

Predictive and Prognostic Molecular Factors in High Grade Gliomas

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Abstract: Gliomas are the most common primary brain tumor in adults. In addition to the histological grade, knowledge at the molecular level of these tumors is important in the management of these tumors. 1p/19q-codeletion is an important molecular factor seen in oligodendroglial grade tumors and also confers a favorable prognosis as well as predicts good response to chemotherapy and radiotherapy. IDH mutation also helps in better prognosticating patients with grade III gliomas. Patients of glioblastoma with methylated MGMT promoter, confers a survival advantage when treated with temozolomide and thus acts as a predictive marker. These various molecular factors help's not only in prognosticating glioma patients but also aids in tailoring treatment.

Keywords: Molecular factors; high grade gliomas.

INTRODUCTION

Gliomas are the most common primary brain tumor in adults. The clinical spectrum of this disease ranges from grade I gliomas including pilocytic astrocytoma [with a median survival of over 20 years] to the highly fatal Glioblastoma with a median survival of 12 to 14 months [1]. Histopathological grading of gliomas is based on the WHO system which takes into account 4 factors for grading of these tumors namely nuclear atypia, mitoses, endothelial proliferation and necrosis.

With the knowledge at the molecular level of these tumors and their correlation with clinical outcomes has brought a second thought in the scientific community whether the pure histological classification of these tumors is sufficient or not. This is of importance because the although anaplastic gliomas generally have a poor survival outcome than LGG's, but when other molecular factors are taken into consideration the anaplastic oligodendroglomas with 1p19q co-deletion treated with adjuvant chemoradiotherapy has definitely a better survival outcome than many grade II gliomas. In this era of transformation to personalized medicine it is important to take these factors also into consideration before prognosticating and treating these patients.

Prognostic factors are those factors which influence the outcome of patients irrespective of treatment while predictive factors are those which predict a response to a particular intervention. In this review we would like to review the various predictive and prognostic factors other than grade of gliomas and their importance in management of these tumors.

Anaplastic (Grade III) gliomas

The WHO grade III gliomas include anaplastic astrocytoma and anaplastic oligodendroglomas. The terminology of anaplastic oligo-astrocytoma is no more

used and the tumors with mixed features are either classified as anaplastic astrocytoma or anaplastic oligodendroglomas depending on the 1p and 19q co-deletion [2]. The astrocytic tumors are associated with mutated TP53, while the oligodendroglial tumors are associated with 1p/19q co-deletion.

The p53 gene, called the “guardian of the human genome” is a tumor suppressor gene located on the short arm of Chromosome 17 [3]. The p53 gene alterations are very important in the initiation, recurrence and progression of grade III astrocytic tumors. Nayak *et al.* reported 53.8% incidence of p53 protein positivity in anaplastic astrocytomas [4]. Many studies have found mutual exclusion between 1p and 19q co-deletion and p53 [5]. The gene alterations of TP 53 being more common in astrocytoma histologies and mutual exclusion with 1p and 19q co-deletions make it a poor prognostic factor. It was not found to be a significant predictive factor for any treatment modality.

1p/19q-codeletion is an important molecular factor seen in oligodendroglial grade III tumors and may assist in the characterization of tumors with oligodendroglial phenotype [6]. Shukla et al in a study of 43 cases found that 1p and/or 19q co-deletion was seen in 65% (13/20) of oligodendroglomas, while astrocytic tumors are more likely to show p53 over-

expression (57.1%). P53 expression and 1p/19q status was found to be mutually exclusive in many studies [7]. In another study by Singh *et al.* 1p and 19q co-deletions were seen in 72.7% of oligodendrogliomas [8].

1p/19q-codeletion has been shown to be a positive prognostic factor and a positive predictive factor for chemotherapy. The RTOG 94-02 trial by Cairncross *et al.* had evaluated the role of chemoradiotherapy for anaplastic oligodendroglioma [9]. The trial included 291 patients who were randomized to PCV chemotherapy plus radiotherapy vs. radiotherapy alone. On analysis of the data, he found that patients with co-deleted 1p/19q status had a better overall survival than non co-deleted patients. It was found that by addition of chemotherapy in co-deleted patients the median survival almost doubled from 7.3 years to 14.7 years. The EORTC 26951 trial by van den Bent *et al.* also addressed the same issue of adjuvant chemotherapy in anaplastic oligodendroglioma [10]. The trial included 368 patients who were randomized to radiotherapy alone vs. radiotherapy plus 6 cycles of PCV chemotherapy. The trial had concluded that addition of chemotherapy is beneficial in terms of overall survival in anaplastic oligodendroglioma and the benefit is more in 1p/19q-codeleted tumors. These two phase III trials confirmed the prognostic and predictive significance of 1p/19q-codeletion and it must be done in all grade III tumors.

In a study by Wang *et al.* involving 1305 patients, it was found that IDH 1 mutation was generally seen in patients with 1p/19q-codeletion whereas IDH mutation was extremely rare in gliomas with EGFR amplification [11]. The IDH1 mutation represents 90% of all IDH mutations. IDH1 mutations are associated with astrocytic tumors whereas IDH2 mutations are associated with oligodendrogliomas. The analysis of data of this trial revealed that presence of IDH mutation confers a positive prognosis to the patient with a hazard ratio of 0.358 for overall survival which was statistically significant. Zhang *et al.* also reported his data of 203 anaplastic glioma patients in which he found that anaplastic oligo-astrocytoma and astrocytoma patients with IDH gene mutation showed similar prognosis with anaplastic oligodendroglioma patients with wild-type IDH gene [12]. Stratification of grade II-III gliomas into subsets by the presence or absence of IDH mutation helps in better prognosticating these patients [13].

Studies have also shown that polymerase epsilon gene mutations to be associated with high grade gliomas and its presence is associated with an improved prognosis in these patients [14]. Thus it is very important to do a molecular analysis in these patients in that it not only sub group's grade III tumors but also provides valuable prognostic and predictive factors which will help in better managing these patients.

Grade IV gliomas

The WHO grade IV tumors include Glioblastoma [GBM], Gliosarcoma, and Glioblastoma-O [Glioblastoma with oligo-dendroglial differentiation]. The Glioblastoma-O [GBM-O] occurs more in younger patients compared to other forms of and has a higher frequency of IDH1 mutations and had a lower frequency of PTEN deletions. The GBM-O is also associated with higher survival than that of other GBMs [15]. The glioblastoma can be further sub divided into primary and secondary glioblastoma. The primary GBM is characterized by over expression of EGFR while secondary GBM is characterized by IDH1 mutation, 1p/19q-codeletion and over expression of TP-53 [16]. Most of the cases of GBM may be primary but prognosis is better for patients with secondary GBM [17].

Epidermal Growth Factor Receptor (EGFR) gene over expression occurs in about 50% of the cases of GBM [18]. Newcomb *et al.* when analyzed the survival of 80 patients with GBM, could not find any association between survival and altered expression of p16, p53 and EGFR [19]. Similar to the results in grade IV gliomas IDH 1 mutation is associated with significantly longer progression free survival and overall survival than patients with wild-type IDH1 in GBM [20].

The Stupp *et al.* trial had shown that addition of temozolomide to radiotherapy improves median survival of GBM patients from 12.1 months to 14.6 months and two year survival from 10.4 percent to 26.5 percent [1]. But whether the addition of temozolomide [TMZ] to radiotherapy gives survival benefit to all patients of GBM was unanswered. MGMT is DNA-repair gene and its promoter methylation is associated with longer survival in patients of glioblastoma who receive alkylating agents. Hegi *et al.* did MGMT methylation study in 206 patients in the trial correlated it with benefit of adding temozolomide in these patients [21]. Patients with methylated MGMT promoter, a survival benefit was observed in patients treated with temozolomide and radiotherapy [median survival was 21.7 months vs. 15.3 months]. But no statistically significant difference in overall survival was obtained by adding temozolomide in patients who are not MGMT methylated, though PFS was better by adding TMZ. Iaccharino *et al.* also found that MGMT promoter methylation has a favorable impact on clinical outcomes in patients with GBM [22]. MGMT promoter methylation has also been tested in Indian patients and was found to be positive in 62% of the patients and MGMT methylation was slightly higher in GBM-O subgroup [60% vs. 71%] [23]. But some researchers have also questioned the prognostic value of MGMT in GBM but may be due to small sample size they have used [24].

Yang *et al.* did a metaanalysis, which involved 50 clinical trials and 6,309 patients to evaluate the role of MGMT in glioblastoma [25]. GBM patients with MGMT promoter methylation had longer OS with a HR of 0.524 by univariate analysis and 0.427 by multivariate analysis. Zhang *et al.* also did a metaanalysis which involved 30 clinical trials and 2,986 patients to evaluate the role of MGMT in glioblastoma [26]. The metaanalysis had concluded that MGMT promoter methylation was associated with better progression free and overall survival in patients with GBM regardless of therapeutic intervention. Thus MGMT methylation has emerged as a prognostic marker and a predictive marker for response to temozolomide in patients with GBM [27].

Epithelial cell transformation sequence 2 (ECT2) is another marker that has been found in high grade gliomas and is important in cancer invasion and progression [28]. In a study by Cheng *et al.* it was found that expression of ECT2 is correlated with WHO grading and gave an unfavorable survival for these patients. LOH 10q is another genetic abnormality in GBM, is more frequently in older adults [29]. Its presence is associated with shorter survival in patients with GBM. HOXA9 target genes are another group of genes found in GBM with key roles in cell proliferation, DNA repair, and stem cell maintenance. Its expression is associated with poor prognosis and was shown by Pojo *et al.* in a study involving more than 600 patients and its expression was associated with temozolomide resistance [30]. Similarly Meng *et al.* had reported that N-myc interactor was very important in tumorigenesis of GBM and was associated with unfavorable prognosis in GBM [31]. TERT promoter mutations also are a bad prognostic factor and indicate a worse course of disease in GBM patients [32].

The expression of Enhancer of Zeste Homolog 2 (EZH2) expression and Tectonic family member 1 (TCTN1) in GBM have been shown to be associated with poor outcomes [33, 34]. Brett-Morris *et al.* has also reported that Spermidine/spermine N1 acetyltransferase 1 (SAT1) which is an enzyme involved in polyamine catabolism and its expression in GBM leads to radio resistance of these tumors [35]. Over 50 genes that have been identified to be associated with GBM and rare cases of genetic predisposition for GBM have been reported [36]. Researchers are also trying to develop genetic signatures that are used in prognosticating patients with GBM better [37, 38]. The development of these molecular signatures and further validation in clinical trials may not only help in prognosticating these patients in future but also in tailoring treatment for these patients.

CONCLUSION

We must go beyond the histological grading of gliomas as it helps in better understanding of disease process and natural history. There are various molecular

prognostic factors that help's in prognosticating the glioma patients in addition to the grade and clinical features. There are also various predictive molecular that aids in tailoring treatment based on an individual basis. These molecular classifications must be taken into account when further revision of WHO grading is done as in some cases is more accurate in prognosticating the patient than grade of the tumor. It is also important that we use this data in future clinical trial designs to optimize the outcome of glioma patients.

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