Glioblastoma (GBM) is the most common and most aggressive type of primary brain tumour in adults. It represents 54% of all gliomas and 16% of all brain tumours (Ostrom et al. 2016). Despite surgery and treatment with radiotherapy plus an oral alkylating agent, temozolomide (TMZ), tumours invariably recur, and the patient survival is an average of ~14–16 months. In this review we summarise the current understanding of multiple factors that may affect survival of patients with GBMs. In particular, we discuss recent advancements in surgery and detection of genomic-based markers with prognostic values, such as IDH1/2 mutations, MGMT gene promoter methylation, and TERT gene promoter alterations. We address the issue of tumour heterogeneity and evolution that may result in different parts of the same tumour exhibiting different GBM subtypes and in subtype switching, which may restrict the usefulness of the expression-based classification as a prognostic marker before relapse. The determinants of long-term survival in patients with IDH1/2 wt GBM, beyond MGMT promoter methylation, remain to be identified, and even the absence of both IDH1/2 mutations and MGMT promoter methylation does not preclude long-term survival. These findings suggest that host-derived factors, such as immune system responsiveness may contribute to long-term survival in such patients. We report the results of high-throughput approaches, suggesting links between long-term survival and enhanced immune-related gene expression. The further search for new gene candidates, promoter methylation status, and specific features of host immunity should provide prognostic biomarkers for the evaluation of survival of IDH1 wild-type/non-G-CIMP GBMs.

Key words: glioblastoma, immunology, long-term survival, IDH, MGMT, TERT, evolution surgery.

Introduction

Glioblastoma (GBM) is the most common and most aggressive type of primary brain tumour in adults. It represents 54% of all gliomas and 16% of all brain tumours [1]. Therapeutic options are narrow and consist of surgery and treatment with radiotherapy plus an oral alkylating agent, temozolomide (TMZ). Despite the benefits from radiotherapy/TMZ treatment, the patient survival is an average of ~14–16 months and tumours invariably recur, leading to a fatal outcome.

Despite many efforts, the prognosis for this type of cancer is still very poor and practically unchanged since 2000, when temozolomide [2, 3] was introduced into clinical practice. Despite many efforts, in patients undergoing aggressive treatments, progression-free survival (PFS) is 7–8 months, median survival is 14–16 months, and 5-year overall survival (OS) is 9.8% [4, 5]. Despite the poor prognosis, some patients manage to survive for a relatively long time, which is of interest to both clinicians and researchers. In the case of glioblastoma, long-term survivors are often defined as patients who have survived for more than 2 years after diagnosis [6] and a small fraction of GBM patients (9.8%) survive for exceptionally long periods. Studying the clinical and molecular characteristics of these rare instances of long-term survival (LTS) among GBM patients may provide insights into both GBM pathobiology and help to identify potential new prognostic biomarkers.

Surgery and new surgical approaches

Aggressive infiltration of the brain parenchyma by glioblastoma cells makes tumour resection a real challenge for physicians and, at present, prevents complete cure. Surgical treatment, albeit of great importance, is not sufficient and fully effective due to the fuzzy boundary between tumour and healthy tissue, and patient safety during the surgery. However, among other positive prognostic factors, such as age at diagnosis, the patient’s wellbeing, tumour histologic type and its genetic profile, surgical treatment and its extent is the only one which can be directly influenced. Complete macroscopic tumour removal (gross total resection, GTR) in comparison to subtotal removal or biopsies statistically prolongs PFS as well as OS in both low-grade (> 120 months with GTR vs. 56 months if STR or 23 if no treatment was undertaken) [7] and malignant gliomas, including gliosarcoma, where survival after GTR is increased up to 20 months (8.8 months with no GTR) [8–10]. The subtotal resection unfortunately has a comparable impact on the OS as the execution of the brain biopsy alone and results in poor prognosis [11]. In the case of sub-total resection of the tumour during primary surgery
or its relapse, extension of the resection during secondary operation is associated with an increase in OS to a level comparable to the time when GTR was achieved at the time of first surgery (18.5 months and 9.7 months) [12, 13]. Typically, GBM presents as a solitary lesion. Nonetheless, multiple synchronous lesions are present in 0.5 to 20% of cases. It has been shown, that surgery targeting all lesions amenable for resection gave similar outcomes to matched cases of unifocal GMB [14].

According to the generally accepted definition, total tumour removal is achieved when neuroimaging studies confirm complete removal of contrast-enhancing regions or hyperintensive T2/FLAIR regions [15]. In order to maximise surgical resection, intraoperative MR imaging, intraoperative ultrasonography and intraoperative tumour staining can be used to maximise surgical resection [16]. Combined with the awake surgery and eloquent brain mapping the complete glioma resection is up to 96% [17]. Without the use of advanced imaging techniques, total tumour removal was achieved on average only in 68% of patients [18]. A randomised, controlled, multicentre trial has shown that fluorescence-guided resection with use of 5-ALA was superior to white light resection both in terms of GTR (65 vs. 35%) and 6-month PFS (42 vs. 21%) [19]. There is a growing number of other fluorescent agents, including ones targeting EGFR, PPARPs, or integrins, which could be utilised for research or clinical purposes in the future [20]. Retrospective analysis of resected tumours has shown that gliomas harbouring IDH mutations are more amenable for surgical treatment, thus having a better prognosis after maximal surgical excision [21].

Genomic correlates of better survival and response to chemotherapy

Chemotherapy of brain tumours has limited options due to poor penetration of drugs through the blood-brain barrier. High cellular and genomic heterogeneity of glioblastoma is an additional obstacle that significantly limits therapeutic options [22]. Despite the failure of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, EGFR remains a dominant molecular alteration in GBM subtypes and represents a promising target, with various targeting drugs, including vaccines, antibody drug conjugates, and chimeric antigen receptor (CAR) T cells. Immune therapies under investigation include checkpoint inhibitors, vaccines against tumour-associated antigens and tumour-specific antigens, activated dendritic cells, heat shock protein-tumour conjugates, and CAR T cells [23]. So far, these approaches have failed to result in the successful application of targeted therapies, and chemotherapy with DNA damaging drugs remains the main option. Standard treatment is maximal tumour resection followed by 6-week chemoradiotherapy (60 Gy + temozolomide 75 mg/m²). Hydrochlorothiazide is then used for a minimum of 6 months (150-200 mg/m² for 5 days every 28 days) [24].

Methylation of the MGMT gene promoter

Promoter methylation of the O(6)-methylguanine-DNA-methyltransferase (MGMT) gene has been considered a prognostic marker and has become more important in the treatment of glioblastoma. MGMT is a DNA repair protein that removes alkyl groups from the guanine O6 position. When MGMT promoter is methylated, the protein is not present and cells tend to be more sensitive to alterations induced by alklylation, which leads to cell death by apoptosis [25]. Response to treatment with alkylating agents (temozolomide or carmustine for glioblastoma) is dependent on the methylation state of the MGMT gene promoter [26]. This translates into a clinical effect — survival of patients with methylated MGMT promoter treated with TMZ was significantly higher (21.7 months) compared with patients with non-methylated MGMT (15.3 months) [27]. Interestingly, MGMT promoter methylation was statistically significantly related to survival over 3 years, but was no longer significant in patients who survived 5 years or more [28]. Surprisingly, MGMT gene methylation is prognostic but not predictive of response to TMZ chemotherapy in anaplastic glioma [29]. These results can be explained either by the fact that MGMT methylation is associated with an otherwise positive prognostic factor, IDH1/2 mutation in the anaplastic gliomas. Moreover, loss of chromosome 10, occurring in the majority of GBM cases, leads to an absolute lack of MGMT function.

IDH1/2 mutations

Isocitrate dehydrogenase (IDH1/2) mutations are found in nearly 70% of low-grade gliomas [30] and around 12% of glioblastomas [31]. Mutations in IDH1/2 are associated with an excessive methylation of the genome which results in glioma-specific CpG island methylator phenotype (G-CIMP) [32]. IDH mutations are linked to cellular metabolic changes [32, 33] and production of 2-hydroxylglutarate, an oncometabolite, which when accumulated leads to inhibition of DNA demethylase TET2 and altered DNA methylation [34], inhibition of proline hydroxylases, induction of ROS (reactive oxygen species) by decreasing NADPH level in the cell [35], aberrant chromatin conformation due to enhanced histone methylation [36, 37] and induction of HIF-1 mediated angiogenesis [38]. So far, attempts at predicting tumour IDH1/2 status, based on detection of 2-hydroxyglutarate (2-HG) in serum, have failed. 2-HG concentration in serum from patients with gliomas does not correlate with IDH1/2 mutation status or tumour size [39]. Irrespectively, magnetic resonance spectroscopy peak at 2.25 ppm was shown to strongly correlate with IDH1/2 mutation and 2-HG concentration in resected specimens [40]. IDH mutations are commonly associated with MGMT promoter methylation as a part of the specific methylation phenotype (79% of G-CIMP vs. 46% for non-G-CIMP) [41]. IDH1/2 mutation demarcates oligodendroglioma, astrocytoma, and secondary GBM from primary GBM and lower-grade gliomas with biology similar to GBM. The effect on long-term survival was directly related to the presence of mutations in IDH1/2 genes [42]. IDH1/2 mutated tumours were more frequently unilobar lesions. In contrast, IDHwt lesions were more prone to occur in the brainstem and in multiple lobes and were significantly more often found in a location bearing high surgical risk [43].
portant role in glioblastoma pathogenesis, IDH mutations alone are hardly associated with long-term GBM survival [44, 45]. Moreover, a recent study shows that there was no survival benefit for IDH1-mut GBMs when controlled for location: 25.2 months overall survival for IDH1-mut patients and 23.6 for IDH1-wild type patients [46, 47]. On the other hand, IDH mutations when paired with MGMT promoter methylation status are statistically significant prognostic factors for long-term survival and response to treatment of GBM patients [47–49].

Global DNA methylation profiling of tumours isolated from long-term (> 36 months) and short-term (6–10 months) surviving GBM patients (IDH1 wild-type/non-G-CIMP) revealed hypermethylation of multiple CpG islands compared to the promoter region of LOC283731 which correlated with improved patient outcome. The prediction was most pronounced in younger GBM patients (< 60 years old) [50]. In a recent study of DNA methylation profiles, a set of CpG loci differentially hypermethylated between short-term and long-term GBM cases was identified, including genomic regions coding for members of the homeobox gene family (HOXD8, HOXD13 and HOXC4), the transcription factors NR2F2 and TFAP2A, and DICKOPF2, a negative regulator of the WNT/β-catenin signalling pathway [51].

**TERT promoter mutations**

Recent findings on cancer genetics have found that over 85% of tumours show up-regulated telomerase complex which may lead to cancer cell immortality by preventing telomeres shortening and enabling infinite cell proliferation [52–54]. Mutations in the promoter region of TERT gene lead to up-regulation of its mRNA and protein resulting in telomere elongation in gliomas [55]. Highest frequency of hotspot mutations of the TERT gene promoter in gliomas are found in gliosarcomas (81%), oligodendrogliomas (78%) and primary glioblastomas (83–54%) [56, 57]. Gliomas harbouring TERT promoter mutations have worse prognosis in comparison to TERT wild-type gliomas (27 vs. 14 months), excluding TERT-IDH double mutated subgroup which seems to have a very good prognosis reaching overall survival even higher than 17 years [52, 58, 59]. The poor survival of TERT promoter-mutated gliomas was associated with higher radiotherapy resistance [60]. The prognostic value of TERT promoter mutation was absent in completely resected GBMs treated with temozolomide leading to assumptions that TERT-mut GBMs are a subgroup of tumours which need to be treated as aggressively as possible [61]. A meta-analysis of nine studies with adjusted outcomes showed that TERT promoter mutations were associated with a worse prognosis of patients with gliomas [62].

**Tumour evolution under therapy**

Recent integrative studies of molecular data and clinical variables in recurrent GBMs showed GBM evolution, heterogeneity and specific alterations associated with treatment. Whole-genome and whole-exome sequencing of multiple regions from primary and paired recurrent GBMs revealed both the occurrence of the same mutations in both samples (suggestive of clonal evaluation) and divergent tumours that share few genetic alterations with the primary tumour. The study showed TMZ induced hypermutation [63]. A recent study combining genomic and transcriptomic data from 114 GBM patients shows that despite 45% of mutations being shared by diagnostic and relapse samples, the dominant clone at diagnosis was generally not a linear ancestor of the dominant clone at relapse. In particular, 11% of patients exhibited replacement of one mutated gene (at diagnosis) with a differently mutated version of the same gene (at relapse). This mutational switching was enriched ~200-fold in genes implicated in GBM, such as EGFR, TP53, and PDGFR. Moreover, two-thirds of patients with primary GBM displayed different transcriptional subtypes at diagnosis and relapse [64]. This observation of subtype switching, together with recent findings that different parts of the same tumour can exhibit different GBM subtypes [65] may restrict the usefulness of the expression-based classification as a prognostic marker before relapse.

**Immunological correlates of long term survival in glioblastoma**

It has been shown that IDH1/2 wild-type GBM patients with long-term survival exhibit no specific markers distinguishing them from IDH1/2 wild-type GBM patients with poor outcome. Long-term surviving patients with and without IDH1/2 mutations, share an increased prevalence of MGMT promoter methylation. The determinants of long-term survival in patients with IDH1/2wt GBM, beyond MGMT promoter methylation, remain to be identified, and even the absence of both IDH1/2 mutations and MGMT promoter methylation does not preclude long-term survival [45]. These findings suggest that host-derived factors, such as immune system responsiveness may contribute to long-term survival in such patients. First high-throughput approaches have suggested links between long term survival and decreased retinoic acid signalling [66] or enhanced immune-related gene expression [67].

Gene expression microarray profiling of high grade astrocytomas from long-term survivors revealed the increased expression of immune function-related genes (such as CD3D, CD3E, CD3G, CD8B, TRAC, TRAT1, VAV1, and ZAP70 expressed by T cells) was associated with longer survival. Notably, the T cell signature was predominant within this prognostic immune gene set. This association of immune function and cell-specific genes with survival was confirmed independently in a larger public GBM gene expression microarray data set [67]. Transcriptomic studies and pathway analysis of differentially regulated genes implicated tumour-promoting, microglia-driven inflammatory processes in short-term GBM survivors. Transcriptomic analyses and multicolor immunofluorescence staining have provided further evidence for higher numbers of pro-tumourigenic, M2-like microglia in short-term surviving patients with GBMs [68]. This is consistent with the pro-tumourigenic role of glioma infiltrating microglia/macrophages (GAMs) and correlation between numbers of
activated GAMS and glioma grade [69, 70]. These findings provide important insights into the association of innate immune response and survival in IDHwt GBMs.

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