

Symposium

Therapy for glioma: Indian perspective

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Abstract

Central nervous system (CNS) are rare neoplasms with considerable heterogeneity and variation. The most common primary lesions of CNS are gliomas. A majority of the data about the demography and management of gliomas has emerged from the west. However, there may be considerable variation in the presentation, behavior, and response to treatment between patients in the western world and the Asian population. This article discusses gliomas with special reference to data from oncology centers in India.

Key words: Central nervous system, gliomas, treatment

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Introduction

Tumors of the central nervous system (CNS) are rare neoplasms constituting 1-2% of all malignancies.^[1] Depending upon the age, histology, and site in the CNS, these tumors have varied presentations and contrasting clinical outcomes.^[2,3] Among CNS neoplasms, gliomas are the most common tumors. These tumors include astrocytomas, oligodendrogliomas, and ependymomas. Most of the literature in epidemiology, molecular features, and management of gliomas has emerged from the west. 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.^[4]

Hence, the interpretation and results from developed countries cannot be applied directly to developing countries. This article addresses this issue with the available evidence from the oncology centers in India.

Epidemiological aspects

The cancer registration system of developing and developed countries is different. There are dedicated cancer registries in most of the developed world to document all cases and thus a prospective database is available for comparison.^[5,6] In contrast, most of the epidemiological data in India is based on population-based cancer registries, which represent only a small proportion of the population. The situation is even

more difficult for the less common CNS tumors. Epidemiological information about these tumors in India, therefore, has mainly been based on reports from individual centers.

A prospective study from the Tata Memorial Hospital provided a one-year demographic data and relevant tumor-related information on all 656 patients registered in the Neuro-oncology Clinic.^[7] Astrocytomas were the most common primary tumors. Gliomas constituted 38.7% (254 cases) of CNS tumors, with high-grade gliomas comprising 151 (59.5%) and low-grade gliomas 79 (33.1%) cases. Pilocytic astrocytoma was seen commonly in children. Among the 19 oligodendrogliomas, 12 cases were grade-II and seven were anaplastic. Most of these tumors were seen in middle-aged males. Ependymomas presented either with posterior fossa mass or as a spinal tumor. Most of the cases were below 18 years of age (43.5%). All spinal ependymomas were grade-II, whereas, eight intracranial ependymomas were of anaplastic histology. Eighteen patients presented with clinical and radiological signs of brain stem glioma. To be specific, the median age of presentation of pilocytic, fibrillary and, anaplastic astrocytomas, and glioblastomas were 16, 35, 36, and 50 years as compared to the corresponding values of 23, 33, 49, 62 years recorded in developed countries.^[8] One reason for this could be that the average life span of people in developing countries is generally shorter than those living in the developed countries. For instance, the average life expectancy in India is 62 years for men

and 63 years for women, whereas, it is 73 and 79 years, respectively, in developed countries.^[9] This can explain the relatively lower proportions of high-grade gliomas when compared to the western data (16 vs. 23%).

Molecular studies

The concept of different genetic pathways leading to glioblastoma multiforme (GBM) has gained considerable acceptance. Two major groups are now described — primary or *de novo* GBM and secondary GBM. Primary GBMs occur in elderly patients and are characterized by mutation in the phosphate and tensin homolog gene (PTEN) and the epidermal growth factor receptor (EGFR). Secondary GBMs are a feature of a younger population and have p53 and *platelet-derived growth factor* (PDGF) mutations. A study evaluated the genetic alterations in 30 pediatric GBM cases (age ≤ 18 years) with immunohistochemical staining for p53, p16, and p27 protein expression, EGFR alterations, and PTEN deletion.^[10] Although EGFR protein overexpression was noted in 23% of the cases, the corresponding amplification of the EGFR gene was rare (5.5%). Deletion of the PTEN gene was also equally rare (5.5%). One case showed polysomy (chromosomal gains) of chromosomes 7 and 10. Loss of p16 and p27 immunoexpression was observed in 68 and 54% of the cases, respectively. In pediatric *de novo* / primary GBMs, deletion of PTEN and EGFR amplification were rare, while p53 alterations were more frequent as compared to primary adult GBMs. Frequency of loss of p16 and p27 immunoexpression was similar to their adult counterparts. This suggested that pediatric malignant gliomas were distinctly different from adult GBMs, highlighting the need for the identification of molecular targets that could be adopted for future novel therapeutic strategies.

Another study assessed for the possible existence of molecular pathways, to determine whether there was any correlation between these different variants and clinical parameters, such as, age, duration of symptoms, and outcome.^[11] Immunophenotyping was performed to study the simultaneous expression of the p53 protein and EGFR in 58 cases of adult supratentorial GBMs. By this method, four variants of GBM could be distinguished: 34% were p53 positive only, 38% were EGFR positive only, 14% were double negative (p53 negative / EGFR negative), and 14% were double positive (p53 positive / EGFR positive). Interestingly, all nine cases of secondary GBM, in which there was clinical and histological evidence of progression from a pre-existing low-grade lesion, were p53 positive. Differences were observed with regard to the age distribution of the four variants, in that the

p53 negative / EGFR negative tumors occurred most frequently in the younger age group (21 - 40 years). In the elderly group (61 - 80 years), two-thirds of the tumors were p53 negative / EGFR positive primary GBMs, and no case of a double positive or double negative variant was encountered. The differences in duration of symptoms and symptom-free survival according to age group and genetic subset were not statistically significant. There were no differences in outcome within each age category for any GBM variant, although the longest mean symptom-free survival was noted among patients aged between 41 and 60 years, with a p53 positive / EGFR negative variant.

Clinical data

No study regarding the long-term clinical outcome of low-grade gliomas has been published from an Indian center. There, however, exist many reports about the outcome of patients with GBM. As established from western data, the cornerstone of the management of these tumors has been surgery, followed by postoperative radiotherapy. Temozolomide (TMZ) is an oral alkylating agent with considerable antitumor activity in brain tumors. Concomitant TMZ along with radiotherapy (RT) followed by six cycles of adjuvant TMZ has become the standard treatment in such patients, following a randomized European and Canadian trial, which demonstrated a significant improvement in the median and two-year survival in patients receiving or not receiving TMZ.^[12] However, it is of interest to assess if the same results can be replicated in clinical practice in the Indian context.

A study reported the experience with concomitant and adjuvant TMZ with RT in patients with newly diagnosed GBM.^[13] Forty-two newly diagnosed histopathologically proven patients with GBM underwent treatment as per the Stupp's protocol. The patients were 13 - 69 years of age with a median age of 49.5 years (31 males, 11 females). Fifty percent of the patients underwent a gross total resection of tumor, 43% had partial resection, and 7% an open or stereotactic biopsy only. Fifty-three percent of the patients had a postoperative Karnofsky Performance Score (KPS) of 60 - 80%. All patients received concomitant radiation and TMZ, with 74% of the patients completing six cycles of adjuvant TMZ. At a median follow-up of 12.5 months, the one- and two-year survival was 67 and 29%, respectively. The median overall and progression-free survivals were 16.4 and 14.9 months, respectively. Patients with pretreatment KPS of 480% had significantly better overall survival as compared with those having KPS of 80% (median survival 22.12 vs. 11.97 months; $p=0.026$). Treatment

was generally well tolerated with 9% of the patients developing grade 3 anemia, 2% grade 3 leucopenia, and 7% grade 3 or 4 thrombocytopenia, respectively, during the treatment. This analysis confirmed the good overall tolerability to TMZ in the Indian population, both in the concomitant and adjuvant settings and concurs well with that in the published literature.

In another study, patients with a histopathological diagnosis of GBM, treated at a single institution, were analyzed.^[14] After surgery, pts were planned for postoperative RT to a dose of 60 Gray (Gy) in 30 fractions, in six weeks, with concurrent chemotherapy (CT), with either TMZ 75 mg/m² PO daily for six weeks or Paclitaxel (PT) 60 mg/m² i/v weekly with RT or Carboplatin (CB) 150 mg i/v weekly with RT. Patients treated with TMZ were planned for further adjuvant TMZ as per Stupp protocol. 110 patients were included in the analysis. Two patients receiving TMZ had grade 4 thrombocytopenia. Both recovered and there were no treatment-related mortalities. At a median follow up of 31 weeks (range 7-157, mean 38 weeks), 72 (66%) patients were evaluated for response. Of these, 43 patients had progressive disease, 18 had complete response, 10 had partial response, and 1 patient had stable disease. The median time to progression was 32 weeks (range 11-90 weeks)

In yet another trial, 47 patients with newly diagnosed GBM, treated with Stupp regimen, were assessed.^[15] The median overall survival was 17 months. Multivariate analysis revealed that an age of 60 years or older ($p < 0.03$), a postoperative performance score ≤ 70 ($p = 0.04$), non-total tumor resection ($p = 0.03$), tumor size > 4 cm ($p = 0.01$), time interval between surgery and RT ($p = 0.03$), and proliferation index overexpression ($p = 0.001$) were associated with a worse prognosis.

Nimotuzumab is a Humanized Monoclonal Antibody with Anti EGFR Activity.^[16] A multicentric trial is assessing the safety and efficacy of Nimotuzumab "An open Label, Prospective, Multicentric Study to Evaluate the Safety and Efficacy of BIOMAb - EGFR TM (Nimotuzumab) as Induction and Maintenance Therapy in Combination with Radiotherapy Plus Temozolamide (concomitant and adjuvant)." This study is presently being conducted in various oncology centers in India and the results are awaited.

Lonidamine (LND) is an indazole carboxylic acid that has been shown to be synergistic with RT in tissue culture and animal models. Clinical experience has shown that LND is well-tolerated drug. A study assessed the combination treatment of TMZ and LND to see the increase in radiation response of

malignant human brain tumour cells *in vitro*.^[17] The effects of continuous treatment for two days on proliferation response and cytotoxicity were studied after trypsinization, by cell count and uptake of trypan blue dye (0.5%). For the study of radiation ((60)Co-Gamma-rays, 2 Gy) response, the drugs were removed 4 hours after irradiation and cultures were grown further in a drug-free, normal growth medium for another 20 hours or 44 hours. The continuous presence of TMZ or LND for two days significantly inhibited cell proliferation in a concentration-dependent manner. Post-irradiation presence of either of these drugs for 4 hours significantly reduced the proliferation response, 24 and 48 hours after treatments. This suggested that combination of TMZ and LND at clinically achievable, low-plasma concentrations could inhibit tumor growth, and LND could reduce the dose of the temozolamide required for radiosensitization of brain tumors. This study is important for developing countries in view of its potential as a resource sparing, low-cost option in GBMs.

Recurrent gliomas bear an even more dismal outcome than primary lesions. Of late, however, newer agents such as Bevacuzimab (Aniti VEGF) and Irinotecan have been tested in recurrent gliomas. A study tested Bevacizumab (Avastin) Plus Irinotecan in a Phase II setting, in recurrent GBM patients. Seventeen patients received Avastin 10 mg/kg plus CPT -11 125mg/m² q for two weeks. Four patients had a complete response (CR), seven had partial response (PR) / stable disease, and six patients progressed. Based on the promise shown by Bevacuzimab in the western data, it is soon going to be tested in a Phase III trial in GBM, upfront along with RT + TMZ (RTOG)

Brainstem tumors represent 10% of the CNS tumors, accounting for 30% of the pediatric posterior fossa tumors. These tumors are intractable, with most patients having relentless progression of the disease, and therefore, a dismal outcome. In view of their location, most of the lesions are not operable and RT remains the cornerstone of therapy. Various approaches tried in these tumors include use of chemotherapy and altered RT schedules, but all have reported uniformly dismal outcomes.^[18]

A study performed the clinicopathological correlation of 45 cases of brain stem gliomas and determined the occurrence and prognostic significance of p53 expression.^[19] Thirty patients were diagnosed by surgical biopsy and 15 at autopsy. In 25 cases p53 immunohistochemistry (Avidin Biotinylated technique) was performed. Fifty-one percent of the gliomas were observed in the first decade of life. Diffuse astrocytomas

were seen in 40 cases (5% were Grade I, 47.5% Grade II, 32.5% Grade III, and 15% Grade IV) and pilocytic astrocytomas in five cases. Grade IV patients had 2-3 mitoses /10 high-power fields and had a poorer survival rate. Grade II astrocytomas were treated with excision and RT, while grade III and IV tumors were treated with RT and chemotherapy (CCNU). Improvement was noted in 20% of the patients, postoperatively. The outcome was better in patients who were treated surgically.

In a prospective study, pediatric patients with newly diagnosed pontine gliomas were treated with focal RT to a dose of 54 Gy / 30 fractions, along with concurrent daily TMZ (75 mg/m², day 1 - day 42). Four weeks after completing the initial RT + TMZ schedule, adjuvant TMZ (200 mg/m², days 1-5) was given every 28 days, to a maximum of 12 cycles. Response was evaluated clinically and radiologically with magnetic resonance imaging (MRI) and positron emission tomography (PET) scans. At the time of analysis, 19 patients died due to disease progression and one patient was alive with progressive disease. The median overall survival and progression-free survival was 9.15 months and 6.93 months, respectively. As admitted by the authors themselves, this was not better than the results generally known historically and through previous experiences.^[20,21]

Quality of life issues

With improving treatment modalities, the survival of patients has improved. Issues such as quality of life have therefore become more important in contemporary neuro-oncology practice.^[22] However, deterioration in the quality of life can be because of surgery, radiotherapy, medication, and tumor itself. A study prospectively assessed the activities of daily living (ADL) in young patients with low-grade gliomas treated with stereotactic conformal radiotherapy (SCRT), in 38 children and young adults (age 5-25 years, median 12.5 years) with low-grade gliomas.^[23] The mean of the total modified Barthel's ADL score (Barthel's Index, BI) at baseline, before starting SCRT, was 94.5 (standard deviation 14.8, range 45-100). At the two-year and three-year follow-up, mean BI was 97.1 and 99, respectively. On follow-up, maximum improvement in individual BI was seen in the ambulation-related domain in patients with impaired visual function ($P = 0.027$), low KPS ($P = 0.015$), and age less than 13 years ($P = 0.103$). The mean pre-radiotherapy baseline BI of three patients, who eventually developed local recurrence, was only 64 (SD 32.1) as compared with a baseline score of 97.18 seen in patients whose tumor remained controlled at follow-up ($P = 0.001$). Young patients

with low-grade gliomas after surgical intervention had a lower than normal BI before starting RT, suggesting a decrease in ADL possibly due to tumor- and surgery-related factors. At the two-year and three-year follow-up after SCRT, there was no further decrease in mean BI. A significant improvement in BI was seen in visually handicapped patients, patients with poor performance status, and younger patients.

To summarize, there are limited studies addressing the demography, clinical features, and outcome in gliomas, in the Indian context. For gliomas, the demographic trend in Indian data as compared to the west is revealing. However, as far as disease management and outcome is concerned, the results are in close concurrence with the reported western data in terms of disease-free and overall survival outcomes.

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