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Anti-Tumour Treatment

Photodynamic therapy of malignant brain tumours: A complementary approach to conventional therapies

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ABSTRACT

The poor outcome of primary malignant brain tumours is predominantly due to local invasion and local recurrence and their prognosis is highly dependent on the degree of resection. They have no border and, at best, a marginal zone that remains invisible to the surgeon. Photodynamic therapy (PDT) appears to be an interesting modality to fill the need for a targeted treatment that may reduce recurrence and extend survival with minimal side effects.

In this review, we summarize the different technologies of brain tumour PDT employed such as interstitial PDT, and PDT-associated surgical resection, describing new light delivery devices. The role of dosimetry – one of the key factors behind successful brain tumour PDT - is discussed. This can be achieved by integrating results from *in vivo* studies. In this context, the development of new therapeutic photosensitizer delivery systems is also an area of significant research interest. Multifunctionality can be engineered into a single nanoplatform to provide tumour-specific detection, treatment, and follow-up. Such multitasking systems appear to be complementary to conventional technologies.

Preface

Photodynamic therapy (PDT) was first proposed as a useful tool in oncology over 25 years ago. For brain tumors, PDT has several potential advantages over surgery, radiotherapy or chemotherapy.[1] Photodynamic techniques such as photodynamic diagnosis (PDD),[2,3] fluorescence-guided tumour resection (FGR)[4–6] and PDT are currently undergoing intensive clinical investigations as adjuvant treatment of malignant brain tumours.[6–9] Recent developments focus on new photosensitizer delivery systems, light delivery devices, real-time dosimetry and strategies for performing image-guided PDT, all combined to improve the effectiveness and the safety profile of this innovative technique that has the potential to become an exciting addition to the range of treatment options under investigation for brain tumours.

At a glance

Photodynamic therapy was developed as an additional therapy (enhancing the effect of surgery) or as a treatment for inoperable tumours. It involves giving the patient a drug (usually called photosensitizer) that makes tissues sensitive to light. A light source (typically laser light) is used during the procedure and in some cases for up to a few days afterwards to activate the light-sensitive substance with the aim of destroying the tumour cancerous lesions. The procedure has been used by enthusiasts for almost 25 years.

Major adverse events occasionally reported in the literature include: cerebral edema, raised intracranial pressure, hypersensitivity reaction, skin photosensitization.[10]

Specialists classified the procedure as novel and of uncertain safety and efficacy (see Ip Overview of photodynamic therapy for brain tumors-National Institute for Health and Clinical Excellence). The key efficacy outcomes for this procedure are overall and progression-free survival, completeness of resection and quality of life.

The optimal light exposure dose is still being studied. The technique is constantly evolving with new photodynamic agents and nanoplatforms, as well as novel light delivery systems. Surgeons need to be trained to make appropriate use of the technology, including light sources.

Introduction

Brain tumours may develop as a primary tumour from glial, neuronal or meningeal cells, or metastases from tumours elsewhere

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in the body. Intrinsic brain tumours (such as astrocytoma, oligodendroglioma, meningioma) are graded using the World Health Organization (WHO) classification from I (low-grade and least aggressive) to IV (high grade and most aggressive).[11] Prognosis with high-grade tumours is often poor, with survival measured in months, and worst with recurrent tumours. Malignant brain tumours are diagnosed 5–10 times a year in every 100,000 of the population and are responsible for 3% of all cancer deaths worldwide. They are the second most common cause of cancer deaths among young people and the sixth most common cause of productive-years loss. The symptoms of a brain tumour vary depending on its location, size and infiltration. Different locations can cause discrete disturbances such as limb weakness or speech impediment, while any brain swelling caused by the tumour can lead to raised intracranial pressure, headaches, vomiting and impaired consciousness.

One of the most common primary malignant brain tumours is high-grade glioma, comprising more than 40% of all intracranial tumours and consisting of glioblastoma multiforme (GBM 29%) and anaplastic astrocytoma (AA 11%). Standard treatment of high-grade gliomas usually consists of cytoredictive surgery followed by radiation therapy and chemotherapy; however these tumour types usually recur despite treatment (Table 1).

Once the tumour progresses, treatment options include repeated surgical resections, radiosurgery, chemotherapy with standard agents, novel therapies, or a combination of the above (Table 2).

The use of two or more modalities of treatment in combination, alternately or together, can offer many benefits, and is already in clinical practice. Only a few randomized trials have been done at the time of progression and most trials are phase II trials, limited by the number of patients treated. The integration of the oral cytotoxic agent temozolomide into current protocols of post-operative first-line treatment for high-grade glioma improves progression-free rates and overall survival.[12] But despite post-operative radiotherapy plus temozolomide for newly diagnosed GBM and improvements in the molecular characterization of high-grade glioma, these tumours continue to relapse. Other complementary strategies consist in re-treatment with stereotactic radiotherapy (mostly with additional chemotherapy) or re-resection plus either photodynamic therapy (PDT), temozolomide, or systemic and local chemotherapy.

The poor outcome for these tumours stems from local invasion and local recurrence. Surgical resection is the mainstay of treatment, removing tumour material with the aim of reducing intracranial pressure without worsening of neurological functions. However, in most cases curative resection is not possible because of the infiltrating growth of the tumour into normal brain parenchyma. The wide majority of GBM recur locally and patients often succumb to and die from local recurrence, indicating that a more aggressive local therapy is required to eradicate it. However, complete radical surgical excision is hindered by the elusive nature of these tumours: a significant number of cells are not visible and require the aid of surgical microscopy. Moreover, side effects of radiotherapy can have considerable influence on health and quality of life. In this unfavorable context, PDT appears as an innovative

Table 1
Treatment of glioma.

Surgery	
	Important prognostic factors, such as age, performance status, and presumed extent of maximal safe resection should be considered. Surgical resection may increase survival in select patients. Decreasing tumor mass may also improve the efficacy of adjuvant therapy, as may the removal of hypoxic tissue, known to be resistant to chemotherapy.
Radiation techniques(12)	
Conventional radiotherapy	Multifractionated focal external beam radiation therapy (EBRT). Current therapeutic goals for treatment of GBM involve gross total resection followed by EBRT.
Intensity-modulated radiotherapy (IMRT)	IMRT is a new radiation technique, using inverse treatment planning coupled with computer-controlled multi leaf collimation during treatment delivery to create highly complex dose-intensity patterns, leading to a conformal radiation doses to targets.
Radiosurgery	Gamma knife radiosurgery is administered as a single dose, whereas Cyberknife stereotactic radiosurgery (SRS) or linear accelerator radiosurgery may be fractionated.
Brachytherapy	An important experience with temporary brachytherapy was accumulated. However, this technique is rarely used today as both local failure and symptomatic radiation necrosis were common.
Photodynamic therapy (PDT)	(explained in this review)
Chemotherapy(13)	
	Concurrent radiation and the oral alkylating agent temozolomide followed by adjuvant temozolomide has become the standard of care for patients with newly diagnosed GBM. Nitrosoureas are the most commonly used second-line chemotherapeutic agent, but carboplatin, etoposide, irinotecan, or a combination of these agents is also commonly used. It seems that the methylation status of methylated methylguanine methyltransferase (MGMT) may be an important molecular marker for selecting temozolomide as a first-line treatment.
Targeted therapies(14)	