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Editorial

High-grade gliomas: reality and hopes

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Abstract

In this issue of the *Chinese Journal of Cancer*, European experts review current standards, trends, and future prospects in the difficult domain of high-grade glioma. In all fields covered by the different authors, the progress has been impressive. For example, discoveries at the molecular level have already impacted imaging, surgery, radiotherapy, and systemic therapies, and they are expected to play an increasing role in the management of these cancers. The European Organization for Research and Treatment of Cancer (EORTC) has pioneered new treatment strategies and contributed to new standards. The articles in this issue will cover basic molecular biological principles applicable today, novel surgical approaches, innovations in radiotherapy planning and delivery, evidence-based standards for radiotherapy alone or combined with chemotherapy, current standards and novel approaches for systemic treatments, and the important but often neglected field of health-related quality of life. Despite the advances described in these articles, the overall prognosis of high-grade glioma, especially glioblastoma, remains poor, and more research is needed to address this problem.

Key words High-grade glioma, glioblastoma multiforme, surgery, radiotherapy, chemotherapy, health-related quality of life

Among more than 100 different histological subgroups of brain tumors, high-grade gliomas (HGG) are the most frequent entities, accounting for over 50% of primary malignant brain tumors, depending on age and country. The incidence of HGG has increased in past decades and has become quite significant in the older population. In spite of recent important advances in understanding basic molecular mechanisms of HGG, spectacular improvements in imaging, surgery, and radiotherapy, as well as the discovery of a series of new promising drugs and targeted agents, the overall prognosis remains poor, with a few exceptions. In the past, a common mistake was to include all HGG in the same tumor category, for example, WHO grade 3 and grade 4 tumors were included in the same treatment or research protocols, despite that their characteristics and prognoses are widely different. On histopathologic assessment, grade 4 gliomas or glioblastoma multiforme (GBM) present features like necrosis and intense microvascular proliferation, which are not found in grade 3 anaplastic astrocytoma (AA) or anaplastic oligodendriglioma (AO). Furthermore, AO exhibits cells with a characteristic "fried-egg" appearance, which is not found in pure AA. In addition different tumor subtypes show distinct cytogenetic abnomalities, some of which are critically important for their diagnostic, prognostic, and predictive values. Examples include the O-6-methylguanine-DNA methyltransferase (*MGMT*) methylation, epidermal growth factor receptor (*EGFR*) amplification, and vascular endothelial growth factor-A (VEGF-A) overexpression in GBM, or the 1p/19q chromosomal co-deletion in AO. Sequential accumulation of genetic aberrations, deregulation of growth factor signaling pathways, and other genetic abnomalities are postulated to contribute to a continuum from low-grade (grade 2) to high-grade (grade 4) glioma. In practice, however, only 10% of GBMs develop from grade 2 gliomas, and currently, the management of the former does not differ from that of "spontaneous" GBM. As will be seen in this issue of the *Chinese Journal of Cancer* dedicated to HGG, the progress made in the basic biological understanding of these tumors has impacted not only systemic treatments but also the newest imaging modalities, surgical management, and radiotherapy planning and delivery. Currently, the treatment backbone of HGG almost always includes surgery, radiotherapy, and chemotherapy. The pivotal European Organization for Research and Treatment of Cancer-National Cancer Institute of Canada (EORTC-NCIC) trial published in 2005 and updated in 2009 has established the standard treatment for GBM[1,2].

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Although a significant minority of patients can survive for several years[3,4], a majority will succomb to the disease. Progress has also been made in AA and AO[5,6], for which the prognosis is less gloomy; however intensive research is needed and important trials are ongoing[7,8]. Health-related quality of life (HRQoL) is a tool of growing importance in HGG[9,10]. It should be included in any prospective trial to aid clinicians in making final treatment decisions.

In this issue, we have gathered a series of comprehensive reviews on different aspects of HGG. These articles have been written by European experts who are heavily involved in clinical research on HGG, most being major contributors of the EORTC Brain Tumor Group and Radiation Oncology Group.

Hofer *et al*.[11] provide a clear and practical guide for clinicians, looking at the role of molecular markers in the diagnosis and treatment of HGG. Currently, 1p/19q chromosomal co-deletion, *MGMT* methylation, and *IDH* mutations have made their way into clinical practice, and a growing number of other markers are under investigation.

Wolbers[12] describes surgery of HGG with the newest developments in preoperative planning, multimodal neuronavigation, and different means to allow safe and maximal cytoreduction, the latter associates with improved prognosis. Intraoperative imaging by fluorescence guidance seems to be particularly promising in this regard, and newer developments like implantable telemetric light or probes are being tested. Future and exciting developments include direct infusion of biological agents and transfer of genetic material into the tumor using various vectors, as well as other novel approaches.

Radiotherapy plays a central role in the treatment of HGG, and has undergone important advances due to rapid progress in informatics, imaging, and the delivery of high-precision beams. Dhermain[13] reviews the current European and the US standards in radiotherapy planning and delivery and discusses their limitations. New concepts for planning should include judicious use of advanced imaging techniques to provide not only anatomic but also functional information on cellularity [diffusion magnetic resonance imaging (MRI)], angiogenesis (perfusion MRI) metabolic activity (positron emission tomography (PET), cellular proliferation [magnetic resonance spectroscopy (MRS)], and so on. Co-registration of these imaging techniques is essential but there are a number of drawbacks, highlighting the need for a better standardization. These imaging tools should be aimed at more efficiently delivering “the right dose to the right target” and should take into account the challenging problem of tumor heterogeneity and focal areas of radio-resistance.

Villà *et al*.[14] give a comprehensive overview of the major trials that have set the standards of care in GBM. Surprisingly, it appears that in spite of well conducted randomized controlled trials, a substantial proportion of patients have not yet been offered the best treatments. Randomized controlled trials have established the role of postoperative radiotherapy versus no radiotherapy, and the optimal radiotherapy dose, and have explored all sorts of radiotherapy fractionations. For example, in elderly patients, hypofractionation is as efficient as conventional fractionation and spares the patients significant treatment time. Chemotherapy and chemoradiation have also been tested in randomized controlled trials. Villa *et al*.[14] analyze the pivotal EORTC-NCIC trial, including the major role of MGMT.

Hottinger *et al*.[15] provide a critical analysis of the current standards of care and novel approaches in the management of GBM, from a medical oncology and neuro-oncology point of view. Starting from the published trials in adult patients (EORTC-NCIC) and in elderly patients, they carefully evaluate novel therapies. Regarding angiogenesis, targeting VEGF seemed to be a very attractive approach, given VEGF overexpression in GBM. However, two recent randomized controlled trials on primary GBM had disappointing results, raising a number of questions regarding the addition of VEGF to chemoradiation. Furthermore, inhibiting integrins with the drug cilengitide produced encouraging results in phase 2 studies, in particular for patients whose tumors exhibit *MGMT* methylation, but the efficacy of this approach was not confirmed in a large randomized controlled trial. Various agents directed against EGFR have been tested, but here again results were disappointing. Similarly, inhibitors of mTOR and protein kinase C did not produce desired effects. Still, a number of other novel approaches such as immunotherapy and alternating electric fields are being tested in randomized controlled trials, but clearly, further intensive research is needed.

Finally, Dirven *et al.*[16] remind us that the recognition of palliation and improvement of the quality of life (QoL) are at least as important as overall survival or progression-free survival, especially in cancers with a poor prognosis like GBM. Health-related quality of life (HRQoL) is a concept that takes into account physical, psychologic, and social parameters and also includes symptoms induced by the disease and treatment. The EORTC has developed the QLQ-C30 generic questionnaire for cancer patients and the QLQ-BN-20 brain tumor-specific questionnaire. Other groups have also developed questionnaires that are currently being used to assess HRQoL. Collectively, these questionnaires allow investigators to efficiently measure the effect on the disease as well as the impact of treatments like surgery, radiotherapy, and chemotherapy on QoL. For example, studies show that HRQoL scores decreased overall after surgery or radiotherapy, but other trials of chemotherapy and chemoradiation disclosed no negative effect or even a slight improvement. In their comprehensive analysis, Dirven *et al*.[16] remind us that in clinical trials, the benefits of a new treatment strategy should be carefully weighed against the side effects of the treatments, not only in terms of overall and progression-free survivals but also in terms of HRQoL. HRQoL is also expected to impact daily clinical decision-making and health care policy.

In summary, many studies on HGG have been conducted and have improved the overall understanding and management of these malignant brain tumors, but overall prognosis remains rather poor and continuous and extensive research should be carried out.

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