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Chemotherapy for malignant gliomas

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Chemotherapie maligner Gliome

Zusammenfassung. Nach einer Durststrecke von mehreren Jahrzehnten konnte in der Therapie des Glioblastoma multiforme, des häufigsten und bösartigsten primären Hirntumors bei Erwachsenen, endlich eine Verbesserung der Prognose erreicht werden. Durch die konkomitante und adjuvante Therapie mit Temozolomide, einer oralen alkylierenden Substanz, konnte eine signifikante Verlängerung der Überlebenszeit der Patienten erzielt werden (Studie EORTC 26981/22981, NCIC CE3). Diese Therapie wird von den meisten Patienten gut vertragen. Während der konkomitanten Phase sind wöchentliche Blutbildkontrollen dringend angezeigt. Die häufigste und schwerwiegendste beobachtete Toxizität waren Grad III und IV Thrombozytopenien und Lymphozytopenien bei etwa 5 % der Patienten. In der EORTC-Studie war eine Prophylaxe gegen Pneumocystis carinii Pneumonie vorgeschrieben. Eines der wichtigsten Ergebnisse der Studie war auch, dass die Lebensqualität der Patienten durch die ganze Therapiephase hindurch stabil gehalten werden konnte.

Wieweit sich dieses Therapiekonzept auf andere Hirntumore übertragen lässt oder welche Dosismodifikationen von Temozolomide oder Kombinationen mit anderen Substanzen, insbesondere mit „small molecules", die Effektivität der Therapie steigern können, sollte in weiteren Studien untersucht werden.

Schlüsselwörter: Maligne Gliome, Chemotherapie.

Summary. Concomitant and adjuvant treatment with Temozolomide, an oral alkylating agent, has significantly improved the survival of patients with newly diagnosed glioblastoma multiforme (study EORTC 26981/22981, NCIC CE3). When given with the appropriate cautiousness including weekly clinical and laboratory controls during the concomitant phase, this therapy is generally well tolerated. The observed toxicity is mainly haematological. Grade III and IV toxicities mainly thrombocytopenia or lymphocytopenia occur in around 5 % of patients. A prophylaxis against pneumocystis carinii pneumonia was mandatory in the EORTC study. Most importantly, the quality of life of the patients was maintained throughout the therapy.

This success has boosted the whole field of neurooncology, after a dry spell of more than thirty years for glioblastoma multiforme. Whether this concept will be applicable to other brain tumours and which schedule modifications or combinations with biologicals will improve the effectivity of therapy in brain tumours should be explored in further studies.

Key words: Malignant glioma, chemotherapy.

Introduction

The use of chemotherapy for patients with malignant gliomas was debated controversially for decades [1, 2]. Radiotherapy was the mainstay of postoperative treatment of patients with malignant gliomas since the seventies of the twentieth century, when Walker et al showed that adjuvant radiotherapy doubled the median survival length of patients with glioblastoma multiforme (GBM) from 3 to 4 months to 9 to 12 months [3, 4] The additional use of chemotherapy, mostly of nitrosoureas able to cross the blood-brain barrier, like ACNU, BCNU, CCNU and fotemustine remained controversial, as a significant increase of survival could not be demonstrated in a randomized phase III trial [1, 2, 5]. Although it was repeatedly demonstrated that patients treated with chemotherapy in addition to radiotherapy had an increased the probability to become long term survivors, an unequivocal benefit could never be demonstrated [5]. Two meta-analyses pooling data of more than 3000 patients showed that the proportion of 2-year survival increased from 15 % to 20 % with nitrosourea-based chemotherapy [6, 7]. Whereas in the USA adjuvant therapy with nitrosoureas was considered a sort of standard in absence of a better alternative, half of the European patients got chemotherapy only in relapse.

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For several years most treatment options were tested in small phase II studies, often monocentric, revealing a lot of futile and several promising efforts, only rarely explored further potential progress. In this context of multiply disappointed hopes, the EORTC brain tumour group together with the National Cancer Institute of Canada started a cooperative study for patients with newly diagnosed glioblastoma multiforme with an innovative design with continuous oral low dose chemotherapy with Temozolomide together with radiation therapy. This concept yielded unequivocal prolongation of survival in this devastating disease [8].

Chemotherapy of newly diagnosed glioblastoma multiforme with Temozolomide

The regimen established by the study EORTC 22981–26981/NCIC CE3 is now recognized as the new standard therapy for patients with newly diagnosed GBM.

Oral chemotherapy starts with the first day of radiation therapy and consists of Temozolomide (TMZ) 75 mg/m^2 taken 120–60 minutes before radiation. In this low dose, most patients do not experience nausea and vomiting, so the use of a prophylactic anti-emetic medication is optional and can be tailored to the individual needs of the patient. The absorption of TMZ shows only a slight decrease after meals (only 10 % reduction of the AUC, delayed peak concentration), implicating that patients can take the medication at any time of the day according to their scheduled time of radiotherapy and at the same time during weekends [9]. This schedule is maintained for the entire duration of radiotherapy e. g. six weeks, for 30 radiations of 2 Gy each.

Safety monitoring and pneumocystis carinii prophylaxis

During this course of chemotherapy weekly controls of the blood counts and differential counts are mandatory. In the "Stupp-study", severe haematological toxicity was a rare event, affecting less than 5 % of patients in the combined treatment arm, but the rare events of severe thrombocytopenia and of severe leucopenia and lymphocyte depression occur abruptly and deserve immediate stop of chemo-radiotherapy and taking of adequate measures [8]. Extended application of TMZ leads to depletion of CD4 lymphocytes [10–12]. Furthermore, it must be considered that patients with brain tumours under medication with corticosteroids might be in a profound immunodeficient state. Hughes et al observed that more than 20 % of patients with anaplastic gliomas receiving radiotherapy and 24 mg daily of dexamethasone without any further medication showed CD4 counts of less than 200/µl, which is the cut-off point for starting a prophylaxis against pneumocystis carinii pneumonia [13]. In a national consensus, it is recommended to perform pneumocystis carinii prophylaxis in case of: Lymphocytes = 500/mm^3.

Usually, the haematological toxicity is rapidly and spontaneously reversible after the stop of chemotherapy, but cases with 5 weeks of severe thrombocytopenia requiring repeated transfusions and of severe and even fatal pneumocystis carinii pneumonia have been observed. In the protocol of the EORTC study 26981, a pneumocystis carinii prophylaxis was mandatory for all patients. The need for this prophylaxis has been debated since then, pointing out that only a minority of patients develop the low CD4 counts requiring a prophylaxis and that it should be given to patients with lower than 200 CD4 lymphocytes/µl. This is intellectually convincing but CD4 counting, at least in our country, costs tenfold the sum needed for the most expensive prophylactic treatment, which is a strong argument for giving inhalative prophylaxis with pentacarinate to all patients and saving the money for CD4 testing [14].

Adjuvant treatment

The adjuvant treatment begins four weeks after the end of the chemoradiotherapy, when eventual haematological toxicity has resolved. TMZ is given for 5 days in the dose of 150 mg/m^2 daily. For this higher dose most patients need antiemetic prophylaxis. For the first cycle a blood count should be done at day 21. The next cycle starts day 28 with a dosage of 200 mg/m^2 of TMZ when blood counts are appropriate and no other severe toxicity has occurred. This regimen should be continued for 6 cycles. In the EORTC study, approximately 50 % of the patients in the combined treatment arm completed the full length of 6 adjuvant cycles. The reason for discontinuation was mostly disease progression, toxicity only the exception. Several patients of our centre complained about stomach pain after TMZ, which responded to proton pump inhibitors and symptomatic treatment.

The study includes regular assessments of the subjective quality of life by the patients. Taphoorn et al could demonstrate that the quality of life of the patients could be maintained throughout the whole duration of therapy [14].

Monitoring of treatment response

MRI should be done every three months to monitor treatment response. In the EORTC Study, the first MRI was foreseen four weeks after the end of the chemoradiotherapy, but at this time point MRI scans might falsely suggest disease progression, as post(radio)therapeutic changes might not have resolved. As patients might experience symptoms of increased cranial pressure and even progressing neurological symptoms [15] which recur spontaneously or after anti-oedematous treatment, it is preferable to do the first MRI scan at least 6, better even 8 weeks after the end of radiotherapy, even if this delay might appear unacceptably long for patients and their families.

Outcome of concomitant and adjuvant treatment with Temozolomide in patients with newly diagnosed glioblastoma

Patients treated according to the concomitant and adjuvant TMZ regimen achieved a significantly longer median time to progression (6.9 vs. 5.0 months), a longer median survival (14,6 vs. 12,1mo) and, most impressive, the percentage of patients alive after two years was 10 % in the arm with radiotherapy only and 26 % in the com-

bined treatment arm. All these differences were highly significant. Subgroup analysis showed that patients benefited independently of age or prior tumour resection. Women lived in median two months longer than men. Patients with a performance status of WHO grade 2 did not show a benefit from the combined treatment.

Using tumour samples of 206 patients enrolled in the study, Monika Hegi could demonstrate that the strongest factor influencing treatment response was the silencing of the DNA repair enzyme MGMT by methylation of its promoter region. 46 % of patients with a methylated MGMT promoter who received the combined treatment were alive at 24 months, compared to 14 % of patients, who received the same treatment, but whose MGMT promoter was unmethylated and who showed no difference in survival to patients in the radiotherapy only arm. In the EORTC study, 45 % of the examined patients had a silenced MGMT promoter [16].

Esteller has shown that MGMT promoter methylation is essential for the response of patients with glioblastoma to the therapy with nitrosoureas, and his findings have been confirmed by Silber and Kamiryo [17–19]. This implicates that presently all therapies that have shown some effectiveness in the treatment of newly diagnosed glioblastoma multiforme rely on MGMT silencing and that for the patients with unmethylated MGMT promoter region either overcoming this resistance or other therapeutic strategies will be needed.

In this situation, several new trials have started or will start soon that investigate possibilities to overcome MGMT resistance by dose dense temozolomide schedules or combination of TMZ with O6 benzylguanine or with nitrosoureas [20]. New agents with a different mode of action like antagonists to the epithelial growth factor like erlotinib [21] or VEGF (vascular endothelial growth factor) and PDGF (platelet derived growth factor) receptor antagonists like PTK 787 [22] or imanitinib mesylate [23, 24] or cilengitide, a snake venom antagonizing the tumour vasculature (an alphaVbeta3 inhibitor) [25], or an antagonist to the protein Kinase C beta, enzastaurin [26] which suppresses angiogenesis and leads to apoptosis are investigated in trials with and without combination to TMZ.

Are there alternatives to Temozolomide?

Most patients with malignant gliomas or their relatives ask for the concomitant treatment with Temozolomide. However, some patients opt for an alternative intravenous treatment with fotemustine/dacarbacine given every three weeks in an outpatient schedule and where outcome is quite similar to TMZ, without the risk of the pneumocystis carinii pneumonia and with slightly more haematological toxicity at the end of the treatment schedule [27]. This treatment is particularly suitable for patients with compliance problems. Furthermore, the length of the survival durations of GBM patients achieved in the NOA study 01 combining ACNU with VM26 (17.3 months) or with ARA-C (15,1months) in an adjuvant setting – thus without concomitant treatment are worthy of consideration and discussion [28].

Patients with relapsed glioblastoma

In patients who have shown a good response to the initial treatment and/or – in the absence of measurable disease postoperatively – in patients who relapse after a delay that suggests a response to the initial therapy (in practice at least 6 months after the treatment stop), as in other tumour entities, reinduction with the initial treatment appears safe and effective. Alternatively, nitrosourea based chemotherapy as PCV, BCNU and CCNU can be given in relapse, when response to an alkylating agent can be expected.

However, in patients with progression under treatment or with early relapse, a change of treatment strategy is mandatory. To date, there is no standard therapy for this condition, but several compounds have been tested successfully. Some patients might benefit from a PDGF-R antagonist like imatinib, given orally with or without Hydroxyurea, as demonstrated by Raymond et al. and by Dresemann et al. [23, 24]. All the compounds mentioned previously which are now tested upfront in patients with newly diagnosed GBM are under current investigation or have already been investigated in patients with relapse.

Patients with anaplastic astrocytoma

In most older studies, combining patients with anaplastic gliomas WHO III and patients with glioblastomas, the patients with anaplastic gliomas showed a higher proportion of treatment response and longer periods of survival [5]. Currently, treatment of patients with anaplastic gliomas is done in analogy to treatment of glioblastoma multiforme. A cooperative study of EORTC/NCIC/RTOG is planned to explore the treatment response of patients with anaplastic gliomas without 1p/19q deletion to a regimen similar to that of the study 22981 with the possibility to prolong the adjuvant treatment phase.

Patients with malignant oligodendroglioma

The renewal of the whole field of neuro-oncology has started with the finding of Gregory Cairncross who described in 1994 that oligodendroglioma is a chemotherapy sensitive disease, using the standard regimen in neuro- oncology PCV, a combination of procarbacine, CCNU and vincristine [29]. This regimen is very effective, yielding objective responses in nearly all patients treated, but this range of responses could be reproduced with TMZ, without the severe haematological toxicity of PCV, limiting the median number of cycles given to three, in the majority of patients [30].

In further molecular studies, it could be shown that patients whose tumours bore deletions of the short arm of the chromosome 1p and /or the long arm of chromosome 19q are those who respond to radiotherapy and to chemotherapy with either PCV or temozolomide, resulting in survival durations of longer than 6–7 years, in patients with the deletions compared to 2–3 years in patients without the deletions. The latest findings in this rare glioma entity suggest that the sequence of therapies seems not to be important in oligodendroglioma, as long as the treatment options are used [1]. A formal study exploring the effectiveness, cognitive outcome and

patient's satisfaction would be needed to answer the question whether chemotherapy or radiotherapy should be the start of the treatment of a newly diagnosed oligodendroglioma with 1p/19q loss.

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