Photodynamic Therapy in Adult Intra-axial Brain Tumours

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Abstract

The management of high-grade gliomas is challenging considering their infiltrative nature, involvement of the eloquent cortex, and high recurrence rate. Photodynamic therapy (PDT) is an emerging modality that selectively destroys tumour cells while preserving normal brain tissue. Its safety, and the concurrent use with surgery, radiation, and chemotherapy, is some of its appealing tenets. Here, we present a review of the literature regarding the mechanism, safety, and efficacy of PDT.

Keywords: brain tumour, glioma, adjuvant treatment.

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Introduction

High-grade gliomas have remained a challenge for oncologists despite multimodal management strategy, particularly in recurrent settings. The infiltrative nature of glioma in the peritumoural oedematous area is linked to a high recurrence rate (80%). Novel therapies have been developed to control recurrence, including the administration of therapeutic agents directly into or near the tumour bed.[1]

A method of visual identification and selective elimination of tumour cells is the newly studied photodynamic therapy (PDT). It includes the introduction (intravenous, intraperitoneal, local or oral) of a light-sensitive chemical agent called a photosensitizer (PS) followed by its activation at a certain wavelength of light. Photosensitizing agent selectively accumulates in malignant cells due to an impaired blood-brain barrier (BBB) and high metabolism. It triggers an oxidative reaction when activated by the light rays of the appropriate wavelength, generating singlet or triplet oxygen species. In the singlet state, energy is converted into heat or emitted as light (fluorescence). In the triplet state, reactive oxygen species (ROS) are generated. ROS react with macromolecules containing unsaturated double bonds and damage the membranes of intracellular organelles. It disrupts cell signaling pathways, destroys DNA, and eventually leads to tumour cell death.[2] PDT also affects microvasculature causing local ischaemia and activating macrophages, producing a strong immune response against tumours.[1] (Figure 1)

There are two types of PDT. Interstitial PDT (iPDT) is applied via the stereotactic insertion of fiber optic cable into the tumour for photo-stimulation. Tumour volume less than 5cm^3 is a criterion of total response after iPDT. The iPDT is comparable to laser interstitial thermal therapy (LITT) for the treatment of glioblastoma. Both are minimally invasive stereotactic techniques; however, iPDT has the added benefit of selective neoplastic cell targeting.[3] This type of photo-irradiation can be completed following tumour resection or as adjuvant therapy alone.[4]

Intracavitary PDT is applied to the resection cavity after maximum safe resection in the operating room or during post-operative recovery. It is commonly applied by placing a balloon filled with diffusing liquid (typically a lipid suspension) coupled to a fibre optic guide and an external light source into the intracranial resection cavity. After tumour resection, the balloon is positioned in the cavity and inflated to conform to the geometry of the cavity without causing excessive compression of surrounding brain tissue. Intracavitary photo-irradiation covers a larger surface area than interstitially inserted fibres.[5, 6]

Literature review

The first RCT to test PDT as treatment for glioblastomas was conducted by Muller and Willson.[7] The treatment arm included 43 patients who underwent resection followed by porfimer sodium-mediated PDT and was compared in 34 patients who underwent tumour resection alone. Post-operative radiotherapy was administered to all patients. Median survival was 11.0 months in the treatment group compared to 8.0 months in the control group. A 38% increase in median survival with PDT as well as more than 6.0-months survival rate in the treatment group was statistically significant, but Kaplan–Meier curves crossed over at 15 months.[7]

A phase II clinical trial of intraoperative PDT with thalaporfin sodium (TS) included 27 patients with newly diagnosed or recurrent primary parenchymal brain

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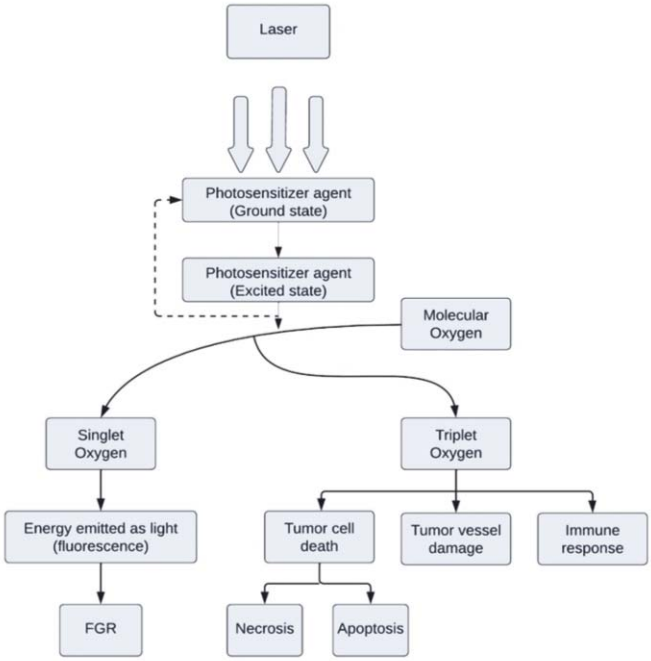

Figure: Mechanism of action of PDT.
Mechanism of Photodynamic therapy (FGR: Fluorescence guided resection).

tumours.[8] In the analysis cohort of 22 patients, the 12-month survival and 6-month progression-free survival (PFS) after surgery and PDT were 95.5 and 91.0%, respectively, versus 100% in 13 patients with newly diagnosed glioblastoma. Side effects on the skin that can be associated with the use of talaporfin sodium were reported in 7.4% of patients. Skin photosensitivity test results were relatively mild and completely disappeared within 15 days after administration of photosensitizer in all patients. Other side effects noted were a transient increase in liver enzymes (glutamyltransferase (59.3%), alanine aminotransferase (48.1%), aspartate aminotransferase (37.0%), blood alkaline phosphatase (25.9%), and blood lactate dehydrogenase (22.2%).[8]

A series compared 15 patients with small newly diagnosed (<4 cm) and unresectable glioblastomas who underwent 5-ALA iPDT with 112 patients who underwent complete tumour resection alone. All patients received standard radiotherapy and temozolomide. The iPDT group demonstrated a significantly longer median PFS of 16.0 vs. 10.2 months and a 3-years survival of 56.0 vs. 21.0%. Of note, 6 of the 15 patients in the iPDT group experienced PFS more than 30 months.[5]

Another case series of 41 patients diagnosed with primary brain tumours, treated with PDT with either Porfimer sodium or mTHPC was published.[9] In 7 patients, PDT was repeated at the time of the relapse. In 22 episodes PDT was part of the initial treatment of primary brain tumours and in 26 episodes was part of the treatment at relapse. The median PFS observed was 10 months for glioblastoma, 26 months for Anaplastic Astrocytoma, and 43 months for Oligodendroglioma (ODG). Median OS was 9 months for glioblastoma, 20 months for AA, and 50 months for ODG. The disparity in PFS and OS data results from not censoring patients for PFS when they die from non-tumour-related causes. Median OS since first diagnosis was 17 months for glioblastoma, 66 months for AA and 122 months for ODG. One scalp burn requiring plastic surgery with cutaneous graft was observed. Other cutaneous toxicities were one case of blisters on the forearm and other of erythema in forearm.[9]

Fluorescence-guided surgery (FGS) shares similarities to PDT because it employs a haematoporphyrin derivative as the active compound, along with visualization by externally supplied light. In this manner, it is reasonable to consider these techniques together, one for visualization, and the other for tumour cell eradication. Indeed, FGS, along with photodiagnosis, is considered as a PDT-technology.[4] One study used 5-ALA for FGS and intraoperative PDT in 20 patients with recurrent GB. After 5-ALA FGR, 1–4 cylindrical laser diffusers were inserted into the resection cavity and PDT was performed (200 mW/cm) with continuous irrigation to maintain optical clarity and ventilation with 100% oxygen.[10] The median PFS was 6 months, which is comparable to the standard treatment for recurrent glioblastoma. Infection at the surgical site was noted in 1 patient after 6 months as the only side effect. In 16 (80%) of 20 cases, cytotoxic oedema along the resection margin was detected, which regressed or disappeared after 4–5 months.[10]

Another series included ten patients with newly diagnosed glioblastoma treated between May 2017 and June 2018 who underwent maximal resection guided by 5-ALA FGS, followed by intraoperative PDT.[12] Postoperatively, patients underwent adjuvant therapy (Stupp protocol)[11]. The 12-months PFS rate was 60% (median 17.1 months), and the 12-months OS rate was 80% (median 23.1 months) with no serious toxicities.[12]

A systematic review on PDT reported that patients harbouring high-grade gliomas, 33 (13%) were considered long-term survivors (> 2 years) after iPDT. For de novo glioblastoma, iPDT allows an increase of PFS from 6.9 months to 14.5 months.[13] More surprisingly, for recurrent glioblastoma, the PFS was also 14 months after iPDT whereas it is usually between 5 to 7 months. Regarding the OS, it seems to improve with iPDT. Instead of 14.6 months in Stupp et al,[11] median OS in this review

was 19 months for de-novo Glioblastoma.[13]

Another retrospectively analyzed cohort consisted of 16 patients with biopsy-proven de novo glioblastomas for whom a standard of care treatment was not possible due to the location of the tumour or other contraindications.[14] They underwent 5-ALA mediated iPDT with radiation therapy and temozolomide. A total of 10 of 16 patients experienced prolonged OS (24 months or more). The dominant prognosis-affecting factor was the MGMT promoter methylation status. When comparing the entire iPDT cohort with the standard-of-care (SOC) cohort according to Stupp et al.[13] The iPDT cohort (n = 287), showed superior PFS (median of iPDT of 16.4 months vs. median of Stupp of 6.9 months) and OS (median of iPDT of 28.0 months vs. median of Stupp of 14.6 months), a two-year overall survival (OS) rate of 26.5%.[14]

Conclusion

PDT emerges as a promising modality for managing malignant gliomas, effectively addressing various current treatment challenges. It offers targeted tumour treatment, organ-sparing techniques, low systemic toxicity, and eliminates the need for extensive hospital stays. Although it shows encouraging survival indices in high-grade gliomas and has proven feasibility and safety, definitive conclusions await confirmation through phase III clinical trials.

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Conflict of Interest: None.

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References

1. Akimoto J. Photodynamic therapy for malignant brain tumours. Neurol. Med. Chir.2016;56:151-7
2. Quirk BJ, Brandal G, Donlon S, Vera JC, Mang TS, Foy AB, Lew SM, Girotti AW, Jogal S, LaViolette PS, Connelly JM. Photodynamic therapy (PDT) for malignant brain tumors–where do we stand? Photodiagnosis Photodyn Ther. 2015;12:530-44.
3. Hsia T, Small JL, Yekula A, Batool SM, Escobedo AK, Ekanayake E, You DG, Lee H, Carter BS, Balaj L. Systematic review of photodynamic therapy in gliomas. Cancers. 2023;15:3918.
4. Cramer SW, Chen CC. Photodynamic therapy for the treatment of glioblastoma. Front Surg. 2020;6:81. doi: 10.3389/fsurg.2019.00081
5. Schwartz C, Ruhm A, Tonn JC, Kreth S, Kreth FW. Interstitial photodynamic therapy of de-novo glioblastoma multiforme WHO IV. Neuro Oncol. 2015;17:v214–20. doi: 10.1093/neuonc/nov235.25
6. Stylli SS, Kaye AH, MacGregor L, Howes M, Rajendra P. Photodynamic therapy of high grade glioma–long term survival. J Clin Neurosci. 2005;12:389-98
7. Muller PJ, Wilson BC: Photodynamic therapy of brain tumor—a work in progress. Laser Surg Med. 2006;38: 384–389.
8. Muragaki Y, Akimoto J, Maruyama T, Iseki H, Ikuta S, Nitta M,et.aal. Phase II clinical study on intraoperative photodynamic therapy with talaporfin sodium and semiconductor laser in patients with malignant brain tumors. J Neurosurg. 2013;119:845- 52. doi: 10.3171/2013.7.JNS13415
9. Vanaclocha V, Sureda M, Azinovic I, Rebollo J, Cañón R, Sapena NS, Cases FG, Brugarolas A. Photodynamic therapy in the treatment of brain tumours. A feasibility study. Photodiagnosis Photodyn Ther. 2015;12:422-7.
10. Schipmann S, Müther M, Stögbauer L, Zimmer S, Brokinkel B, Holling M, Grauer O, Molina ES, Warneke N, Stummer W. Combination of ALA-induced fluorescence-guided resection and intraoperative open photodynamic therapy for recurrent glioblastoma: case series on a promising dual strategy for local tumor control. J Neurosurg 2020;134:426-36.
11. Stupp R, MasonWP, Van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. NEJM. 2005;352:987–996.
12. Vermandel M, Dupont C, Lecomte F, Leroy HA, Tuleasca C, Mordon S, Hadjipanayis CG, Reyns N. Standardized intraoperative 5-ALA photodynamic therapy for newly diagnosed glioblastoma patients: a preliminary analysis of the INDYGO clinical trial. J Neurooncol. 2021;152:501-14.
13. Leroy HA, Guérin L, Lecomte F, Baert G, Vignion AS, Mordon S, Reyns N. Is interstitial photodynamic therapy for brain tumors ready for clinical practice? A systematic review. Photodiagnosis Photodyn Ther. 2021;36:102492.
14. Foglar M, Aumiller M, Bochmann K, Buchner A, El Fahim M, Quach S, Sroka R, Stepp H, Thon N, Forbrig R, Rühm A. Interstitial photodynamic therapy of glioblastomas: a long-term follow-up analysis of survival and volumetric MRI data. Cancers. 2023;15:2603.