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Editorial Comment

Future trends in the treatment of brain tumours

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1. Introduction and current status

An international meeting on new developments in brain tumours was held in Padova on 16–17 March focusing on the challenges and perspectives of treating gliomas. Malignant gliomas, despite their low incidence (approximately 5–8/100 000 inhabitants/year), are among the most lethal and difficult to treat forms of tumours, often affecting the young, and carry a heavy social, psychological and economical burden. The appropriate management of brain tumours requires a combination of surgery, radiotherapy (RT) and chemotherapy. Whenever possible, patients should be referred to specialised centres, where different specialists with training in the field of neuro-oncology devote their efforts to these types of neoplasms.

Nowadays, according to the World Health Organization (WHO) classification of brain tumours issued last year [1], the histological diagnosis of a brain tumour must be completed by an immunohistochemical analysis and, preferably, by an assessment of chromosomal or other genetic alterations which may identify different subtypes of glial tumours and predict clinical outcome and response to therapy. Loss of PTEN and epidermal growth factor (EGF) receptor amplification define *de novo* glioblastoma, while alterations of p53, platelet-derived growth factor (PDGF) receptor alpha and p16 are mainly associated with secondary glioblastoma arising from a previous low-grade astrocytoma. The prognostic role of these genetic alterations, however, is not yet clear. In oligodendrogliomas, on the contrary, allelic loss of chromosomes 1p and 19q is now a recognised predictive element for durable responses to chemotherapy and prolonged survival [2]. Discrepancies in the recognition of mixed forms and in the grading of malignant gliomas are not uncommon among neuropathologists, and so expert panel review should be mandatory for multi-centre clinical trials.

2. Future trends for high grade gliomas

Preferably, the surgery performed is as extensive as possible, although this depends on the site of disease and the neurological performance of the patient. By means of ultrasound aspirator and microsurgery techniques, perioperative morbidity and mortality at present are low, albeit not completely absent. There is the hope that in the future, by means of intra-operative imaging (echography or magnetic resonance), computer-assisted surgical navigation systems and functional mapping of cortical motor areas, the neurosurgeon better recognises the extension of the infiltrating tissue, and may perform larger resections with less neurological risks.

No clinical trial has as yet demonstrated a consistent advantage of neo-adjuvant chemotherapy delivered before RT [3], even though this is probably the most suitable setting to evaluate the activity of new drugs.

A RT dose escalation above the 'standard treatment' (60 Gy in 30–33 fractions, for a total of 6 weeks) does not appear to be warranted, due to the lack of an increased response, and the risk of late neurotoxicity. A shorter treatment (up to 30–45 Gy) may be considered

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indicated in patients with a poor life expectancy, such as elderly patients with glioblastoma multiforme, because the uncertain survival advantage obtained with a full-dose regimen is counter-balanced by a longer period of treatment [4].

Hyperfractionation regimens or accelerated RT schedules have been studied in randomised trials, without significant benefit. Likewise, brachytherapy has not been shown to increase overall survival (OS) and causes a higher incidence of symptomatic radiation necrosis [5].

Today, the main perspectives of research in the field of radiotherapy of brain tumours are:

- the development of effective radio-enhancers: for instance, an allosteric modifier of haemoglobin, RSR13, increases oxygen release in peripheral tissues; it is administered 30 min before radiotherapy concomitantly with inhalation of oxygen [6].
- the use of radiosurgery, which is under investigation in the European Organization for Research and Treatment of Cancer (EORTC) 22972/MRC BR10 trial in which patients with high grade gliomas are randomised after surgery to receive or not a 20 Gy/4 fractions stereotactic boost after standard RT.
- the concomitant administration of chemotherapeutic drugs synergistic with RT (such as temozolomide (TMZ), see below);
- Boron Neutron Capture Therapy, consisting of administration of a B^{10} carrier (such as boron-Phenylalanine) that crosses the brain–blood barrier and accumulates in the tumour cells. Low-energy neutron irradiation reacts with B^{10}, and generates two charged particles (Lithium ions and alpha-particles) that damage tumour cell DNA and proteins. Phase I/II studies are ongoing, but high costs and elaborate safety measures would limit its accessibility.

Since the late 1980s, chemotherapy has been extensively applied in patients with malignant gliomas, both in the adjuvant setting and at the appearance of recurrence. Randomised trials on *de novo* malignant gliomas have shown median survivals of 9–11 months, improving 1 or 2 months by the application of systemic chemotherapy. In recurrent gliomas, objective response rates (except for oligodendrogliomas) do not exceed 30%, and time to progression (TTP) is relatively short. Meta-analysis has demonstrated a 8–15% prolongation of median survival. Besides, chemotherapy may palliate symptoms, and can improve the patients' quality of life, and constitutes the endpoint for medical treatment [7].

Methodological errors in past clinical trials, such as low statistical power, heterogeneous inclusion criteria (mixed histologies and different performance status), and different endpoints of efficacy (reduction/stabilisation of disease, TTP or OS), were perhaps one obstacle to the progress of the medical treatment of brain tumours.

A recent randomised trial by the Medical Research Council (MRC) Brain Tumor Working Party did not show an impact on survival of adjuvant procarbazine CCNU vincristine (PCV) chemotherapy in both grade III and IV astrocytomas [8]. In this study, however, OS rates (13 and 9 months, respectively) were somewhat poorer than other large series [9]. A selection bias or undertreatment may have contributed to this, as 20% of patients received only 45 Gy of radiotherapy.

TMZ, an imidazole derivative that alkylates DNA, is the most promising new drug in recent years, with an optimal profile of clinical tolerability, even in elderly patients. Response rates range from 5.4% [10] to 23.8% [11] in glioblastoma patients, with a progression-free survival at 6 months (PFS-6) of 26% [10] and 31.8% [11].

Moreover, a stabilisation or improvement in quality of life can be observed in most patients. The clinical benefit of synergy with radiation therapy by Stupp and colleagues [12] in a pilot study obtained a remarkable 1-year OS of 67%. A currently open large, randomised phase III study within the framework of the EORTC will evaluate the impact on survival of TMZ concomitant with standard external RT followed by six adjuvant cycles, every 4 weeks.

These observations on the presumed efficacy of TMZ has stimulated the enthusiasm of researchers who now explore new pharmaceutical combinations, such as TMZ and cisplatin, TMZ and liposomal doxorubicin, TMZ and BCNU and TMZ and CPT-11. Ongoing phase I and II trials are also evaluating the association of TMZ with interferon-alpha, tamoxifen and the anti-angiogenic agent thalidomide. Combinations with 13-*cis* retinoid acid and marimastat (an oral metalloproteinase inhibitor) are on their way towards phase III studies, as survival is the best endpoint of efficacy for these differentiating and anti-invasive, although not cytotoxic drugs.

High-dose chemotherapy with autologous stem cell rescue did not prove advantageous for high grade glioma patients, perhaps with the exception of medulloblastoma [13]. Today, most efforts are directed towards the development of new drugs or alternative strategies to overcome drug resistance.

O^6-Alkyl-guanine-DNA-alkyl-transferase (AGT) is one of the main targets, because experimental models and clinical experiences have shown a positive association with both response to chemotherapy and survival. Promotor methylation appears to be the principal mechanism of control of expression of this suicide DNA repair enzyme. Although their findings were criticised, Esteller and colleagues could establish a strong relationship between *AGT* promotor methylation and response to BCNU and OS in high grade astrocytomas

[14]. It is unknown whether *AGT* promotor methylation has an intrinsic prognostic role, or if its application is only relevant in patients treated with alkylants. Moreover, post-transcriptional modifications of *AGT*, nor concomitant methylation of other putative regulatory genes have been investigated. Therefore, further confirmatory studies are needed before larger scale applications of *AGT* methylation can be applied.

In any case, 1p and 19q loss and methylation of the *AGT* gene promotor are the first molecular markers that strongly correlate with response to chemotherapy and survival. We hope that, with the availability of new tests, in the near future the chemosensitivity of gliomas can be predicted, and medical treatments be tailored to single patient needs.

Current approaches that aim at inhibiting AGT and enhancing cytotoxicity of BCNU and TMZ are:

- pre-exposure to other agents that alkylate guanine in the O^6 position, and saturate AGT in the tumour cells. A phase II study was conducted by Brandes and colleagues [15] in 58 glioblastoma patients at first recurrence (after surgery and radiotherapy) who were treated with procarbazine (100 mg/m^2, on days 1–5), vincristine (1.4 mg/m^2, max 2 mg on day 3) and BCNU (80 mg/m^2 on days 3–5), every 8 weeks. A response rate (complete and partial response (CR + PR)) of 29% was obtained, PFS-6 was 42.3% (95% confidence interval (CI): 31.2–57.3%), and median OS was estimated to be 13.8 months.
- O^6-benzylguanine (OBG) is a direct inhibitor of *AGT*, and is devoid of side-effects. Phase I studies demonstrate that a dose of 100 mg/m^2 is able to deplete *AGT* [16], and phase II trials evaluating its association with BCNU are ongoing [17].
- Protracted and/or fractionated administration of TMZ is able to deplete *AGT* $>90\%$ [18], therefore new schedules have been elaborated: 200 mg/m^2 bolus and then 90 mg/m^2 every 12 h for nine doses [19], 21 days on and 7 off (maximum tolerated dose (MTD): 100 mg/m^2/daily) [20]; 7 days on and 7 days off (MTD 150 mg/m^2/daily) [21], daily for 42 days (MTD 75 mg/m^2/daily) [22]. These pilot studies proved that alternative schedules are feasible, but that haematological toxicity is dose-limiting with a significant incidence of prolonged lymphopenia and their potential is under study.

Anaplastic oligodendroglioma is the subtype of glioma most sensitive to chemotherapy (response rates $\geqslant 70\%$, with a 20% CR), and currently two large randomised studies are evaluating the role of six cycles of PCV ('neoadjuvant') before RT (Radiation Therapy Oncology Group) (RTOG 9402) or after ('adjuvant') RT (EORTC 26951). Notwithstanding the high responsiveness to medical treatment, a benefit from high- dose chemotherapy has not been demonstrated, and the incidence of severe toxicity is substantial with 20% toxic deaths [23]. Using TMZ as a second-line monochemotherapy, van den Bent and colleagues reported 26% responses [24], while other groups [25] obtained 40.8% responses with a PFS-6 of 53% and limited haematological toxicity. Studies employing TMZ alone or in combination with other agents as first-line therapy in recurrent anaplastic oligodendrogliomas are eagerly awaited.

3. Future trends for low-grade gliomas

The treatment of low-grade gliomas is still controversial. Compared with high grade subtypes, few clinical trials have been published to date, mainly because low-grade gliomas have a relatively low incidence, and require a long follow-up. The correct timing of surgery, RT and chemotherapy depends mainly on the patient's age and performance status, the localisation of disease, and the presence (or not) of progressive clinical symptoms. According to the randomised EORTC 22844 trial, early RT delays progression, but does not improve survival in these patients, and low-dose treatments (up to 45 Gy) seem to be as effective as the standard 60 Gy dosage [26]. Low-grade gliomas respond to chemotherapy [27,28]. For these patients, however, clinical improvement is usually the major endpoint, instead of a radiological shrinkage of tumour extension, which, indeed, is often difficult to achieve. If RT is postponed, neuro-psychological functions remain unchanged [29], while protracted alkylating chemotherapy may expose the patients to the risk of secondary tumours and infertility. TMZ was recently tested in low-grade gliomas [27,28], and showed no more than 12% objective responses. None the less, the high rate of stable disease (ranging from 28 to 65%), and the frequent clinical improvement of symptoms makes TMZ an alternative for low grade glioma patients.

4. Primary central nervous system lymphoma

Recent trials of first-line chemotherapy with high dose methotrexate (MTX) (>3 g/m^2) with or without other chemotherapeutic drugs in patients with primary central nervous system lymphoma (PCNSL) were discussed. The role of intrathecal MTX remains uncertain, as well as the need to add ARA-C or other cytotoxic drugs to MTX, which was confirmed to be the most effective drug. In patients that achieve a CR after chemotherapy, consolidation with whole brain RT may be postponed, or substituted with further monthly cycles of MTX. This approach appears to be particularly advantageous in elderly patients, who are more susceptible to the

damaging effects of large fields of radiation to the brain [30]. In fact, in a recent study conducted at the Memorial Sloan Kettering Cancer Centre (MSKCC) [31], non-irradiated patients >60 years had the same survival as irradiated elderly patients, most of whom died because of RT-induced leucoencephalopathy without any sign of recurrence. The most promising drugs for second-line treatment of PCNSL are TMZ, topotecan and rituximab (anti-CD20 antibodies); the role of high-dose chemotherapy with autologous stem cell rescue appears promising in light of the study of Sussain and colleagues [32], who reported 72% CR in 22 patients, with a 3-year disease free survival of 53%, albeit at the price of fatal toxicity in 5 patients (23%).

5. Future directions and development

Worldwide efforts are focused on finding new effective drugs for malignant gliomas, and probably most of the new drugs that will be tested in the future will not be cytotoxic. In fact, advances in the knowledge of the molecular events that underlie tumour formation and invasion prompt the researchers to develop molecules that target the specific pathways altered in glioma cells, for example the activation of membrane or cytoplasmic kinases (such as EGF receptor, protein kinase C and cyclin-dependent kinases (CDKs), the loss of physiological checkpoints in the cell cycle (such as p53 and $p105^{Rb}$), and the production of growth factors (PDGF and insulin-like growth factor (IGF)), angiogenic factors (vascular endothelial growth factor (VEGF)) or metalloproteinases (collagenases and elastases).

A swift evaluation of new compounds requires rapid phase I and II trials to be conducted in close collaboration between pharmaceutical companies and hospitals, with adherence to Good Clinical Practice rules. According to the current trend in neuro-oncology, PFS-6 is felt to be a reliable and objective endpoint of efficacy for phase II studies on new drugs, especially when dealing with agents not expected to induce a tumour shrinkage.

Within the framework of the EORTC, there is a Specific Program of Clinical Research devoted to new drugs (New Drug Development Program), which is currently promoting pilot studies on new drugs for brain tumour patients, in cooperation with the Early Clinical Study Group and the Brain Tumor Group. A multi-level programme of quality assurance concerning the collection and elaboration of pharmacokinetic and clinical data guarantees an optimal functioning of this highly specialised network devoted to the screening of new potential anticancer agents.

Gene therapy is a modern and innovative strategy of treatment for glioblastoma multiforme; small clinical trials showing some responses and no important side-effects have already been carried out. The association of a suicide gene, such as the Herpes Simplex *TK*, with immunomodulating cytokines, such as interleukin (IL)-2 or IL-4, so-called immunogene therapy, is an alternative strategy.

Short penetration of the gene vector in tumour nodules is responsible for low transfection efficacy *in vivo*, and this is probably one of the major obstacles to a strong and long-lasting antitumour effect by gene therapy. Liposomes or systems of convection-enhanced injection will probably allow the potentiation of the delivery of genetic material to glioma cells *in vivo*, and positron emission tomography (PET) may be extremely useful to monitor the process of gene transfer *in vivo*. Oncolytic viruses such as ONYX-015, which lyses cells that are devoid of a functional p53 protein, or a new engineered adenovirus that replicates only in cells in which $p105^{Rb}$ is altered, represent alternative approaches for selective targeting of tumour cells.

6. Conclusion

Extensive research devoted to the understanding and to improving the treatment of malignant gliomas over the past three decades has yielded few, but important, advances. One of these is insight into the origin and biology of brain tumours. A remarkable increase in the number of new agents being developed that are aimed at either the cell cycle, signal transduction, receptor membranes or inhibiting invasion of brain tumour cells has become apparent. Together with new ways of packaging these agents and improved modes of local delivery, we believe that in the next 5–10 years the outcome of brain tumours will be substantially improved.

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