Pharmacology & Therapeutics 139 (2013) 341–358

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: G. Eisenhofer

Current status of local therapy in malignant gliomas — A clinical review of three selected approaches

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ARTICLE INFO

Keywords:
Malignant gliomas
Local therapy
Carmustine wafers
Convection-enhanced drug delivery
Local gene therapy
Review

ABSTRACT

Malignant gliomas are the most frequently occurring, devastating primary brain tumors, and are coupled with a poor survival rate. Despite the fact that complete neurosurgical resection of these tumors is impossible in consideration of their infiltrating nature, surgical resection followed by adjuvant therapeutics, including radiation therapy and chemotherapy, is still the current standard therapy. Systemic chemotherapy is restricted by the blood–brain barrier, while methods of local delivery, such as with drug-impregnated wafers, convection-enhanced drug delivery, or direct perilesional injections, present attractive ways to circumvent these barriers. These methods are promising ways for direct delivery of either standard chemotherapeutic or new anti-cancer agents. Several clinical trials showed controversial results relating to the influence of a local delivery of chemotherapy on the survival of patients with both recurrent and newly diagnosed malignant gliomas. Our article will review the development of the drug-impregnated release, as well as convection-enhanced delivery and the direct injection into brain tissue, which has been used predominantly in gene-therapy trials. Further, it will focus on the use of convection-enhanced delivery in the treatment of patients with malignant gliomas, placing special emphasis on potential shortcomings in past clinical trials. Although there is a strong need for new or additional therapeutic strategies in the treatment of malignant gliomas, and although local delivery of chemotherapy in those tumors might be a powerful tool, local therapy is used only sporadically nowadays. Thus, we have to learn from our mistakes in the past and we strongly encourage future developments in this field.

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1. Introduction

Gliomas are frequently occurring, primary brain tumors with an incidence of 6.04 per 100,000 person-years in the United States (CBTRUS, 2011), and of 3 to 5 per 100,000 per year in Europe (Crocetti et al., 2012). They are classified on a scale of I to IV, defined by the World Health Organization, on the basis of histopathological features (Louis et al., 2007). Grades III and IV are considered high-grade or malignant. The annual incidence of malignant gliomas is ~5 cases per 100,000 people (Louis et al., 2007; CBTRUS, 2011). The most common and

Abbreviations: AG, anaplastic gliomas; AEs, adverse effects; AV, adenoviruses; AV-HSV-tk, adenovirus herpes simplex virus-thymidine kinase; CB, cintredekin besudotox; CEDD, convection-enhanced drug delivery; CNS, central nervous system; CSF, cerebrospinal fluid; CT, chemotherapy; CW, carmustine wafers; GCV, ganciclovir; EGFR, epidermal growth factor receptor; HSV, herpes simplex virus; HSV-tk, Herpes simplex virus-thymidine kinase; IL, interleukins; GBM, glioblastoma multiforme; MG, malignant gliomas; MRI, magnetic resonance images; PE, *Pseudomonas* exotoxin; PFS, progression-free survival; RT, radiotherapy; RV, retrovirus RV; RV-VPC, RV-mediated HSV-tk gene transfer delivered by injections of VPC; TGF-β, Transforming growth factor-beta; TMZ, temozolomide; VPC, virus-producing cells.

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0163-7258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pharmthera.2013.05.003

biologically aggressive subtype of high-grade gliomas is the glioblastoma multiforme (GBM), World Health Organization (WHO) grade IV. GBM and AG (grade III) account for ~76% of all gliomas (Aldape et al., 2003; CBTRUS, 2011). Characteristic for GBM are the hallmark features of uncontrolled cellular proliferation, diffuse infiltration, propensity for recurrence, necrosis, microvascular proliferation, resistance to apoptosis, and high genomic instability.

MG occur in all age groups, but are more common in older adults, with an increase in incidence coinciding with an increase in age, the highest of whom being 75 to 84 years old (CBTRUS, 2011). Despite advancements in surgery and adjuvant therapy, the prognosis remains poor, with a median survival of less than 15 months (Stupp et al., 2005), and with 3–5% of GBM patients surviving five years after diagnosis. Patients with AG have a modestly better prognosis, with an estimated median survival of between 3 years (for anaplastic astrocytoma) and 7 years (for anaplastic oligodendroglial tumors) (Nieder et al., 2004; Prados et al., 2004; van den Bent et al., 2006).

A number of environmental, genetic and other factors are implicated according to risk nature for the development of MG. Some of those established risk factors are: prior exposure to therapeutic doses of ionizing radiation (Hodges et al., 1992; Smith-Rooker et al., 1992; Wrensch et al., 1993), genetic predisposition as genetic syndromes, e.g. Li–Fraumeni Syndrome (Nichols et al., 2001) or other hereditary syndromes such as neurofibromatosis types 1 and 2, tuberous sclerosis, and Turcot Syndrome (Wrensch et al., 2002). Approximately 5% of patients with MG have a family history of gliomas. However, most familial cases have no identified genetic cause.

Additional factors such as alcohol, smoking, dietary intake of nitroseamines and other dietary issues have been investigated as potential risks for MG, but so far none have been proved to be involved in the gliomagenesis (Berleur & Cordier, 1995; Lee et al., 1997; Wrensch et al., 2002).

2. Current standard treatment of malignant gliomas

2.1. Surgical resection

The standard therapy for newly diagnosed MG includes surgical resection followed by combined RT/CT and adjuvant chemotherapy. Surgery effectively induces reduction of tumor mass, and patients should undergo maximal surgical resection whenever possible to achieve a better overall survival (Stummer et al., 2006, 2008; Sanai & Berger, 2011). In addition, CT seems to be more efficacious when minimal residual disease is present (Keles et al., 2004). Current advances in neurosurgical equipment, such as intraoperative brain mapping (Sanai et al., 2008), intraoperative MRI (Gasser et al., 2011; Senft et al., 2011), and application of 5-aminolevulinic acid derived tumor fluorescence for intraoperative identification of MG tissue, have obtained an improved safety and an increased extent of resection in glioma patients (Stummer et al., 2006). However, complete neurosurgical resection of these tumors is impossible in consideration of their infiltrating nature. As a result, surgery must be followed by adjuvant therapy modalities like RT, CT, or both.

2.2. Radiation therapy

Radiation therapy with an external beam irradiation has been shown to be effective in the treatment of newly diagnosed MG (Andersen, 1978; Walker et al., 1978). The median survival is increased from 5 months to 9 months with adjuvant RT compared to surgery alone or best supportive care only (Andersen, 1978; Walker et al., 1980). The optimal dose of radiation in the treatment of MG patients has long been debated, with several large cooperative trials using different dosages. The study results were that 60 Gy was superior to 45 Gy, improving patients' survival by 3 months (Walker et al., 1979; Chang et al., 1983; Bleehen & Stenning, 1991). Increasing the radiation doses up to 70 Gy and higher have not proved to be more effective (Chang et al., 1983). Standard practice is to administer 58 to 60 Gy in 1.8 to 2.0 Gy fractions 5 days a week for 30 to 35 fractions. The administration of 40 Gy as a focal dose to the tumor area, including the surrounding edema, with an additional boost of 20 Gy given to the enhancing tumor plus a 1- to 2-cm margin, is currently the favorable schema of radiation (Garden et al., 1991). However, gliomas are a heterogeneous tissue and most cells seem to be resistant to RT (Baumann et al., 1992, 2009) implicating that even after application of the clinically best tolerated maximum dose of 60 Gy, tumors will not be eradicated completely.

2.3. Chemotherapy

The fundamental problem with systemic CT for brain tumors is that most chemotherapeutic agents do not pass the blood–brain or blood–tumor barrier to reach an effective dose within the tumor. Therefore, in addition to the systemic application, local and CEDD applications have been established.

Standard systemic adjuvant CT is based on alkylating agents which have been used in the therapy of primary brain gliomas for several decades, consisting of either nitrosoureas or other alkylating agent-based CT, like TMZ. This group of medications is one of the few with the ability to penetrate the blood–brain barrier, achieving cytotoxic concentrations in cerebrospinal fluid and brain parenchyma. Nitrosoureas induce the process of alkylation to inhibit DNA repair through the inhibition of DNA replication. Alkylating agents can be administrated as monotherapy or in combination with other agents like procarbazine and lomustine.

TMZ, imidazotetrazine derivative of the alkylating agent dacarbazine, is an orally administrated, second-generation alkylating chemotherapeutic agent, introduced to the therapy of primary brain tumors in the 1990s. It has since been approved in several randomized clinical trials for the therapy of recurrent and newly diagnosed MG. The precise mechanisms by which TMZ acts to kill tumor cells are not completely understood. However, it offers improved outcomes when used alone or in combination with irradiation. Tumor resistance against alkylating agents is an unsolved clinical problem due to intratumoral overexpression of the MGMT protein (O^6-methylguanine-DNA methyltransferase). The *MGMT* gene is located on chromosome 10q26, and encodes a DNA-repair protein that removes alkyl groups from the O^6 position of guanine, an important site of DNA alkylation. The repair of the DNA induces the consumption of the MGMT protein, which must be regenerated by the cell. When left unrepaired, chemotherapy-induced lesions trigger cell apoptosis (Ochs & Kaina, 2000). Epigenetic silencing of the *MGMT* gene by promoter methylation has been associated with longer overall survival in MG patients who received alkylating CT with carmustine or TMZ (Esteller et al., 2000).

2.4. Current treatment of newly diagnosed anaplastic gliomas

After surgical tumor debulking, patients with AG received, according to the NOA-04 study, either conventional radiation, consisting of 60 Gy in the schema described above, or chemotherapy with TMZ or PCV (procarbazine, lomustine, and vincristine) (Wick et al., 2009). In the latter trial, initial radiotherapy or chemotherapy after surgical resection achieved comparable results in patients with AG.

However, according to newly published data, patients with anaplastic oligodendrogliomas and anaplastic oligoastrocytomas—subgroups of the AG—should be treated with PCV plus radiation therapy especially if the gliomas are co-deleted for chromosomes 1p and 19q (Cairncross et al., 2013; van den bent et al., 2013). At this point, it should be mentioned that vincristine is a well-known neurotoxic chemotherapeutic agent with several dose-dependent and cumulative long-term side effects, such as: paresthesias, progressive weakness, seizures, and bi-hemispheric white matter changes on