Lipoplatin™ Monotherapy ICF
REGULON AE
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Medical Administration Dept.

Informed Consent & Liability Release

Introduction

You have been diagnosed with Malignant Tumor.

This document allows you to be informed of a new drug, Lipoplatin or Nanoplatin, that could be an alternative way of treating your disease, combined with radiation of low dose (2Gy). The suggested treatment is 200 mg/m^2 Lipoplatin on Day 1 as a 5-6 h infusion in 1 Lit 5% Dextrose or saline followed by 200 mg/m^2 Lipoplatin on Day 2 and combined with 2 Gy radiation to the tumor lesions on Day 2. The concept is to allow the nanoparticles to extravasate to all tumors and metastases in about 6-36 hours. The low-dose radiation, other than damaging the DNA of the cancer cells will also activate the heavy metal atom of Platinum in Lipoplatin and increase many-fold its cancer killing activities. This treatment will be totally void of Grade 2,3 or 4 side effects usually seen by indiscriminately all FDA-approved drugs; there will be only Grade 1 hematological toxicity to about 20% of the patients not requiring treatment. There will be no kidney toxicity even of Grade 1 at the above proposed dose. Thus patients with kidney insufficiency, elderly patients (over 75 years) and other sensitive groups can receive the above treatment.

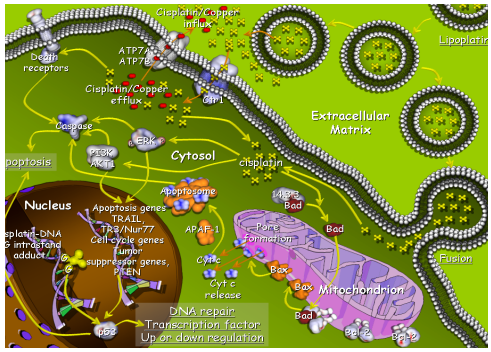
Before you consent, please read the following information.

Information on Lipoplatin™

The new drug, Lipoplatin, is under approval by the European Medicines Agency (EMA) and also plans for its application for fast-track approval 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 and operating out of Greece for the EU clinical development. 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 (3.5 times) efficacy to cisplatin in monotherapy studies compared to historic cisplatin monotherapy 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 in F98 glioma cells and orthotopic animal models at the University of Sherbrooke, Department of Radiation Biology. 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 instead of the 6 hours half-life of cisplatin; **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 possible **antimetastasis** properties thus limiting the detachment of cancer cells from the primary tumor and their spreading into other organs of the body as shown in preclinical studies; **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 as shown in preclinical studies.

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:

Lipoplatin, at a dose of 200mg/m^2 will be administered intravenously as a 4- to 6-hour infusion on Day 1 without prehydration. You may receive dexamethasone and antiemetics according to the opinion of the Physician. One fraction dimensional conformal radiotherapy of accelerated 2.0 Gy (the radiation therapist will determine the field to be irradiated) will be administered on Day 2. We propose 10 such cycles every week or D1,2 treatments every 14 days depending on the severity of your condition.

After the anticipated success you will be placed under **maintenance therapy** involving a similar treatment every 2 to 6 weeks depending on the initial severity of your condition and the success of the treatment and the type of malignancy. This will be decided by an expert Medical Team. **You may also be given alternative treatment with natural products, vitamins and hyperthermia**.

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 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.

Partient's Right Thumb Print

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Patient Full Name

_____ _____

Patient Signature Date

_____

Witness Full Name

_____ _____

Witness Signature Date

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Investigator's Full Name

_____ _____

Investigator Signature Date