Granulocyte Colony-Stimulating Factor–Primed Donor Lymphocyte Infusion after Salvage Chemotherapy for Treatment of Relapsed Acute Leukemia after Allogeneic Stem Cell Transplantation

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1. Introduction

The management of posttransplantation relapse is extremely difficult. Although standard reinduction chemotherapy may induce complete remission, long-term disease-free survival is unlikely because of high treatment-related toxicity and disease recurrence [1,2]. Moreover, if reestablishment of donor hematopoiesis is not achieved by reinduction chemotherapy, the profound marrow aplasia that will ensue may result in catastrophic consequences [3]. Here, we describe 3 patients with relapsed acute leukemia after allogeneic bone marrow transplantation (BMT) who developed profound marrow aplasia after aggressive reinduction chemotherapy and who subsequently received granulocyte colony-stimulating factor (G-CSF)-primed donor lymphocyte infusion (DLI) containing abundant CD34⁺ cells. This strategy was applied in an attempt to reestablish donor hematopoiesis as well as to induce a maximal graft-versus-leukemia effect. Although recent reports have demonstrated the plausible efficacy of this approach, none of our 3 patients showed a satisfactory response.

2. Case Reports

2.1. Case 1

A 34-year-old man with acute lymphoblastic leukemia (ALL) carrying the Philadelphia chromosome with minor BCR/ABL transcripts received an allogeneic BMT from his HLA-identical sister during his first remission in October

1999. The initial posttransplantation course was unremarkable; however, the patient relapsed at day 152. The patient was then given intensive salvage chemotherapy using a dose-adjusted RELAL-88 5-day induction regimen (vindesine, mitoxantrone, cyclophosphamide, intermediate-dose cytarabine, prednisolone, and methotrexate) [4]. After completion of this chemotherapy regimen, the patient achieved a hematologic remission. The patient was then treated with DLI from the original donor, as previously described [5]. Despite these aggressive interventions, which resulted in temporary molecular remission [5], the patient again relapsed at day 561. The patient received the same therapeutic strategy applied at the initial relapse. However, the aggressive chemotherapy performed on day 578 resulted in profound myelosuppression; therefore, at day 605 the patient received G-CSF-primed DLI rather than unprimed DLI. No further chemotherapy and no graft-versus-host disease (GVHD) prophylaxis were administered before the G-CSF-primed DLI. Although the patient developed grade II acute GVHD affecting the gut and liver, treatment with prednisolone and FK506 stabilized the patient well. The hematologic recovery was rapid and observed as early as 11 days after the infusion of G-CSF-primed DLI, but this strategy failed to induce a complete hematologic response, as indicated by the small number of blasts still detected in a bone marrow aspirate obtained on day 616. The minimal residual disease state assessed by real-time reverse transcriptase-polymerase chain reaction analysis of minor BCR/ABL messenger RNA performed before and after treatment was 650,000 and 1600 copies/ μ g transfer RNA, respectively. Six months after G-CSF-primed DLI, the patient died of relapse after an abrupt increase in peripheral blood leukemic blasts.

2.2. Case 2

A 27-year-old woman with Philadelphia chromosome-negative ALL underwent an allogeneic BMT from her HLA-identical brother during the early relapse phase in December

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Figure 1. Clinical courses of the 3 patients. The serial changes in the numbers of neutrophils (solid lines) and blasts (dashed lines) are shown. Granulocyte colony-stimulating factor (G-CSF)-primed donor lymphocyte infusions (DLI) contained $1.47 \times 10^6/\text{kg}$ $\text{CD}34^+$ cells and $2.34 \times 10^8/\text{kg}$ $\text{CD}3^+$ cells (case 1), $1.15 \times 10^6/\text{kg}$ $\text{CD}34^+$ cells and $2.78 \times 10^8/\text{kg}$ $\text{CD}3^+$ cells (case 2), and $1.76 \times 10^6/\text{kg}$ $\text{CD}34^+$ cells and $3.58 \times 10^8/\text{kg}$ $\text{CD}3^+$ cells (case 3). SCT indicates stem cell transplantation.

2003. However, the patient relapsed as early as 3 months after the initial transplantation. Abrupt discontinuation of cyclosporine resulted in no response. Therefore, the patient received the same chemotherapy applied in case 1 on day 105, but she developed severe aplasia. Consequently, G-CSF-primed donor lymphocytes were infused on day 133. The patient received no conditioning therapy and no GVHD prophylaxis. Although a relatively low number of $\text{CD}34^+$ cells were infused, the patient showed rapid hematologic recovery and became transfusion independent, as is shown in Figure 1. The patient also developed grade II acute GVHD of the skin, which was treated with methylprednisolone (1 mg/kg per day). Improvement in the skin GVHD permitted tapering of the dosage. However, 17 days after G-CSF-primed DLI, the patient suddenly died of treatment-related arrhythmia. An autopsy revealed no evidence of ALL recurrence.

2.3. Case 3

A 23-year-old man with acute myelogenous leukemia underwent an allogeneic BMT from an HLA-identical brother during his first remission in September 2003 but relapsed 5 months later. The patient received standard reinduction chemotherapy consisting of cytarabine and

idarubicin but did not achieve a hematologic remission. Therefore, the patient was put on further aggressive chemotherapy with the time-sequential application of mitoxantrone plus intermediate-dose cytarabine followed by high-dose cytarabine plus etoposide on day 227 [6]. However, the patient developed severe aplasia after chemotherapy; consequently, G-CSF-primed lymphocytes were infused on day 255. This attempt appeared to induce no hematologic response, as determined by the existence of 60% leukemic blasts in the patient's bone marrow sample obtained on day 276. However, the patient was followed up and was in good general condition without an abrupt increase in peripheral leukemic blasts until day 342, when a second transplantation was scheduled. This patient also did not receive any GVHD prophylaxis, but he did not develop acute or chronic GVHD.

3. Discussion

Several reports have indicated that the combination of chemotherapy and DLI provides little impact on overall survival in patients with relapsed acute leukemia [7]. Recently, Glass et al reported the use of G-CSF-primed DLI, instead of unprimed DLI, after chemotherapy for treatment of patients with relapsed leukemia [8]. These authors' intention was to circumvent some of the problems associated with

unprimed DLI. First, the infusion of a high number of donor CD34⁺ cells might avoid aplasia after DLI. Second, the transfer of a complete progenitor cell graft might allow the wider use of aggressive chemotherapy prior to DLI. Although this approach is very close to that taken in a second transplantation, the crucial ways in which it differs from a second transplantation are the use of nonmyeloablative chemotherapy and the absence of prophylactic immunosuppression for acute GVHD. The available data from 2 prospective studies have disclosed a high rate of complete remission with this strategy. Levine et al reported a maximal response rate of 59% in selected patients [9]. Another study by Choi et al has also shown promising results: the complete remission rate and the 2-year overall survival rate were 63% and 31%, respectively [10]. These results were surprisingly superior to the historical data for DLI (complete remission rates of 0%-29%) [11]. Our approach was essentially the same as that of these studies, including the use of G-CSF-primed DLI and the absence of GVHD prophylaxis, although our patients received DLI with a relatively long interval (28-29 days in our study versus 7-15 days in the previous 2 studies). We performed G-CSF-primed DLI as stem cell rescue rather than as front-line therapy. However, in contrast to the previous 2 reports, our experience of these 3 patients provided only dismal outcomes, with 1 sudden death associated with treatment-related toxicity. Although our small study population, including advanced leukemia with short remission duration after initial BMT, may prohibit drawing meaningful conclusions, these data will be the basis for further studies with larger numbers of patients to assess this new treatment strategy.

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