Cytotherapy, 2013; 15: 1237–1244

International Society for Cellular Therapy
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Lowering the alemtuzumab dose in reduced intensity conditioning allogeneic hematopoietic cell transplantation is associated with a favorable early intense natural killer cell recovery

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Abstract

Background aims. The anti-CD52 monoclonal antibody alemtuzumab is employed in allogeneic hematopoietic cell transplantation (alloHCT) for the prevention of graft-versus-host disease (GVHD). However, its optimal dosing in this setting has not been determined yet. We compared three different alemtuzumab dose levels in reduced intensity conditioning (RIC) alloHCT with respect to lymphocyte recovery and outcome. *Methods.* In 127 consecutive patients with predominantly advanced stage hematologic malignancies, a first alloHCT after RIC was performed, applying a fludarabine-based protocol (in 93% FBM: fludarabine, bis-chloroethyl-nitrosourea [BCNU], and melphalan). For GVHD prophylaxis, cyclosporine and alemtuzumab at three different dose levels (40 mg, 20 mg, 10 mg) were administered. Recovery of the peripheral blood (PB) lymphocyte sub-populations and clinical outcome were determined with regard to the alemtuzumab dose. *Results.* Natural killer (NK) cell concentrations in PB around day +30 correlated inversely with the alemtuzumab dose, whereas other PB lymphocyte subtypes remained essentially unaffected by dosing of alemtuzumab. Lower alemtuzumab doses were associated with a tendency toward improved overall survival mainly during the early post-transplantation months. With regard to the PB NK cell concentration around day +30, "early intense NK cell reconstituters" tended to show an overall survival benefit. *Conclusions.* An alemtuzumab dose reduction to only 10–20 mg provides sufficient GVHD prophylaxis and supports improved NK cell regeneration early after alloHCT in PB ("NK cell saving effect"), which may have a positive effect on overall survival.

Key Words: *alemtuzumab, hematopoietic cell transplantation, natural killer cells, NK cell saving effect, reduced intensity conditioning*

Introduction

Allogeneic hematopoietic cell transplantation (alloHCT) offers a potentially curative therapeutic option for patients with otherwise fatal hematologic malignancies such as leukemia and lymphoma. Because of significant toxicity, conventionally dosed conditioning (chemotherapy or radiation or both) regimens are limited in their applicability to younger patients without major co-morbidities. However, in recent decades, so-called reduced intensity conditioning (RIC) protocols have emerged, providing the benefits of alloHCT to older patients and patients with poorer performance status (1).

Conventionally and reduced intensity dosed regimens both require a means of immunosuppression for the prevention of graft-versus-host disease (GVHD) and graft rejection. However, too much immunosuppression is disadvantageous in terms of loss or reduction of the desired graft-versus-leukemia/lymphoma effect, an increased risk of reactivated (e.g., cytomegalovirus) or acquired infection, and the side effects of the immunosuppressive agent itself (e.g., corticosteroids). The most beneficial composition of alloHCT protocols regarding the kind and dosage of chemotherapeutic and GVHD prophylactic agents is an ongoing challenge (2).

The humanized monoclonal antibody alemtuzumab (Campath-1H, MabCampath) binds to the human CD52 molecule, a small (12 amino acids), glycosylphosphatidylinositol anchored cell surface glycoprotein abundantly expressed on B and T lymphocytes, natural killer (NK) cells, monocytes, macrophages and some dendritic cells (3,4). Subsequently, these target cells are eliminated by complement-dependent cytotoxicity (5), by antibody-dependent cellular cytotoxicity and by the induction of apoptosis (6). Although alemtuzumab has emerged as an

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(Received 10 October 2012; accepted 21 May 2013)

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http://dx.doi.org/10.1016/j.jcyt.2013.05.016

attractive therapeutic option for chronic lymphocytic leukemia in the last decade (7), anti-CD52 antibodies of the Campath-1 family (initially Campath-1M *in vitro*, later Campath-1G *in vivo*) originally were introduced in the early 1980s for the control of GVHD and graft rejection by T-cell depletion (3,8,9). In 1997, alemtuzumab found its way into non-myeloablative RIC regimens, where it initially was applied at a total dose of 100 mg (20 mg/day intravenously on days −8 to −4 before transplantation) (10).

At our institution, we established a non-myeloablative, reduced-toxicity protocol in 1998. This FBM regimen comprises fludarabine, bis-chloroethyl-nitrosourea (BCNU) and melphalan, and employs cyclosporine and mycophenolate mofetil for GVHD prophylaxis (11,12). In 2003, we began a clinical trial aimed at identifying the lowest possible alemtuzumab dose within a fludarabine-based reduced toxicity conditioning protocol (mostly FBM) for alloHCT in combination with cyclosporine, able to provide sufficient GVHD prophylaxis while possibly reducing the risk of graft-versus-leukemia/lymphoma effect impairment and infection. The initial dose of 40 mg alemtuzumab could be reduced further to 20 mg and 10 mg (13). The safety of an alemtuzumab dose reduction approach in a related setting was confirmed more recently (14).

We report on the immune reconstitution data as an integral part of our study. We demonstrate a faster increase in peripheral blood (PB) lymphocyte counts early after transplantation in patients receiving a reduced dose of alemtuzumab mediated by an accelerated NK cell recovery and its impact on the clinical outcome.

Methods

Study population and treatment protocol

For this survey, 127 consecutive patients were identified from the University Medical Center Freiburg alloHCT database who received alloHCT between July 2003 and May 2007 for hematologic malignancies and were not eligible for conventional dose conditioning because of age, performance status or co-morbidities; their characteristics are listed in Table I. Diagnoses included acute myelogenous leukemia (n = 69), myelodysplastic syndromes (n = 15), B-cell non-Hodgkin's lymphoma (n = 11), chronic lymphocytic leukemia (n = 10), T-cell non-Hodgkin's lymphoma (n = 5), myeloproliferative neoplasms (n = 4), myelodysplastic/myeloproliferative neoplasms (n = 2), chronic myelogenous leukemia (n = 3), acute lymphoblastic leukemia (n = 7), and multiple myeloma (n = 1).

All patients received their first alloHCT with PB stem cells as the predominant stem cell source (124 of 127; 97.6%) and bone marrow in only three cases (3 of 127; 2.4%). Grafts were derived from sibling (58 of 127; 45.7%) or unrelated (69 of 127; 54.3%) donors. All patients received a fludarabine-based, reduced toxicity, non-myeloablative conditioning regimen, which in most cases (118 of 127; 93%) was FBM: fludarabine (30 mg/m^2 × 5), bis-chloroethyl-nitrosourea (BCNU; 200 mg/m^2 × 2; 150 mg/m^2 × 2 in patients ≥55 years old) and melphalan (140 mg/m^2 × 1; 110 mg/m^2 × 1 in patients ≥55 years old). In the remaining 9 of 127 (7%) patients, melphalan was replaced by thiotepa because of its superior penetration across the blood-brain barrier in situations with an increased risk of cerebrospinal fluid involvement. For GVHD prophylaxis, we administered cyclosporine (5 mg/kg daily starting from day −3) and alemtuzumab (MabCampath; Genzyme Corporation, Cambridge, MA, USA) intravenously at three different dose levels: cohort A (July 2003 to July 2005) received 20 mg × 2 (day −2 and −1), cohort B (August 2005 to May 2006) 10 mg × 2 (day −2 and −1) and cohort C (June 2006 to May 2007) 10 mg × 1 (day −1) (13).

Recovery of the lymphocyte sub-populations in PB was determined by flow cytometry around day +30 (range, 25−35) and day +100 (range, 80−120) after alloHCT. Clinical outcome (overall survival, GVHD, relapse rate and fatal infections) was recorded with a median follow-up of 754 days (range, 1−2124 days). The transplantation protocols were approved by the University Medical Center Institutional Review Board, and all patients gave written informed consent for treatment and prospective data collection in accordance with the Declaration of Helsinki.

Flow cytometry analysis of lymphocyte sub-populations in PB

PB was stained with fluorochrome-conjugated antibodies (fluorescein isothiocyanate-labeled/phycoerythrin-labeled; all obtained from BD Biosciences, Heidelberg, Germany) against CD45/CD14 (leukocyte sub-populations), CD3/HLA-DR (T lymphocytes, activated T lymphocytes), CD3/CD4 (T4 lymphocytes), CD3/CD8 (T8 lymphocytes), CD19/CD5 (B lymphocytes) and CD3/CD16+CD56 (NK cells, natural killer T [NKT] cells), according to the manufacturer's instructions. After red blood cell lysis (BD PharmLyse; BD Biosciences), samples were analyzed by means of a FACSCalibur flow cytometer (BD Biosciences) equipped with CellQuest Pro

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