SUPPLEMENTARY APPENDIX

Allogeneic stem cell transplantation for advanced cutaneous T-cell lymphomas: a study from the French Society of Bone Marrow Transplantation and French Study Group on Cutaneous Lymphomas

Adèle de Masson,[1] Marie Beylot-Barry,[2] Jean-David Bouaziz,[1]* Régis Peffault de Latour,[3]* François Aubin,[4] Sylvain Garciaz,[5] Michel d'Incan,[6] Olivier Dereure,[7] Stéphane Dalle,[8] Anne Dompmartin,[9] Felipe Suarez,[10] Maxime Battistella,[11] Marie-Dominique Vignon-Pennamen,[11] Jacqueline Rivet,[11] Henri Adamski,[12] Pauline Brice,[13] Sylvie François,[14] Séverine Lissandre,[15] Pascal Turlure,[16] Ewa Wierzbicka-Hainaut,[17] Eolia Brissot,[18] Rémy Dulery,[19] Sophie Servais,[20] Aurélie Ravinet,[21] Reza Tabrizi,[22] Saskia Ingen-Housz-Oro,[23] Pascal Joly,[24] Gérard Socié,[3]** and Martine Bagot;[1]** French Study Group on Cutaneous Lymphomas and Société Française de Greffe de Moëlle et Thérapie Cellulaire

[1]Service de Dermatologie, Université Paris VII Sorbonne Paris Cité, INSERM UMR-S976, CHU Saint-Louis, Paris, France; [2]Service de Dermatologie, CHU de Bordeaux, Université Bordeaux II, France; [3]Service d'Hématologie-Greffe, Université Paris VII Sorbonne Paris Cité, INSERM UMR-S940, CHU Saint-Louis, Paris, France; [4]Service de Dermatologie, CHU de Besançon, France; [5]Service d'Hématologie, Institut Paoli-Calmettes, Marseille, France; [6]Service de Dermatologie, CHU Estaing, Clermont-Ferrand, France; [7]Service de Dermatologie, CHU Saint-Eloi, Montpellier, France; [8]Service de Dermatologie, Centre de Recherche en Cancérologie de Lyon, Hospices Civils de Lyon, Université Claude Bernard Lyon 1, France; [9]Service de Dermatologie, CHU de Caen, Caen, France; [10]Service d'Hématologie, CHU Necker-Enfants Malades, Paris, France; [11]Laboratoire de Pathologie, Hôpital Saint-Louis, Paris, France; [12]Service de Dermatologie, CHU Pontchaillou, Rennes, France; [13]Service d'Hématologie-Oncologie, CHU Saint-Louis, Paris, France; [14]Service des Maladies du Sang, CHU d'Angers, France; [15]Service d'Hématologie, CHU de Tours, Tours, France; [16]Service d'Hématologie, CHU de Limoges, Limoges, France; [17]Service de Dermatologie, CHU de Poitiers, Poitiers, France; [18]Service d'Hématologie, CHU de Nantes, France; [19]Service d'Hématologie Clinique, CHU Claude Huriez, Lille, France; [20]Service d'Hématologie Clinique, CHU de Liège, Belgique; [21]Service d'Hématologie Adultes, CHU Estaing, Clermont-Ferrand, France; [22]Service d'Hématologie, CHU de Bordeaux, Hôpital Haut-Lévêque, Bordeaux, France; [23]Service de Dermatologie, CHU Henri-Mondor, Créteil, France; and [24]Service de Dermatologie, CHU Charles-Nicolle, Rouen, France

*These authors contributed equally to this work. **These authors contributed equally to this work.

 doi:10.3324/haematol.2013.098145
Manuscript received on September 14, 2013. Manuscript accepted on November 4, 2013.
Correspondence: martine.bagot@sls.aphp.fr

Supplementary Methods

Patients

Data collection and inclusion criteria

We retrieved all patients with diagnosis of primary cutaneous T-cell lymphoma as defined in the World Health Organization (WHO)- European Organisation for Research and Treatment of Cancer (EORTC) classification of cutaneous lymphomas[1] who underwent allogeneic HSCT from the French national registry of the Société Française de Greffe de Moëlle et Thérapie cellulaire from July 1st, 2002 to February 7th, 2013. The Société Française de Greffe de Moëlle et Thérapie cellulaire is a voluntary organization comprising 80 transplantation centers which are required to report all consecutive HSCT and follow-up data annually.

The diagnosis of transformed mycosis fungoides relied on the presence of more than 25% of large cells on biopsy of a mycosis fungoides lesion.[4] The diagnosis of Sézary syndrome was always associated to an absolute Sezary cell count of 1000 cells/mm^3 or more, a CD4/CD8 ratio of 10 or higher, and an identical dominant T-cell clone evidenced in skin and blood by polymerase chain reaction technique (with denaturing gel gradient electrophoresis). The diagnosis of primary cutaneous anaplastic large-cell lymphoma required the presence of large cells with an anaplastic, pleomorphic or immunoblastic phenotype and the expression of CD30 by the majority of tumor cells, with no clinical evidence or history of mycosis fungoides, lymphomatoid papulosis or other type of primary cutaneous T-cell lymphoma[1].

In each case, the diagnosis was reviewed by an expert panel of dermatologists and pathologists from the French Study Group on Cutaneous Lymphomas.

Patients were selected for transplant if they displayed:

- nodal (N3) or visceral (M1) involvement and evolutive disease after at least 1 line of systemic treatment (excluding skin-directed therapies for epidermotropic T-cell lymphomas),
- or tumor-stage mycosis fungoides (T3) or Sézary syndrome (T4 and B2) with no evidence for nodal (N3) or visceral involvement but relapsed or refractory disease after at least 3 lines of systemic treatments.

Patients with non-epidermotropic T-cell lymphomas were not included in the analysis if they had evidence of an initial extracutaneous localization, to avoid including patients with a primary nodal lymphoma and a secondary cutaneous involvement. Out of 40 patients selected, 2 were excluded because they presented with MF of International Society for Cutaneous Lymphomas (ISCL)-EORTC maximal stage I, and 1 was excluded because he presented with nodal involvement at the diagnosis of primary cutaneous anaplastic large-cell lymphoma.

Baseline, pre-transplant and post-transplant assessments

Evaluations at baseline and at least monthly during the follow-up included complete history, physical examination, and assessment of the body-surface area involved with patches, plaques, and tumors. A cytomorphological and immunophenotypical examination of the peripheral blood lymphocytes to identify circulating Sézary cells were performed in each case of epidermotropic T-cell lymphoma.[21-23] At baseline (at the time of diagnosis, or of any large-cell transformation) and 3 months after allogeneic HSCT, all patients underwent a staging computed tomography or positron emission tomography/computed tomography scan, and any abnormal lymph node was characterized histologically by an excisional biopsy. Pre-transplant global disease response was defined by comparing the disease status immediately prior to HSCT to the disease status before the onset of the last systemic treatment line before HSCT. This global disease response was defined as follows: complete response (CR, 100% clearance

of skin lesions, and no evidence of lymph node, visceral or leukemic involvement on pre-transplant staging), very good partial response (VGPR, > 90% regression of measurable disease in skin, lymph nodes and any visceral or blood tumor burden), partial response (PR, > 50% regression), progressive disease (PD, evidence of new skin lesions, tumors, lymph node, organ involvement or increased blood tumor burden), and stable disease (SD, fails to attain the criteria for CR, VGPR, PR or PD). Current status at last follow-up was defined as the disease status at last follow-up compared to the disease status just before allo-HSCT and was assessed with the same criteria used for baseline evaluation: CR, PR, SD and PD.

End Points and Definitions

Outcome analysis focused on engraftment, transplant-related mortality, relapse or progression, progression-free survival (PFS), overall survival (OS), acute and chronic GVHD, and disease response at last follow-up (CR, PR, SD or PD). Engraftment was defined as an absolute neutrophil count greater than 500/mm^3 for 3 consecutive days.

Statistical analysis

The database was closed for analysis in April 2013. Probabilities of PFS and OS were estimated from the time of HSCT using Kaplan-Meier estimates. The occurrences of engraftment, acute and chronic GVHD, transplant-related mortality and progression were calculated using cumulative incidence estimates taking into consideration the competing events.[25] Transplant-related mortality was defined as any death which could not be attributed to disease relapse or progression, including patients who died in complete remission of the lymphoma, and patients who experienced a localized cutaneous relapse and died thereafter from HSCT-related causes (e.g., thrombotic microangiopathy, stage 3 acute GVHD, disseminated adenovirus infection). Disease-associated death was considered a competing

event of transplant-related mortality, and transplant-related mortality a competing event of progression in cumulative incidences estimates. The following factors were analyzed for their association with transplant-related mortality, progression, PFS, and OS by univariate analysis using a Cox regression model: age of the recipient at time of allo-HSCT, disease type, disease status at time of allo-HSCT (CR or VGPR *versus* PR or PD), donor origin (sibling *versus* matched unrelated donor), conditioning regimen (reduced intensity conditioning *versus* myeloablative conditioning), use of antithymocyte globulin. Acute and chronic GVHD, treated as time-dependent covariates, were analyzed for their association with progression and transplant-related mortality in Cox univariate analysis. Factors with significant impact in univariate analysis were also analyzed by Cox regression multivariate analysis. Statistical analysis was performed using the cmprsk and survival packages of R version 2.14.1 for Mac statistics software. Reported p-values are two-sided and were considered statistically significant if less than .05.