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# Risk Factors for Steroid-Refractory Acute Graft-versus-Host Disease after Allogeneic Stem Cell Transplantation from Matched Related or Unrelated Donors

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A B S T R A C T

We performed a retrospective study to identify pretransplantation risk factors for steroid-refractory (SR) acute graft-versus host disease (aGVHD) after allogeneic stem cell transplantation from matched donors in 630 adult patients who underwent transplantation at our center between 2000 and 2012. The cumulative incidence (CI) of SR aGVHD was 11.3% ± 2.3%. The identified independent risk factors were matched unrelated donor (hazard ratio [HR], 2.52; $P = .001$), female donor for male recipient (HR, 1.84; $P = .023$) and absence of antithymocyte globulin (HR, 2.02; $P = .005$). Three risk groups were defined according to the presence of these risk factors. In the whole cohort, the CI of SR aGVHD was 3.5% ± 1.7% in the low-risk group (0 risk factor, n = 115), 9.3% ± 1.6% in the intermediate-risk group (1 risk factor, n = 323), and 19.3% ± 2.9% in the high-risk group (2 or 3 risk factors, n = 192). Our study suggests that pretransplantation characteristics might help identify patients at high risk for SR aGVHD. A risk adapted first-line treatment of aGVHD could be evaluated in those patients.



## INTRODUCTION

Acute graft-versus host disease (aGVHD) remains the most frequent and challenging complication after allogeneic stem cell transplantation (allo-SCT). The most consistently reported risk factors are well defined and include HLA-mismatched donor, HLA-matched unrelated donor, older patient age, a female donor for a male recipient, prior alloimmunization of the donor, and type of graft-versus-host disease (GVHD) prophylaxis [1-3]. Less consistently reported risk factors include higher intensity of the conditioning regimen with irradiation, older donor age, recipient cytomegalovirus (CMV) seropositivity, and use of peripheral blood (PB) stem cells [1-3].

Steroid-refractory (SR) aGVHD is of particular interest because of its very poor prognosis, with a median survival of 6 months and a long-term survival ranging from 20% to 30% [4,5]. Based on these results, several studies have sought to identify risk factors for poor outcome at the onset of aGVHD. Westin et al. [6] identified grade III and IV and hyperacute (before day 14) aGVHD as predictors for SR aGVHD. Robin et al. [7] reported that initial liver involvement was a clinical predictor of poor outcome, and McMillan et al. [8] proposed a novel aGVHD risk score based on severity of skin, gut, and liver involvement. More recently, Castilla-Llorente et al. [9] identified steroid resistance, age > 18 years, increased serum bilirubin, and overt gastrointestinal bleeding as significant risk factors for mortality after stage 3 and 4 gut aGVHD. Unfortunately, the lack of satisfactory drugs to treat

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**Table 1**
Patient and Transplantation Characteristics of the Study Population (n = 630)

| Characteristics | n (%) |
|---|---|
| Age at transplantation, median (range), yr | 50 (18-67) |
| Year of transplantation, median | 2007 |
| 2000-2003 | 124 (19.7) |
| 2004-2006 | 137 (21.7) |
| 2007-2009 | 170 (27) |
| 2010-2012 | 199 (31.6) |
| ABO incompatibility | |
| None | 334 (53) |
| Major | 99 (15.7) |
| Minor | 115 (18.2) |
| Bidirectional | 33 (5.2) |
| Missing data | 49 (7.9) |
| Recipient sex | |
| Male | 411 (65.2) |
| Female | 219 (34.8) |
| Female donor for male recipient | 151 (24) |
| Recipient/donor CMV status | |
| R−/D− | 238 (37.8) |
| R−/D+ | 77 (12.2) |
| R+/D− | 121 (19.2) |
| R+/D+ | 191 (30.3) |
| Missing data | 3 (0.5) |
| Diseases | |
| AML | 229 (36.4) |
| MDS | 46 (7.3) |
| ALL | 104 (16.5) |
| NHL | 76 (12.1) |
| HD | 18 (2.8) |
| MM | 78 (12.4) |
| AA | 19 (3.1) |
| CLL | 28 (4.4) |
| CML | 18 (2.8) |
| MPS | 14 (2.2) |
| Status at transplantation | |
| CR1, PR1, or CP | 290 (46) |
| >CR1, >PR1, or AP | 207 (32.9) |
| Untreated | 37 (5.9) |
| Refractory | 96 (15.2) |
| Conditioning regimen* | |
| NMA | 77 (12.2) |
| RIC | 296 (47) |
| MAC | 257 (40.8) |
| ATG† | |
| Yes | 326 (51.7) |
| No | 304 (48.3) |
| Dose of ATG† | |
| Median dose, mg/kg | 5 |
| 2.5 mg/kg§ | 70 (21.5) |
| 5 mg/kg | 200 (61.3) |
| 7.5 mg/kg§ | 18 (5.5) |
| ≥10 mg/kg | 28 (8.6) |
| Missing data | 10 (3.1) |
| ATG, Thymoglobulin | 8 |
| ATG-Fresenius | 1 |
| Horse ATG | 1 |
| Donor | |
| Matched related | 363 (57.6) |
| Matched unrelated | 267 (42.4) |
| Source of stem cells | |
| PB | 441 (70) |
| BM | 188 (29.8) |
| Missing data | 1 (0.2) |
| Median CD34+ cells in the graft, median (range) | 5.4 × $10^6$ (.6-31.9) |
| Missing data | 17 (2.7) |
| GVHD prophylaxis | |
| CsA | 173 (27.5) |
| CsA+MTX | 343 (54.4) |
| CsA+MMF | 106 (16.8) |
| Others | 8 (1.3) |

R indicates recipient; D, donor; AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; ALL, acute lymphoid leukemia; NHL, non-Hodgkin lymphoma; HD, Hodgkin's disease; MM, multiple myeloma; AA, aplastic anemia; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; MPS, myeloproliferative syndromes; CR, complete remission; PR, partial remission; CP, chronic phase; AP, accelerated phase; MTX, methotrexate; MMF, mycophenolate mofetil.

* According to Bacigalupo et al. [15].

† Rabbit ATG (Thymoglobulin, n = 324; ATG-Fresenius, n = 1) or horse ATG (n = 1).

‡ Rabbit ATG, Thymoglobulin.

§ Doses exclusively used in patients who underwent transplantation with RIC regimen.

SR aGVHD currently limits the practical value of these predictors and a preventive strategy based on analysis of pretransplantation characteristics might also be relevant. As the specific pretransplantation risk factors for SR aGVHD are not as clearly defined as for aGVHD, we conducted a retrospective study in adult patients who underwent transplantation from matched related (MRD) or matched unrelated donors (MUD) at our center between 2000 and 2012.

## PATIENTS AND METHODS

### *Patients*

This retrospective study included adult patients (≥18 years) who received an allo-SCT from an MRD or MUD between January 1, 2000 and December 31, 2012 at the university hospital of Bordeaux. All patient records were reviewed to ensure the quality of data. To reduce heterogeneity of the study population, patients who underwent transplantation from mismatched unrelated (n = 76) or syngeneic (n = 2) donors were excluded, as well as patients who underwent transplantation with cord blood (n = 94) or in vitro T cell–depleted grafts (n = 2).

During the period of study, our transplantation policy was always to favor a sibling donor over an unrelated donor, to use reduced-intensity conditioning (RIC) or nonmyeloablative (NMA) regimens in patients >50 years or with significant comorbidities, and to use myeloablative (MAC) regimens in patients ≤50 or 55 years, according to ongoing protocols. Antithymocyte globulin (ATG) was mostly used with RIC regimens; more often with unrelated donors, but its use did not depend on the disease, nor on the status of disease. No haplo-identical or mismatched related transplantation was performed during the period of the study. MUD were matched at the allele level (4 digits) for HLA-A, -B, -C, -DRB1, -DQB1. The HLA typing method did not significantly change during the period of the study.

### *Definitions*

The clinical diagnosis of aGVHD was based on a combination of symptoms affecting the skin, the liver, and/or the gastrointestinal tract after transplantation [10]. The diagnosis of aGVHD was supported by biopsy whenever indicated and possible. To reduce heterogeneity, aGVHD occurring after donor lymphocytes infusions were not included. The grading of aGVHD was made according to the 1994 consensus conference [11]. First-line systemic therapy with methylprednisolone or prednisone 2 mg/kg/day was started in patients with grade II to IV aGVHD according to the European Society for Blood and Marrow Transplantation – European LeukemiaNet (EBMT-ELN) and American Society for Blood and Marrow Transplantation (ASBMT) recommendations [5,12]. The initial dose was maintained for 7 to 14 days and tapered off in responding patients. *SR aGVHD* was defined as aGVHD progressing after 3 to 5 days of treatment, unchanged after 7 days, or in incomplete response after 14 days, according to the recent EBMT-ELN and ASBMT recommendations [5,12]. Because the study period began in 2000, we chose to retrospectively select SR aGVHD if they clearly corresponded to 1 of the 3 clinical situations recently defined by the EBMT-ELN and ASBMT groups [5,12]. We did not consider the start of a