REGULATORY STATUS OF CHLORIN-CHLOROPHYLL

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Summary

We use a sophisticated formulation of Chlorin-Chlorophyll combined with a robotised light source. As of this date we believe our innovation has progressed to the point where a cure has become possible. Once significant proof has been obtained in consecutive patients we will submit our data to the regulator.

Of course, it is impossible to predict whether our innovation will turn out to be successful. And there is a moral obligation to immediately submit our dossier once the treatment is proven to be as revolutionary as we think it is. Consequently, we will only submit when we have a protocol that incorporates the techniques matured to manage serious side effects.

As of this date we document in a way that supports oversight of our research. To enable that oversight, we use case-based reasoning. Our documentation contains the logic behind the improvements to our innovation.

Introduction

On a global scale Chlorin-Chlorophyll is used for skin cancer, although it is only approved in Russia. Our goal is to obtain approval for all cancers in the European Union in conjunction with a powerful light source. To this end we are conducting an observational study.
We believe that it is impossible to cure cancer without side effects. For the authorities it is difficult to deal with serious side effects when Chlorin-Chlorophyll is not yet approved.

A Risk Averse Approach to Experimental Medicine is an Oxymoron

In regular medicine since the 1970's at least a hundred thousand cancer patients have been treated with photodynamic therapy (PDT). The scientific literature on PDT for cancer is immense. In general, it has been proven that when cells that have accumulated a photosensitizer are exposed to a specific wavelength of light, they produce a reactive, singlet oxygen that reduces the vitality of those cells and eventually kill them. [1,2,3] This works well for small localized cancers. Especially small skin cancers heal with few side effects and with comparable cure rates to standard therapy of almost 100 percent.

The regulation of PDT for cancer began with a porphyrin mixture, a drug grade hematoporphyrin derivative (HpD) that was found to have an affinity for tumour tissue and showed clinically relevant phototoxicity. [4] Over decades, the HpD formulation was standardized as a porfimer sodium (Photofrin). In 2003 it was approved by the US Food and Drug Agency (FDA) for skin cancer. Another first-generation drug, temoporfin (Foscan) was approved by the FDA in 2003. In 2001 the European Medical Agency (EMA) approved temoporfin for the palliative treatment of patients with advanced head and neck cancer who have exhausted other treatment options. [5] In 2011 the FDA approved line extensions for porfimer. One for precancerous Barrett oesophagus and the other to relieve symptoms of oesophageal cancer. The latter line extension reaches no more than 1 centimetre into the cancer tissue [6] This line extension for advanced oesophagus cancer does not improve life expectancy.[7] Several porphyrin derivatives have been approved by the FDA since the late 1980's, e.g. 5-aminolevulinic acid-ALA, verteporfin (Visudyne), 5-aminolevulinic acid-ALA (Levulan), and methyl aminolevulinate (Metvix).

The trials submitted for the registered sensitisers are designed in ways that cannot cure cancer. The sensitisers and light sources have insufficient power. None of the registered sensitisers are effective for cancer. [8]

Superiority of Chlorin-Chlorophyll Photosensitiser

Superior chorophyll photosensitizers with better accumulation in cancer cells and superior luminescence e.g., chlorins, purpurins, and bacteriochlorins have been developed in the laboratory and tested in animal studies. The most superior is chlorin-chlorophyll, discovered in the US. In 2001 it was approved for skin cancer in Russia under the brand name Radachlorin (Registration number: ЛС-001868). Ethical committees have approved several clinical trials to evaluate the efficacy of chlorin-chlorophyll, for instance for bronchial cancer. [9] Chlorin-chlorophyll has been approved for another indication than cancer. It is approved for age related macular degeneration. [10]

Superiority of Chlorin-Chlorophyll over the registered drug porfimer is shown below:

- Chlorin-chlorophyll captures photons with incoming wavelengths that penetrate deeper into the body than porfimer sodium.
- Chlorin-chlorophyll has shown no toxicity in animal studies in the absence of light. In the presence of light, the LD-50 toxicity was at 500 mg per kilo bodyweight. In contrast porfimer sodium is toxic in the absence of light.
- Three hours after an intravenous dose, a large and optimal spread has been reached between chlorin-chlorophyll enriched cancer cells and chlorin-chlorophyll devoid non-cancerous cells. With porfimer sodium a lesser spread is reached only after 48 hours.
- Chlorin-chlorophyll is cleared from the body in 48 hours, whereas porfimer sodium is cleared only after 4-6 weeks. Porfimer sodium accumulates not only in cancer cells, but also in the reticulo-endothelial system and the skin. Patients need to stay out of the sun for 6 weeks.
- Chlorin-chlorophyll is low cost because it is a natural product from algae, used as a food supplement. Porfimer, although out of patent, is still more expensive.

Regulation for Innovation

The scientific literature consistently shows an unfulfilled need for higher energy light sources than the approved 1-Watt lasers.[11] Risk averse regulation of experimental medicine restricts the adoption of light sources with sufficient power for human cancer. Yet, light emitting diodes (LED's) are powerful enough for human cancer. They can be assembled in a range of geometries and sizes at low cost.

However, the required power for human cancer is not even on the radar. Presently, the most commonly used PDT light source is a 0.5 to 1-Watt diode lasers. The 1-Watt DIOMED 630 PDT (Diomed Inc.) is registered by the FDA in 2003 for palliative PDT in patients with partial or complete obstruction caused by oesophageal cancer and to reduce lung obstructions in patients with endobronchial non-small cell lung cancer (NSCLC). In 2003, the 0.95-Watt Ceralas PDT 762 nm laser (CeramOptec of Biolitec AG) was registered by the FDA for PDT in patients with subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia and presumed ocular histoplasmosis.

Innovation Requires Cased-Based Reasoning

Case-based reasoning allows the developmental process to be stringently controlled. Consecutive cases are documented. The reasoning underpinning the ongoing development of the solution is also documented. The concept of case-based reasoning centres on using the experience of all previous cases to build the best rationale for the 'next case'. *See Figure 2 – Case Based Reasoning.*

The literature shows that the case rationale should include inputs from the patient. Several recent studies show that real-time drug/light dosimetry

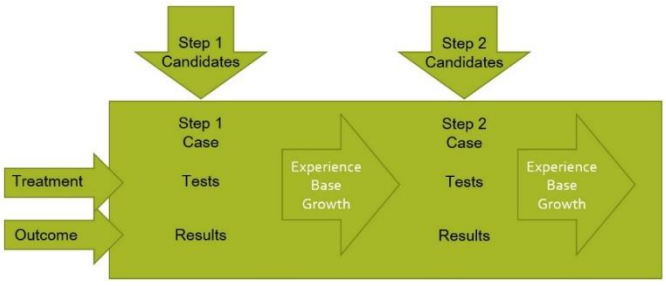

Figure 2 – Cased Based Reasoning

measurement and feedback system for monitoring tumour luminescence during a PDT session are required to optimise the treatment. [12]

However, today experiments are designed in a way that a solution is tested without allowing continuous case by case learning. The experiments described below did not allow for incremental learning. However, they do show that powerful unapproved light sources were used in practice.

1200-Watt LED arrays have been shown suitable for flat surface illumination of wide-area superficial lesion.[13] In a PDT experiment a LED was percutaneously implanted successfully into chemotherapy resistant solid tumours. [14] Parenchymal organs such as the liver and pancreas have been approached with intra-tumour placement of a LED array, during surgery. [15] For intra-operative PDT of a brain tumour, a LED-probe may be arranged in a cylinder tip to fit into a balloon catheter. [16] Brain cancer has also been approached successfully with LED coupled to an implanted optical fibre or a directly implanted LED. [17]

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Introduction

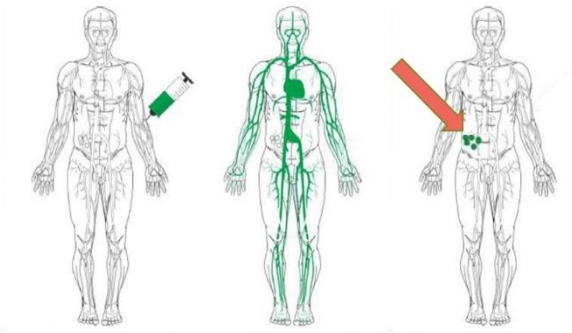

Figure 16 – Chlorin-Chlorophyll Light Therapy

Chlorin-Chlorophyll was invented in the US. In the noisy environment of the internet and in conversations with doctors it's easy to become confused. However, light induced therapies have a history of successes with small cancers going back decades. Light therapy is approved in the USA for skin cancer. Chlorin-Chlorophyll is approved in Russia to treat skin cancers and as a complementary treatment to chemo / brachy radiation treatment in other cancers. The results with skin cancer are excellent giving a complete cure in almost all patients. In 2001 the Russian Ministry of Health approved it as Radachlorin (Registration number: ЛС-001868) for skin cancer. Globally, it is considered safe. Ethical committees allow its use with many other cancers than skin cancer.

The Eigenherstellungs Framework requires the use of superior molecules, when available, above registered inferior ones. Currently there is no better sensitiser than Chlorin-Chlorophyll, *See Figure 16*. Within the German framework we began by treating localised cancers up to 5 cm deep in the body or reachable by natural openings such as the rectum and oesophagus. Our latest light sources bring a dramatic reduction in the burden of cancer. At the least, the patient gains years of life and if there is a recurrence repeated treatment is perfectly possible.

Our development cycle to build improved light sources is two to four months. The developments are intended to eradicate the cancer completely and in the future, could even be used prophylactically.

Benefits of Passive Immunisation

Chlorin-chlorophyll has the following advantages over the registered drug Porfimer:

- In preclinical research produced three times more reactive oxygen
- Can use a light source that penetrates deeper into the tissues of the body
- Has no toxicity in animal studies in the absence of light
- Works in three hours after an intravenous dose, rather than 48 hours
- Is cleared from the body in 48 hours rather than after 4-6 weeks
- Accumulates in cancer cells and not in other tissues
- No need to stay out of the sun for weeks

History of Regulated Light Sources for PDT

In the 1970s, the red light from a xenon arc lamp was one of the original sources. It is a non-coherent, low intensity light source that produces a spectrum of wavelengths that only partially match the photosensitizer of the time. From there on, better lamps, fibres, lenses and filters have been sufficient for skin cancer. The most commonly light source is the 0.5 to 1 Watt diode laser,

with monochromatic light of a narrow bandwidth. The 1-Watt DIOMED 630 PDT was registered by the FDA in 2003 for more advanced indications. The laser may be used for the reductions of partial or complete obstruction of oesophageal cancer and endobronchial non-small cell lung cancer. Although not formally accepted by the regulator, ethical committees have accepted the use of LED's. In the case of brain and other hard to reach cancers ethical committees have even approved LED's combined with fibre optics.

Pulsing Light Sources Improve Patient Experience

After his own diagnosis Wim Huppes had to make choices. He survived for several years through experimenting before coming to understand that the Chlorin-Chlorophyll light therapy is the most effective cancer treatment available. To learn more, he worked as a volunteer in both alternative and regular clinics in Germany where they were delivering this therapy. Wim was inspired by the fact that global results with skin cancers are excellent. There is almost no scar tissue, which is of high value to patients with genital and facial cancers. In Germany he witnessed that treatment of early stage prostate cancer worked, but their techniques were not reliable enough to compete with surgery. All larger cancers, including breast, pancreatic, brain, ovarian, cervix, lung, resulted in partial responses. Although Wim was excited by the potential only regulated low power 1-Watt light sources were used. Wim saw that more powerful light sources were needed. Humans are around 80 kilos, yet they received the same power used in tests with rodents that are just around 10 grams.

Using sufficient power, we were able to eradicate cancer. However, in the first patient the cancer was almost carbonised (turned nearly to charcoal) occurred causing severe pain. A surgeon could then remove the carbonised tumour. Even this was an excellent medical result but an unpleasant experience. With repeated use of sufficient power, it was possible to use the light more gently. We then noticed "Cancer Fever" with almost all patients. Today Chlorin-Chlorophyll is available as an immunising therapy. The body responds with its natural self-healing process. With our improved light sources, we transformed light therapy into an immunotherapy. *See Figure 17 for an example of one of our current light sources*

Figure 17 – LED Tube of 300-Watt

We continue to improve the light sources because we want to further improve the patient experience. Based on the published research on cell lines and in rodents, it was clear that a short flash exposure of increased power could further improve the patient experience. We now have LED light sources that emit an enormous flash of exactly the right wavelength. They are assembled in a range of geometries and power appropriate for the need of the patient.

The Superiority of Chlorin-Chlorophyll

The dyes such as Chlorin-Chlorophyll are called sensitisers by regulatory agencies. Since the 1970s, globally, at least a hundred thousand cancer patients have been treated with light therapy, also called photodynamic therapy (PDT). Several derivatives of the early drug hematoporphyrin have been approved. In 2001, the European Medical Agency (EMA) approved temoporfin (Foscan) for the palliative treatment of patients with advanced head and neck cancers. In 2003, porfimer sodium (Photofrin) was approved by the FDA for skin cancer. In 2011,

the FDA approved a line extension for Photofrin to treat oesophageal cancer. Other approvals of the FDA include verteporfin (Visudyne), 5-aminolevulinic acid-ALA (Levulan), and methyl aminolevulinate (Metvix). All these approved compounds work well for small localized cancers. Larger cancers show partial responses. For instance, for oesophageal cancer PDT is used not as a cure but only to remove enough local cancer to allow the insertion of a feeding tube. All the previously mentioned sensitisers were patented but none were superior to Chlorin-Chlorophyll. As a natural substance Chlorin-Chlorophyll cannot be patented although there is solid scientific literature including the longstanding work in Russia. For further details please read the Chlorin-Chlorophyll documentation