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The treatment of glioblastoma – state of the art

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A comparison is made of the different approaches being taken to overcome glioblastoma. At this stage, treatment is not yet standard or successful, but at least it is improving.

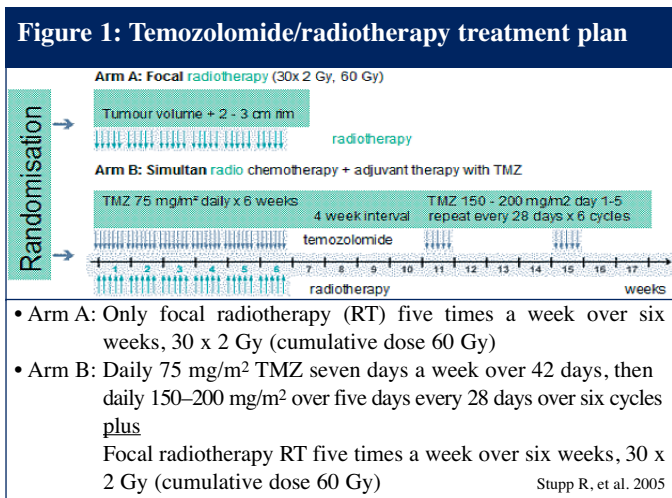
Glioblastomas rank amongst the most malignant types of tumour in man, although the incidence with three cases per 100,000 population is relatively low. In Germany, 2,500 new cases/year are diagnosed, and of these 50% of patients pass away in the first year. The treatment of choice is where possible radical operation and subsequent radiotherapy of the extended tumour region with a total cumulative dose of 60 Gy in conventional fractionation, i.e. over a period of six weeks. Temozolomide (TMZ), marketed as Temodal in Europe and Temodar in the US, has become the standard treatment in Germany. Chemotherapy is given in parallel, in addition to radiation. The dose during radiotherapy is 75 mg/m² administered daily, including weekends (see Figure 1). The capsules are taken with a little water on an empty

This is the case in 50% of all glioblastoma patients. If the gene is activated, the lesions caused by chemotherapy can only be repaired inadequately or not at all, which leads to increased necrosis of the tumour cells. In a controlled study by Hegi et al. it was verified that the 2-year survival rate of patients with a methylated gene, who were treated post-operatively according to the Stupp plan combined with radio/chemotherapy plus temozolomide possessed a significantly higher survival probability: 46% compared to 13.8% in the control group.

Astonishingly, the patients with methylated genes only profit from this nine months after the beginning of therapy. The reason for this is not known.

When administered orally, bioavailability of temozolomide is almost 100%, accumulation being unknown. Excretion is predominantly renal. Maximum plasma levels are attained after about one hour, up to 40% of the plasma levels are achieved in the cerebrospinal fluid. In pharmacokinetic terms, there are no differences in metabolism between children, adults or elderly patients.

With regard to side effects, haematological toxicity should be particularly mentioned. Side effects and their relative frequency during combined treatment and during chemotherapy alone can be seen in Table 1.



stomach in the morning. Sensitive patients will also need an antiemetic. After radiotherapy has finished, four to six courses of chemotherapy alone are administered, at 4-week intervals, each for five days in an increased single dose of 150–200 mg/m². The total dose is likewise administered on an empty stomach every morning, generally after preliminary treatment with antiemetics. This combined treatment, which was advocated by Roger Stupp et al. in the *New England Journal of Medicine* in 2005, caused overall survival to significantly increase from 12.1 months to 14.6 months. Progression-free survival (PFS) improved from five months to 6.9 months and the 2-year survival rate went up from 10.4% to 26.5%.

The prognosis criteria for prolonged survival are well known: younger age, good general condition as well as a methylated MGMT (methyl-guanine methyl transferase) status. The MGMT gene activates the promoter region of the tumour to overexpression, resulting in a bad response to treatment. If this gene is methylated, i.e. inactivated, response to treatment is significantly better.

Table 1: Haematological toxicity

	Simultaneous TMZ treatment n = 284	Adjuvant TMZ treatment n = 223	Total length of study n = 284
Side effects	Number of patients (%)		
Leukopenia	7 (2)	11 (5)	20 (7)
Neutropenia	12 (4)	9 (4)	21 (7)
Thrombocytopenia	9 (3)	24 (11)	33 (12)
Anaemia	1 (<1)	2 (1)	4 (1)
Total	19 (7)	32 (14)	46 (16)

In arm A temozolomide was administered at a concentration of 150 mg/m² over six cycles in the classical way within five days, 150 mg/m² of procarbazine was administered in arm B over 28 days, there was then a week's interval, then repetition with a total of three cycles. Overall survival after six months came to 60% in the TMZ group versus 44% in the procarbazine group, whereby the difference was significant. Six-month PFS was 21% in the TMZ group, 8% in the PCB group (p = 0,008). All in all, with regard to the duration of the relapse-free interval, temozolomide was greatly superior to procarbazine. There was also a slight advantage in the temozolomide group regarding toxicity in reference to severe side effects degrees III and IV, as

Table 2: Summary of studies - treatment for relapsed glioblastomas

Study	Regime	Genomic Medicine Biorepository (GMB)	Chemonaive patients (%)	Relative Risk RR (%)	PFS-6 6-month progression-free survival	95% CI	Time to progression TTP (weeks)	95% CI
Wong et al. 1999	Beta interferon, menogaril 13-cis-retinoic acid, difluoromethylornithine, carboplatin, fluorouracil, procarbazine	225	n.s.	6	15	10-19	9	8-10
Kapelle et al. 2001	Procarbazine, vincristine, lomustine	63	68.2	11	29	n.s.	13	n.s.
Fine et al. 2003	BCNU and thalidomide	38	50	24	27	15.9-45.9	14.9	8.3-24.6
Yung et al. 2000	TMZ (150-200 mg/m ² over 5 days, every 28 days)	112	35	5.4	21	13-29	12.4	n.s.
Brandes et al. 2003	TMZ (150-200 mg/m ² over 5 days, every 28 days)	42	0	19	24	14-42	11.7	9-22
Groves et al. 2002	TMZ (150-200 mg/m ² over 5 days, every 28 days) plus marimastat	44	43	13.6	3.9	24-54	17	13-26
Jackle et al. 2003	TMZ (150-200 mg/m ² over 5 days, every 28 days) plus 13-cis-retinoic acid	40	NR	5	32	21-51	16	9-26
Brandes et al. 2004	TMZ bd (750-1,000 mg over 5 days) plus cisplatin	50	100	20.4	34	23-50	18.4	13-25.9
Hau et al.	Pegylated liposomal doxorubicin with/without tamoxifen	28	58	7.1	7.1	n.s.	n.s.	
Rich et al. 2004	Iressa (gefitinib)	53	17	0	13	n.s.	8.1	7.9-9.1
Friedman et al. 2000	Irinotecan only	48	n.s.	17	n.s.		18	n.s.
Brandes et al. 2004	BCNU plus irinotecan	42	0	21.4	30.3	18.5-49.7	16.9	11.7-23.5
Brandes et al. 2004								n.s.: not specified

far as nausea and vomiting are concerned. Haematotoxicity was minimally worse in the temozolomide group.

There have been many trials seeking better results by changing temozolomide's dosing schedule; in particular, trials have been run to administer temozolomide in daily reduced single doses over a period of three weeks. There are trials offering temozolomide on a weekly basis; it was reported at the Trends in Central Nervous System Malignancies Conference 2009, Budapest, Hungary, that classical application according to Stupp produces better results with lower toxicity.

Herrlinger et al. published a study in 2006, in which lomustine, an alkylating agent, was administered in addition to the combination of radio/chemotherapy with temozolomide. The treatment plan comprised radiation therapy with 60 Gy over six weeks combined with both temozolomide 100 mg/m² day 2 to 6 and lomustine in a concentration of 100 mg/m² on the first day. The cycle duration was six weeks, five cycles being applied on average. Radiotherapy was administered conventionally. In the group as a whole, the 2-year overall survival rate amounted to 44.7%; after six months the PFS rate was 61.3%. Median PFS was calculated as nine months with a confidence interval of 95% (5.3-11.7). This means that adding lomustine improved the outcome in this study, the prognosis resembling the Stupp data for the subgroup of the prognostically favourable methylated patients.

There are few alternatives when the situation relapses, which is the case with almost every patient. Here, as usual, clinical evidence tends towards repeated radiation as the best form of therapy. Further administration of temozolomide is also recommended, particularly if the last course was quite a long time ago. Alternatively, mitotic inhibitors are available. Standard chemotherapy combinations comprising procarbazine, lomustine and

vincristine are recommended. At the 2009 American Society of Clinical Oncology meeting, two contributions encouraged treatment of relapses with irinotecan and bevacizumab.

Vredenburg et al. presented their results with reference to bevacizumab and irinotecan in 2007. Two treatment groups were formed; bevacizumab 10 mg/kg body weight and irinotecan 140 mg/m² were administered to the first group, while the same antibody concentration plus 125 mg/m² of irinotecan were given to the other group. The efficacy of irinotecan was increased by giving preliminary anti-epileptic treatment, since irinotecan is a pro-drug, activated during metabolism. CYP3A4 production is promoted in advance by anti-epileptic drugs. Treatment is by IV administration every two weeks over a 6-week cycle until progression. This treatment is standard in our clinic after renewed radiation carried out during the preliminary stages with a cumulative dose of 30 Gy in classical hyperfractionation with two fractions/day of 1.2 Gy.

To compare with traditional chemotherapy, Yung et al. presented a controlled study in 2000, in which temozolomide was tested against procarbazine. This was a randomised multicentre phase II study, in which 225 adult patients with glioblastomas were subjected to chemotherapy when they relapsed after radiotherapy. The primary end point was PFS after six months and tolerance to the therapy. The secondary end point was overall survival as well as the quality of life.

Table 2 surveys the relapse therapy of glioblastoma as well as the corresponding results, which includes all the cases involved in preliminary phase I and phase II studies. Controlled comparisons are completely absent.

Literature can be requested from the authors.