Local Treatment of Malignant Gliomas by Direct Infusion of Specific Monoclonal Antibodies labeled with $^{131}$I: Comparison of the Results Obtained in Recurrent and Newly Diagnosed Tumors

Pietro Riva, Agostino Arista, Giancarlo Franceschi, Massimo Frattarelli, Carmelo Sturiale, Nada Riva, Michela Casi, and Rosetta Rossitti

Abstract

Two murine monoclonal antibodies, BC-2 and BC-4, raised against tenascin and labeled with $^{131}$I were infused locally in the site of neoplastic disease by means of a removable (16 patients) or indwelling (34 patients) catheter. Fifty patients bearing a malignant glioma were treated. Twenty-six of these were suffering from recurrent disease; their tumors relapsed within 9 months (median) after treatment. The remaining 24 cases had a newly diagnosed tumor, and local radioimmunotherapy (RIT) was given immediately after surgery and radiochemotherapy. All efforts were made to reduce the tumor before the infusion of the radiopharmaceutical. Therefore, 22 cases with relapsing glioma underwent additional debulking surgery, which led to total or subtotal removal of tumor in 9 of the patients. Altogether, 28 patients had intraleseional RIT when the disease was minimal or microscopic. Conversely, 22 cases underwent local RIT with a tumor the diameter of which was >2 cm. In many cases, the infusions were repeated up to six times to achieve complete destruction of the neoplastic tissue. The local treatment did not give rise to systemic or to cerebral adverse effects. The labeled monoclonal antibodies, given directly in the site of the lesion, concentrated in very high amount in the neoplastic tissue and remained fixed in the target for a long period of time. For these reasons, the radiation dose to the tumor was remarkable (on average >30,000 cGy/cycle) and consequently led to promising results. The median survival was, in total, 20 months (18 in recurrent tumors and 23 in newly diagnosed lesions). Moreover, median survival was 17 months in patients with bulky tumors (both recurrent and newly diagnosed tumors) and 26 months in patients with minimal or microscopic disease. The median time to progression was 3 months in recurrent and 7 months in newly diagnosed gliomas. Finally, RIT produced 3 CRs (all in recurrent tumors), 6 PRs (4 in recurrent and 2 in newly diagnosed), and 11 stabilizations of disease (4 in recurrent and 7 in newly diagnosed). In 19 cases (13 recurrent and 6 newly diagnosed) the progression of tumor was recorded.

Eleven patients (2 recurrent and 9 newly diagnosed) who were treated by RIT when their disease was minimal and nondetectable by radiological methods remained disease-free and were classified as NED. The overall response rate (NED plus CR plus PR) was 40% (34.6% recurrent and 45.8% newly diagnosed). These data provide evidence for the capability of this new therapeutic technique to achieve, in a significant number of cases, lasting control of malignant gliomas and suggest the opportunity to apply this treatment in an adjuvant setting.

Introduction

Current therapeutic modalities (surgery, external radiotherapy, and chemotherapy) currently utilized control malignant gliomas and can prolong patients’ survival, achieving a median duration of 12 months (1–3) and as long as 17 months (4). Nevertheless, they do not lead to complete remission of these tumors, which in almost all cases recur (5). Therefore, local techniques to selectively destroy the neoplastic tissue without affecting the normal brain have been developed or are under study (6–9). The locoregional administration of radiolabeled monoclonal antibodies (10, 11) reacting specifically with antigens present in the tumor represents a promising approach in this field. Experimental (12, 13) and clinical (14, 15) studies have demonstrated that the intratumoral injection of specific immunoglobulins linked to a suitable isotope yields a very favorable biodistribution of the radiopharmaceutical. In fact, the accretion of radioimmunoglobulins in the lesion as well as their residence time in the neoplastic tissue are enhanced in comparison with that achievable by i.v. administration. Moreover, the direct application of radiolabeled MoAbs into the tumor delivers a very high radiation dose to the target cells. Promising outcomes were obtained in a Phase I clinical study in patients with recurrent tumor (16, 17). A second group of patients with newly diagnosed malignant gliomas was given intraleseional RIT, and the biological and clinical effects of the treatment were evaluated and compared in both groups.

Materials and Methods

MoAbs. Two murine IgG1 antibodies, BC-2 and BC-4, the biological and histopathological characteristics of which have been described previously (18) were used. Their target is TN, an exomeric glycoprotein that is found in impressive quantity in the stroma as well as in the cytoplasm of tumor cells of malignant gliomas (19, 20). Conversely, normal cerebral tissue completely lacks TN antigens (21). This feature is favorable for glioma targeting by means of MoAbs because a high concentration of these biological probes can be achieved in the tissue (22). The MoAbs were labeled with $^{131}$I by means of the Iodogen method, as published (23), with good labeling efficiency; immunoreactivity was preserved satisfactorily (24, 25).

Patients. Altogether 50 evaluable patients were accrued in this study, the protocol of which was approved by the Ethical Committee of “M. Bufalini” Hospital (Cesena, Italy) and by the Italian Health Ministry. The patients were subdivided into two groups: group A, patients with recurrent malignant gliomas (26 patients); and group B, patients with newly diagnosed malignant gliomas (24 patients).

The mean age of the patients in group A was 49.6 years and ranged between 26 and 70 years. In group B, the patients’ mean age was 52.5 years (range, 26–68 years). In the majority of cases of groups A and B, the tumor diameter evaluated by CT scan before the first surgical operation was >3 cm, as shown in Table 1. Large tumor size represented an unfavorable prognostic factor (26, 27). Tumors were located in all lobes of the brain: temporal (11), parietal (10), frontal (8), parieto-occipital region (5), parieto-temporal region (5), fronto-parietal region (5), occipital (3), fronto-temporal region (3), 3rd ventricle (1), and spinal cord (1).

The histology of the tumors, classified according to the WHO (28), in group A were glioblastomas (19) and anaplastic astrocytomas (5). The Karnofsky performance status (29) was 100–80 in 35 cases (70%), 70–50 in 10 cases (20%), and 40–30 in 5 cases (10%). Patients with recurrent malignant glioma (group A) had a clinical course which can be summarized as follows: (a) surgical operation to resect their newly diagnosed primary tumor; (b) external

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2 To whom requests for reprints should be addressed. Phone: (547) 352664; Fax: (547) 352660.

3 The abbreviations used are: MoAb, monoclonal antibody; TN, tenascin; CT, computed tomography; SPECT, single-photon emission computed tomography; DTPA, diethylenetriaminopentaacetic acid; HAMA, human antinouse antibody; PD, progressive disease; NED, no evidence of disease; CR, complete remission; PR, partial remission.
radiotherapy at the maximum tolerated dose (60–70 Gy) delivered to a limited field; (c) chemotherapy given in 20 patients by combining different drugs; (d) in all cases the tumor relapsed after a median time of 9 months; (e) thus, they were referred for intralesional RIT; (f) 22 of 26 patients underwent an additional surgical operation that was carried out with the support of the operating microscope, aiming to achieve total or subtotal removal of the regrowing glioma tissue before the local infusion of radioactive drug. This goal was achieved in 9 cases, whereas in the remaining 13 patients a neoplastic remnant, the diameter of which was, on average, 4.08 cm (range, 2.2–6.1 cm), remained; and (g) finally, MoAbs conjugated with $^{131}I$ were infused intratumorally. 

Conversely, the patients in group B with a newly diagnosed malignant glioma had intralesional RIT immediately after surgical operation and radiochemotherapy. In this group, surgery achieved more effective reduction of tumor burden. In fact, 15 of 24 patients had a minimal or microscopic residual disease after surgery. In the remaining nine cases, the mass left by the intervention had an average diameter of 2.95 cm (range, 2–4.1 cm). In all patients, immunohistochemistry (30) confirmed the expression of TN in sufficient amount (at least three plus). All patients gave their informed written consent before the infusion of radiolabeled MoAbs.

**Protocol of RIT.** The methodology used has been described in detail (16, 31, 32) and is briefly summarized here. The patients were pretreated with antiepileptic drugs, steroids, antibiotics and thyroid-blocking agents. To inject the MoAbs exactly in the site of the disease, an indwelling Rickham catheter, with a reservoir located under the skin, was utilized in the majority of cases (34 of 50). This device was set up by the surgeon during the operation which produced a cavity at the site of the tumor. The tip of the catheter was placed inside the cavity. In this way, antibodies injected through the external reservoir reached the cavity and homogeneously diffused through it to reach and bind their specific target. In 16 cases, 12 of these bearing recurrent lesions (group A) and 4 with newly diagnosed tumors (group B), a removable catheter was used. It was inserted surgically or stereotactically and had to be removed within 2 weeks to avoid local infections. The radiolabeled MoAbs were bolus administered within 30 s. The volume of radiopharmaceutical was always <1.5 ml to prevent an increase of the intracranial pressure. In the first 26 patients, escalating doses of $^{131}I$ starting from 185 MBq and reaching 2405 MBq, increasing 85 MBq at each level, were administered. In this way, the maximum tolerated dose was determined to be 2405 MBq. In the second series of cases (24), higher $^{131}I$ doses ranging from 1850 to 2405 MBq (mean, 2146 MBq) were used. This amount of radiopharmaceutical proved to be safe and effective and was chosen to be utilized in subsequent applications. The procedure of injection and the subsequent management of the patients were carried out according to radioprotection regulations.

**Multiple RIT Cycles.** RIT courses were repeated many times, when the course of the disease made it possible. The first three therapeutic injections were given at short intervals (30–60 days). Subsequent injections were given after 3–4 months with respect to the response of the tumor to the treatment. In 17 cases, patients’ RIT infusions were interrupted owing to the progression of the tumor.

In those patients who experienced a favorable response, RIT courses were interrupted only when the patients did not have evidence of disease for at least 6 months. This was assessed by radiological investigations (CT scan, magnetic resonance imaging, and brain SPECT with $^{99m}$Tc-labeled DTPA), which had to be completely normal. This rule was adopted empirically, on the basis of the experience gained during the course of the trial. The maximum number of injections given to the same patient was six; four cases had six administrations. As an example of this particular strategy, the clinical course of the patient is reported. She was operated on July 1993 to remove a huge left temporo-parietal (diameter, 3.69 cm) glioblastoma. Then she underwent external radiotherapy to a total dose of 5400 cGy; in addition, she was given chemotherapy. Finally, she was given intralesional RIT according to the following schedule: first course ($^{131}I$-labeled MBq 1850), on December 1993; second course ($^{131}I$-labeled MBq 1443), on February 1994; and third course ($^{131}I$-labeled MBq 1238), on April 1994. At the end of this period, the brain CT scan and SPECT ($^{99m}$Tc-labeled DTPA) showed no sign of tumor. Nevertheless, she had additional infusions on August 1994 ($^{131}I$-labeled MBq 1961) and December 1994 ($^{131}I$-labeled MBq 2479) as a precautionary measure. The patient is completely free of disease 26 months from diagnosis and 21 months from first RIT course (Fig. 1).
pharmacokinetics of the anti-TN antibodies when they were administered again.

Pharmacokinetics and Dosimetry. The MoAbs, injected directly in the site of the tumor that contained large amounts of specific TN antigens concentrated in high quantity in the target and did not spread to the normal brain or distant organs. Moreover, the residence time of the radiopharmaceutical in the tumor was long (Fig. 2) because the intralesional route of injection avoided the removal of the MoAbs.

As a consequence, the radiation doses that were given to the patients with newly diagnosed malignant glioma were remarkably high. The irradiation of the lesions of the patients with newly diagnosed malignant glioma were higher than that in patients with recurrent tumors, the fact that the tumor load was less in the former group than 1 mm. By means of these data, the doses delivered to the neoplastic tissue and to the liver, kidney, bone marrow, urinary bladder, and thyroid etc. were calculated applying both Medical International Radiation Dosimetry and Monte Carlo formalisms (33, 34).

Follow-up. Every month a physical examination and a complete hematological investigation were performed. In particular, a HAMA (35) assay was done using an ELISA method (36). Brain CT scan and brain SPECT (99mTc-labeled DTPA) were carried out every 3 months. When the patient became free of disease for at least 1 year, the clinical and radiological controls were obtained every 6 months. The median survival time of all patients were measured from the time of initial diagnosis until death or last follow-up visit and was statistically evaluated according to Kaplan et al. (37). The median time to tumor progression was calculated beginning from the first RIT course, applying the methodology described by Kaplan et al. (37). The objective response to the treatment was assessed clinically and radiologically (CT scan, brain SPECT with 99mTc-labeled DTPA, and, if necessary, magnetic resonance imaging), utilizing the WHO score (38). In this respect, objective measurements of the three main diameters of the lesions obtained both by CT scan and by SPECT were carried out. On the basis of the results of these investigations the responses to treatment were classified as PD, stabilized disease, PR, and CR (38). Twenty-four patients (9 in group A and 15 in group B) received local RIT after radical removal of the neoplastic tissue and subsequent radiochemotherapy. In these cases, the radiological examinations before RIT did not provide evidence of macroscopic tumor. In fact, these patients had a postoperative cavity, macroscopically free of disease, although occult neoplastic cells around the cavity were almost certain.

If these patients did not relapse after one or more RIT infusions, this result was classified as NED.

Results

Toxicity. The local administration of large amounts of 131I and immunoglobulins did not produce systemic or cerebral adverse effects. All hepatic, renal, metabolic, and hematological functions were unchanged. A few patients suffered mild and transient ailments, such as headache and nausea after the therapeutic infusions, which spontaneously decreased and disappeared no later than 24 h afterwards.

HAMA. Sixty-nine % of the patients developed HAMA owing to the spread of the murine IgG or of their degradation products into the blood stream. HAMA output was recorded in 64% of cases belonging to group A (16 of 25) and in 75% of group B (18 of 24). HAMA was dose dependent because in cases who had three or more cycles, it was always present. Conversely, HAMA was observed in only 35.4% of those patients who underwent 1–2 administrations (Table 2). The patients who became HAMA positive and were given additional administrations of MoAbs did not show allergic or anaphylactic symptoms. Moreover, HAMA did not cause any modification of the

<table>
<thead>
<tr>
<th>Table 2 HAMA production</th>
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<tbody>
<tr>
<td>Cycle</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<td>4</td>
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<p>| Table 3 Pharmacokinetics and dosimetry (mean values) |</p>
<table>
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<tr>
<th>All patients</th>
<th>Group a</th>
<th>Group b</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID % x g.</td>
<td>2.4 ± 1.8</td>
<td>2.11 ± 1.8</td>
</tr>
<tr>
<td>CgY</td>
<td>42,300 ± 30,000</td>
<td>30,000 ± 26,000</td>
</tr>
</tbody>
</table>

| Table 4 Objective response to RIT (WHO criteria) in 50 cases |
|-----------------|-----------------|-----------------|-----------------|
| Group a | % | Time | Group b | % | Time | Total | % | Time |
| PD     | 13 | 50  | 6   | 25  | 9   | 19   | 38  | 6   |
| SD     | 4  | 15.4| 7   | 29.2| 9   | 11   | 22  | 10  |
| RR     | 4  | 15.4| 10  | 8.3 | 11  | 6    | 12  | 10  |
| CR     | 3  | 11.5| 42  | 2   | 3   | 3    | 42  |
| NED    | 2  | 7.7 | 20  | 3.75| 11  | 11   | 22  | 13  |

a Group a, number of patients with recurrent tumor.

b Group b, patients with newly diagnosed tumor.

c T.D. % x g, percentage of injected dose concentrated in g of tumor 24 h after the injection.
d eff. T/2, effective half-life of the radiolabeled MoAbs in the tumor (in hours).
e cGy, radiation dose delivered to neoplastic tissue/cycle in cGy.

Fig. 2. Planar scintigraphy obtained, in anterior view, 63 days (i.e. more than 2 months) after the intralesional injection of radionabeled antibodies BC-2 and BC-4 (4 mg. of protein and 2220 MBq, i.e., 60 mCi, of 131I). This image demonstrates that the MoAbs intralesionally injected remain in the site of injection for a period of time extremely extended. About 2% of injected dose is still concentrated in the cavity left by surgery, which was performed 21 months before. Only a small amount of free radioiodine has been picked up by the thyroid. This patient, who underwent the surgical removal of left frontal glioblastoma, received 5 RIT applications and is in complete remission 23 months since the first MoAb injection.
The irradiation dose to liver, kidney, and bone marrow did not exceed 150 cGy/cycle and did not produce untoward effects.

Survival. The intraleisional RIT approved to prolong the lives of the patients in comparison with the values usually reported for current treatments (surgery and radiochemotherapy), wherein median survival is usually <12 months (39). In fact, the overall RIT median survival was 20 months; in group A it was 18 months and in group B it was 23 months. In cases (belonging to both groups A and B) who were treated with a tumor remnant with a diameter >2 cm, median survival was 17 months. By contrast, median survival was 26 months in patients who underwent RIT with minimal or microscopic lesions. The median time to tumor progression was 3 months in group A and 7 months in group B.

Clinical Response. Altogether, the local infusion of radiolabeled MoAbs led to 3 CRs (all in recurrent tumors), 6 PRs (4 in recurrent and 2 in newly diagnosed), and 11 stabilizations of disease (4 in recurrent and 7 in newly diagnosed). In 19 cases (13 recurrent and 6 newly diagnosed), PD was recorded. Eleven patients (2 recurrent and 9 newly diagnosed) who received intraleisonal RIT when their lesion was minimal and not detectable by means of radiological examinations, remained disease free and were classified as NED (Table 4; Fig. 1). The overall response rate, which included PR plus CR plus NED results, was 40% (34.6% recurrent and 45.8% newly diagnosed).

Relapse of the Tumor after RIT. In 14 cases who received one or more RIT courses, the tumor, which was apparently absent at the time of first RIT course, relapsed in spite of administration of radioactive antibodies. The recurrence of glioma occurred in five patients of group A and in nine patients of group B. Moreover, in 6 patients (2 group A and 4 group B) the neoplastic tissue reappeared in the bed of the primary lesions. By contrast it recurred outside the site of the original tumor in eight cases (Table 5).

Histological Modifications Produced by Local RIT. Seventeen patients, 6 in group A and 11 in group B, underwent an additional operation because they presented radiological and clinical data that were judged as suspicious of relapsing disease after one or more RIT applications. In all cases, large areas of necrosis were found in the site of the primary tumor. In three cases, neoplastic cells were completely absent and few malignant cells were present in the remaining cases.

Discussion

This study is still in progress and a larger number of cases has to be treated to improve the significance of the results. Nevertheless, some conclusions can be drawn. The local infusion of radiopharmaceuticals proved to be a safe technique that was well tolerated. This was due to the particular route of administration, which restricted the radioactive antibodies to neoplastic tissue, thus preventing or greatly reducing their diffusion to normal brain or critical organs. In particular, the indwelling catheter utilized for the infusion was made of plastic material so that it was tolerated by the tissues and could be left in place for two or three years. At the same time, it guaranteed deposition of the radiopharmaceutical in neoplastic tissue, avoiding unwanted spread to normal brain. Thus, the intraleisonal administration of radiolabeled MoAbs seemed to approach the features of the “magic bullet” proposed by Ehrlich (40). Repeated RIT applications could be safely performed.

This represented a therapeutical advantage with respect to other locoregional radiating techniques that can be used only one time (41, 42). HAMA was observed in many cases but did not affect tumor targeting when repeated courses were carried out. β-Rays of 125I have a restricted energy and cannot penetrate into tissue >1 mm. The presence of physiological or anatomical obstacles could prevent the targeting of tumor clusters. “Barriers” were represented by areas of necrosis, hemorrhagic infiltrations, and tumor zones with high interstitial pressure. For these reasons, relapse in the tumor bed occurred in some cases. In spite of these limitations, the clinical outcomes can be judged as promising and are similar or better than the outcomes obtained with other aggressive approaches. For example, Wen et al. (43) by utilizing stereotactic brachytherapy with 125I seeds, in addition to customary regimens, obtained a median survival of 18 months in 56 patients with newly diagnosed glioblastoma. Moreover, in cases undergoing reoperation the median survival was 22 months. By using stereotactic radiosurgery, in 51 cases a 10-month survival was recorded (44), but in small, radiographically well-defined malignant gliomas a median survival of 26 months was observed (45, 46).

Similarly intraoperative radiation therapy delivering a large radiation dose to the neoplastic tissue in a group of 30 cases led to a survival of 25 months (47). The use of a radiosensitizer combined with hyperfractionated irradiation (48) did not give a significant benefit to the patients (median, survival 11 months). Finally, the i.v. injection of radiolabeled MAbs (49) produced only one CR and two PRs of brief duration in 14 cases.

The survival thus far recorded in our patients points to evidence that the prognosis of this disease can be ameliorated and the patients’ lifespan made longer in group A (18 months) and group B (23 months). Moreover, the application of intraleisonal RIT to small or microscopic lesions, in an adjuvant setting, yielded additional prolongation of the survival (26 versus 17 months recorded in bulky diseases). The objective response to intraleisonal RIT was quite good, taking into account the aggressive and invasive nature of these tumors.

In fact, 11 NED, 3 CR, and 6 PR were obtained altogether, corresponding to a 40% response rate. Moreover, in group B the percentage of NED and CR was higher with respect to group A (37.5 versus 19.2%, respectively), whereas the progression of the disease (PD) was significantly lower (25% group B versus 50% group A). This represents the most interesting issue of our study. The clinical experience acquired during 4 years gave evidence that this innovative therapeutic technique is able to reduce or completely destroy the neoplastic tissue, to prevent the regrowth of the tumor, and to control the progression of malignant gliomas for a long time. The best model for the application of intraleisonal RIT is represented by patients with newly diagnosed tumors in whom previous treatment (radical surgery, radiochemotherapy, and chemotherapy) has reduced neoplastic tissue to minimal or microscopic disease. Additional progress could be achieved by the use of 90Y, the energetic β particles of which can penetrate up to 1 cm into the tissue, thus, reaching more distant neoplastic elements and enhancing the probability of destroying the glioma cells. At the same time its physical properties (absence of γ emission and quite short half-life, 2.5 days) greatly reduce the length of hospitalization.

Table 5 Malignant glioma relapse after RIT

<table>
<thead>
<tr>
<th>Tum. bed</th>
<th>%</th>
<th>Time</th>
<th>Outside</th>
<th>%</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>2</td>
<td>14.2</td>
<td>6</td>
<td>3</td>
<td>21.4</td>
</tr>
<tr>
<td>Group B</td>
<td>4</td>
<td>28.5</td>
<td>8</td>
<td>5</td>
<td>35.7</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>42.7</td>
<td>7</td>
<td>8</td>
<td>57.1</td>
</tr>
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</table>

*Tum. bed*: number of patients, who received RIT when their disease was apparently absent and was not shown by radiological examinations, in whom the malignant glioma relapsed in the bed of primitive lesions after one or more RIT courses.

*Tumor relapse either in tumor bed or outside the primary lesion. In particular, the particular route of administration, which restricted the radioactive antibodies to neoplastic tissue, thus preventing or greatly reducing their diffusion to normal brain or critical organs. In particular, the indwelling catheter utilized for the infusion was made of plastic material so that it was tolerated by the tissues and could be left in place for two or three years. At the same time, it guaranteed deposition of the radiopharmaceutical in neoplastic tissue, avoiding unwanted spread to normal brain. Thus, the intraleisonal administration of radiolabeled MoAbs seemed to approach the features of the “magic bullet” proposed by Ehrlich (40). Repeated RIT applications could be safely performed.

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