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Combined treatment of glioblastoma patients with locoregional pre-targeted ^{90}Y -biotin radioimmunotherapy and temozolomide

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Aim. In a previous phase I-II study, the safety profile and anti-tumor efficacy of pre-targeting locoregional radioimmunotherapy (LR-RIT), based on the "3 step" method, was assessed in 24 high-grade glioma patients. The encouraging results in terms of low toxicity and objective response rate (25%) prompted us to continue our study.

Methods. An analysis of 73 patients with histologically confirmed glioblastoma multiforme (GBM), treated with the "3 step" ^{90}Y -biotin based LR-RIT, is herein reported. All patients had a catheter implanted at 2nd surgery and underwent at least 2 cycles of LR-RIT (range 2-7) with 2 months interval. Thirty-five out of 73 patients were also treated with Temozolomide (TMZ). Two cycles of TMZ (200 mg/m²/day, for 5/28 days) were administered in between each course of LR-RIT. Overall survival (OS) and progression free survival (PFS) were retrospectively calculated.

Results. Stabilization of disease was achieved in 75% of patients, while 25% progressed.

In the 38 patients treated with LR-RIT alone, median OS and PFS were respectively 17.5 months (95%CI=[17-20]) and 5 months (95%CI=[4-8]), while in the 35 treated with the combined treatment (LR-RIT+TMZ) respective values were 25 months (95%CI=[23-30]) and 10 months (95%CI=[9-18]) (p<0.01). The addition of TMZ to LR-RIT did not increase neurological toxicity, and no major hematological toxicity was observed.

Conclusion. These results confirm the safety and the efficacy of ^{90}Y LR-RIT in recurrent GBM patients; the addition of TMZ significantly improved the overall out-

Work supported by grants of the Italian Association for Cancer Research and Italian Ministry of Health.

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comes; a further controlled prospective, randomized study is fully justified.

KEY WORDS: Radioimmunotherapy - Temozolomide - Glioblastoma - Monoclonal antibodies - Avidin - Biotin.

Glioblastoma multiforme (GBM) is one of the most rapidly growing and devastating neoplasms.¹ The traditional management of this tumor involves a multi-modal strategy consisting of surgical resection, external beam radiotherapy (EBRT) and, in some cases, a nitrosoureas or procarbazine-based chemotherapy.^{2, 3}

The principal procedure in the treatment of GBM is the surgical attempt to radically remove the neoplastic tissue. On the other hand, radiotherapy has been demonstrated the most effective adjuvant therapy to surgery.^{4, 5} Many studies are in progress to enhance the efficacy of radiotherapy and, among different treatment modalities, brachytherapy, radiosurgery and intraoperative radiotherapy are the most frequently studied.

Radioimmunotherapy, as systemic⁶⁻⁹ or locoregional-

al application¹⁰⁻¹³ has the potential to become an option in the management of GBM, complementing the above mentioned treatment regimens.

The systemic application of monoclonal antibodies (MoAbs) for therapeutic purposes is restricted by many factors: high interstitial pressure inside the neoplastic tissue, limited blood supply to the tumor, inhomogeneous and inconstant antigen expression, possible presence of physiological barriers (necrosis and/or fibrosis), formation of immunocomplexes and catabolism of immunoglobulins. Although often impaired in tumor, the blood-brain barrier further hampers the accumulation of antibodies in the malignant tissue. The amount of immunoglobulin actually localized within neoplastic glial tissue has been measured to be less than 0.01% of *i.v.* administered MoAbs per gram of tumor tissue.¹⁴⁻¹⁶

Among strategies proposed to overcome these drawbacks and to improve the tumor/non tumor uptake, the "3-step" pre-targeting method based on avidin-biotin system should be considered.^{17, 18} Our group has studied and applied this new method, both as systemic or locoregional radioimmunotherapy (LR-RIT), in glioblastoma patients.^{6, 8, 9, 19}

Different MoAbs have been utilized for radioimmunotherapy of glioblastoma. In many trials antitenascin MoAbs have been employed.²⁰ Tenascin, a tumor associated extracellular matrix glycoprotein, is overexpressed in the stroma of GBM, but absent in the normal brain tissues. The locoregional application of anti-tenascin MoAbs allows their penetration through the neoplastic tissue, where they bind to their specific antigens.²¹ Additionally MoAbs, when labeled with high energy beta-emitting radionuclides, are able to destroy a large number of tumor cells in antigen negative areas, due to the "cross-fire effect".

The results reported so far with LR-RIT indeed demonstrated its effectiveness in glial malignancies.^{10-13, 19} In a previous phase I study we concluded that pre-targeted locoregional radioimmunotherapy with 90Y-biotin in glioma patients was a safe procedure. Median overall survival for glioblastoma patients, was 20 months and the maximal tolerated dose (MTD) per cycle, limited by neurotoxicity, was established within the range of 1 110 mBq.¹⁹

Recently Temozolomide (TMZ), a novel alkylating agent with excellent properties of penetration into brain, was introduced as standard treatment for recurrent high-grade gliomas.²² This prompted us to add it to our LR-RIT in order to increase the efficacy of the treatment.

The role of combining locoregional radioimmunotherapy with TMZ in patients with recurrent glioblastoma multiforme, after conventional modalities of treatment, is addressed in this analysis.

Materials and methods

Patients evaluation

Over the past 6 years, more than 100 GBM patients were treated with LR-RIT in our Institute. Patients were required to have unifocal and sovratentorial lesion, histologically-proven glioblastoma, immunohistochemical demonstration of tenascin expression in tumor and a life expectancy of more than 2 months. A catheter connected with a subcutaneous Ommaya or Rickam reservoir had to be present into the surgical cavity to allow the injection of reagents.

Seventy three patients who were treated with a second surgical debulking (plus catheter implantation) due to recurrent or progressive disease after conventional management and were given at least 2 cycles of LR-RIT, were included into this analysis. Another group of about 30 patients had catheter implantation and LR-RIT after first surgical debulking thus they are not included in the present study.

According to the received treatments, the patients were then divided into 2 groups: a group A (38 patients), who received only LR-RIT and a group B (35 patients), who received LR-RIT in association with TMZ.

Baseline evaluation was performed before the first cycle of LR-RIT. All patients underwent a physical examination, in order to determine the Karnofsky performance status (KPS). A brain cerebral MRI or CT scan with contrast enhancement was obtained in order to evaluate residual tumor, to calculate the volume of SRC (considering maximum diameter of the SRC and assuming SRC as regular sphere), and to check the correct placement of the catheter.

Before the "3-step" reagents delivering, a small activity (3-5 MBq) of ^{99m}Tc-pertecnetate, in a volume of 0.5 ml of saline solution, was injected to prove scintigraphically the catheter viability and to assess ventricular communication with the surgical cavity.

In patients not operated in the study Centers (Milan or Rome) a central pathology review was performed to confirm the diagnosis of GBM.

The evaluation was repeated at 2-3 month intervals, up to disease progression.

Complete blood count and blood chemistry was drawn every 2 weeks for the patients who received LR-RIT; for the patients who had TMZ in addition to LR-RIT, the complete blood count was checked weekly.

Response evaluation was assessed according to Macdonald's criteria²³ in which 4 response categories are proposed: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Response in this scheme is based on major changes in tumor size on the enhanced CT or MR imaging scan. Scan changes are interpreted in light of steroid use and neurological findings. Toxicity were defined according to WHO criteria.²⁴

The study was performed after approval by the Ethical Committee of the European Institute of Oncology. All patients signed a consent form after receiving detailed information on the aim and potential risks of the study and agreed to the collection of data.

Therapy

LOCOREGIONAL RADIOIMMUNOTHERAPY

Reagents (anti-tenascin monoclonal murine antibodies BC4, native avidin, ⁹⁰Y-biotin) and radiolabeling procedure were described in our previous report.¹⁹ Under sterile conditions, 2-5 mg of biotinylated anti-tenascin MoAb were injected into the surgical cavity, through the indwelling catheter. Eighteen to 24 h later, 5-15 mg of native avidin was administered and, finally, 14-16 h later, ⁹⁰Y-biotin was administered.

The injected activity ranged from 370 to 925 MBq per cycle, depending on the surgical cavity volume: in cavities of 3 cm (with calculated volume of about 14 cc), 4 cm, 5 cm and >5 cm in diameter, amount of ⁹⁰Y-Biotin was respectively 370, 555, 740 and 925 MBq. The administered activity did not differ based on amount of residual enhancing tumor.

Before each step, patients were pre-medicated with intravenous steroids and Mannitol solution.

Bremsstrahlung scintigraphic images were performed within 1 h after ⁹⁰Y-biotin administration. Protocol scheduled at least 2 cycles of LR-RIT for each patient, with 2 month interval.

CHEMOTHERAPY

In 1999 our standard treatment was modified and systemic TMZ chemotherapy was added to LR-RIT. TMZ was administered orally at 150 mg/m²/d for 5

consecutive days, every 28 days, for the first cycle. Dose was increased to 200 mg/m²/d (only in naive-chemotherapy patients) if no hematological toxicity occurred. Prophylactic anti-emetics were routinely prescribed during chemotherapy. On average, 2 cycles of TMZ were given between 2 consecutive cycles of LR-RIT. Chemotherapy was continued unless unacceptable toxicity or disease progression was observed.

Statistical methods

The potential association between baseline factors and treatment groups was tested using Student's *t*-test, Wilcoxon's test or Pearson χ^2 test. The various combinations of sites of the GBM were grouped into: Occipital, Frontal, Parietal and Temporal. When fitting the models, a proper comparison was possible only for the last 3 groups, as only 4 patients had a GBM located in the Occipital zone.

Progression free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method and for OS we considered time from first surgery to death or last follow-up, while for PFS we considered time since evaluation at our institute to progression or last follow-up. A Cox proportional hazard model²⁵ was fitted to adjust for a potential confounding effect of age and to assess treatment effects and associations with prognostic factors. When fitting such models: cavity diameter was grouped into 3-4 cm *vs* 5-5+ cm, depth of the tumor was grouped into cortical *vs* non-cortical. All the analyses were done in S-Plus (S-PLUS 2000 Professional Release 2, MathSoft, Inc. Seattle, WA).

Results

Baseline characteristics

We analyzed a sample of 73 patients, with an overall median age (min=29, max=77) of 52 years, treated with LR-RIT (52%) and LR-RIT+TMZ (48%). As standard treatment, all patients had received a first surgery: the tumor removal was macroscopically complete in 31 patients and partial in 42. Subsequently, all the patients but 1, received adjuvant EBRT, with a median dose of 60 Gy (min=54 Gy, max=72 Gy) equally distributed in the 2 groups, and 41% also received adjuvant nitrosoureas-based chemotherapy. None of the non-radically operated patients achieved a complete response after adjuvant radio- or chemotherapy. All

TABLE I.—*Characteristics of the patients at baseline.*

	All patients	LR-RIT (Group A)	LR-RIT + TMZ (Group B)
Number: N (%)	73	38 (52%)	35 (48%)
Sex			
F	24	10	14
M	49	28	21
Age: median (min, max)	52 (29, 77)	50 (29, 67)	54 (37, 77)
Site: N (%)			
Frontal	26 (36%)	15	11
Parietal	19 (26%)	6	13
Temporal	24 (33%)	15	9
Occipital	4 (5%)	2	2
Depth: N (%)			
Cortical	31 (42%)	17	14
White Matter	38 (52%)	19	19
Ventricular Infiltration	4 (6%)	2	2
Crossed Midline Brain: N (%)			
Yes	14 (19%)	9	5
No	59 (81%)	29	30
Cavity Diameter (cm): N (%)			
3	10 (14%)	2	8
4	31 (42%)	16	15
5	20 (28%)	12	8
>5	12 (16%)	8	4
Median KPS (min, max)	70 (70, 100)	70 (70, 100)	80 (70, 100)
MRI/CT			
Evident disease (infiltrating)	65 (29)	34 (17)	31 (12)
Dubious alterations	8	4	4

patients underwent also a second surgery (plus catheter implantation), that was macroscopically radical in 11 cases. The median time interval between the first and the second surgery was of 6 months (1st quartile=4, 3rd quartile=8).

At our first evaluation, patients presented a median Karnofsky score of 70. Instrumental imaging (MRI/CT) revealed clear evidence of persistent disease (as a pathologic enhanced rim all around the surgical cavity) in 65 patients (among them, 29 had tendency to infiltrate the brain adjacent tissue), while in other 8 only dubious alterations were visible. In the whole group, the location of GBM was frontal in 36% of cases, temporal in 33%, parietal in 26% and occipital in 5%. The midline of the brain was crossed in 19% of the cases. Considering the depth of the tumor, 42% of lesions were cortical, while 52% were located more deeply in the white matter and 6% were infiltrating the wall of ventricular system.

Except for those patients with ventricular infiltration, the basal ^{99m}Tc-perchnetate scintigraphy document-

TABLE II.—*Overall treatment received, since diagnosis.*

	All patients	LR-RIT (Group A)	LR-RIT + TMZ (Group B)
First Surgery			
N. (%)	73	38 (52%)	35 (48%)
Radical	31 (42%)	12	19
Not Radical	42 (58%)	26	16
Adjuvant 3D-Conf EBRT	72*		
Median Gy (min, max)		60 (54, 72)	60 (54, 60)
Adjuvant (Nitrosourea-based) CT			
N. (%)	30 (41%)	13	17
Second Surgery + Catheter			
N. (%)	73	38	35
Radical	11 (15%)	7	4
Not Radical	62 (85%)	31	31
LR-RIT cycles			
Median (min, max)	3 (2, 7)	3 (2, 5)	3 (2, 7)
LR-RIT cumulative activity (MBq)			
Median (min, max)	1 850 (927, 4 440)	2 035 (925, 3 330)	1 665 (740, 4 440)
Temozolomide cycles			
Median (min, max)	—	—	6 (4, 16)

*) Delivered to all but 1 patients after the first surgery.

ed isolated surgical cavities, without leakage or communication with the CSF space.

Regarding LR-RIT, the median number of cycles was 3 (min=2, max=7), and a median cumulative activity was 1 850 MBq (1st quartile=40, 3rd quartile=60).

In patients who received TMZ in addition, the median number of cycles was 6 (min=4, max=16).

Tables I and II show respectively the distribution of patients' characteristics and the overall treatments received by patients since their diagnosis.

Apart from patients treated with LR-RIT+TMZ being slightly, but non significantly, older (Wilcoxon's test p=0.30), and with a smaller, but non significantly, cavity diameter (Fisher's Exact test: p-value=0.13) both groups were comparable.

Response

In the majority of patients (75%) a stabilization of disease was obtained. An example of long lasting progression free survival is shown in Figure 1. Eighteen patients (25%) remained in progression.

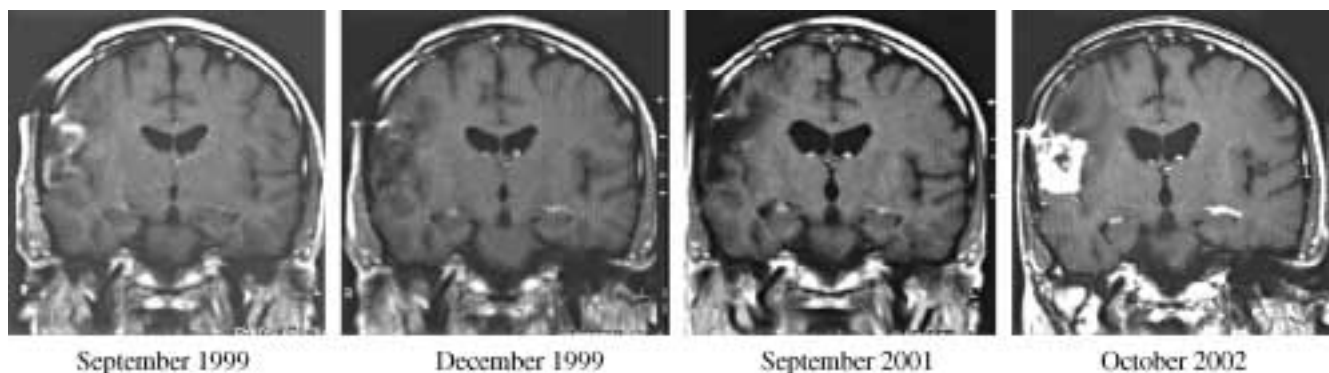


Figure 1.—Male, 52 years of age, diagnosed with GBM in right parietal lobe, treated with surgery and EBRT (60 Gy). In June 1999 he was re-operated due to recurrence. A control MRI performed in September 1999 revealed dubious alterations in the surgical bed. The patient was enrolled for LR-RIT (3 cycles) in association with TMZ (12 cycles). Further MRI control did not show Gadolinium enhancement until October 02. Subsequently, a third neurosurgery was performed, as a salvage therapy, to palliate the symptom of cerebral edema. Histological examination documented necrotic tissue mixed with viable tumor cells.

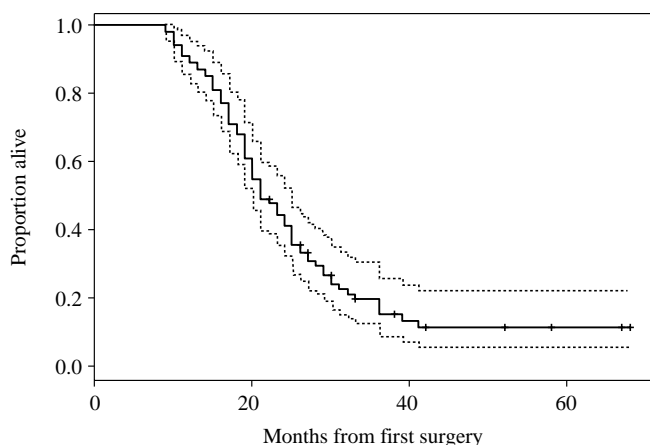


Figure 2.—Kaplan-Meier estimated OS in the whole group of patients and 95% CI.

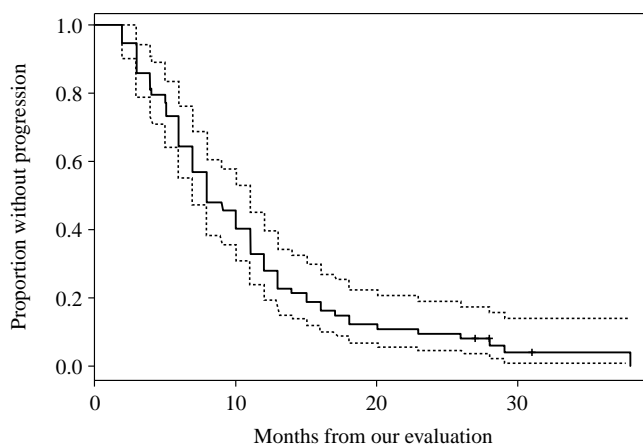


Figure 3.—Kaplan-Meier estimated PFS in the whole group of patients and 95% CI.

Although statistically not significant, there was a tendency toward higher response rate in the LR-RIT+TMZ group. The median follow-up time after LR-RIT was 14 months (1st quartile=10, 3rd quartile=18).

Overall and progression free survival

Overall, in this group of 73 patients, the estimated median PFS from the evaluation at our Department was 8 months (95%CI=[6 mm, 10mm]) and the estimated median OS from the first surgery was 21 months (95%CI=[19 mm, 25 mm]) (Figures 2, 3).

In the group treated with LR-RIT alone, the OS and the PFS were 17.5 months (95%CI=[17 mm, 20 mm])

and 5 months (95%CI=[4 mm, 8 mm]) respectively. Patients treated with LR-RIT+TMZ had a statistically significant improved OS and PFS {median OS=25 months (95%CI=[23 mm, 30 mm]) and median PFS=10 months (95%CI=[9 mm, 18 mm]); log-rank test associated p-value<0.01 and <0.01 respectively} (Figures 4, 5).

In the final Cox model, we considered the factors in Table I plus radicality of the first surgery and treatment received. These prognostic factors were all well balanced across the 2 treatment groups. When fitting the final model we found no evidence of a treatment by site interaction. In Table III are reported the coefficients for the main effects of the final models for PFS and OS. We found that, after adjust-

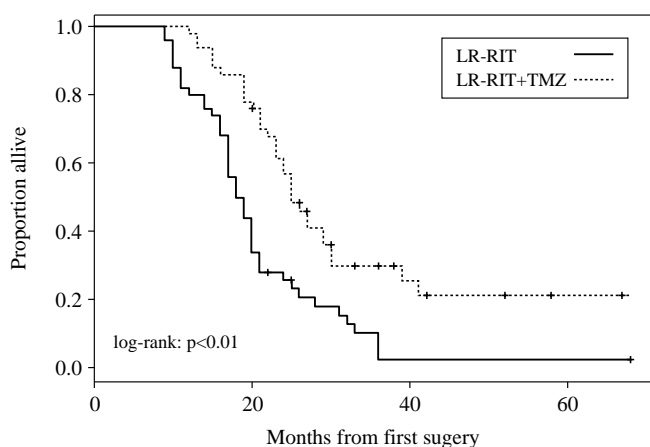


Figure 4.—Kaplan-Meier estimated OS and treatment group.

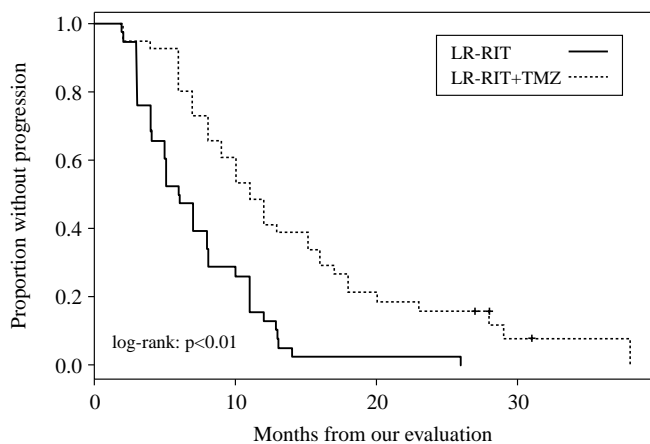


Figure 5.—Kaplan-Meier estimated PFS and treatment group.

ing for age and Karnofsky score, radicality of first surgery was a very important prognostic factor, strongly reducing both the risk of disease progression and death.

We couldn't find a significant association between temporal, parietal or frontal location and OS or PFS. Although non significant, the coefficient for the cavity suggests an increased risk for a diameter equal or greater than 5 cm; a similar consideration applies to a cortical *versus* a non-cortical location of the tumor. From the final row of Table III, we can see that the importance of the addition of TMZ to LR-RIT is confirmed by these data, as it strongly characterized the prognosis of these patients, together with the radicality of the first surgery (Figures 4, 5).

TABLE III.—Estimated relative hazard and 95% confidence interval from Cox PH model: Overall Survival (OS) and Progression Free Survival (PFS).

	OS		PFS	
	Relative hazard	95% CI	Relative hazard	95% CI
Age (per year)	1.06	1.03, 1.09	1.02	0.96, 1.06
Karnofsky per unit	0.99	0.95, 1.01	0.97	0.94, 1.00
Depth				
Non cortical <i>vs</i> cortical	1.60	0.77, 3.30	1.51	0.73, 3.15
Radically 1 st surgery				
Yes <i>vs</i> No	0.50	0.27, 0.93	0.37	0.16, 0.82
Midline brain crossed				
Yes <i>vs</i> No	0.64	0.26, 1.60	0.49	0.15, 1.57
Cavity diameter				
5, >5 cm <i>vs</i> 3, 4	1.35	0.68, 2.65	0.80	0.34, 1.88
Infiltration				
Yes <i>vs</i> No	1.68	0.72, 3.96	1.59	0.55, 4.54
Treatment				
LR-RIT+TMZ <i>vs</i> LR-RIT	0.36	0.19, 0.66	0.21	0.10, 0.45

Toxicity

Four patients experienced a mild allergic reaction at second cycle of LR-RIT (during MoAbs [3 patients] and avidin [1 patient] administration). Two more patients presented a brief attack of myoclonic epilepsy, within a few minutes after ⁹⁰Y-biotin injection.

In 3 patients, who received 4 cycles of LR-RIT a delayed, progressive exacerbation of haemiparesis occurred. A subsequent palliative surgical debulking demonstrated a prevalent part of necrotic tissue mixed with tumor. In 2 patients a skin infection around the reservoir was reported.

Twenty-two out of the 35 patients who received LR-RIT+TMZ presented transient hematological toxicity: a grade II-III lymphocytopenia (in 12/22) and/or a grade II-III thrombocytopenia (in 8/22). No hematological, renal or liver toxicity was reported in the remaining patients.

Discussion

Since a definitive cure or a long-term remission for glioblastoma seems unlikely in the near future, the common goal of most experimental protocols is the attempt to control disease progression, prolong sur-

vival of patients and improve their quality of life. Although, a large number of treatments for recurrent GBM are reported in the literature, there is no substantial evidence to establish general guidelines in the case of GBM relapse.

Considering that more than 80% of recurrent GBM arise within 2 cm from the original margin of contrast-enhancing tumor,²⁶⁻²⁹ in case of GBM relapse, locoregional therapeutic approaches, can be applied. They include reoperation and various types of radiotherapy (conformal conventionally fractionated radiotherapy, hypo-fractionated stereotactic radiotherapy, interstitial brachytherapy and radiosurgery). Reoperation may improve neurological status and prolong survival in some cases; however, radiation therapies can provide similar benefit in a less invasive manner.³⁰

Clinical experiences employing more innovative approaches, such as local hyperthermia, intra-tumoral injection of interleukin-2 activated lymphocytes, α -interferon, recombinant toxins and various chemotherapeutic agents, have been reported over the last few years.³¹⁻³⁴

Locoregional radioimmunotherapy, with its ability to destroy a large number of tumor cells, was reported as a very effective and safe therapy. In our phase I study,¹⁹ involving a small group of patients with high-grade astrocytoma treated with pre-targeted LR-RIT, the median overall survival for GBM patients was 20 months. These results were in agreement with those from other LR-RIT trials and indicated that locoregional approach with radionuclides can compete with other radiotherapy modalities.^{11-13, 20}

A major aim of the current study was to verify the efficacy, in terms of response and survival, of pre-targeted RIT performed in a larger group of recurrent glioblastoma patients. When we consider the whole group of 73 patients, objective response rate (including PR and SD) was 75%, while the OS and PFS were respectively 21 and 8 months. In the subgroup of 35 patients who underwent only LR-RIT, the respective survival values were 17.5 (OS) and 5 (PFS) months, while in the subgroup of combine therapy (LR-RIT+TMZ) the respective estimates were 25 and 10 months.

Since this is not a randomized study, the comparison between 2 treatments' efficacy cannot be regarded as conclusive. However, a median overall survival of 21 months compares quite favorably with selected retrospective results. In the major clinical study eval-

uating survival in glioblastoma patients treated with surgery, with or without EBRT, Walker *et al.* reported median survival of 35 and 14 weeks respectively in patients treated with surgery followed by radiotherapy or best supportive care only.⁵ The most recent report of Brain Tumor Cooperative group NHI Trial 87-01 reported median survival of 68.1 weeks in patients with GBM intensively treated with surgery, interstitial and external radiotherapy and carmustine.³⁵ On the other hand in a review, which included more than 1 400 patients with recurrent high-grade gliomas (anaplastic astrocytoma and GBM) median time to progression was only 14 weeks.³⁶ Our results, in recurrent patients treated with surgery, radiotherapy and LR-RIT, appear to be more favorable both in terms of OS and PFS.

The role of chemotherapy in glioblastoma, either in an adjuvant setting or at recurrence, has often been controversial. Recently, in relation with positive results assessed in pre-clinical and clinical trials,^{37, 38} the new alkylating drug, TMZ was approved for the treatment of relapsing GBM. Since then, TMZ has been studied in different treatment schedules both in primary and recurrent GBM.³⁹ More recently, a combination with EBRT was introduced.⁴⁰

The rationale for combining TMZ and radiotherapy is based on preclinical data suggesting additional or, at least, synergistic activity against GBM cell lines.⁴¹ In clinic, Stupp *et al.*⁴⁰ recently reported a median survival of 16 months in 64 GBM patients treated with external radiotherapy and TMZ. At present, a randomized trial of European Organization for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC), comparing the combination of TMZ and radiotherapy to the radiotherapy alone, is ongoing.

From the beginning of 1999, in our Department, TMZ was proposed in association with LR-RIT to the new enrolled patients. In our opinion, the basis for combining LR-RIT and TMZ include spatial cooperation (TMZ should eliminate microscopic disease outside the radiation LR-RIT field), toxicity independence (the 2 treatments have different toxicity profiles) and the destructive effect of radiation on brain-blood barrier, with improved permeability for chemotherapeutic agents.⁴² The OS and PFS, of patients receiving the combined treatment, confirmed the hypothesis of better results with combined treatment. In fact, the effectiveness of these treatments was at least additional: both OS and PFS increased respectively from

17.5 and 5 months for the group treated with LR-RIT alone, to 25 and 10 months in combined treatment (LR-RIT+TMZ).

Regarding the safety, LR-RIT alone or combined with TMZ was very well tolerated. Remarkably, there is a low incidence of early and late neurotoxicity. Only 3 patients suffered from progressive neurotoxicity that required surgical debulking. In all cases histopathology revealed a mixture of necrosis and tumor cells, with the prevalence of the former at the boundaries of the resected mass. This frequency for radionecrosis is much lower than in brachytherapy or stereotactic radiotherapy series.^{43, 44}

Reversible grade II and III lymphocytopenia and/or thrombocytopenia were observed in 62% of patients treated with LR-RIT and TMZ that is comparable to studies applying TMZ and external radiotherapy.^{40, 45} Patients' subjective tolerance of the catheter was very good: we observed only 2 complications (skin infection) connected with catheter implantation.

Conclusions

Our study confirms the efficacy and safety of LR-RIT in glioblastoma, with a significant increase in survival compared to the one obtained with surgery and external radiotherapy alone. In particular, this study shows that this improvement in survival can be further increased by the multimodal approach of combining LR-RIT with TMZ.

We are aware of possible bias in our retrospective study, such as in the selection of patients or in incomplete treatment in patients that were not included into the analysis. Nevertheless, these results represent the basis for further prospective trials. A strict timing and schedule of radioimmunotherapy could play an important role in the overall outcomes of glioblastoma. The best results will be probably obtained when LR-RIT is performed after initial surgery. Since it is very well tolerated, the catheter could be inserted even at the first surgical intervention. The 2-4 week interval, between surgery and external radiotherapy could be a suitable period to start LR-RIT.

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