Autologous Stem Cell Transplantation: Release of Early and Late Acting Growth Factors Relates With Hematopoietic Ablation and Recovery

By Ugo Tasta, Robert Martucci, Sergio Rutella, Giovanni Scambia, Simona Sica, P. Benedetti Panici, Luca Pierelli, Giacomo Menichella, Giuseppe Leone, Salvatore Mancuso, and Cesare Peschle

We have monitored the serum concentrations of hematopoietic growth factors (HGFs; ie, stem cell factor [SCF], leukemia inhibitory factor [LIF], interleukin-3 [IL-3], IL-6, IL-8, and granulocyte colony-stimulating factor [G-CSF]) in 15 lymphoma/leukemia and 6 ovarian cancer patients undergoing autologous bone marrow (BM) or peripheral blood (PB) stem cell transplantation (SCT). Thus, the analysis was performed during and after high-dose chemotherapy (from day −6 to day −1), at the time of SCT (day 0), and thereafter (through day +17). Despite the heterogeneity of these patients and their conditioning regimens, a consistent kinetic pattern was observed for all analyzed cytokines. Particularly, (1) SCF serum concentration did not significantly fluctuate. (2) High levels of LIF (~250 to 450 pg/mL) before chemotherapy rapidly declined to markedly lower concentrations (~10 ng/mL) starting from day −1 through day +17; (3) conversely, IL-3 level was low before treatment, sharply increased during chemotherapy, and rapidly returned to baseline level after SCT. Hypothetically, the sharp LIF decrease and IL-3 increase during chemotherapy may underlie the induction of stem cell cycling and differentiation caused by hematopoietic ablation. Furthermore, (4) IL-6 concentration was low before and immediately after chemotherapy, but increased starting from day +5, peaked at day +6 through 9, and then declined to baseline level from day +10 onward; (5) a strictly similar pattern was consistently observed for both G-CSF and IL-8 levels, in agreement with our previous studies. It is relevant that peak IL-6, G-CSF, and IL-8 concentrations were directly correlated to peak neutrophil numbers in the recovery phase, thus suggesting an important role for these cytokines in granulocyte rescue; in line with this interpretation, hematologic patients undergoing PBSCT (10 of 15) exhibited higher peaks of IL-6, G-CSF, and IL-8 and a more pronounced increase of neutrophil/platelet number than did hematologic cases undergoing BMST (5 of 15). Altogether, these studies indicate a coordinate pattern of cytokine release during hematopoietic ablation/recovery after chemotherapy and autologous SCT; the fluctuations of IL-6 and IL-3 levels during chemotherapy are seemingly related to stem cell recruitment, whereas the post-SCT increase of IL-6, G-CSF, and IL-8 may underline the neutrophil recovery.

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MATERIALS AND METHODS

Patients. Fifteen patients with hematologic malignancies were treated in the Department of Hematology, Catholic University (Rome, Italy) (Table 1). Autografting was performed at either complete remission or a stage of “minimal residual disease.” Eight patients had non-Hodgkin’s malignant lymphoma, 5 acute myeloid leukemia (AML), and 2 Hodgkin’s lymphoma. Ten patients received PBSCT and 5 received BMST. The BuCy2 protocol was used as conditioning regimen, as reported elsewhere. Briefly, patients were treated with busulfan (4 mg/d/kg of body weight) on days −6 through −3, with cyclophosphamide (60 mg/d/kg of body weight) on days −2 and −1 and then transplanted with autologous BM or PBSCs on day 0. The methodology for PBSCT harvesting has been described.

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Six patients with untreated ovarian cancer eligible for chemotherapy were treated in the Department of Gynecology and Obstetrics, Catholic University (Table 2). All patients had histologic evidence of stage III or IV epithelial ovarian cancer (according to the International Federation of Gynecology and Obstetrics) and a residual tumor of greater than 0.5 cm after cytoreductive surgery. The chemotherapy regimens and methods for harvesting PBSCs have been described. Briefly, patients received cisplatin (100 mg/m², intravenously [IV]) on day -4, and carboplatin (1,800 mg/m², IV) as continuous infusion over 24 hours on day -3; autologous PBSCs were administered on day 0.

Written informed consent was obtained from each patient, and the study has been approved by the Hospital Human Subjects Investigational Review Board (Catholic University).

None of these patients received growth factor therapy after chemotherapy and during the first month after chemotherapy and SCT. Samples taken after SCT correspond to days +1 through +20. The day-0 sample was drawn in the morning before SCT. Samples taken after SCT correspond to days +1 through +20 (only a limited number of samples were available at days +18 through 20). Blood was drawn on EDTA and plasma was separated by centrifugation (15 minutes at 4,000 rpm) shortly after collection, aliquoted, and stored at -80°C until used. Early morning (7 to 8 AM) samples were always used for cytokine evaluation.

Cytokine assays. Serum concentrations of HGFs (SCF, LIF, IL-3, IL-6, G-CSF, and IL-8) were evaluated by sensitive and specific immunoassays (R&D System-British Biotechnology, Cowly, Oxford, UK).

The detection thresholds are 5 pg/mL for SCF, LIF, and G-CSF; 10 pg/mL for IL-3 and IL-8; and 0.3 pg/mL for IL-6. In addition to the controls performed by the supplier, further controls were performed to determine assay specificity (ie, absence of cross-reactivity for each assay against a large panel of recombinant cytokines/proteins). Each cytokine level represents the mean value observed in three separate determinations. The intra-assay variability for the various cytokine determinations was 5% to 10%. The interassay variability of plasma cytokine immunoenzymatic analysis was 5% to 20%, using an identical immunoassay batch for each cytokine.

Statistical methods. Statistical comparisons were performed using the Mann Whitney U test for nonpaired groups, Wilcoxon test for paired analysis, or the binomial proportion test. Statistical significance was defined as P < .05.

RESULTS

Clinical data. Cytokine serum concentrations were evaluated in 15 leukemia/lymphoma and 6 ovarian cancer patients. The 15 hematologic patients (Table 1) underwent an identical chemotherapy regimen (BuCy2 protocol) before transplantation: 10 patients received transplants of autologous PBSCs and the remaining 5 of BMSCs. The 6 ovarian cancer patients (Table 2) received high-dose chemotherapy followed by PBSCT.

Table 1. Hematologic Patients: Main Clinical Features, Infused Cells, and PBMC Recovery

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (X/;ke)</th>
<th>Diagnosis</th>
<th>Origin</th>
<th>MNC (&gt;10⁹/kg)</th>
<th>CFU-GM (&gt;10⁹/kg)</th>
<th>WBC &gt;1 x 10⁹/L (d)</th>
<th>PMNC &gt;0.5 x 10⁹/L (d)</th>
<th>Platelets &gt;50 x 10⁹/L (d)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>NHL</td>
<td>PB</td>
<td>1.17</td>
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<td>10</td>
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</tr>
<tr>
<td>3</td>
<td>38</td>
<td>AML</td>
<td>BM</td>
<td>1.3</td>
<td>67.2</td>
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<td>11</td>
</tr>
<tr>
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<td>38</td>
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<td>BM</td>
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<td>11</td>
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<tr>
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<td>46.1</td>
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</table>

Abbreviations: NR, not reached; MNC, mononuclear cells; WBC, white blood cells; NHL, HL, non-Hodgkin's, Hodgkin's lymphoma.

Table 2. Ovarian Cancer Patients: Main Clinical Features, Infused Cells, and PBMC Recovery

<table>
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<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Infused Cells</th>
<th>PMNC Recovery</th>
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<tbody>
<tr>
<td></td>
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<td>MNC (&gt;10⁹/kg)</td>
<td>CFU-GM (&gt;10⁹/kg)</td>
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<tr>
<td>1</td>
<td>35</td>
<td>1.17</td>
<td>40.3</td>
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<td>0.58</td>
<td>46.1</td>
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PBSC or BMSC infusion data and kinetics of PB granulocyte and platelet recovery after high-dose chemotherapy and SCT are summarized in Tables 1 and 2. Hematopoietic recovery was prompt and sustained in the 10 PBSCT hematologic patients (Table 1); the 5 BMSC patients showed delayed recovery of neutrophils (patients no. 11, 12, and 13) and particularly of platelets (patients no. 3, 10, 11, 12, and 13; Table 1). Granulocyte and platelet recovery was slightly more rapid in the ovarian cancer patients than in the leukemia/lymphoma cases undergoing PBSCT (Table 2). Neutropenic fever was reported for most patients (average number of days with >38°C, 3.5; range, 0 to 6), but only 5 cases presented clinically and microbiologically documented infectious episodes (the cytokine release pattern in these 5 patients was similar to that observed in the remaining cases). All patients survived at least 100 days after transplantation.

**Kinetics of SCF, LIF, IL-3, IL-6, G-CSF, and IL-8 serum levels.** SCF, LIF, IL-3, IL-6, G-CSF, and IL-8 plasma levels were evaluated in all 21 patients before and after high-dose chemotherapy/SCT.

SCF, LIF, IL-3, and IL-6 serum concentrations were evaluated in a first set of experiments. SCF, a cytokine present at relatively high levels in the serum of normal subjects,29 exhibited only slight fluctuations before and after SCT (Fig 1, top). A moderate increase at day 0 was present in 8 of 15 hematologic patients (results not shown). Among hematologic patients, AML BMSCT and lymphoma PBSCT showed similar LIF levels (P = .77). Furthermore, no significant difference was found between hematologic patients undergoing PBSCT versus ovarian cancer patients (P = .80).

Plasma LIF concentrations exhibited a unique pattern (Fig 1, middle). Before chemotherapy LIF was present at high level (mean values, 656, 460, and 218 pg/mL in hematologic BMSCT, hematologic PBSCT, and gynecologic patients, respectively; normal LIF serum values are <30 pg/mL; results not shown), then LIF values rapidly and gradually declined until day −2 (~10 pg/mL) and stabilized thereafter. Nineteen of the 21 patients showed a marked decrease of LIF concentration (data not shown). No significant difference was found between hematologic PBSCT versus ovarian cancer patients (P = .79) or among hematologic patients undergoing either BMSCT or PBSCT (P = .88).

IL-3 serum levels were low before transplantation, but markedly increased during ablative chemotherapy, peaked on day 0, and then progressively returned to baseline levels after SCT (Fig 1, bottom). The initial IL-3 increase was observed for 20 of 21 patients (data not shown). Plasma IL-3 levels were not significantly different in hematologic PBSCT versus ovarian cancer patients (P = .90) or among hematologic patients undergoing either BMSCT or PBSCT (P = .77).

Serum IL-6 levels were low before and during chemotherapy (day −6 to 0) and in the first days after SCT (Fig 2, top). A sharp increase was observed at day +6. All 21 patients exhibited this marked increase (data not shown). In hematologic PBSCT cases, markedly elevated levels of IL-6 (ie, >50 pg/mL) were observed only at day +6; in ovarian cancer, high levels were present from day +6 to +9. IL-6 levels were significantly different in hematologic PBSCT versus ovarian cancer patients (P = .02). Furthermore, among hematologic patients, those undergoing PBSCT exhibited higher IL-6 levels than those undergoing BMSC (P = .05).

We also evaluated the plasma concentrations of G-CSF and IL-8. In agreement with our previous report,31 all patients exhibited a pronounced increase of both G-CSF and IL-8 levels at day +6 (Fig 2, middle and bottom), ie, 5 to 6 days before neutrophil recovery. As for IL-6, the G-CSF increase is more prolonged in the ovarian cancer than in the lymphoma PBSCT group (day +4 to +11 values, P = .003): in the latter patients, G-CSF peaks occurred at day +6, whereas in the former group, G-CSF peaked at days +6 to +9. However, in these two groups of PBSCT patients, IL-8 exhibited similar kinetics and values (P = .89). Furthermore, among hematologic patients, those undergoing PBSCT showed significantly higher levels of both G-CSF (P = .05) and IL-8 (P = .027) than those undergoing BMSC.

**Correlation between cytokine production, neutrophil/platelet decrease, and recovery.** We first evaluated a possi-
EARLY AND LATE ACTING CYTOKINES

Fig 2. Kinetics of IL-6, G-CSF, and IL-8 serum concentrations in 10 lymphoma, 5 leukemia, and 6 ovarian cancer patients undergoing SCT after high-dose chemotherapy (see legend to Fig 1). Mean ± SEM values are presented.

Fig 3. Neutrophil and platelet recovery in 10 lymphoma, 5 leukemia, and 6 ovarian cancer patients undergoing high-dose chemotherapy and SCT. Mean ± SEM values are presented.

PBSCT hematologic patients in both platelet (P = .004) and neutrophil recovery (P = .003).

In the two groups of patients undergoing PBSCT, peak levels of IL-6, G-CSF, and IL-8 (but not of IL-3) strictly correlated with peak numbers of neutrophils and platelets after SCT (except for the lack of significant correlation between G-CSF and platelet values in gynecologic cases; Table 4).

Hematologic patients undergoing BMSCT exhibited a very delayed platelet recovery and an incomplete neutrophil recovery; the latter parameter did not correlate with the cytokine peaks (Table 4).

DISCUSSION

Hematopoiesis is a multistep cell proliferation and differentiation process that is sustained by a pool of hematopoietic SCs (HSCs). HSCs can self-renew and differentiate into hematopoietic progenitor cells (HPCs), which are committed to a specific lineage(s). HPCs are functionally defined as colony-forming units (CFUs) or burst-forming units (BFUs), ie, HPCs of the erythroid (BFU-E, CFU-E), the granulomonocytic (CFU-GM, -G, -M), and the megakaryocytic (BFU-MK, CFU-MK) series, as well as multipotent CFU for the GM, E, and MK lineages (CFU-GEMM). In BM, HPCs differentiate into morphologically recognizable precursors that mature to terminal elements circulating in PB.

HGFs control the survival, proliferation, and differentia-
tion of stem and/or progenitor cells; in addition, they affect a variety of functional activities of differentiating/terminal cells.\textsuperscript{35-39} HGFs exert either a multilineage or unilineage stimulus according to a hierarchical pattern.\textsuperscript{27-39} IL-3 acts on the early progenitor pool, ie, CFU-GEMM, BFU-E, CFU-GM, and early megakaryocytic progenitors. GM-CSF exerts similar effects but possibly stimulates progenitors at a more distal differentiation stage. Erythropoietin, G-CSF, IL-5, and M-CSF are largely specific for end-stage HPCs of the erythroid, granulocytic, eosinophilic, and monocytic lineages, respectively.\textsuperscript{30-42}

In enriched HPC culture, diverse GFs exert little activity themselves, but potentiate the stimulatory activity of other HGFs, particularly IL-3. These early acting GFs include SCF,\textsuperscript{43} IL-6,\textsuperscript{44} IL-11,\textsuperscript{45} basic fibroblast GF,\textsuperscript{46} and LIF.\textsuperscript{47,48} A defect of SCF underlies the HSC defect in WW or eagles, respectively.\textsuperscript{49} SCF is one of the HSC GFs?~ In addition to SCF, another recently identified HGF, FLT3 ligand, seemingly acts on primitive hematopoietic cells.\textsuperscript{50}

The evaluation of cytokine activity in BM or other tissue sites is technically difficult. However, the measurement of circulating HGFs is simple to perform and secreted they affect a variety of functional activities of differentiating/terminal cells.\textsuperscript{35-39} IL-3 acts on the early progenitor pool, ie, CFU-GEMM, BFU-E, CFU-GM, and early megakaryocytic progenitors. GM-CSF exerts similar effects but possibly stimulates progenitors at a more distal differentiation stage. Erythropoietin, G-CSF, IL-5, and M-CSF are largely specific for end-stage HPCs of the erythroid, granulocytic, eosinophilic, and monocytic lineages, respectively.\textsuperscript{30-42}

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Although the relationship between the G-CSF/IL-8 increase and the platelet rescue needs further analysis, the role of IL-6 in megakaryocytopoiesis is well established. In vitro, this cytokine stimulates megakaryocyte maturation, as shown by increased megakaryocyte size and development of polyploidy.\(^{52,55}\) Furthermore, in vivo studies in rodents\(^ {46}\) and primates\(^ {45}\) have shown that injection of recombinant human IL-6 leads to a twofold to eightfold elevation of platelet counts. Finally, serum IL-6 levels are significantly elevated in patients with reactive thrombocytosis.\(^ {96}\) These findings have led to the speculation that IL-6 and thrombopoietin are identical proteins.\(^ {97}\) The present study supports the hypothesis that IL-6 plays an important role in megakaryocytopoiesis during hematopoietic recovery after ablative therapy and SCT.

In conclusion, this study shows a coordinate pattern of cytokine release during hematopoietic ablation/recuperation after chemotherapy and autologous SCT; the fluctuations of LIF and IL-3 levels during chemotherapy are seemingly related to stem cell recruitment, whereas the post-SCT increase of IL-6, G-CSF, and IL-8 may underlie the neutrophil recovery.

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