Review

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RICHARD E. KAST * , Laura Milla Sanabria , Anton P Kast , Erasmo Barros da Silva Jr

Posted Date: 25 July 2024

doi: 10.20944/preprints202407.1970.v1

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Noninvasive, Drug Augmented, Ultra Low Intensity Transcranial Light Photodynamic Treatment of Glioblastoma: LIT-PDT

Richard E. Kast [1,*], Laura Milla Sanabria [2], Anton P Kast [1] and Erasmo Barros da Silva Jr [3]

[1] IIAIGC Study Center, Burlington, Vermont, USA
[2] Universidad Nacional de Río Cuarto-CONICET, Río Cuarto, Argentina
[3] Neurosurgery Department - Neuro-Oncology, Instituto de Neurologia de Curitiba, Rua Jeremias Maciel Perretto, 300 - Campo Comprido, Curitiba 81210-310 Brazil
* Correspondence: richarderickast@gmail.com

Abstract: This paper presents the rationale for using ultra low intensity transcranial light photodynamic treatment (LIT-PDT) for treating glioblastoma. Glioblastoma is currently treated with maximal safe resection, temozolomide and ionizing irradiation. Mortality in 2024 remains at over 80% within several years from diagnosis. 5-aminolevulinic acid (5-ALA) is a heme precursor that is selectively taken up preferentially by malignant cells, including glioblastoma. Photon energy can be transduced to molecular oxygen by a 5-ALA metabolite, PpIX, transforming oxygen to the singlet state, a reactive oxygen species (ROS) that destroys or damages vital glioblastoma cell structures. In PDT, light energy ~ 100 to 200 J / cm^2, at 630 nm is delivered intraoperatively after resection and preoperative oral 5-ALA. This generates ROS cytotoxicity in residual glioblastoma cells within the resection cavity wall. 630 nm light poorly penetrates skin, skull, and brain tissue. That currently restricts PDT to a single intraoperative session using high flux light. LIT-PDT addresses some current shortcomings of 5-ALA PDT treatment. Part 1 analyzes published data indicating that continuous ultra low light flux, 17 μW / cm^2, over 24 hours for a total delivery of 1.5 J / cm^2, is effective for 5-ALA PDT treatment. That opens the way for repetitive, extracranial light to deliver enough energy for low flux, long duration PDT to any deep brain structure using less than 12 W total distributed over the entire scalp area. In Part 2, by analysis of 5-ALA and PpIX physiology, it became apparent that four non oncology drugs - ciprofloxacin, deferiprone, telmisartan and ziprasidone, will increase energy capture by GB cells, thereby increasing PDT treatment cytotoxicity. A phased pilot study of LIT-PDT treatment is being planned.

Keywords: 5-ALA; glioblastoma; photodynamic treatment; repurposing

1. Introduction

This paper analyzes prior studies to show that a new treatment for glioblastoma (GB) that uses ultra low intensity transcranial light photodynamic treatment with drug augmented photodynamic treatment (LIT-PDT) can be an effective treatment. In PDT treatment, oxygen is transformed to its reactive singlet state by light, catalyzed by a 5-aminolevulinic acid (5-ALA) metabolite, PpIX. This singlet state is a reactive oxygen species (ROS) that oxidizes, and thereby destroys or damages, vital GB cell structures leading to cell death [1–3]. After oral administration 5-ALA is preferentially taken up by GB cells and converted to PpIX to a greater degree than the surrounding brain tissue. This has two important consequences. 1) PpIX fluoresces red after illumination with 415 nm light, enabling more complete intraoperative identification of tumor margins and hence more complete resection. 2) PpIX will transfer 635 nm light energy to ground state oxygen to generate ROS, preferentially killing GB cells [1–3].

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Survival at 2 years after a diagnosis of GB remains <20% despite multimodal treatment. This paper presents a data analysis and synthesis of two data sets that can be combined to make a new treatment for GB. The first data set, Section 2 below, analyzes peer-reviewed PDT treatment of GB using orally administered 5-ALA as the photosensitizer. Our analysis concludes that ultra low light fluences delivered noninvasively, transcranially, over 24 hours is both feasible, safe, and predicted to be more effective than short duration, intraoperative high fluence 5-ALA PDT as currently used in treating GB.

The second data set, presented in Section 3 below, analyzes peer-reviewed data on four drugs from general medical practice - the antibiotic ciprofloxacin (cipro), the iron chelator deferiprone, and either the hypertension treatment drug telmisartan or the antipsychotic drug ziprasidone to increase effect of 630 nm light PDT in treating GB. They all have good evidence of increasing 5-ALA PDT effectiveness.

However, although many variables will influence survival, in the summer of 2024, standard treatment of GB with maximal safe resection, followed by irradiation and temozolomide, in a general GB population, still results a median overall survival under 2 years due to tumor recurrence [4,5].

Dozens of clinical trials of new medicines, and different forms and schedules of ionizing irradiation tried over the last 20 years have failed to greatly prolong survival [6,7]. The addition of the wearable Optune® device (Novocure Ltd., Haifa, Israel) that delivers 200 KHz electromagnetic radiation (radio frequency, non-ionizing) to the brain and tumor area has demonstrated good tolerability, some GB mitotic slowing and other potentially advantageous metabolic changes but only slight prolongation of median overall survival [8]. Using intraoperative PpIX fluorescence leads to better tumor demarcation, resection and slightly longer time to progression [9]. Ten years ago it was said that GB's fatal recurrence rate is almost 100% [10]. Despite some improvements in the standard of care, the same can be said today.

The usual first GB recurrence is within the first 20 mm of the resection cavity wall, and most of these are within the original irradiation field [11]. Extending resection, so-called extra marginal resection may prolong time to recurrence but not prevent it. At the time of diagnosis GB has already spread throughout the entire brain.

Based on our analysis of the transcranial light brain penetration studies of Tedford et al and Mathews et al, vide infra, we determined that i) noninvasive transcranial 630 to 660 nm light can deliver an ultra low fluence rate (17 μW / cm^2) to a GB, to the post-resection peritumoral area, and to the entire brain and, ii) prolonged and repetitive delivery of such fluence is effective in mediating 5-ALA PDT killing of GB cells [12,13].

Thus the LIT-PDT Regimen includes two components: 1) ultra low light levels delivered continuously noninvasively over 24 hours with 5-ALA PDT, and 2) three orally administered drugs from general, non oncology medicine - ciprofloxacin, deferiprone, and telmisartan or ziprasidone - will augment capture of 630 nm photon energy, increasing ROS generation after 5-ALA. Details follow.

2. Multiple array, Ultra Low Fluence, Transcranial, Repetitive, 5-ALA PDT

In PDT of GB as currently constituted, oral 5-ALA is preferentially taken up by GB cells and metabolized to PpIX. PpIX transfers 630 nm light energy to ground state O_2 ($^3O_2$), thereby generating singlet O_2 ($^1O_2$), one of several ROS [14–17]. See Table 1. for oxygen related ROS definitions.

Ferrochelatase mediates iron incorporation into PpIX, transforming PpIX to non-ROS generating heme. PpIX accumulates in large quantities in GB cells after 5-ALA administration due to increased uptake of 5-ALA compared to non-GB brain tissue, and reduced ferrochelatase activity and increased heme demand in GB cells [15,18–21].

Intraoperative 5-ALA PDT heretofore has been by using ~200 J / cm^2 total, of 635 nm light delivered to the resection cavity wall in five fractions of 12 minutes with 2 minute pause between the four periods. The light exposure is performed with the direct placement of up to 4 diffusers or through an Intralipid ™ filled Foley catheter intracavitary diffuser, for a delivery total of 720,000 mW.s = 720 J / cm^2 total, fractionated over 1 hr [22].

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This, delivered intraoperatively as a single session before closure immediately after fluorescence guided resection [19,21–23]. Exploration began twenty years ago of low fluence, mW 5-ALA PDT, delivered over extended periods of time to increase selective tumor cell kill through apoptosis. [24–26]. See Table 2 for definitions of light measurement terms.

Table 1. Glossary of some oxygen related terms.

O_2	**ground state triplet oxygen molecule, $^3O_2$ stable, atmospheric oxygen**
$^3O_2$	another designation of O_2, the common form of atmospheric oxygen.
•OH	hydroxyl radical, a neutral, highly reactive ROS.
$^1O_2$	singlet oxygen molecule, half-life of microseconds, an ROS.
O_2 •⁻	superoxide anion radical, an oxygen molecule with one unpaired outer shell electron, negative charge −1, an ROS.
O_3	ozone, trioxygen molecule, an ROS.
H2O2	hydrogen peroxide, a non radical, non ionic, ROS.

Table 2. Light dosing terms defined. .

term	definition	units
fluence	the energy delivered to a given area	J / cm^2
flux	the momentary power received by a given area	W / cm^2
irradiance	the momentary power received by a given area	W / cm^2
light dose	J/cm^2 delivered over a specified time interval	J / cm^2

Note: we speak of area and denote per cm^2 but we are really referring to a volume of tissue, cm^3, with the understanding that tumor tissue proximal to light sources will receive slightly greater energy, the tumor tissue distal to the light source slightly less energy.

The limitations of 5-ALA PDT as currently practiced are restricted to a single intraoperative PDT session. This means that high fluence light is required. As a consequence necrosis predominates as mode of death, as opposed to the preferable apoptosis that would predominate if ultra low fluence could be used. Approximately 4 to 13 mm deep to the surface of the resection cavity receives enough photon energy to generate cytotoxic ROS during intraoperative PDT [23,27]. Also blood clots and surgical debris may interfere in the efficacy of the intracavitary light delivery. Also, in current practice intraoperative high light flux PDT quickly exhausts available O_2 supply even when ventilating the patient with 100% oxygen during the treatment. PDT requires O_2 to be effective.

Prolonged or repetitive PDT leaving the resection cavity open with the attendant risks and procedure complications [28], or fully implantable light and power sources, the Globus Lucidus [29], have been in development to allow long term, repeated PDT. However we know that PpIX positive GB cells reside within the first 20 mm of the resection cavity wall [30,31]. Those cells will not receive enough short term light to be killed by intraoperative PDT, even by high flux delivery of 200 J / cm^2 [12,13].

In vitro work by Mathews et al however has opened up another avenue to overcome the current limitations of one shot intraoperative PDT. Mathews et al [13] and others [32,33] have shown that ultra low fluence (<50 μW / cm^2] delivered continuously over 24 hours can be repeated with resulting deep blockage of GB growth. Cytotoxicity was primarily by apoptosis, not necrosis. Mathews et al

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even showed no growth using four 24 hr periods of 17 μW / cm² flux, 1.5 J / cm² total delivered, 635 nm light, separated by 3 day intervals [13]. Note that 1.5 J / cm² per 24 illumination day is less than 1% of the fluence used in today's clinical intraoperative 5-ALA PDT:

$$86{,}400 \text{ s / day} \times 17 \text{ μW / cm}^2 = 1.5 \text{ J / cm}^2 . \quad (1)$$

If given once at a single session, Mathews reported that 12 J / cm² was the required light dose to achieve similar growth suppression, an 8 times higher total energy delivery compared to the repeated 24 hour low flux treatment [13].

This small fluence can be delivered non-invasively, transcranially, to GB tissue from the scalp surface by using fully external multi LED 630 nm light array, through intact human skin and skull. The calculation behind this statement:

Lapchak measured light attenuation across the human calvaria and found that 4.2% of the incident power was transmitted with minor corrections for variations in depth and hydration [34–36]. Tedford et al measured attenuation versus depth in human brain parenchyma to be 2.4 / cm² depending slightly on wavelength and geometry [12]. Assuming the head is broadly illuminated so that scattering may be neglected, we can reasonably estimate light power at the tumor in terms of power incident on the scalp reduced by these factors.

$$p = P \times 0.042 \times \exp(-d / 2.4 \text{ cm}) \quad (2)$$

where

p = delivered power density at the tumor in W / cm²

P = incident power density at the scalp in W / cm²

d = depth of the tumor beneath the cortex in cm

Matthews found in vitro that a protocol of long-term exposure at low power was effective on glioma spheroids at 17 μW / cm². Inverting the formula, we can solve for the incident power density P sufficient to deliver a desired power density p at the tumor as a function of the tumor depth d. See Table 3 for the resultant predicted external 630 nm flux requirement noninvasively applied to the head to achieve 17 μW / cm² at a GB post-resection area at the listed depth from the external light source.

$$p = P \times 0.042 \times \exp(-d / 2.4 \text{ cm}) . \quad (3)$$

The listed external flux can be easily delivered by many of the current commercially available photobiomodulation helmets for home use, for which no prescription is needed. If we take an average scalp area to be 700 cm² then total light energy delivered to the entire scalp area would be ~12 W to reach the deepest GB.

Table 3. Incident power density (flux) of 630 nm light at the scalp skin surface required to deliver 17 μW / cm² to GB tumor tissue at the listed brain depths deep to the scalp surface. Values calculated according to the attenuation formula.

GB tissue depth	external flux required to achieve 17 μW / cm²
at 3 cm →	1.4 mW / cm²
at 5 cm →	3.3 mW / cm²
at 7 cm →	7.5 mW / cm²
at 9 cm →	17 mW / cm²

So Part 1 of the LIT-PDT program is to deliver post resection 17 μW / cm² 630 nm illumination to the resection area / 24 hrs after oral preoperative 5-ALA. Light will be delivered by an external multi LED array cap, giving broad head illumination such that light scattering may be neglected.

Prolonged transcranial 630 nm light delivery from 10 to 20 W light sources has a well established safety history of use in humans, a procedure called photobiomodulation [37–41].

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Photobiomodulation refers to use of external low level (<20 mW / cm^2) LED arrays to deliver transcranial light at ~630 nm (red) light to the brain with the aim of improving brain function deficits.

Dozens of clinical studies in humans have explored 630 nm photobiomodulation treatment to reduce impairments of Alzheimer's disease [42,43], cognitive or executive function [44,45], Parkinson's disease [46], traumatic brain injury [47,48], autism [49], and others [50–52]. While the results on brain function have not shown to have unequivocal benefit, all the studies have shown good safety with minimal or no side effects from this light delivery.

A wide variety of these photobiomodulation helmets delivering broad head illumination at 630 nm are currently commercially available for home use without prescription. Most of these can easily deliver 17 μW / cm^2 to any part of the brain. Figure 1 shows a schematic of LIT-PDT illumination of a GB tumor area

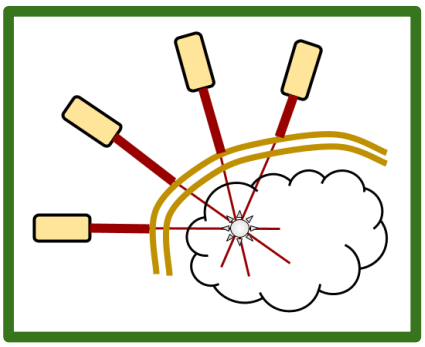

Figure 1. Schematic drawing of transcranial 630 nm LED illumination of GB. The schematic indicates beams of light but the strong light diffusion by brain tissue results in light hitting the GB resection area from many angles.

3. The LIT-PDT Drugs

Drug repurposing refers to use of previously approved drugs that induce basic physiology changes that are beneficial in treating conditions other than their traditional or originally approved use.

The two of the four drugs discussed here, cipro, deferiprone, were discussed previously as potential adjuncts to PDT [53]. Table 4 lists the four augmentation drugs with their common use in general medical practice and their primary intended use in LIT-PDT. Figure 2 shows a schematic of the drugs' locus of action in augmenting 5-ALA-PDT.

Table 4. List of the three augmentation drugs with their general medical use and their use in LIT-PDT.

drug	general medicine use	use in LIT-PDT
ciprofloxacin	antibiotic	increased protoporphyrin
deferiprone	iron chelation	iron chelation
telmisartan	hypertension	ABCG2 inhibition
ziprasidone	psychosis	D2 blocking

Table 5. An illustrative example of a possible schedule of events for the first GB case in a planned phased pilot study of LIT-PDT. This will be done without drug augmentation. Drug augmentation would start after safety of a transcranial illumination regimen has been established. PDT duration of this first use is predicted as 32 hours.

time	5-ALA dose	illumination

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- 36 hr	1st 20 mg/kg p.o.	off
-33 hr	none	on
-28 hr	2nd 20 mg/kg p.o	on
-9 hr	3rd 20 mg/kg p.o.	on
-1 hr	none	off
0 hr - surgery	none	off
+ 4 hr, H&E, etc	none	off

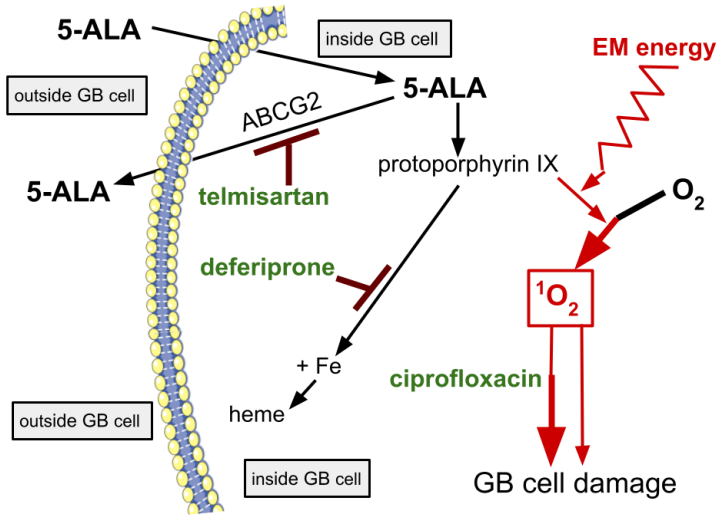

Figure 2. A simplified schematic of 5-ALA entry into GB cells and its indirect action in creating cytotoxic ROS after cells' exposure to EM irradiation. By inhibiting 5-ALA export, febuxostat increases intracellular 5-ALA. By inhibiting diversion of PpIX to heme synthesis, deferiprone increases intracellular PpIX.

3.1. Ciprofloxacin

Cipro is a rather common broad-spectrum antibiotic in use in humans around the world. As an antibiotic, cipro works by inhibiting bacterial DNA gyrase while also stabilizing DNA strand damage created by DNA gyrase and topoisomerase IV. Repositioning cipro as a cancer cell cytotoxic drug has a research database empirically demonstrating such an effect but the mechanism by which it does so has not yet been firmly established [54–57].

Cipro exhibits an unexplained specificity in killing a variety of malignant cells at the 40 t0 80 µg/mL range while sparing non-transformed cells [58]. In vitro results indicated that cipro could be used as an adjuvant to treat GBM by increasing apoptosis and ROS production in these cells [59,60]. In glioma GL26 cells, cipro decreased cell viability and inhibited proliferation [61]. In the GB A-172 cell line, cipro induced an increased Bax/Bcl-2 ratio and tumor cell death. Also in the A-172 line cipro increased the cytotoxic effects of TMZ [59,60]. Other studies also showed the cytotoxic, anti-proliferative and pro-apoptotic effect of cipro towards the GB cell line U87MG GB cells [62].

In preclinical study, cipro augmented 5-ALA cytotoxicity to GB. Using Caesium-137 gamma irradiation, 0.66 MeV, 1 Gy / min, 8 Gy total, GB cytotoxicity and intracellular ROS increased in vitro with added 5-ALA alone. Adding cipro to 5-ALA further increased that irradiation' s cytotoxicity. The effect was not large but it was clear and statistically significant [63].

Empirically cipro enhanced 5-ALA PDT cytotoxicity to chordoma cell lines in vitro when there was no effect of light alone, cipro alone, or 5-ALA alone [64]. Empirically cipro enhanced 5-ALA PDT

 doi:10.20944/preprints202407.1970.v1

cytotoxicity to meningioma cell lines in vitro when there was no effect of light alone, cipro alone, or 5-ALA alone [65].

Recognizing the preclinical database of inherent cytotoxicity to malignant cells, Gera et al gave 1000 mg/day cipro along with traditional chemotherapy with etoposide in acute myeloid leukemia in a phase 1b trial. That trial gave evidence of modest benefit from adding cipro [66].

3.2. Deferiprone

Deferiprone is an iron binding drug in human use to reduce iron overload. In preclinical study, a series of FDA/EMA approved, related iron binding drugs augmented 5-ALA cytotoxicity to GB by the same mechanism. By binding iron, iron becomes less available for incorporation into PpIX to create heme. That metabolic impediment results in a buildup of intracellular PpIX [67–72]. This process can be intuitively appreciated by Figure 2, as the left hand arrow going off from PpIX decreases, more PpIX is available to the right hand arrow process going off to singlet oxygen, $^1O_2$.

Among the several FDA/EMA approved iron chelators for human use, deferiprone would be best for use in GB 5-ALA use because it achieves good brain tissue levels [73,74]. The other approved iron chelators do not. Deferiprone has been in use for 40 years and has a good history of tolerability, safety, and reduction of brain iron content [74,75].

Since PpIX clearance is mediated by ferrochelatase, by limiting access to intracellular iron, iron chelators diminish PpIX conversion to heme, thus increasing intracellular PpIX for PDT or intraoperative fluorescence [76–79].

3.3. ABCG2 and Telmisartan or Ziprasidone

ABCG2, also known as BCRP, is a 144 kDa homodimer drug efflux pump. It is the primary export pump for 5-ALA [80–83]. Many drugs that inhibit GB's ABCG2 efflux transporter will increase intracellular 5-ALA levels, increase PpIX accumulation, and increase 5-ALA PDT GB cell killing [84–86]. Accordingly, as part of the LIT-PDT Regimen, one of the currently marketed drugs that inhibits ABCG2 should be added to 5-ALA PDT GB treatment. Independently of potential benefits of use during 5-ALA PDT, ABCG2 inhibition increases brain tissue levels of temozolomide [87], the mainstay cytotoxic chemotherapy drug in GB.

A wide range of currently FDA/EMA marketed drugs, although marketed for other indications, have been shown to also inhibit transport function of ABCG2: aprepitant, dabigatran, meloxicam, ziprasidone [88], aripiprazole [89], telmisartan [90], febuxostat [91], lapatinib [81,84], rifapentine [92] among others. Of these we focus on two drugs, telmisartan and ziprasidone that coincidentally have documented growth inhibiting effects on GB of their own, alone, independently of light, PDT, or 5-ALA.

3.3.1. Telmisartan

Telmisartan is an angiotensin II receptor 1 blocking drug (an ARB) used to lower high blood pressure. It also exerts agonism at PPAR-gamma/alpha and exhibits neuroinflammation reducing effects [93,94]. Telmisartan inhibits ABCG2 drug transport [90,95,96]. IC IC50 was 17 μM at ABCG2 [90].

Unrelated to PDT, a review in 2016 outlined the potential advantages of adding telmisartan to standard GB treatment [97]. Since then further data on glioma growth inhibition by telmisartan alone has accrued [98–100]. Preclinical studies in a variety of other cancers have similarly shown growth suppression by telmisartan, independently from any effects on PDT [101–107]. These findings would favor using telmisartan to augment 5-ALA PDT as a drug with 5-ALA independent anti-GB effects as well as inhibition of ABCG2.

3.3.2. Ziprasidone

Almost all currently approved and marketed drugs to treat psychosis act to block dopaminergic signaling at dopamine receptor 2 (D2). Ziprasidone is one of the 20+ D2 blocking drugs currently

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approved and marketed to treat psychosis. Inhibitory IC50 of ziprasidone at ABCG2 was 2.8 μM [108].

See reviews from 2014 and 2020 on D2 drive in GB growth and the importance of inhibiting D2 signaling during GB treatment [109,110]. Since the original review in 2014, many papers have confirmed the GB growth drive from D2 agonism and the potential for D2 blocking drugs to inhibit GB growth [111–119]. These findings would favor using ziprasidone to augment 5-ALA PDT as a drug with 5-ALA independent anti-GB effects as well as inhibition of ABCG2.

The lower IC50 would favor ziprasidone as would the added benefit of D2 inhibition but risk of akathisia or unpleasant mental side effect potential would be votes against its use. In theory both telmisartan and ziprasidone could be used simultaneously - there is no predictable drug-drug interaction. It is unknown if the ABCG2 inhibiting effects would be additive to 5-ALA PDT. Nor do we know if the inherent anti-GB effects of telmisartan and ziprasidone, unrelated to 5-ALA or PDT, would be additive or not.

4. LIT-PDT and GB Ecosystems

As with most ecosystems in nature, different interacting communities exist within a GB. These cell communities are connected by pairwise interactions leading to a mutual interdependence of the different populations, each on each other.

In cancer generally and in GB specifically, current cancer research has identified multiple ecological roles played by each malignant cell subpopulation (community) and between malignant cell subpopulations and trophic non-malignant cell populations (monocyte lineage cells, neutrophils, lymphocytes, fibroblasts, endothelial cells, et al). These many dyads tend to be mutually supporting and have different spectra of vulnerabilities to growth inhibition, so we reason that the more mutually supporting ecosystems we can inhibit or kill, the more effective the treatment will be [120–125].

A special case of mutually supporting ecosystems in cancer - the stem/non stem cells' relationship - requires specific addressing. Throughout the common deadly cancers, including in GB, tumors tend to relapse after an initial tumor reduction with initial chemo or radiotherapy. Recurrence tends to arise from small numbers of the relatively treatment resistant GB stem cell subpopulation. Stem cells in the recurrent tumor are even more resistant to treatment than were the primary tumors' stem cells. GB stem cells are at the apex of an entropic hierarchy and impart therapy resistance [20,126,127].

We have indications that GB stem cell subpopulations are more resistant to 5-ALA PDT [128,129]. However GB stem cells can respond to PDT [130–134], highlighting the importance of defeating resistance pathways as the augmentation drugs - telmisartan and ziprasidone advocated in this paper - are designed to do.

5. Discussion and Conclusions

Cipro, deferiprone, and febuxostat are well tolerated drugs, usually without side effects. Although surprises cannot be excluded, there is no a priori reason to suspect drug-drug interaction that would change that low side effect risk when these three are used together.

Low fluence light delivery in 5-ALA PDT has several advantages over the current use of high fluence intraoperative PDT. Lower fluence over a longer time results predominantly in apoptosis and less inflammation. Higher fluence 5-ALA PDT over a shorter time results in predominantly necrosis with relatively more inflammation and edema [25,135]. A second advantage of low fluence light is that we can repeatedly and noninvasively deliver it.

The safety of the human brain's exposure to low wattage extracranial 630 nm has been well established by the large body of research on photobiomodulation [136–141].

Preclinical study of Mathews et al explored 17 μW / cm^2 flux over considerably longer exposure times (24 hours, 1.5 J / cm^2 total) but repeating this every fourth day [13]. A further advantage of low flux delivery is reduced immunosuppression elements [142].

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A pilot study is planned. 36 hours prior to primary surgery, one newly diagnosed GB will receive 5-ALA by mouth, then 32 hours of continuous noninvasive 630 nm transcranial illumination of fluence calculated to deliver 17 μW / cm² / 24 hours. Calculated as follows:

24h x 60 min x 60 sec = 86,400 sec in 1 day.

17 μW / cm² x 86,400 sec =

1,468,800 μW.sec / cm² / day = 1.5 J / cm² / d, the in vitro dose that Mathews et al showed stopped all GB cell growth [13].

Thus the predicted total 630 nm light energy received by the tumor resection area will be 2.3 J / cm² delivered over a continuous illumination time of 32 hours. Depending on results the next step would be the same illumination schedule, 32 hours on, off for 88 hours (1⅓ day on, 3⅔ days off) , for 4 cycles prior to surgery. Further schedules would be determined by these initial histology results. Evaluation of effect by necrosis, apoptosis, and K67 markers, and standard H&E pathology report.

As a consequence of this paper's analysis of the data, a phased pilot study of LIT-PDT warranted and planned.

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