Feasibility and toxicity of CCNU therapy in elderly patients with glioblastoma multiforme

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In our institution, 103 glioblastoma multiforme (GBM) patients aged from 55 to 83 years were treated since November 1994 as follows. All patients underwent surgical intervention (gross total resection, $n = 35$; subtotal resection, $n = 38$; stereotactic biopsy, $n = 30$). Subsequently all patients were offered radiotherapy and chemotherapy with CCNU. Results were as follows: 101 patients started radiotherapy, 93 patients completed it (96% of the patients aged <65 years and 85% of the patients ≥ 65 years). All patients received at least 1 cycle of chemotherapy (median 3 cycles). Chemotherapy-associated toxicity was generally mild, more pronounced in females and did not increase with age. Median time to progression was 10.5 ± 3.2 months for the patients <65 years and 5.1 ± 1 months for patients ≥ 65 years. median overall survival was 17.5 ± 3.8 months in patients <65 years and 8.6 ± 1 months in patients ≥ 65 years ($p < 0.0001$). In multivariate analysis, age and female sex remained independent prognostic factors. Our data indicate that a treatment concept including concomitant radio- and chemotherapy is feasible even in elderly patients with GBM. *Anti-Cancer Drugs* 14:137–143 © 2003 Lippincott Williams & Wilkins.

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Introduction

With the continuous raising of life expectancy in industrialized countries, the age groups prone to malignant tumors, including brain tumors such as glioblastoma multiforme (GBM), have become the fastest growing populations. Not unexpectedly, an increase in the occurrence of GBM in the elderly has been noted in Europe, North America, Australia and Japan [1–5]. This increase might in part be due to better diagnostic facilities. However, even in the 1990s a large proportion of patients with high-grade gliomas were still not specifically treated [6–8].

In contrast to geriatric medicine, where 'elderly' people are defined as people aged from 65 to 75 years, 'old' people as aged from 75 to 85 years and 'very old' people as more than 85 years old, there is obviously no consensus about the definition of the beginning of advanced age in patients with malignant brain tumors: 'old' age might start as early as 50 [9–11], 55 [12], 60 [13–15], 65 [8,13,16–17] or, finally, 70 years [18,19]. A detrimental effect of age for response to therapy has been described in GBM patients as early as 40 [20] and 45 years, as documented as an independent adverse prognostic factor in multivariate analysis [6,8,9,14,16].

The generally accepted therapy of GBM consists of maximal feasible resection, radiotherapy and, controversially, to date mostly nitrosourea-based chemotherapy [8,14,20–24]. For elderly patients all these treatment modalities are constantly being discussed. Moreover, Lowry noted an increase of the proportion of patients with no treatment at all from 4% in the 1980s to 18% in the 1990s [8].

In contrast, a recent meta-analysis by Stewart has found no influence of age on the rate of response to therapy in more than 2300 patients with high-grade malignant gliomas [25].

The molecular mechanism of susceptibility to nitrosourea-based chemotherapy was described as age independent [11]. In most centers, according to surveys of the last 15 years, nearly one-fourth to one-third of all patients with the histologic diagnosis of GBM were >65 years.

For this study we analyzed the outcome of GBM patients aged ≥ 65 year and compared it to the outcome of patients aged 55–64 years, treated since November 1994 in our institution, to evaluate the currently used

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multimodal treatment and discuss further management modalities.

Materials and methods

Patients

From November 1994 to August 2000, 103 consecutive patients >55 years (range 55–83 years) with histologically proven primary GBM were treated at our institution. There were 49 patients aged 55–64 years and 54 patients aged 65–83 years. Patient's characteristics and treatment modalities are shown in Table 1. Only patients who met the neuropathological WHO criteria for GBM as malignant, mitotically active astrocytic tumors with necrosis and/or neovascularization were enrolled [26,27].

Data were prospectively recorded during treatment and follow-up visits. Routine check-up consisted of the evaluation of status, gross neurological status, Karnofsky score, blood counts and blood chemistry. All patients with a Karnofsky score of at least 60% at 2 weeks after surgery were offered radiotherapy and chemotherapy.

Neurologic symptoms

Neurologic symptoms at presentation are summarized in Table 2. Localizing symptoms were observed in 75% patients and by headache in 43%. Only 27% of patients experienced seizures. The symptom burden at presentation did not differ significantly between the two patients groups.

Table 1 Medical and treatment characteristics in 103 patients with GBM

	<65 years of age		≥65 years of age		All
Age at diagnosis and gender					
male	32		33		65
female	17		21		38
Karnofsky index (1 week after surgical intervention)					
60%	4		10		14
70%	14		15		29
80%	13		10		23
90%	17		10		27
100%	9		1		10
	Male	Female	Male	Female	
Tumor localization					
frontal	8	5	10	5	28
temporal	12	10	8	5	33
parietal	6	1	5	5	18
occipital	3	2	3	1	9
bilateral	5	0	2	1	8
infratentorial	1	0	0	0	1
multifocal	1	1	1	1	4
stem ganglia	1	1	0	0	2
Surgery					
microscopic complete resection	14	10	3	7	35
subtotal resection	10	7	15	5	38
stereotactic biopsy	13	3	9	5	30
Radiotherapy					
initiated	32	23	27	17	101
completed	32	19	27	15	93
no radiation	1	0	1	0	2
Chemotherapy					
First-line chemotherapy					
CCNU	32	17	33	21	103
Second-line chemotherapy					
temodal	7	4	1	2	10
dacarbacine/fotemustine	5	2	0	0	7
Third-line therapy					
thalidomide	3	2	0	0	5

Table 2 Neurologic symptoms at presentation

	<65 years of age			≥65 years of age		
	Male	Female	All (%)	Male	Female	All (%)
n	32	17		33	21	
Vertigo	11	5	(32)	7	8	(28)
Headache	14	8	(45)	10	12	(41)
Seizures	9	5	(28)	9	5	(26)
Localizing symptoms	24	10	(71)	23	10	(61)
No. of symptoms at diagnosis						
1	15	9	(49)	21	10	(57.5)
2	11	8	(39)	8	7	(28)
3	2	1	(6)	4	1	(9)
4	3	0	(6)	1	2	(5.5)

Neurosurgical procedures

The surgical procedures were performed according to the standard procedure for microneurosurgery with an operation microscope (Contraves; Zeiss, Oberkochen, Germany) and from 1995 on with a pointer device neuronavigation system (Easy Guide Neuro; Philips, Eindhoven, The Netherlands). Gross total resection was defined as a resection of ≥95% of the radiological visible tumor by postoperative compute tomography or magnetic resonance tomography scans performed within 72 h after the surgical intervention. Subtotal resection was defined as a removal of <95% of radiologically visible tumor. Stereotactic biopsies were carried out by using a stereotactic microscope (MKM; Zeiss) for tumor targeting and resection guidance [28]. When necessary, steroids (dexamethasone 4–8 mg i.v.) were given before surgical intervention to reduce brain edema. Repeated neurosurgery at tumor relapse or tumor progression was not routinely foreseen and based on individual decisions.

Radio-oncologic treatment

Radiotherapy was planned using a three-dimensional treatment planning system based on magnetic resonance sectional imaging. The planning target volume, i.e. the tumor volume including a security margin of 2 cm, was defined by the radio-oncologist based on preoperative and postoperative imaging diagnostic data. Immobilization masks were used for patient fixation to ensure a reproducible set-up. Two different treatment schedules were applied with equivalent biologic effective doses (BED). A radiation dose of 66 Gy (2 Gy/fraction) ($n=86$) or 51 Gy (3 Gy/fraction) ($n=12$) was delivered to the planning target volume using a multiple field technique with individually designed shielding blocks or standard multileaf collimators. Radiotherapy started within 6 weeks after surgical intervention and lasted for 4–7 weeks. Written informed consent was mandatory before start of radiotherapy.

Chemotherapeutic treatment

Eligibility criteria for chemotherapeutic treatment included a Karnofsky score $\geq$60% at 2 weeks after neurosurgical intervention. Adequate liver function (SGOT, SGPT and alkaline phosphatase levels $< 2 \times$ the normal range; bilirubin in serum < 1.5 mg/dl) as well as adequate renal function (creatinine $< 1.5 \times$ of the normal range) and bone marrow function (leukocyte count $> 3000/\mu$l, hemoglobin > 10 g/dl, platelet count $> 100\,000/\mu$l) were requested. Patients with intercurrent illnesses or acute infections were not eligible. Written informed consent was mandatory before start of radiotherapy.

Chemotherapy was started between day 10 and 14 after surgery. All patients received CCNU 100 mg/m^2 orally, administered in 6-week intervals.

Seventeen patients received second-line chemotherapy, 14 patients aged <65 years and three elderly patients. It consisted of temozolomide 150 mg/m^2 orally day 1–5 ($n = 10$) or fotemustine/dacarbacine 100/200 mg/m^2 for up to 1–9 cycles ($n = 7$).

Thalidomide was given to patients ($n = 5$) beyond first relapse. We started with 50–100 mg orally and increased the dosage to 200 mg daily.

Toxicity and response evaluation

For toxicity evaluation, the WHO scale was used and toxicity grades reflect the most severe degree observed. In case of hematotoxicity necessitating a delay of chemotherapy, blood cell counts were performed in weekly intervals.

Magnetic resonance imaging (MRI) scans were routinely performed every 3 months and immediately when disease progression was suspected clinically. Disease progression was defined according to Macdonald's criteria with an increase of $\geq$25% of an enhancing tumor or any new tumor on MRI scans, clinical worsening with or without the need to increase the dosage of steroids [29]. As response evaluation on MRI in patients with various degrees of resection is not unambiguous, we report time to progression, progression-free survival at 6 months and duration of overall survival.

Supportive care

All patients were carefully prepared for the surgical intervention and managed perioperatively by an interdisciplinary team. During chemotherapy, they were seen by a medical oncologist prior to each chemotherapy cycle, in between when clinically necessary and after stopping chemotherapy in 3-month intervals. At chemotherapy administrations, all patients were given serotonine antagonists prophylactycally. Attempts were made to taper and finish steroids as soon as possible in order to prevent or minimize steroid side effects such as steroid diabetes, Cushingoid appearance, myopathy and loss of the diurnal cycle. All patients were given dietary advice, physiotherapeutic treatment when needed as well as advice for recommended physical activity.

Patients and their relatives were informed about community resources for cancer patients, and those were organized with the help of hospital- and community-based social workers.

Statistical considerations

Survival time was calculated from the day of surgical intervention until the day of last follow-up or death. Analysis was performed according to tumor localization, according to age, gender and treatment modalities.

Survival curves and median survival were estimated based on Kaplan–Meier's non-parametric method [30]. Log-rank tests were used to assess the strength of association between survival time and each of the parameters as a single variable. Statistical evaluations were performed with the GraphPad PRISM program package (version 3.00).

Spearman's coefficient of correlation was used as appropriate. The Cox proportional-hazards model was used for multivariate analysis using SPSS 10.0 (SPSS, Chicago, IL).

A p value ≤ 0.05 was considered statistically significant.

Results

Therapy

All patients underwent surgical intervention. In 35 patients gross total resection was possible; subtotal resection was achieved in 38 patients. Stereotactic biopsies as the only neurosurgical intervention were performed in 30 patients. Within at least 6 weeks after surgery 101 patients (one refused radiotherapy, one died early) started with radiotherapy and 93 patients finished it. Two patients aged <65 years and eight elderly patients had to discontinue radiotherapy at lower doses than 60 Gy, due to worsening of clinical status or tumor progression. CCNU chemotherapy as first-line therapy was given to 103 patients (Table 1). The median number of chemotherapy cycles given was 3 in patients <65 years as well as in patients $\geq$65 year; 18% of patients <65 years and 27% of patients $\geq$65 years had only one cycle of chemotherapy. After relapse, second-line chemotherapy was given to 14 patients <65 years and three patients $\geq$65 years.

Side effects of chemotherapy

Hematological side effects were recorded in 59 of 103 patients treated with CCNU (Tables 3 and 4). The most

Table 3 Hematoxicity of chemotherapy in 103 patients with GMB

	<65 years of age		≥65 years of age		All
	Male	Female	Male	Female	
WHO grade I and II					
red blood cells	0	4	1	3	8
platelets	5	4	4	5	18
leukocytes	6	5	1	4	16
WHO grade III and IV					
red blood cells	2	0	0	3	5
platelets	0	1	3	3	7
leukocytes	1	1	0	3	5

Table 4 Toxicity of chemotherapy according to Karnofsky index (KI) (WHO grading)

	KI 60% ($n=14$)	KI 70% ($n=29$)	KI 80% ($n=23$)	KI 90% ($n=27$)	KI 100% ($n=10$)
Red blood cells					
grade 1	0	1	2	0	0
grade 2	1	2	1	1	0
grade 3	0	0	1	0	0
grade 4	1	0	1	1	1
all	2	3	5	2	1
Leukocytes					
grade 1	0	1	1	2	2
grade 2	1	3	2	3	1
grade 3	0	0	3	0	0
grade 4	1	0	1	1	0
all	2	4	7	6	3
Platelets					
grade 1	1	1	4	1	1
grade 2	1	3	5	2	0
grade 3	0	2	1	0	1
grade 4	1	0	1	1	0
all	3	6	11	4	2

common side effect was thrombocytopenia, occurring mostly after 3–5 cycles of chemotherapy. In two patients, dosage of CCNU had to be reduced from 100 to 75 mg/m^2. Noteworthy, more female ($n=37$) than male ($n=25$) patients experienced hematological side effects.

The non-hematological side effects observed were mainly fatigue, dry skin and cortisone-induced myopathy. There was one case of pneumonia in every age group. We noted no episodes of bleeding or cerebral hemorrhage. We did not observe organ toxicity to the respiratory system, especially lung fibrosis. Nausea and vomiting, and other gastrointestinal, renal or neurological side effects were not observed.

The side effects were not clustered in patients with lower performance score or advancing age.

Close-meshed controls

For patients who were deceased at the time of writing ($n=78$), we measured the duration of the period between their last follow-up and the date of death. This period varied from 0.2 to 11.5 months (median 1.2 months). It was longer in patients aged 70–74 years ($n=13$) and, unexpectedly, in patients with a performance score ≥90% ($n=15$).

Survival

Tumor progression occurred in 84 patients. Median time to progression was 10.5 ± 3.2 months in patients <65 years and 5.1 ± 0.8 months in patients ≥65 years. Six months after diagnosis, 65% of patients <65 years and 42% patients ≥65 years lived free of progression; after 1 year this was still 30% of the younger and 9% of the older patients, respectively.

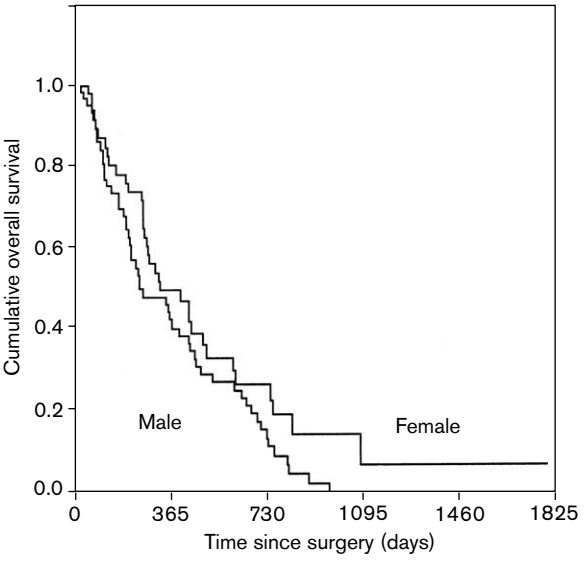
There was a difference in survival with respect to gender (Fig. 1) in favor of woman ($p<0.0001$) but no significant difference, according to Karnofsky index (KI; Fig. 2) (Table 5) or according to tumor location in the left or right hemisphere ($p=0.007$). Patients with tumors of deep brain structures, involvement of the corpus callosum ($n=8$) or multifocal glioblastomas ($n=4$) showed a median survival of 6.1 months, compared to patients with hemispheric tumors with 11.2 months ($p>0.05$).

Patients who were able to finish radiotherapy ($n=93$) had a median survival of 12.9 months, whereas in 11 patients who could not complete radiotherapy, median survival was 3.4 months ($p<0.0001$). The median duration of overall survival was 17.5 ± 3.8 months for patients <65 years and 8.6 ± 1 months in patients ≥65 years (Fig. 3).

Discussion

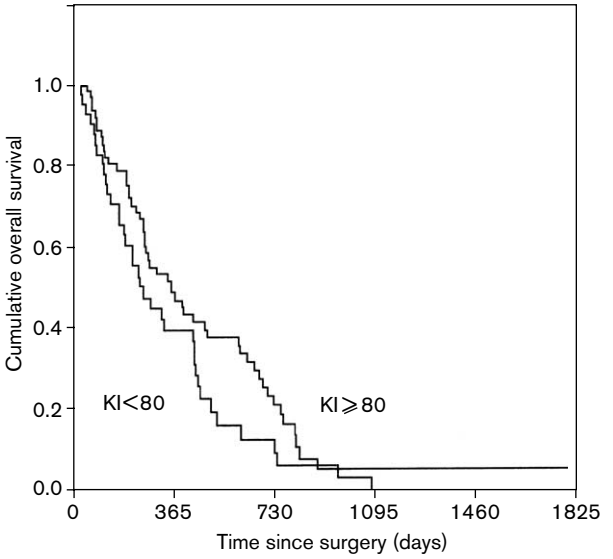
Our study demonstrates the feasibility of a consequent multimodal therapeutic concept in patients ≥65 years,

Fig. 1



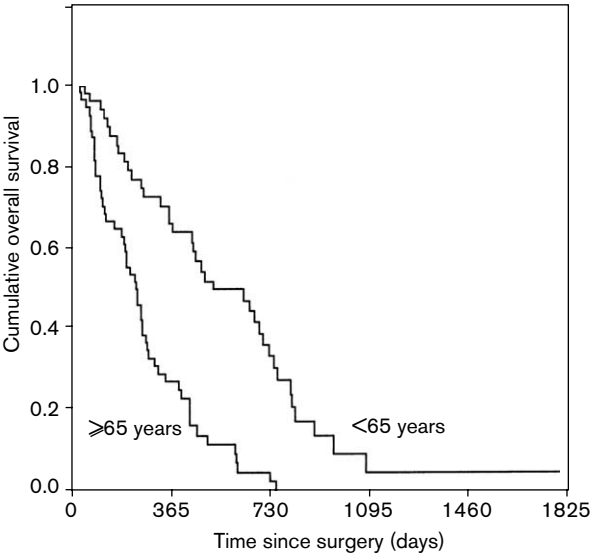
Survival of patients with GBM according to gender ($p<0.001$).

Fig. 2



Survival of patients with GBM according to performance score.

Fig. 3



Survival of patients with GBM according to age.

Table 5 Multivariate analysis of cumulative overall survival of 103 patients with glioblastoma (Cox regression)

Factor	*p* value	Relative risk	95% confidence interval
Age at primary surgery (<65 versus ≥65 years)	<0.001	3.998	2.387–6.694
Sex	0.006	1.89	1.203–2.968
Postoperative Karnofsky performance status (<80 versus ≥80)	0.636	–	–
Extent of resection (subtotal versus total)	0.146	–	–

with acceptable side effects also in these patients. Although the median duration of survival of glioblastoma patients <65 years was longer than that of elderly patients, the survival duration in our cohort of uniformly treated patients compares favorably to data in the literature (Table 6). The very low proportion of elderly patients in clinical trials in oncology has previously raised substantial concern among the oncologic societies [31].

The goal of treatment in a nearly incurable disease as GBM, especially in elderly patients, is to maintain the best achievable quality of life for the longest achievable period. The ways to reach this goal are controversial. The impact and the value of all commonly accepted therapeutic options are critically discussed for their suitability in elderly GBM patients.

In younger patients, maximum feasible tumor resection is related to prolonged survival [12,15,17,32], but in elderly patients this benefit must be weighted against the increased risk of postoperative, mostly thromboembolic, complications. Cytoreductive surgery has been described to be of modest benefit for elderly patients [12,18,32]. On the other hand, stereotactic biopsy is a safe procedure with a very low death and morbidity rate of only 3%, but does not achieve the relief of symptoms related to resection. In our cohort, the observed morbidity was higher in patients who had tumor biopsy only than in patients with tumor resection, confirming that the patients allocated to tumor biopsy were in fact the group of patients with the worst prognostic factors.

Following surgical intervention all patients were offered radiotherapy. During radiotherapy, patients might suffer from acute toxicity of radiotherapy, and also from fatigue and from reactive depression. These factors might cumulate and aggravate the difficulties for elderly patients with daily transport or a prolonged stay in the hospital. In other centers, patients have been offered shortened schedules of radiotherapy, either with increased single fractions, accelerated treatment and/or a lowered total dose, resulting in a shorter, more easily feasible treatment period [11,33]. In our cohort, all but 12 patients were able to finish radiotherapy with 66 Gy. The favorable survival data of our patients support that elderly patients with a reasonable performance score should be offered radiotherapy, precluded that individual patient transportation and 'support at home' are ensured.

Thus far, the impact and the usefulness of chemotherapy in elderly patients has been questioned. In several trials,

Table 6 **Survival duration of older adult patients with GBM**

Author	Year	Patients (*n*)	Age [median (range)] (years)	Aged >70 years (%)	Tumor resection (*n*)	Tumor biopsy (*n*)	Radiotherapy (*n*)	Chemotherapy (*n*)	OAS (months)
Adams [34]	1983	384	ND (18–70)	ND	218	166	382	188	8.0
Whittle [32]	1991	80	63 (60–74)	ND	39	29	31	ND	4.0
Curran [10]	1993	1037	53 (ND)	ND	498	95	570	ND	8.8
Kelly [14]	1994	128	71.1 (65–83)	ND	40	88	96	ND	4.2
Meckling [19]	1995	103	74.2 (ND)	100	66	15	22	ND	3.9
Mohan [18]	1998	102	74.5 (70–87)	21	49	53	77	16	6.3
Villà [17]	1998	85	70 (65–81)	42	32	53	43	10	4.0
Piribauer (this study)	2002	103	65 (56–83)	31	70	30	101	103	10.6

age >70 years was considered an exclusion criterion [6,10,34]. Other studies recruited patients without age limit [10,12,14,17,24,35]. The application of chemotherapy to elderly patients has to be monitored cautiously, avoiding either over- or undertreatment. Major reasons for undertreatment are withholding chemotherapy because of fear of severe side effects, the lack of an effective thrombocytic growth factor or as the trend to avoid compliance problems with elderly people. Often every worsening of the patient's status is interpreted as a side effect of chemotherapy by the patients, their relatives or even the family physician. To overcome these problems, we routinely offer telephone follow-up for patients and their primary carers. Although data of the patients of this cohort demonstrate the feasibility of chemotherapy with acceptable toxicity in almost all patients, a close follow-up with the patient himself or a relative appears mandatory for the early recognition of eventual complications.

Another pivotal prognostic factor to be kept in mind is the association between chronic disease and chronic depression, especially in the elderly. This was pointed out by the Longitudinal Aging Study Amsterdam (LASA) where two groups of >300 patients each of depressed and non-depressed older adults were followed for several years. Depression was significantly related to an increased risk of cognitive decline and of death [36]. Quite analogous, Colleoni *et al.* have provided evidence that depressed breast cancer patients are more prone to refuse chemotherapy or to preliminary stop this therapy than non-depressed patients, and perhaps therefore show a significantly shortened survival period [37]. We intend to address these effects by our initiative to improve logistic support and close follow up.

Most clinicians still rely on intuition and anecdotal experience to choose oncologic treatment for the elderly. Convinced of the futility of the treatment of GBM in the elderly, physicians often spare the patients at least the intense confrontation with their disease necessary to obtain informed consent as well as the side effects of chemotherapy.

Oncologic comprehensive geriatric assessment would definitely be very helpful in elderly patients with GBM [31,38,39]. This would allow an assessment of the potential benefits and disadvantages of treatment strategies within prospective trials.

Conclusion

A multimodal treatment concept including concomitant radio- and chemotherapy appears feasible even in older adult patients with GBM. Nevertheless, the patient's situation, and their wishes and ability to comply with the postsurgical therapies need individual consideration and decision. The implementation of oncologic geriatric assessment in the process of decision making in elderly GBM patients should facilitate the design of prospective trials.

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