Interferon Enhancement of Radioimmunotherapy for Colon Carcinoma

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ABSTRACT

Recombinant human γ-interferon (INF-γ) has recently been shown to enhance localization of radiolabeled monoclonal antibodies (MAb) to human colon carcinoma xenografts in athymic mice. The present study investigates the ability of γ-interferon to enhance radioimmunotherapy of a low carcinomaembryonic antigen—expressing human colon cancer (WiDr) in athymic mice. Growth curve analysis, antibody localization, and dose estimation studies were performed. A significant tumor growth delay, measured as the time to reach 1.0 g, was noted for animals receiving specific anti-carcinoembryonic antigen 99mTc-MAb (ZCE025, 120 μCi) plus INF-γ (61.8 days) as compared to animals that received specific 99mTc-MAb with phosphate-buffered saline (34.9 days; P < 0.005). INF-γ (100,000 units) was given i.p. every 8 h for 2 days before and 4 days after 99mTc-MAb therapy. The time required to reach 1.0 g for animals treated with nonspecific 99mTc-MAb (ZME018) was significantly less either with (38.3 days) or without (34.4 days) INF-γ. The difference was more apparent when compared to animals receiving INF-γ alone (30.0 days) or phosphate-buffered saline alone (28.9 days; P < 0.001). Increased antibody localization in the tumors of animals treated with INF-γ plus specific 99mTc-MAb (43.2% injected dose/g) was seen in comparison to animals treated with specific 99mTc-MAb without INF-γ (18.2% injected dose/g). The estimate of radiation dose delivered to the tumors, based on biodistribution data over time, revealed significantly higher levels in animals treated with specific 99mTc-MAb with INF-γ (2477 cGy) compared to animals treated without INF-γ (1217 cGy). These results provide support for the use of γ-interferon as an immunomodulating agent prior to radioimmunotherapy.

INTRODUCTION

MAb directed against specific tumor-associated antigens can now be produced in large quantities by hybridomas. CEA is a well-characterized antigen expressed in over 95% of colon cancers as well as 20–70% of breast, lung, and stomach cancers (1). Radiolabeled monoclonal antibodies directed against CEA have been successfully utilized in animal and human trials for imaging of colon, lung, and breast carcinomas (2-4).

γ-Interferon has demonstrated a variety of immune modulatory actions which include enhancement of HLA class I and II antigens as well as enhancement of tumor-associated antigens on a variety of cell lines (5, 6). Previous animal studies have shown that recombinant human INF-γ can increase the amount of CEA expression and MAb localization in cell lines with a low expression of CEA. Nude mice bearing a low CEA-expressing tumor were exposed to INF-γ (100,000 units i.p. every 8 h for 4 days), showed a significant increase in tumor CEA expression (5,598 ng CEA/g tumor) compared to nontreated animals (809 ng/g; P < 0.01). Antibody localization was also significantly increased in tumors of INF-γ-treated animals. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1Supported in part by USPHS Training Grant CA09477, Program Project Grant CA43904, Cancer Center Core Grant CA33572, and by a grant from The Margaret Early Foundation, Los Angeles, CA.

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3The abbreviations used are: MAb, monoclonal antibody; INF-γ, γ-interferon; CEA, carcinoembryonic antigen; % ID/g, percentage of injected dose/g; RIT, radioimmunotherapy; PBS, phosphate-buffered saline.

Received 9/4/90; accepted 2/22/91.

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reconstituted in PBS with 1% bovine serum albumin just prior to use and stored at 4°C. Animals were given 10⁷ units IFN-γ in 0.1 ml by i.p. injection every 8 h for 2 days prior to and for 4 days following the ⁹⁰Y-MAB injection. This regimen has been previously shown to result in optimal biological effectiveness of IFN-γ (7). Control animals received PBS with 1% bovine serum albumin for the same treatment interval.

Tumor Growth. Six days after tumor injection, the animals were divided into six groups. The specific therapy groups received PBS or IFN-γ on days 6 through 12 following tumor injection and 120 µCi ⁹⁰Y-labeled anti-CEA MAb ZCE025 (specific ⁹⁰Y-MAB) on day 8. The nonspecific therapy groups received PBS or IFN-γ on days 6–12 and 120 µCi ⁹⁰Y-labeled anti-melanoma MAB (nonspecific ⁹⁰Y-MAB) on day 8. Two additional control groups received either PBS alone or IFN-γ alone on days 6–12. Tumor weight was approximately 0.05 g at the time of ⁹⁰Y-MAB treatment.

A separate experiment was conducted to evaluate the effect of IFN-γ and RIT when tumors were larger, approximately 1.0 g, at the time of ⁹⁰Y-MAB treatment. The groups were similar to those in the previous experiments, with the exclusion of the nonspecific ⁹⁰Y-MAB treatments. All animals received IFN-γ or PBS on days 10–16 following tumor injection, with specific therapy groups receiving ⁹⁰Y-MAB on day 12.

Tumor size was calculated using the formula for an ellipse rotated about its major axis

\[
\text{volume} = \frac{4}{3} \pi ab^2
\]

where \(a\) is the longer radius and \(b\) is the shorter radius. The accuracy of this measurement formula is within 10–20% of the actual weight based on previous studies. A density of 1.0 g/cm³ was assumed. Individual and mean growth curves were plotted until the tumors reached 4.0 g. Analysis of individual growth curves was performed by stepwise regression analysis of the natural log of tumor size against time. Statistical analysis of the resulting slopes was performed using Welsch’s test and an analysis of variance.

Antibody Localization and Dose Estimation. A separate group of tumor-bearing mice was treated with 120 µCi of specific or nonspecific ⁹⁰Y-MAB with or without IFN-γ in the manner described above. The animals were sacrificed 12, 24, 72, 120, and 192 h after ⁹⁰Y-MAB therapy, and the tumor, blood, spleen, liver, kidney, lung, heart, muscle, and bone were removed. The tissue samples were weighed and counted concurrently with a known fraction of the injected ⁹⁰Y dose to correct for radionuclide decay. The tissues were suspended in a standard volume of normal saline, and the brake radiation (Bremsstrahlung) from the β decay was measured on a gamma counter. Specific activity present in normal saline, and the brake radiation (Bremsstrahlung) from the β decay was measured on a gamma counter.

The radiation dose to the tumor and other organs was estimated using biodistribution data (14). Based upon the times of biodistribution, the deposited β dose was calculated for six time blocks: 0–0.5 day, 0.5–1.0 day, 1.0–3.0 days, 3.0–5.0 days, 5.0–8.0 days, and 8.0 days–complete decay. For each of the first five time intervals, the formula used was

\[
\Delta D_t = 2.13 \times E_y \times C_i \times \Delta t
\]

where \(\Delta D_t\) is the interval β dose in cGy, \(E_y\) is the mean decay energy of the β for ⁹⁰Y (0.931 MeV), and \(\Delta t\) is the elapsed time interval in h. \(C_i\) is the concentration of the isotope present during the time period expressed in µCi/g. This was calculated using the biodistribution data for the tumor (% ID/g × 120 µCi) and correcting for decay. Integration of the β dose formula over time to infinity gives an estimate of the total β dose deposited in the tumor in the final time period (day 8 to complete decay). This integration yields

\[
D_{\beta} = 73.8 \times E_y \times C_{day} \times T_{el}
\]

where \(T_{el}\) is the effective half-life in days. Since the tumor growth experiment encompasses more than 10 half-lives of the radionuclide, it is reasonable to assume essentially complete decay.

The accumulated β dose \(D_{\beta}\) may then be corrected for finite tumor size by using formulae described by Loevinger, based on

\[
D_{\beta}(0,b) = D_{\beta}(1 - 0.33(1 + \gamma b)e^{1 - \gamma t})
\]

where \(D_{\beta}(0,b)\) is the dose at the center of a spherical source of β-particles with uniform unit density \([\gamma = 6.5 \text{ cm}^{-1}; b = \text{radius (cm)}]\). A final correction factor of approximately 0.75 for calculating the average dose within a sphere is derived from a graphic analysis of tumor size and \(D_{\beta}(0,b)\) (15).

RESULTS

Tumor Growth. Curves of mean tumor size for the six groups accumulated in four separate experiments are shown in Fig. 1. Individual growth curve analysis for each animal was performed by regressing the natural log of tumor mass against the day of measurement. A biphasic growth pattern was seen for the majority of animals. There was a higher degree of error when the data points were tested for a monophasic growth rate or multiple rates. Separate slopes were fit to the measurements, and a transition point was determined to be 1.0 g using the method of Draper and Smith (16). The rate of growth (or doubling time) for each animal in the early phase prior to the transition point of 1.0 g was analyzed and tested for statistical significance against other groups within a particular experiment. Average doubling times for all animals are reported in Table 1. One of the total of 160 animals was excluded from the final statistical analysis. Three animals in the group treated...
with IFN-γ plus specific 90Y-MAb (total n = 26) and one animal treated with specific 90Y-MAb without IFN-γ (total n = 26) demonstrated marked tumor growth delay with tumors never reaching 1.0 g. Although these animals represent the greatest effectiveness of the treatment regimen, they also tended to overinflate the average values and lessen the statistical significance. They are therefore recorded separately here. The tumor doubling times prior to 1.0 g for the animals treated with IFN-γ plus specific 90Y-MAb [11.30 ± 0.43 (SEM) days] were significantly different from all other groups: PBS/specific 90Y-MAb (6.84 ± 0.30 days); IFN-γ/nonspecific 90Y-MAb (7.18 ± 0.23 days); PBS/nonspecific 90Y-MAb (6.69 ± 0.32 days); IFN-γ alone (5.28 ± 0.25 days); PBS alone (5.38 ± 0.29 days). These values are shown in Table 1.

Each growth curve was then analyzed for the time required to reach the 1.0-g size (Table 2). This time increased significantly in animals receiving specific 90Y-MAb plus IFN-γ (11.76 ± 1.82 days) compared to control animals receiving specific 90Y-MAb without IFN-γ (34.95 ± 1.47 days) or animals receiving PBS alone (28.86 ± 1.52 days) or IFN-γ alone (30.00 ± 1.29 days). Animals treated with nonspecific therapy with or without IFN-γ took 38.33 ± 1.31 and 34.44 ± 1.46 days, respectively, to reach the 1.0-g size. For the comparison of the IFN-γ/specific 90Y-MAb group to all other groups, P < 0.001.

A separate experiment in which animals were treated with specific 90Y-MAb 12 days following tumor injection, when tumor size was approximately twice as large (0.1 g), showed similar but less significant results. The time required for the tumor to reach 1.0 g following treatment with IFN-γ plus specific 90Y-MAb was increased to 44.44 ± 3.58 days compared to 26.51 ± 1.04 days for PBS alone (P < 0.005).

Antibody Biodistribution. Antibody localization studies following specific 90Y-MAb therapy with and without IFN-γ were performed at the following time points: 12, 24, 72, 120, 192 h (n = 40) (Fig. 2). Enhanced MAb localization in the tumor was documented for the group treated with specific 90Y-MAb plus IFN-γ. The uptake of 90Y reached a peak of 42.3% ID/g at approximately 3 days and remained high to 8 days. Animals treated with specific 90Y-MAb without IFN-γ showed no significant increase in tumor uptake of MAb. Antibody localization studies were also obtained following nonspecific 90Y-MAb therapy with and without IFN-γ at 72 and 120 h (Fig. 2). The nonspecific therapy groups showed no enhancement of MAb localization by the tumor with or without IFN-γ. In this colon carcinoma cell line with low CEA expression, the tumor uptake in the nonspecific 90Y-MAb groups was not significantly different from the uptake in the PBS/specific 90Y-MAb group. The biodistribution of normal tissues was performed for blood, liver, spleen, kidney, lung, muscle, heart, and bone. Normal tissue uptake of radiolabeled MAb was not influenced by prior treatment with IFN-γ. The results for the 72-h biodistribution are shown in Fig. 3. Analysis of other time points showed no effect of IFN-γ on normal tissue biodistribution.

Dose Estimation. Absorbed dose estimation was calculated for tumors in animals treated with specific anti-CEA 90Y-MAb. The cumulative deposited β doses and appropriate correction factors based on tumor size are listed in Table 3. In the groups
CI-associated antigens, the enhancement of major histocompatibility within a tumor in order to increase overall uptake of radiolabeled MAb. Animal studies have shown significant therapeutic benefit using 90Y-labeled anti-CEA MAb to treat human tumor xenografts. Several regulatory actions which include the enhancement of tumor-associated antigen expression can be increased in a variety of low CEA-expressing colon carcinoma cell lines following therapy with IFN-γ (6, 7). Enhanced tumor CEA expression was noted by immunohistochemistry, and total CEA measurements were made by enzyme immunoassay. In addition, increased localization of radiolabeled MAb at the tumor resulting in enhanced scintiscan images has been observed in the animal model. Our in vitro and in vivo studies suggested that the effect of IFN-γ may require 1–3 days for the increased antigen expression to actually be manifested on the cell membrane. Optimal enhancement was achieved when a relatively sustained blood level of IFN-γ was maintained by either frequent injections or a continuous delivery system via an osmotic pump. These levels have been maintained in humans at doses below the maximum tolerated dose (8–10 × 10^6 units/m^2) (18, 19). Sustained levels of IFN-α have also been demonstrated to be associated with optimal enhancement of CEA expression and antibody uptake (20).

In this study, the tumor uptake of radiolabeled anti-CEA 90Y-MAb was significantly increased following the administration of IFN-γ. High levels of antibody uptake were maintained from day 3 to day 8 following 90Y-MAb therapy. It is interesting to note that previous in vitro and in vivo studies suggested that the enhanced antigen expression of IFN-γ returns to baseline levels by the third day after IFN-γ removal (5). In this experiment, IFN-γ was discontinued on the fourth day following 90Y-MAb therapy, and sustained levels of antibody uptake were still apparent 4 days after IFN-γ removal. Tumor uptake of nonspecific anti-p97 (anti-melanoma) 90Y-MAb was not enhanced by treatment with IFN-γ. Normal tissue uptake of 90Y-MAb was not changed in animals receiving IFN-γ.

Analysis of individual growth curves revealed a biphasic growth pattern with more rapid growth and shorter doubling times for smaller tumors and slower growth and longer doubling times for larger tumors. A transition point of 1.0 g was identified, which is similar to the transition size reported for the LS174T colon carcinoma cell line in our laboratory (21). The tumor doubling times after a size of 1.0 g was reached were not significantly different among all groups. This suggested that resurgent tumors after RIT had similar growth rates when compared to untreated tumors. The decreased growth rate prior to the 1-g size was thought to reflect the degree of tumor cell killing prior to the resurgence of viable tumor cells. A significant tumor growth delay, measured as the time to reach 1.0 g, was noted in animals treated with IFN-γ specific 90Y-MAb (61.76 days) when compared to the controls: PBS/specific 90Y-MAb (34.95 days); IFN-γ/nonspecific 90Y-MAb (38.33 days); PBS/nonspecific 90Y-MAb (34.44 days); IFN-γ alone (30.00 days); or PBS alone (28.86 days). This growth delay was most pronounced when the tumors were treated at an earlier time point with small tumors (0.05 g), although similar effects were seen for larger tumors (0.1 g).

In an effort to quantify the effectiveness of radioimmunotherapy plus IFN-γ, the difference between the IFN-γ group and the PBS control group in the time for the tumors to reach 1.0 g (range, 21–51 days; mean, 33 days) can be used to estimate the magnitude of tumor cell killing based on the doubling times of the PBS control treatment group (5.38 days). Assuming a constant doubling time of 5.38 days, the delay of 21–51 days could be estimated to be a delay of 4–10 tumor doublings (2^4–2^10 = 16–10^5), which is equivalent to an estimated 10^5–10^6 cell kill. However, in these experiments, animals were inoculated with 10^6 cells and were treated with 90Y-MAb at day 8 or 3 days after a size of 1.0 g (range, 21–51 days; mean, 33 days) can be used to estimate the magnitude of tumor cell killing based on the doubling times of the PBS control treatment group (5.38 days). Assuming a constant doubling time of 5.38 days, the delay of 21–51 days could be estimated to be a delay of 4–10 tumor doublings (2^4–2^10 = 16–10^5), which is equivalent to an estimated 10^5–10^6 cell kill. However, in these experiments, animals were inoculated with 10^6 cells and were treated with 90Y-MAb at day 8 or

### DISCUSSION

The results of therapy for human colon carcinoma have not changed dramatically in the past 40 years, due partly to the inadequacy of present adjuvant therapy for microscopic disease in patients undergoing resection. Radiolabeled monoclonal antibodies directed specifically at a tumor-associated antigen would appear to be the ideal therapy for tumor cells. Several animal studies have shown significant therapeutic benefit using 90Y-labeled anti-CEA MAb to treat human tumor xenografts that show a high expression of CEA (9, 17). Unfortunately, most human colon carcinomas are actually a heterogeneous collection of cells with variable CEA expression. Thus, radioimmunotherapy in humans will require an effective method for increasing the antigen expression of low CEA-expressing cells within a tumor in order to increase overall uptake of radiolabeled anti-CEA MAb.

IFN-γ has been shown to possess a variety of immunomodulatory actions which include the enhancement of tumor-associated antigens, the enhancement of major histocompatibility complex class I and II antigens, and the modulation of interleukin 2, tumor necrosis factor, and Fc receptor synthesis. Recent in vivo studies in our laboratory as well as in vitro studies at the NIH have shown that the degree of tumor-associated antigen expression can be increased in a variety of low CEA-expressing colon carcinoma cell lines following therapy with IFN-γ (6, 7). Enhanced tumor CEA expression was noted by immunohistochemistry, and total CEA measurements were made by enzyme immunoassay. In addition, increased localization of radiolabeled MAb at the tumor resulting in enhanced scintiscan images has been observed in the animal model. Our in vitro and in vivo studies suggested that the effect of IFN-γ may require 1–3 days for the increased antigen expression to actually be manifested on the cell membrane. Optimal enhancement was achieved when a relatively sustained blood level of IFN-γ was maintained by either frequent injections or a continuous delivery system via an osmotic pump. These levels have been maintained in humans at doses below the maximum tolerated dose (8–10 × 10^6 units/m^2) (18, 19). Sustained levels of IFN-α have also been demonstrated to be associated with optimal enhancement of CEA expression and antibody uptake (20).

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### Table 3 Estimation of absorbed radiation dose for animals treated with anti-CEA 90Y-ZCE025 (120 μCi) either with or without IFN-γ

<table>
<thead>
<tr>
<th>Dose/time interval (cGy)</th>
<th>Plus IFN-γ</th>
<th>PBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12 h</td>
<td>121</td>
<td>111</td>
</tr>
<tr>
<td>12–24 h</td>
<td>402</td>
<td>321</td>
</tr>
<tr>
<td>24–72 h</td>
<td>2224</td>
<td>1252</td>
</tr>
<tr>
<td>72–120 h</td>
<td>1865</td>
<td>635</td>
</tr>
<tr>
<td>120–192 h</td>
<td>1650</td>
<td>476</td>
</tr>
<tr>
<td>192 h – ∞</td>
<td>1290</td>
<td>366</td>
</tr>
<tr>
<td>Total D_{av}</td>
<td>7552</td>
<td>3161</td>
</tr>
<tr>
<td>Mean tumor size (g)</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Size correction factor*</td>
<td>0.437</td>
<td>0.513</td>
</tr>
<tr>
<td>Correction factor for av. dose</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>Total av. tumor dose (cGy)</td>
<td>2477</td>
<td>1217</td>
</tr>
</tbody>
</table>

*Correction factor for estimating radiation loss from small objects (15).
12. Tumors were identifiable at days 6–7 and became measurable accurately by days 10–12. In the PBS control group, tumors reached 1.0 g (106 cells) at day 30. An increase from 106 cells at inoculation to 109 cells at 1 g would be equivalent to 10 doublings over 30 days. However, during the measurable period between days 10 and 30 for the PBS control group a doubling time of 5.38 days was noted, accounting for 4 doublings. Therefore, by extrapolation, we can estimate that 6 doublings occurred between days 0 and 10 after inoculation. This suggests that the doubling time at day 8, when 90Y-MAb therapy was given, was under 2 days. Based on an estimated doubling time of 2 days, a delay of 21–51 days comparing IFN-γ plus 90Y-MAb to control (time to reach 1 g) would result in a delay of 10–25 doublings (210–225 = 1024–3.3 x 107) or a 103–107 cell kill. Because only 106 cells were inoculated, and 109 cells were estimated to be present at the time of therapy, we would expect that animals receiving a tumor cell kill over 106 would have a high likelihood of being cured. Indeed, three animals in the specific 90Y-MAb plus IFN-γ group had demonstrated stable disease and had not reached the 1-g size at 120 days. If this phenomenon is translated into the human model, with measured doubling times of approximately 30 days for human colon carcinoma, the use of RIT may stabilize disease for a period of 1 year or more. In an adjuvant setting, with a potential for microscopic residual disease estimated to be under 106 cells remaining following resection, the use of RIT could provide significant therapeutic benefit and even potential long-term control or cure. These estimates are based on the assumption that the delay in the time for tumors to reach a given size reflects only on the tumor cells killed and not on changes in the proliferative rate of treated cells. In actuality, both events are probably in effect simultaneously. However, since all tumors in all treatment groups demonstrated similar growth rates and no significant change in tumor histology after 1-g tumor size (data not shown), the proliferative rate was not believed to be the predominant factor.

Estimation of dose delivery for radioimmunotherapy has been a challenging area of investigation. The method most commonly used in the animal model utilizes the biodistribution data accumulated over a time period, with the dose approximating the area under a curve generated by these points. This estimation assumes no escape of β-particles from the tumor or organ. Since the tumors studied were quite small (0.03–0.08 g), such β escape probably accounted for an overestimation of the dose absorbed. Our approach has explicitly included such edge effects with corresponding reductions in estimated dose (Table 3). However, our formula did not consider the effect of β-radiation entering from adjacent tissue or circulating activity and thus underestimated the absorbed dose. In the present study, a higher estimated dose was delivered to the tumors of animals treated with IFN-γ plus specific anti-CEA 90Y-MAb (2477 cGy) compared to those treated with PBS plus specific anti-CEA 90Y-MAb (1217 cGy).

In summary, the present experiments demonstrate that therapy with γ-interferon can increase the amount of 90Y-labeled anti-CEA MAb localized to xenografts of a low CEA-expressing human colon carcinoma, WiDr. The animals treated with IFN-γ and specific 90Y-MAb showed a significant growth delay when compared to specific 90Y-MAb without IFN-γ, nonspecific 90Y-MAb, PBS alone, or IFN-γ alone. Considering the doubling time of 5.38 days for the control group at the time of therapy and the difference in the time to reach 1.0 g (range, 21–51 days), the tumor cell kill was calculated to be in the range of 10−10−1. A tumor cell kill of 10−1–10−2 may actually be calculated if one estimates a shorter doubling time during the earlier growth phase. The dose delivered to the tumor was calculated to be approximately 2477 cGy in the IFN-γ-treated animals compared to 1217 cGy in animals that did not receive IFN-γ. The use of IFN-γ to enhance CEA expression may have broad implications for MAb imaging and therapy in humans. Further studies are required to ascertain the uniformity of this observation in different models and ultimately in humans with CEA-producing cancers.

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Cancer Res 1991;51:2335-2339.

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