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REVIEW

Experimental use of photodynamic therapy in high grade gliomas: A review focused on 5-aminolevulinic acid

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Summary Photodynamic therapy (PDT) consists of a laser light exposure of tumor cells photosensitized by general or local administration of a pharmacological agent. Nowadays, PDT is a clinically established modality for treatment of many cancers.

5-Aminolevulinic acid (ALA) induced protoporphyrin IX (PpIX) has proven its rational in fluoro-guided resection of malignant gliomas due to a selective tumor uptake and minimal skin sensitization. Moreover, the relatively specific accumulation of photosensitizing PPIX within the tumor cells has gained interest in the PDT of malignant gliomas. Several experimental and clinical studies have then established ALA-PDT as a valuable adjuvant therapy in the management of malignant gliomas. However, the procedure still requires optimizations in the fields of tissue oxygenation status, photosensitizer concentration or scheme of laser light illumination. In this extensive review, we focused on the methods and results of ALA-PDT for treating malignant gliomas in experimental conditions. The biological mechanisms, the effects on tumor and normal brain tissue, and finally the critical issues to optimize the efficacy of ALA-PDT were discussed.

Contents

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Introduction

Glioblastoma (GBM) is the most common and deadliest malignant brain tumor. The current standard of treatment for GBM involves maximal surgical resection followed by radiation therapy (RT) and concomitant chemotherapy with oral cytotoxic chemotherapy, temozolamide (TMZ), followed by maintenance administration of TMZ. The median survival for primary GBM with this combined treatment is 15 months (*versus* 12 months with RT only) and the 2-year survival rate increases to 26% compared to 10% in RT arm [1,2]. The three main causes of the poor prognosis associated with GBM are: (1) the tumor cells extensively infiltrate the surrounding brain tissue, limiting the efficacy of surgical resection; (2) the blood—brain barrier (BBB) prevents the optimal delivery of chemotherapy agents; (3) GBM is refractory to most cancer cytotoxic agents or rapidly develops resistance.

In the event of recurrences, associated with a poorer prognosis, other treatments added to an optional new surgery may be proposed. They include carmustine implants, TMZ rechallenges, or others chemotherapy such as bevacizumab [3—5]. Novel strategies, such as fluorescence-guided resection (FGR) [6], immunotherapy [7], gene therapy [8], anti-angiogeneic agents or targeting of growth-promoting pathways [9], provide additional avenues to increase survival benefits.

During the last decade, photodynamic therapy (PDT) has emerged as a promising treatment strategy in the management of various cancers in urology, gynecology or dermatology [10—13]. PDT relies on the selective accumulation of photosensitizers (PS) in tumor to generate the destruction of the cells. Illumination of the tumor with an excitation light tuned to the absorption band of the PS leads to the tumor destruction while sparing normal tissues. Thus the efficacy of PDT depends on numerous parameters, including tissue oxygenation status, photosensitizer concentration, and light regimen.

The mechanisms of PDT-mediated tumor destruction involve a direct cellular toxic effect, vascular damages and an immune reaction, which might be important for long-term tumor control [14,15]. In light of our work on developing interstitial PDT in a U87 glioma rodent model, we present an extensive review of the experimental use of PDT in high grade gliomas, with a specific focus on the use of 5-aminolevulinic acid induced protoporphyrin IX, as well as a detailed study of the illumination and oxygenation conditions.

PDT of gliomas

The choice of photosensitizer

Ideal PS should absorb light in the red or far-red wavelengths, for increased tissue penetration, and should have the ability to cross the BBB. In addition, an ideal PS candidate would offer high tumor tissue selectivity, reduced skin and systemic toxicity through a rapid elimination of the PS by the patient [14,16]. Many compounds have already been investigated for PDT of gliomas.

Hematoporphyrin derivative (HpD; Photofrin®) was the first PS to be studied reported in detail [16,17]. Despite its interesting characteristics, poor tumor selectivity and long-lasting skin photosensitivity constituted several drawbacks that led to the development of new PS [18,19]. Compounds such as m-THPC (m-tetrahydroxuphenyl chlorin, Foscan®), 5-ALA (5-aminolevulinic acid), BOPP (boronated porphyrin) and talaporfin sodium have been mainly used in clinical trials for gliomas (Table 1) [6,20—26]. Their activation peaks are respectively at 652, 635 and 630 nm. Others PS have been assessed in experimental studies, including hypericin, SIM01 and Pc4 [27,28].

5-ALA is a second-generation PS that is already authorized in European Union for fluorescence-guided resection [20,29]. It is a precursor that is converted into the potent