Evolution of radiotherapy and chemotherapy practice in malignant gliomas

Anusheel Munshi, Sayan Paul
Department of Radiation Oncology, Fortis Memorial Research Institute, Gurgaon, Haryana, India

ABSTRACT

Malignant astrocytomas of the brain carry a poor prognosis. This article traces the evolution of radiotherapy and chemotherapy practice including the development of concurrent chemo-radiation schedules in the context of these tumors.

Key words: Chemotherapy, glioma, radiotherapy

INTRODUCTION

Tumors of the central nervous system (CNS) are rare neoplasms constituting 1-2% of all malignancies.[1] Approximately, 85-90% of primary CNS tumors are intracranial tumors, while the rest are in the spine.[1-3] Depending upon the age, histology and site in the CNS, these tumors have varied presentations and contrasting clinical outcomes.[4] Among CNS neoplasms, gliomas are the most common tumors. These tumors have annual incidence of 3-4/1,00,000 population.[1-3] At least, 80% of malignant gliomas are glioblastomas.[5] Treatment options include surgery, radiotherapy (RT) and systemic chemotherapy, in varied schedules and combinations.[6] Glioblastoma multiforme (GBM), the most common intraparenchymal brain tumor in adults, is highly invasive and has a poor prognosis. Long-term survival, even with optimal treatment remains poor. Typical median survival time for patients with GBM and anaplastic astrocytoma ranges from 10 to 12 months and 30 to 40 months, respectively. However, it is well-known that geographical, genetic and phenotype differences in populations can alter the incidence, natural history, behavior and response to treatment of cancers.[7]

MOLECULAR ASPECTS

Primary GBM's tend to occur in older patients (mean age, 55 years), whereas secondary GBM's tend to occur in younger adults (45 years of age or less).[8,9] The difference between these two entities can occasionally be recognized radiographically. Regions of non-enhancing tumor are evident in secondary glioblastomas, as well as pathologically, when a surgical specimen contains low-grade disease. The two types of glioblastoma arise through different molecular pathways. Primary glioblastomas are associated with a high rate of overexpression or mutation of the epidermal growth factor receptor, p16 deletions and mutations in the gene for phosphatase and tensin homologs.[9-11] Secondary glioblastomas have genetic alterations involving the *p53* gene and overexpression of platelet-derived growth factor A and its receptor, platelet-derived growth factor receptor.[12]

Three molecular markers have redefined the outlook for malignant gliomas: 1p/19q chromosomal codeletion, O (6)-methylguanine methyltransferase (MGMT) promoter methylation and mutations of isocitrate dehydrogenase (IDH) 1 and 2. The assessment of these molecular markers has so far not been implemented in clinical practice because of the lack of precise therapeutic implications. It is considered that these markers are more prognostic than of predictive value, irrespective of whether patients were receiving RT, chemotherapy or both (1p/19q, IDH1/2). Also, with the advent of Temozolomide and lack of a viable alternative, testing was considered of limited value because testing itself has complexity and cost implications. However, in 2012, long-term follow-up of the Radiation Therapy Oncology Group (RTOG) 9402 and European Organization for Research and Treatment of Cancer (EORTC) 26951 trials demonstrated an overall survival benefit from the addition to RT of chemotherapy with procarbazine/

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Address for correspondence: Dr. Anusheel Munshi,
Department of Radiation Oncology, Fortis Memorial Research Institute, Gurgaon - 122 002, Haryana, India. E-mail: anusheel8@hotmail.com

Lomustine/vincristine confined to patients with anaplastic oligodendroglial (AO) tumors with (vs. without) 1p/19q co-deletion.[13]

SURGERY IN MALIGNANT GLIOMAS

Surgery remains the cornerstone of the management of malignant glioma. However, surgery alone results in a short median survival time of about 4 months. Surgical options in a malignant glioma patient include stereotactic biopsy, open biopsy or debulking procedure and major tumor resection. Optimal debulking surgery using an adequate tissue sample appears to offer the best outcome in eligible patients with good performance status.[14] Although the aim is complete or near-complete surgical removal, it has to be within the constraints of preservation of neurologic function and underlying patient health.[14,15] An exception to the general recommendation for attempted resection is the case of deep-seated tumors such as pontine gliomas. These tumors are diagnosed on clinical evidence and treated without initial surgery approximately 50% of the time. Two primary goals of surgery in malignant gliomas therefore include (1) establishing a histologic diagnosis (2) reducing intracranial pressure by removing as much tumor as is safely possible while preserving neurological function.[16] In view of poor patient outcomes in malignant gliomas after surgery alone, adjuvant treatment is strongly recommended.

RT

Radiation therapy has a significant role in the treatment of patients with high-grade gliomas. Use of RT in malignant gliomas is based on two trials in 1970's, which demonstrated improvement in survival. In the landmark study by Walker *et al.*, a total of 303 patients were randomized. Patients were divided into four random groups and received bis-chloroethylnitrosourea (BCNU) (80 mg/m^2/day on 3 successive days every 6-8 weeks) and/or RT (5000-6000 rads to the whole brain through bilateral opposing ports) or best conventional care, but no chemotherapy or RT. Median survival of patients was best conventional care: 14 weeks; BCNU: 18.5 weeks; RT: 35 weeks; and BCNU plus RT: 34.5 weeks.[17] A randomized trial compared 60 Gy (in 30 fractions over 6 weeks) with 45 Gy (in 25 fractions over 4 weeks) and showed superior survival in the first group (12 months vs. 9 months median survival; hazard ratio [HR] =0.81; 95% confidence interval (CI): 0.66-0.99). This trial made 60 Gy as the accepted standard dose of RT for malignant gliomas.[18] A statistically significant survival advantage was found comparing post-operative radiation therapy with no radiation therapy in a systematic review and meta-analysis of five randomized trials (risk ratio=0.81; 95% CI: 0.74-0.88).[19]

On the other hand, there have been some approaches in radiation therapy that have failed to deliver in the context of malignant gliomas. These include stereotactic radiosurgery and brachytherapy. A randomized trial tested radiosurgery as a boost added to standard external beam radiotherapy (EBRT), but found no improvement in survival, quality-of-life or patterns of relapse compared with EBRT without the boost.[20,21] Similarly, brachytherapy has been used to deliver high doses of radiation locally to the tumor while sparing normal brain tissue. A randomized study was undertaken to assess the role of brachytherapy as a boost (using I 125 seeds) to external beam radiation therapy in the initial management of patients with malignant astrocytomas. This study did not find any benefit of using brachytherapy.[22] This approach fell out of favor in view of the technical challenges and no proven benefit over external RT.

Conformal external beam radiation is the most commonly used approach.[23] EBRT using either 3-dimensional conformal radiation therapy or intensity-modulated radiation therapy is considered an acceptable technique in radiation therapy delivery. In general, 2-3 cm margins on the magnetic resonance imaging-based volumes (T1-weighted and fluid attenuated inversion recovery to create the planning target volume are used. Dose escalation using radiosurgery has not improved outcomes.[23]

CHEMOTHERAPY

Traditionally, chemotherapy was considered to have little or no benefit in the management of brain tumor. This perception is changing in recent years. The first agents to make some breakthrough in malignant gliomas were nitrosoureas. For many years, the nitrosourea carmustine (BCNU) was the standard chemotherapy added to surgery and radiation for malignant gliomas. The use of this agent was based upon a randomized trial (RTOG -8302) of 467 patients conducted by the brain tumor study group that compared four regimens after initial resection.[24] This study used the arms of semustine (methyl-CCNU), radiation therapy, radiation therapy plus carmustine and radiation therapy plus semustine. The radiation therapy plus carmustine arm had the best survival rate.

More recent randomized trials evaluated various chemotherapy regimens as alternatives to nitrosourea, different RT techniques and pre-irradiation multi-agent

chemotherapy. Several observations in the late 1980s led to the development of independent research strategies for patients with GBM tumors, anaplastic astrocytoma lesions and patients with anaplastic oligodendroglioma (AO), including selective use of brachytherapy, various radiosensitizing agents and the development of a novel statistical approach to patient grouping by prognostic characteristics and survival (recursive partitioning analysis classes). In 2002, a patient-level meta-analysis of 12 randomized trials was published. It suggested modest impact on survival using nitrosourea containing chemotherapy regimens for malignant gliomas (combined HR death=0.85; 95% CI: 0.78-0.91).[25]

In 2005, a large multicenter trial of glioblastoma patients conducted by the EORTC National Cancer Institute of Canada that showed a survival advantage.[26,27] In this landmark study, 573 patients with glioblastoma were randomly assigned to receive standard radiation to the tumor volume with a 2-3 cm margin (60 Gy, 2 Gy per fraction, over 6 weeks) alone or with temozolomide (75 mg/m^2 orally per day during radiation therapy for up to 49 days, followed by a 4-week break and then up to six cycles of five daily doses every 28 days at a dose of 150 mg/m^2 increasing to 200 mg/m^2 after the first cycle). Patients in the combined therapy group were given prophylactic therapy for pneumocystis carinii during the period of concomitant radiation therapy and temozolomide. Overall survival (OS) was statistically significantly better in the combined radiation therapy/temozolomide group (HR for death=0.6; 95% CI: 0.5-0.7; survival at 3 years was 16.0% vs. 4.4%). The oral agent, temozolomide, has since replaced the nitrosoureas as the standard systemic chemotherapy for malignant gliomas. Studies are to determine whether it is the concurrent component or the sequential component of Temozolamide, which is more crucial during the chemoradiation schedule.[28] Table 1 presents the important trials in high-grade gliomas in the context of radiation and chemotherapy.

The optimal treatment strategy for AO tumors is still evolving. Molecular profiling of oligodendrogliomas have shown distinctive genetic patterns characterized by co-deletions of chromosome arms 1p and 19q, MGMT methylation and IDH1 mutations; they are all prognostic factors for patients with AO. Long-term follow-up data of the RTOG 9402 and the EORTC 26951 studies demonstrate clear evidence that for patients with codeleted 1p19q AO, early radiation with chemotherapy offers a significant improvement in overall survival compared with early radiation only, there is benefit even with salvage chemotherapy at tumor relapse, these trials establishes the 1p19q allelic loss as a predictive marker.[13,37] RTOG 9402 shows median survival for 1p19q codeleted patients is 14.7 years compared with 7.3 year in non-codeleted patients with the addition of PCV chemotherapy with radiation establishing the role of addition of chemotherapy in 1p19q codeleted patients with radiation.[13]

Ependymoma is the third most common primary brain tumor in children. Tumors are classified according to the WHO pathological grading system. Prior studies have shown pathological grades are important prognostic factor. Regardless of tumor location or pathological grade, gross total resection (GTR) is associated with a better outcome than subtotal resection (STR). GTR is associated with the lowest rates of mortality, the best overall survival and the longest progression free survival (PFS). However, pathological classification, tumor location and method of treatment play a role in outcomes. Cage *et al*. in a study showed that GTR is associated with the best overall and PFS rates. Patients with WHO Grade II tumors had better overall survival after GTR + EBRT and better PFS after GTR alone. Patients with WHO Grade III tumors had better overall survival after STR + EBRT. Patients with infratentorial tumors had improved overall survival compared with those with supratentorial tumors. Progression-free survival was best in those patients with infratentorial tumors following STR + EBRT. Consideration of all of these factors is important when counseling families on treatment options.[38]

LOCALIZED TUMOUR BED CHEMOTHERAPY

Because malignant glioma-related deaths are nearly always the result of an inability to control intracranial disease (rather than the result of distant metastases), the concept of delivering high doses of chemotherapy while avoiding systemic toxicity is attractive. A biodegradable carmustine wafer has been developed for that purpose. The wafers contain 3.85% carmustine and are implanted into the tumor bed lining at the time of open resection. There have been two randomized placebo-controlled trials of this focal drug delivery method both showed a trend towards OS advantage associated with the carmustine wafers. The first was a small trial closed because of a lack of continued availability of the carmustine wafers after 32 patients with high-grade gliomas had been entered.[39] Although OS was better in the carmustine wafer group (median 58.1 vs. 39.9 weeks; P=0.012), there was an imbalance in the study arms (only 11 of the16 patients in the carmustine wafer group vs. 16 of the 16 patients in the placebo-wafer group had Grade IV

Table 1: Important trials on chemo radiotherapy in high-grade gliomas

Author, year	No. of patients	Histology	Chemotherapy schedule	Radiotherapy	Chemo therapy	DFS	OS
Walker *et al*., 1978[24]	303	AA	Concurrent	50-60 Gy	BCNU	-	Best supportive care 14 weeks BCNU 18 weeks RT-35 weeks RT+BCNU 34.5 weeks
Yamamoto *et al*., 1984[29]	122	GBM/AA	Induction+ concurrent		VCR, ACNU, VM26	-	RT+CT versus RT 1 year 55% versus 43% 2 years 42% versus 23% 3 years 27% versus 7% 5 years 22% versus 5%
Sandberg-Wollheim, *et al*., 1991[30]	171	GBM/AA	Concurrent	WBRT 58 Gy	PCV	-	Concurrent CT-RT versus CT<50 years Median time to progression: 81 weeks versus 21 weeks Median survival: 124 weeks versus 66 weeks>50 years MTP 23 weeks versus 17 weeks MS 51 weeks versus 39 weeks
Fine *et al*., 1993[31]	16 RCTs, 3000 patients	GBM/AA	Concurrent+ sequential			-	10.1% increase in OS with CT at 1 year 8.6% increase in OS with CT at 2 years
Krishnasamy *et al*., 1995[32]	42	GBM/AA	Concurrent+ sequential	45 Gy/25#+ neutron boost 450NcGY/6#	Cont 5 FU and Hydroxyurea×6 day Adjuvant PCV up to 1 year	-	Median survival for GBM 62 weeks (single arm study)
Stewart, 2002[25]	12 RCTs, 3004 patients	GBM/AA	Concurrent and adjuvant	40-60 Gy in 25-35#		-	6% increase in survival with CT at 1 year 5% increase in survival with CT at 2 years
Stupp *et al*., 2005[26]	573	GBM	Concurrent and adjuvant	60 Gy/30#	TMZ 75 mg/m^2 con+150-200 mg/m^2 adjuvant 6 cycles	-	Median survival 14.6 months (with CTRT) versus 12.1 months (RT alone)
van den Bent *et al*., 2006[33]	368	Anaplastic ODG/AOA	Sequential	59.4 Gy/33#	PCVx 6 cycles	23 months versus 13.2 months	40.3 months (RT+CT) versus 30.6 months (RT)
Shibui *et al*., 2012[34]	111	GBM/AA	Concurrent	RT in both arm	ACNU+PCZ versus PCZ	19.5 months versus 19 months	6.2 months versus 6.3 months
Friedman *et al*., 2013[35]	3	GBM	Concurrent and adjuvant	TMZ+ bevacizumab	-	Two patients disease free at 38 months, 49 months	-
EORTC brain tumor group study 26951, 2013 van den Bent *et al*.[36]	368	AO	Adjuvant	59.4 Gy/33	6 cycle PCV	2.6 year versus 1.7 year	4.9 year (RT+CT) versus 4.7 year (RT)
RTOG 9402, 2013 Cairncross *et al*.[13]	291	AA/AOA	Concurrent		PCV		In 1p19q codeleted patients CT+RT versus RT 14.7 year versus 7.3 years In Non-codeleted patients CT+RT versus RT 2.6 years versus 2.7 years

EORTC – European organization for research and treatment of cancer; RTOG – Radiation therapy oncology group; RCT – Randomized controlled trials; AA – Anaplastic astrocytoma; AO – Anaplastic oligodendrogliomas; AOA – Anaplastic oligoastrocytoma; GBM – Glioblastoma multiforme; VCR – Vincristine; ACNU – Nimustine hydrochloride; BCNU – Carmustine or bis-chloroethylnitrosourea; VM26 – Teniposide; PCV – procarbazine; lomustine (CCNU); and vincristine; TMZ – Temozolomide; ACNU+p – Nimustine hydrochloride+Platin; PCZ – Procarbazine; WBRT – Whole brain radiotherapy; RT – Radiotherapy; CT – Chemotherapy, CRT – Chemoradiotherapy; MTP – Median time to progression; OS – Overall survival; DFS – Disease free survival; CTRT – Chemoradiotherapy; ODG – Oligodendroglioma; MS – Median Survival; FU – Follow Up

glioblastoma). The second study was a multicenter study of 240 patients with primary malignant gliomas, 207 of whom had glioblastoma. At initial surgery, they received the carmustine versus placebo wafers, followed

by radiation therapy (55-60 Gy).[40,41] Systemic therapy was not allowed until recurrence, except in the case of AO, of which there were nine patients. Unlike the initial trial, patient characteristics were well-balanced between the study arms. Median survival in the two groups was 13.8 months versus 11.6 months; $P=0.017$ (HR=0.73; 95% CI: 0.56-0.96). A systematic review combining both studies estimated a HR for overall mortality of 0.65; 95% CI: 0.48-0.86; $P=0.003$.[42] However, both these trials had drawbacks including inferior control arms and non-use of temozolomide. These issues and the cost implications of therapy have prevented placement of wafers from becoming standard therapy in GBM's.

SURVIVAL TRENDS FOR HIGH-GRADE GLIOMA OVER THE PAST YEARS IN GENERAL POPULATION

There is some evidence that the survival benefits seen in clinical trials have translated into benefits seen in population-based registries as well. In a relevant study, patients diagnosed between 2000 and 2006 with a GBM who underwent surgery and post-operative RT were selected from the Surveillance, Epidemiology and End Results database. Patients were grouped into time periods: 2000-2001, 2002-2003, 2004 and 2005-2006 (which represented those treated after the EORTC/NCIC trial presentation in 2004). Relative survival (RS) was estimated by the Kaplan-Meier method and Cox multivariable regression modeling was used to estimate proportional HR. Over time, there was improvement in the median and 2 year RS of 12 months and 15% for 2000-2001, 13 months and 19% for 2002-2003, 14 months and 24% for 2004 and 15 months and 26% for 2005-2006 ($P<0.0001$ compared with 2000-2001 and 2002-2003; $P=0.07$ compared with 2004).[43] Table 2 highlights the trials that led to increments in survival.

ELDERLY PATIENT WITH MALIGNANT GLIAL TUMOURS

Most patients with glioblastoma are older than 60 years. Paradoxically, most studies and treatment guidelines are based on trials in patients aged only up to 70 years. Some work addressing elderly patients with high-grade gliomas has been published recently. Of note is a randomized study assessed Temozolomide versus standard 6 week RT versus hypofractionated RT in patients older than 60 years with glioblastoma.[45] Patients treated with temozolomide who had tumor MGMT promoter methylation had significantly longer survival than those without MGMT promoter methylation (9.7 months [95% CI: 8.0-11.4] vs. 6.8 months [5.9-7.7]; HR: 0.56 [95% CI: 0.34-0.93], $P=0.02$), but no difference was noted between those with methylated and unmethylated MGMT promoter treated with RT (HR: 0.97 [95% CI: 0.69-1.38]; $P=0.81$) For all patients who received temozolomide or hypofractionated RT ($n=242$) overall survival was similar (8·4 months [7.3-9.4; $n=119$] vs. 7.4 months [6.4-8.4; $n=123$]; HR: 0.82, 95% CI: 0.63-1.06; $P=0.12$) Another randomized study reconfirmed that temozolomide alone is non-inferior to RT alone in the treatment of elderly patients with malignant astrocytoma. MGMT promoter methylation seems to be a useful biomarker for outcomes by treatment and could aid decision-making.[46]

Table 2: Important landmark trials that contributed in evolution of treatment strategy in GBM

Year	Landmark trial	New standard of care	Increment in OS
1980	Walker, *et al.*[24]	Radiotherapy with nitrosoureas	Modest increase in survival with addition of carmustine with radiation
1991	Bleehen and Stenning (UK MRC)[18]	60 Gy radiation dose better than 45 Gy	3 months increment in survival
2001	Lacroix, *et al.*[44]	Extent of resection important prognostic factor	13 months versus 8.8 months median survival in>98% resection versus<98% resection
2002	Stewart: Systematic review and meta-analysis[25]	Addition of chemotherapy to radiation	15% relative decrease in the risk of death. Absolute increase in 1-year survival of 6%
2003	Laws, *et al.*[15]	Resection	Resection rather than biopsy improves survival
2005	Stupp *et al.*[26]	Surgery followed by concurrent and adjuvant chemoradiation with temozolomide	Median survival improved by 2.5 months
2009	Stupp, *et al.*[26]	Surgery followed by concurrent and adjuvant chemoradiation with temozolomide	16.3% improvement in OS at 2 years
2013	Cairncross, *et al.* (RTOG 9402)[13]	In 1p19q codeleted AO/AOA adding chemotherapy to radiation benefits	Median survival 14.7 years as compared to 7.3 years

AA – Anaplastic astrocytoma; AO – Anaplastic oligodendroglioma; AOA – Anaplastic oligiastrocytoma; GBM – Glioblastoma multiforme; OS – Overall survival

TREATMENT OPTIONS PRESENTLY UNDER CLINICAL EVALUATION

In view of the overall dismal outcome of high-grade gliomas, further research in developing RT and chemotherapy practices is needed. Heavy particle

radiation, such as proton beam therapy, carries the theoretical advantage of delivering high doses of ionizing radiation to the tumor bed while sparing surrounding brain tissue. The available data for this technique are preliminary. Novel biologic therapies under clinical evaluation for patients with brain tumors include Dendritic cell vaccination, Tyrosine kinase receptor inhibitors, Farnesyltransferase inhibitors, Viral-based gene therapy, Oncolytic viruses, Epidermal growth factor-receptor inhibitors, Vascular endothelial growth factor inhibitors and other anti-angiogenesis agents.[47-49]

To summarize, treatment of malignant gliomas of the brain has evolved from surgery predominant approaches to approaches including radiation and chemotherapy in the adjuvant treatment.

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