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CURRENT TREATMENT PROTOCOLS AND NEW STRATEGIES FOR GLIOBLASTOMA MULTIFORME

Oncology

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common and aggressive malignant neoplasm of brain. Its incidence is approximately 6.5 per 100000 person in United States and increase with age. Current standard treatment is maximal safe resection followed by radiation along with concurrent and adjuvant temozolamide. But despite best available treatment, survival is very minimal. Thus there is a need for newer treatment approaches by which we can improve the survival in GBM in near future. In this article we review the current treatment protocol and newer approaches which are still under investigation like radioimmunotherapy, peptide vaccines against EGFRvIII, Proton therapy etc.

KEYWORDS

Temozolamide, Radioimmunotherapy, Peptide Vaccine, Proton Therapy

Introduction

Glioblastoma multiforme is the most common and aggressive malignant neoplasm of brain. Its incidence is approximately 6.5 per 100000 person in United States. Incidence increased with age to reach 50 per 100000 person at age > 75 years[1].

It accounts for 45.6 % of primary malignant brain tumors[2] and 75 % of all high grade gliomas[3]. The histopathological features of Glioblastoma include nuclear atypia, mitotic activity, vascular proliferation and necrosis. Glioblastoma is diffusely infiltrative, involving large portions of brain. It is also classified as WHO grade IV gliomas according to its behaviour, outcome and prognosis.

Glioblastoma is very fatal malignant tumor. It requires multimodality treatment. Current standard management is maximal safe resection followed by post op radiation with concurrent and adjuvant Temozolamide. Despite this aggressive treatment, median survival is about 14.6 months, 2 year survival around 27%[4] and 5 year survival only 9.8 % approximately.

Prognosis of Glioblastoma is very poor. In spite of best available treatment all patients recur with time. There are various prognostic factors. Age and KPS are the two most important prognostic factor. Patients with age < 50 years and KPS >70 do better[5]. Other factors are methylated MGMT promoter gene, Angiogenesis, EGFR gene amplification, presence of an EGFR deletion mutant variant III (EGFRvIII) and IDH 1 mutation (secondary Glioblastoma) etc.

A variety of new treatment approaches are being investigated to prolong the survival. This includes targeted therapy which can act by inhibiting tumor proliferation, angiogenesis, invasion via various receptors and molecular pathways, radio sensitizers, radioimmunotherapy, vaccines and alteration in radiation techniques. Here we shall discuss the current available treatment protocol and new approaches which can improve the outcome in future.

Surgery: Surgery is first and most important part of glioblastoma management. It results in immediate symptomatic relief from mass effect, improve neurologic function, reduce tumor bulk and provide tissue for histology and molecular analysis. Complete resection is associated with survival advantage[6]. But with surgical resection alone median survival is around 6 months. Thus some adjuvant treatment is necessary.

Radiation: Randomized trials have demonstrated a clear survival advantage of surgery followed by post op radiation. Median survival became 12.1 month approximately[4] Initially WBRT was used postoperatively but now IFRT (involved field radiotherapy) is the standard because according to Hochberg et al[7] and Wallner et al[8] 78% of recurrence occur within 2 cm and 56% recurrence occur in within 1 cm of margin of initial tumor bed. In Brain Tumor Cooperative Group trial (BTCG 80-01)[9] there was no difference in outcome in patients treated with WBRT 60.2 Gy vs. WBRT 43 Gy followed by IFRT 17.2 Gy.

Optimal radiotherapy dose for glioblastomas is 60 Gy in 30 fractions in 6 weeks.(walker et al)[10]. Radiation dose escalation has no survival benefit[11-12]. But dose escalation using *Proton therapy* provides some survival benefit in some early trials so it requires further prospective randomized trial to validate the results.

For IFRT treatment there are 2 protocols for tumor delineation and treatment techniques. The RT Oncology Group (RTOG) favours a two-step cone down technique, with an initial phase clinical target volume (CTV1) including the entire T2- high signal intensity, comprising of peritumoral edema and enhancing lesion) plus 2 cm margin and the initial planning target volume (PTV1) is an additional margin of 3–5 mm, for dose of 46 Gy in 23 fractions, followed by a boost field (CTV2) defined as the T1-enhancement and the surgical cavity plus 2 cm and PTV2 with an additional margin of 3–5 mm for dose of 14 Gy in 7 fractions. The European Organisation of Research and Treatment of Cancer (EORTC) recommend a single-phase technique in which GTV is defined as the T1 contrast enhancement region or the surgical tumor bed plus any residual enhancing tumor that is seen on the planning scan. The CTV includes GTV with a margin of 2–3 cm, which can be modified in anatomic regions such as bony structures and adjacent normal meninges. The PTV margin to CTV is 0.5–0.7 cm to ensure adequate CTV coverage. A total dose of 60 Gy in 30 fractions is usually delivered.

Chemoradiation: Glioblastoma is generally resistant to chemotherapy because of inherent invasiveness, existence of BBB, Interaction between anti-convulsant drugs and chemotherapy, genetic mutation, high angiogenicity, EGFR gene amplification or the EGFR vIII mutation, methylation of the O6-methylguanine-DNA methyltransferase (MGMT) and base excision repair pathway[13-14].

Before the advent of Temozolamide, various chemotherapy were used to treat Glioblastoma. Nitrosourea agents used along with radiation which shows very minimal improvement in survival but other drugs like cisplatin, carboplatin and paclitaxel, did not exhibit any improvement in survival.

A large multi-institutional phase III cooperative group trial by Stupp et al[4] conducted by the EORTC Brain and Radiotherapy Groups and National Cancer Institute of Canada Clinical Trials Group (EORTC-NCIC Trial). In this trial, patients with newly diagnosed glioblastoma were randomly assigned to receive focal RT alone (fractionated focal irradiation for a total of 60 Gy in 30 fractions over 6 weeks) or RT plus concomitant TMZ (75 mg/m2, 7 days per week from the first to the last day of radiotherapy), followed by six cycles of adjuvant TMZ (150–200 mg/m2 for 5 days every 28-day). At a median follow-up of 28 months, the median survival was 14.6 months with RT plus TMZ and 12.1 months with RT alone (2.5 months benefit with RT plus

TMZ). The 2-year survival rate was 26.5% with RT plus TMZ and 10.4% with RT alone. This provided the level 1 evidence of benefit of systemic chemotherapy in glioblastoma and TMZ was approved in 2005 after this large trial for GBM treatment. The long-term results and 5-year analysis were published in 2009 by Stupp et al.[15]. Of 286 patients treated with radiotherapy alone, 97% [278] died and of 287 in the combined-treatment group, 89% [254] died during 5 years of follow-up. OS rates at 2, 3, 4 and 5 years were 27.2%, 16.0%, 12.1% and 9.8%, with combined treatment group, vs. 10.9%, 4.4%, 3.0% and 1.9% with radiotherapy alone (P<0.0001). Methylated MGMT promoter was the strongest predictor of benefit from TMZ. Prophylaxis against Pneumocystis carinii pneumonia with oral trimethoprim-sulfamethoxazole during concomitant treatment with radiotherapy and TMZ is required.

Patients whose tumor contained a methylated MGMT promoter; their median survival was 21.7 months (TMZ plus RT) as compared with 15.3 months among those who were treated with RT alone[16]. Thus patients with methylated MGMT promoter benefited most.

Because Glioblastoma has high vascular proliferation and Angiogenesis which promote progression, regulated by VEGF. Bevacizumab (humanized monoclonal antibody against VEGF) blocks the binding of VEGF to its receptor on the surface of endothelial cells and prevents the migration and proliferation of endothelial cells, thereby decreasing tumor vascularisation and vasogenic brain edema resulting in hypoxia and cell death. Various trials conducted to see the efficacy of Bevacizumab in treating Glioblastoma. RTOG 0825 and AVAglio trial (patients randomly assigned to RT plus TMZ with placebo or Bevacizumab) shows that Bevacizumab did not improve overall survival (OS) but median PFS (progression free survival) was better in both trials[17-18]. Retrospective analysis of AVAglio data suggests that patients with IDH1 wild-type proneural glioblastoma may derive an OS benefit from first-line bevacizumab treatment (17.1 vs. 12.8 months, respectively; P=0.002)[19].

Cilengitide is an anti-angiogenic small molecule targeting the integrins αvβ3, αvβ5 and α5β1. They mediate communication between glioblastoma cells and the brain microenvironment and are over-expressed on tumor cells and vasculature. These are involved in angiogenesis, cellular survival, proliferation, migration, and invasion. In the multicentre, open-label, phase III CENTRIC EORTC 26071-22072 study[20], Stupp et al. investigated the efficacy of cilengitide in patients with newly diagnosed glioblastoma with methylated MGMT promoter. The addition of cilengitide to temozolamide chemoradiotherapy did not yield any improvement in outcome.

EGFR (Epidermal Growth Factor Receptor) is over-expressed in approximately 40- 50% of patients with glioblastoma, and of those nearly 50% harbour the specific EGFRvIII mutant. Clinical trials evaluating the efficacy of EGFR inhibitors in glioblastomas have shown disappointing results.

Some newer radiosensitizing agents were also tested. Motexafin gadolinium (MGd) was used concurrently with RT plus TMZ but there was no significant survival advantage[21].

Investigational approaches:

Radioimmunotherapy- In it monoclonal antibodies against EGFR tagged with ^{125}I has been evaluated in the treatment of high-grade gliomas. In a phase II trial by Brady et al.,[22] 25 patients with malignant gliomas (10 with anaplastic astrocytoma and 15 with GBM) were treated with surgical resection or biopsy, followed by definitive external-beam radiotherapy and one or multiple doses (35 to 90 mCi per intravenous or intra-arterial infusion) of ^{125}I-labeled monoclonal antibody. The total cumulative dose ranged from 40 to 224 mCi. Median survival was 15.6 months and in an updated report that included a total of 180 patients with a minimum follow-up of 5 years, median survival was 13.4 months for those with GBM[23].

Another potential target is *Tenascin,* an extracellular protein overexpressed in malignant gliomas but not found in normal tissue. Radiolabeled monoclonal antibodies to tenascin have been evaluated in phase I or II trials showing activity against newly diagnosed and recurrent malignant gliomas[24]. In a phase II trial by Reardon et al., ^{131}I-labeled murine antitenascin monoclonal antibody was injected directly into the surgical resection cavity in 33 patients with untreated malignant glioma. Patients were subsequently treated with external-beam radiotherapy and 1 year of alkylator-based chemotherapy. Even after accounting for prognostic factors, median survival (86.7 weeks) was longer than that of historical controls. Treatment-related toxicities were mild; only 1 patient required reoperation for radionecrosis[25].

Targeted therapy

More recently, Peptide vaccines targeting EGFRvIII have been tested in multicentric phase II trials of newly diagnosed EGFRvIII-expressing GBM following gross total resection and conventional radiotherapy with concurrent temozolomide. Both peptide vaccines rindopepimut (CDX-110) and PEPvIII consist of 13 amino acids unique to EGFRvIII and conjugated to keyhole limpet hemocyanin. In both trials, results compared favourably to historical controls. But interesting fact is that 82% of cases in the PEPvIII trial lost EGFRvIII expression at recurrence, suggesting the capacity of the EGFRvIII-targeted vaccine to potentially eliminate EGFRvIII-expression tumor cells in most patients. Similar results have been observed in preclinical models[26]. Now phase III trials are going on to test EGFRvIII vaccination.

CCI-779 and Everolimus are the other agents which are also being investigated as preclinical experiments suggest that these agents are potential radiosensitizers.

Conclusion: For Glioblastoma, maximal safe resection followed by post op radiation with concurrent and adjuvant Temozolamide is still the current standard management. But with this survival is less. Several newer approaches are being investigated in various trials, like Radiation dose escalation using proton therapy, radiolabelled monoclonal antibody to Tenascin, Peptide vaccines (PEPvIII and CDX-110) against EGFRvIII and Everolimus, to improve the survival. In initial trials they have shown promising results but large multicentric randomized trials are needed for any conclusion.

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