Editorial

Low grade glioma: a journey towards a cure

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Data from recent clinical, translational, and basic science research provide us with a powerful propelling energy towards a new design of clinical trials. The updated survival data from the RTOG 9802 (see below) hint at the possibility that among the long-term survivors, there might be some with a cure.

In all the fields of human oncology no entity has had the misnomer as that of a low grade glioma (LGG). Histologically it has been considered a "benign" or "low grade" tumor. Yet biologically in due time it almost always progresses towards a malignant killer. Furthermore LGG as a single histological grade contains heterogeneity of molecular entities each with its own biological behavior that calls for a personalized approach to treatment. For that reason there is a need to revisit data from past and recent clinical trials in order to adapt a new mindset in the design of LGG clinical trials. In order to adopt best evidence for treating the individual patient this new mindset must re-examine the applicability of past clinical data in light of the recent molecular data. Whereas past clinical trials have enrolled all LGG patients into one entity going forward the design of new clinical trials must take into consideration the incorporation and subsequent validation of the new molecular data.

As clinicians we approach each patient with the mindset that we live in the era of personalized medicine with a duty and emphasis upon true informed consent and the patient-physician shared decision-making. In treating LGG, revised survival data from past clinical trials with incorporation of molecular profile has shown that there is no on "size fits all" when it comes to treatment. There is always the individual approach to the individual patient.

The molecular era

The Cancer Genome Atlas Research Network has provided us with an integrative genomic analysis of diffuse LGG subdividing them into three different groups with different but important prognosis: IDH mutation with co-deletion of 1p/19q, IDH mutation without 1p/19q co-deletion, and IDH wild type (1). The 2016 WHO classification of tumors of the central nervous system has integrated these molecular markers with the traditional histological grading system (2).

Traditionally, in the design of clinical trials we have stratified patients into low-risk and high-risk LGG based upon the Pignatti criteria (3). These criteria have served us very well despite their two limitations: first there was no central pathological validation of the local pathology and second the analysis did not include molecular markers. Also keep in mind that EORTC (4) clinical trial that randomized patients with LGG between early *vs.* deferred radiation did not take into consideration either clinical, histological or molecular risk factors and it excluded patients with GTR. We now have biomarkers with important and different prognostication that will need to be incorporated in our treatment decisions and as such it would be unwise to indiscriminately recommend the "watch-and-see" approach.

The role of the extent of resection (EOR)

This is the one modality of treatment for LGG that is not the subject of controversy. In surgical neuro-oncology as important as it is how much the surgeon takes out is more important how much is left behind. In the RTOG 9802 trial the size of residual disease on the postoperative MRI correlated with the risk of progression (5) Although it remains to be answered whether GTR is equally important in all three LGG molecular subtypes, yet should radiotherapy become necessary it is wise that the volume to be radiated is as small as possible to minimize the late

cognitive effects of radiotherapy. Although systemic reviews and meta-analysis to quantify the association of the EOR with the likelihood of survival found no prospective or high class I or II studies, yet there appears to be an association between the EOR and improved OS as well as PFS (6-8). Despite ongoing controversy (9,10), additional benefits of the EOR in the hands of the experienced neurosurgeon are the following improvements in:

(I) Seizure control;
(II) QOL;
(III) PFS;
(IV) Symptomatic relief;
(V) Decadron-dependency;
(VI) Delayed malignant transformation.

Role of radiotherapy, chemotherapy or combination of radio-chemotherapy

In the landmark trial of RTOG 9802, 254 patients with high-risk LGG as defined by the Pignatti criteria were randomized to radiotherapy with or without adjuvant PCV chemotherapy. Of the patients who had progressed on the radiation-only arm more than 70% were treated with PCV. The immediate combination therapy resulted in a gain of PFS (10.4 *vs.* 4.0 years) and of median OS (13.3 *vs.* 7.8 years). PFS at 10 years was 51% *vs.* 21% in favor of the combination therapy (11). This trial has proven that when the decision is made to proceed with radiotherapy it would be best that adjuvant chemotherapy be used immediately following the completion of radiotherapy rather than waiting to start the chemotherapy for the time of progression. Neither arm of the study showed deterioration in the neurocognitive function as measured by the ("insensitive") MMSE. Molecular data was available in only 45% of the patients. The benefit was particularly in favor of the patients with oligodendroglioma molecular profile (IDH mutation and co-deletion of 1p/19q).

In a single arm trial of RTOG 0424 newly diagnosed patients with high-risk LGG were treated with radiotherapy plus concurrent as well as adjuvant temozolomide (12). Although the 3-year OS at 73% and the PFS at 59.2%, both better than at the time best known historical controls, yet we should keep in mind the median PFS of 4.5 years was inferior to that of 10.4 years in the RTOG 9802. This study also has pending analysis of QOL as well as a battery for neurocognitive function as secondary endpoints. Biomarker analysis is pending.

Recently the EORTC has reported on a randomized, phase 3, intergroup trial (EORTC 22033-26033) in which patients with high-risk LGG (using the Pignatti criteria) either newly diagnosed or progressive disease previously untreated after surgery were randomized to either radiotherapy or dose dense temozolomide (75 mg/m^2/day for 21 days every 28 days for 12 cycles (13). This, at the time of study initiation, was the only study to prospectively stratify tumor by molecular subtypes before treatment randomization. The authors have made it clear, however, that the study was not empowered for the analysis of the molecular subgroups but only for hypothesis generation. The median PFS was 46M for RT group *vs.* 39M for TMZ group (P=0.22). PFS was 62, 48 and 20 months for patients with IDH mutation and 1p/19q co-deletion, IDH mutation and no co-deletion, and IDH wild type respectively. The PFS at 5 years showed significant difference between RT and TMZ only for the patients with IDH wild type: 42 months for RT *vs.* 19 months for temozolomide (P=0.004).The median OS, necessary for future individualized treatment choices based upon the predictive effects of different biomarker subtypes, had not been reached.

Of note is that PFS for the RT only arm in this study (46 months) was similar to that of RTOG 9802 RT only arm (48 months).

There are three take home messages from this study: (I) since the IDH mutation with 1p/19q co-deletion had the best outcome regardless of treatment there is a strong argument in favor of initiating patients with this combination biomarker on chemotherapy, especially if there is a large postoperative residual tumor. (II) The second take home message is since patients with the IDH wild type tumors had the worst prognosis regardless of treatment there is an argument, supported by data from RTOG 9802 as well as the Cancer Genomic Atlas, that these patients should be considered as pre-GBM. (III) The third take home message as pointed out by the authors is that the study could not establish "a preferred treatment modality" with high variability of the individual disease course where some patients showed progression within few months while others were symptom free for many years, once again emphasizing the need for an individualized approach to treatment. As for the MGMT status, while it is important to check it in patients with the IDH wild type it does not provide any additional predictive or prognostic value in patients with IDH mutation (13).

There was no difference in the effects of RT or temozolomide upon the HRQOL or NCF as measured by

the (insensitive) MMSE (14).

Following the final report of RTOG 9802, the NCI suspended accrual to the one study, ECOG E3F05, which was designed for comparison of RT *vs.* RT plus TMZ.

The role of temozolomide as single agent in newly diagnosed LGG with postoperative residual disease: the UCSF experience

As mentioned above, the RTOG 9802 study showed significant improvement in both the OS and PFS for the patients who received PCV immediately following RT but not for those whose PCV was deferred to the time of progression. A natural question that arose from this trial was what would happen if alkylating chemotherapy was to be given at time of postoperative diagnosis and RT was deferred to the time of progression in the group with the most favorable molecular profile (the oligodendroglioma).

In a single arm, phase II trial the UCSF group has investigated standard temozolomide as a single agent in 120 patients with newly diagnosed LGG with postoperative residual disease by MRI (15). The primary end point was objective radiological response rate. The study looked at three molecular subtypes: 1p/19q co-deletion (45%), IDH mutation with intact 1p/19q (38%) and IDH wild type (16%). The majority of the patients (53% had not received salvage RT at time of last follow-up. Although the partial response rate was low at 6% yet there was a high rate (86%) of stable or improved disease. The median PFS was 4.2 years with a median OS of 9.7 years, which compare favorably to 4.0 and 7.8 years in the RT only arm of RTOG 9802 and 4.5 years PFS on RTOG 0424. Molecular subtype was associated with rate of disease progression, PFS and OS. Pretreatment tumor volume was associated with PFS and OS. Compared to 8% of patients with IDH mutation and 56% of patients with wild type IDH, patients with co-deleted tumors showed no evidence of progression during treatment, thus raising the possibility that these patients may be candidates for deferred or even omitted RT in favor of chemotherapy.

Summary for the future

(I) Minimizing inter-observer variability: a strong argument in favor of molecular stratification of LGG is the considerable variability in both the typing and grading of LGGs (16,17). In the Gorlia *et al.* study, 21% of cases reviewed had to be excluded due to differing central pathology review diagnosis, 17% being qualified as HGGs (16). For the future clinical trials quality controls would, as much as resources would allow, be a major plus if efforts are made to minimize the same problem when it comes to molecular profiling.

(II) There is an obvious need to evaluate and validate risk profile for patients with LGG to combine both Pignatti clinical criteria as well as the newly established molecular subtypes. Along with this validation comes the consideration for a prognostic model. In the past the one prognostic model for PFS and OS that was reported by Gorlia *et al.* (16) used data from 339 patients from the EORTC clinical trials for the development of the prognostic model and 450 patients from North American cooperative groups for the validation of the model. The study established three risk groups: low, intermediate and high. Criteria used to develop the prognostic models included clinical, radiological and histological criteria. Inclusion of molecular markers in the development of future prognostic profiles will substantially improve their predictive power.

(III) It is very clear that future clinical trials will have to address some very important issues as to the timing and choice of therapy for patients with LGG. Considering the impressive survival data from the RTOG 9802 it is conceivable that there might have been some cures amongst those with long-term OS. With that in mind, future clinical trials must incorporate HRQOL and neurocognitive function as important outcomes. Hopefully, with long term survivors it will be lesser of a challenge to capture long-term neurocognitive function. The time might come when neurocognitive function becomes an important primary endpoint in this disease entity, keeping in mind that the MMSE is not sensitive enough to identify early and important neurocognitive changes.

(IV) There is a need to best identify the subtype of LGG who are best candidates for "watch-and-see" approach. In this regard the data from both the EORTC (13) and the UCSF (15) in using temozolomide and deferring RT is an encouraging step in that direction. That being said, we need to keep in mind that 45% of patients with oligodendroglioma grade II and 74% of grade II astrocytoma recur as grade III-IV (18). Thus, the patients with favorable molecular subtypes will need

a closer monitoring of clinical as well as radiological status. We should also seek for paired tissue to examine if and how often does alkylating chemotherapy result in "super-mutated" aggressive tumor at time of recurrence.

(V) In the era of molecular data question arises if future clinical trials should combine both groups of lower grades II and III glioma with IDH mutation. Reuss *et al.* examined the relationship between age and histological grade *vs.* IDH mutation in predicting survival in patients with lower grades II and III. They combined three independent series containing 1,245 patients (out of a total of 1,360) with lower grades II and III and showed that IDH mutation type predicted survival much more robustly than WHO histological grading with overall survival of 10.9 and 9.3 years respectively for the patients with IDH-mutant grades II and III (19). In the same study, they also showed that age at presentation was identical for the same two groups of patients. These findings with far-reaching consequences for the practicing clinician need to be validated in prospective studies (19).

In another study, Olar *et al.* examined the IDH mutation status and role of histological grade, age, and mitotic index in the overall survival in patients with glioma grades II and III (20). They found that the prognostic impact of the grade was "modest" in the patients with the IDH-mutation type in comparison to IDH-wild type (HR 1.21 *vs.* 1.74, respectively). Mitotic index was significantly associated with outcome in the group with IDH-wild but not the IDH-mutation (HR 4.41 *vs.* 1.10 and P<0.0001 versus P<0.5, respectively). Age was significantly associated with outcome only in the IDH-wild type (20). There is an obvious need to take consideration of this date in the design of future clinical trials.

Lastly, we live in the age of personalized medicine with emphasis upon patient-physician shared decision making. Patient-centered goals are for improved survival, minimizing toxicity, improving HRQOL, and protecting neurocognitive function. I strongly believe these patient-centered goals and objectives are best pursued when patients are enrolled on clinical trials. Every patient with LGG is a candidate for a clinical trial until it is proven otherwise.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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