Informed consent form for Lipoplatin monotherapy and low-dose radiation

Updated: January 2019

Introduction

You have been diagnosed with Malignant Tumor.

This document allows you to be informed on a new drug, Lipoplatin that could be an alternative way of treating your disease, combined with radiation of low dose (2Gy per dose twice per week or once per week for 8-12 weeks). Before you consent, please read the following information.

Information on Lipoplatin

The new drug, Lipoplatin, is under consideration for approval in EU (by the European Medicines Agency, EMA), in the Russian Federation, UAE, Turkey. Regulon also plans for fast-track Marketing Authorization by the U.S. Food and Drug Administration (FDA). Lipoplatin has been granted the orphan drug designation by EMA for pancreatic cancer.

Lipoplatin™ is a liposomally-encapsulated form of cisplatin, developed by Regulon, Inc. based in California, USA. Cisplatin is a well-known chemotherapy drug used in the treatment of epithelial malignancies representing more than 85% oh human tumors. The Lipoplatin nanoparticles have been shown to concentrate in primary tumors and metastases following intravenous administration. In human studies the levels of Lipoplatin in the tumor were 10-200 times higher compared to adjacent normal tissue. This is a unique passive targeting not found in other drugs. The targeting of tumors is facilitated from the imperfections in the endothelium of tumor vasculature compared to the vasculature in normal tissue but also from the avidity of tumors for nutrients such as the lipid shell of Lipoplatin. According to this mechanism, the tumor cells with their avidity for nutrients uptake the Lipoplatin nanoparticles mistaken as “food”. Furthermore, Lipoplatin nanoparticles have the ability to penetrate the membrane of tumor cells in a few minutes from the extravasation & tumor targeting because of a fusogenic lipid, DPPG, present in the Lipoplatin bilayer, thus emptying their toxic payload inside the tumors. This gives a great advantage compared for example to other liposomal drugs or chemotherapy drugs that cannot penetrate the cell membrane; the inability to cross the cell membrane is the main reason tumor cells become resistant to chemotherapy in patients and this remains a major hurdle in cancer treatment today.

Lipoplatin has been tested on animals in preclinical studies, as well as in more than 1300 patients in Phase I, II and III clinical studies. These studies are required for FDA or EMA approval and Regulon is in the process of application for centralized marketing authorization by EMA initially in lung and pancreatic cancers to be followed by additional cancer indications. Lipoplatin

has shown a much higher efficacy to cisplatin and better toxicity profile, with only Grade I toxicities, when used as monotherapy.

Lipoplatin was also shown to have the best radiosentitizing activity among all platinum drugs. This radiosensitizing activity was 14-times better than cisplatin in F98 glioma cells. Thus when Lipoplatin nanoparticles are administered and concentrate into tumors in about 24 hours, a subsequent radiation of the tumors will enhance its anticancer activity many times without the side effects of classical chemotherapy.

In conclusion, Lipoplatin: **1**. has the ability to circulate in body fluids for long time (2-3 days half-life) because of the PEGylation of the liposomes; **2**. To find tumors and metastases and concentrate 10-200 times more in tumors than in adjacent normal tissue; **3**. To penetrate the cell membrane of the tumor cells and bypass drug resistance; **4**. To attack the cells that make up the vasculature of the tumors (called endothelium) sprouted during neoangiogenesis so the tumors can grow fast, a mechanism that gives strong antiangiogenesis properties to Lipoplatin. This feature is not found in cisplatin or in most other chemotherapy drugs; **5**. To kill tumor cells (epithelial cells in origin) via the strong chemotherapy properties of cisplatin but in addition to cause apoptosis – cell death- via modulation in signaling and via the mitochondrial pathway. **6**. To have antimetastasis properties thus limiting the detachment of cancer cells from the primary tumor and their spreading into other organs of the body; **7**. To have 14-times better radiosensitizing activity than cisplatin meaning that when combined with radiation therapy to have an activity to kill tumor cells 14 times greater than cisplatin.

Possible side effects

The side effects from Lipoplatin are very mild, Grade I. The drug causes no side effects and patients go to work or to their daily activities after chemotherapy. For comparison patients treated with ciplatin vomit, loose their hair, have kidney damage and peripheral neuropathy. The classical chemotherapy affects every single organ or tissue in the body. Lipoplatin's invention is a tremendous achievement in oncology.

The proposed treatment with 2Gy as a dose of radiation after each treatment (to a total of 20 Gy instead of the 60 Gy given as a routine) also does not cause side effects but has a synergistic action to make Lipoplatin several times more effective (14 times in tissue culture studies) in damaging your tumors without affecting the normal tissues in your body!

Procedures

If you choose to be treated with Lipoplatin plus low dose radiation, the treatment schedule is as follows:
Before Lipoplatin administration the patient is treated with the following premedication

1. 250 mg Solu Cortef (Hydrocortisone Sodium Succinate). SOLU-CORTEF Sterile Powder is an anti-inflammatory glucocorticoid that contains hydrocortisone sodium succinate as the active ingredient.

2. Half an ampule of FENISTIL (5 mg) GlaxoSmithKline. Fenistil contains dimetindene maleate, an antihistamine/anticholinergic that is a selective H1 antagonist and is used as an antiallergic drug. It is used topically to treat skin irritations, such as insect bites. Dimentidene is also administered orally to treat allergies, such as hay fever. Unlike first generation antihistamines, it causes only minimal drowsiness.

3. One ampule TAGAMET (CIMETIDINE - INJECTION) a histamine H_2 receptor antagonist that inhibits stomach acid production. USES: Cimetidine is used to treat ulcers of the stomach or intestines and prevent them from returning after treatment. This medication is also used to treat certain stomach and throat problems caused by high acidity (e.g., Zollinger-Ellison syndrome, erosive esophagitis) or a backward flow of stomach acid into the esophagus (gastroesophageal reflux disease-GERD).

Lipoplatin monotherapy treatment details

A dose of 200 mg/m^2 dose (approximately 2-3 vials of Lipoplatin 300-450 mg total in cisplatin) are diluted in 500 ml saline or 5% dextrose and infused iv with the help of a peristaltic pump over 4 h.
No post or pre- or post-hydration is given to minimize loss of Lipoplatin through the urine.
The Lipoplatin **treatment is given on Days 1,4 followed by low-dose radiation on the subsequent day.**
The treatment is repeated for 8 or more consecutive weeks.
The patient is then reevaluated with PET/CT

Low-dose RT

A dose of 2 Gy against the major lesions (determined from the PET/CT) is given on the following day. The optimal timing is 6-36 h from Lipoplatin infusion start so that the nanoparticles have accumulated in the tumors and the low-dose radiation damages 14-fold more the tumor cell mass because of a radiosensitizing activity of Lipoplatin determined to be 14-times better than that of cisplatin in animal models in Canada.
The treatment is given on Days 2,5

Frequency of Lipoplatin RT

This treatment can be applied 2 times per week or weekly depending on the performance status of the patient, the type of tumor and the urgency to debulk cancer lesions.

In several cases Lipoplatin is infused on Mondays and Thursdays (150-200 mg/m^2) followed immediately after infusion by radiation (at 6h from infusion start) for convenience to avoid bringing the patient to the hospital more frequently.

After the anticipated success you may be placed under **maintenance therapy** (involving a similar treatment every 4 to 6 weeks depending on the initial severity of your condition and the success of the treatment and the type of malignancy) or be left with no Lipoplatin treatment but reevaluated every 3 or 6 months. This will be decided by your oncologist and an expert Medical Team. **You will also be given alternative treatment with natural products with anticancer activity, vitamins and advice on your food regimen**.

Food Supplements

Regulon and the treating oncologists will supply all patients with a number of food supplements with known anticancer activity from plant extracts. These do not cause any side effects; on the contrary they can make the patients feel better In addition, the patient will be advised to take vitamin B-100, Vitamin C and Vitamin E to boost the immune system to fight cancer, to diminish the danger of cardiovascular disease and reduce neuropathies, pain and ease symptoms from adverse reactions.

Side effects

Regulon attests that this proposed treatment does not cause the side effects of classical chemotherapy. Patients who received 200 mg/m^2 Lipoplatin monotherapy on day 1 and another 200 mg/m^2 Lipoplatin monotherapy on Day 2 showed only Grade 1 (very mild) side effects. Side effects are numbered Grade 1,2,3, and 4. Most other chemotherapies cause Grade 3 and 4 toxicities.

The Philosophy of Regulon for cancer treatment with plant extracts

You will also receive proprietary plant extracts in the form of Regulon's cocktail (Regulon's Immuno boost Anticancer Extract) or gelatin-coated pills containing extracts from anticancer plants. Regulon will also offer advise to you on foods to eat and those to avoid, vitamins and food supplements. In conclusion, your quality of life will be better than you ever hope to have as a cancer patient. Our philosophy is to keep you in good condition and for the maximum of years possible providing the best treatment available globally!

The success of Regulon's treatment

The success of Regulon's treatment is tremendous including terminally ill cancer patients who were given a few weeks to live by their treating physicians. Under clinical development Lipoplatin has treated over 1,800 patients and in compassionate sales at least 2,000 additional patients.

Lipoplatin Monotherapy plus low-dose radiation cases develop a new era in cancer treatment and are considered a tremendous advancement in medical history.

VERY IMPORTANT

Although the oncologist and the radiation therapist may have proposed a full radiation with 30-60 Gy and therapy with other drugs according to the guidelines, I desire to be treated with Lipoplatin monotherapy and low-dose radiation.

CONSENT

I have read, or have had read to me, the description of the optional treatment regimen, as outlined above. The investigator or his/her representative has explained it to me and has answered all of the questions I have at this time. I have been told of the potential risks, discomforts, side effects and adverse reactions.

_____ _____

Patient Signature Date

Patient's full name

_____ _____

Witness Signature Date

Witness's full name

_____ _____

Oncologist's Signature Date

Oncologist's full name