Radioimmunotherapy for Breast Cancer Using Escalating Fractionated Doses of ¹³¹I-labeled Chimeric L6 Antibody with Peripheral Blood Progenitor Cell Transfusions

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Abstract

Radioimmunotherapy (RAIT) using a humanized murine monoclonal antibody, chimeric L6 (ChL6), has produced objective tumor regression in 50% of chemotherapy-refractory patients with metastatic breast cancer in our prior studies. Because myelosuppression limited dose escalation, we evaluated the ability of granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood progenitor cell (PBPC) transfusions to ameliorate this problem. ¹³¹I-labeled ChL6 was given at a starting dose of 150 mCi/m² (2.5 times the maximum tolerated dose without PBPCs) for a planned three treatments. When blood radioactivity declined to less than 1 μCi/ml after treatment, PBPCs were transfused, and G-CSF was administered. Patient 1 had minimal myelosuppression, received two cycles of therapy, and then developed human antimonoclonal antibody (HAMA). Patient 2 had prolonged thrombocytopenia that resolved after additional PBPC transfusion. Progressive disease as well as HAMA prevented further treatment. Patient 3 received all three cycles of 150 mCi/m² at 8-week intervals. Thrombocytopenia (<25,000/μl) occurred but was transient (0–7 days). Because HAMA developed in all prior patients who received G-CSF with ChL6 RAIT, including patients 1 and 2, who received PBPC, patient 3 was given cyclosporin for 14 days. She did not develop HAMA or significant toxicity following 3 cycles of RAIT. Cumulative radiation doses to her lungs and tumor were estimated at 3,100 and 11,200 cGy, respectively. For 9 months, she had a reduction in bone pain, a decline in serum tumor markers, and decreased tumor uptake of F-18-deoxyglucose on a positron emission scan. Her performance status improved, and she had no pulmonary toxicity. We conclude that: (a) PBPC transfusion can modify the myelotoxicity of RAIT and can permit repetitive dosing; (b) cyclosporin is a promising means to abrogate HAMA; and (c) fractionation of intensive-dose RAIT may increase the antitumor effect and reduce normal organ toxicity.

Introduction

RAIT³ is a promising new strategy for treating breast cancer. In a Phase I dose escalation trial with ¹³¹I linked to ChL6, a human chimera of the L6 murine monoclonal adenocarcinoma antibody (1–3), more than one-half of heavily pretreated, chemorefractory, metastatic breast cancer patients had at least 50% reduction in tumor size. Clinical results, quantitative imaging, and radiopharmaceuticals have been reported previously for a subset of these patients (4–6). ¹³¹I-labeled ChL6 therapy was free of significant toxicity, except for dose-limiting myelosuppression; e.g., 60–70 mCi/m² doses produced WHO grade 3–4 hematological toxicity after the first or second treatment. The addition of G-CSF did not alter the prolonged thrombocytopenia. Further dose escalation requires a means for ameliorating myelosuppression. In this report, we present details concerning hematological toxicity observed in the first three breast cancer patients treated with repeated doses of 150 mCi/m² ¹³¹I-labeled ChL6 with G-CSF-mobilized PBPC support.

Materials and Methods

ChL6 was developed by substituting the murine antibody constant regions G2a and κ with human constant domains G1 and κ (Oncogene, Seattle, WA; Ref. 7). ChL6, like the murine antibody (L6), binds to adenocarcinomas, including 50% of human breast cancers, but demonstrates 50–100-fold more efficiency in mediating antibody-dependent cytotoxicity (3, 7). The radiopharmaceutical was prepared by chloramine T radioiodination with ¹³¹I (ICN Biomedicals, Irvine, CA) as described previously (8, 9). More than 95% of the ¹³¹I was bound to the ¹³¹I-labeled ChL6 radiopharmaceutical by high-performance liquid chromatography and cellulose acetate electrophoresis, and more than 70% of the preparation reacted with the breast cancer HER-2/neu cell line (10). The final sterile, pyrogen-free radiopharmaceutical contained 10 mCi ¹³¹I/mg antibody and 1 mCi ¹³¹I/ml solution (8, 9).

Patient Eligibility. Patients with metastatic breast cancer documented to be L6 antibody positive by immunoperoxidase staining of fresh or frozen tissue (11) were eligible if they had measurable disease unresponsive to or recurrent after at least one prior standard combination chemotherapy regimen. Additional requirements included a normal complete blood count, the absence of other serious medical illnesses, normal organ function, Eastern Cooperative Oncology Group performance status of 2 or better, an interval of at least 4 weeks from chemotherapy administration, and a negative serum HAMA (4). Patients with tumors occupying more than 25% of the axial skeleton, extensive liver or pulmonary disease, prior monoclonal antibody therapy, or central nervous system disease were excluded.

Progenitor Cell Harvest. After patient eligibility was established, and written informed consent was obtained in accordance with institutional review board guidelines, a central venous catheter was placed, and the patient began receiving G-CSF at 8 μg/kg/day s.c. (12, 13). Apheresis began on day 4 and continued daily until a target of 15 × 10⁶ MNCs/kg patient body weight was obtained to permit three treatments at a dose of 5 × 10⁶ MNC/kg (14, 15). Aliquots of all components were prepared for hemopoietic progenitor cell harvesting using a methylcellulose culture system supplemented with FCS, BSA, and phytohemagglutinin-stimulated, leukocyte-conditioned medium (all reagents from Terry Fox Laboratory, Vancouver, British Columbia, Canada). All cultures contained interleukin-3 (R&D Systems, Inc., Minneapolis, MN). Cells were plated in quadruplicate at a concentration of 2 × 10⁶ cells/ml in 35-mm Lux Petri dishes (Nunc Inc., Naperville, IL). After 14 days of incubation in a 5% CO₂, 37°C, humidified atmosphere, colonies of CFU-GM were enumerated using an inverted microscope (16). Results were expressed as mean colony-forming cells/patient weight (i.e. CFU/kg total cells/kg = CFU/kg). To determine the number of CD33- and CD34-positive cells, a 10⁶ cell aliquot of the apheresis harvest was incubated for 20 min with phycoerythrin-conjugated CD33 and FITC-conjugated CD34 antibody (HPA-2; Becton Dickinson, Mountain View, CA). After red cell lysis, the washed leukocyte suspension was fixed, and 50,000 cells were analyzed by FACScan (Becton Dickinson; Ref. 17). Results were expressed as percentage of CD34-positive cells. For each apheresis harvest, the yield of CD34-positive cells was calculated per kg patient body weight (% CD34⁺ x 0.01) (cells/kg) = CD34⁺ cells/kg.

The progenitor cells were cryopreserved in Fenswal Cryocyte bags (Baxter, Deerfield, IL) using 10% DMSO, controlled-rate freezing (18), and liquid nitrogen storage. After sufficient cells were stored, G-CSF was discontinued, and at least 1 week elapsed before RAIT permitted reversal of the G-CSF.

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³ The abbreviations used are: RAIT, radioimmunotherapy; ChL6, chimeric L6; CFU-GM, colony-forming units for granulocytes and macrophages; G-CSF, granulocyte colony-stimulating factor; HAMA, human antimonoclonal antibody; MNC, mononuclear cell; PBPC, peripheral blood progenitor cell; ID, injected dose.
stimulatory effects on the bone marrow. The numbers of MNCs, CD34-positive, and CFU-GM given with each transfusion are shown in Table 1. RAIT. Eligible patients received 200 mg unconjugated ("cold") antibody prior to the $^{131}$I-linked antibody to block normal vascular endothelial receptors and to permit maximum tumor uptake, as shown previously (4). This cold antibody was followed by a 10-MCi imaging dose to assess tumor uptake and to verify the absence of normal organ targeting. Twenty-four hours later, a second 200-mg cold dose was given, followed by the therapeutic dose of 150 mCi/m$^2$ $^{131}$I-labeled ChL6. To block thyroid uptake of $^{131}$I, patients were given Lugol’s solution (20 drops daily) beginning 3 days before and for approximately 14 days after treatment (when residual $^{131}$I was less than 5%ID). Plasma samples were obtained before, during, and after antibody infusion, and the clearance rates of the radioactivity are shown in the radiopharmacokinetic curves in Fig. 1.

Calculated dosimetry is shown in Table 2 for blood and bone marrow. The radiation-absorbed dose delivered to the marrow from radionuclide in the blood was calculated using the cumulative activity measured for the blood. Counts in each sample were converted to amounts of $^{131}$I/ml by comparison with a calibrated $^{131}$I standard. The %ID in 1 ml whole blood was extrapolated to the %ID of $^{131}$I in the patient’s entire blood volume using a formula that related blood volume to body weight [blood volume (ml) = weight (kg) $\times$ 67.6 ml/kg]. The cumulated activity in the blood was determined using a biexponential fit for the blood clearance data and integration of the area under the curve of blood concentration versus time (Fig. 1). The cumulated activity of the blood was adjusted to that for the bone marrow by assuming a concentration or specific activity of 0.25 in the marrow when compared with blood. The $S$ factor for nonpenetrating radiation (2.72 $\times$ 10$^{-2}$) was obtained using methods of the Medical Internal Radiation Dose Committee to determine the equilibrium-absorbed dose constant for nonpenetrating radiation (0.408) in a marrow mass of 1500 g (19–21). Tumor uptake occurring in bone and/or marrow may add to the local marrow exposure by severalfold (21). The cumulative blood dose from the time of the stem cell infusion is based on biological clearance calculated from the kinetic curves in Fig. 1 and the $^{131}$I decay.

Patients were hospitalized and nursed, using special precautions until whole-body radioactivity was less than 30 mCi, approximately 2 millirem/h at 1 m. Previous in vitro studies using $^{131}$I concentrations of 0.02–2 $\mu$Ci/ml showed no adverse effect on CFU-GM growth (data not shown). Therefore, PBPCs were transfused after the blood radioactivity fell below 1 $\mu$Ci/ml. The patient then began a 2-week course of daily s.c. G-CSF (8 µg/kg). Subsequent RAIT cycles were planned at 6–8-week intervals for a maximum of three cycles, unless unacceptable toxicity, tumor progression, or HAMA response intervened. Because the first two patients developed HAMA, the third patient was given a 14-day course of cyclosporin at a dose of 5 mg/kg every 12 h p.o. beginning 3 days prior to each therapeutic $^{131}$I-labeled ChL6 cycle in an attempt to prevent HAMA (22, 23). Serial blood counts were obtained (Fig. 2), and patients were evaluated for clinical response and development of HAMA (4).

Results

Progenitor Collection and Transfusion. Five apheresis procedures were performed to collect $12.8 \times 10^6$ MNCs/kg from patient 1 and $13.2 \times 10^6$ MNCs/kg from patient 2. For patient 3, 10 aphereses were required to obtain a total of $9.2 \times 10^8$ MNCs/kg. Although patient 3 had a lower MNC yield, the total CD34 and CFU-GM content of her collections were well above our current threshold per infusion of $2 \times 10^9$ CFU-GM/kg and $2 \times 10^9$ CD34-positive cells/kg (24) (Table 1).

Hematological Toxicity and Recovery. The first patient’s blood level of radioactivity declined to less than 1 mCi/ml, and the PBPC transfusion was given 9 days following her first treatment and 7 days following her second treatment with 150 mCi/m² $^{131}$I-labeled ChL6. A more rapid decline in radioactivity after dose 2 (Fig. 1) was caused by development of occult HAMA, as documented subsequently during recovery from the second treatment. The patient’s neutrophil count never dropped below 1000/µl. The nadir platelet count occurred 21 days after both treatments, but myelosuppression was less during cycle 2 and resolved rapidly. Serial platelet counts are shown in Fig. 2. No grade 3 or 4 toxicity was noted after either cycle. Because Patient 1 developed a HAMA response, she could not receive a third cycle of therapy.

The second patient received 150 mCi/m² $^{131}$I-labeled ChL6 followed on day 9 by a PBPC infusion containing the requisite $5 \times 10^8$ MNCs/kg. However, this infusion contained less than one-fourth of the CFU-GM content given to patient 1 after each cycle of treatment (Table 1). Patient 2 experienced minimal neutropenia, with only 2 days below 1,000 neutrophils/µl and 1 day below 500 neutrophils/µl. However, grade 4 thrombocytopenia occurred, and she required a total of two platelet transfusions (Fig. 2). When it seemed that her thrombocytopenia might be prolonged, the remainder of her progenitor cells were transfused on day 40. No further platelet transfusions were needed, and her platelet count rose gradually to the nearly normal range (100,000/µl). Because she developed progressive disease, a 4-week course of external-beam radiotherapy to the chest and axilla was begun 6 days after the second progenitor infusion, and this could have blunted subsequent platelet recovery. The patient was not eligible for retreatment due to disease progression 30 days after her first cycle of $^{131}$I-labeled ChL6, as well as a positive HAMA.

Patient 3 received her first PBPC transfusion 9 days after her initial

Table 1 Characteristics of progenitor cell transfusions given following 150 mCi/m² $^{131}$I-labeled ChL6 antibody

<table>
<thead>
<tr>
<th>Progenitor transfusion</th>
<th>MNC (X10^6/kg)</th>
<th>CD34+ (X10^6/kg)</th>
<th>CFU-GM (X10^6/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient/transfusion</td>
<td>1/1</td>
<td>5</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>1/2</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>2/1</td>
<td>5</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>2/2</td>
<td>8</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>3/1</td>
<td>3</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>3/2</td>
<td>3</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>3/3</td>
<td>3</td>
<td>4.0</td>
</tr>
</tbody>
</table>

* Second transfusion given due to prolonged thrombocytopenia; no second course of $^{131}$I-labeled ChL6 given.
cycle of 150 mCi/m² 131I-labeled ChL6. Neutropenia was minimal, with neutrophil counts between 500 and 1,000/μl for only 2 days. Severe thrombocytopenia occurred but was brief (Fig. 2). She received a second dose of 150 mCi/m² 131I-labeled ChL6, followed in 9 days by a second peripheral stem cell infusion. Again, neutropenia was minimal (with no count below 1,000/μl), but low-grade thrombocytopenia (27,000–47,000/μl) persisted for 3 weeks (Fig. 2). A return of platelets to ≥100,000/μl occurred 42 days following the second stem cell infusion. After the third cycle of 150 mCi/m², neutropenia between 500 and 1,000/μl lasted 2 days. The platelet nadir, 16,000/μl, occurred on day 19 after RAff. Platelets were fewer than 25,000/μl for 7 days and fewer than 59,000/μl for 24 days (Fig. 2). During the three treatment cycles, patient 3 received a total of six red cell and two platelet transfusions.

**Antitumor Response.** Patients 1 and 2 did not have objective reduction of their tumors. Patient 2 progressed after one treatment. Patient 3 had a clinical antitumor effect, with a decline in markedly reduced bone pain such that she was able to discontinue narcotic analgesics. In addition, a positron emission tomographic scan showed normalization of F-18 fluoroodeoxyglucose uptake in the metastatic liver lesions by the second treatment, and computed tomography of the abdomen following treatment demonstrated 6 months of stabilization of previously rapidly expanding hepatic lesions. Patient 3 received a cumulative lung dose of 3,100 cGy but had no pulmonary symptoms and unchanged pulmonary function tests and blood gases during the 9-month follow-up period. The estimated radiation dose to the tumor was 11,200 cGy.

**Discussion.** 131I-labeled ChL6 is the first RAIT documented to produce objective tumor regression in the majority of patients with metastatic breast cancer and is, therefore, a promising new approach to treatment (5). Although the antibody itself may be therapeutic by stimulation of immune effector cell function (2, 3), studies of the ChL6 monoclonal antibodies alone as therapy in cancer patients demonstrated no clinical response (25). The antibody does facilitate targeting of the isotope to the tumor by creating a vascular leak and enhanced delivery of the radioisotope (5), which may be a critical component leading to the demonstrated therapeutic effects. If sufficient radiation is delivered, RAff is tumoricidal, not only to cells targeted by the radiolabeled antibody, but also to antigen-negative or nontargeted tumor cells within several cell diameters (26).

The present report shows, for the first time, that myelosuppression, the dose-limiting toxicity of RAIT, can be ameliorated by growth factor-mobilized PBPC transfusions (6, 23). Negligible acute or delayed toxicity to other organ systems has been observed, the hematological toxicity has been manageable, and dose escalation continues.

In contrast to other high-dose RAIT studies, we have designed a fractionated, multiple-radioisotope-cycle, intensive radiotherapy approach. In diseases that respond well classically to radioactive antibody treatments, e.g., lymphoma, tumor bulk determines to a significant degree the clinical efficacy of treatment (26). We reasoned that in patients with solid tumors with advanced disease, multiple cycles of treatment would be needed to achieve a meaningful clinical effect. Thus, we designed the trial to establish the maximum tolerated dose in the context of a three-cycle regimen. This fractionated approach could minimize toxicity as well. Our first three patients have received one to three doses of approximately 250 mCi each. Press et al. (27) reported on 19 lymphoma patients receiving single, intensive courses of RAIT with 234–777 mCi 131I. Fifteen of the patients received autologous bone marrow transplants after 2 days with an absolute neutrophil count below 200 (days 14–31 after radioantibody). In this lymphoma study, patients were hospitalized for a prolonged period while they recovered from myelosuppression, whereas our patients were discharged as soon as their whole-body radioactivity satisfied standards approved by Radiation Safety and immediately following their progenitor cell transfusion, approximately 9 days after treatment. They were then followed with serial blood tests and transfusions as needed on an outpatient basis. We have chosen to give the progenitor cell transfusions prophylactically, not waiting for severe or prolonged myelosuppression. The degree of myelosuppression seen in our prior

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**Table 2 Blood and bone marrow radiation doses for patients treated with 150 mCi/m² 131I-labeled ChL6 and PBPC transfusions**

<table>
<thead>
<tr>
<th>Patient</th>
<th>131I-labeled ChL6 (mCi)</th>
<th>Blood dose (cGy)</th>
<th>Marrow dose (cGy)</th>
<th>Blood 131I (μCi/ml) on day of PBPC</th>
<th>Blood dose (cGy) after PBPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Rx* 1</td>
<td>244</td>
<td>341</td>
<td>85</td>
<td>0.39 (9)</td>
<td>1.8</td>
</tr>
<tr>
<td>1-Rx 2</td>
<td>248</td>
<td>242</td>
<td>61</td>
<td>0.03 (7)</td>
<td>0.02</td>
</tr>
<tr>
<td>2-Rx 1</td>
<td>257</td>
<td>418</td>
<td>104</td>
<td>0.56 (7)</td>
<td>3.7</td>
</tr>
<tr>
<td>3-Rx 1</td>
<td>259</td>
<td>492</td>
<td>123</td>
<td>0.47 (9)</td>
<td>5.1</td>
</tr>
<tr>
<td>3-Rx 2</td>
<td>258</td>
<td>563</td>
<td>141</td>
<td>0.73 (8)</td>
<td>14.3</td>
</tr>
<tr>
<td>3-Rx 3</td>
<td>254</td>
<td>406</td>
<td>102</td>
<td>0.59 (8)</td>
<td>8.0</td>
</tr>
</tbody>
</table>

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* Calculated from radiopharmacokinetic curve shown in Fig. 1; Methods standardized by the Society of Nuclear Medicine, Medical Internal Radiation Dose Committee, were then used to calculate the cumulative blood dose in cGy from mCi h (19, 21).
* The radiation dose to the bone marrow was calculated from the blood activity by assuming the concentration of blood in marrow is 25% of marrow mass. Tumor uptake, particularly in bone and/or marrow, could add to the marrow exposure and is not estimated.
* Number of days between 131I-labeled ChL6 treatment and the stem cell infusion is shown in parentheses.
* Cumulative blood dose from the time of stem cell infusion is estimated based on biological clearance calculated from the kinetic curves in Fig. 1 and the 131I decay.
* Rx, rait cycle.
patients treated with 60 mCi/m², we think, warrants prophylactic hematopoietic support at and above the 150-mCi/m² level to reduce myelosuppression best.

Mobilized PBPCs were chosen because they are particularly well suited to ameliorating thrombocytopenia. Using intensive-dose chemotherapy, transfusion of mobilized PBPCs alone or with bone marrow results in significantly more rapid platelet engraftment than is observed in standard autologous bone marrow transplantation (13, 15, 29). As in all autologous transplants, only the use of genetically marked stem cells could document that our patients were engrafted by the infused progenitors and not by "endogenous reconstitution" (30). However, platelet recoveries in our first and third patients were more rapid than those we have observed in prior patients receiving a 2.5-fold lower dose of 131I-labeled ChL6 (5, 6), and the degree of myelosuppression we have observed is less than that reported with similar single 131I-linked monoclonal antibody doses of approximately 250 mCi (28).

The dose of mobilized PBPCs required for adequate engraftment is not known. We chose initially a dose based on MNCs using our own experience and reports of other investigators (24, 31), because it is an instantly available measure, and absolute values are not dependent on differences in laboratory techniques. However, our second patient’s slow recovery from myelosuppression was due, at least in part, to the low progenitor cell content of her infusion despite an adequate MNC dose. Currently, we are using a target CFU-GM dose, greater than 2 × 10³/kg, because it may be more reliable. Because reagents and laboratory techniques vary, this absolute number, although similar to that suggested by other authors (30), may not be applicable to other laboratories. Further refinement of the subset analysis of CD34 may prove to be a more reproducible measure of engrafting potential (32).

The number of PBPCs mobilized by G-CSF in the breast cancer patients described in this report is lower than the number we observed using chemotherapy coupled with G-CSF (23) and lower than that reported for G-CSF mobilization in patients undergoing autologous transplantation with intensive-dose adjuvant chemotherapy for high-risk localized breast cancer (31). The reason for relatively poor stem cell mobilization is likely a combination of prior chemotherapy and the advanced disease state that exists in these Phase I study patients. New growth factors or combinations of growth factors may be more effective in mobilizing cells for these patients (33, 34).

The timing of the progenitor cell infusion was chosen at a point when the residual total-body burden and circulating radioactivity levels would not damage the infused cells. We based this on the measured blood level on the day of infusion (Table 2) and extrapolated data on the possible radiation dose to stem cells, as well as in vitro progenitor cell culture results. At present, we suggest that a blood level of less than 1 μCi/ml as 131I-labeled antibody is a reasonable target prior to stem cell infusion and correlates, in most patients, with a whole-body 131I content of less than 30 mCi, a level that permits a patient to be discharged under the Nuclear Regulatory Commission’s suggested guidelines. The whole-body level we require before progenitor cell infusion probably equates to the criterion used by Press et al. (28) for RAIT patients receiving bone marrow transplantation, i.e., 2 milliCi/h at 1 m.

In this study, up to three individual therapy doses of approximately 250 mCi given at 6–8-week intervals have not produced significant nonhematological toxicity, such as the pulmonary and pericardial toxicity that was observed using similar total doses given on a single occasion (28). Individual differences in normal organ exposure due to tumor burden and location and careful evaluation of nonhematological toxicity will continue as we proceed with dose escalation in this trial. Repetitive use of RAIT with 131I-labeled ChL6 in breast cancer patients has been limited by the development of HAMA, including two of three patients reported here. Treatment with cyclosporin may be responsible for the suppression of HAMA in patient 3 and may enhance the use of repetitive RAIT as we proceed with this study. Once the maximum dose is established, a combination of RAIT with cytotoxic therapies having different and complementary mechanisms of action may enhance further this new clinically useful modality for the treatment of breast cancer.

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References


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