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Six year survival after prolonged temozolomide treatment in a 30 year old patient with glioblastoma

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Abstract

Glioblastoma (GBM) is the most malignant primary brain tumour in adults. Since 2005 surgery followed by radiotherapy with concomitant Temozolomide (TMZ) is the standard care for patients with a GBM. Despite these improved treatment strategies, survival of GBM-patients remains poor, and there are very few patients who survive for a long time. Also there is no standard therapeutic strategy after six cycles of TMZ, and further treatment is at the physician's discretion. We report a case of a young patient with a glioblastoma who, not only showed dramatic clinical and radiological improvement after TMZ treatment but who now also (under continued TMZ therapy) survives over 6 years, with complete remission clinically and radiologically. Up till now there are no studies describing TMZ treatment in GBM patients for as long as 6 years.

Key words: Glioblastoma; long-term survivors; Temozolomide; MGMT methylation.

Introduction

Glioblastoma (GBM) is the most frequent and most malignant primary brain tumour in adults. The 5-year survival decreased with age from 13% to less than 1% from the youngest (15-45 years) to the oldest age group of patients (75 years and over). Data from a recent phase III trial show a 2 year survival rate of 13-26.5% (Stewart 2002; Stupp *et al.*, 2005).

The results of the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) Clinical Trials Group showed 1- and 2-year survival rates of 61% and 26.5% in patients treated with concomitant radiotherapy plus daily Temozolomide (TMZ) followed by an additional six cycles of TMZ (Stupp *et al.*, 2005).

This regimen is now the standard care for patients under the age of 70 with a newly diagnosed GBM.

During the last few years several molecular markers have been identified in gliomas with prognostic and/or predictive value.

Combined loss heterozygosity of chromosome arms 1p and 19q in (oligodendro)gliomas, is a predictor for better response to chemotherapy as well as radiotherapy, and predicts longer survival (Jeuken *et al.*, 2004). In contrast, loss of 19q alone, found in especially astrocytomas, is associated with malignant progression (Jeuken *et al.*, 2006).

Amplification with over-expression of EGF-R, as well as PTEN and/or CDKN2A deletions seems to be correlated with a worse prognosis and response to therapy (Jeuken *et al.*, 2006).

O6-methyguanine-DNA-methyltransferase (MGMT) is involved in DNA repair of alkyl adducts and plays a major role resistance to chemotherapeutic agents.

Tumours with a methylated MGMT-promotor are reported to be more sensitive to alkylating agents such as carmustine (BCNU), procarbazine, lomustine (CCNU) and TZM. Hegi et al found a median survival of 21.7 months and a 2 year survival of 46% in patients with MGMT promoter methylation vs 12.7 months and a 2-year survival of 13.8% in patients without MGMT promoter methylation (Hegi *et al.*, 2005).

As up till now there is no standard therapeutic strategy after six cycles of TMZ, the EORTC/NCIC trial leaves the question of adjuvant treatment duration unanswered. Further treatment is at the physician's discretion.

Here we describe a young patient with rapid progressive neurological deterioration due to a GBM. After initial radiotherapy, we treated her with long term TMZ and she has been showing a complete

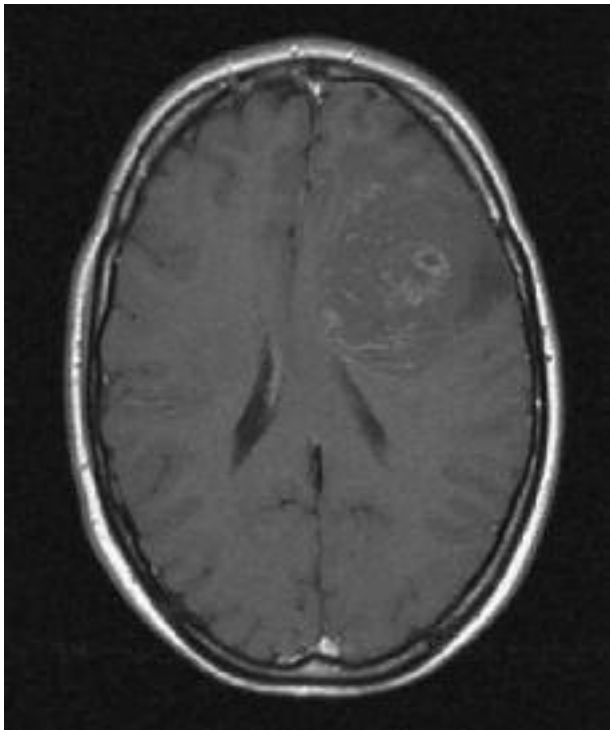

FIG. 1. — T1 weighted MRI with contrast injection before treatment, showing, in the left frontoparietal region, a partly enhancing mass with a focal ring-shaped enhancement, suggestive of high grade glioma with focal necrosis.

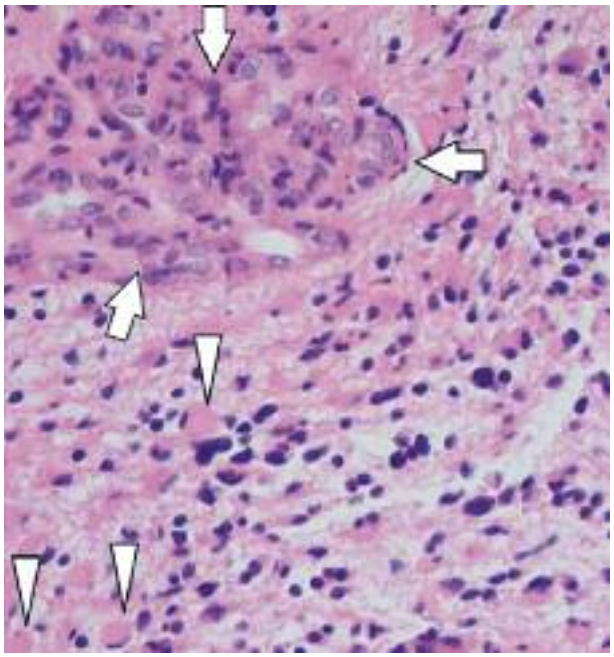

FIG. 2. — Histology of the brain tumor; the tumor cells reveal astroglial morphology with an eosinophilic cell body of variable size (some gemistocytic tumor cells indicated by arrowheads) and eosinophilic cell processes; Additionally, the tumor cells show marked nuclear pleiomorphism; according to the WHO 2000 and 2007 classification the presence of florid microvascular proliferation (indicated by arrows) in this diffuse infiltrative astroglial neoplasm leads a diagnosis of glioblastoma (Hematoxylin & Eosin staining, original magnification × 200).

clinical and radiological response for over 6 years now.

Case report

A 25 year old, previously healthy woman sought medical attention for hemiparesis and difficulties with speech which developed in the course of 2 months. A T1 weighted MRI showed a large (61 by 50 by 48 mm) partly contrast-enhancing mass in the left frontoparietal region with a focal ring-enhancement, suggestive of high-grade glioma with necrosy (Fig. 1). She underwent gross total resection of the tumour that was histopathologically characterized as GBM (Fig. 2). Post-operatively the patient developed a focal insult for which she received phenytoin 2dd 200 mg. A few weeks after the operation radiotherapy was started, with a total dose of 60 Gy (given in 30 daily fractions of 2 Gy for 30 days) and she received 13.5 mg dexamethason. Two and a half months later she quickly deteriorated and was admitted to our hospital in a somnolent state. Neurological examination revealed a total right sided paralysis and aphasia. A brain CT-scan showed, compared to the previous MRI, tumour progression with a severe space-occupying effect (Fig. 3). At that time the dexamethason dose was slightly increased to 15 mg daily, and TMZ treatment was started with a schedule of 150 mg/m(2)/day for 5 days every 4 weeks. A month later she was able to walk again and an MRI of the brain showed no signs of further tumour progression.

Another month later she did very well clinically and it was decided to increase the TMZ to 200 mg/m(2)/day for 5 days every 4 weeks. The corticosteroids were continued in a low dose (8 mg daily) for about a year.

After twelve cycles she developed thrombocytopenia and the thirteenth cycle of TMZ was postponed. At that moment the MRI showed less tumour enhancement. A few weeks later the TMZ treatment could be continued and up till now she receives TMZ with a schedule of 75 mg/m(2)/day for 5 days every 6 weeks without side effects.

MRI's showed a continuing reduction of the tumour enhancement and of the space occupying lesion. Eventually, 4 years after the start of TMZ no space occupying lesion or enhancement is seen (Fig. 4). Treatment with TMZ was continued up till now (Fig. 5).

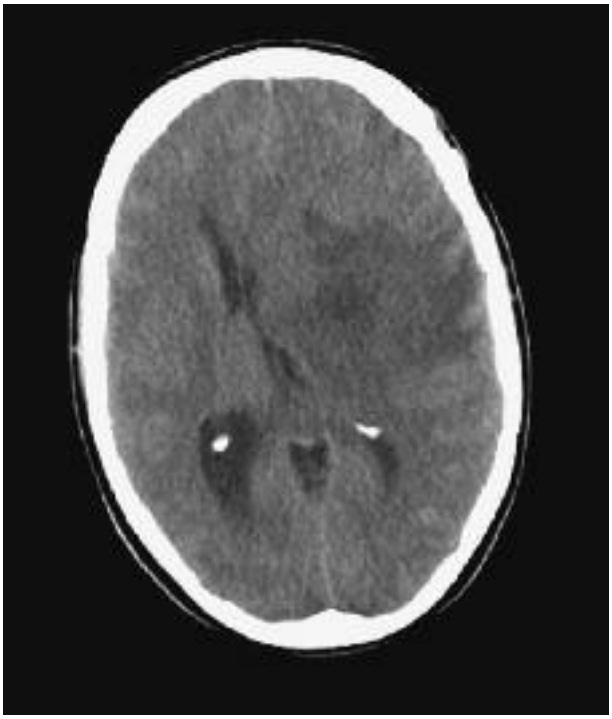

FIG. 3. — CT-scan without contrast injection, 2.5 months post-operative, showing tumour progression with severe space-occupying effect.

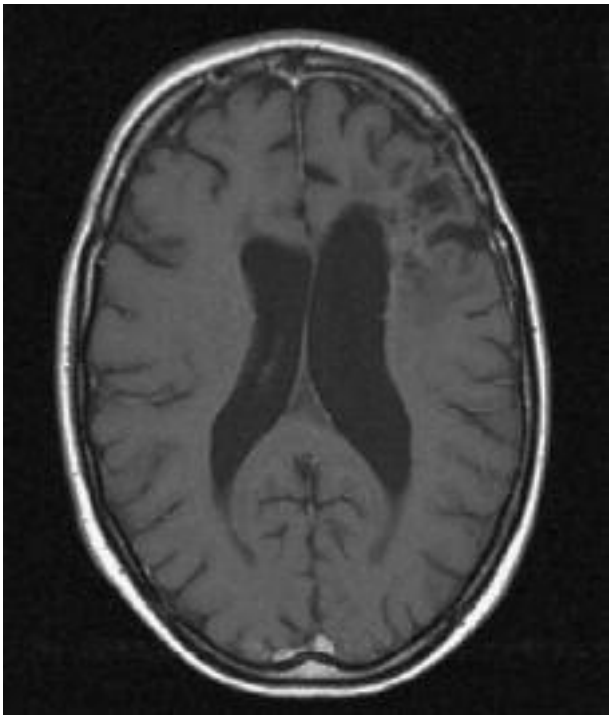

FIG. 4. — T1 weighted MRI with contrast injection 4 years after the start of temozolomide, showing no residual tumour mass.

Currently she has a Karnofsky Performance status of 90 points, she has no physical or cognitive limitations except for epileptic insults which are treated with levetiracetam.

Pathological and molecular analysis of the brain tumour

Microscopic analysis of the tumour fragments substituted for histophatological analysis revealed an astroglial tumour of variable but for a major part high cellularity, marked nuclear pleiomorphism, dispersed mitoses, and focal florid microvascular proliferation (Fig. 2). Clear cut necrosis was absent in the material sent for histophatological analysis based on these features, at that time a diagnosis of GBM was made. This diagnosis was fully compatible with the radiological images that in addition strongly indicated necrosis in this tumour.

Molecular analysis was performed on DNA isolated from an archival paraffin block (tumor load of 70%) using multiplex ligation dependent probe amplification (MLPA) as described previously (Jeuken *et al.*, 2006; Jeuken *et al.*, 2007). Copy number changes were investigated for chromosome arms 1p and 19q (MLPA assay P088 , RC Holland, Amsterdam, The Netherlands). Furthermore, using MLPA assay ME011 (MRC Holland), copy number changes and the presence of DNA methylation were investigated for MGMT. Although, in contrast to the included reference genes and control DNAs, methylation was only detected for MGMT. Of the 3 methylation sensitive MGMT probes, methylation ratios of 0.91, 0.56, and 0.17 were detected for probes L1261, L5144, and L5146 respectively (MRC Holland). Overall this average of 0.54 is classified as moderate methylation of the MGMT promoter (Jeuken *et al.*, 2007).

Discussion

We describe a young patient with a glioblastoma who, not only showed dramatic clinical and radiological improvement after TMZ treatment but who now also (under continued TMZ therapy) survives over 6 years, with complete remission clinically and radiologically.

Despite improved treatment strategies, survival of GBM-patients remains poor, and there are not many patients who survive for a long time.

The long-term survivors are defined as those patients with a median survival time of more than 3 years. Accordingly to Martinez up to 5% of all GBM patients show such a long-term survival

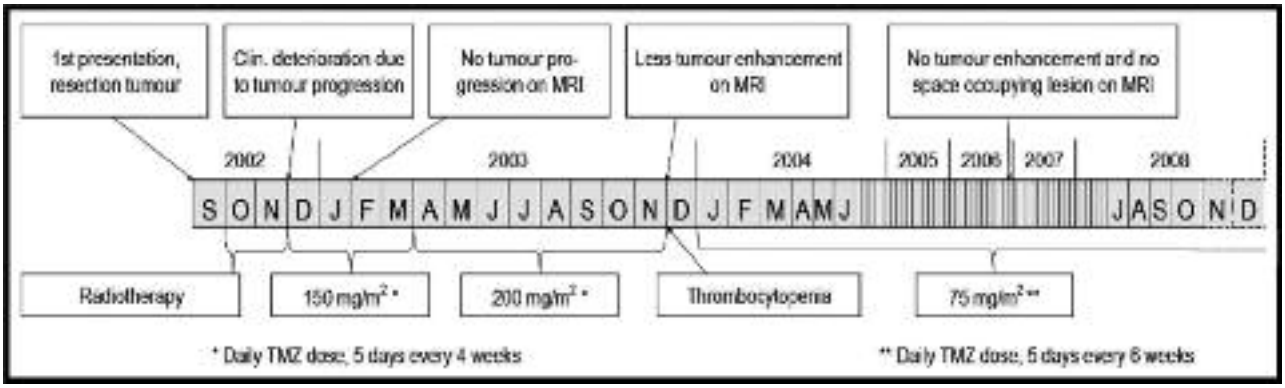

FIG. 5. — Timeline visualising the 6 years of treatment

(Martinez *et al.*, 2007). However Scott *et al.* found that in their population based study only 2.2% of the patients survived more than 3 years (Scott *et al.*, 1999). Very few patients with glioblastoma survive for 10 years (Morita *et al.*, 1996). So far no characteristics definitely identify GBM patients destined for long-term survival. Although Gorlia at al recently found several factors that are reported to be correlated with improved survival, such as a more extensive tumour resection and Karnofsky Performance status (= Mini-Mental State Examination (MMSE) score of 27 or higher). Younger age is a strong predictor of survival (Gorlia *et al.*, 2008).

Also specific cytopathological characteristics could be associated with long-term survival, but causal statements can not be made so far (McLendon *et al.*, 2003). For example it has been shown that GBMs showing an unexpected long survival often contain a loss of 1p and 19q, prognostic factor known to predict good prognosis especially in oligodendroglial tumours. In this case however, this prognostic factor was not identified.

Regarding response to TMZ treatment, molecular studies have shown that specific tumour characteristics, like a silenced MGMT gene by promoter methylation, are associated with a prolonged survival after treatment with RT and concomitant TMZ followed by adjuvant TMZ, although it is not the only factor determining outcome (Hegi *et al.*, 2005). Concordantly, we detected methylation of the MGMT promoter in this tumour that responds extremely well to TMZ.

As mentioned earlier there is no standard therapeutic strategy after six cycles of TMZ, and further treatment is at the physician's discretion.

The protracted administration of TMZ, even at low doses, was shown to lead to significant and prolonged depletion of MGMT-activity. Although this may potentially enhance the anti-tumour activity of the agent, to date there are no conclusive data available demonstrating that these more dose-dense regimes offer clinically relevant increased anti-tumour activity (Khan *et al.*, 2002; Wick *et al.*, 2004).

These results provide a rationale to prolong TMZ treatment at least beyond six cycles, which may even be as long as the disease is present.

So far there are few studies on long-term TMZ treatment.

In a study from Hau *et al.* patients with a GBM received up to 40 cycles of TMZ, and first line treatment lasted up to 40 months. In patients receiving at least 12 cycles no excessive toxicity was found. (Only 1% for infections) Long-term TMZ appears to be feasible and well tolerated in this patient population (Hau *et al.*, 2007).

Colman *et al.* suggests that continued therapy with TMZ until tumour progression or toxicity, may improve progression-free survival (Colman *et al.*, 2002). They also showed that long-term treatment (19 cycles) with TMZ is associated with an acceptable safety profile.

In the case of our patient we started TMZ after the clinically deteriorating course, and because of the excellent clinical results followed by good radiological results, we continued TZM in a lower dose for 6 years. This long-term treatment with TMZ did not result in toxicity and as far as we know there are no studies describing TMZ treatment in GBM patients for as long as 6 years.

Although the moderate methylation of the MGMT-promotor as well as the young age of the patient could partly contribute to this therapeutic success, we suggest that the long term survival of this patient is considered to be mostly due to a prolonged response to TMZ.

It could be argued that the initial progression was a form of pseudoprogression. However, the patient

was not treated with chemoradiotherapy and pseudoprogression is especially seen after this concomitant therapy. Recently it has been shown that pseudoprogression is significantly correlated with MGMT-promoter methylation status. However in our patient only a moderate degree of MGMT-promoter methylation was determined (Brandes *et al.*, 2008). Furthermore, the clinical course of this patient, with continuing response to TMZ, forms a strong argument against this hypothesis (Brandsma *et al.*, 2008).

More systematic studies are needed to resolve the question for how many cycles and at what doses TMZ should be continued, or which regimen must be used when tumour progression c.q. reoccurrence would occur. This case report demonstrates that prolonged treatment with TMZ is feasible for some patients who initially show favourable response.

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