Importance of Timing of Radioimmunotherapy after Granulocyte Colony-Stimulating Factor Administration for Peripheral Blood Stem Cell Harvest

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Abstract

Nine radioimmunotherapy (RAIT)-naive patients with medullary thyroid cancer received high doses of 131I-MN-14 F(ab), anti-carinoembryonic antigen monoclonal antibody (232–486 mCi), five in combination with bone marrow harvest, without prior granulocyte colony stimulating factor (G-CSF) injections (group 1) and the other four using peripheral blood stem cell harvest (PBSC) preceded by G-CSF administration of 10 µg/kg per day for 5 days for stem cell mobilization, 6–8 days before RAIT (group 2). The amount of radioactivity (mCi) given in both groups were similar (312 ± 93 versus 424 ± 65; P = NS). The percent platelet loss at nadir, duration of grade 4 thrombocytopenia, and time to complete recovery (TTCR, measured from the day of treatment), were 83 ± 17%, 2.5 ± 0.7 days, and 45 ± 8 days in group 1, respectively, compared with 88 ± 6%, 3.0 ± 2.6 days, and 50 ± 24 days in group 2 (P = NS), respectively. In contrast, the percent WBC loss at nadir, duration of grade 4 leukopenia, and TTCR of WBCs were 3.0–2.6 days, and 50–24 days in group 2 (P = NS), respectively. The difference in WBC toxicity after RAIT with bone marrow harvest and PBSC is thought to be due to the administration of G-CSF for PBSC harvest before RAIT. Preclinical data of RAIT in mice showed that the time of G-CSF administration before RAIT is critical: increased WBC toxicity was seen in mice given RAIT 3 or 7 days after a 5-day course of G-CSF (81 and 57% WBC loss, respectively) compared with those given no G-CSF or G-CSF 10 or 14 days before RAIT (45–50% WBC loss). In conclusion, our data indicate that the timing of RAIT after the administration of G-CSF for PBSC may influence WBC toxicity and recovery after this treatment and may have important implications on the design of high-dose RAIT trials combined with PBSC.

Introduction

High-dose or myeloablative RAIT3 is increasingly becoming an attractive option for the treatment of patients with relapsed, refractory hematological and nonhematological malignancies (1–5). Usually, either BMH or PBSC is used to collect a sufficient number of hematopoietic stem cells to be given after high-dose therapy for reconstitution of the ablated or severely damaged bone marrow. Although both methods are currently accepted as a source of hematopoietic stem cells, PBSCs are more frequently used due to the relative ease of harvesting without the need of an operative procedure, the lower cost, and the quicker establishment of adequate peripheral blood counts after myeloablative therapy compared with BM transplant. PBSCs are “mobilized” using either cytotoxic chemotherapy or cytokines, such as G-CSF, which is typically administered for 3 days before PBSC harvesting at a dose of 10 µg/kg per day continued for 2–3 days during the harvesting procedure. High-dose RAIT is then given after harvesting of a sufficient number of PBSCs of usually ≥2 × 10⁶ CD34+ cells/kg (6). However, there are no particular guidelines with regard to when high-dose RAIT can be given after such a dose-intensive administration of G-CSF. Interestingly, it is generally recommended that G-CSF administration after conventional chemotherapy should not occur until at least 24 h after the last dose of drug has been given, because the cytokine induces proliferation of the committed myelopoietic stem cells. This promitotic effect of G-CSF could potentially sensitize the marrow compartment, rendering RAIT more toxic. The appropriate interval between G-CSF mobilization and RAIT dosing has not been established. It may be argued that the byproduct of a more therapeutic higher dose of RAIT is myeloablation, and concern about the severity and duration of marrow damage is not relevant in this setting. However, one cannot discount the possibility that the surviving fraction of “endogenous” stem cells plays an important role in the speed

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3 The abbreviations used are: RAIT, radioimmunotherapy; BM, bone marrow; BMH, bone marrow harvest; CBC, complete blood count; CEA, carcinoembryonic antigen; G-CSF, granulocyte colony-stimulating factor; MAb, monoclonal antibody; MTC, medullary thyroid cancer; MTD, maximum tolerated dose; PBSC, peripheral blood stem cell; PBSC, peripheral blood stem cell harvest; PCNA, proliferating cell nuclear antigen; pRBC, peripheral red blood cells; pWBC, peripheral white blood cells; TTCR, time to complete recovery.
and durability of marrow reconstitution after myeloablative therapy. Hence, minimizing permanent damage to the stem cell reserve in the marrow space may be important.

In this report, we describe our clinical observations of the potential influence of G-CSF administration on WBC toxicity and recovery after high-dose RAIT with $^{131}$I-MN-14 (F(ab)$_2$, anti-CEA MAb in patients with MTC who had either BMH without prior G-CSF injections, or PBSCH preceded by G-CSF administration for stem cell mobilization 6–8 days before RAIT. To further corroborate our clinical observations, animal studies on the influence of G-CSF administration before RAIT are also described.

Materials and Methods

Patient Selection and Registration. The patients reported herein were part of a Phase I dose escalation trial with $^{131}$I-MN-14 (F(ab)$_2$, anti-CEA MAb in patients with MTC who had either BMH without prior G-CSF injections, or PBSCH preceded by G-CSF administration for stem cell mobilization 6–8 days before RAIT. To further corroborate our clinical observations, animal studies on the influence of G-CSF administration before RAIT are also described.

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Prior therapy</th>
<th>Time from last therapy to MAb treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>M</td>
<td>Total thyroidectomy with right modified neck and upper mediastinal dissection, left modified neck dissection</td>
<td>5 mo</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>M</td>
<td>Total thyroidectomy with right radical neck dissection, cervical radiation (60.5 Gy), chemotherapy with Adriamycin DTIC, cytoxin, and vincristine (4 cycles)</td>
<td>13 mo</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>M</td>
<td>Total thyroidectomy with right radical neck and mediastinal dissection, cervical and mediastinal radiation (10 Gy), right upper femur radiation (30 Gy)</td>
<td>11 mo</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>M</td>
<td>Total thyroidectomy with right radical neck dissection, cervical radiation (55.8 Gy)</td>
<td>4.25 yr</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>M</td>
<td>Cervical and mediastinal radiation (40 Gy), total thyroidectomy, chemotherapy with Taxol (3 cycles)</td>
<td>1.0 yr</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>F</td>
<td>Right thyroid lobectomy with right modified neck and mediastinal dissection, left thyroid lobectomy</td>
<td>8 mo</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>M</td>
<td>Right thyroid lobectomy with right radical neck dissection, cervical radiation (60 Gy), I-131 therapy (150 mCi)</td>
<td>15.7 yr</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>F</td>
<td>Total thyroidectomy, bilateral modified radical neck dissection, cervical and mediastinal radiation (56 Gy), mediastinal dissection</td>
<td>10.7 yr</td>
</tr>
<tr>
<td>9</td>
<td>51</td>
<td>M</td>
<td>Total thyroidectomy and left functional neck dissection, Marimastat (oral anti-cancer drug) therapy</td>
<td>1.5 mo</td>
</tr>
</tbody>
</table>

and received $\geq 1.5 \times 10^8$ nucleated cells, whereas those receiving PBSCH received $\geq 2 \times 10^8$ CD34+ cells/kg.

All patients were at least 4 weeks beyond any major surgery, radiation, or chemotherapy and must have recovered from any prior treatment-induced toxicity. The patients had a performance status of $\geq 70$ on the Karnofsky scale (Eastern Cooperative Oncology Group score 0–2), a minimal life expectancy of 3 months, no severe anorexia, nausea, or vomiting, normal hepatic and renal function, WBCs $\geq 3,000$ cells/mm$^3$ or a granulocyte count of $\geq 1500$ cells/mm$^3$, and a platelet count of $\geq 100,000$. Subjects were excluded from treatment if they were pregnant or had extensive irradiation to $>25\%$ of their red marrow. All patients were mentally responsible and signed an informed consent. The therapy trial was conducted under an investigational new drug application (BB-IND-5673) from the Food and Drug Administration, and the protocol was approved by the Institutional Review Board of each participating institution.

The radioactive dose administered was based on radiation dose estimates to the critical organs (kidneys, liver, and lung), which was determined by a pretherapy tracer study performed 1 week before the therapy infusion. The tracer infusion consisted of 8 mCi of $^{131}$I-MN-14 (F(ab)$_2$, 1–50 mg of MAb protein, depending on the plasma CEA level; Ref. 1). All antibody infusions were given i.v., proceeding slowly over the first 5 min and then at a more rapid rate to complete the infusion within 15–45 min.

Table 2 lists the therapeutic infusions of $^{131}$I-MN-14 (F(ab)$_2$ in nine patients, including both the critical organ radiation-absorbed dose level and radioactivity amounts given. According to recommendations by the Food and Drug Administration, the starting dose level was set at 900 cGy to the kidneys, with the radiation delivered to the lung or liver not exceeding 1200 cGy at the first dose level. The radiation dose was then to be escalated in 300-cGy increments (1200 cGy to the kidney, not
Table 2  Antibody infusions of 131I-MN-14 F(ab)_2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Injection</th>
<th>wk</th>
<th>mCi</th>
<th>mg</th>
<th>Dose level entered (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>8.0</td>
<td>28.1</td>
<td>900/1200*</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>269.0</td>
<td>23.3</td>
<td>900/1200*</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0</td>
<td>8.0</td>
<td>10.0</td>
<td>900/1200*</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
<td>8.0</td>
<td>0.6</td>
<td>900/1200*</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>1</td>
<td>233.5</td>
<td>17.1</td>
<td>900/1200*</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0</td>
<td>8.0</td>
<td>10.0</td>
<td>900/1200*</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>0</td>
<td>8.0</td>
<td>10.0</td>
<td>900/1200*</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>1</td>
<td>416.0</td>
<td>40.9</td>
<td>900/1200*</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>0</td>
<td>8.0</td>
<td>10.0</td>
<td>900/1200*</td>
</tr>
</tbody>
</table>

*This patient was given a reduced dose of only 656 cGy to the kidneys, because the calculated mCi amount at the 900-cGy level to the kidney exceeded the maximum allowable radioactivity (250 mCi ± 20% of 131I) that could be given at our affiliated hospital at that time (see text).

After a 5-day course of G-CSF (2 μg/day per mouse). Total pWBCs were determined at 3–4-day intervals by collection of 50 μl of blood from the retro-orbital sinus. RBCs were osmotically lysed, and total WBCs were counted in a Becton Dickinson (Mountain View, CA) flow cytometer. The mean ± SD of WBC count in groups of five mice was determined and compared with untreated mice and mice receiving RAIT without previous G-CSF.

In a follow-up study, the percentage of marrow cells positive for PCNA was determined 3, 5, 7, 10, and 14 days after the 5-day course of G-CSF (7–9). Marrow cells were collected, permeabilized, and incubated with FITC-anti-PCNA MAb. Samples were analyzed by FACScan.

Statistical Analysis. Student’s t test was used to compare the WBC and platelet parameters (baseline counts, toxicity grades, etc.) between the various groups of mice or between the two groups of patients treated. P < 0.05 was considered statistically significant.

Results

Difference in Patient Characteristics and MAb Infusions between the Two Groups. No apparent differences were observed between patients who had BMH (group 1) and those who had PBSCH (group 2) before RAIT with regard to age or prior therapy. However, two of the four patients in group 2 were female, whereas all five patients in group 1 were male. The average (mean ± SD) radioactive dose received in group 1 was 312 ± 93 (range, 232–416) mCi compared with 424 ± 65 (range, 337–486) mCi in group 2 (P = NS). The time to reinfusion of BM in group 1 ranged from 7 to 10 (mean ± SD, 8.2 ± 2.3) days, whereas the time to reinfusion of PBSCH in group 2 ranged from 9 to 14 (mean ± SD, 11 ± 2.4) days (P = NS compared with group 1).

Comparison of Platelet and WBC Toxicity between the Two Groups. Table 3 shows the platelet and WBC toxicity in the two groups of patients. There were no statistically significant differences among baseline platelet counts, absolute nadir platelet counts, percent platelet loss or mean platelet toxicity grade at nadir, duration of grade 4, and time to complete recovery (measured from the day of treatment) of platelet toxicity between groups 1 and 2. In contrast, statistically significant differences were found in the absolute WBC nadir counts (P < 0.02), percent WBC loss or mean WBC toxicity grade at nadir (P < 0.02 and 0.03, respectively), duration of grade 4, and time to complete recovery of WBC toxicity (P < 0.03 and 0.05, respectively) between groups 1 and 2. Patients in group 2 who received high-dose RAIT in combination with PBSCH preceded by G-CSF for stem cell mobilization had significantly more WBC toxicity and a longer duration to complete recovery of such toxicity than those in group 1, who had high-dose RAIT in combination with BMH without prior G-CSF injections. These differences were seen despite the lack of any significant difference in the baseline WBC between both groups of patients (mean WBC counts, 6.2 ± 3.4 in group 2 versus 7.1 ± 2.9 in group 1). Similar findings were observed in a separate analysis of the neutrophil counts, with statistically significant differences found in the absolute neutrophil nadir counts, percent neutrophil loss or mean neutrophil toxicity grade at nadir, duration of grade

exceeding 1500 cGy to the lungs and liver, etc.), until the MTD has been determined. The first patient planned to receive the 900-cGy dose level to the kidneys was actually treated at a lower dose of only 656 cGy, because the calculated mCi dose at the 900-cGy level to the kidney exceeded the maximum allowable radioactivity (250 mCi ± 20% of 131I) that could be given at our affiliated hospital at that time (see text).

Evaluation of Hematological and Nonhematological Toxicity. Toxicity was graded according to the National Cancer Institute common toxicity criteria. All patients were followed for hematological toxicity by monitoring CBC weekly. If a grade 2 leukopenia or thrombocytopenia occurred, monitoring was increased to twice per week with CBC performed three times per week in the event of grade 3 or 4 myelotoxicity. CBC was monitored until the WBC toxicity and platelet parameters were reached and a stable blood count was documented for at least 2 consecutive weeks. Organ toxicity was assessed at 4, 8, 12, and 24 weeks after therapy. Thereafter, follow-up tests were planned to be performed every 6 months, whenever possible, for up to 5 years, to monitor any chronic toxicity from treatment. Detailed results with regard to monitoring hematological and nonhematological toxicity and the toxicity observed after therapy are described elsewhere (1).

Mice Studies. BALB/c female mice (20 g in weight) were given a dose of 240 μCi of 131I-MN-14 3, 7, 10, or 14 days after a 5-day course of G-CSF (2 μg/day per mouse). Total pWBCs were determined at 3–4-day intervals by collection of 50 μl of blood from the retro-orbital sinus. RBCs were osmotically lysed, and total WBCs were counted in a Becton Dickinson (Mountain View, CA) flow cytometer. The mean ± SD of WBC count in groups of five mice was determined and compared with untreated mice and mice receiving RAIT without previous G-CSF.

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Timing of RAIT after G-CSF Administration

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4, and time to complete recovery of neutropenia between groups 1 and 2 (Table 3). Here again, no significant differences were found in the baseline neutrophil counts between both groups of patients.

Animal Experiments in Support of the Clinical Findings. To investigate experimentally the influence of G-CSF administration before RAIT on WBC toxicity, mice were given RAIT with 240 μCi of 131I-MN-14 IgG (i.e., ~90% of the "nonmyeloablative" MTD in mice) either without the preadministration of G-CSF or 3, 7, 10, or 14 days after a 5-day course of G-CSF (2 μg/day per mouse). Fig. 1 shows the results of these experiments. Mice given RAIT alone experienced a 45–50% loss in pWBC between days 7 and 14 after therapy. Those given RAIT 3 days after G-CSF mobilization had an 81% loss in pWBC 7 days after RAIT. A 7-day spacing resulted in a 57% loss in pWBC. When the spacing between G-CSF and RAIT was 10 or 14 days, no additional toxicity above that observed with RAIT alone occurred. The additional WBC toxicity observed with the 3- or 7-day interval between G-CSF and RAIT could be explained by hyperproliferative marrow activity after G-CSF. Using PCNA as a marker for proliferative activity, we observed an increase in percentage of marrow cells that were PCNA positive from 58.2 ± 25.0 (n = 9) to 92.2 ± 1.3 (n = 4) on day 3, 92.4 ± 1.7 (n = 4) on day 5, and 94.1 ± 3.8 on day 7 (P < 0.05 on days 3 and 5; P < 0.02 on day 7). By day 10 after G-CSF, the percentage of PCNA-positive marrow cells had returned to 68.3 ± 17.1 (n = 4; P = NS).

Discussion

This report presents a clinical observation on a difference in WBC, but not platelet, toxicity between BM and PBSC rescue after high-dose RAIT with 131I-MN-14 F(ab)_2 in patients with MTC. Although this difference was observed in relatively small groups of patients who had either BMH or PBSCH in preparation for high-dose RAIT, it was quite striking, particularly when one considers the differences in the duration of grade 4 leukopenia and neutropenia and time to complete recovery of WBC or neutrophil counts between both groups. The conditions for reinfusing BM or PBSCs were similar, and the number of CD34+ cells was comparable in both groups. Although the mean radioactive dose given in the group of patients who had PBSCH (group 2) was somewhat higher than that in patients who had the BMH (group 1), and, therefore, the mean time to reinfusion of stem cells was longer in this group, these differences were not statistically significant. Moreover, clearly lower WBC toxicity was seen in patients in group 1 who received similar radioactive doses and, hence, had a time to reinfusion of stem cells similar to that of patients in group 2. It is also unlikely that these differences would have made such a dramatic impact in the case of WBC but not platelet toxicity. In fact, our previous studies, albeit using nonmyeloablative doses of 131I-MN-14 F(ab)_2 in MTC patients, have shown a similar correlation between the radioactive dose given or red marrow dose delivered and both platelet and WBC toxicity (10).

Our investigations with regard to the reason for increased WBC but not platelet toxicity after PBSCH compared with BMH has led us to suspect that a major component of the procedure used for harvesting PBSCs, but not BM (namely, the administration of a relatively high dose of G-CSF of 10 μg/kg per day for 5 days), may be responsible for this finding. The administration of high-dose RAIT within ~1 week after this dose-intensive G-CSF therapy may be occurring at a time when the endogenous granulocyte precursors could be quite hyperproliferative, and, hence, are more sensitive to radiation, although exogenous G-CSF has already declined to pretreatment levels. It is important to note here that normal WBC or neutrophil counts in the peripheral blood within a few days after the last administration of G-CSF (i.e., before RAIT) may not be synonymous with the cessation of proliferative activity of granulocyte precursors in the bone marrow. In fact, it is conceivable that such activity may still be ongoing to "fill in" certain pools of "late" granulocyte precursors at the various steps of granulopoiesis, which could have been largely depleted through differentiation to peripheral granulocytes during the dose-intensive G-CSF administration. However, more studies are needed to prove this supposition and to elucidate whether endogenous cytokines other than G-CSF may be involved in such a process.

The experimental data obtained in mice support our suspicion that prior administration of G-CSF is probably responsible for the increased WBC toxicity after RAIT. The timing of G-CSF administration before RAIT was shown to be critical; increased WBC toxicity was seen in mice given RAIT 3 or 7 days after G-CSF administration before RAIT in mice.
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G-CSF Spacing

Days Post RAIT Treatment

Fig. 1 Total WBCs in BALB/c mice after RAIT. Left panel, mice received 5 days of G-CSF (2 µg/day) with spacing of 3 days (▼) or 7 days before RAIT (▼) compared with mice given RAIT alone without G-CSF (●) and untreated mice (●). Mice given RAIT alone experienced a 45–50% loss in pWBC between days 7 and 14 after therapy. Those given RAIT 3 days after G-CSF mobilization had an 81% loss in pWBC 7 days after RAIT. Recovery showed an erratic profile in which peaks (days 24, 31, and 42) and dips (days 28, 35, and 38) were observed in the pWBC profile. A 7-day spacing resulted in a 57% loss in pWBC. Right panel, 10-day (▼) and 14-day (▼) spacing between G-CSF and RAIT compared with mice given RAIT alone without G-CSF (●) and untreated mice (●). No additional toxicity above that observed with RAIT alone occurred. 0, day of RAIT.

days after a 5-day course of G-CSF compared with those given no or G-CSF 10 or 14 days before RAIT. The more severe WBC toxicity with the 3- or 7-day compared with a 10-day spacing correlated with differences in PCNA expression at the time of RAIT, suggesting that the hyperproliferation of the committed myelopoietic stem cells and, hence, their increased radiosensitivity are probably responsible for the increased WBC toxicity observed.

Although it is not absolutely clear whether the 10- or 14-day time span between G-CSF administration and RAIT shown to be safe in mice will be sufficient in humans, we have instituted an “obligatory” interval of at least 2 weeks between the last day of G-CSF and initiation of RAIT. This period appears reasonable, and it is likely to be sufficient to at least ameliorate any potential residual effect of prior G-CSF on WBC toxicity. Unfortunately, due to logistical reasons, the treatment of the last two patients (not included in this report) given high-dose 131I-MN-14 F(ab)2 combined with PBSCH was delayed by >2 weeks (18 and 41 days) after the last day of G-CSF administration, and, hence, the adequacy of the 2-week interval could not be accurately assessed in this trial. However, our recent experience in MTC patients given high doses of 90Y-humanized MN-14 IgG combined with PBSCH with doses up to 50 mCi/m2 (range, 20–50 mCi/m2), even combined with a single 60-mg/m2 dose of doxorubicin given 24 h after RAIT, suggests that this 2-week interval may be adequate. Grade 4 leukopenia and neutropenia has been transient (i.e., <1 week), and recovery of pWBC and neutrophil counts to baseline has occurred within 7 weeks in all patients.

In conclusion, our data indicate that the administration of G-CSF for stem cell mobilization before high-dose RAIT can influence WBC toxicity and recovery after therapy. The spacing between G-CSF and RAIT is also important. This could have implications on the design of high-dose RAIT trials combined with PBSCH with respect to the timing of such therapy in relation to G-CSF administration.

References


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