TREATMENT OF ADULT LOW AND HIGH GRADE GLIOMAS : PAST PRESENT AND FUTURE; LITERATURE REVIEWED

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ABSTRACT

Some controversy about management of gliomas has been discussed in several reports in the literatures. For low grade gliomas, conservative or aggressive treatment is considered a proper management in each case. The unpublished result of ongoing Radiation Therapy Oncology Group (RTOG) clinical trial about treatment of low grade gliomas may give some more answer in this topic. For high grade gliomas, multimodality treatment is accepted and the benefit of chemotherapy is proven at the present time. It is hoped that biotherapy will be another effective novel approach in the future for high grade gliomas.

INTRODUCTION

The term "gliomas" is referred to the tumor originated from glia cells. The World Health Organization (WHO) classifies gliomas according to their morphologic characteristics into astrocytic, oligodendroglia and mixed tumors.[1] Management of gliomas has so far produced variable therapeutic outcome due to heterogeneity of disease (variable in histology), genetic alteration and immune abnormality of host. Modality of treatment is varied from the past to present and may be in the future. The objective of this paper was to show the proper management of adult gliomas by reviewing the articles related to treatment topics in "PubMed" online, paying a particular attention since the year 2000 and searching for references or related articles in the past to see the trend for a proper management at present and possibly in the future.The treatment is addressed specifically to low and high grade gliomas.

TREATMENT OF LOW GRADE GLIOMAS

Due to slow growing behavior of these tumors, controversy about management in survillance, surgery, radiotherapy and chemotherapy has been discussed in many articles.

Surveillance or defer treatment of low grade gliomas is referred to delay any aggressive treatment after biopsy has been done. This concept may be appropriate for very slow growing and indolent behavior of disease such as low grade oligodendroglioma in young age group (< 21 years) with a non-enhancing mass on Magnetic Resonance Image (MRI) presented with seizures and no other neurologic symptoms, concerning surgical complications or when patient wants to be observed.[2-5]

Surgery has been the main treatment modality for a long time with benefit in obtaining tissue diagnosis and cytoreduction to improve neurological status and decreased local recurrence or malignant transformation. Aggressive surgical procedure can prolong survival and improve quality of life in cases with minimal morbidity from the procedure.[5,6,7] However, in the multivariate analysis, extent of resection is not a significant prognostic factor for overall survival.[3,8,9] The extent of surgery is still a matter of debate by now. To avoid severe surgical complication in deep seated or eloquent area, functional or cortical mapping surgical procedure is applied to get the maximum tumor removal with the least morbidity.[10-13]

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The controversy of radiation treatment in low grade gliomas is debated with regard to toxicity, efficacy and optimal time to begin the treatment. However, there is still no sufficient data from randomized control trials to answer these questions. The recommendation for radiotherapy regimen to avoid severe toxicity is to use a daily dose not more than 2 Grey (Gy) and total tumor dose between 50-55 Gy with the improvement of radiotherapy technique, such as a conformal 3 dimensional treatment to give exactly treatment volume to tumor and minimally normal tissue effect.[5,6,8,14-18] There is still no definite standard dose for low-grade glioma. Median dose from most reports is 54-55 Gy. Efficacy of radiotherapy has been discussed between the believer and non-believer group subject to each opinion. For the group who believes in the efficacy of radiotherapy, it is argued that it can decrease tumor burden and prevent dediffertiation from low to high grade.The most effective benefit is that it can prolong the time of progression of the disease. Moreover, at a present time of the modern radiation technology, the side effect from treatment is less than before.[18-20] For the non-believer group, they have found no overall survival benefit from radiation treatment and still afraid of radiation complications. Moreover, if tumors progression are detected in those cases, they believe they can handle it with resurgical procedure.[21-23] The optimal time of postoperative radiotherapy can be defined into early (withih 8 weeks of surgical day) and late (more than 8 weeks) treatment. The criteria can be concluded that early radiotherapy is considered in cases with age more than 40 years (or 50 years in some report), astrocytoma histology, the largest tumor diameter more than 6 centimeters, tumor crossed midline and presented with neurological deficits before surgery. These are unfavorable prognostic factors which are reasonable to give early radiotherapy to improve the time to progression or progressive free survival. Delay radiotherapy is considered in young age group with good performance status who had less than 2 unfavorable prognostic factors, oligodendroglioma or oligodendroglial predominant, and presented with seizure only before surgery.[5,8,9,14,18,22-30] However, there is still no exact conclusion in these comments of radiotherapy ideas. Altered fractionation, stereotactic radiotherapy or dose escalation with proton/photon treatment in low grade gliomas do not gain benefit from conventional treatment.[29]

Chemotherapy (such as nitrosourea, lomustine, temozolomide) is claimed to be an effective treatment and can delay radiotherapy if afraid of complication or used in recurrent or progressive disease. However, there is still quesionable in true benefit and toxicity of chemotherapy in low grade gliomas although some response is seen in case with chromosome 1p and 19q deletion.[5,29-35]

The ongoing Radiation Therapy Oncology Group (RTOG) protocol 98-02[36] is the study of phase II observation in a favorable low-grade glioma (age < 40 years and gross total resection) and phase III radiation with or without Procarbazine, CCNU, Vincristine (PCV) in unfavorable low grade glioma (age equal or less than 40 years or subtotal resection/ biopsy).This report may give some clue for the treatment in the future.

TREATMENT OF HIGH GRADE GLIOMAS

The genetic alteration in high grade gliomas, such as loss of tumor suppressor gene, loss of cell cycle control, increased angiogenesis and invasiveness, is the factors that contribute to aggressiveness of this malignancy and make it hard to handle the good outcome of treatment.[37-39] For glioblastoma multiformae, the necrotic area in the central zone can activate surrounging pseudopalisade area which contains hypercellular tumor cells and can activate hypoxic-induced factor (HIF) and induce progressiveness of necrotic zone.The invasiveness genes (such as Matrix Metallo Protease, MMP2) can produce edematous area around the tumor cells which make it hard to define the exact tumor margin.[37-39] Nowadays, the recommended standard treatment of high grade gliomas is surgery followed by postoperative

radiotherapy with or without chemotherapy.[40-43]

Surgical problem is discussed between less or more aggressive procedure. Maximal tumor removal without neurological deficits to reduce the number of cancer cells is the optimal treatment. Less surgical procedure followed by radiation treament is recommended when the tumor is located in deep seated or eloquent area which concerns morbidity from extensive surgery.[44] Indeed, extensive tumor removal more than 90% is effective in palliative symptoms, improve neurological status, control intracranial pressure with definitive histology and may improve overall survival. However, most of the cases presented with high grade gliomas could not receive extensive surgery without severe morbidity.In fact, aggressive tumor resection is still debatable because it fails to find a statistical correlation between extent of resection and survival.[42,44-47] The latest Cochrane systematic review is still under-powered to show clinical effectiveness of surgical resection compared to biopsy.[48] Cortical or functional mapping surgical procedure is the other way to get rid of maximum tumor tissues with minimal morbidity.[10-13] Resurgery is considered in two conditions, early and late period. Early resurgery after MRI for 48 hours after first time surgery is to get rid of all residual tumor. Intraoperative image guidance such as MRI or transcranial ultrasound is used to detect residual tumor and gain a possibility to achieve a more complete tumor resection.[11,49-51] Delay resurgery for those who have recurrence, one must be concerned about age, performance status, initial surgical procedure, site and time interval from previous surgery to make a treatment decision. Resurgery for recurrent tumor can relieve symptoms, improve general condition and reduce the need of steroid treatment. Information from resurgical specimen can provide valuable time for additional treatment.[40,52,53]

Standard postoperative irradiation 60 Gy , 1.8-2 Gy/ fraction is the recommended treatment for high grade gliomas.[40-42,54,55] Clinical Targeted Volume (CTV) is still debated. Most papers have recommended CTV to cover area of high signal T2 weighted in MRI or contrast enhancement computerized tomographic (CT) scan plus hypodensity peripheral zone as the initial treatment volume.Gross tumor volume (GTV) on MRI or contrast enhancement CT scan plus 1 cm margin is defined as a boosted volume after 45-50 Gy.[42,54-56] Short radiation treatment course is routinely recommended in those who have high Recursive Partitioning Analysis (RPA) score as a palliative treatment.[54,57-60] No significantly prolonged survival was detected by using altered fractionation, brachytherapy, radiosurgery, radiosensitizer or Intensity Modulated Radiation Therapy (IMRT) in high grade gliomas.[54,61-63] Radiotherapy is limited by normal brain tissue tolerance dose. To minimize toxicity in reirradiated cases, limited field irradiation at recurrent site is necessary. Brachytherapy (iodine 125 implantation,GliaSiteâ), fractionated stereotactic radiosurgery or IMRT has been reported with improvement in quality of life and some survival benefit in some subgroup of patients (such as small size tumor, unifocal lesion, good performance status).[64-68] The advance technology of image fusion (PET, SPECT, CT, MRI) is a helpful tool for radiation oncologist to determine the exact tumor volume for reirradiation.[69]

Chemotherapy (such as carmustine, lomustine, nimustine) may gain survival benefit in young age, good performance status and maximal surgical debulging mass in many trials as an adjuvant therapy.[41,42,55,70,71] No additional incremental benefit of neoadjuvant chemotherapy in high grade gliomas was detected.[72-75] Temozolomide is used as a combined treatment with radiotherapy (concurrent and adjuvant) which showes survival benefit results compared with radiotherapy alone.[73,74] Anaplastic oligodendroglioma with loss of heterozygous (LOH) chromosome 1p and 19q has correlation with more chemoresponsiveness than other high grade gliomas.[75] Chemotherapy used in recurrent cases produces a small number of complete response rate. Partial response rate is around 30% with either single or combinative agents.[41,42] To circumvent the blood brain barrier and deliver chemotherapeutic agent to brain tissue, convection enhanced delivery or

infusion pump is the technique used to deliver drugs directly into the area where the catheter is applied. This technique can limit the side effect from systemic chemotherapy.[76]

Nowadays, knowledge about molecular genetics in the development of gliomas is more understood than before. There are three main genetic alteration pathways to turn original glia cells into malignant gliomas. The first way is inactivation of phosphatase and tensin homolog deleted on chromosome ten (PTEN) on chromosome 10q and epidermal growth factor receptors (EGFR) amplification and/or rearrangement leading to primay glioblastoma multiforme. The second way is loss of p53 with inactivation of cyclin-dependent kinase inhibitor 2A(CDKN2A),RB1 and CDK4 amplification and finally loss of chromosome 10q is the pathway of develop secondary glioblastoma multiforme from astrocytoma dedifferentiation. The third way is the development of glioblastoma multiforme with oligodendroglial component from loss of chromosome 1p, 19q , 10q and CDKN2A.[37-39] Other several factors involved such as MMP9 and vascular endothelial growth factor (VEGF) which promotes invasion and neovascularization, hypoxic-induced factor (HIF) which enhances gelatinase activity and increase migration of pseudopalisade cells in hypercellular zone, down regulation of invasion inhibitory protein 45 (IIp45) which leads to tumor suppressor gene loss, and many other factors, can activate aggressiveness of high grade gliomas.[38,39] Understanding of this knowledge can lead to the novel biological treatment concept of high grade gliomas such as gene therapy, molecular therapy, immunotherapy and targeted therapy. Current clinical trials of these novel therapeutic agents have been reported (most of them are phase I and II) as a single or combination treatment, mostly with recurrent diseases. They have many mechanisms of action such as anti-tenascin Mab (monoclonal antibody), PDGFR (platelet-derived growth factor receptor) inhibitors, EGFR inhibitors,VEGF inhibitors, cell cycle inhibitor and so on.[42,77-79] The strategies to kill selectively glioma cells are the use of prodrug/ suicide gene therapy, oncolytic viruses and apoptosis-inducing agents.[78] The concept of prodrug/ suicide gene therapy is to kill the transducted or infected herpes simplex virus thymidine kinase cells (glioma cells, higher mitotic activity than normal cells) by phosphorylated ganciclovier. This process is called GCV/TK system. Unfortunately, no significant advantage over standard treatment has been found.[80] Oncolytic virotherapy is to use the natural ability of lytic viruses to kill their host cells(infected glioma cells). The prototype is dl 1520(ONYX-015) replication adenovirus which is found to be safe but limited in efficacy as a single agent while promising results are shown in combination treatment with radiotherapy or chemotherapy.[81,82] The idea of apoptosis induction is triggering the natural mechanism of programmed cell death in tumor cells. Malignant gliomas mostly express DR5 (TRAIL-R2, type I transmembrane receptors containing an intracellular death domain) which are sensitive to TRAIL-induced apoptosis.[83,84] Immunotherapy of malignant gliomas is based on the hypothesis that glioma cells accumulate immunotolerance neoantigens during transformation without any inflammation or tissue destruction at an early stage of oncogenesis. So, cancer vaccine is designed to break down the immune tolerant or to activate occult T-cell population which escapes immune tolerance. Dendritic cell vaccination is the active immunotherapy designed to act against malignant glioma. Phase I clinical trial has promoted a cytotoxic inflammatory reaction at tumor site, suggesting the successful generation of a systemic immune response. Other vaccination, such as xenogenic protein vaccine, cytokine-expressing vaccine and novel bacterial vaccine are still in the animal model trials.[85-87]

CONCLUSION

The management of gliomas is still controversy in each modality. Due to slow growing behaviors of low grade gliomas, more conservative management is considered to avoid severe complications from treatment, such as surveillance, minimal aggressive surgical procedures, or limit radiation dose and

improve technique to minimize radiation complication or just wait and see after operation in some selected case. Chemotherapy is still of questionable benefit for low grade gliomas. We must wait for final results of RTOG 98-02 to answer some questions about the controversial management. For high-grade gliomas, surgery and postoperative radiotherapy is still the standard treatment. After the benefit of additional chemotherapy is proven, this modality is more accepted than before. Recurrent tumor is still a big problem due to aggressive behavior of this disease. Individual judgement in retreatment which whatever surgery, radiotherapy or chemotherapy is dependent upon each decision hoping to improve quality of life and prolong life in some patients. Understanding the knowledge of genetic alteration of high grade gliomas leading to the novel concept of biotherapy, with the hope to get rid of more tumor cells and improve treatment outcome. However, this concept is still in clinical trial but expected to be the new frontier treatment in the future.

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