5 months compared with 11.5 months in patients treated with docetaxel alone. Disease progression was delayed

by six months in combination-therapy patients compared with four months in the docetaxel-alone group. The side effects of the combination therapy were gastrointestinal and hand-foot syndrome, an inflammatory skin condition; side effects of the docetaxel group were fever and joint pain (240).

Adjuvant treatment of early breast cancer has experienced major changes in the last 25 years. Since the mid 1970s when cyclophosphamide, methotrexate and 5-fluorouracil (CMF) resulted in statistically significant and clinically meaningful improvements in disease-free and overall survival, the use of adjuvant chemotherapy has become common practice worldwide. In recent years anthracycline-containing polychemotherapy regimens, especially regimens containing epirubicin-taxane combinations, were found to provide a significant benefit over CMF with a significant prolongation in relapse-free and overall survival rates (reviewed in ref. 27).

Cisplatin combinations in breast cancer. The combination of gemcitabine and cisplatin has proven effective as first-line chemotherapy for patients with breast cancer, inducing a response rate of 80% in one phase II study. Five additional studies as second or third line chemotherapies in breast cancer patients demonstrated a median response rate of 43% with a moderate toxicity profile, particularly for patients whose disease progressed after treatment with anthracyclines and/or taxanes (reviewed in ref. 241). Eliminating minimal residual disease in breast cancer patients and with the aim to achieve the highest rate of complete response in order to enhance disease-free survival is a challenge in the treatment of advanced or metastatic breast cancer. In a Phase II trial, 60 women with metastatic breast cancer and at least a partial response to induction chemotherapy received three separate high-dose cycles of chemotherapy with peripheral blood progenitor support and G-CSF. The first intensification was paclitaxel (825 mg/m^2), the second melphalan (180 mg/m^2) and the third consisted of cyclophosphamide 6000 mg/m^2 (1500 mg/m^2/day x 4), thiotepa 500 mg/m^2 (125 mg/m^2/day x 4) and carboplatin 800 mg/m^2 (200 mg/m^2/day x 4) (CTCb). Following the paclitaxel infusion most patients developed a reversible, predominantly sensory polyneuropathy. Of the 30 patients with measurable disease, 12 converted to CR, nine converted to a PR, and five had a further PR, giving an overall response rate of 87%. The toxic death rate was 5% (242).

Both paclitaxel and cisplatin are active as second-line chemotherapy for patients with breast carcinoma. A synergistic cytotoxicity of these two drugs has been demonstrated in vitro. A phase II clinical trial using 175 mg/m^2 paclitaxel as 3h infusion plus 50 mg/m^2 cisplatin as 24-hour infusion every 3 weeks was administered as first line chemotherapy; when appropriate, chemotherapy was followed by resection of the primary tumor (mastectomy) and/or adjuvant radiotherapy. There were 3 complete responses (CRs) and 24 partial responses (PRs) among 46 patients, for an overall response rate of 58.7%. Grade 3-4 nausea and emesis and Grade 3-4 myelosuppression occurred in six patients and four patients, respectively (243).

Carboplatin plus weekly paclitaxel has been used as first- and second-line therapy in patients with advanced breast cancer in a Phase II multicenter trial. One hundred patients with advanced breast cancer were divided into two groups of 20 and 80. The small group of patients was treated with weekly paclitaxel 135 mg/m^2 and carboplatin at AUC of 2. Toxicity mainly consisting of neutropenia (50%) and leukopenia (35%) was observed in this group. The large group was treated with 100 mg/m^2 paclitaxel. Sixty-one patients received prior chemotherapy, 37 of whom received prior doxorubicin linked with cardiotoxicity. The overall response rate (ORR) among 95 assessable patients was 62%, including 8% complete responses and 54% partial responses. The median time to response was 1.8 months, the median duration of response was 13.3 months, the median time to progression was 4.8 months and the median survival was 16 months. The 62% ORR achieved with weekly paclitaxel plus carboplatin is among the highest achieved with chemotherapy for advanced breast cancer (244).

Carboplatin 200 mg/m^2 i.v. and mitomycin C 10 mg/m^2 i.v. on day 1 every 4 weeks has been used as an effective salvage therapy in metastatic breast cancer. In case of granulocytopenia or thrombocytopenia below grade 3, the carboplatin dosage was escalated to 300, 400, and 450 mg/m^2 in the next treatment cycle with 300 mg/m^2 as recommended dose (245).

The combination of cisplatin and vinorelbine in metastatic breast cancer gave objective responses in 27 out of 52 patients (52.9%; complete response 9.8%). Median time to progression was 8.5 months and median survival was 16.6 months (246). Eighty-one women <60 years of age in Netherlands with breast cancer and extensive axillary lymph node involvement received three courses of FE120C (5-fluorouracil 500 mg/m^2, epirubicin 120 mg/m^2, cyclophosphamide 500 mg/m^2) followed by surgery. The patients were then randomized to receive either a fourth FE120C course alone or a fourth FE120C course followed by high-dose chemotherapy (cyclophosphamide 6 g/m^2, thiotepa 480 mg/m^2, carboplatin 1600 mg/m^2). After a median follow-up of 6.9 years, 47 (48%) patients were alive, of whom 36 (38%) were without disease in this study. The 5-year overall survival rates were not much different (62.5% and 61%, between the two groups, respectively); the number of tumor-positive axillary lymph nodes after induction chemotherapy were significant factors determining overall survival (247).

Two randomized, double-blind, placebo-controlled clinical trials have studied the effects of pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) on platelet recovery in breast cancer patients undergoing autologous bone marrow transplantation. The purpose of MGDF administration was to reduce the duration of severe thrombocytopenia. 75 breast cancer patients underwent a bone marrow harvest and myeloablative STAMP V chemotherapy and were randomized to receive placebo or one of three doses of PEG-rHuMGDF. The study drug was administered daily starting on the day of bone marrow infusion until the platelet count was greater than or equal to 50 x 10^9/L (without transfusion) or for a maximum of 28 days (248).

17. Metastatic melanoma

The incidence of cutaneous melanoma has been rapidly increasing, with an estimate of 47,700 new cases (one in 5,000) diagnosed in 2000 in the United States (Table 1). In the early phase of its natural history, melanoma is cured in most cases by surgery, but once the metastatic phase develops, it is almost

always fatal. The overall survival for patients with metastatic melanoma ranges from 4.7 to 11 months, with a median survival of 8.5 months. Metastasis involves lungs, lymph nodes, liver, and other visceral organs.

The treatment of metastatic melanoma remains unsatisfactory. Systemic therapy has not been successful up to now, with very low response rates to single-agent chemotherapy. Standard treatment for patients with metastatic melanoma has not been defined. Conventional chemotherapy has been disappointingly ineffective. Although the most active single agent is dacarbazine (Bayer), numerous trials support the activity of platinum analogs against melanoma. Dacarbazine has a response rate of 15% to 20% and remains the reference agent for the treatment of metastatic disease. Additional single-agents include cisplatin, carmustine, paclitaxel and docetaxel. Multicenter studies using combinations of dacarbazine, cisplatin, carmustine, and tamoxifen gave overall response rates from 10% to 20% and there is no evidence that the addition of tamoxifen improves the response rate. Combination of cisplatin, vinblastine, and dacarbazine has been associated with a 20% to 25% response rate.

A phase II study in patients with metastatic melanoma used paclitaxel as a 3-hour infusion of 175 mg/m^2, and carboplatin dosed to yield an area under the curve of 7.5 administered during 30 minutes. 20% of the patients had partial responses, 47% had stable disease, whereas 33% showed evidence of progressive disease (249). Previously untreated melanoma patients with in-transit metastases received a systemic regimen in 21 day cycles composed of dacarbazine 800 mg/m^2 i.v. on day 1, vinblastine 1.6 mg/m^2 i.v. on days 1-5, and cisplatin 100 mg/m^2 on day 3 by 24 h intra-arterial infusion via the iliac or subclavian artery in 1Lit of heparinized saline. This treatment regimen gave a 67% response rate (250). Application of electrodes around the tumor and intratumoral injection of cisplatin in melanoma lesions increased the response rate from 38% to 78%; thus, electrochemotherapy with cisplatin is a highly effective approach for treatment of cutaneous malignant melanoma nodules (251). This study also demonstrates that one major hurdle in cisplatin chemotherapy is the limitation of cisplatin passage across the cell membrane; the electric current makes holes into the membrane allowing passage of the drug inside the malignant cell.

Levels of O^6-methylguanine-DNA methyltransferase (MGMT) in melanoma tumors in patients treated with dacarbazine-based chemotherapy have been examined and the data support the concept that MGMT contributes to resistance to dacarbazine; objective responses to chemotherapy were seen in 12 patients, while 53 patients failed to respond to treatment (252). Bcl-X_L is an antiapoptotic member of the Bcl-2 family universally expressed in human melanoma and contributing to the chemoresistance of melanoma cells; overexpression of Bcl-X_L in stably transfected human melanoma cells significantly reduced sensitivity to cisplatin-induced apoptosis (253).

Immunochemotherapy (biochemotherapy) of metastatic melanoma. The immunotherapy of metastatic melanoma using interferon (IFN)-α and interleukin (IL)-2 as single agents gave response rates of 15% to 20%. Higher response rates but with an unclear impact on overall survival on multiple phase II studies were obtained using a combination of immunotherapy and cytotoxic chemotherapy (reviewed in refs. 254,255). Immunological mechanisms seem to be responsible for the increased response rate, and particularly macrophage activation seems to be involved in tumor reduction. A schedule combining GM-CSF with biochemotherapy (cisplatin, dacarbazine, IL-2, IFN α-2b, tamoxifen) has been applied to 19 patients with advanced malignant melanoma in a Phase I study and gave a median overall survival was 6.2 months. GM-CSF may augment the cytotoxic lymphocyte response by activating antigen-presenting cells. There was a dose-response relationship with GM-CSF in terms of host immunological response in this study (256).

Immunochemotherapeutic combinations containing IL-2 theoretically represent the most effective therapies for metastatic melanoma, particularly in association with cisplatin. Treatment with high-dose IL-2 can cause severe toxicity and is normally administered in an inpatient setting. The antitumor activity of IL-2 can be enhanced by the immunomodulating pineal neurohormone melatonin (MLT), which has also been shown to increase the cytotoxicity of cancer chemotherapy and reduce its toxicity. A study using a low-dose IL-2 and cisplatin in association with MLT as a second-line therapy for metastatic melanoma patients progressing after dacarbazine plus IFN-α gave an objective tumor response of 31% (4 out of 13 patients) (257).

Phase II studies of biochemotherapy (combining IL-2, IFN-α, and cisplatin-based chemotherapy) have reported response rates ranging from 40 to 60%, with durable complete remissions in approximately 10% in patients with metastatic melanoma. Other studies have shown that the addition of IL-2 and IFN-α2b in multiagent chemotherapy for advanced melanoma increases overall response, albeit without clear evidence of an improvement in overall survival. Toxicity, however, with IL-2 / IFN-α / cisplatin, is often severe and can be life-threatening (258). A multicenter prospective randomized clinical trial (176 patients) with metastatic melanoma has compared chemotherapy (cisplatin and dacarbazine with or without carmustine every 21 days for 6 cycles) with biochemotherapy (using the same chemotherapy and immunomodulant low-dose subcutaneous IL-2 for 8 days and IFN α-2b 3-times a week, for 6 cycles). The overall survival (OS) was 9.5 months in the chemotherapy-arm (89 patients), versus 11.0 months in the biochemotherapy-arm. In the chemotherapy-arm there were three complete responders and 15 partial responders (OR 20.2%) compared to OR 25.3% in the biochemotherapy-arm; toxicity was fairly similar in both arms. Thus, the addition of low-dose immunotherapy did not produce a statistically significant advantage in OS, time to progression, or OR (259). Tamoxifen and cisplatin exhibit cytotoxic synergy in human melanoma cells. An overall response rate of 50%, with a complete response rate of 6% and a median survival of 9.5 months was reported using high-dose tamoxifen with dacarbazine, vinblastine, cisplatin, interleukin-2, and IFN-α2b in patients with metastatic melanoma (260). High dose tamoxifen (240 mg/day) and weekly cisplatin (80 mg/m^2 for a total of 3 weeks) followed by a second 3 week cycle of cisplatin gave an overall response rate of 32% in patients with metastatic melanoma (261).

A possible relationship between the clinical response to biochemotherapy and the serum caspase-1 level has been examined in 81 metastatic malignant melanoma patients and 50 normal volunteers. Patients received cisplatin, recombinant IL-2 (Proleukin) and IFN-α (Roferon A) in two induction cycles (biochemotherapy). The median caspase-1 level in melanoma patients was significantly higher than in healthy volunteers; the level of caspase-1 was significantly higher in biochemorefractory patients compared to patients responding to biochemotherapy and disruption in apoptosis pathways might be involved in progressive advanced melanoma (262). A Phase II study of biochemotherapy in metastatic melanoma patients showed an overall response rate of 29% (three complete responses, 15 partial responses) among the 63 patients evaluable for response; the response rate among previously treated and previously untreated patients was 6% and 38%, respectively. The low response rate among previously treated patients indicates that biochemotherapy is not useful as second-line therapy (263). A pilot Phase II study was performed on 48 patients with Stage III melanoma to explore the safety and activity of neoadjuvant biochemotherapy; two cycles of biochemotherapy were administered prior to and after complete lymph node dissection. Each cycle consisted of cisplatin, 20 mg/m^2 i.v. on Days 1-4; vinblastine, 1.6 mg/m^2 i.v. on Days 1-4; dacarbazine, 800 mg/m^2 i.v. on Day 1; IL-2, 9x10^6 IU/m^2/day i.v. over 24 hours on Days 1-4; and IFN-α, 5x10^6 IU/m^2/day subcutaneously on Days 1-5, every 3 weeks. Clinical responses were observed in 14 of 36 patients (38.9%) with measurable disease, including 13 partial responses (36.1%) and 1 complete response (2.8%) (264). Measurements of macrophage activation (neopterin), nitric oxide production (nitrite), and tumor necrosis factor-alpha (TNF-α), IL-1α, IL-1β, IFN-γ, IL-6, IL-10, and soluble IL-2 receptor (sIL-2R) were performed in melanoma patients during chemo- and biochemo-therapy. Six of the nine biological responses (nitrite, neopterin, IFN-γ, IL-6, soluble IL-2R, and IL-10) significantly increased in the biochemotherapy-treated patients (cisplatin, vinblastine, and dacarbazine, IL-2, TNF-α) but not in the cisplatin, vinblastine, and dacarbazine- treated patients (265).

18. Malignant peritoneal or pleural mesothelioma

Malignant peritoneal mesothelioma is an aggressive neoplasm that rapidly spreads within the confines of the abdominal cavity to involve most accessible peritoneal and omental surfaces. Malignant mesothelioma is almost invariably fatal. The incidence of the disease is rising rapidly in many countries, and there is no generally accepted standard treatment for patients with unresectable disease. One regimen involves laparotomy with omentectomy, resection of peritoneal implants; repeated courses of intraperitoneal chemotherapy with doxorubicin, cisplatin, and interferon gamma; second-look laparotomy and intraoperative hyperthermic perfusion with mitomycin and cisplatin; and whole abdominal radiation (266).

Patients with malignant pleural mesothelioma usually die of respiratory failure from extensive disease progression in the thorax. Because radiotherapy is associated with significant complications, and surgery is feasible in only a small percentage of patients the use of a systemic chemotherapy is the only treatment option. Doxorubicin has historically been considered the gold-standard chemotherapy, although its true response rate is only 15%. Although nearly every class of cytotoxic agent has been evaluated in mesothelioma, including antifolates, the anthracyclines, and the platinums, response rates are below 20%. An impressive 48% response rate has been reported for the combination of gemcitabine with cisplatin (reviewed in ref. 267).

Cisplatin was the most active single-agent regimen and the combination of cisplatin and doxorubicin had the highest response rate (28.5%) against unresectable malignant mesothelioma in a review of 83 clinical trials published from 1965 to 2001 (268). The combination of pemetrexed disodium and cisplatin was associated with very encouraging regression rates in mesothelioma patients treated as part of a phase I trial. A subsequent trial showed similarly encouraging activity (10 partial responses out of 25 evaluable patients [40%]) in mesothelioma patients treated with pemetrexed and carboplatin while a large, prospectively randomized, phase III trial of cisplatin alone versus cisplatin and pemetrexed with vitamin support has been completed (reviewed in ref. 20).

A phase I clinical and pharmacokinetic study of pemetrexed and carboplatin in patients with malignant pleural mesothelioma has been completed. Both pemetrexed and carboplatin doses were escalated. The MTD was determined to be 500 mg/m^2 pemetrexed and carboplatin of AUC 6, and three of the five patients treated at this dose level experienced a dose-limiting toxicity. The recommended phase II dose of the combination was pemetrexed 500 mg/m^2 and carboplatin AUC 5 mg/mL.min. A response rate of 32% was achieved, the median time to progression was 305 days, and the median survival time was 451 days (269). A multicenter randomized controlled trial proposes mitomycin, vinblastine and cisplatin (MVP) versus vinorelbine (Navelbine, Pierre Fabre Oncology, Winchester, UK) thought to provide good symptom control as recorded by patients. The outcome measures were overall survival, palliation of symptoms, performance status, analgesic usage, toxicity, quality of life, tumor response, and recurrence/progression-free survival (270).

19. Malignant Gliomas

Malignant gliomas (WHO Grade III and IV) continue to be a significant medical problem. The incidence of brain nervous system tumors is approximately 18,000 new cases in the United States in 2000 and 176,000 new cases world-wide; see Table 1). Brain tumors are the second leading cause of cancer mortality in people under 35 years of age and the fourth leading cause in those under 54 years of age. The cause of primary brain tumors is unknown. Environmental agents, familial tendencies, viral causes, and other possibilities are under investigation.

The most common childhood brain tumors are: Astrocytoma, Medulloblastoma, Ependymoma. The most common adult brain tumors are: i). Metastatic brain tumors from lung, breast, melanoma, and other cancers; ii). glioblastoma multiforme; iii). anaplastic (malignant) astrocytoma; iv). meningioma. Less frequently occuring are: Acoustic neuroma, adenoma, brain stem glioma (that may be an astrocytoma,

anaplastic astrocytoma, glioblastoma multiforme, or a mixed tumor), chordoma, choroid plexus papilloma, CNS lymphoma, cysts, craniopharyngioma, ependymoma, gangliocytoma, ganglioglioma, hemangioblastoma, medulloblastoma, neurofibromatosis, oligodendroglioma, optic nerve glioma, pineal region tumors, pituitary adenoma, pnet (primitive neuroectodermal t umor), spinal tumors, and tuberous sclerosis.

Glioma is a general name for tumors that arise from the glial (supportive) tissue of the brain. Gliomas are the most common primary brain tumors. Astrocytomas, ependymomas, oligodendrogliomas, and tumors with mixtures of two or more cell types are the most common gliomas.

Treatment usually involves a multi-modal approach, including surgery, radiation therapy, and chemotherapy. These combined modalities, however, have had a limited impact on survival.

Median survival for glioblastoma multiforme (GBM), the most common malignant glioma, ranges from 40 to 50 weeks, with most patients dead of disease within two years (271-273). Despite recent technical advances in surgery and anaesthesia, the effectiveness of surgical resection alone for treatment of glioblastoma remains dismal, with a median survival time of 4 to 6 months. This reflects the unique infiltrative and migratory growth characteristics of malignant gliomas, which make total resection impossible (274). To date, radiotherapy has been the most effective treatment for malignant gliomas. Adjuvant chemotherapy has provided little clinically relevant survival advantage to patients with GBM and modest benefit to patients with anaplastic astrocytoma (275). Failure of these treatments most often occurs with local tumour progression, which is unresponsive to conventional chemotherapy, and eventually leads to death. Therefore, alternative treatment approaches are needed which are based less on physical or mechanical principles and more on specific biological features of gliomas.

Glioblastoma multiforme (GBM) makes up as many as 30% of all primary brain tumors. Despite the employment of multimodal antitumor treatment, the overall survival is small. 17 patients underwent subtotal tumor ablation and were administered local chemotherapy with cisplatin incorporated into biodegradable 6-carboxylcellulose polymer (cisplatin-depot) of a total dose of 45 mg (Group A). 21 patients underwent subtotal tumor ablation without cisplatin-depot implantation (Group B). Two to three weeks after the surgery all the patients in Groups A and B started a course of radiation therapy. A total dose of cranial irradiation was 20 Gy followed by a boost tumor bed irradiation up to the conventional dose of 60 Gy. The median overall survivals for patients of Group A were 427.5 days versus 211.0 days in Group B (276).

Medulloblastoma is the most common primary brain tumor in children and accounts for 25% of newly diagnosed cases. Surgical resection, posterior fossa, craniospinal irradiation and chemotherapy for selected, high-risk patients have extended the 5-year survival rates to > 70%; The most active chemotherapy agents include cisplatin, CCNU, cyclophosphamide, vincristine and carboplatin. Neurocognitive function and quality of life are often impaired following radiation therapy (RT) to the developing brain (reviewed in ref. 277).

After surgical resection, high-risk medulloblastoma children patients were treated with craniospinal radiation therapy and four consecutive cycles of high-dose cyclophosphamide, cisplatin (75 mg/m^2 per cycle), and vincristine, each followed by stem-cell rescue, every 4 weeks. A 2-year progression-free survival of 93.6% was achieved in the average-risk patients and 73.7% in the high-risk patients (278).

The combination of cisplatin chemotherapy and radiation therapy for the treatment of medulloblastoma has been shown to cause significant ototoxicity, impairing a child's cognitive function and quality of life. Both cisplatin chemotherapy and radiation therapy contribute to this. Intensity-modulated radiation therapy (IMRT) has been successfully used to achieve lower rates of hearing loss by decreasing the radiation dose delivered to the cochlea and eighth cranial nerve (auditory apparatus) while still delivering full doses to the desired target volume (279).

Brain stem gliomas (BSG) were treated with intensive induction chemotherapy and simultaneous external beam irradiation in 11 children. Induction chemotherapy was two cycles of ifosfamide (days 1-3), etoposide (days 4-6), methotrexate (days 15 and 22), cisplatin (days 29-31) and cytarabine (days 29-31), separated by a 3-week interval. Maintenance chemotherapy with carmustine, carboplatin and vincristine (8 cycles over a 1-year period) was given in those patients who responded clinically or radiographically to induction chemotherapy. This intensive combined modality treatment was toxic but yielded objective responses in more than 50% and long-term survivors in one third of childhood BSG patients (280).

In a Phase I study, 29 children with high-grade glioma (median age 11.1 years) and with tumors located in cerebral cortex, deep cerebral locations, cerebellum, and in spinal cord were treated with simultaneous radiochemotherapy; the regimen was fractionated radiation (1.8 Gy up to 59.4 Gy) given simultaneously with two cycles of chemotherapy (cisplatin 20 mg/m^2/d x 5d, etoposide 100 mg/m^2/d x 3d, and cisplatin, etoposide, ifosfamide: 1.5 g/m^2/d) (281). Fifty-two pediatric patients of whom 27 with Grade 4 malignant glioma and 25 with Grade 3 anaplastic astrocytoma between the ages of 3 - 17 years were randomized to receive either 54 grays of irradiation (n = 22 patients) followed by chemotherapy with lomustine, vincristine, and cisplatin (maintenance chemotherapy) or sandwich chemotherapy (n = 30 patients), which consisted of ifosfamide, etoposide, methotrexate, cisplatin, and cytosine arabinoside followed by irradiation and tumor surgeries. The extent of resection was the most important prognostic factor but early, intensive chemotherapy increased survival rates in patients who underwent complete resection (282).

A simple chemotherapy regimen based on cisplatin and etoposide was used in children with low-grade glioma (LGG) to avoid radiotherapy. 10 monthly cycles of cisplatin (30 mg/m^2/d on days 1 to 3) and etoposide (150 mg/m^2/d on days 1 to 3) were used. Objective tumor response and toxicity were evaluated by magnetic resonance imaging and neurologic and functional tests at 3-month intervals. An objective response was obtained in 24 of 34 patients (70%). In 31 previously untreated children, the

overall survival was 100% and progression-free survival was 78% at 3 years, with a median follow-up of 44 months (283).

Thirty-two patients with newly diagnosed brainstem gliomas were randomly assigned to three courses of carboplatin, etoposide, and vincristine versus cisplatin, etoposide, cyclophosphamide, and vincristine. This was followed by hyperfractionated external-beam radiotherapy (HFEBRT) at a dose of 72 Gy. Response rates were 10%-27% for the various combinations. Neither chemotherapy regimen meaningfully improved the response rate, event-free survival, or overall survival relative to previous series of patients with brainstem gliomas who received radiotherapy with or without chemotherapy (284).

Stereotactic radiosurgery is a valuable adjunctive strategy in the management of recurrent or unresectable pilocytic astrocytomas; however, in a recent study multimodal treatment included fractionated radiation therapy, stereotactic intracavitary irradiation of tumor, chemotherapy, cyst drainage, ventriculoperitoneal shunt placement, and additional cytoreductive surgery. 33 (89%) of 37 patients were alive at a median follow-up period of 28 months after radiosurgery (285).

In a Phase II study 28 patients, 14 with anaplastic astrocytoma (AA) and 14 with glioblastoma (GB) were treated with intravenous administration of carboplatin (300 mg/m^2) on day 1 and etoposide (60 mg/m^2) on day 1 to 5, repeated every 6 weeks. Partial response was seen in 5 of 14 patients (36%) with AA and in 2 of 14 patients (14%) with GB, and stabilization of the disease (SD) in six (43%) in each group. The mean survival/survival after recurrence was 51 months/25 months in the AA group, and 17 months/9 months in the GB group (286).

Intra-arterial delivery of chemotherapy is an expensive and technologically burdensome treatment requiring proximity to a major center with neuro-oncological and neuroradiological clinical services. In a phase II study intra-arterially infused cisplatin 60 mg/m^2 on day 1 and oral etoposide 50 mg/m^2/day given at days 1-21, with a 7 day rest interval between courses on 20 patients with recurrent malignant glioma gave an overall response rate of 40%. The median survival time from treatment for the responders (n = 8) was 56.5 weeks and for the non-responders (n = 12) was 11 weeks (287). Treatment of recurrent malignant supratentorial astrocytomas was tested with carboplatin, administered intravenously at a dose of 400 mg/m^2 on day 1, and etoposide, administered intravenously at a dose of 100 mg/m^2 from day 1 to day 3 for 3 days. This was followed by treatment with a recombinant mutant human TNF-α given intravenously for up to 5 injections for 2 weeks. Treatment was repeated every 8 to 12 weeks for up to four cycles. Patients were previously treated with surgery, radiation therapy and chemotherapy with a nitrosourea and involved 3 patients with anaplastic astrocytomas, one patient with anaplastic oligoastrocytoma and 6 patients with glioblastomas. Of 9 evaluable patients, three (33%), including one glioblastoma, partially responded to the treatment (PR) with time to tumor progression (TTP) of 231, 121 and 57 weeks, respectively (288).

Experimental drugs against gliomas. Activation of signaling by the epidermal growth factor receptor (EGFR) through gene amplification or rearrangement is common in human malignancy, especially in a large fraction of de novo glioblastomas multiforme (GBMs). The most common mutant EGFR, (AEGFR) lacks a portion of the extracellular domain, enhances tumorigenicity in vivo, and causes resistance to cisplatin from suppression of cisplatin-induced apoptosis by the constitutively active tyrosine kinase activity of the receptor; inhibition of AEGFR signaling by the tyrosine kinase inhibitor, tyrphostin AG1478, could sensitize tumor xenografts to cisplatin and may provide the basis for the development of a novel therapeutic strategy for the very aggressive AEGFR-expressing GBM (289).

Increased expression of focal adhesion kinase (FAK) was consistently observed in low- and high-grade astrocytomas and during glioblastoma progression after radiotherapy and is a potential target for anti-invasive strategies against infiltrating glioma cells (290). Most tumors, including gliomas, are resistant to tumor necrosis factor (TNF) cytotoxicity unless protein or RNA synthesis is inhibited. The combined use of pretreatment with cisplatin followed by TNF-alpha had synergistic effects on glioma cells and thus cisplatin can sensitize glioma cells to TNF-α-induced apoptosis (291). Antisense oligonucleotides against human telomerase RNA in combination with cisplatin against malignant glioma cells with telomerase activity showed synergistic effect at 1 microg/ml cisplatin and additive effect at 5 microg/ml cisplatin (28).

20. Other cancers where cisplatin is being used

Endometrial cancer is believed to have a better prognosis than cervical cancer. However, advanced endometrial cancer with distant metastases has a poor prognosis and there is no established therapy. Two patients with endometrial cancer with multiple lung metastases (stage IVb) were treated with paclitaxel at 210 mg/m^2 over 3h and carboplatin at AUC of 5. Six courses of the regimen were given every 3-4 weeks. Multiple lung shadows in chest X-P and computed tomography (CT) were reduced in number and size after two courses and either disappeared or remained as scars after six courses (292).

A phase II clinical trial using combination of mitomycin, doxorubicin, and cisplatin (MAP) in patients with advanced uterine leiomyosarcoma as first line chemotherapy gave a complete response in 3 out of 37 patients (9%) and partial response in 5 out of 37 patients (14%) after receiving from one to six (median three) cycles (293).

A combination of cisplatin, interferon-α, doxorubicin and 5-fluorouracil has been used for unresectable hepatocellular carcinoma (294). Children with unresectable or metastatic hepatoblastoma (HB) were sequentially treated with one course of carboplatin (700 mg/m^2). This was followed by three courses of carboplatin at 700 mg/m^2 on day 0; 5-FU (1,000 mg/m^2/d) on days 0 to 2; and vincristine at 1.5 mg/m^2 on days 0, 7, and 14. After that therapy, patients whose tumors were resectable underwent surgery and then received two additional courses of carboplatin/vincristine/5-FU. Children whose tumors remained unresectable received high-dose cisplatin at 40 mg/m^2/d, days 1 to 5 and etoposide at 100 mg/m^2/d), days 2 to 4. The five-year EFS estimates were 59% for stage III disease (n = 22) and 27% for stage IV disease (n = 11), respectively (295).

A Phase II study with 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX-4 regimen) in 59 patients with metastatic renal cell carcinoma, pre-treated or not by cytokines (29 versus 30), gave three minor responses, no complete or partial response, a median progression-free survival of 3 months, and a median survival of 10.6 months. There was no difference between pre-treated and non-treated patients (296).

Fifty-one children (median age 7 months) with retinoblastoma were treated with a combination of transpupillary thermotherapy delivered shortly after i.v. injection of carboplatin (560 mg/m^2). Each tumor was treated separately with a diode laser using a microscope. Tumor regression was obtained for 99 tumors (96.1%) after a median follow-up of 30 months (297). Continuous infusion of carboplatin (28 mg/m^2/d), 5-FU (1 g/m^2/d for 4 days as a continuous infusion) and radiotherapy (50 Gy in 25 fractions over 5 weeks) has been used for localized carcinoma of the thoracic esophagus (154). Children with Wilms tumor (nephroblastoma) were treated with high-dose melphalan, etoposide and carboplatin and autologous peripheral blood stem cell rescue in order to improve their probability of survival. Fourteen of 23 patients were alive after a median observation time of 41 months, 11 of 14 were in continuous complete remission, and 3 in complete response after relapse post high-dose chemotherapy. The estimated survival and event-free survival for these patients were 60.9% and 48.2%. Because of the nephrotoxicity of this regimen, dose adjustment on glomerular filtration rate has avoided permanent renal failure (298).

Metastatic brain tumors are the most common complication of systemic cancer and affect 20-40% of all adult cancer patients. Although whole-brain radiotherapy and surgical resection of accessible, solitary lesions have been the mainstay of treatment, recently chemotherapy has become a more viable treatment option. Local chemotherapy with biodegradable polymers or tempozolomide and intra-arterial administration of carboplatin, have demonstrated activity against recurrent metastatic disease (68, reviewed in ref. 299).

The importance of first versus second/third line chemotherapies. Despite high response rates to first line chemotherapy, the majority of patients with advanced cancer will relapse and will be candidates for further chemotherapy (88). A great number of studies demonstrate the much higher effectiveness of chemotherapy regimens given as first line treatments; the gun smoke in low response rates in second and third line treatment points to chemoresistance developed during the first line chemotherapy provided that the patients in comparable studies were randomized for disease stage.

For example, the response rates in the various regimens against advanced NSCLC used as 1st versus 2nd line treatment are dramatically different. Chemotherapy-naive patients treated with paclitaxel plus carboplatin gave a response rate of 28.0% and those treated with paclitaxel plus gemcitabine gave a response rate of 35.0% (51). The overall response rate was 52.1% for chemotherapy-naive patients with locally advanced NSCLC treated with carboplatin plus paclitaxel and sequential radiation followed by consolidation carboplatin and paclitaxel (58). Attenuated doses of paclitaxel and carboplatin on chemotherapy-naive NSCLC patients over 65 years of age gave an objective response rate of 40% (52). Irinotecan, paclitaxel and carboplatin on previously untreated Stage IIIB/IV NSCLC patients gave a tumor responses rate of 32% (72). A phase III study using gemcitabine plus carboplatin or gemcitabine plus cisplatin in chemotherapy-naive patients with stage IIIB/IV NSCLC gave comparable response rates of 47% and 48% (46). A phase III randomized trial using a combination of gemcitabine with ifosfamide or with the cisplatin-carboplatin on chemotherapy-naive patients with metastatic stage IV NSCLC gave objective response rates of 23-29% (47). A randomized phase III on chemonaive patients with advanced or metastatic NSCLC using cisplatin plus vinblastine vs gemcitabine plus carboplatin gave response rates of 15% vs 27% (48). On the other hand, second-line chemotherapy with paclitaxel in patients with NSCLC who had failed first-line platinum-based regimens gave an overall objective response rate of only 8% (53). Treatment with irinotecan and vinorelbine of NSCLC patients in stage IIIB and IV previously treated with cisplatin, paclitaxel, and gemcitabine gave a 9% partial response (300). A phase II study of nedaplatin and vindesine on patients with relapsed or refractory NSCLC who had previously received chemotherapy, thoracic radiotherapy, and/or surgery showed a partial response of 3 out of 40 patients (7.5%) in patients who had received prior chemotherapy, compared to 4 out of 8 (50%) chemotherapy-naive patients (66). Docetaxel as first line treatment against NSCLC gave response rates from 19% to 54% with a median duration of survival ranging from 6.3 months to 11 months, whereas on previously-treated patients with NSCLC the overall response rate (ORR complete+partial) was ranging from 16% to 25% with a median survival ranging from 7.2 months to 10.5 months (reviewed in ref. 11). Pemetrexed (Alimta) as single-agent against NSCLC in previously untreated patients resulted in a response rate of around 20% compared to a response rate of 9% as a second-line single agent (reviewed in ref. 31). An overall response rate of 72.2% was reported using cisplatin, etoposide, and gemcitabine (PEG) on previously untreated patients with SCLC (304) whereas response to second-line therapy remains consistently poor (reviewed in ref. 302). A 29.4% response rate was documented on previously treated SCLC patients with sensitive tumors (68 of 110 patients who responded to first-line treatment and progressed in more than 3 months after treatment discontinuation) using cisplatin and topotecan; the response rate was 23.8% on patients with refractory tumors (42 of 110 patients who failed first-line treatment in less than 3 months from treatment discontinuation) after the same treatment (303).

21. Conclusions and perspectives

Platinum drugs remain a cornerstone of present day chemotherapy regimens not only for epithelial malignancies of the lung, ovarian, bladder, testicular, head & neck, and gastrointestinal but also against a number of metastatic or advanced malignancies including cancers of the breast, melanoma, prostate, mesothelioma, nasopharyngeal, pancreatic, leiomyosarcomas and most other advanced cancers. Understanding details on activation of signal transduction by cisplatin, carboplatin, oxaliplatin and most other platinum compounds leading to apoptosis, mostly responsible for the toxic

side effects of platinum compounds, is likely to reveal novel strategies and improve combination therapies and efficacy. Tumor cells can activate different signaling pathways compared to normal cells and this is an advantage in new drug development. Cisplatin damage can modulate signaling pathways in cancer cells and therefore combination therapies of platinum compounds with signaling blockers seems to have bright prospects in the anticancer field. Inhibition of the JNK, ras, MAP kinase and other pathways by treatment of tumors with kinase inhibitors are bright prospects for new drugs to be used in combination with platinum compounds. Also important appear to be epothilone B and its related BMS 247550 now in clinical trials (reviewed in 304) whereas new epothilones are under preclinical development (305-308). Other drugs under clinical evaluation include the protein kinase Cβ inhibitor compound 317615 (309), ZD1839 (also known as Iressa) against head and neck, prostate, colon and breast cancers (reviewed in refs. 310-312), the hypoxic cytotoxin tirapazamine (313) and DMXAA (314), bevacizumab, a monoclonal antibody to vascular endothelial growth factor (315), IMC-C225, a chimeric monoclonal antibody that targets EGFR (reviewed in 316,317), vinflunine, is a new uniquely fluorinated Vinca alkaloid (reviewed in ref. 318) decitabine, a new DNA hypomethylating agent used in clinical trials with cisplatin (319), and emerging gene therapy drugs such as adenoviral E1A (320) and p53 (321).

Intriguing results from large randomized trials indicate that single agent platinum might be well incorporated into taxane regimens. Additionally, a range of other agents could be tested as part of first-line regimens, having demonstrated activity in relapsed patients such as topotecan, gemcitabine, cell signaling inhibitors and liposomal doxorubicin. As a greater understanding of the molecular basis of various cancers is gained, the inclusion of biologic-based therapies will hopefully advance our ability to treat patients with specific cancers more effectively. New formulations of experimental and already tested platinum compounds will continue to play an important role in cancer treatment especially in their combinations with radiation therapy, taxanes and other microtubule stabilizers (paclitaxel, docetaxel, epothilones), topoisomerase I and II inhibitors, angiogenesis inhibitors, signal transduction blockers, and the emerging gene therapy drugs. Cisplatin, carboplatin, the trinuclear platinum agent BBR3464, the platinum complex ZD0473, oxaliplatin and Lipoplatin (reviewed in ref. 5) could be developed in combination with agents such as taxanes, gemcitabine, vinorelbine, epothilones in patients with advanced and/or refractory solid tumors (43).

Development of platinum drug resistance by tumors is a major clinical limitation. This is often linked to resistance to other chemotherapy drugs (doxorubicin, taxanes) from crosstalk of mechanisms involving import of these molecules across the cell membrane. The experimental strategies under investigation aimed at overcoming cisplatin resistance such as introduction of functional genes (p53, p21, bax), or of genes that intervene with apoptotic pathways such bax, $BclX_L$, bcl-2 (reviewed in ref. 5) are likely to contribute to tumor treatment especially in combination with regimens using platinum drugs. Novel avenues include the development of hammerhead ribozymes or employment of oligonucleotides designed to cleave specific mRNAs and thus diminish the levels of a protein in a tumor cell. For example, suppression of the gene expression multidrug resistance 1 (MDR1) can reverse multidrug resistance to doxorubicin and etoposide (although not to cisplatin) in cell cultures (reviewed in ref. 5). One could also inhibit factors that upregulate production of glutathione or other molecules involved in detoxification of cisplatin with the purpose of increasing cisplatin sensitivity in resistant tumors. If such effects can be done by specific tumor targeting employing for example the liposome encapsulation technology implemented in Lipoplatin, Doxil, or Spi-77 the effect would be very dramatic without interfering with their metabolism in normal tissues.

In future gene therapy applications, the preferential tumor targeting with toxic genes or other anticancer genes (tumor suppressor genes, genes participating in signaling pathways, ribozyme genes targeting specific mRNA molecules) using the type of liposomes used for liposomal encapsulation of genes and viruses (322) is also anticipated to bring a major advancement in molecular oncology.

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