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Review Article

The Current Treatment Approach for Anaplastic Gliomas

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Abstract

Grade 3 gliomas include 6–10 % of all newly diagnoses of primary brain tumors and comprise 6–15% of all primary brain tumors. Three histological subtypes are characterized: anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytoma (AOA). During the past decade, understanding of molecular and prognostic significance of genetic alterations in anaplastic gliomas (AG) has changed treatment strategies of these tumors, particularly for oligodendroglial subtype. The initial treatment for AG is maximal safe resection. The management after initial surgery of AG with 1p/19q codeletion includes radiotherapy (RT) and PCV (procarbazine, CCNU, vincristine) chemotherapy as established by EORTC 29651 and RTOG 9402 trials. The sequence of RT and chemotherapy has not been defined; therefore both neoadjuvant and adjuvant chemotherapy may be applied. The second treatment option is RT plus Temozolomide chemotherapy for 1p19q co-deleted tumors. The treatment of uni- or nondeleted AG is either RT only or primary alkylator-based chemotherapy only with deferred RT as determined in NOA-04. The combined therapy with radiation plus Temozolomide in patients with newly diagnosed AA patients is an alternative treatment option. We should await mature results from CATNON study to help determine whether use of concurrent Temozolomide during radiation, in addition to 12 cycles of adjuvant Temozolomide, provides increased benefit. There has been no standard therapy for patients with recurrent AG. At progression, the option of second surgery should be explored. Alkylating chemotherapy is the treatment of choice for most patients previously untreated with chemotherapy. Re-irradiation is another option for recurrent AG.

ABBREVIATIONS

AA: Anaplastic Astrocytoma; **AG**: Anaplastic Glioma; **AO**: Anaplastic Oligodendroglioma; **AOA**: Anaplastic Oligoastrocytoma**; ATRX**: α-Thalassemia/ Mental Retardation X-Linked Gene; **CNS**: Central Nervous System; **CTV**: Clinical Target Volume**; G-CIMP**: Glioma-CpG Island Methylation Phenotype; **EANO**: European Association for Neuro-Oncology; **EGFR**: Epidermal Growth Factor Receptor; **EORTC**: European Organization for Research and Treatment of Cancer; **FLAIR**: Fluid attenuation inversion recovery; **GBM**: Glioblastome; **Gy**: Gray**; GTV**: Gross Tumor Volume; **HGG**: High-Grade Gliomas; **IDH**: Isocitrate Dehydrogenase; **MGMT**: Methylguanine Methyltransferase Promoter Methylation; **MRC**: Medical Research Council; **MRI**: Magnetic Resonance Imaging; **NCCN**: National Comprehensive Cancer Network; **PDGFR**: Platelet Derived Growth Factor Receptor; **PFS**: Progression Free Survival; **PTEN**: Phosphatase And Tensin Homolog; **PTV**: Planning Target Volume; **RT**: Radiotherapy; **RTOG:** Radiation Therapy Oncology Group; **OS:** Overall survival; **TERT:** Telomerase Reverse Transcriptase

INTRODUCTION

Grade 3 gliomas include 6–10 % of all newly diagnoses of primary brain tumors and comprise 6–15% of all primary brain tumors [1, 2]. Three histological subtypes are characterized: anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytoma (AOA). Although they are less aggressive compared to WHO grade 4 glioblastoma (GBM), the most common as well as malignant, the prognosis is highly variable depending on histopathology and molecular markers, with a median overall survival (OS) ranging between 2 years for anaplastic astrocytoma (AA) and 4 years for anaplastic oligodendroglioma (AO) [2].

During the past decade, understanding of molecular and prognostic significance of genetic alterations in anaplastic gliomas (AG) has changed the treatment strategies of these tumors, particularly for oligodendroglial subtype. Recently, new molecular markers have been developed and some of these markers can be used diagnostically; moreover some of them seem to have a role as prognostic and predictive factors, as well as response to specific chemotherapy regimens and radiotherapy

(RT) [3]. Also, these genetic alterations affected the classification of the glial tumors; therefore in 2016 World Health Organization (WHO) classification of tumors of the central nervous system has been updated. According to WHO 2016 classification system, AA further divided into three categories as: anaplastic astrocytoma-isocitrate dehydrogenase (IDH) mutant; anaplastic astrocytoma-IDH-wild type; and anaplastic astrocytoma- not otherwise specified (NOS). On the other hand, Anaplastic oligodendroglial tumors further divided as: anaplastic oligodendroglioma-IDH-mutant and 1p/19q-codeleted; anaplastic oligodendroglioma-NOS; and anaplastic oligoastrocytoma-NOS [4]. The search for genetic alterations showed that in the overwhelming majority of cases AG are compatible with either astrocytoma or oligodendroglioma and true oligoastrocytomas are excedingly rare.

Gadolinium-enhanced magnetic resonance imaging (MRI) is the optimal imaging modality to suggest AG. MRI may also provide information that indicates the specific tumor type. High-grade gliomas (HGG) are typically hypointense on T1-weighted images, and enhance heterogeneously following contrast infusion. Enhancing tumor can be distinguished from the surrounding hypointense signal of edema on T1-weighted sequences [5]. MRI reveals AA to be an ill-defined, T1-weighted hypointense and T2-weighted hyperintense mass with surrounding vasogenic edema [6].

Historically, the management of patients with AG was based upon the results from studies in patients with HGG. The recognition of the molecular and prognostic differences between oligodendroglial and other glial tumors caught attention of the investigators around the world for searching the molecular biologic characteristics of gliomas in an effort to improve the outcome. Among AG, there is high correlation between oligodendroglial morphology and 1p/19q co-deletion. The 1p/19q codeletion was first identified as both a prognostic and predictive biomarker in the EORTC (European Organization for Research and Treatment of Cancer) 26951 and RTOG (Radiation Therapy Oncology Group) 9402 trials [7, 8]. After this, several biological markers including mutation of IDH1, presence of the glioma-CpG island methylation phenotype (G-CIMP), methylguanine methyltransferase (MGMT) promoter methylation, α-thalassemia/ mental retardation X-linked gene (ATRX) mutation, telomerase reverse transcriptase (TERT) promoter mutation, p53 mutation, phosphatase and tensin homolog (PTEN) mutation, epidermal growth factor receptor (EGFR) and platelet derived growth factor receptor (PDGFR) overexpression or amplification and gene expression profiles have been identified as potential prognostic factors in AG [9, 10]. Tumors with 1p/19q co-deletion almost always have IDH1/2 mutations, and often have MGMT promoter methylation and TERT promoter mutations [11, 12]. By contrast, TP53 mutation and loss of ATRX expression are rare in 1p/19q-co-deleted gliomas, but common in diffuse and anaplastic astrocytomas. This finding could help to better dissect the controversial entity of anaplastic oligoastrocytoma [11, 13].

The initial treatment for AG is maximal safe resection [10, 11]. A new classification using molecular markers may improve the initial management of AG and tailor treatment according to the presence or absence of prognostic markers as mentioned above. The management after initial surgery of AG with 1p/19q codeletion includes radiotherapy (RT) and PCV (procarbazine, CCNU, vincristine) chemotherapy as established by the EORTC 29651 and RTOG 9402 trials [7, 8]. The treatment of uni- or nondeleted AG is either RT only or primary alkylator-based chemotherapy only with deferred RT as determined in the NOA-04 [14].

Surgery

Surgery provides tissue to establish the diagnosis and is used to relieve symptoms due to mass effect in patients with suspected AG. Particularly for AA, surgery may improve the symptoms due to tumor infiltration of the brain, edema and seizures. Surgery also reduces the number of tumor cells that may lead to relapse. As with other HGG, maximal safe resection is the preferred approach, but partial resection or biopsy may be required, depending upon the location and extent of the tumor [15].

There are no randomized trials that have established the benefit of maximal surgical resection compared with a more limited resection, and such studies are unlikely to be conducted. A prognostic role regarding the extent of resection has been demonstrated retrospectively in most trials of AG [16]. In a retrospective cohort of 335 HGG patients, Beiko et al., showed that the survival benefit associated with surgical resection differs based on IDH1 genotype in HGG [17]. The authors concluded that that resection of enhancing and non-enhancing tumor was significantly correlated with overall survival in IDH1 mutant AAs and GBMs and not in wildtype HGG. Thus, individualized surgical strategies for AG may be considered based on IDH1 status. Also NOA-04 trial demonstrated that extent of resection is found as a prognostic factor in AG patients [14]. The therapeutic option following surgery varies according to the histological subtype, molecular differences as well as the clinical status of the patient.

Postoperative treatment of anaplastic astrocytoma

The traditional standard of care for AA includes maximum safe resection as feasible or biopsy, followed by 54-60 Gray (Gy) of partial brain irradiation given in 1.8–2 Gy fractions [11]. Adequate doses of RT are required to maximize the survival benefit; however the use of higher doses has failed to show a survival benefit [18].

Adjuvant RT is an option for all subtypes

The target volume delineation for WHO grade III gliomas is conflicting. According to European Association for Neuro-Oncology (EANO) guideline, RT volume includes T2-weightened or Fluid attenuation inversion recovery (FLAIR) abnormality plus a 1-2 cm safety margin. The planning tumor volume (PTV) receives approximately 50 Gy and the contrast enhancing volume receives an additional 10 Gy; all administered in 1.8–2.0 Gy fractions per day, 5 fractions per week, for a total of 60 Gy [11, 19]. In ongoing CATNON study the GTV is defined as the entire region of high signal intensity on the T2-weighted MRI images or FLAIR sequences plus the region of enhancement on postoperative CT/MRI if available, or as the region of enhancement on preoperative CT/MRI if postoperative imaging is not available, plus the tumor resection margin. In some cases, no enhancement can be seen,

and GTV is defined according to the T2 abnormality. The CTV is defined as a 1.5 to 2.0 cm volumetric expansion of the GTV, and the PTV will add 0.5 to 0.7 cm, depending on the centers. A total dose of 59.4 Gy in 33 fractions of 1.8 Gy is recommended [20]. The National Comprehensive Cancer Network (NCCN) guideline defines the gross tumor volume (GTV) using pre- and postoperative MRI imaging using T1 and FLAIR/T2 images [21]. To account for sub-diagnostic tumor infiltration, the GTV is expanded 1-2 cm (clinical target volume: CTV) for grade III tumors. Fields are usually reduced for the boost treatment. The recommended dose is 55.8-59.4 Gy in 1.8 Gy/fraction or 57 Gy in 1.9 Gy/fraction in grade III tumors.

Although Medical Research Council (MRC) study failed to show the survival benefit of the addition of PCV chemotherapy to RT for the subgroup patients with AG [22], the German NOA-4 study showed that alkylating chemotherapy alone was as effective as was RT alone with respect to progression free survival (PFS) and OS [14]. In the NOA-4 phase III trial, patients (N=318) were randomly assigned 2:1:1 (A:B1:B2) to receive conventional radiotherapy (arm A); procarbazine, lomustine (CCNU), and vincristine (PCV; arm B1); or temozolomide (arm B2) at diagnosis. Their results suggested that the either initial RT alone or initial chemotherapy alone may be the treatment option, since both have comparable results. Therefore the present standard of care outside clinical trials remains RT or alkylating chemotherapy alone for patients with AA.

According to the NCCN guidelines another postoperative treatment option for newly diagnosed AA is RT and chemotherapy [21]. The CATNON trial designed to elucidate the benefit of adding chemotherapy to RT in newly diagnosed AG without 1p/19q co-deletion [23]. The CATNON trial enrolled 748 patients newly diagnosed AG patients and all patients received RT 59.4 Gy in 33 fractions, and in a 2 x 2 factorial design were randomized to: RT alone; RT with concurrent daily 75 mg/m^{2}Temozolomide; RT followed with 12 cycles of 150-200 mg/m^2 adjuvant Temozolomide day 1-5/4 weeks; or RT with both concurrent and 12 cycles of adjuvant Temozolomide. The preliminary results of the CATNON trial found that the patients who receive RT plus 12 cycles of adjuvant Temozolomide have improved survival compared with those who do not receive adjuvant Temozolomide (hazard ratio [HR] 0.65, 95% CI 0.45-0.93). The study is continuing in order to elucidate the role of concurrent Temozolomide. Based on these data combined therapy with radiation plus Temozolomide in most patients with newly diagnosed AA patients are an alternative treatment option. We should await mature results from the CATNON study to help determine whether use of concurrent Temozolomide during radiation, in addition to 12 cycles of adjuvant Temozolomide, provides increased benefit.

Postoperative treatment anaplastic oligodendroglial tumors

Although adjuvant RT has been considered standard of care for anaplastic oligodendroglial tumors, their sensitivity to nitrosoureas and Temozolomide has long been recognized, and ongoing controversies do not focus on whether to give RT or alkylating chemotherapy at all, but rather when and in what sequence [11]. The role of PCV was first reported in small series of patients with recurrent oligodendroglioma and oligoastrocytoma [24]. These studies led to randomized phase III trials RTOG 9402 and EORTC 26951 to clarify the role of PCV chemotherapy in AO and AOA. Long-term results of RTOG 9402 and EORTC 26951 indicated that patients whose tumors harbored a 1p19q co-deletion benefitted from early addition of PCV chemotherapy to RT; a significant improvement in OS was demonstrated compared with early RT, even with salvage chemotherapy at tumor relapse [7, 8]. Thus, 1p/19q co-deletions have also predictive value for benefit from chemotherapy, in addition to the characterization of a prognostically more favourable subgroup of patients with anaplastic oligodendroglial tumors. Therefore the optimal treatment for anaplastic oligodendroglial tumors should include both RT and chemotherapy; however the treatment decisions should be individualized. The presence of 1p/19q co-deletions may help to determine the optimal treatment approach.

According to NCCN guideline 1p19q co-deleted tumors should be treated with RT and neoadjuvant or adjuvant PCV [21]. This option is supported by EORTC 26951 and RTOG 9402 studies. The second treatment option is RT plus Temozolomide chemotherapy for 1p19q co-deleted tumors, since Temozolomide is easier to administer, has better tolerance, and has been shown to improve survival in other types of malign gliomas [6, 21].

The optimal sequence of RT and chemotherapy when given as a combined approach for AO has been uncertain. In the EORTC 26951 trial, PCV chemotherapy was administered after the end of RT; on the other hand in the RTOG 9402 study, four cycles of PCV were administered before the RT. Therefore NCCN guideline recommends the PCV either before or after the RT.

There is an increasing knowledge about the long-term toxicities of RT. The radiation-induced cognitive impairment is one of the most important long-term side effects of RT. The sensitivity of the oligodendroglial tumors to chemotherapy and the concerns about the radiation related neurotoxicities including cognitive impairment have led to the use of only chemotherapy rather than RT as the initial treatment particularly for patients with 1p19q co-deletions. Long-term results of NOA-4 study which compared the RT versus Temozolomide versus PCV alone, might answer this question [14]. Preliminary results of NOA-4 study demonstrated that there is no differential activity of primary chemotherapy versus RT in any subgroup of anaplastic glioma [24,25]. However, the similar OS after initial RT only or initial chemotherapy only implies that combined RT plus chemotherapy is likely to result in improved survival compared with initial chemotherapy alone [6]. NOA-04 long-term data do not support a differential efficacy of primary Temozolomide monotherapy or PCV polychemotherapy versus RT in any of the histological or molecular subgroups of anaplastic glioma. Specifically, the patients with the best prognosis (ie, patients with CIMPcodel anaplastic gliomas) do not seem to benefit selectively from one of the therapies. Although statistically not significant NOA-4 trial updated version showed that Temozolomide is inferior to PCV. The median overall survival rates were 8 years for initial RT group, and 6.5 years forinitian chemotherapy group either with Temozolomide or PCV [25]. Although the difference was not statistically significant, it may be clinically significant.

Non-co-deleted tumors should be treated as AA [21]. The postoperative treatment options for non-co-deleted tumors include RT alone; RT plus Temozolomide or PCV or Temozolomide chemotherapy. Temozolomide may be reasonable option for chemotherapy as the preliminary results of the CATNON trial indicate that RT with 12 cycles of adjuvant Temozolomide improves survival over RT alone. In addition subgroup analysis of earlier randomized trials found that the benefit of PCV when used in combination with RT was attenuated or absent in patients with non-co-deleted anaplastic oligodendroglial tumors. Lastly Temozolomide is easier to administer, has better tolerance, and has been shown to improve survival in other types of malign gliomas [6, 21].

TREATMENT OF RECURRENT DISEASE

There has been no standard therapy for patients with recurrent AG. The treatment choice for recurrent disease depend on multiple factors including the location of the tumor, the performance status of the patients, initial treatment modality, radiographic data, response to the initial treatment as well as the time to recurrence [26].

Re-resection may be used in selected patients particularly those with asymptomatic tumor mass, good performance status. Also the tumor should be located in non-eloquent brain parts [19]. Although surgery may improve function, the survival benefit has not benefit substantiated. Nonetheless obtaining tissue from the recurrent tumor may change treatment option, since progression to glioblastoma is demonstrated in such patient population. However, only 20-30% of recurrent HGG patients are candidates for a second surgery [11].

Re-irradiation is another option for recurrent anaplastic gliomas. Focal RT approaches are often employed with limited volume recurrences; however the role of reirradiation in patients with recurrent HGG is uncertain, and there is a lack of prospective data. Based on retrospective series, selected patients with small recurrent tumors and a good performance status may benefit from repeat radiation using modern high-precision techniques [27].

Both PCV and Temozolomide have activity in patients who have failed an initial chemotherapy regimen, although response rates are lower and the duration of disease control is generally shorter compared to treatment at first diagnosis or at first recurrence after RT [6]. Response rates ranging between 50-70% in recurrent AG are reported when treated with alkylating chemotherapy [10, 28-30].

The management of patients who have progressed on either Temozolomide or PCV is experimental. Other agents that have shown some activity as second-line chemotherapy in patients with anaplastic oligodendroglial tumors including paclitaxel, irinotecan, carboplatin, and etoposide plus cisplatin; however response rates have been approximately <15% [10, 30-32].

Although not approved for recurrent AG, bevacizumab may be another option for recurrent AG after failure with RT or chemotherapy [10]. Taillibert et al., evaluated the bevacizumab-irinotecan regimen in a consecutive series of 25 patients with recurrent oligodendroglial tumors retrospectively [33]. All patients had not responded to previous treatment either with RT or chemotherapy. They demonstrated an objective response rate of 72% with the combination of bevacizumab plus irinotecan, with a median progression-free survival of only 140 days [33].

FUTURE DIRECTIONS AND ONGOING STUDIES

Understanding the molecular pathology of AG has been increasingly changed the managements of patients with AG. There are ongoing two important trails that aimed to solve many questions about AG. The first one is “CODEL” trial, which is a phase III Alliance for Clinical Trials in Oncology/EORTC intergroup trial, which was planned to define treatment for newly diagnosed 1p/19q-codeleted AG patients. The patients with patients with 1p19q co-deleted anaplastic or low-grade gliomas were randomly assigned to: RT followed by PCV; or RT with concurrent and adjuvant Temozolomide (NCT00887146). Following EORTC 26951/RTOG 9402 reports, the original CODEL trial, which contained an RT-alone control arm, was closed.

The second ongoing study is phase III EORTC/North American intergroup trial (“CATNON”). In CATNON study patients with non-co-deleted anaplastic gliomas are randomly assigned to one of four treatment arms: RT; RT with concurrent Temozolomide; RT followed by Temozolomide; and RT with concurrent and adjuvant Temozolomide (NCT00626990). The preliminary results of the CATNON trial found that the patients who receive RT plus 12 cycles of adjuvant Temozolomide have improved survival compared with those who do not receive adjuvant Temozolomide (hazard ratio [HR] 0.65, 95% CI 0.45-0.93). The study is continuing in order to elucidate the role of concurrent Temozolomide.

CONCLUSIONS

- Anaplastic gliomas (AG) include 6–10 % of all newly diagnoses of primary brain tumors and comprise 6–15% of all primary brain tumors.
- During the past decade, understanding of molecular and prognostic significance of genetic alterations in AG has changed treatment strategies of these tumors, particularly for oligodendroglial subtype.
- According to updated WHO 2016 classification system, AA further divided into three categories as: anaplastic astrocytoma- isocitrate dehydrogenase (IDH) mutant; anaplastic astrocytoma-IDH-wild type; and anaplastic astrocytoma- not otherwise specified (NOS). On the other hand, Anaplastic oligodendroglial tumors further divided as: anaplastic oligodendroglioma-IDH-mutant and 1p/19q-codeleted; anaplastic oligodendroglioma-NOS; and anaplastic oligoastrocytoma-NOS.
- The initial treatment for AG is maximal safe resection.
- The management after initial surgery of AG with 1p/19q codeletion includes RT plus neoadjuvant or adjuvant PCV (procarbazine, CCNU, vincristine) chemotherapy based upon RTOG 9402 and EORTC 26951 studies. The sequence of PCV and RT has not been defined yet; therefore PCV may be used in either neoadjuvant or adjuvant setting.

- All patients with AG with 1p/19q codeletion should receive both RT and chemotherapy. Chemotherapy option may be either PCV or Temozolomide.
- The treatment of uni- or nondeleted AG is either RT only or primary alkylator-based chemotherapy only with deferred RT as determined in NOA-04. For these patients RT plus Temozolomide may be another treatment option.
- CATNON study will determine whether use of concurrent Temozolomide during radiation, in addition to 12 cycles of adjuvant Temozolomide, provides increased benefit. Adequate doses of RT are required to maximize the survival benefit in AG patients. Many radiation oncologists use a dose of 59.4 Gy in 1.8 Gy fractions for grade III tumors. Dose escalation > 60 Gy has not been shown any survival benefit. Additionally the optimal treatment volume for HGG patients' remains a controversial issue and varies among cooperative groups.
- There has been no standard therapy for patients with recurrent AG. The treatment choice for recurrent disease depend on multiple factors including the location of the tumor, the performance status of the patients, initial treatment modality, radiographic data, response to the initial treatment as well as the time to recurrence.
- Re-resection may be used in selected patients particularly those with asymptomatic tumor mass, good performance status.
- Alkylating chemotherapy is the treatment of choice for most patients previously untreated with chemotherapy.
- Re-irradiation is another option for recurrent AG. However the role of re-irradiation in patients with recurrent HGG is uncertain, and there is a lack of prospective data.
- Although not approved for recurrent AG patients, bevacizumab may be a treatment option for recurrent AG patients, who did not respond alkylating chemotherapy and RT.
- Ongoing CODEL and CATNON studies will solve the many questions about AG.

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