CYTOKINE PRIMING OF ACUTE MYELOID LEUKEMIA MAY PRODUCE A PULMONARY SYNDROME WHEN ASSOCIATED WITH A RAPID INCREASE IN PERIPHERAL BLOOD MYELOBLASTS

To the Editor:

The use of granulocyte-macrophage colony-stimulating factor (GM-CSF) administered before or in combination with chemotherapy represents a new strategy in the treatment of acute myeloid leukemia (AML). This cytokine is a known growth promoter of leukemic colony-forming cells and can recruit quiescent cells into cycle, possibly increasing their chemosensitivity. However, in vivo GM-CSF priming for 18 to 48 hours has been associated in some patients with rapid increases in myeloblast counts in peripheral blood. We have examined the safety and proliferative effects of GM-CSF priming for 72 hours in 16 patients with relapsed or refractory AML. The median age was 53 years (range 20 to 72) and median duration of prior remission in the relapsed patients was 5.4 months (range 1.3 to 33 months). Previous chemotherapy in the relapsed AML patients was conventional cytosine arabinoside-daunorubicin ('7 plus 3') or the same combined with etoposide 75 mg/m²/d for 7 days. GM-CSF (synthesized in Escherichia coli; Schering-Plough, NJ) was administered at a dose of 5 µg/kg/d by subcutaneous injection for 3 days before commencing chemotherapy. No patients developed dyspnea with the first dose of GM-CSF. In patients 6 and 13 this "priming period" was shortened to 2 days because the peripheral blood white cell count exceeded 30 × 10⁹/L by the second day. GM-CSF was continued for the first 4 days of standard chemotherapy with cytosine arabinoside 100 mg/m²/d continuous intravenous (IV) infusion for 7 days plus daunorubicin 50 mg/m²/d IV on days 1 through 3.

Serial bone marrows confirmed that GM-CSF priming produced a rapid increase in myeloblasts in peripheral blood. For patient 6 (Table 1), the peripheral blast cell count increased from 3.6 × 10⁹/L to 26.4 × 10⁹/L over the first 72 hours. Similarly, the bone marrow labeling index increased from 9.9% to 12.9%.

Table 1. Effect of GM-CSF Priming on Peripheral Blood Blast Count and Marrow Labeling Index

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>FAB</th>
<th>Total WCC (x10⁹/L)</th>
<th>Blast Cells (x10⁹/L)</th>
<th>Bone Marrow Labeling Index (%)</th>
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<tbody>
<tr>
<td></td>
<td>0 h</td>
<td>72 h</td>
<td>0 h</td>
<td>72 h</td>
</tr>
<tr>
<td>1</td>
<td>M3</td>
<td>3.1</td>
<td>4.7</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>M4</td>
<td>3.6</td>
<td>26.4</td>
<td>0.6</td>
</tr>
<tr>
<td>3</td>
<td>M4Eo</td>
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<td>3.1</td>
<td>0.4</td>
</tr>
<tr>
<td>4</td>
<td>M1</td>
<td>1.3</td>
<td>2.7</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>M4</td>
<td>1.6</td>
<td>11.9</td>
<td>0.2</td>
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<td>32.3*</td>
<td>20.0</td>
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<td>1.9</td>
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<td>M7</td>
<td>6.3</td>
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</tbody>
</table>

* Values at 48 hours when chemotherapy began.
† Patient with relapse in skin.
significant increases (ie, >1%) in \(^3\text{H}\)-thymidine labeling index of marrow myeloblasts in 8 of 11 patients (Table 1). It is of note that there was little or no change in the labeling index in patients 13 and 15 although GM-CSF priming increased peripheral blood blasts by 12.8 and 15.6 \(\times 10^9/L\), respectively. Thus, GM-CSF in some patients may promote the egress ("release") of bone marrow cells into blood, an effect that has also been described in normal subjects.\(^7,8\)

There were four induction deaths, three of which resulted from a pulmonary syndrome that developed within the first 4 days of chemotherapy. All three early deaths were associated with a substantial increase in blast count of between 15.6 and \(27 \times 10^9/L\) during the GM-CSF priming period. Patient 7 developed respiratory failure and pulmonary infiltrates on day 2 followed by cerebral hemorrhage in the setting of florid disseminated intravascular coagulation. Autopsy showed pulmonary edema and intra-alveolar hemorrhages and edema as well as multiple hemorrhages throughout the brain. Patients 11 and 15 developed dyspnea, fever, and pulmonary infiltrates on chest x-ray which progressed despite antibiotics. Neutrophil counts at the onset of the pulmonary syndrome were 0.2 to 1.7 \(\times 10^9/L\) and platelets were 9 to 25 \(\times 10^9/L\). These three patients were ages 33, 64, and 62 years and had no preexisting cardiac or pulmonary disease except for mild mitral incompetence in patient 15. It is possible that pulmonary toxicity associated with the abrupt hyperleucocytosis contributed to the early fatal outcome in these three patients because a similar pulmonary syndrome has been described after rapid increases in peripheral blood blast counts of 15 to 30 \(\times 10^9/L\) in patients with acute promyelocytic leukemia receiving all-trans retinoic acid.\(^9,10\)

Cytokine priming should be given with great caution to patients with AML because the sudden release of myeloblasts from the bone marrow may be associated with serious pulmonary toxicity.

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REFERENCES

Cytokine priming of acute myeloid leukemia may produce a pulmonary syndrome when associated with a rapid increase in peripheral blood myeloblasts [letter]

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