Int. J. Radiation Oncology Biol. Phys., Vol. ■, No. ■, pp. 1–6, 2009

0360-3016/09/$–see front matter

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doi:10.1016/j.ijrobp.2009.07.1733

CLINICAL INVESTIGATION

CONCURRENT LIPOSOMAL CISPLATIN (LIPOPLATIN), 5-FLUOROURACIL AND RADIOTHERAPY FOR THE TREATMENT OF LOCALLY ADVANCED GASTRIC CANCER: A PHASE I/II STUDY

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Purpose: Liposomal drugs have a better tolerance profile and are highly accumulated in the tumor environment, properties that promise an optimal radiosensitization. We investigated the feasibility of the combination of 5-fluorouracil/lecovorin–based radio-chemotherapy with the administration of high weekly dose of a liposomal platinum formulation (Lipoplatin™).

Methods and Materials: Lipoplatin was given at a dose of 120mg/m^2/week, 5-fluorouracil at 400mg/m^2/week (Day 1), whereas radiotherapy was given through 3.5-Gy fractions on Days 2, 3, and 4. Two groups of 6 patients received four and five consecutive cycles, respectively.

Results: Minimal nephrotoxicity (18.2% Grade 1) and neutropenia (9% Grade 3) was noted. Fatigue Grade 2 appeared in 25% of cases. Abdominal discomfort was reported by 18% of patients. No liver, kidney, gastric, or intestinal severe acute or late sequellae were documented, although the median follow-up of 9 months is certainly too low to allow safe conclusions. A net improvement in the performance status (from a median of 1 to 0) was recorded 2 months after the end of therapy. The response rates assessed with computed tomography, endoscopy, and biopsies confirmed 33% (2 of 3) tumor disappearance in patients treated with four cycles, which reached 80% (4 of 5) in patients receiving five cycles.

Conclusions: Lipoplatin radio-chemotherapy is feasible, with minor hematological and nonhematological toxicity. The high complete response rates obtained support the testing of Lipoplatin in the adjuvant postoperative or preoperative radio-chemotherapy setting for the treatment of gastric cancer.

Liposomal cisplatin, Lipoplatin, Radiotherapy, Chemotherapy, Gastric cancer.

INTRODUCTION

Gastric cancer is a tumor, with an overall mortality of 75% based on Surveillance Epidemiology and End Results data (http://seer.cancer.gov/statfacts/html/stomach.html). Radical surgery may lead to cure rates as high as 80% in patients with node-negative disease, but these drop to 10% to 40% in patients with extramural tumor invasion and/or lymph node involvement (1). Adjuvant chemotherapy trials have shown a small survival benefit reducing the death risk by no more than 4% (2,3). Adjuvant radio-chemotherapy, on the other hand, seems to offer a more significant benefit in terms of loco-regional control; and after the favorable results of the INT-0116 trial, a combination of 5-fluorouracil with radiotherapy is considered the standard postoperative regimen (4). The CALGB-80101 study (http://www.cancer.gov/clinicaltrials/CALGB-80101) is expected to elucidate whether platinum-based chemotherapy before and after 5-fluorouracil radio-chemotherapy can further improve osteoperative outcomes (5).

Cisplatin is, indeed, an active drug in gastric cancer as shown in Phase II trials (6). Moreover, cisplatin is a key drug in the practice of radiosensitization and has an established role in the radio-chemotherapy of locally advanced lung, head-and-neck, and gynecological cancer and other malignancies. Inclusion of cisplatin in the concurrent radio-chemotherapy phase of adjuvant therapy for gastric cancer or in radical radio-chemotherapy regimens applied for

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Conflict of interest: Teni Boulikas is the inventor of Lipoplatin™ and he has interests in Regulon. No other authors have conflicts of interest to declare.

Received June 6, 2009, and in revised form July 14, 2009. Accepted for publication July 16, 2009.

Table 1. Patient, disease and medical treatment characteristics

No. of patients	12
Age (y)	
median	71
range	51–79
Sex	
Male	9
Female	3
PS	
0–2	1
Origin	
Cardio-esophageal	8
Gastric body	4
T-stage*	
T3	6
T4	4
Recurrent*	2
N-stage*	
negative	3
positive	9
Previous chemotherapy	
No	9
Yes‡	3
Main symptomatology	
Dysphagia	9
Hemorrhage	4
Pain	9
Ascitis	3

†Based on computed tomography or magnetic resonance imaging, American Joint Committee on Cancer system.
* After previous surgery.
‡ Progressive disease to chemotherapy.

the treatment of inoperable gastric disease is founded on a strong rationale. The severe nausea/vomiting and malaise, as well as the renal toxicity expected from the combination of abdominal radiotherapy with cisplatin, is probably the main reason why randomized trials have avoided adopting such a combination, resorting to drugs of mild toxicity but also of doubtful sensitizing efficacy such as 5-fluorouracil.

Stealth liposomal formulation of cytotoxic drugs aims to confer a prolonged circulation half-life time of the encapsulated drug that is slowly released as liposomes degrade (7). Their size and structure, being a major obstacle for their extravasation in normal tissues, facilitate the differential accumulation of the drug in cancerous tissues with increased vascular permeability (8,9). Highly selective localization of liposomes in tumors could be of great importance when chemotherapy is to be combined with radiotherapy, as radio-sensitization of the normal tissues encompassed within the radiation fields is substantially reduced and the high intratumoral concentration of the drug promises an optimal sensitization effect.

In the current Phase II study, we investigated the feasibility of the combination of the widely used 5-fluorouracil/lecovorin–based radio-chemotherapy with the administration of high weekly dose of a liposmal platinum formulation (Lipoplatin™) (10) for the treatment of inoperable or recurrent gastric cancer.

METHODS AND MATERIALS

Twelve patients with locally advanced inoperable gastric adenocarcinoma were recruited in a Phase I/II study examining the feasibility, toxicity, and efficacy of radiotherapy in combination with Lipoplatin. The median follow-up of patients was 9 months (2–24 months). The study was approved by the institutional Ethics and Scientific Committees and by the Hellenic Drug Administration (EOF) (Aα-KD-72/01/04).

Lipoplatin was made available for the current study by Regulon AE Hellas. Lipoplatin is formed from cisplatin and liposomes composed of dipalmitoyl phosphatidyl glycerol (DPPG), soy phosphatidyl choline (SPC-3), cholesterol, and methoxy-polyethylene glycol-distearoyl phosphatidylethanolamine (mPEG2000-DSPE) (11).

Criteria

Table 1 reports the patient and disease characteristics. Patients with locally advanced gastric cancer, gastric cancer inoperable for medical reasons, or recurrent carcinomas were recruited. Patients were required to have a performance status of 0 to 2, normal renal and kidney function, and normal hematological parameters. Patients with severe renal, liver, cardiovascular, or pulmonary diseases, and patients who had hematological malignancies or who were pregnant, were excluded. Previous radiotherapy was also an exclusion criterion. Patients with extensive metastatic disease or patients with uncontrolled brain metastasis were excluded. Local control of pain or hemorrhage would greatly improve the quality of life in patients with minor metastatic disease, so such patients were also eligible. Patients with relapse after chemotherapy or patients with chemo-resistant disease could be included in the protocol.

Pretreatement and treatment evaluation

Baseline studies included physical examination, whole blood count (WBC) with differential and platelet count, complete biochemical profile, bone scan, and computed tomography or MRI of the chest and upper abdomen. Patients were followed with white blood cell counts and with serum urea, creatinine, and liver enzyme tests once a week during the treatment period. Acute radiation toxicity registered daily on treatment days. The National Cancer Institute (NCI) Common Toxicity Criteria Version 2 scale (www.fda.gov/cder/cancer/toxicityframe.htm) was used to assess chemotherapy and acute radiation toxicity.

Response to treatment was assessed with computed tomography (CT), endoscopy, and biopsies performed during endoscopy, 2 months after treatment completion. Duration of response was measured from the time the criteria of the objective response were first met with CT and endoscopy done every 3 months. We defined CR as disappearance of the CT-measurable in-field lesion within 2 months after treatment completion, disappearance of the endoscopically detectable lesion, and histological confirmation of lack of viable tumor at biopsies. Partial response referred to a regression, by more than 50%, of the detectable mass at CT scan and/or to a massive regression of the endoscopically detectable tumor.

Chemotherapy regimen

Radio-chemotherapy was administered on a weekly basis. 5-Fluorouracil (400 mg/m^2), leucovorin (200 mg flat dose), and Lipoplatin (120 mg/m^2) were administered on day 1 of each week. The choice of the Lipoplatin dose was based on the previous experience from our institute on a Phase II trial in lung cancer (12). Lipoplatin was diluted in 1L of D/W (dextrose 5% in water) and was administered as a 3 h infusion at an outpatient basis. Methylprednisolone 250 mg,

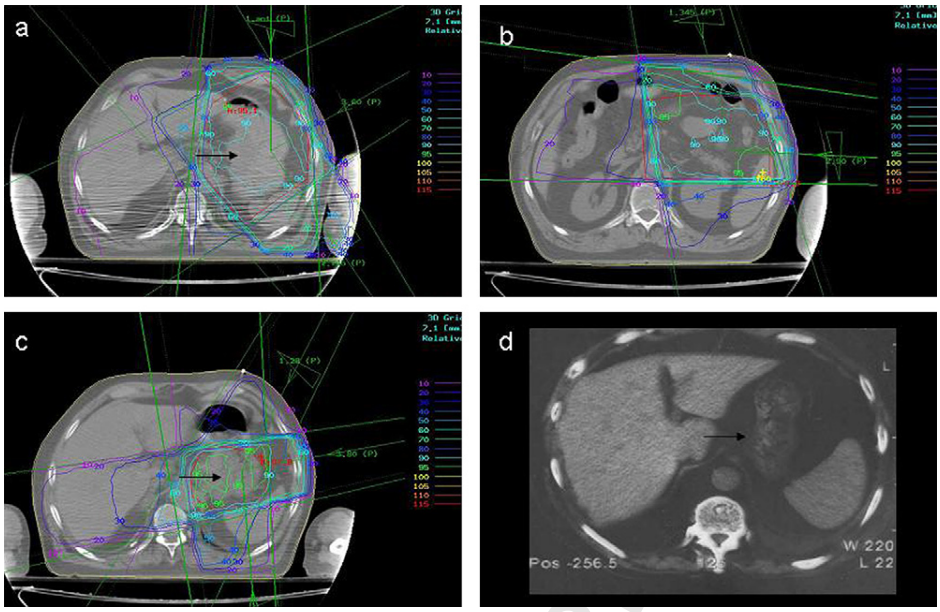

Fig. 1. A half beam planning splitting the target area to two portions, above and below the apex of the left kidney, is shown in (a) and (b), respectively. A three-field technique was used at the upper region, which was useful to keep liver and spleen dose to low levels (a). A two oblique–field technique was applied at the lower region, providing a good protection of the kidneys and liver (b). The fifth radiotherapy cycle used booster individualized radiotherapy fields directed to the detectable tumoral mass, after a new computed tomographic simulation (c). One year after therapy, the patient remains has remained alive with no evidence of disease (d).

dimethindene maleate 8 mg, ondasetron 16 mg, and ranitidine 50 mg were administered intravenously to prevent vomiting and infusion-related reactions such as back pain, flash, and dyspnea, which may appear during liposomal drug infusion.

Patients with hemoglobin levels of less than 11.5 g/dl were supported with subcutaneous administration of erythropoietin. Any drop if neutrophils to less than 2,000/ml (greater than Grade 1 toxicity) was supported with G-CSF, whereas neutropenia of Grade 3 or more was also followed by a 1-week delay. Platelet toxicity of Grade 3 or more was also followed by delay of chemotherapy until platelet toxicity regressed to Grade 1.

Radiotherapy details

Radiotherapy was given on days 2, 3, and 4 of each week at a dose of 3.5 Gy/day, using a 6- to 18-MV linear accelerator (LINAC; ELECTA). The fields applied followed the guidelines in the consensus statement of Smalley *et al.* (13). A conformal three-dimensional planning CT scan was performed (Plato, Nucletron), encompassing the whole gastic, cardiac area, and lower esophagus, together with the adjacent nodal regions extending below the diaphragm, to the liver and spleen edges and downward up to the level of the second to third lumbar vertebra. Overall, a half beam technique was used, splitting the target area to two portions, above and below the apex of the left kidney. A three-field technique was used at the upper region, which was useful to keep liver and spleen dose to low levels (Fig. 1a). A two–oblique-field technique was applied at the lower region, providing a good protection of the kidneys and liver (Fig. 1b). As no respiration movement–correction radiotherapy facilities were available, adequate margins were considered during planning, and the patients were instructed to avoid large volume breathing.

Six patients were planned to receive four weekly cycles, and another six patients 5 weekly cycles of the regimen. The fifth radiotherapy cycle used booster individualized radiotherapy fields directed to the detectable tumoral mass, after a new CT-simulation (Fig. 1c).

The weekly dose of radiotherapy was 10.5 Gy (3.5 Gy×3 days), which is equivalent to 13.1 Gy given with standard fractionation, assuming an α/β ratio of 4 Gy for late normal tissue effects. The four cycles of radiotherapy administer a physical dose of 42 Gy in 4 weeks, which is equivalent to 52.4 Gy (for $\alpha/\beta = 4$ Gy). The five cycles give a physical dose of 52.5 Gy to the tumor, which is equivalent to 65.6 Gy (for $\alpha/\beta = 4$ Gy).

Statistical analysis

The statistical analysis and graphical presentation of survival curves was performed using the GraphPad Prism 4.0 version package (GraphPad, San Diego CA, www.graphpad.com). Survival curves were plotted using the method of Kaplan and Meier.

RESULTS

Lipoplatin tolerance

Of 12 patients, 1 patient (8.3%) experienced a reaction to the Lipoplatin infusion during the first cycle. This was accompanied by flash, back pain, and sensation of breathing difficulty, without blood pressure drop or cardiac dysfunction. The symptoms regressed rapidly some minutes after infusion interruption and breathing support with oxygen. The patient exited the trial.

Of 11 evaluable patients, 2 patients (18.2%) developed Grade 1 renal toxicity. Nausea Grade 1 was noted in 2 of 11 patients (18.2%). Three patients (25%) complained of Grade 2 fatigue during radio-chemotherapy, but asthenia was not the cause of treatment delays.

Neutropenia was uncommon. Grade 2 and 3 toxicity was noted in 2 of 11 (18.2%) and in 1 of 11 (9%) patients, respectively. None of the patients developed febrile neutropenia, and rapid restoration of neutrophil counts was obtained after G-CSF administration. One patient (9%) developed Grade 3 platelet toxicity, whereas 10 of 11 showed no platelet toxicity. None of the patients developed any grade of anemia, and the pre-RT low hemoglobin levels in some patients increased rapidly with the use of erythropoietin.

Radiotherapy tolerance

Radiotherapy was well tolerated and the overall nausea and vomiting of the regimen was limited, as mentioned above. Abdominal discomfort was mentioned by 2 of 11 patients (18.2%), but this was not the reason for treatment delays. None of the patients complained of anorexia- or radiotherapy-related dysphagea and, in contrast, these features improved during radiotherapy. No case of diarrhea was recorded.

Within a median follow-up of 9 months (2–24 months), none of the patients experience any severe late toxicity, whether treated with four (12×3.5 Gy) or five (15×3.5 Gy) cycles of radiotherapy.

Response and survival

Symptomatic response to therapy was evident since the first treatment cycles. Dysphagia and pain were substantially improved in all treated patients. Hemorrhage was also controlled in all 4 patients. The median PS of patients improved from 1 to 0 at 2 months after the end of therapy.

Of 6 patients receiving four cycles of the regimen, 2 patients (33.3%) achieved histologically confirmed CR, 3 (50%) achieved PR, and 1 (16.7%) had stable disease. Four of 5 patients receiving five cycles of the regimen showed CR (80%). The 12-month local relapse free survival is 51%, whereas the median value has not been reached (Fig. 2a). The 12-month overall survival is 70% and the median 16 months (Fig. 2b). Comparison analysis of the four- vs. five-cycle results is not feasible because of the short follow-up of the later group.

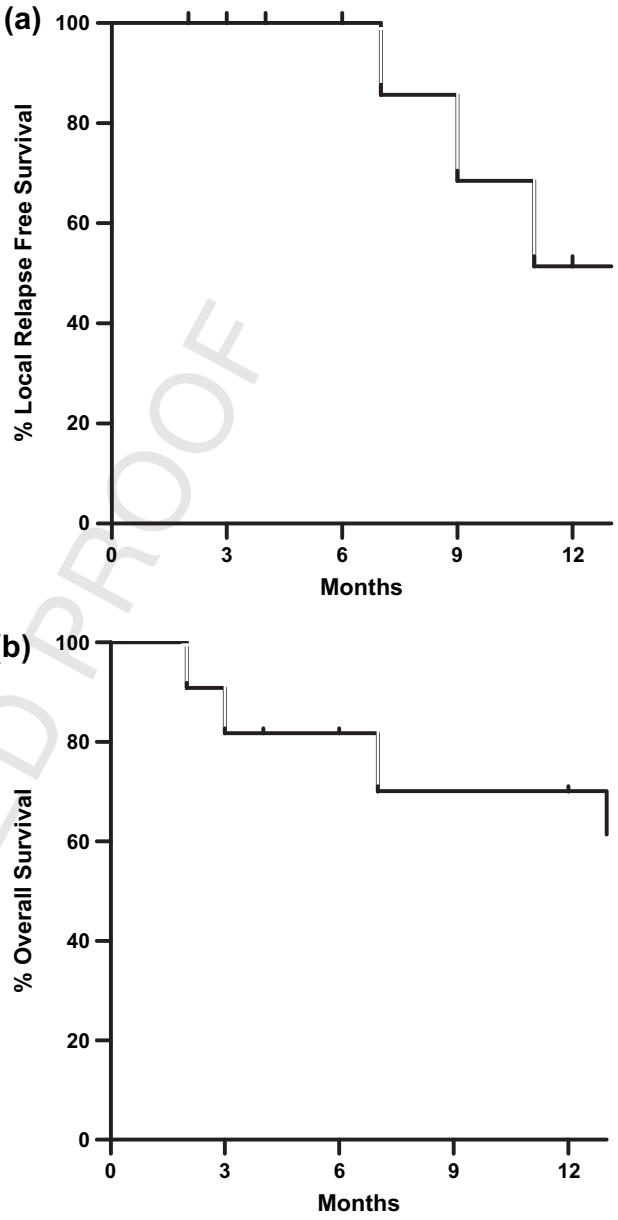

Fig. 2. Kaplan-Meier survival curves of 11 patients treated with lipoplatin, 5-fluorouracil, and radiotherapy: (a) local-relapse–free and (b) overall survival.

DISCUSSION

Lipoplatin is a liposome formulation of cisplatin designed to reduce cisplatin toxicities without counteracting its efficacy (11). Comparative studies in rodents and dogs showed a clear superiority of Lipoplatin over cisplatin in terms of kidney tubular damage (14,15). Moreover, Arienti *et al*. showed a higher antitumor activity of Lipoplatin in established cell lines from various tumors (16). The observed favorable toxicity and anti-tumor efficacy of Lipoplatin compared with cisplatin suggest a higher therapeutic index for Lipoplatin.

Plasma pharmacokinetics in human beings showed a half-life of 60 to 117 hours (10), which explains the low nephrotoxicity of Lipoplatin and suggests a superior gradual accumulation of the cisplatin in the tumor environement. This was shown in a phase I study by Boulikas *et al*. after direct measurement of the platinum levels in tissue biopsies, showing 10 to 50 times higher accumulation in malignant compared with the adjacent normal tissues (17). In this study, the highest platinum levels among all tissues examined were found in gastric cancer specimens, most likely reflecting the high degree of vascularization of these tumors and the ability of the nanoparticle formulation for extravasation through the compromised endothelium of the tumor (17). In a Phase I trial performed at our institution in lung cancer patients, Froudarakis *et al*. suggested that the maximum tolerated dose of Lipoplatin, when given together with gemcitabin, is 120 mg/m^2 for two weekly cycles, repeated every 21 days (12).

Based on the above data, we postulated that Lipoplatin represents a candidate drug to test its activity together with radiation. The high intratumoral accumulation of liposomes and the favorable tolerance profile of the drug could reveal liposomal cisplatin as an optimal radiosensitizing approach. The administration of a weekly dose of 120 mg/^{2} of cisplatin through the liposomal carriers is three-fold higher than the up to 40 mg/m^2 dose of cisplatin used in the clinical practice of radio-chemotherapy.

Inoperable gastric cancer is a suitable model of an incurable human cancer in which the toxicity and efficacy profile of Lipoplatin based radio-chemotherapy could be studied. Radiotherapy tolerance at the upper abdominal area is certainly problematic, as stomach, small intestine, pancreas, and certain areas of the liver and kidneys are inevitably included in the fields. Nevertheless, radio-chemotherapy with 5-fluorouracil is the standard adjuvant postoperative regimen and is probably the only challenging regimen for the radical treatment of inoperable cases (5). However 5-flurouracil/leucovorin, despite demonstrated activity against gastric cancer, is far from being the optimal radiosensitizer. Indeed, cisplatin is the only drug that has shown a net improvement in therapeutic index of radiotherapy (18–20).

We therefore started a Phase I/II trial aiming to examine the tolerance and efficacy of four and five consecutive weekly cycles of 120 mg/m^2 of Lipoplatin administered together with a hypofractionated regimen of radiotherapy, given as a 3- weekly fraction of 3.5 Gy. Large radiotherapy fractions have been used in the past as a palliative regimen for gastric cancer. Pfister *et al.* used 16 fractions of 2.5 Gy (biological dose of 44 Gy for α/β=4 Gy) with good tolerance and long lasting palliation (20). Although the α/β value of gastric cancer is unknown, several human carcinomas, including colon adenocarcinoma, tend to have a low α/β value, so large radiotherapy fractions may be more effective. Suwinski *et al.* recently suggested a 5-Gy value for colorectal cancer (21). The 12 and 15 fractions of 3.5 Gy used in the current study correspond to a biological dose of 52 Gy and 66 Gy, respectively, for normal tissues and cancer tissues with α/β value as low as 4 Gy. Both dose levels are higher than the ones used for palliation, and the latter one should certainly be considered as a high-dose radical regimen, given the high radio\sensitivity of organs in the upper abdomen. A conformal technique was used to keep the dose within the levels of individual organ tolerance.

The administration of four and five consecutive cycles of Lipoplatin at the dose of 120 mg/m^2 as a 3-h infusion showed an excellent tolerance by the majority of the patients with minimal nephrotoxicity (18.2% Grade 1 increase in creatinine) and neutropenia (9% Grade 3). Neutrophils were rapidly restored using G-CSF. Platelet toxicity, a common side effect of cisplatin, was limited to 1 patient who showed a Grade 3 platelet drop but in whom counts returned to normal after 1 week delay of the Lipoplatin cycle. Grade 2 fatigue appeared in 25% of cases during therapy but did not jeopardize the course of therapy.

Radiotherapy showed also an excellent tolerance, with abdominal discomfort reported by 18% of patients. No liver, kidney, gastric, or intestinal severe acute or late sequellae were reported, although the median follow-up of 9 months is certainly too short to allow definite conclusions.

A net improvement in the performance status (from a median of 1–0) was recorded 2 months after the end of therapy. Symptoms of dysphagia, pain, and hemorrhage were significantly improved or completely resolved. The response rates assessed with CT, endoscopy, and biopsies confirmed 33% tumor disappearance in patients treated with four cycles and 80% in patients receiving five cycles.

CONCLUSION

We conclude that inclusion of Lipoplatin in the 5-flurouracil–based radio-chemotherapy is feasible, with minor hematological and nonhematological toxicity. The regimen results in excellent symptomatic control. The high complete response rates obtained suggest that Lipoplatin should be tested in adjuvant postoperative or preoperative radio-chemotherapy regimens for the treatment of gastric cancer.

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