Improved, personalized treatment of glioma necessitates long-term follow-up of cognitive functioning

KEYWORDS: cognitive functioning • follow-up • glioma • quality of life • treatment

Over the last few decades, substantial progress has been made in the treatment of patients with glioma, primary brain tumors arising from the supporting tissue of the brain. Although glioma is still an incurable type of cancer (almost all patients inevitably die of their disease), the introduction of new chemotherapeutic regimens has led to significant improvements in survival for patients with several subtypes of glioma.

The addition of temozolomide to standard radiotherapy for patients with glioblastoma (GBM; WHO grade IV glioma) not only resulted in increased median survival of the patient group as a whole but also in an improved 2-year survival (26 vs 10%). In addition, for the first time in history, a substantial number of GBM patients surviving for more than 5 years after diagnosis has been recorded [1]. Recently, a clinical trial in elderly patients with high-grade glioma showed that patients with a methylated O6-methylguanine-DNA methyltransferase promoter had a better response on temozolomide than patients with tumors with an unmethylated promoter [2]. Furthermore, two large randomized Phase III trials of the European Organisation for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) recently reported that the addition of procarbazine, lomustine and vincristine (PCV) chemotherapy to standard radiotherapy led to a doubling of median overall survival from approximately 7 to more than 14 years for a genetically defined (combined loss of heterozygosity of chromosomes 1p and 19q) subset of patients with a WHO grade III oligodendroglioma [3]. These two examples illustrate that genetically defined subsets of patients with high-grade gliomas can be distinguished by clinical behavior and response to therapy. Additionally, there are more new developments to report: coexpression of EGF receptor variant III (EGFRvIII) and phosphatase and tensin homolog deleted in chromosome 10 (PTEN) in GBM has been demonstrated to be associated with responsiveness to EGFR tyrosine kinase inhibitors [4]. This has resulted in the development of randomized Phase II and III studies on rindopepimut (CDX-110; Celldex, MA, USA) for GBM patients who have mutated EGFRvIII [5].

These developments imply that the number of treatment alternatives for GBM patients will increase in the coming years, and hence the prognosis of patients will hopefully further improve. With increased survival, the condition of the patient and therefore the quality of survival become essential. If effective treatment, in terms of prevention of tumor regrowth, would result in deterioration of cerebral functioning and, subsequently, in worse health-related quality of life (HRQOL), longer survival is less meaningful. The human brain is an extremely complex organ and we only understand small parts of its functioning. We know that brain functioning may be compromised by the presence of a brain tumor, and also by irradiation and by various kinds of chemotherapy, and that this will ultimately result in cognitive deterioration [6,7]. In contrast to older studies, the most recent Phase III clinical trials in glioma patients included HRQOL monitoring during the study [8,9]. Furthermore, some of the recently developed clinical trials even perform cognitive testing in (subsets of) patients at specified time points (e.g., EORTC Catnon Phase III study on anaplastic astrocytoma without codeleted 1p/19q). So far, the few completed Phase III trials of glioma patients that included standardized HRQOL monitoring demonstrated a transient decline during and shortly after (neo)adjuvant and concomitant chemotherapy,
while in the subsequent 2–3 years a steady recovery was found [8–10].

The best way to monitor cerebral functioning is repeated testing of cognitive functions. Apart from a report on cognitive functioning in an RTOG trial on anaplastic oligodendroglioma, no reports on cognitive functioning in large trials have been published yet [10]. The authors of this report concluded that cognitive functioning did not deteriorate during the first 5 years after treatment. However, they used the mini-mental state examination (MMSE) for the assessment of cognition, and we think that for proper detection of changes in cognition during treatment a more extensive neuropsychological test battery instead of the MMSE, should have been used [11]. Such an extensive test battery also covers cognitive domains such as attention and executive functioning.

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Unfortunately, information on HRQOL and cognitive functioning during the whole disease course (as opposed to only during the active treatment phase) of glioma patients is virtually lacking. We know that treatment-related cognitive deterioration may progress for many years after treatment in both low- and high-grade glioma patients [12–15]. Three years after initial treatment, seven out of 17 GBM patients, most without tumor recurrence, performed abnormally on a standardized neuropsychological test measuring attention, (working) memory and language [16], whereas in two other studies more than 5 years after initial treatment the vast majority of high-grade glioma patients suffered from cognitive deficits and only few patients functioned independently [12,15]. We recently assessed cognitive functioning and HRQOL in a subset of 32 long-term surviving patients who participated in the previously mentioned EORTC trial on addition of PCV to postoperative irradiation in anaplastic oligodendroglioma. We concluded that cognitive function was variable, but that most patients functioned independently with a relatively stable and acceptable HRQOL during the course of the disease. In this small sample, we could not identify an effect of the addition of PCV on cognition, nor on HRQOL, as long as patients did not suffer from tumor recurrence [17].

It is important to acknowledge that we do not have any proper information on the long-term impact of new chemotherapeutic drugs on cognitive functioning. With an increase in treatment options and the introduction of personalized or ‘tailored’ chemotherapy, information on HRQOL and cognitive function during and particularly after treatment is important when discussing treatment options with patients who have been diagnosed with a glioma. Currently, it is impossible to provide patients and their families with adequate information on these aspects as our knowledge is restricted to short-term side effects and anecdotal reports on long-term sequela. This lack of information may partly be explained by a drop in compliance of study patients (and their treating physicians) to fill out HRQOL questionnaires and to undergo neuropsychological testing. Moreover, in most trials, no further information, apart from survival, is allowed to be collected when tumor progression occurs. Retrieval of additional information on long-term survivors of experimental trials usually requires renewed approval of medical ethical committees. We think it is important that the design and organization of future treatment trials with all kinds of new, and often promising, drugs in brain tumor patients will facilitate lifelong close monitoring of cognitive functioning, in order to gain more insight into long-term central neurotoxicity.

References


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Editorial


