

Malignant Glial Tumors in the Immuno Oncology Era: New Challenges, New Hopes

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Description

Brain tumors are among the less common types of cancer in adults. Based on the data from the Central Brain Tumor Registry of the United States [CBTRUS] in 2014, the incidence of malignant brain Tumor has been reported as 7.25 per 100,000 with a total count of 115,799 cases with a higher rate in females [1]. However, the worldwide incidence of primary malignant brain tumors has been reported as 3.4 per 100,000 with a higher rate in males compared to females [3.9 per 100,000 vs. 3 per 100,000, respectively]. Besides, the incidence is higher in developed countries [5.1 per 100,000] than in less developed countries [3 per 100,000] [2].

Malignant glial tumors are the most common type of primary malignant CNS tumors in adults and Glioblastoma Multiforme is the most common and also the most aggressive form of these malignant glial tumors that accounts for 60% this heterogeneous group of tumors. Moreover, the prognosis of Glioblastoma Multiforme is generally poor with an estimated 2 year survival of 8.7% and the median survival of only 12-18 months [3].

Although local treatments such as surgery and radiation therapy are effective to reduce the size and burden of the tumor, these modalities are rarely considered as curative therapeutic approach as the malignant cells easily infiltrate the adjacent brain tissue and there is no limiting boundary or capsule around the tumor. The high mitotic activity of the tumor and the limited efficacy of locoregional therapeutic approaches necessitates additional treatments, such as chemotherapy, enhancing the efficacy of treatment, both as a radiosensitizing agent and extending anti-tumor activity in the whole brain tissue. Temozolamide has been found the most effective agent among available chemotherapeutic agents that are potentially able to cross the brain blood barrier and distribute in the brain tissue [4]. Despite the integration of multidisciplinary approach with optimal surgical tumor resection and concurrent chemoradiation followed by chemotherapy as an adjuvant treatment, the risk of recurrence is as high as 90% with a recurrence even closer than 4 cm from the primary tumor site [3]. Anti-angiogenesis monoclonal antibody bevacizumab has also shown its efficacy in prolongation of survival as a second line treatment modality, either alone or in combination with chemotherapy, namely irinotecan with 6 months progression free survival of 42.6% to 50.3% and duration of response of 4.3 to 5.6 months, respectively [5,6]. Although molecular aspects of Glioblastoma Multiforme suggest the role of EGFR in tumor progression, clinical trials with EGFR inhibitors such as Erlotinib and Gefitinib did not show significant response tumor response [7].

Immunotherapy has been considered an attractive therapeutic approach in oncology based on the extensive molecular and clinical studies focusing on properties and interactions between immunosuppressive behavior of the tumor itself and long lasting potentially curative anti tumor directed cell mediated cytotoxicity. However, adequacy of immune system to face malignant tumors of the central nervous system, such as Glioblastoma Multiforme with resultant activation of a powerful, long lasting cell mediated cytotoxicity response might face challenges. Lack of the lymphatic system, as well as the paucity

of powerful antigen presenting cells in the CNS are potential reasons for this inadequacy [8,9]. Besides, Glioblastoma Multiforme cells secrete immune suppressive cytokines such as TGF- beta and Interleukin-10 and prostaglandin E2. These tumor cells also down-regulate adhesion or co-stimulatory molecules, as well as induce inhibitory cells, such as myeloid-derived suppressor, immunosuppressive microglia or regulatory T cells [10-12]. Active immunotherapy through anti GBM cancer vaccines has been approached in different preclinical, phase I and phase II clinical trials in the past decade. Tumor Associated Antigens [TAA] have been introduced either as the whole tumor cell lysate from either autologous GBM resected tumors or allogeneic resected tumor or even GBM cell lines, or tumor specific neo antigens, such as Epidermal Growth Factor Receptor variant III [EGFRvIII], that is specifically found on the surface of GBM cells carrying specific mutant gene and has never been expressed on the surface of normal cells, as well as synthetic peptide cocktails [13-16]. Dendritic cells, heat shock proteins and cytokines, such as GM-CSF and interleukins have also been integrated into anti GBM vaccines to strengthen the antigen presenting process and overcome the potential immune suppressive role of GBM tumor cells, leading to a long lasting cell mediated cytotoxicity induction against malignant cells with a survival benefit in these groups of patients, respectively [17-20]. Currently, there are several active phase I, II and III clinical trials evaluating the efficacy of different types of anti GBM vaccines, both as a first line approach and in relapsing and progressive cases in both adults and paediatric patients. Rindopepimut [Rintega®, CDX-110] is a therapeutic vaccine targeting the neo antigen EGFRvIII, which is expressed in approximately one-third of Glioblastoma tumors. The FDA granted Rindopepimut a Breakthrough Therapy Designation for patients with EGFRvIII-positive Glioblastoma, based on a randomized, placebo-controlled phase II trial [ReACT] showing its survival benefit among recurrent patients. It has also received Orphan Drug Designation in Europe in 2011. An international phase III trial of Rindopepimut in newly diagnosed glioblastoma completed its enrollment in December 2014 and is no longer accruing [NCT01480479].

Another randomized, placebo-controlled phase III trial testing DCVax-L, a dendritic cell vaccine derived from autologous tumor cells, for newly diagnosed glioma [including Glioblastoma Multiforme and Astrocytoma] [NCT00045968], as well as a couple of phase II clinical studies, namely randomized, placebo-controlled phase

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Ib trial studying ICT-107, a dendritic cell vaccine that targets six different antigens associated with Glioblastoma Multiforme, in patients with newly diagnosed glioblastoma following resection and chemoradiation [NCT01280552], a phase II study on Heat Shock Protein Peptide Complex-96 [HSPPC-96] vaccine in patients with recurrent resectable Gglioma [NCT01814813], and another phase II study on ERC1671 [Gliovac], a cancer vaccine composed of autologous antigens, derived from the patient's own surgically removed tumor tissue, which is administered together with allogeneic antigens from glioma tissue resected from other GBM cases, in patients with recurrent or progressive, bevacizumab-naïve Glioblastoma Multiforme or Gliosarcoma [NCT01903330] are among the active ongoing clinical trials investigating the efficacy of anti GBM vaccines. Final results of these ongoing clinical trials might show the light on the efficacy of active immunotherapy through anti GBM vaccines, the selection criteria for the patients who might benefit the most of this treatment modality, as well as the best sequence of therapeutic approach using chemoradiation, anti angiogenesis monoclonal antibodies and active immunization following surgery.

Glioblastoma Multiforme has also been considered as an attractive target for oncolytic viruses. Its anatomical distribution within the brain as a single organ and lack of distant metastasis in one hand and high rate of tumor cell mitotic activity and bunch of active post mitosis regenerating cells around the primary tumor, makes GBM one of the most investigated tumor types in these studies [21]. Oncolytic viral treatment follows specific steps and each step mandates its characteristic needs and specificities; first the virus should attach to specific tumor cell receptors, which is preferably found on the tumor cells and not normal cells and this cell surface integration might be engineered to target tumor specific antigens such as EGFRvIII [22]. The next step is the cytoplasmic phase with the activation of antiviral mechanisms, such as Protein Kinase R [PKR] and interferons leading to apoptosis. Finally, in the nuclear phase, replication of oncolytic viruses within nuclei of the tumor cells need specific characters, such as specific cell cycle phase or even mutations such as p53 [23]. Interaction between tumor, oncolytic viruses and the host immune system is complex. Cytokines, such as interferons and interleukins, inflammation and its mediators, such as prostaglandins and finally innate and adaptive immune system play their roles in this complex interaction and direct the outcome. Oncolytic viruses augment tumor associated antigen release through their cytolytic activity, hence activating the immune system against tumor cells that would eventually lead to long lasting cell mediated antitumor cytotoxicity. Besides, host immune system might activate against oncolytic virus itself, leading to antiviral antibody production with resultant suppression of its antitumor activity [24,25].

Malignant glial tumors in pediatric patients are about 8-12% of all Pediatric CNS tumors with a poor prognosis and 5 year survival of 15-35% [26]. Molecular aspects of pediatric malignant glial tumors are also different from adult tumors. Epidermal Growth Factor Receptor [EGFR] overexpression that is a common finding in adult tumors is quite rare in pediatric category presenting in less than 10% of cases. On the contrary, p53 mutation is reported in almost all cases of pediatric unlike adult cases of malignant glial tumors, and most importantly, Platelet Derived Growth Factor Receptor A [PDGFRA] amplification is by far the most commonly encountered genetic finding. V600E point mutation in BRAF is also reported in 10% of cases of pediatric high grade glial tumors [27-30]. Considering the BRAF/RAS/MAPK/ERK signalling pathway and its crucial role in tumor proliferation, migration and angiogenesis and identification of this mutation in malignant pediatric gliomas offers a new potential therapeutic modality for these patients with poor prognosis [31].

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