Current Status of Therapy of Solid Tumors: Brain Tumor Therapy

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Treatment of malignant brain tumors with conventional approaches is largely unsuccessful because curative doses generally cannot be delivered without excessive toxicity to normal brain. Radioimmunotherapy is emerging as an attractive alternative for glioma therapy because of the potential for more selectively irradiating tumor cells while sparing normal tissues. Several institutions are engaged in phase I and phase II trials investigating the therapeutic potential of monoclonal antibodies (mAbs) labeled with the β-emitters ^{131}I and ^{90}Y and the α-emitter ^{211}At in patients with recurrent and newly diagnosed brain tumors. The current status of these trials will be discussed with regard to efficacy, toxicity, and future directions.

Key Words: brain tumor; glioma; ^{211}At; radionuclide therapy; ^{131}I

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In the United States alone, more than 17,000 cases of primary malignant brain tumors are diagnosed per year, and the incidence appears to be increasing. For patients with glioblastoma multiforme (GBM), the most common and virulent primary brain tumor, median survival has been 40–50 wk from the time of diagnosis (*1*), even when aggressive multimodality treatments are applied. Most cases of GBM recur adjacent to the original tumor site, and management of recurrent disease is even less effective, with a median survival of only 16–24 wk being reported (*2*). External-beam radiotherapy and chemotherapy are the standard treatment approaches for brain tumors; however, the lack of specificity of these modalities for malignant cell populations compromises their effectiveness. Toxicity to normal brain generally hinders the delivery of curative doses to tumor and severely reduces the quality of life for the few patients with significant survival prolongation.

Because of its potential for more selectively irradiating tumor cells, radioimmunotherapy is an attractive strategy for patients with brain tumors. A potential impediment is the interference of a partially intact blood–brain barrier with the delivery of labeled macromolecules to intracranial tumors. However, early studies demonstrated that the absolute magnitude of the accumulation of labeled monoclonal antibodies (mAbs) in brain tumors after intravenous delivery was comparable to that observed in other solid tumor types (*3*). Nearly all cases of GBM recur within a 2-cm rim around the original tumor, and controlling tumor cells within this region is the primary goal of radioimmunotherapy. Unfortunately, small clusters and single tumor cells also frequently are present beyond this rim at distances of 4–7 cm from the original tumor site or even in the contralateral hemisphere (*4,5*). Although evidence from autopsy specimens suggests that diffusion of labeled mAbs administered locally to brain tumor patients may be greater than expected based on molecular weight considerations alone (*6*), delivery of curative doses of radiation to these distant tumor sites will be a formidable task.

Many early radioimmunotherapy trials on brain tumor patients involved intravenous administration of antibodies, primarily those reactive with the epidermal growth factor receptor (*7,8*). Although some positive responses were reported, more encouraging survival benefits have been reported when the radiolabeled mAb was administered locoregionally, either into nonresected tumor or into the surgically created tumor resection cavity. This strategy is exemplified by a study from Hopkins et al. using mAbs reactive with a neural cell adhesion molecule present on GBM as well as normal neural tissue (*6*). Because most brain tumor radioimmunotherapy trials have involved mAbs reactive with tenascin, the remainder of this article will focus on these studies.

TENASCIN AND BRAIN TUMORS

Tenascin-C (hereinafter referred to as tenascin) is a 6-armed glycoprotein that that is overexpressed in the extracellular matrix of gliomas and malignancies. The level of tenascin expression increases with advancing tumor grade (*9*). Important for its role as a target for radioimmunotherapy is the fact that more than 90% of GBM cases exhibit high levels of tenascin expression (*10*). In addition, tenascin is located primarily around tumor blood vessels, with this feature becoming more predominant with advancing tumor grade (*11*). This offers the exciting prospect of using radiolabeled antitenascin mAbs as an antivascular therapeutic, with all the attendant advantages (*12*).

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Several antitenascin mAbs, which bind to different epitopes on the tenascin molecule, have been used for targeted radiotherapy. Antibody BC-2 binds to an epitope found on both the A1 and the A4 alternatively spliced fibronectin type III repeats, and mAb BC-4 reacts with an epitope in the epidermal growth factor–like repeat found on all tenascin isoforms (*13*). The 81C6 mAb reacts with an epitope present within the alternatively spliced fibronectin type III CD segment (*14*). Antibodies reactive with alternatively spliced regions of the tenascin molecule instead of those present on all isoforms should be preferred because they should increase the relative reactivity with tumor compared with liver and spleen, normal organs that express tenascin (*10*).

ROUTE OF ADMINISTRATION

Investigators in the Brain Tumor Program at Duke University Medical Center have been evaluating the therapeutic potential of ^{131}I-labeled 81C6 mAb in patients with GBM and other malignant brain tumors. Diagnostic-level studies were first performed on patients to facilitate the design of radioimmunotherapy trials. Three observations were key in this process: First, after intravenous injection, levels of ^{131}I-labeled 81C6 in GBM biopsy samples were up to 5 times higher than levels of coinjected ^{125}I-labeled control mAb and up to 200 times higher than levels in normal brain (*3*), confirming the importance of mAb specificity. Second, a paired injection study demonstrated that, compared with intravenous injection, intracarotid administration offered no advantage in tumor delivery (*15*). Third, a protein dose escalation protocol followed by SPECT demonstrated that delivery of mAb by the intravenous route would not yield therapeutically relevant tumor doses without an unacceptable radiation dose in tenascin-expressing liver and spleen (*16*). For these reasons, radioimmunotherapeutic trials with antitenascin mAbs have involved intracompartmental (locoregional) administration of the labeled protein, into either tumor, spontaneous tumor cysts, or, most frequently, surgically created glioma resection cavities.

ANTITENASCIN MABS LABELED WITH β-EMITTERS

Trials at Duke University Medical Center

More than 300 patients with GBM and other primary brain tumors have been treated at Duke University Medical Center by direct injection of ^{131}I-labeled 81C6 antitenascin mAb into a surgically created tumor resection cavity via a Rickham catheter inserted during the resection procedure. Entry criteria for phase I studies included histopathologic confirmation of diagnosis, tumor localization within the supratentorial compartment, immunochemical documentation of tumor reactivity with 81C6, and a maximum of 1-cm residual enhancement on postoperative MRI. Before radioimmunotherapy, intactness of the resection cavity and patency of the catheter were demonstrated by radionuclide imaging. Most patients subsequently received systemic chemotherapy and newly diagnosed patients also received conventional radiotherapy after ^{131}I-labeled 81C6 treatment.

The maximum tolerated dose determined in a phase I study on patients with recurrent brain tumor was 3,700 MBq of ^{131}I-labeled murine 81C6 (*17*). Thirty-four patients (26 with GBM) received between 740 and 4,440 MBq of labeled mAb, and dose-limiting toxicity was neurologic. The median survival for all patients and those with recurrent GBM was 60 and 56 wk, respectively. In patients with newly diagnosed tumors evaluated in a parallel phase I study, the maximum tolerated dose was 4,440 MBq, with neurologic toxicity again the dose-limiting factor (*18*). A total of 42 patients, 32 with GBM, received administered activities ranging between 740 and 6,660 MBq of ^{131}I-labeled murine 81C6, and median survival was 79 and 69 wk in all patients and in those with newly diagnosed GBM, respectively (Fig. 1).

Most patients were followed by serial ^{18}F-FDG PET and contrast-enhanced MRI; however, neither technique could distinguish between tumor recurrence and radiation necrosis. The contrast-enhancing rim seen on MRI always was hypermetabolic on PET, making differential diagnosis impossible. Figure 2 shows coregistered images of a patient after surgery and at various intervals between 5 and 70 wk after ^{131}I-labeled 81C6 therapy. As early as 5 wk after therapy, an enhancing region at the cavity margins, characterized by increased ^{18}F-FDG accumulation, was seen. Biopsies at 24 and 52 wk indicated lack of tumor and evidence of radiation necrosis.

A phase II trial was then performed at an administered activity of 4,440 MBq of ^{131}I-labeled 81C6 on 33 newly diagnosed brain tumor patients, including 27 with GBM (*19*). The median survival observed in all patients and in those with GBM was 87 and 79 wk, respectively. To better assess the survival benefit of this radioimmunotherapy, we

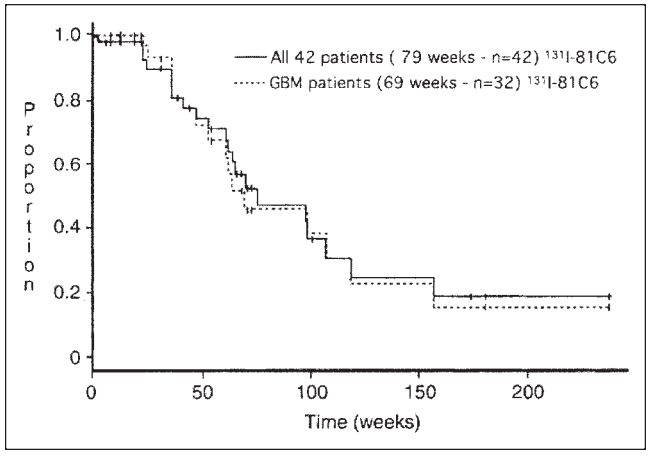

FIGURE 1. Kaplan–Meier plot of survival of GBM patients and of all patients after locoregional treatment with ^{131}I-labeled murine 81C6 mAb. Median survival for patients with GBM and for all patients was 69 and 79 wk, respectively. (Reprinted with permission of (*18*).)

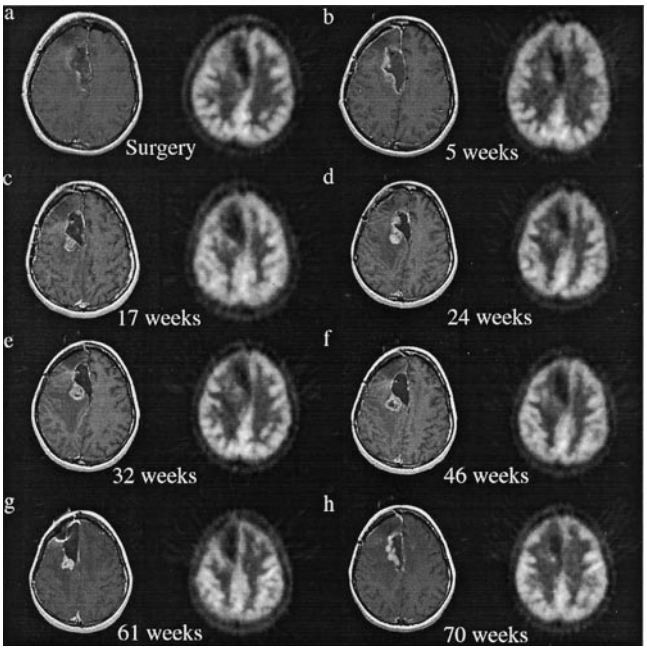

FIGURE 2. Coregistered MRI and ^{18}F-FDG PET images after surgery and as a function of time after treatment with ^{131}I-labeled murine 81C6 mAb. At 5 wk, cavity margins exhibited increased ^{18}F-FDG uptake and enhancement on MRI. Biopsy samples obtained from this patient at 24 and 52 wk showed radiation necrosis and macrophage infiltration but no tumor involvement. (Reprinted with permission of (*18*).)

compared our results with those for conventional chemotherapy and radiotherapy in patients with similar characteristics based on the recursive partitioning data reported by Curran et al. (*20*). With the caveat that the sample size of our study was limited, the results obtained with ^{131}I-labeled 81C6 therapy compared favorably with those reported for similar patient subpopulations treated by conventional methods. For example, we observed a median survival of 65 wk in patients (n = 16) over 50 y old with a Karnofsky performance status greater than or equal to 70%, compared with a median survival of only 39 wk for those reported by Curran et al.

In evaluating the potential merit of new therapeutics, in addition to increasing survival, minimizing side effects and maximizing quality of life are important considerations. Stereotactic radiosurgery and ^{125}I interstitial brachytherapy are alternative strategies for providing a boost dose of radiation to brain tumors, and the survival results that we have obtained with ^{131}I-labeled 81C6 compare favorably with these. Moreover, the need for reoperation to debulk radionecrosis and relieve symptomatic mass effect with radioimmunotherapy was only about 2%, compared with 34%–64% for the other boost-radiation-therapy procedures (*19*).

Patient-specific dosimetry is an important component of any radioimmunotherapy protocol because it offers the possibility of relating tumor response and normal tissue toxicities to a measurable parameter. Our investigational new drug application for ^{131}I-labeled 81C6 requires administration of the labeled mAb on a fixed megabecquerel basis, and thus, the radiation doses received by these patients vary considerably. The primary factors accounting for this variation are differences in cavity size and clearance rate among the patients treated. For example, in newly diagnosed patients, the cavity volume ranged from 2.1 to 80.9 cm^3 and the residence time ranged from 10 to 113 h, yielding average absorbed doses to the 2-cm shell region surrounding the cavity of 3–59 Gy (*21*).

Isodose contours are useful for showing variations in radiation-absorbed dose as a function of distance from the resection cavity interface. This is exemplified by Figure 3, which presents the isodose contours coregistered with contrast-enhanced MRI for a patient who received 3,700 MBq of ^{131}I-labeled 81C6 and had a cavity volume of 51 cm^3 (*22*). The average doses at the cavity interface and the 1-cm- and 2-cm-thick annulus from the cavity margins were 30,000, 2,700, and 1,700 cGy, respectively, compared with an average dose to normal brain of 400 cGy. However, as can be seen from these isodose contours, the radiation dose received by different regions of normal brain varies considerably.

To determine the dose to the cavity interface that maximizes tumor control while minimizing radiation necrosis, we investigated the relationship between radiation dose to the 2-cm cavity margin and histopathology (*21*). Biopsy samples used in this study were obtained from 16 patients in whom progressive changes had been seen on serial MR images. The relationship, based on biopsy results, between absorbed dose to the cavity interface and initial dose rate is shown in Figure 4. Patients who received less than 44 Gy to the 2-cm cavity margin were more likely to exhibit tumor recurrence albeit without radiation necrosis, whereas those receiving more than 44 Gy had a higher incidence of radiation necrosis. This has led us to initiate an additional phase I trial on newly diagnosed brain tumor patients in which a dosimetry study is used to calculate the activity of ^{131}I-labeled 81C6 needed to deliver an average of 44 Gy to the 2-cm resection cavity margin. The results obtained to date are highly encouraging.

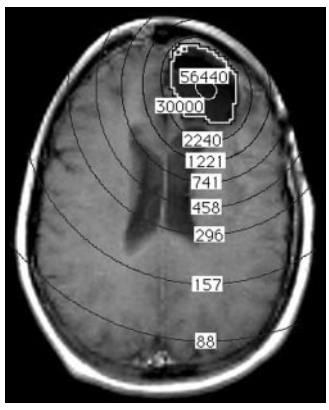

FIGURE 3. Axial MR image (gadolinium enhanced, T1 weighted) coregistered with isodose contours for a patient treated with 3,700 MBq of ^{131}I-labeled murine 81C6. Volume of surgically created tumor resection cavity in this patient was 51.2 cm^3. (Reprinted with permission of (*22*).)

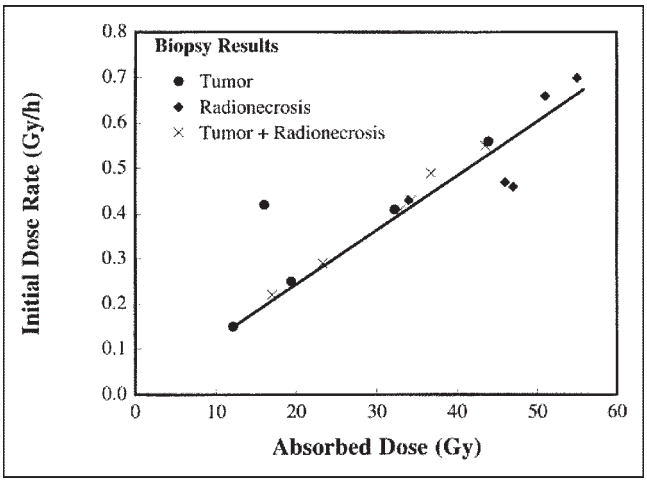

FIGURE 4. Relationship between absorbed dose and initial dose rate in 16 patients on whom biopsies were performed after treatment. (Reprinted with permission of (*21*).)

Trials at Other Institutions

The treatment of anaplastic astrocytomas and glioblastoma with radiolabeled antitenascin mAbs BC-2 and BC-4 has been investigated extensively by Riva et al. (*23*). The relative efficacy of BC-2 and BC-4 was not investigated, as no distinction was made between the 2 mAbs. On the other hand, patients were evaluated on the basis of tumor size. In a phase II study using ^{131}I-labeled antitenascin mAbs on 91 patients (74 with glioblastoma, 9 with anaplastic astrocytoma, 7 with anaplastic oligodendroglioma, and 1 with oligodendroglioma), 52 patients were classified as having small (<2 cm^3) or undetectable residual tumor, with the remaining having larger tumors. Of these, 44 were recurrent tumors and 47 were newly diagnosed malignancies. The treatment protocol consisted of 3–10 locoregional injections of ^{131}I-labeled mAb with cumulative activities of up to 20.35 GBq.

The median effective half-life of ^{131}I in the tumor was 57.1 h, and the mean radiation dose delivered to the walls of the surgically created resection cavity was 150 Gy. The median survival for patients with glioblastoma, anaplastic astrocytoma, and anaplastic oligodendroglioma was 19, >46, and 23 mo, respectively, with no distinction made between recurrent and newly diagnosed patient populations. In glioblastoma patients with smaller-volume disease, the response rate, 56.7%, was better than that in those with larger tumors (17.8%).

The Italian group also performed a similar study with ^{90}Y-labeled BC-2 and BC-4 (*23*). A total of 43 evaluable patients (35 with glioblastoma, 6 with anaplastic astrocytoma, and 2 with oligodendroglioma) were treated. Of these, 16 had small or undetected residual tumor and 19 had larger lesions; 19 had recurrent and 16 had newly diagnosed disease. Patients received between 3 and 5 cycles of ^{90}Y-labeled mAb with a cumulative activity of up to 3.145 GBq. The median effective half-life of ^{90}Y in the tumor cavity was 43.2 h, and the mean radiation dose delivered to the cavity interface was 280 Gy. The median survival was 90 mo for patients with anaplastic astrocytoma and 20 mo for patients with glioblastoma. The response rate for ^{90}Y-labeled mAb treatment in patients with smaller-volume disease, 56.3%, was nearly identical to that observed with ^{131}I in the study described above. On the other hand, the response rate with ^{90}Y, 26.3%, was somewhat higher that that observed with ^{131}I, consistent with the longer β-particle range of the radiometal.

A recent report described a 2-institution study involving locoregional injection of either ^{131}I- or ^{90}Y-labeled BC-4 in 37 patients with malignant brain tumors (13 patients with anaplastic astrocytoma and 24 with glioblastoma) (*24*). The treatment protocol involved multiple cycles (mean of 3 and maximum of 8) of labeled mAbs at intervals of 6–8 wk. The median survival for patients with glioblastoma was 17 mo, and the 5-y survival probability reported for those with anaplastic astrocytoma was about 85%. Acute side effects were generally minor and generally limited to headache and nausea and, for 2 patients treated with ^{90}Y, skin necrosis. Survival results were not stratified with regard to radionuclide, and it was not clear whether the patients had recurrent or newly diagnosed brain tumors.

ANTITENASCIN MABS LABELED WITH α-EMITTERS

One strategy for increasing the therapeutic efficacy of radioimmunotherapy is to use more potent radionuclides. β-Particles have a radiobiologic effectiveness that is similar to conventional external-beam irradiation, and their cytotoxicity is highly dependent on the presence of oxygen, dose rate, and position of the tumor cells in the cell cycle. On the other hand, α-particles are radiation of high-linear-energy transfer and are much less dependent on these factors, which often confound tumor treatment with low-linear-energy transfer radiation. α-Particles have a range in tissue of only a few cell diameters, and in vitro studies have demonstrated that human tumor cells could be killed as a result of only a few α-particle traversals per cell (*25*).

^{211}At is a particularly promising α-emitter for targeted radiotherapy because its 7.2-h half-life is compatible with the pharmacokinetics of many types of tumor-targeting vectors, and α-particle emission is associated with 100% of its decays. Furthermore, it emits polonium x-rays, which can be used for imaging the distribution of ^{211}At-labeled radiopharmaceuticals in patients.

Currently, we are conducting a phase I trial on recurrent-brain-tumor patients of ^{211}At-labeled human/mouse chimeric 81C6 administered into surgically created glioma resection cavities (*26*). The chimeric construct with human IgG_2 constant regions, because of its enhanced in vivo stability, was studied instead of the murine protein used previously (*27*). ^{211}At was produced on the Duke University Medical Center cyclotron and coupled to chimeric 81C6 by reaction with *N*-succinimidyl 3-[^{211}At]astatobenzoate. Sev-

enteen patients (3 with anaplastic oligodendroglioma and 14 with glioblastoma) have been treated with 74 MBq ($n = 5$), 148 MBq ($n = 6$), 248 MBq ($n = 5$), or 370 MBq ($n = 1$) of ^{211}At-labeled chimeric 81C6.

The pharmacokinetics, monitored by serial imaging and blood sampling for 24 h after administration, indicated a high degree of retention of the labeled protein in the tumor resection cavity. More than 95% of ^{211}At decay occurred in the cavity, and less than 0.2% of the injected dose was found in the blood pool. The average radiation dose received by the cavity interface was about 3,000 Gy, compared with 0.01 Gy for normal tissues including the liver and spleen, which express tenascin. Responses have been encouraging, with a median survival of 60 wk observed. Notable is the fact that 2 patients with recurrent GBM survived for nearly 3 y. After a hiatus to develop more reliable radiochemical methodologies for preparing higher activity levels of ^{211}At-labeled chimeric 81C6, dose escalation is continuing.

SUMMARY AND FUTURE DIRECTIONS

To date, more than 600 patients with malignant brain tumors have been treated with radiolabeled antitenascin mAbs by direct injection of the molecule into surgically created resection cavities. Compared with external-beam therapy and chemotherapy, the conventional treatment for patients with these malignancies, this radioimmunotherapy procedure has improved survival in patients with both recurrent and newly diagnosed brain tumors. Compared with other methods to boost radiation dose to brain tumors, such as interstitial brachytherapy and stereotactic radiosurgery, radioimmunotherapy offers similar or more favorable responses with significantly lower toxicity to normal brain.

With regard to optimization of this promising treatment strategy, more controlled studies will be needed to define the ideal radionuclide and dose schedule to achieve local control of residual tumor. A more challenging task will be the treatment of small multicellular deposits and single glioma cells farther from the primary tumor site. Intracerebral microinfusion (also known as convection-enhanced delivery) might be helpful in achieving this goal because this technique could be useful for increasing the delivery of labeled mAbs or fragments to tumor cells that have infiltrated distant regions of the brain (*28,29*). The potential utility of this delivery approach has been demonstrated in brain tumor patients treated with a conjugate of transferrin and a genetic mutant of diphtheria toxin administered by high-flow interstitial microinfusion (*30*). Another promising alternative being investigated is delivery of the radionuclide via a smaller molecule such as a peptidic vector (*31*). In summary, the feasibility of brain tumor–targeted radionuclide therapy has been demonstrated. The efficacy of this treatment strategy may improve in the future through the use of optimized radionuclides, carrier molecules, and delivery techniques.

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