Leukemia Research 54 (2017) 12–16

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Immune stimulation during chemotherapy increases incidence of acute graft versus host disease in acute myeloid leukemia: A study on behalf of SFGM-TC and ALFA

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ARTICLE INFO

Article history:
Received 23 November 2016
Received in revised form
30 December 2016
Accepted 4 January 2017
Available online 5 January 2017

Keywords:
Infections
Toxicities
GVHD
Transplantation
AML

ABSTRACT

60–70% of AML patients have an indication of allogeneic hematopoietic stem cell transplantation (allo-HSCT) during their treatment. Graft versus host disease (GvHD), the major cause of mortality and comorbidities post-transplantation, develops by immunological mechanism and decides greatly prognosis and quality of life (QoL) of graft recipient. Current GvHD prophylaxis is not personalized. Infections, toxicities and leukemic infiltration complicate the first chemotherapy phases prior to allo-HSCT. They, to certain extent, induce local immune stimulation. Impact of immune stimulation of this period on incidence of GvHD has not been evaluated. We retrospectively studied 238 AML patients transplanted at first remission from 21 French centers in the ALFA-0702 protocol and found that cutaneous and digestive immune stimulation during induction increases the incidence of skin and gut aGVHD, respectively. Furthermore, prolonged febrile duration correlates with elevated incidence of grade II–IV aGvHD. Thus, we identified a group of patients with higher risk of aGvHD. The benefit of personalized GvHD prophylaxis should be explored in a prospective cohort to decrease incidence of aGvHD in these patients and improve their QoLs.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is one of curative treatment options for acute myeloid leukemia (AML) patients. The immunologic graft versus leukemia (GvL)

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http://dx.doi.org/10.1016/j.leukres.2017.01.002
0145-2126/

effect and intensity of conditioning participate in curative effect [1]. AML is the most common indication for allo-HSCT. Patients without favorable cytogenetic profile are conventionally recommended to be transplanted with a HLA-identical sibling donor. Since high-resolution HLA-typing enables better recipient-donor matching, outcome of transplantation with unrelated donors has been improved [2]. Moreover, the feasibility and efficiency of reduced-intensity conditioning (RIC) have been demonstrated in different studies with both related and unrelated donors [3–5] and increased the number of allo-HSCT in AML patients in the last decade. Furthermore, allo-HSCT significantly improves survival compared with conventional treatments in AML patients with intermediate and unfavorable cytogenetics at first complete remission [6]. European LeukemiaNet AML working party suggested to use allo-HSCT if the expected disease-free survival (DFS) is at least 10% more based on an individual's risk assessment [7].

Graft-versus-host disease (GvHD) is the major barrier to a successful allo-HSCT. It necessitates the use of corticosteroids which disturbs immune recovery and increases the risk of infection and relapse. Therefore, the benefit of allo-HSCT can be compromised by elevation of non-relapse mortality (NRM) secondary to severe GvHD. To prevent GvHD, prophylaxis based on calcineurin inhibitors (CNI) like cyclosporine or tacrolimus are usually used. Choice of GVHD prophylaxis is not personalized. In spite of current prophylaxis, 70% of allograft recipients still suffered from II–IV grade aGvHD [8]. It is described to be a three-phase process according to current understanding of its pathophysiology [9]. First, tissue damage induce a pro-inflammatory environment. Second, antigen presenting cells (APCs) and inflammatory cytokines activate donor T lymphocytes, NK cells and amplify allogeneic immune response. Finally, activated donor T cells mediate cytotoxic damage against host cells [9]. Factors influencing either phase of the onset of GvHD are shown to be able to impact its incidence and/or severity [10].

Extramedullary leukemic infiltration, infection and drug toxicities often complicate the first phase chemotherapy prior to transplantation. These complications can induce tissue damages and immune activation. Impact on GVHD incidence of this kind of immune stimulation prior allo-SCT has however not be evaluated.

2. Materials and methods

2.1. Patients

From 2009 to 2013, 238 AML patients, enrolled prospectively in ALFA-0702 trial (patients aged 18–60 y, de novo AML, patients with favorable cytogenetics excluded), transplanted in first complete remission with bone marrow or peripheral blood stem cell from 21 French centers were included in our study. Clinical data prior to allo-HSCT were collected from the ALFA database. Clinical data after allo-HSCT were collected from the SFGM-TC database (ProMise). This study was conducted in accordance with the Declaration of Helsinki. Patient records/information was anonymized and de-identified prior to analysis. Clinical data prior allo-HSCT were collected in centers including in ALFA-0702 clinical trial (www.clinicaltrials.gov NCT00932412) and clinical data after allo-HSCT were collected in the same centers belonging to the French Society for Stem Cell Transplantation (SFGM-TC) and sharing ProMISe (Project Manager Internet Server) (CNIL number authorization: Number 1238249), which is the central data management system.

2.2. Complications during chemotherapy

Prophylactic antibacterial and antifungal therapy were initiated and continued through recovery of peripheral counts. In induction, posaconazole 200 mg was administred every 8 h from day 4 and in each arm of consolidation, posaconazole 200 mg will be administred every 8 h from day 6 and lévofloxacine 500 mg was administred every 8 h from day 1.

Complication includes infectious and non-infectious events in our study; the former defined as microbiologically documented infections or clinically considered infections, while the latter is composed of drug toxicities, extramedullary leukemic infiltration and complication with uncertain origin. Complication grading was defined according to CTCAE v4.0.

2.3. GVHD

Standard GvHD prophylaxis was cyclosporine (CSA) combined to methotrexate (MTX) in 126 (53%), CSA combined to mycophenolate mofetil (MMF) in 55 (23%), CSA alone in 31 (13%) and others prophylaxis in 26 (11%) patients. GvHD grading was defined according to revised Glucksberg criteria and the maximum grade was used.

2.4. Statistical analysis

Characteristics of the cohorts were presented and compared depending presence or not of GVHD, and of various complications. Continuous variables are described using median [Interquartile range] (minimum; maximum) and qualitative variables using count and percentage. Non continuous variables were compared using khi square test. Withney and Kruskall-Wallis tests were used for continuous variables. Overall survival (OS) was calculated from the date of HSCT until death or last follow-up. Progression free survival (PFS) was calculated from the date of HSCT until death, relapse or last follow up. GvHD free/relapse free survival (GRFS) is calculated from the date of HSCT until the diagnosis of extended chronic GvHD or relapse of disease. OS, PFS and GRFS were assessed by Kaplan Meier method. Statistical analysis was performed with SPSS v.22 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Characteristics of patients

We retrospectively enrolled 238 de-novo AML patients transplanted in first complete remission (CR) from 21 French centers from 2009 to 2013 in the ALFA-0702 trial. Median age at transplant was 47 years old (18–60) and M/F sex ratio was 132/105 respectively. Cytogenetics was intermediate-1, intermediate-2 and unfavorable in 4, 124, 105 patients respectively according to ELN classification. ECOG status was 0, 1, 2 in 110, 109 16 patients, respectively (Table 1).

3.2. Characteristics of infections and drug toxicities prior allo-HSCT

During the chemotherapies 75, 91 and 23 patients underwent skin, gut and hepatic complications during induction respectively, while 16, 32 and 9 patients suffered from skin, gut and hepatic complications during consolidation respectively (Table 2). Majority of the complications occur during inductions. During induction, 16.4%, 30.6% and 6.3% of the patients underwent skin, gut and liver CTCAE grade ≥ 3 complications, respectively. No significant difference was found between complications and conditioning regimen ($p = 0.154$, $p = 0.314$ and $p = 0.984$ for skin, gut and liver complications, respectively) and; complications and GVHD prophylaxis ($p = 0.214$, $p = 0.884$ and $p = 0.331$ for skin, gut and liver complications, respectively).