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The role of chemotherapy in the treatment of low-grade glioma
A review of the literature

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Abstract

Low-grade gliomas (LGG) are a group of uncommon neuroglial tumors of the central nervous system. They are characterized by a grade I or II according to the WHO classification. Grade I tumors are non-invasive and amenable to surgical resection with curative intent. Diffuse infiltrating LGG (WHO grade II) are tumors with a highly variable prognosis. Curative resection can only rarely be achieved and progression is characterized by transformation into a high-grade glioma (WHO grade III-IV). There are only limited evidence-based treatment recommendations for the management of progressive LGG because of a lack of data from prospective randomized trials. Most often radiotherapy is offered to patients with symptomatic and/or progressive disease. Three randomized trials have failed to demonstrate a survival improvement with either early versus delayed radiation or with a higher dose of radiation. The potential role of chemotherapy for the treatment of LGG has only been addressed in phase II trials. The PCV-chemotherapy regimen is associated with considerable toxicity that limits its applicability. The results with temozolomide (TMZ) chemotherapy have been more promising. Patients with chemosensitive LGG as predicted by heterozygotic loss of chromosomal arms 1p and 19q or methylation of the promoter of the MGMT-gene in the genome of the glioma cells respond to TMZ. Radiotherapy will be compared to chemotherapy as first line treatment for LGG in two phase III studies that are planned for by the brain tumor group of the European Organization for Research and Treatment of Cancer (BTG-EORTC) and Radiation Therapy Oncology Group (RTOG).

Key words : Low-grade, glioma, chemotherapy, temozolomide, astrocytoma, oligodendroglioma.

List of abbreviations

LGG : low-grade glioma ; O = Oligodendroglioma ; OA = Oligoastrocytoma ; A = Astrocytoma ; RT = radiation therapy ; TMZ = temozolomide ; PCV = Procarbazine, CCNU, Vincristine ; TTP = time to progression ; PFS = progression-free survival ; OS = overall survival ; BTG-EORTC = European Organization for Research and Treatment of Cancer ; RTOG = Radiation Therapy Oncology Group ; Gd-MRI = Gadolinium enhanced magnetic resonance imaging ; WHO = World Health Organization ; EGFR = Epidermal Growth Factor Receptor ; PDGFR = Platelet Derived Growth Factor Receptor ; ASCO = American Society for Clinical Oncology ; GBM = Glioblastoma Multiforme ; MGMT = O6-methyguanine-DNA-methyl transferase ; AGAT = O6-alkylguanine-DNA-alkyltransferase ; HRQoL = health-related quality of life ; CML = chronic myeloid leukemia ; GIST = gastrointestinal stromal tumor.

Introduction

Low-grade glioma (LGG) is a denominator for a group of central nervous system neuroglial tumors with a WHO grade of I or II (Table 1). The actual incidence of LGG is not well defined but LGGs are estimated to represent about 25% of all primary central nervous system gliomas (with an estimated incidence of 100-150 new cases in Belgium on an annual basis). The majority of these lesions (75%) are completely or partially composed of tumor cells with oligodendroglial differentiation characteristics while a minority are pure astrocytic gliomas. WHO grade I glioma (such as the pilocytic astrocytoma) is in most patients readily curable by neurosurgical resection. Grade II lesions, in contrast, are diffuse infiltrating gliomas that are incurable by resection and irradiation in the vast majority of patients. Patients with grade II glioma face an extremely variable prognosis ; survival may range from less than one year up to more than fifteen years. Unfortunately, with the available treatment modalities recurrence and evolution into a lethal high-grade glioma (WHO grade III-IV) cannot be prevented.

Most neuro-oncologists consider a maximum safe surgical resection as the standard approach in a patient suspected of having a LGG. Histopathological examination of the resected tissue should allow for an accurate histopathologic diagnosis. In case of a tumor-associated mass effect

Table 1

Overview of the different neuroepithelial histological types of low-grade glioma according to the WHO classification of tumors of the central nervous system

Astrocytic tumors
Astrocytoma
Pilocytic astrocytoma
Pleiomorphic xanthoastrocytoma
Subependymal giant-cell astrocytoma
Oligodendroglial tumors
Oligodendroglioma
Mixed gliomas
Oligoastrocytoma

surgical removal can offer symptomatic relief. An impact of resection on survival is likely to exist but its extent remains unclear.

Following an accurate diagnosis of LGG, a "wait and see" policy is recommended for asymptomatic patients who are free of obvious tumor progression on T1/T2 weighted images on serial Gadolinium-enhanced MRI (GdMRI) of the brain. One should be however cautious and always compare follow-up MRI images with the images made at baseline. In slow growing tumors like LGG, comparison of sequential GdMRI images might falsely lead to the conclusion of no progression while comparison against the baseline images might indicate a slow progression. Non-Gd-enhancing LGG who are characterized as hypo- or iso-metabolic by radioisotope imaging (radiolabeled Methionine-, FDG-PET, or by alpha-methyl Tyrosine SPECT) are expected to have a better prognosis (Kaschten, Stevenaert *et al.* 1998 ; Padma, Said *et al.* 2003 ; Weckesser, Matheja *et al.* 2002). Clinical characteristics such as age over 40 years at diagnosis, astrocytoma histology, largest tumor diameter of more than 6 cm, tumor crossing the midline and the presence of a neurological deficit before surgery have been identified as negative prognostic clinical factors for survival in adult patients with cerebral LGG (Pignatti, van den Bent *et al.* 2002).

Radiotherapy

In patients with persistent clinical symptoms after surgery or in patients who experience symptomatic progression of their LGG, radiation therapy should be offered. Regarding the modality of radiation therapy, the results of 3 randomized clinical trials are available. A prospective randomized trial conducted by the European Organization for the Research and Treatment of Cancer (EORTC 22845/MRC BR4) investigated the outcome of early postoperative versus delayed radiation at time of progression (a dose of 54 Gy was administered in both treatment arms). An interim analysis in 1998 showed that time to progression was delayed in the early radiotherapy group but no difference was found in terms of overall survival (Karim, Afra *et al.* 2002). The long-term results of this trial have been presented at the latest annual meeting of the Society for Neuro-Oncology (Toronto, November 2004). With a median follow-up of 7.75 years, progression-free survival was significantly longer in the early radiotherapy arm. Survival after progression was longer in the control arm. Consequently, overall survival did not differ between both treatment groups (Van Den Bent , Afra *et al.* 2004).

No benefit was found for higher doses of fractionated radiation therapy in two randomized trials that respectively compared 59.4 Gy to 45 Gy and 64.8 Gy to 50.4 Gy (Karim, Maat *et al.* 1996 ; Shaw, Arusell *et al.* 2002). Therefore fractionated radiotherapy to the tumor and a 1-2 cm margin at a dose of 50-54 Gy is nowadays considered as the optimal treatment in symptomatic patients with tumor progression following surgery (Buatti, Meeks *et al.* 2002).

Long-term remissions can be observed following radiation therapy. However the majority of LGG patients will experience a recurrence of their glioma that inevitably will progress to a high-grade glioma (WHO grade III or IV). A substantial proportion of patients will be candidates for a second resection of their tumor and if no resection can be performed, a biopsy should be considered in order to accurately document the dedifferentiation grade of the recurrent lesion since this information is important for the determination of the patient's prognosis. Also, in case of a localized recurrence, re-irradiation can be considered an option, especially if the patient has had a considerable recurrence free interval following the first irradiation. Unfortunately, the benefit and toxicity of secondary surgery and/or radiation therapy have not been adequately established in large prospective studies.

Chemotherapy

At recurrence, and especially when the tumor is not amenable to resection or a second session of radiotherapy, chemotherapy is the only available etiological treatment option. Also, because of the lack of perspective for further improvement in the outcome of LGG patients treated by surgery and radiotherapy alone and because of the potential long term toxicity associated with radiotherapy, there has been a reappraisal of chemotherapy as a possible first-line treatment option following surgery.

Only a limited number of small phase II reports illustrate the efficacy of chemotherapy in LGG (Table 2). Encouraged by the high objective response rates (60-80%) observed in patients with anaplastic oligodendroglioma treated with PCV combination chemotherapy (procarbazine, CCNU and vincristine) this regimen has also been evaluated in patients with LGG (Cairncross, Macdonald *et*

Table 2

Overview of recently published prospective chemotherapy studies in patients with low-grade glioma

Chemo	Publication	Setting	Histology and patient number	Tumor response rates (%)	PFS	OS
PCV	Buckner, Gesme *et al.* 2003	6 cycles up-front followed by RT	17 O, 11 OA	52	NR	NR
	Stege, Kros *et al.* 2005	Up-front and at recurrence (non-enhancing)	7 O, 14 OA	81	Median = > 24 months for newly diagnosed patients	NR
TMZ	Brada, Viviers *et al.* 2003	Up-front	11 O, 2 OA, 17 A	57	3-years = 66%	3-years = 82%
	Hoang-Xuan, Capelle *et al.* 2004	Up-front	60 O	17	1-year = 73%	NR
	Quinn, Reardon *et al.* 2003	Pretreated patients	20 O, 5 OA, 16 A	61	Median = 22 months	NR
	Pace, Vidiri *et al.* 2003	Pretreated patients	4 O, 10 AO, 29 A	46	1-year = 39%	NR

PCV = Procarbazine, CCNU, Vincristine ; TMZ = Temozolomide ; O = Oligodendroglioma ; OA = Oligoastrocytoma ; A = Astrocytoma ; Up-front = before radiation in chemonaïve patients ; RT = radiation therapy ; NR = not reported ; PFS = progression-free survival ; OS = overall survival.

al. 1994 ; van den Bent, Kros *et al.* 1998). Mason *et al.* reported that none of 9 symptomatic patients with LGG (8 were treated at presentation) deteriorated during the first 6 months of therapy (median time to progression (TTP) 35 months, range 22-45). However, hematological toxicity was seen in all patients (Mason, Krol *et al.* 1996). In an abstract presented at ASCO 1997, L Thoron *et al.* reported their experience in 10 patients (median age 37 years) who had undergone an incomplete resection of a large (6-12 cm Ø) LGG. Objective tumor regression was seen in 3/10 patients. Toxicity was substantial with only 2 patients able to complete more than 4 cycles of PCV and a notably impaired quality-of-life in all patients. Hematological toxicity and hypersensitivity reactions to procarbazine limited therapy. Unfortunately 2 patients died because of toxicity following cycle 2.

A Dutch retrospective study reported the activity of up-front PCV chemotherapy in 16 newly diagnosed patients with large oligodendrogliomas or mixed oligoastrocytomas (for which radiotherapy would suggest treatment volumes of > 50% of the hemispheres) and 5 patients with recurrent non-enhancing oligodendroglioma and oligoastrocytomas after radiotherapy (Stege, Kros *et al.* 2005). In the newly diagnosed and responding patients, radiotherapy was withheld until the time of disease recurrence. Eight patients received the intended six cycles. Thirteen patients had to discontinue treatment due to toxicity (9 with asymptomatic myelosuppression, 3 with hepatotoxicity, one because of a secondary unrelated malignancy). Thirteen of the 16 newly diagnosed patients and three of five patients with recurrent tumors responded. Only one of the newly diagnosed and one of the recurrent patients experienced disease progression while receiving chemotherapy (median time to disease progression for the newly diagnosed patients was > 24 months). Several patients showed a significant clinical improvement despite only a modest improvement of the tumor image on the MRI scans. Combined loss of chromosomes 1p and 19q was documented in 7 patients but could not be correlated with response or survival in this small patient cohort.

Buckner *et al.* reported the most complete data on the efficacy of PCV chemotherapy administered before radiotherapy (Buckner, Gesme *et al.* 2003). In their phase II study, 28 patients with an incomplete tumor resection were treated with 6 cycles of PCV followed by radiotherapy. The aim of the study was to determine the efficacy of 6 cycles of PCV in terms of objective response rate. The application of the Macdonald tumor response criteria however proved to be problematic since only 13/28 tumors demonstrated contrast enhancement. Therefore anti-tumor activity was reported in terms of “radiological regression”. This was observed in 29% (8/28) of patients according to the interpretation of the MRI images by the treating physician and in 52% (13/25) of patients according to a blinded central neuroradiological review. Regressions occurred in non-enhancing and enhancing tumors. Toxicity was substantial with 28% (8/28) of the patients being unable to complete the 6 cycles of PCV as scheduled by the protocol. Myelosuppression was the most frequent toxicity with 75% of grade 3 or 4 leukopenia and 64% of grade 3 thrombocytopenia. Myelosuppression was cumulative in nature (related to the use of the nitro-

sureum CCNU). Other toxicity consisted of grade 2 anorexia, nausea/vomiting, abdominal pain, diarrhea, allergy, alopecia and grade 2/3 neurological toxicity, lethargy and sensory changes related to peripheral neuropathy. Notwithstanding the observed unacceptable toxicity profile of PCV chemotherapy in LGG patients, a phase III US Intergroup trial (R9802) is ongoing that will compare radiotherapy alone with RT + PCV.

Four prospective studies are available in which LGG patients are treated with Temozolomide (TMZ) chemotherapy. TMZ is an orally administered, second-generation imidozotetrazine derivative that is degraded spontaneously at physiological pH to the cytotoxic DNA-alkylating substance methyltriazeno-imidazole-carboxamide (MTIC). Unlike dacarbazine (DTIC), TMZ does not require hepatic activation. Because of these features, TMZ has superior penetration into the central nervous system (Ostermann, Csajka *et al.* 2004). A high cellular content of the repair enzyme O6-methyguanine-DNA-methyl transferase (MGMT-gene or AGAT) has been correlated with resistance to TMZ and methylation of the MGMT-promoter has been associated with tumor response (Esteller, Garcia-Foncillas *et al.* 2000 ; Paz, Yaya-Tur *et al.* 2004). Throughout a large number of phase II studies, TMZ has shown consistent activity against recurrent high-grade glioma (Yung, Prados *et al.* 1999 ; Yung, Albright *et al.* 2000 ; Brada, Hoang-Xuan *et al.* 2001 ; Brandes, Ermani *et al.* 2001). A recent large randomized phase III study demonstrated radiotherapy with concomitant TMZ followed by 6-months of adjuvant TMZ to be superior to radiotherapy-alone in newly diagnosed glioblastoma multiforme (GBM) (Stupp, Dietrich *et al.* 2002 ; Stupp, Mason *et al.* 2005). Methylation of the MGMT-gene promoter predicted for survival benefit derived from radiotherapy with concomitant/adjuvant TMZ (Hegi 2004 ; Hegi, Diserens *et al.* 2005).

In all the studies on LGG, TMZ was administered at a dose of 200 mg/m^2/day $\times$ 5 days every 28 days. Toxicity has been mild throughout these studies and largely comparable with what has been observed in studies on high-grade glioma (predominant hematological toxicity was seen with grade 3/4 intensity in about 8-13% of patients). Throughout these four studies a particular relevant clinical benefit was reported for patients presenting with treatment refractory epilepsy.

In both a British and a French study all patients had a confirmed histology of WHO grade II glioma and were radio- and chemotherapy naïve at the initiation of chemotherapy (no previous therapy other than surgery was allowed) (Brada, Viviers *et al.* 2003). In both studies the objective radiological responses were characterized by a slow reduction in the tumor size. In the British study on 30 patients (17 astrocytoma, 11 oligodendroglioma, 2 mixed oligoastrocytoma) an objective partial response was seen in 3 patients with an additional 14 minor responses (17/29 evaluable patients, 57%). Only one patient progressed under chemotherapy and 83% of patients completed the 12-month treatment period (defined by the protocol as the maximum duration of therapy in responding patients). Ninety-six percent of patients with impaired health-related quality of life (HQoL) had improvement in at least one HQoL domain and 54 % of patients with epilepsy had a reduction in seizure frequency. The 3-year progression free survival (PFS) was 66% and the 3-year survival 82%.

The French study investigated the response rate of low-grade oligodendroglial tumors to TMZ as initial treatment and evaluated the predictive value of chromosome 1p deletion on the radiological response. Sixty patients received a median number of 11 TMZ cycles. Clinically, 51% of patients improved, particularly those with uncontrolled epilepsy. The objective radiological response rate was 17% (partial response), 14% minor responses were seen, 61% of patients had stable disease and 8% experienced disease progression. The median time to maximum tumor response was 12 months (range 5 to 20 months). Loss of chromosome 1p was significantly associated with objective tumor response (Hoang-Xuan, Capelle *et al.* 2004).

The American study reported by Quinn *et al.* concerned 46 patients (median age 41y, range 7-61y) who had received prior therapy (radiotherapy in 52%, resection in 15% and nitrosurea based chemotherapy in 22% of patients) and 70% of the neuroimaging studies revealed an enhancing tumor lesion (Quinn, Reardon *et al.* 2003). There was 1 case of toxic death due to intracerebral hemorrhage, neutropenia, thrombocytopenia and sepsis. An encouraging objective response rate of 61% (24% complete response + 37% partial response) with an additional 35% of patients with disease stabilization (= 96% tumor control) was observed. The median progression-free survival was 22 months, the 6-months progression free survival-percentage was 98% and the 12 months progression free survival-percentage 76%.

In an Italian study on 43 pretreated patients with progressive LGG (29 A, 10 AO, 4 O) 30 patients were pre-treated with RT and 16 with PCV (Pace, Vidiri *et al.* 2003). An objective response was observed in 46.5% of patients (4 CR + 16 PR) and an additional 39% of patients achieved disease stabilization. Median duration of response was 10 months ; respectively 76% and 39% of patients were free of progression at 6 and 12 months.

Future perspectives

At present only a limited amount of data is available regarding the possible role of chemotherapy in the management of LGG. The available evidence

suggests that the PCV combination chemotherapy regimen is too toxic. Besides an unacceptable incidence of acute toxicity, a prolonged administration of nitrosurea-based chemotherapy would hypothetically also raise the risk of late toxicity such as secondary leukemia in patients with a considerably better prognosis than patients with high-grade glioma. The cumulative myelotoxicity of nitrosurea also interferes with a prolonged administration of this chemotherapy in a substantial number of responding patients. TMZ, on the other hand, has a more favorable toxicity profile, can be administered orally and has no known cumulative toxicity. Although late toxicity such as secondary leukemia cannot be ruled out with this alkylating agent, there are currently no observations of an increased risk associated with the prolonged use of TMZ. One should however consider the limitations imposed by the fact that current TMZ prescription is limited to high-grade glioma or metastatic melanoma patients who have a poor survival prognosis.

Early studies of the efficacy of chemotherapy for LGG have been complicated by the difficulty to evaluate radiological tumor response as a substantial proportion of LGG are non-enhancing on MRI and because tumor regression is much slower as compared to other cancers and high-grade glioma. Implementation of metabolic imaging might aid the early evaluation of chemotherapy efficacy. Validation of this alternative methodology for response evaluation however awaits confirmation in prospective trials.

The efficacy of chemotherapy in patients with a preceding history of a LGG that recurs after surgery and radiotherapy is more easily assessable as most of these patients will present with a contrast-enhancing tumor. TMZ has an encouraging activity in such patients (45-64% objective response). Most encouraging is the low percentage of both treatment naïve and pretreated patients in which tumor progression has been observed during the first 6 months of chemotherapy, suggesting that it is safe to defer other treatment options if the patient is followed-up carefully.

We lack sufficient data on the time to progression and on the overall survival of LGG treated with chemotherapy. However, the observations made on heterogeneous populations of LGG seem to indicate that the median TTP is well beyond the 1-2 year range. A substantial heterogeneity exists among LGG patients with regard to response to and survival following chemotherapy. This heterogeneity is correlated with the histology and molecular genetic characteristics of the tumor cells. An oligodendroglial histology in combination with a loss of chromosome arms 1p and 19q correlates with chemosensitivity and prolonged time to progression (Cairncross, Macdonald *et al.* 1994 ; Smith, Perry *et al.* 2000 ; Cairncross, Seiferheld *et al.* 2004 ; Van Den Bent , Afra *et al.* 2004). Although this correlation has mainly been established on anaplastic oligodendroglioma, recent publications have shown this is also true for LGG (Ino, Betensky *et al.* 2001 ; Felsberg, Erkwoh *et al.* 2004 ; Hoang-Xuan, Capelle *et al.* 2004). Patients with a LGG that has a 1p/19q deletion are likely to derive a substantial benefit from chemotherapy and could be spared the potential long-term toxicity of radiotherapy. A six- to twelve month treatment course with TMZ might be appropriate in this setting and is unlikely to impose an excessive risk for early or late toxicity. Oligodendroglial or mixed AO LGG that have only a loss of chromosome 1p might still derive a benefit from frontline chemotherapy. This benefit, however, is expected to be smaller in terms of time to progression. Such patients might possibly benefit more from immediate radiotherapy following the achievement of a best response under chemotherapy. Combined metabolic and MRI imaging could potentially identify persistent or progressive disease after a 6 month course of chemotherapy. Any regression obtained under chemotherapy might translate itself in an improved survival following radiotherapy since the tumor dimension is known to be a negative prognostic factor with regards to TTP following radiotherapy (Pignatti, van den Bent *et al.* 2002).

MGMT-promoter methylation has recently been identified as a strong predictive factor for a survival benefit from combined radiotherapy plus concomitant TMZ followed by 6 months of adjuvant TMZ. A subgroup of LGG patients with a worst prognosis defined by clinical parameters, might be candidates for such a combination treatment at the condition of a demonstrated MGMT-promoter methylation in the glioma cells (Pignatti, van den Bent *et al.* 2002 ; Mollemann, Wolter *et al.* 2004).

Finally there will also be patients with LGG who will not derive any benefit from chemotherapy. These are patients with a high risk for chemotherapy related complications (such as patients with a high risk for infections or a bleeding diathesis) or tumors that can be predicted to be chemoresistant (as characterized by a pure astrocytic histology, absence of 1p/19 loss of heterozygosity and a non-methylated MGMT-promoter).

Whether and how we can improve the outcome of patients with LGG can only be answered in prospective clinical trials. Both the EORTC and RTOG will conduct a phase III trial in which symptomatic LGG patients will be randomized between radiotherapy and TMZ chemotherapy. Despite its encouraging activity, implementation of TMZ chemotherapy for the treatment of LGG will not likely provide a definite solution for most patients with this disease. A rapid gain in insight into the molecular-genetic background of LGG is likely to provide us within the next years with rational tar-

gets for molecular therapy. Already, EGFR and PDGFR targeted small molecule tyrosine-kinase inhibitors are in clinical trial for high-grade glioma. In contrast to their high-grade counterparts, LGG are genetically much more stable cancers. In analogy with the successes achieved with targeted therapy for the treatment of the genetically stable phase of chronic myeloid leukemia (CML) or gastrointestinal stromal tumors (GIST), the rewards of targeted therapy approaches for LGG might be by far more rewarding as compared to their application in high-grade tumors. How to implement most efficiently this growing knowledge and the available therapeutic armamentarium is a challenge for the near future.

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