Failure of Recombinant Stem Cell Factor to Enhance Engraftment of L-Leucyl-L-Leucine Methyl Ester Treated Canine Marrow After Irradiation

To the Editor:

T-cell depletion from marrow has been used to reduce the risk of graft-versus-host disease (GVHD) in patients undergoing allogeneic marrow transplantation; however, this was accompanied at the price of an increased incidence of graft failure. L-Leucyl-L-leucine methyl ester (Leu-Leu-OMe), a lysosomotropic compound, has been shown to selectively deplete cytolytic T cells and their precursors, natural killer cells, and monocytes, but not helper T cells from peripheral blood and marrow. In dogs, Leu-Leu-OMe treatment of marrow resulted in a substantial reduction of progenitor cell colonies even when accessory cells were added back to the culture. Pecora et al. showed a reduction of committed progenitors when human marrow was incubated with Leu-Leu-OMe. Although Leu-Leu-OMe treatment did not interfere with engraftment of autologous marrow after conditioning with 9.2 Gy total body irradiation (TBI), transplantation of Leu-Leu-OMe treated marrow from dog leukocyte antigen (DLA)-identical littermates resulted in graft failure in most dogs. Studies in mice have suggested improved engraftment of T-cell–depleted histoincompatible marrow after sublethal TBI by treating donor marrow with recombinant murine granulocyte-macrophage colony-stimulating factor (GM-CSF) and by administration of recombinant human interleukin-1 (IL-1). We failed to show graft enhancement in mice have suggested improved engraftment of T-cell-depleted marrow when accessory cells were added back to the culture. Here we investigated whether posttransplant treatment with rc-SCF enhances engraftment of “T-depleted” Leu-Leu-OMe treated marrow from DLA-identical littermates.

Selection of DLA-identical littermate pairs for transplantation, preparation, and in vitro treatment of marrow with Leu-Leu-OMe have been described. Briefly, aspirated marrow was diluted in medium (Waymouth’s MB751/1, Fred Hutchinson Cancer Research Center media shared facility) and centrifuged to obtain buffy coat medium (Waymouth’s MB751/1, Fred Hutchinson Cancer Research Center). Aspirated marrow was incubated with 1,000 pmol/L Leu-Leu-OMe at a concentration of 20 × 10^6 cells/mL for 15 minutes at room temperature. After recipients were given 9.2 Gy TBI, Leu-Leu-OMe treated donor marrow was infused. Rec-SCF, 100 ng/kg BID subcutaneously was given until day 21 or until engraftment (absolute granulocyte count greater than 1,500/μL). Results are shown in Table 1 and compared to those in dogs given unmodified (n = 7) or Leu-Leu-OMe treated (n = 8) marrow and no rc-SCF infusions. All seven dogs given unmodified marrow engrafted compared to three of eight given Leu-Leu-OMe treated marrow and no rc-SCF (P = .01). Five of 10 dogs given Leu-Leu-OMe treated marrow and postgrafting rc-SCF engrafted, a result that was not significantly different from that in dogs not given rc-SCF (P = .64).

In conclusion, the study confirmed previous observations of an increased risk of graft failure with Leu-Leu-OMe incubation of the grafted marrow. Treatment of recipients with rc-SCF failed to significantly reduce the high risk of graft failure.

ACKNOWLEDGEMENT

Supported by grants DK42716, CA31787, CA15704, and CA18221 awarded by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Cancer Institute, National Institutes of Health, Department of Health and Human Services (Bethesda, MD). Laboratory support was also available through a grant from the Joseph Steiner Krebsstiftung, Bern, Switzerland, awarded to one of the investigators (R.S.). Rec-SCF was kindly provided by Dr Ian McNiece, Amgen, Inc, (Thousand Oaks, CA).

Table 1. Dogs Given 9.2 Gy TBI and Marrow Grafts from DLA-Identical Littermates

<table>
<thead>
<tr>
<th>Leu-Leu-OMe Treatment</th>
<th>Median No. of Donor Cells (×10^6/kg)</th>
<th>Rec-SCF</th>
<th>Studied</th>
<th>Acute GVHD</th>
<th>Surviving</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>1.7</td>
<td>No.</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Yes.</td>
<td>1.9</td>
<td>Yes.</td>
<td>8</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

P value compares proportion of dogs failing to engraft. 

REFERENCES

5. Blazar BR, Thiele DL, Valler DA: Pretreatment of murine donor grafts with L-leucyl-L-leucine methyl ester treatment of canine marrow and peripheral blood cells: Inhibi-

From www.bloodjournal.org by guest on November 16, 2017. For personal use only.
tion of proliferative responses with maintenance of the capacity for autologous marrow engraftment. Transplantation 46:655, 1988
Failure of recombinant stem cell factor to enhance engraftment of L-leucyl-L-leucine methyl ester treated canine marrow after irradiation [letter]

HP Kiem, W Leisenring, R Raff, HJ Deeg, FG Schuening, FR Appelbaum and R Storb

Updated information and services can be found at:
http://www.bloodjournal.org/content/88/5/1896.citation.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml