An Unmodified Anticarcinoma Antibody, BR96, Localizes to and Inhibits the Outgrowth of Human Tumors in Nude Mice

George J. Schreiber, Karl Erik Hellström, and Ingegerd Hellström
Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, Washington 98121

ABSTRACT

The antitumor effects of an unmodified murine monoclonal antibody, BR96, were examined in nude mice bearing human lung adenocarcinoma xenografts. BR96, a murine IgGsubclass that internalizes and is cytotoxic to cells expressing the antigen in vitro, also elicits strong antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity effector functions. Its in vitro antitumor effects were compared with those of its F(ab')2 fragments, a mouse-human chimeric form, and an IgGsubclass class switched variant of the original (IgG1) BR96. Antitumor effects were observed with antigen-positive tumor lines (but not with tumors which did not bind with BR96) and correlated with the levels of antigen expression as detected in vitro. The chimeric form of BR96 gave the strongest antitumor effects, followed by the murine IgGsubclass, while limited effects were seen with the IgGsubclass and with F(ab')2 fragments of BR96, indicating that Fc-dependent host effector functions are primarily responsible for its in vitro activity. The antitumor effects observed were modest unless the antibody treatment was started on the day following tumor grafting.

INTRODUCTION

Many MAbs directed against tumor antigens have been studied in both animals and humans (1). Various methods have been devised to combine the ability of an antitumor MAb to "target" lesions with the anticancer activity of chemotherapeutic drugs or radioisotopes using the MAb as a transport vehicle rather than as an antitumor component. There is also an interest, however, in identifying MAbs with inherent antitumor activity in vitro, either alone or in combination with host components, and evaluating, in vivo, whether they can offer an attractive complement to existing tumor treatment strategies. This is particularly so, since MAbs capable of eliciting host effector functions offer the potential of less toxicity than may be possible when using immunoconjugates with chemotherapeutic agents or radioisotopes.

We report here in vivo studies with a MAb, BR96 (2), which was tested in the unmodified form for antitumor activity against human lung carcinomas xenografted into nude mice. BR96 is an IgGsubclass that binds to a variant of a Le antigen expressed on most tumor cells from human carcinomas of colon, lung, breast, and ovary (2). The MAb can be internalized, and it is cytotoxic to a variety of antigen-positive tumor cell lines when tested by itself in vitro and is capable of eliciting ADCC and CDC effector functions (2). An isotype class switched (IgGsubclass) variant of BR96 was also studied, as were a chimeric version of BR96 and F(ab')2 fragments derived from the murine BR96. Significant antitumor effects were seen with the murine IgGsubclass and chimeric versions of BR96, both of which mediate strong ADCC and CDC activities in vitro, while F(ab')2 fragments, which lack ADCC and CDC activities, had a much weaker, but still observable, antitumor effect in vivo.

MATERIALS AND METHODS

Monoclonal Antibodies. Our group has previously described (2) how BR96 was isolated as an IgGsubclass from a hybridoma resulting from the fusion of spleen cells from a mouse immunized with a cell membrane preparation from a cultured human breast adenocarcinoma. Another MAb, BR64, which came from the same fusion and detected a related antigen (2), was used as a control in one experiment like BR96, it can internalize. BR64 is a murine IgGsubclass that lacks ADCC and CDC activity as well as cytotoxic activity by itself. IIG5, which is a murine (IgGsubclass) anti-Pseudomonas aeruginosa flagellar antibody (3) and does not bind to mammalian tissues, served as a control IgG for most of our experiments. Chimeric 96.5 (4) was used as a nonspecific control in experiments with chimeric BR96. G19.4, which is an anti-CD3 (5) murine MAb, served as a control for the ADCC and CDC activities. Two additional MAbs were studied, an IgGsubclass monoclonal antibody (BR964) and a mouse-human chimeric form (Chi BR96), which was derived from a human breast adenocarcinoma cell line using a modification of a homologous recombination procedure which has been reported previously (4).

Tumor Lines. Cell lines H2707, H2981, and H2987 were developed at Bristol-Myers Squibb Pharmaceutical Research Institute in Seattle from human metastatic lung adenocarcinomas. Fluorescence-activated cell sorter analysis of cultured cells of these lines revealed high levels of BR96 binding to H2707 and H2987. The H2981 line did not bind BR96 and was used in experiments as an antigen-negative control line. (2) Histological examination of tissue sections prepared from tumors grown in vivo confirmed the fluorescence-activated cell sorter data by demonstrating the presence of the BR96-defined antigen on all lines except H2981. Subcutaneous implantation of 3.3 million lung carcinoma cells into nude mice resulted in palpable tumors approximately 8 days later.

Animal Model. Female nude Balb/c mice (nu/nu) (Harlan Sprague Dawley, Indianapolis, IN) received s.c. implantations in the rear flank of 10 million cells from one of the lung carcinoma cell lines (H2981, H2987, or H2707). Antibody treatment was initiated 24 h later (day 2) or on day 5 or day 8 postimplant. In each experiment, except when dose effects were examined, mice were given 1 mg MAb/injection (approximately 45 mg/kg); F(ab')2 fragments were given in 0.66-mg doses. Injections were given 3 days apart for a total of five injections. Using this schedule, which is based on the clearance kinetics of murine IgG in mice, a 3-day interval between the five injections resulted in exposure of the tumor to circulating MAb for over 2 weeks. In addition, the 3-day interval is less than the 6- to 7-day doubling time of the tumor lines in vivo. In the initial experiment, two additional 1-mg injections were given after the five injections. Treatment with control MAbs followed the same schedule and was always initiated on day 2.

Tumor volumes were calculated from the measurements of tumor...
INHIBITION OF HUMAN TUMORS IN NUDE MICE BY MAB BR96

Experiments were initially done in which treatment of tumor-bearing mice with unlabeled MAb BR96 (IgG3) was started 24 h postimplantation and was followed by six more injections on days 5, 8, 11, 14, 19, and 21 postimplant. MAb BR64 was used as a control and was given to the animals at the same dose and time points. As seen in Fig. 1 significant antitumor effects were observed following treatment with BR96 (P < 0.005, P < 0.0005, P < 0.0005, days 8, 21, 28 postimplant, respectively), while there were few if any antitumor effects with BR64 as compared to a group given PBS only. No toxicity was apparent in any group. Complete regressions occurred in 2 of 10 animals receiving BR96, and these animals remained tumor-free for the duration of the experiment. Tumors in the remaining 8 mice grew similarly to tumors in mice treated with BR64 or PBS, except for an initial inhibition.

We then examined the antitumor activity of BR96 (IgG3) against staged tumors. Experiments were performed with the antigen-positive H2987 and H2707 lung carcinoma lines. Mice were implanted with approximately 3 times as many cells as necessary to establish palpable tumors by 8 days, and treatment was started either 5 or 8 days post tumor implantation when all mice had palpable tumors in the range of 75-100 mm³. The administration of Mab was repeated five times 3 days apart. Fig. 2 shows data from H2987 xenografts, and Fig. 3 gives results from H2707. While staged tumors were much less responsive to BR96, significant effects were apparent in the form of a delay in tumor growth (P < 0.05, day 32 postimplant of H2987, and P < 0.05, day 29 postimplant of H2707 for each BR96-treated group compared to PBS). There were few if any differences in mean tumor volumes, depending on whether treatment was initiated on day 5 or day 8 postimplant. However, variations in the responses of individual tumors were observed at the end of treatment. Thus 9 of 10 mice bearing H2707 xenografts were tumor-free when the treatment had started on day 2, as compared to 5 of 10 mice and 3 of 10 mice when treatment was started on days 5 and 8, respectively. Analogous but less impressive effects were observed with H2987. The tumor that was present in 1 of the 10 mice carrying H2707 and treated from day 2 was excised, and its cells were suspended

RESULTS

Localization Experiments. Localization studies were performed in mice carrying either H2707 or H2987 tumor xenografts. Radioiodinated intact BR96 of the IgG1 or IgG3 isotypes, ChiBR96, or F(ab')2 fragments prepared from murine BR96 were administered with appropriate controls, at doses representative of those used in the therapy experiments with unmodified MAbS. BR96 MAbs were radioiodinated with 125I, while control MAbs were radioiodinated with 131I using Iodo-Gen (Pierce, Rockville, IL). Separation of labeled MAb from free iodine was performed using a G-25 Sephadex column. All iodinations were performed on the day of administration to the mice.

Mixtures of the specific and nonspecific MAbs were administered simultaneously via the tail vein of each mouse, with each animal receiving approximately 5 µCi (185 kBq) of each radiolabeled MAb. At selected times mice were anesthetized, bled through the orbital plexus, and sacrificed. Selected tissues were removed, weighed, and counted in a dual-channel gamma counter capable of differentiating between the two iodine isotopes. Selected tissues included blood, tumor, liver, spleen, kidney, lungs, and thigh.

The corresponding cpm in each organ was analyzed using a computer program to correct for 131I Compton scatter into the 125I window. Correction for 131I decay was performed by counting a 10-µl aliquot of the injected dose with each set of tissue samples. Calculation of the activity in the blood was estimated assuming that the blood volume of a mouse is equal to 8% of its body weight. Distribution of specific and nonspecific MAbs was expressed by percentage injected dose, calculated by cpm in organ/cpm injected × 100%. The percentage injected dose was then used to calculate the percentage injected dose/g tissue.

The tumor volume was then calculated using the formula

\[ \text{Tumor volume} = \frac{\text{Longest length} \times (\text{Perpendicular width})^2}{2} \]

Significance between groups of treated mice was determined using the t test statistic for two means.

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Fig. 1. Mean volumes of tumors (±SEM) from mice (10/group) implanted with 10⁷ H2987 cells s.c. Mice were given i.v. injections of murine BR96 (IgG3) or BR64 (IgG3) the following day (day 2) and as indicated by arrows, with each mouse receiving 1 mg MAb/injection. Control mice received an equal volume of PBS.

Fig. 2. Mean volumes of tumors (±SEM) from mice (10/group) receiving injections on five occasions 3 days apart. Mice were given BR96 (IgG3) beginning on day 2, 5, or 8 after s.c. implantation of 10⁷ H2987 cells. IgG5 (IgG3) was given (five injections 3 days apart) beginning on day 2. Control mice were given an equal volume of PBS (five injections 3 days apart) beginning on day 2.

Fig. 3. Mean volumes of tumors (±SEM) from mice (10 mice/group) receiving injections on five occasions 3 days apart. Mice were given BR96 (IgG3) beginning on day 2, 5, or 8 after s.c. implantation of 10⁷ H2987 cells. IgG5 (IgG3) was given (five injections 3 days apart) beginning on day 2. Control mice were given an equal volume of PBS (five injections 3 days apart) beginning on day 2.
The effects of the IgG1 dose and MAb form were most
pronounced in the number of mice without palpable H2707
tumors immediately after treatment, 15 days post tumor
implant. All mice that received BR96 (IgG3) at the 1 mg/dose
were without palpable tumors at the end of treatment. The
number of mice without palpable tumors at that time decreased
as the IgG3 dose was lowered. Once treatment stopped the
tumors began to grow rapidly. There were no apparent toxic
effects in any treated animal. Surprisingly, in view of the data
with the IgG1 switch variant, 3 of the 8 mice which received the
one dose tested of F(ab')2 were without palpable tumors at the
end of treatment. Treatment with 0.32 mg/dose of the chimeric
BR96 resulted in 6 tumor-free mice compared to 4 mice of 8 in
the group that received an equal amount of the IgG3. There
were no dose effects observed in the mice that received the
similar range of doses of the IgG1 switch variant. Mice treated
with PBS or the nonspecific MAbs all had palpable tumors at
the end of treatment, 15 days postimplant. In another experi-
ment, increasing the dose to 2 mg/injection did not result in
greater antitumor activity (data not shown).

The antitumor capabilities of BR96 were also examined
against a tumor which does not express the BR96 antigen,
H2981. Mice were implanted s.c. with 10 million tumor cells,
and treatment was started on day 2, with each mouse receiving
1 mg of MAb once every 3 days for five injections. Fig. 7
demonstrates that BR96 (IgG3) had no effect on the H2981
line.

Localization Experiments. The ability of radiolabeled BR96
and immediately assayed for the presence of the BR96 antigen
by fluorescence-activated cell sorter analysis with fluorescein
isothiocyanate-labeled BR96. Most of the intact cells recovered
from this tumor still strongly expressed the antigen to which
BR96 could bind, suggesting that growth of this tumor was not
due to an antigen-negative clone selected for by BR96
treatment.

Dose effects were examined by reducing the injected amount
of murine IgG3 in half-log increments from 1 to 0.032 mg/
injection given to mice bearing H2707 xenografts. The treat-
ment schedule remained five times, 3 days apart, beginning on
day 2. Fig. 4 demonstrates that the antitumor effects decreased
as the dose was lowered, although the difference between the
0.32-mg and 0.1-mg doses was small. To further explore the
mechanisms responsible for the antitumor effects observed
when animals were treated with BR96, the activities of an
isotype switched mouse variant, BR96 IgG1, a mouse-human
chimeric version of BR96, and F(ab')2 fragments prepared from
BR96 were also tested against the H2707 tumor line. The mean
tumor volumes for groups of mice treated with the IgG1 variant
of BR96 (1 mg/dose) are shown in Fig. 5. The IgG1 variant had
no more antitumor effect than the BR64 control MAb, both of
which were slightly better than the PBS control. However, the
chimeric version of BR96 (0.32 mg/dose) resulted in antitumor
effects at least as good as and apparently exceeding those of the
murine IgG3, BR96, as shown in Fig. 6.
to localize to tumor sites was examined in mice transplanted with either the H2987 or the H2707 carcinoma lines, using radiolabeled antibodies as probes. All mice had palpable tumors resulting from the s.c. implantation of 10 million cells approximately 2 weeks earlier. Table 1 summarizes the biodistribution in tumor as compared to blood and several organs. As shown in this table, the largest differences between specific and nonspecific MAb uptake occurred in tumors. There was a difference in blood concentrations of BR96 IgG, and the nonspecific specific MAb uptake occurred in tumors. There was a difference in this table, the largest differences between specific and nonspecific in tumor as compared to blood and several organs. As shown resulting from the s.c. implantation of 10 million cells approx-

Table 1 Summary of biodistribution experiments

<table>
<thead>
<tr>
<th>MAb</th>
<th>Dose (mg)</th>
<th>Tumor H2987</th>
<th>Blood</th>
<th>Tumor</th>
<th>Liver</th>
<th>Spleen</th>
<th>Kidney</th>
<th>Lung</th>
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</thead>
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<tr>
<td>BR96-G1</td>
<td>1.0</td>
<td>10.2</td>
<td>6.8</td>
<td>2.2</td>
<td>1.9</td>
<td>3.4</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>IIG5</td>
<td>1.0</td>
<td></td>
<td>6.3</td>
<td>2.1</td>
<td>2.1</td>
<td>1.6</td>
<td>2.4</td>
<td>3.2</td>
</tr>
<tr>
<td>BR96-G1</td>
<td>0.3</td>
<td>9.0</td>
<td>7.0</td>
<td>1.8</td>
<td>1.6</td>
<td>2.7</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>IIG5</td>
<td>0.3</td>
<td></td>
<td>5.9</td>
<td>2.0</td>
<td>1.8</td>
<td>2.2</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>BR96-G1</td>
<td>0.3</td>
<td>13.4</td>
<td>9.1</td>
<td>3.3</td>
<td>3.0</td>
<td>3.3</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>G19.4</td>
<td>0.3</td>
<td></td>
<td>14.3</td>
<td>5.1</td>
<td>4.3</td>
<td>2.8</td>
<td>3.3</td>
<td>6.0</td>
</tr>
<tr>
<td>ChiBR96</td>
<td>0.3</td>
<td>7.2</td>
<td>8.2</td>
<td>1.4</td>
<td>1.6</td>
<td>2.0</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Chi96.5</td>
<td>0.3</td>
<td></td>
<td>7.5</td>
<td>2.3</td>
<td>1.8</td>
<td>1.6</td>
<td>1.9</td>
<td>3.5</td>
</tr>
<tr>
<td>F(ab')2</td>
<td>BR96</td>
<td>0.65</td>
<td>H2707</td>
<td>&lt;0.25</td>
<td>&lt;0.25</td>
<td>&lt;0.25</td>
<td>&lt;0.25</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>96.5</td>
<td>0.65</td>
<td></td>
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<td>&lt;0.25</td>
<td>&lt;0.25</td>
<td>&lt;0.25</td>
<td>&lt;0.25</td>
<td>&lt;0.25</td>
</tr>
</tbody>
</table>

The highest tumor:blood uptake ratio was seen with the chimeric BR96, although the specific:nonspecific ratio in the tumor was lower than with the other forms of BR96 tested. The tumor:blood ratios for the two murine isotypes were practically identical. This is noteworthy in view of the differences in therapeutic efficacy of the various forms of unlabeled MAb.

The portion of the dose detected in a particular organ was relatively constant over the dose range used. It may therefore be possible to increase the amount of MAb in the tumor by increasing the dose. F(ab')2 fragments were cleared more rapidly than intact antibodies and had poor uptake in tumors.

DISCUSSION

We have shown that MAb BR96 has significant antitumor effects when tested, in the unmodified form, in nude mice xenografted with human lung adenocarcinoma. The antigen to which BR96 can bind must be expressed in vivo for these effects to occur, inasmuch as there was no inhibition of a lung adenocarcinoma lacking the BR96-defined antigen. Consistent with previous in vitro data (2), mice with a higher antigen-expressing tumor line, H2707, displayed greater antitumor effects than mice grafted with line H2987, which expressed less antigen. Our findings are similar to those obtained with certain other MAbs (10–13), including antibodies which can have antitumor activity of their own, the most notable of which being an antibody against a neu oncogene product (14). BR96 differs from the latter antibody in its much broader tumor specificity, however.

The antitumor effects observed with BR96 may have occurred through several different mechanisms. While it is difficult to separate these mechanisms in the nude mouse model, our data suggest that direct killing by BR96 is not a major component against staged tumors, since only limited antitumor effects were seen with BR96 F(ab')2 fragments, which by lacking the Fc portion of the molecule could only have acted directly on the tumor cells and not by involving complement or effector cells. Since the F(ab')2 fragments were cleared rapidly, it is possible, however, that antitumor effects would have been greater had the fragments remained longer in the animal. The IgG1 murine switch variant has a less cytotoxic effect in vitro than any of the other versions of BR96 tested, including F(ab')2 fragments, and it does not elicit ADCC or CDC. While it localized to the tumor in a manner similar to that of the murine IgG1 isotype, its antitumor activity in vivo was much less than those of the murine IgG1 and chimeric BR96 and even less than that of the F(ab')2 fragments.

With the exception of the F(ab')2 fragments, each of the murine isotypes and the chimeric version of BR96 localized at the tumor in comparable amounts. Therefore, the antitumor effects observed in our model were most likely to be due to the elicitation of effector functions such as ADCC or CDC (15, 16), with ADCC probably playing a larger role than CDC, judging from observations made in other systems (15, 17). Chimeric mouse-human IgG1 MAbs have been shown to mediate highly effective ADCC (18–20), and murine MAbs of the IgG1 isotype can often elicit strong ADCC (15). The data reported in this paper are consistent with these observations: the strongest antitumor effects were seen with chimeric BR96 followed by the IgG1 version, while the BR96 IgG1 variant and the F(ab')2 fragments, which do not elicit ADCC or CDC (2) in vitro, had only limited antitumor activity in the mice.

The strongest antitumor effects were seen when treatment was initiated within 2 days after tumor cell implantation. At this time, the tumor would still be very small and should allow easier access, not only for the MAb molecules and complement, but also for effector cells such as natural killer cells and macrophages. Since no toxicity was observed in the mice, it should be possible to continue treatment for a much longer period of time. Additionally, the antitumor effects of unmodified BR96 might enhance the efficacy of other treatment modalities added concomitantly.

One may speculate that the unmodified chimeric and murine IgG1 versions of BR96 may also have therapeutic activity in humans (e.g., toward micrometastases), although it is hard to predict to what extent tumor cells would be destroyed without causing unacceptable damage to those subpopulations of normal cells of the gastrointestinal tract to which BR96 binds (2). The fact that only modest effects were observed in nude mice with staged tumors suggests, however, that unmodified BR96 will be much less effective for therapy than BR96 to which an antitumor agent such as a drug or radioisotope has been coupled, unless procedures can be developed for increasing the ability of BR96 to kill tumor cells in vivo via ADCC and/or CDC.

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3266

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