Role of nuclear medicine in the treatment of malignant gliomas: the locoregional radioimmunotherapy approach

P. Riva, G. Franceschi, N. Riva, M. Casi, M. Santimaria, M. Adamo.

Department of Nuclear Medicine; "M. Bufalini" Hospital, Cesena, and Ist Oncologico Romagnolo, Italy

Abstract. The high-grade malignant gliomas (anaplastic astrocytomas and glioblastoma) have a very bad prognosis since the available methods of treatment (surgery, radiotherapy and chemotherapy) are unable to control the progression of the disease for long. The use of specific monoclonal antibodies labelled with a suitable isotope (iodine-131 or yttrium-90) represents an effective approach to hamper tumour regrowth. Some authors have injected the antibodies intravenously, or have tried to increase the tumour/background ratio with the avidin/biotin system. In many cases the labelled monoclonal antibodies were injected directly into the tumoral bed after the operation. The authors' experiences concern a quite large locoregional radioimmunotherapy study which was performed by using antitenascin antibodies labelled initially with ^{131}I and more recently with ^{90}Y. The clinical results demonstrate the ability of this technique to control, for a long time, the growth of these tumours. The glioblastoma median survival was prolonged to 25 months (^{131}I group) or 31 months (^{90}Y group). The response rate (which comprises PR, CR and NED) was 47.1% (glioblastoma ^{131}I group) or 40% (glioblastoma ^{90}Y group). In many cases a significant tumour shrinking effect was radiologically demonstrated. The use of ^{90}Y proved more favourable in bulky lesions, and reduced the radioprotection problems.

Key words: Malignant gliomas – Radioimmunotherapy – Monoclonal antibodies – Radioiodine – Radioyttrium

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Introduction

Malignant gliomas are quite often encountered in clinical practice. Malignant astrocytomas are the most frequent type, while the incidence of oligodendrogliomas, mixed oligo-astrocytomas and low-grade astrocytomas is lower. The incidence of malignant gliomas is increasing in the elderly [1–4]. Statistical data indicate that about 20.000 new cases are diagnosed annually, in Europe. Thus these tumors represent a real social problem. Unfortunately, they are very ominous diseases and their natural history is adverse: a 5% 2-year survival rate for patients with glioblastomas and a 20% 10-year survival rate for those with low-grade gliomas have been recorded [5]. The main pathological problem is the infiltrative nature of these tumours. Even if nearly complete tumour resection is performed, billions of undetectable tumour cells are left beyond the resection margins [6]. Against this background of limited effectiveness of conventional treatments, various clinical trials are currently being undertaken to assess new methods of controlling such malignancies.

Surgery is the most important therapeutic procedure and it can now be performed with sophisticated techniques that enable detection of neoplastic cell clusters outside the main tumour mass [7]; nevertheless, resection always proves incomplete and surgery should accordingly be considered the primary step of a multimodality approach [8, 9]. External radiotherapy is performed following the operation. Its effectiveness in controlling local infiltration and in prolonging median survival has been demonstrated. [10–12]. However, the normal brain through which the radiation passes constitutes a limiting factor. For this reason, a dose of 60 Gy cannot be exceeded; but this dose is not sufficient to completely sterilise the tumoral bed and this approach is thus not completely curative. Many studies are in progress to enhance the efficacy of these regimens [13–17]. In particular, radiosurgery [18, 19], boron neutron capture [20] and intraoperative radiotherapy [21, 22] are promising techniques. Interstitial irradiation of the tumour by means of iodine-125 seeds or iridium-192 wires has been investigated [23, 24]. The role of chemotherapy in the management of these tumours is still under evaluation. Several drugs, either as single agents or in combination, have been assessed [25–31]. Moreover, some authors have tried to improve the clinical efficacy of these drugs by utilising the intra-arterial [32] or intratumoral [33, 34] route of administration. Research into immunotherapy, biotechnology therapy and gene therapy is also in progress [35–38]. Unfortunately, in spite of all these efforts the prognosis of malignant gliomas remains poor, and while regimens to control the tumours can prolong median survival (12 months for glioblastoma and 25 months

for anaplastic astrocytoma), they do not lead to a definitive cure [39]. For these reasons, malignant gliomas are considered as orphan tumours.

The role of nuclear medicine in the treatment of malignant glioma: systemic and locoregional radioimmunotherapy

Nuclear medicine can play an important role in this field. In particular, the application of monoclonal antibodies (Mabs) conjugated to a suitable isotope could represent a method by which a high radiation dose can be concentrated on or near the tumour cells, while sparing the normal tissues [40]. The first therapeutic application of radiolabelled Mabs in malignant gliomas was carried out by Brady and co-workers [41–44], who employed the Mab 425, which is raised against epidermal growth factor receptors. The antibody was labelled with ^{125}I [1295–3330 MBq (35–90 mCi) per infusion] and injected i.v. or i.a., following surgery and radiotherapy, in patients with anaplastic astrocytoma or glioblastoma. The cycles were repeated frequently. The incidence of adverse effects was very low, and the median overall survival for both groups of patients was 13.5 months. The systemic administration of Mabs for therapeutic purposes is restricted by many factors: high interstitial pressure inside the neoplastic tissue, limited blood supply to the tumour, inhomogeneous and inconstant antigen expression, possible presence of histopathological barriers (necrosis or fibrosis), formation of immunocomplexes with circulating antigens, and catabolism of immunoglobulins [45]. All these factors result in a very low accumulation of the radiopharmaceutical in the target tissue, which in most cases prevents a favourable therapeutic effect [46]. Moreover, the presence of the blood-brain barrier further hampers the accumulation of antibodies in the malignant tissue.

Paganelli et al. [47] have developed a method which could overcome these problems. Three-step radioimmunotherapy was carried out: first, 35 mg/m^2 of anti-tenascin Mab linked to biotin was administered i.v. Then, 36 h later, 30 mg of avidin and 50 mg of streptavidin were infused. Finally, after 18–24 h 1.2 mg of biotin labelled with yttrium-90 (2.22–2.96 GBq/m^2) was injected. In 48 patients with grade III or IV astrocytomas, a median survival of 19 months (grade III) and 11 months (grade IV) was recorded. Tumour mass reduction was radiologically demonstrated in 12 patients and eight of them had a duration of response of 12 months.

A different strategy is represented by the locoregional administration of monoclonal antibodies. This strategy has been employed in different tumours: intraperitoneally in ovarian [48, 49] and gastrointestinal cancer [50], intrapleurally in cases with malignant effusions [51] and intrathecally in neoplastic meningitis [52]. The direct injection of the immunoconjugates into the tumoral bed of malignant gliomas theoretically presents various advantages: the radiopharmaceutical is concentrated in the area of disease and completely spares the normal brain and distant critical organs; furthermore, it can easily react only with its specific antigenic receptors which are expressed by the glioma tissue. In this way a large number of malignant cells can be hit and damaged or killed by the beta rays produced by the isotope. The crucial problem in this approach is the ability of the antibodies to diffuse through the tissue situated around the postoperative cavity. This area is called the brain adjacent tissue (BAT) and includes the occult neoplastic cells that have migrated from the main tumour mass. A complete and homogeneous distribution of the radiopharmaceutical could lead to sterilisation [53] of this zone and enhance the control of the disease.

The locoregional treatment may be intracavitary, when the antibodies are infused into the surgical crater, or interstitial or intratumoral [54, 55], when the Mabs are administered into the residual neoplastic tissue. Locoregional radioimmunotherapy represents a complex technique, which involves different specialists: neurosurgeons, radiotherapists, oncologists, immunologists, nuclear medicine physicians, radiochemists and physicists. The first step is the surgery, which has to be as radical as possible. During the operation an indwelling catheter (Rickam or Ommaya) is inserted to allow the infusion of radioactive antibodies. Before undergoing radioimmunotherapy, the patient receives external radiotherapy at the maximum dose (on average 60 Gy). If the patient presents relapsing disease following surgery and radiation, he is operated on again in order to reduce the tumour burden. Radioimmunotherapy is then administered.

Antibodies employed

Different Mabs have been utilised for locoregional radioimmunotherapy. In many clinical trials antitenascin Mabs (BC-2 or BC4 or 81C6) have been employed [56, 57]. Tenascin is a glycoproteic antigen, which is present in the extracellular matrix of malignant glioma tissue [58, 59]. By contrast it cannot be found in the normal cerebral parenchyma. Tenascin is expressed in large amounts and its quantity does not change over time. For this reason it represents an optimal target for the radioimmunotherapy approach. In fact the antibodies can readily find and bind to their antigenic receptors surrounding the neoplastic cells. Some authors [60, 61] have employed the Mab ERIC-1, which recognises the human neural cell adhesion molecule (NCAM).

Isotopes utilised

The clinical studies that have been performed and published to date have been carried out using iodine-131 [62–64] and, more recently, yttrium-90 [65, 66]. Some

authors have proposed the application of alpha emitters such as astatine-211 [67]. Radioiodine is available and cheap. Its radiochemistry is well known and it can be easily labelled to the antibodies. Nevertheless, it has disadvantages: its link with immunoglobulins is not stable; the radioconjugate is degraded by tissular desiodases; its emission of gamma rays, whilst ineffective for therapy, exposes the medical staff to unwanted radiation and can contaminate the room; and the energy of beta rays is quite weak (333.8–606.3 keV). Furthermore, it penetrates no deeper than 3 mm; thus many malignant cells can be missed and the sterilisation of the BAT can be incomplete. The use of ^{90}Y is more promising: it does not produce gamma rays and the management of the patient is easier. Even patients who are not self-sufficient and bedridden can be treated. Its beta particles are very energetic (2283 keV) and have a longer path through the tissue. Consequently the probability of killing or damaging a larger number of glioma cells, even in more distant territories, is enhanced. On the other hand the labelling procedures are difficult and time consuming and the isotope is expensive. So far, few data are available on alpha emitters, and they do not allow any conclusions to be drawn.

Clinical studies

Not many trials have been performed so far, and the number of patients to have been enrolled is limited. All are phase I and II studies. The first aspect of note is the very low toxicity of this treatment. No significant early or late changes in haematological, renal, hepatic or metabolic parameters have been recorded. The tolerance of normal nearby brain tissue has been found to be satisfactory. The MTD for ^{131}I was 4440 MBq (120 mCi) [68], while that for ^{90}Y was 925 MBq (25 mCi) [69]. Biodistribution studies have demonstrated a remarkable concentration of the radioactive antibodies at the site of injection. The radioactivity in the surrounding normal brain as well as in distant organs was found to be extremely low. When using ^{131}I a small amount of the isotope was taken up by thyroid, and was found in the gastrointestinal tract and the urinary bladder. This was due to free iodine, which broke loose from its link with the Mabs owing to deiodinating enzymes. The ^{90}Y-Mab complex was found to be more stable and prevented the release of free radioyttrium. Nevertheless, some catabolic products can sometimes be observed in the bowel and, less frequently, in the liver. In about 15% of patients a communication between the surgical crater and the cerebral ventricles may be produced by the operation. In this situation more than 80% of the radioactive antibodies bind directly to the neoplastic area which contains the specific antigen. The remaining part of the solution diffuses through the CSF and arrives in the ventricles and the spinal spaces. However, during the time it is concentrated at the tumour site owing to a direct immunological reaction, only a small quantity enters the systemic circulation.

The dose of ^{131}I administered has ranged from 740 MBq [70] to 4440 MBq [71] (20–120 mCi); the amount of ^{90}Y infused has on average been 740 MBq (20 mCi) [66, 72]. In some studies, injections of the radiopharmaceutical were repeated many times (up to 10) on the basis of the clinical course of the disease [73]. In this way the cumulative dose to the tumour was increased and the probability of controlling tumour growth improved. Following the local injection of antibodies, many patients developed HAMA. The HAMA titre was higher when repeated administrations were carried out. However, the presence of HAMA did not hamper further injections of Mabs: in fact in HAMA-positive patients subsequent local injections of the same immunoglobulins did not give rise to any adverse local or systemic effects and did not modify the biodistribution and dosimetry of the radiopharmaceutical.

The clinical results, even if preliminary, are promising. The median survival in a group of 34 glioblastoma patients was 56 weeks [68]; in another study of five patients in whom treatment was given for recurrent cystic glioma, four had partial responses, clinically or radiographically [74]. In another study, among 31 patients (18 with glioblastoma), a partial response occurred in one patient and disease stabilisation was recorded in 13 (42%) [63]. A recent communication [75] reports 56-week survival in a group of 34 patients with glioblastoma.

Personal experience

We started our locoregional radioimmunotherapy studies in 1990. The first part of our research was carried out with ^{131}I-labelled Mabs and lasted until 1997. The second study, in which ^{90}Y was conjugated with the antibodies, was initiated in 1997 and is still ongoing.

^{131}I study

Following a phase I trial [76], a phase II study was performed in 91 cases with the following tumour types: oligodendroglioma (*n*=1), anaplastic oligodendroglioma (*n*=7), anaplastic astrocytoma (*n*=9) and glioblastoma (*n*=74). The patients' median age was 51 years (range 25–72). The Karnofsky status was above 60% in all cases. All patients had been previously operated on and had received radiotherapy; those with relapsing disease were operated on again before radioimmunotherapy. In addition 54 patients received chemotherapy. At the time of radioimmunotherapy, 52 patients presented a small (volume <2 cm^3) or undetectable residual tumour burden. By contrast 39 patients had a larger tumour mass

(mean volume >3 cm^3). Forty-seven patients were harbouring newly diagnosed tumours and 44 relapsed tumours.

^{90}Y study

In the ^{90}Y trial, 43 evaluable cases were treated in a phase II study, which was preceded by a phase I investigation. These cases comprised two oligodendrogliomas, six anaplastic astrocytomas and 35 glioblastomas. The mean age of the patients was 45.8 years (range 26–77). Sixteen had newly diagnosed and 19 recurrent tumours. Nineteen were suffering from macroscopic lesions; 16 underwent radioimmunotherapy with small or minimal disease (tumour volume < 2 cm^3).

Entry criteria

All the patients entered in the study had normal hepatic, renal, cardiac and haematological findings. Sufficient expression of tenascin in glioma tissues (at least 3+), as assessed by immunohistochemistry, was obligatory. Finally a life expectancy of more than 4 months was required. All patients gave their written informed consent to accept radioimmunotherapy according to the protocol approved by the Ethical Committee of "M. Bufalini" Hospital, Cesena, Italy.

Radioimmunotherapy protocol

Prior to intralesional radioimmunotherapy, all patients were operated on to remove as much of the neoplastic tissue as possible. When feasible, a postoperative cavity was produced. During the operation an indwelling Rickam or Ommaya catheter was inserted, and its tip placed in the middle of the surgical crater with the aim of allowing complete diffusion of the radiopharmaceutical. All patients received external beam radiotherapy at the maximum tolerated dose (55–60 Gy). They then underwent local administration of radiolabelled antibodies. Before this procedure they received antiepileptic drugs and steroids (dexamethasone 4–8 mg per day) starting from day minus 3 and continuing up to day plus 10. In the ^{131}I study, they were administered thyroid blocking agents (thyroxine and potassium iodide). The injection of the solution of radioactive monoclonal antibodies was performed within a few minutes through the reservoir of the catheter. The mean dose of antibody was 1.5 mg and the mean quantity of ^{131}I was 1665 MBq (45 mCi), while the mean dose of ^{90}Y was 740 MBq (20 mCi). In the group of patients with newly diagnosed tumours, the first cycle of intralesional radioimmunotherapy was carried out within 10–30 days after completion of the radiotherapy course. In cases of recurrent disease the antibodies were locally administered within 2 weeks following the new operation. After infusion of the radioactive compound, patients were isolated in a shielded room. The mean duration of hospital stay of patients in the ^{131}I group was 7 days (range 5–15 days), as compared with 3 days in the ^{90}Y group. The locoregional radioimmunotherapy courses were always repeated, with the aim of enhancing the cumulative radiation dose and improving the probability of killing most or all neoplastic elements. The first three cycles were carried out at intervals of 30–40 days, after which further infusions, if needed, were performed every 3 months. In the ^{131}I group one patient received ten courses; in the ^{90}Y group one patient received five courses.

Results

Untoward effects

Both single and multiple cycles of locoregional radioimmunotherapy were always well tolerated, as previously reported. Cumulative doses of up to 20.35 GBq (550 mCi) for ^{131}I and 3.145 GBq (85 mCi) for ^{90}Y did not cause any apparent damage to the normal brain surrounding the tumour area.

Biodistribution and dosimetry

The local administration of Mabs led to high uptake at the site of the target tissue. The mean percentage of injected dose concentrated per gram of tumour after 24 h was 3.1% for ^{131}I and 4.9% for ^{90}Y. The mean effective half-life of Mabs in the tumour was 57.1 h for ^{131}I and 43.2 h for ^{90}Y. The mean radiation dose delivered to the whole surgical cavity and to its walls was, respectively, 300 Gy and 150 Gy for ^{131}I and 600 Gy and 280 Gy for ^{90}Y.

Clinical responses

Median survival

The median survival of patients, calculated according to Kaplan-Meier methodology [77], was significantly prolonged by comparison with the results previously achieved using standard regimens.

^{131}I group. The median survival was 31 months in oligodendroglioma (1 patient), 23 months in anaplastic oligodendroglioma, >46 months in anaplastic astrocytoma and 19 months in glioblastoma. However, in this last group it was 25 months if patients were treated when their lesion was small or minimal as a result of previous approaches.

^{90}Y group. The median survival of patients with anaplastic astrocytoma was 90 months. In the glioblastoma group it was, in total, 20 months, while in cases with a reduced tumour burden it was 31 months. The patient with oligodendroglioma is still alive.

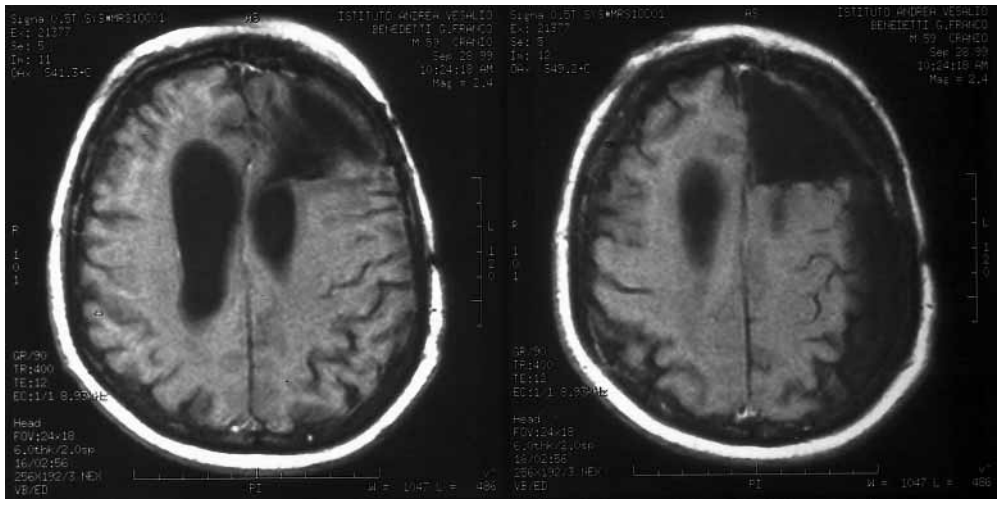

Fig. 1. Patient no. 32, male, 59 years old. The patient was operated on in February 1998 to remove a left frontal glioblastoma. He then received external radiotherapy (62 Gy). in June 1998 he underwent a new, minor, operation to insert an indwelling catheter (Rickam). He was then given 6 cycles of locoregional radioimmunotherapy (cumulative ^{90}Y dose 3426.2 MBq, corresponding to 92.6 mCi). Twenty months after the operation the patient presented no clinical or radiological signs of disease, as demonstrated by this MRI in the transverse section, at two different levels

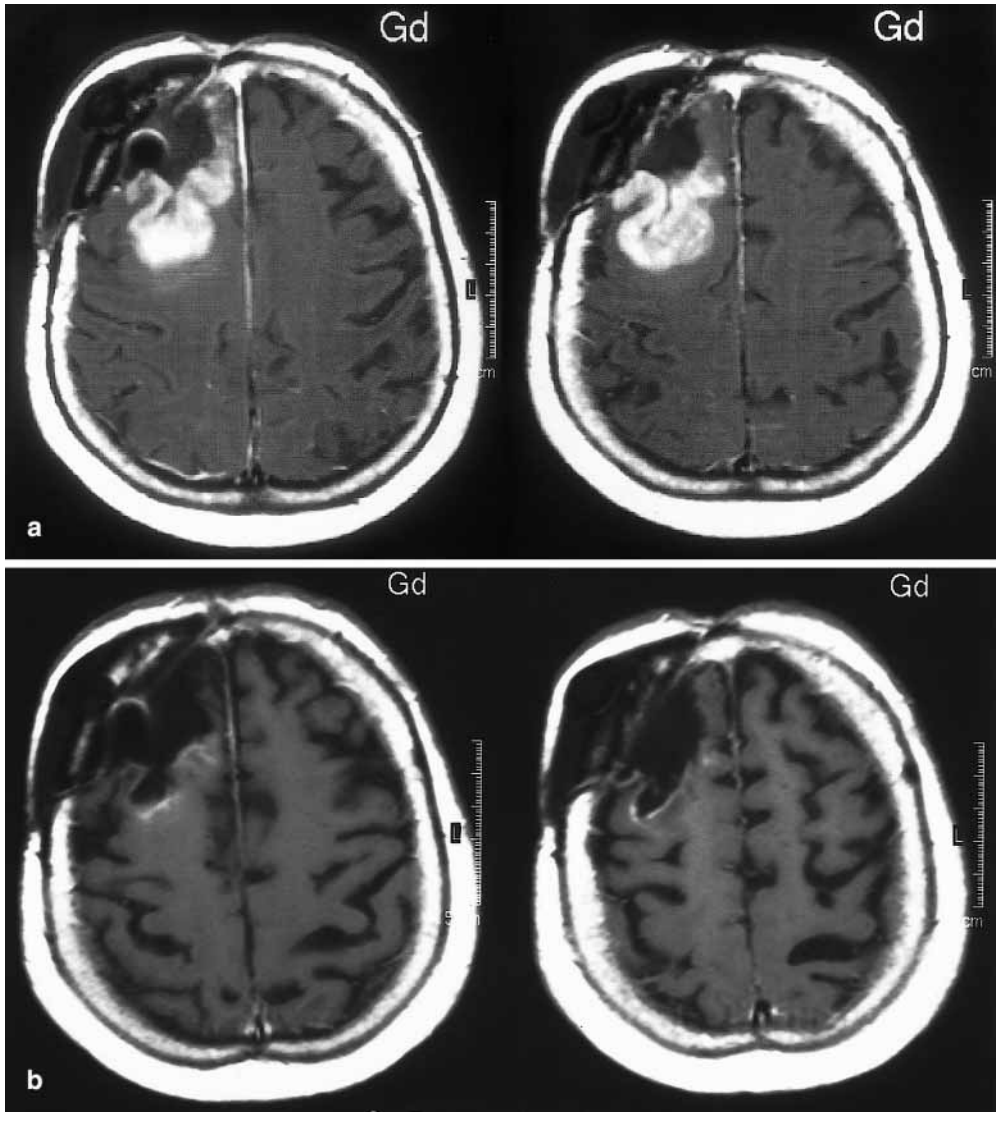

Fig. 2. a Patient no. 95, female, 57 years old. The patient was operated on in February 1998, and then received radiotherapy (59 Gy). However, in January 1999 she underwent a further operation owing to disease relapse. During surgery an indwelling catheter was inserted. She received 6 cycles of local radioimmunotherapy (cumulative ^{90}Y dose 3936.8 MBq, corresponding to 106.4 mCi). MRI, performed in June 1999, demonstrated a huge tumour mass which was growing in spite of two cycles of infusion of radioactive antibodies. **b** Following four courses of radioimmunotherapy the tumour volume is significantly decreased

Objective response

^{131}I group. In the single patient with oligodendroglioma we observed no evidence of disease (NED). Among the seven patients with anaplastic oligodendroglioma (all evaluable), four had progressive disease (PD), two a complete response (CR) and one NED. In the five evaluable patients with anaplastic astrocytoma we recorded one case of PD and four with NED. Finally, in the glioblastoma group (70 evaluable cases out of 74) we registered 27 cases of PD, 10 cases of stable disease (SD), 9 partial responses (PR), 1 CR and 23 with NED. The best outcomes were achieved in patients with minimal lesions and, to a lesser extent, in those with newly diagnosed tumours rather than recurrent disease.

^{90}Y group. The following responses were achieved: oligodendrogliomas: 1 CR, 1 PR; anaplastic astrocytomas: 1 PD, 2 SD, 2 PR, 1 CR and 1 NED; glioblastomas: 14 PD, 7 SD, 5 PR and 9 NED. In more detail, in the 19 cases of glioblastoma with bulky lesions we observed 10 PD, 4 SD and 5 PR. Conversely, in the 16 cases with a small or minimal tumour burden we documented 4 PD, 3 SD and 9 NED (Figs. 1, 2).

Response rate

^{131}I group. The response rate of various histological classes was 100% in oligodendroglioma, 42.8% in anaplastic oligodendroglioma, 80% in anaplastic astrocytoma and 47.1% in glioblastoma. In the subset of patients with glioblastoma, the response rate was 56.7% in those bearing a small tumour mass (<2 cm^3) but only 17.8% in those with a large lesion (>3 cm^3).

^{90}Y group. In patients with oligodendroglioma (n=2) or anaplastic astrocytoma (n=6) the response rate was 66.6%. In the glioblastoma group (n=35) the overall response rate was 40%; in the subset with bulky masses the response rate was 26.3% while in those with slight or undetectable disease it was 56.2%.

Discussion

The effectiveness of a nuclear medicine therapeutic approach in the treatment of malignant gliomas has been demonstrated. For these tumours only a few regimens are available and their ability to control the disease is very poor. Thus the main efforts of oncologists are devoted to other tumours that are more radio- and chemosensitive (breast, ovary, lung, colorectal etc.). The use of unsealed radioisotopes represents a new, interesting method capable of improving the prognosis of these patients. The nuclear medicine physician can play a relevant role in the management of these malignancies. First of all, a good and strict collaboration with the other specialists who attend such patients is mandatory. The neurosurgeon performs the most important step in this regimen: the radical removal of the neoplastic tissue. And if the surgeon knows that he has at his disposal a further weapon, he is more motivated to extend the operation as much as possible and, if necessary, to operate again. In addition, collaboration with the radiotherapist, the oncologist, the radiochemist and the physicist is essential.

The nuclear medicine specialist has to deal with the following specific issues:

1. The antibody has to bind with high affinity to specific receptors situated in the malignant tissue while sparing the normal brain parenchyma.
2. The isotope must penetrate the entire neoplastic area and reach the greatest possible number of glioma cells.
3. The labelling procedures, which not modify the immunoreactivity of the antibody and must give rise to a very stable in vivo conjugate, thus preventing the systemic release of free isotope, which can produce unwanted irradiation of normal organs.
4. The radiopharmaceutical must be administered exactly to the tumour bed, avoiding any damage to the surrounding skin and brain tissues.
5. Monitoring of the patient during his or her hospitalisation in the shielded room.
6. Application and control of the radioprotection procedures.
7. Follow-up of the cases treated and evaluation of the clinical results of the nuclear medicine therapy.

The outcomes so far achieved in trials and the future prospects of improving the clinical effects of this approach warrant further research in order to optimise the therapeutic strategy. The treatment is locoregional and does not affect the critical organs. Thus it can be employed in association with systemic regimens such as chemotherapy, in an attempt to combine the therapeutic properties of two different approaches. The direct administration can selectively concentrate in the tumoral bed an impressive amount of radiation which is specifically directed to the tumour cells: thus the therapeutic index is very high. The beta rays produced by the isotopes employed can kill the glioma elements by virtue of their penetration into the tissue. At the same time the antibodies spread through the tumour and bind with their antigenic receptors. In this way a wider area can be sterilised, offering the theoretical possibility of completely curing malignant gliomas. Unfortunately the clinical and pathological situation of the patients who are referred for this approach often precludes such a favourable outcome. Most patients are submitted to locoregional radioimmunotherapy a long time after the initial surgical intervention, and many undergo the antibody application when the tumour has recurred and a new operation is needed. Furthermore some have macroscopic disease since radical surgery is not possible. In all these situations the area around the site of the primary tumour is in-

filtrated by a massive number of glioma cells, even if this is not evident radiologically. Moreover the malignant elements can be scattered in more distant territories. For these reasons the effectiveness of intracavitary or interstitial radioimmunotherapy is limited. But if the disease is treated at quite an early stage, immediately after surgery and radiotherapy, when the tumour burden has been reduced, there is a greater likelihood of controlling the growth of the tumor.

The results so far achieved indeed demonstrate the effectiveness of the protocol in these ominous malignancies. The most important parameter utilised in neuro-oncology to evaluate the efficiency of an innovative treatment in the field of malignant glioma is the median survival. It is well known that, in large series of patients, this value is 12 months. In our experience, in patients with a small tumour load due to previous approaches, median survival prolonged to 25 (^{131}I) or 31 (^{90}Y) months. This clearly confirms the effectiveness of locoregional radioimmunotherapy. Moreover various innovations offer the possibility of further improving the technique. The most important issue is the molecular weight of the antibodies: the size of Mabs and F(ab') 2 fragments, 155 and 100 kDa, respectively, restricts the depth of tissue penetration. The use of smaller, diffusible high-affinity targeting agents, such as peptides and small designer antibody fragments, should therefore improve the results of the approach [78]. The use of alpha-emitting isotopes with a high LET could lead to a more complete sterilisation of the BAT. The use of different antibodies directed against cell membrane antigens may be of value, as may the injection of antibody cocktails designed to bind more antigen sites. The timing of radioimmunotherapy might also be improved: ideally it should be given immediately after the operation, before external radiotherapy, when the tissue is more vascularized and more permeable. The area of research in this field is wide, and nuclear medicine could become the leading science in the therapy of brain tumours.

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