Regorafenib in glioblastoma recurrence: how to deal with conflicting 'real-life' experiences?

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To date, treatment options for glioblastoma recurrence are scarce. Based on efficacy data from randomized clinical trials, the nitrosourea compound CCNU (lomustine) is considered standard treatment after temozolomide failure. Treatment with lomustine in recurrent glioblastoma yields median overall survival (mOS) ranging from 8.6–9.8 months and median progression-free survival (mPFS) from 1.5–2.7 months.[1–3] In a recently published open-label, randomized, phase II trial (REGOMA trial) of patients with first glioblastoma recurrence, regorafenib was found superior to lomustine with mOS of 7.4 months in regorafenib-treated patients as opposed to 5.6 months in lomustine treated patients.[4] The radiographically assessed disease control rate (defined as complete/partial response or stable disease) was 44% in the regorafenib arm and 20% in the lomustine control arm. A yet unanswered question is whether regorafenib is going to replace lomustine as standard treatment should regorafenib superiority be confirmed in a planned randomized phase III trial.

In several countries, regorafenib is already being used in individual cases on a compassionate-use basis in patients with high-grade glioma. In a recently published single-center experience of regorafenib treatment in recurrent high-grade astrocytoma, we reported our experience with regorafenib under 'real-life' conditions.[5] Almost concurrently, another group reported on their experience with regorafenib for recurrent high-grade glioma.[6] Even though the sample size was rather low (total $n = 30$), the shallow response rate to regorafenib treatment was noteworthy. Furthermore, in most patients, an increase in tumor size up to fivefold in follow-up MR imaging 8 weeks from baseline was evident. These findings stand in contrast to the published results from the phase II REGOMA trial. It also struck us to find an unusually high incidence of Common Toxicity Criteria (CTC) grade 3 adverse events to regorafenib in all but one patient. Among the most debilitating adverse events was a case of hand-foot-syndrome that did not respond to topical dermatological treatment, and eventually led to the requirement for management with opioid analgesics to alleviate patient's symptoms. On the grounds of these preliminary results and the like from a few other centers,[6] one is tempted to call into question how to deal with these unfavorable 'real-life' data in light of a positive randomized phase II trial. Admittedly, there are some limitations to our findings for they merely rely on retrospective observations in a small number of patients. Also, regorafenib was not used at first glioblastoma recurrence but at a more advanced stage of disease of recurrent high-grade astrocytoma of WHO grades III and IV. It is conceivable that regorafenib is active in early glioblastoma recurrence only as opposed to later relapses. Indeed, it is self-evident that findings from a prospective randomized trial make for a higher level of evidence than data derived from case series, which is why we still consider regorafenib in recurrent glioblastoma.

On the other hand, it is noteworthy that the mOS of the lomustine control arm (5.6 months) in the REGOMA trial was considerably lower than that in two other phase III trials (8.6–9.3 months) testing the same population,[1,2] which raises the question how representative the results of the REGOMA trial are. It is to be expected that personalized, targeted treatment will gain traction in the near future in the field of glioblastoma treatment, with the focus being placed on identifying possible responders on molecular or clinical grounds. It should be added that the diverging

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mechanism of action of regorafenib (a multikinase inhibitor of oncogenic receptor tyrosine kinases) and lomustine (an alkylating agent) may be a reason for why regorafenib and lomustine might benefit different patient populations. To further elucidate this idea, it would be instructive to test regorafenib on glioma populations stratified by key molecular alterations.[7] In this context, it is interesting to observe that patients treated with regorafenib experiencing a possibly daunting adverse event, such as hand-foot syndrome, might derive benefit from regorafenib as opposed to those that do not. This is similar to what has been suggested in metastatic colon cancer treated with regorafenib.[6,8] In conclusion, the fundamental question of how to deal with negative 'real-life' data with positive results from a randomized trial at hand remains to be elucidated and may come up again after the next positive phase II/III trial.

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