



HAL
open science

Toxoplasmosis as an Early Complication of Allogeneic Hematopoietic Cell Transplantation

Christine Robin, Mathieu Leclerc, Cécile Angebault, Rabah Redjoul, Florence Beckerich, Ludovic Cabanne, Françoise Foulet, Cécile Pautas, Andréa Toma, Sébastien Maury, et al.

► To cite this version:

Christine Robin, Mathieu Leclerc, Cécile Angebault, Rabah Redjoul, Florence Beckerich, et al.. Toxoplasmosis as an Early Complication of Allogeneic Hematopoietic Cell Transplantation. *Biology of Blood and Marrow Transplantation*, 2019, 25, pp.2510 - 2513. <10.1016/j.bbmt.2019.07.035>. <hal-03488940>

HAL Id: hal-03488940

<https://hal.science/hal-03488940v1>

Submitted on 21 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC 4.0 - Attribution - Non-commercial use - International License

Toxoplasmosis as an early complication of allogeneic hematopoietic cell transplantation

Christine Robin ^{1,2}, Mathieu Leclerc^{1,2}, Cécile Angebault ^{2,3}, Rabah Redjoul ¹, Florence Beckerich ¹,
Ludovic Cabanne ¹, Françoise Foulet ³, Cécile Pautas ¹, Andréa Toma ¹, Sébastien Maury ^{1,2}, Françoise
Botterel ^{2,3,4}, Catherine Cordonnier^{1,2}

¹ Assistance Publique-Hôpitaux de Paris; Henri Mondor Hospital, Department of Hematology and Cellular Therapy, 94000 - Créteil

² University Paris-Est Créteil (UPEC), 94000 - Créteil

³ Parasitology Unit, Microbiology Department, Henri Mondor Hospital, 94000 – Créteil

⁴ EA Dynamyc UPEC, Ecole Nationale Vétérinaire d'Alfort (ENVA), Faculté de Médecine de Créteil, 8 rue du Général Sarrail, 94010 - Créteil, France.

Key words: *Toxoplasma gondii*, toxoplasmosis, allogeneic hematopoietic cell transplantation, trimethoprim-sulfamethoxazole, polymerase chain reaction.

Running head: Early toxoplasmosis after allogeneic HCT

Abstract word count: 73

Manuscript word count: 1821

Number of tables: 1

Number of figures: 0

Number of references: 12

Corresponding author: Christine Robin, MD, PhD

Hematology Department

Henri Mondor Hospital

94000 – Créteil, France

Phone: +33 1 49 81 20 57

Fax: +33 1 49 81 20 67

@mail address: christine.robina@aphp.fr

This work has been partly reported as a poster at the 44th Annual Meeting of the European Society for Blood and Marrow Transplantation, Lisbon, March 18–21, 2018

Abstract

Among 419 consecutive allogeneic hematopoietic cell transplant recipients, we observed 17 (4.0%) cases of toxoplasmosis at a median time of day 45 (6-322) after transplant. Seven of these 17 cases occurred before day 30 after transplant. Because of the lack of PCR screening and trimethoprim-sulfamethoxazole prophylaxis before engraftment, the diagnosis of toxoplasmosis was late and five of these seven patients died. Analyzing these cases, early *Toxoplasma* blood PCR screening, starting from transplant, is crucial.

Introduction

Toxoplasmosis is a rare but well-known complication that can occur after allogeneic hematopoietic cell transplantation (HCT). It almost exclusively occurs through the reactivation of previously seropositive recipients (R+), especially when the donor is seronegative or the patient has been transplanted with cord blood.^{1,2} The incidence varies widely according to several parameters: (a) the seroprevalence of toxoplasmosis in the country—low in North America, over 50% in France³—(b) the administration and compliance to trimethoprim-sulfamethoxazole (TMP-SMX),¹ and (c) whether a regular screening with blood real-time PCR (qPCR) is performed or not. In centers that do not screen their R+ patients using a PCR analysis after transplant, the incidence rate is reported to be around 0.2–2%,^{4,5} and the diagnosis is often done at autopsy.² In centers screening their R+ patients, the incidence is much higher, between 6% and 16%^{1,4} but with more cases of infection than cases of disease. Indeed, a weekly blood qPCR screening of R+ patients allows for the detection of the circulating DNA of the parasite before the appearance of symptoms. Despite the lack of a randomized study, qPCR *Toxoplasma* screening is recommended by international HCT guidelines for the early diagnosis of *Toxoplasma* reactivation—especially when TMP-SMX is not given—to anticipate *Toxoplasma*.⁶

Most cases of *Toxoplasma* are observed between 2 to 6 months after transplant, and even in the larger studies, early cases occurring before day 30 are very rare.^{1,5,7} Because of recent, severe, and early cases of toxoplasmosis in our department, we reviewed all our *Toxoplasma* cases over the last 11 years, focusing on cases observed before day 30 after HCT. The aim of the study was to identify the causes leading to this unexpected finding of early toxoplasmosis and reconsider the pertinence of our procedures accordingly.

Methods

From the laboratory data, we retrospectively collected all cases of *Toxoplasma* infection or disease in allogeneic HCT recipients in our department between January 2007 and June 2018, identifying all patients with a positive qPCR on any body fluid and/or a microscopic examination showing tachyzoites. All patients and donors were assessed for *Toxoplasma* serology before transplant. *Toxoplasma* infection and disease were defined according to the European Society for Blood and Marrow Transplantation's guidelines.⁸ Briefly, *Toxoplasma* infection was defined as a positive qPCR with or without fever but with no organ involvement. *Toxoplasma* disease was defined as *Toxoplasma* infection plus clinical, radiological, or pathological evidence of organ involvement by *T. gondii*. Proven *Toxoplasma* disease was defined as the histologic or cytologic demonstration of tachyzoites in tissue samples obtained either by biopsy or bronchoalveolar lavage (BAL) or at autopsy. Patients who had clinical and radiologic evidence of *Toxoplasma* disease plus ≥ 1 positive PCR test from blood, CSF, or BAL but who had no histologic confirmation were classified as having probable disease. Disseminated toxoplasmosis was defined as clinical, radiological, or histologic evidence of disease in > 1 organ. The cases were considered early before day 30 after transplant. All R+ patients were screened, irrespectively of prophylaxis, by qPCR in blood, targeting a 529 bp-repeat-DNA fragment (AF146527) per previously reported methods⁹ and with the same qPCR technic all over the study time. According to our local procedures from 2000, this screening was performed weekly from engraftment to day 100, then every 1-2 weeks from 3 to 6 months, then at each consultation, according to the outpatient's visits, until the patient was withdrawn from any immunosuppressant.

A positive blood qPCR triggered a diagnostic workup, including fungoscopic eye examination, brain CT scan, or magnetic resonance imaging, lung CT scan, and additional investigations according to the clinical presentation. Asymptomatic but ≥ 1 positive qPCR patients were preemptively treated until

there were two consecutive negative qPCR tests; the treatments were by daily doses of trimethoprim-sulfamethoxazole (TMP-SMX) if they did not receive TMP-SMX at diagnosis or by pyrimethamine (P) with sulfadiazine (S), atovaquone, or dapsone if the diagnosis was done under TMP-SMX. Patients with *Toxoplasma* disease were treated with PS, P-clindamycin, or high-dose TMP-SMX for 3 weeks and then put on secondary prophylaxis. According to French Health Public Law (CSP Art L1121-1.1), the current type of investigation does not require specific informed consent or ethics committee approval.

Results

Four hundred and nineteen patients received an allogeneic HCT during the study period. Data were censored starting on October 30, 2018 so that all patients had a minimal follow-up of 4 months after transplant. Among these 419 patients, 17 (4.0%) developed toxoplasmosis, seven (1.6%) before day 30 (median (range) time: day 22 (6–28)) and 10 (2.4%) after day 30 (median (range) time: day 172 (43–322)) (Table 1). Briefly, all 17 patients were seropositive (R+) for *Toxoplasma*, and all donors (D) except one were seronegative.

Among the seven patients with early toxoplasmosis, none had received TMP-SMX prophylaxis just before, or since transplant, and only two had been screened for qPCR before diagnosis. In these two patients, the second qPCR of the screening was positive at day 25 and day 28, respectively. These patients were preemptively treated, and none of them developed *Toxoplasma* disease. In the five other early cases, the diagnosis was suspected based on clinical manifestations—mostly fever or pneumonia —when qPCR blood screening was not routine. Three patients were neutropenic, and only one had graft-versus-host disease (GvHD). All the seven patients have developed febrile neutropenia between transplant and the diagnosis of toxoplasmosis, including six cases of fever of unknown origin. Two patients have another documented infection before the diagnosis of toxoplasmosis which could have delayed the diagnosis: one probable pulmonary aspergillosis and

one pseudomonas bacteremia. Only one patient had a co-infection at time of toxoplasma infection (pulmonary aspergillosis with pleural effusion which was positive for galactomanne and negative for toxoplasma PCR in the pleural liquid). The delay between first symptoms and toxoplasmosis diagnosis was 0 to 6 days. All five (71%) patients with *Toxoplasma* disease (proven: 1, probable: 4) had pulmonary toxoplasmosis diagnosed at a median of day 22 (range: 6–28). All five patients died one to 33 days after the diagnosis from respiratory (n=2) or multivisceral failure because of disseminated toxoplasmosis (n=3).

Among the 10 cases observed after day 30, there was only one *Toxoplasma* disease (10%) in a patient who was being treated for TMP-SMX prophylaxis but suffering from gut GvHD. At day 319, this patient who refused to come to the hospital during one month, developed seizures, revealing brain toxoplasmosis, which was proven by histology and qPCR on a brain biopsy, while a previous blood qPCR tested negative 4 weeks before. This patient was successfully treated and survived. The other nine patients were preemptively treated based on positive qPCR results. Two of them died within 3 months after the diagnosis of *Toxoplasma* infection, one from leukemia relapse (n=1) and the other from unexplained multivisceral failure with pericarditis (n=1), but both of these patients had a negative blood qPCR at the time of death. A third patient developed *Toxoplasma* infection at day 45 after HCT, concomitantly with uncontrolled acute grade III GvHD and multivisceral failure and remained positive for qPCR in blood until death despite preemptive treatment and without evidence of *Toxoplasma* disease. The median (range) number of toxoplasma PCR performed before the diagnosis - first positive PCR - of toxoplasma infection or disease was 0 (0-1) in the 7 early cases and 25 (5-29) in the 10 cases occurring after day 30.

Discussion

We report that 41% of our toxoplasmosis cases occurred within 30 days after allogeneic transplant when the patients usually did not receive any post-transplant TMP-SMX prophylaxis and were not

screened by qPCR, both being started after engraftment according to our procedures. Although the small size of our patient cohort precludes any statistical comparison, the concomitant lack of prophylaxis and of screening probably explains the high proportion of *Toxoplasma* disease and of the early deaths with or from toxoplasmosis in these early cases when compared with the later cases. Noteworthy, six of these seven patients developed toxoplasmosis when they had no GvHD and had not received any steroid therapy. On the other hand, the 10 patients with toxoplasmosis after day 30 benefited from a regular screening so that nine of them could have been treated preemptively before the onset of any symptom. The only patient who developed CNS toxoplasmosis 10 months after transplant while on treatment of active GvHD had refused consultations during four weeks while he should have benefited from a weekly PCR screening.

In previous series, most toxoplasmosis cases occurred during the second or third months after allogeneic HCT, with a risk persisting across the first year of transplant and sometimes even later.^{10,11} Cases occurring during the first 4 weeks of transplant have been rarely reported but seem to have a high mortality rate.^{1,5,7} Our series clearly identifies toxoplasmosis as an early complication of allogeneic HCT.

However, these cases should have been detected earlier, before any toxoplasma disease, using a weekly blood qPCR screening from transplant. Therefore, in R+ patients, we recommend starting this screening immediately after transplant, not from the point of engraftment. Whether the administration of TMP-SMX given before transplant for PcP prophylaxis in some centers may prevent early toxoplasmosis in HCT recipients has not been addressed in the literature and cannot be determined from our series but seems unlikely as Bactrim cannot be efficient on dormant cysts.

The main limit of the current study is that because of the small number of cases, it was not possible to search for the risk factors for developing early—rather than late—toxoplasmosis among our whole cohort of 419 patients. However, our findings are consistent with previous studies identifying cord blood transplant, donor's seronegativity, and lack of TMP-SMX prophylaxis as risk factors for *Toxoplasma* reactivation.^{1,4}

For a long time, because of the length and deepness of neutropenia after myeloablative conditioning, our efforts during the first 3–4 weeks of transplant have been focused on the optimal management of bacterial and fungal infections, which were the main fears of the transplanters. More recently, because of the predominant use of reduced-intensity conditioning, other infections, initially considered to be complications of the “second” postengraftment phase of transplant, have emerged as major, early problems. Indeed, we recently reported the early onset of pneumocystosis in three out of 18 cases because of the lack of TMP-SMX before engraftment.¹² Similarly, *Toxoplasma* infection may develop early after transplant and should be detected using a weekly qPCR screening from transplant to avoid the development of early *Toxoplasma* disease. From 3 months after transplant, we recommend to go on PCR screening, every 1-2 weeks, as long as the patient receives immunosuppressants.

Conclusion

Because there is no reliable *Toxoplasma* prophylaxis except for TMP-SMX, which should not be given before engraftment because of its hematologic toxicity, we strongly recommend starting a weekly qPCR screening with the transplant and eventually from conditioning in R+ patients to catch early reactivation. The timing between the sample and result is also crucial to optimally start a preemptive treatment and avoid the development of *Toxoplasma* disease.

Conflicts of interest: The authors declare that they have no conflicts of interest.

Author contributions:

CR and CC conceived and designed the study. RR, ML, FB, CP, AT and SM generated and provided the clinical data. CA, FF, and FB provided the laboratory data. CR, LC and CC assembled the data, and ran the analysis. CR, SM, FB and CC analyzed and interpreted the data and drafted the manuscript. All authors approved the final version.

Funding source: No funding was provided for the research.

Acknowledgments: The authors are grateful to the technical staff of the Laboratory of Mycology and to the physicians and nurses of the Department of Hematology.

REFERENCES

1. Martino R, Bretagne S, Einsele H, et al. Early detection of *Toxoplasma* infection by molecular monitoring of *Toxoplasma gondii* in peripheral blood samples after allogeneic stem cell transplantation. *Clin Infect Dis* 2005;40(1):67-78.
2. Mele A, Paterson PJ, Prentice HG, Leoni P, Kibbler CC. Toxoplasmosis in bone marrow transplantation: a report of two cases and systematic review of the literature. *Bone Marrow Transplant* 2002;29(8):691-8.
3. Guigue N, Leon L, Hamane S, et al. Continuous Decline of *Toxoplasma gondii* Seroprevalence in Hospital: A 1997-2014 Longitudinal Study in Paris, France. *Front Microbiol* 2018;9:2369.
4. Meers S, Lagrou K, Theunissen K, et al. Myeloablative conditioning predisposes patients for *Toxoplasma gondii* reactivation after allogeneic stem cell transplantation. *Clin Infect Dis* 2010;50(8):1127-34.
5. Mulanovich VE, Ahmed SI, Ozturk T, Khokhar FA, Kontoyiannis DP, de Lima M. Toxoplasmosis in allo-SCT patients: risk factors and outcomes at a transplantation center with a low incidence. *Bone Marrow Transplant* 2011;46(2):273-7.
6. Gea-Banacloche J, Masur H, Arns da Cunha C, et al. Regionally limited or rare infections: prevention after hematopoietic cell transplantation. *Bone Marrow Transplant* 2009;44(8):489-94.
7. Prestes DP, Mendes C, Batista MV, et al. A case-series of Toxoplasmosis in hematopoietic stem cell transplantation: still a concern for endemic countries. *Bone Marrow Transplant* 2018;53(10):1336-1339.
8. Martino R, Maertens J, Bretagne S, et al. Toxoplasmosis after hematopoietic stem cell transplantation. *Clin Infect Dis* 2000;31(5):1188-95.
9. Costa JM, Bretagne S. Variation of B1 gene and AF146527 repeat element copy numbers according to *Toxoplasma gondii* strains assessed using real-time quantitative PCR. *J Clin Microbiol* 2012;50(4):1452-4.

10. Bretagne S, Costa JM, Kuentz M, et al. Late toxoplasmosis evidenced by PCR in a marrow transplant recipient. *Bone Marrow Transplant* 1995;15(5):809-11.
11. Gajurel K, Dhakal R, Montoya JG. Toxoplasma prophylaxis in haematopoietic cell transplant recipients: a review of the literature and recommendations. *Curr Opin Infect Dis* 2015;28(4):283-92.
12. Redjoul R, Robin C, Foulet F, et al. Pneumocystis jirovecii pneumonia prophylaxis in allogeneic hematopoietic cell transplant recipients: can we always follow the guidelines? *Bone Marrow Transplant* 2018.

1 **Allogeneic stem cell transplantation in therapy-related**
2 **myelodysplasia after autologous transplantation for**
3 **lymphoma: a retrospective study of the SFGM-TC**

4

5 Daniel Jaimes-Albornoz¹, Lionel Mannone², Stéphanie Nguyen-Quoc³, Yves
6 Chalandon⁴, Patrice Chevallier⁵, Mohamad Mohty⁶, Mathieu Meunier⁷, Marie Robin⁸,
7 Marie-Pierre Ledoux⁹, Gaëlle Guillerm¹⁰, Jacques-Olivier Bay¹¹, Xavier Poiré¹²,
8 Natacha Maillard¹³, Mathieu Leclerc¹⁴, Etienne Daguindau¹⁵, Yves Beguin¹⁶, Marie
9 Thérèse Rubio¹⁷, and Emmanuel Gyan^{1,18}

10

11 ¹Department of Hematology and Cellular Therapy, Tours University Hospital, Tours,
12 France; ²Department of Hematology, Nice University Hospital, Nice, France;
13 ³Department of Hematology, Pitié Salpêtrière Hospital, AP-HP, Paris, France;
14 ⁴Department of Hematology, Geneva University Hospital, Faculty of Medicine,
15 University of Geneva, Geneva, Switzerland; ⁵Department of Hematology, Nantes
16 University Hospital, Nantes, France; ⁶Department of Hematology and Cellular
17 Therapy, Saint-Antoine Hospital, AP-HP, Sorbonne University, UPMC Paris 06,
18 INSERM, UMRS 938, Centre de Recherches Saint-Antoine, Paris, France;
19 ⁷Department of Hematology, Grenoble University Hospital, Grenoble, France;
20 ⁸Department of Hematology, Saint-Louis Hospital, AP-HP, Paris, France;
21 ⁹Department of Hematology, Strasbourg University Hospital, Strasbourg, France;
22 ¹⁰Department of Hematology, Brest University Hospital, Brest, France; ¹¹Department
23 of Hematology, Clermont-Ferrand University Hospital, Clermont-Ferrand, France;
24 ¹²Department of Hematology, Saint-Luc University Hospital, Bruxelles, Belgium;

25 ¹³Department of Hematology, Poitiers University Hospital, Poitiers, France;

26 ¹⁴Department of Hematology, Henri-Mordor Hospital, AP-HP, Créteil, France;

27 ¹⁵Department of Hematology, Besançon University Hospital, Besançon, France;

28 ¹⁶Department of Hematology, Liège University Hospital, Liège, Belgium;

29 ¹⁷Department of Hematology, Brabois Hospital, Nancy University Hospital, CNRS

30 UMR 7365, BioPole Lorraine University, Vandoeuvre-les-Nancy, France;

31 ¹⁸Department of Hematology and Cellular Therapy, Tours University Hospital, UMR

32 CNRS, François Rabelais University, Tours, France.

33

34 **Running title:** Allogeneic transplant in secondary myelodysplasia.

35

36 **Key words:** Allogeneic stem cell transplantation, therapy-related myelodysplasia,

37 autologous stem cell transplantation, lymphoma.

38

39 **Correspondence:**

40 Emmanuel Gyan, MD, PhD. Department of Haematology and Cellular Therapy,

41 Tours University Hospital, 37000 Tours, France. Phone: 33 02 47 47 37 12.

42 Fax: 33 02 47 47 38 11. e-mail: emmanuel.gyan@univ-tours.fr

43

44

45

46

47

48

49

50 **ABSTRACT**

51

52 Therapy-related myelodysplastic syndrome (t-MDS) after autologous stem-cell
53 transplantation (ASCT) is a rare complication with no curative option. Allogeneic
54 hematopoietic stem cell transplantation (allo-HSCT) may be considered for eligible
55 patients and has been understudied in t-MDS. We report 47 consecutive patients with
56 t-MDS after an ASCT who underwent allo-HSCT with a median age of 58 years
57 (range: 30-71) at transplantation and a median follow-up of 22 months (range: 0.7-
58 107). The median overall survival (OS) was 6.9 months (95% confidence interval, 0-
59 19). OS rates were 45% (29-60%) and 30% (15-45%) at 1 and 3 years after
60 transplantation, respectively. On univariate analysis prior therapy for t-MDS before
61 allo-HSCT ($p=0.02$) and mismatched donors ($p=0.004$) were associated with poor OS.
62 Three-year non-relapse mortality (NRM) and relapse rates were 44% (25-63%) and
63 41% (22-61%), respectively. Mismatched donors ($p<0.001$) were associated with
64 higher NRM and a high-risk MDS ($p=0.008$) with a higher relapse risk. On
65 multivariate analysis HLA mismatch was associated with higher NRM (HR 6.21; 95%
66 CI 1.63-23.62; $p=0.007$).

67 In conclusion, our results suggest that one third of the patients who develop t-MDS
68 after an ASCT for lymphoma are cured after an allo-HSCT. The use of mismatched
69 donors with standard GVHD prophylaxis should be avoided in such indication for
70 allo-HSCT. It will be worth to see if the implementation of CY post-transplantation
71 will improve the outcome with mismatched donors.

72

73

74

75 INTRODUCTION

76 Treatment options for lymphoid neoplasms include autologous stem-cell
77 transplantation (ASCT). ASCT may be used for the treatment of relapsed or refractory
78 follicular, diffuse large B-cell, Hodgkin's, or T-cell lymphoma and is associated with
79 improved remission rates and prolonged survival.¹⁻³ Adequate patient selection and
80 advances in supportive care have improved outcomes of intensive chemotherapy in
81 recent years. However, such prolongation of survival is also associated with late
82 complications, such as the development of myeloid neoplasm consecutive to the
83 treatment received, including the conditioning chemotherapy of ASCT.⁴⁻⁶

84 The risk of developing therapy-related myelodysplastic syndrome (t-MDS) or acute
85 myeloid leukemia (t-AML) secondary to the use of both alkylating agents and
86 topoisomerase inhibitors ranges from 5 to 7% in most series, although there are
87 studies with very variable and extreme incidences between 1% at 30 months to 11.7%
88 at six years and may continue to increase until 12-15 years after ASCT.^{7,8}

89 Therapy-related MDS is associated with a high incidence of cytogenetic
90 abnormalities, with frequent deletions or monosomies of chromosomes 5 and 7.^{8,9}
91 These abnormalities have been described after the use of alkylating agents,
92 confirming their role in the development of myelodysplasia.^{7,8} Most cytogenetic
93 alterations and acquired mutations are associated with a poor prognosis linked to a
94 low response to chemotherapy and short duration of remission.^{10,11,12}

95 Although allo-SCT has been widely studied in the context of t-AML studies focusing
96 on t-MDS are rare. Furthermore, the best time to perform allogeneic allo-HSCT in
97 this group of patients is unknown as well as predictors that might help patient
98 selection are lacking.^{13,14}

99 We thus launched a retrospective multicentric study to evaluate the results of all
100 consecutive allogeneic transplantation in population MDS secondary to autologous
101 SCT for lymphoma

102

103 **PATIENTS AND METHODS**

104

105 **Data collection**

106 The registry coordinated by the Francophone Society of Bone Marrow
107 Transplantation and Cellular Therapy (SFGM-TC) of the European Project Manager
108 Internet Server database (ProMISe) was used as the data source. An electronic letter
109 of authorization for the collection and use of the data for this retrospective study was
110 sent to each center. All patients had given written consent before transplant for data
111 collection in ProMISe for future research, in accordance with the Declaration of
112 Helsinki. The scientific council of the SFGM-TC approved this study on February 2,
113 2017.

114

115 **Patient selection**

116 For this retrospective study, we considered all consecutive adult patients who received
117 an allogeneic transplant for the treatment of t-MDS to ASCT for lymphoid neoplasms
118 registered from 2006 to 2016 in the ProMISe SFGM-TC database.

119 Patients who received an ASCT and developed secondary t-AML or those who had t-
120 MDS which progressed to t-AML before allo-HSCT were not included. Patients who
121 received ASCT due to neoplasms other than lymphoid neoplasms were not included.

122

123 **Definitions**

124 Lymphoid neoplasms were categorized according to the WHO 2008 classification.
125 The types of MDS followed the WHO 2008 criteria for MDS and were adapted to the
126 WHO 2016 classification.¹⁵ The cytogenetic classification was assessed according to
127 the IPSS score.¹⁶ Lower-risk MDS comprised MDS with low-risk and intermediate-1
128 risk IPSS scores, and higher risk MDS those with intermediate-2 and high-risk IPSS
129 scores. MDS-EB-1 and MDS-EB-2 were defined according to WHO and were
130 analyzed together. The other categories of MDS with <5% blasts in bone marrow
131 (MDS SLD, MDS MLD, MDS-RS-SLD, MDS-RS-MLD, MDS del(5q), MDS-U)
132 were analyzed together. The response criteria in MDS in patients who received some
133 type of treatment after or before allo-HSCT was defined according to the International
134 Working Group response criteria¹⁷.

135 Acute GvHD was described according to the criteria of the International Bone
136 Marrow Transplantation Registry.¹⁷ For the analysis of CMV serostatus, the most
137 hazardous combination, defined as a CMV-seronegative recipient and CMV-
138 seropositive donor, was compared with the other possible combinations. Intensity of
139 the allo-HSCT conditioning regimen was analyzed according to previously
140 established working definitions.¹⁸ Only two categories were considered in the
141 analysis: myeloablative and reduced-intensity conditioning, due to the multiple
142 schemes and doses used. HLA mismatch was defined as the presence of at least one
143 difference in the HLA-A, -B, -Cw, DR, or DQ loci. For the analysis, no mismatch
144 HLA comprised identical-sibling donor and matched unrelated donor 10/10 (MUD),
145 and HLA mismatched those with mismatched unrelated donor 9/10 (MMUD) and
146 cord blood units 4/6 and 5/6.

147 Overall Survival (OS) was defined as the period from the day of allo-HSCT until the
148 day of death from any cause or date of the last recorded follow-up.

149 Non-relapse mortality (NRM) was defined as death from any cause other than relapse
150 of MDS, including progression to AML, from the day of allo-HSCT.

151 Relapse was defined as a relapse of MDS or progression to AML according to the
152 WHO criteria.

153

154 **Statistical analysis**

155 The characteristics of the patients and the factors related to lymphoma, ASCT, t-
156 MDS, and allo-HSCT are summarized with descriptive statistics. The primary
157 endpoint of the study was OS, which was calculated using the Kaplan-Meier method.

158 The frequency of NRM and relapse was calculated by cumulative incidences.

159 The prognostic effects of the factors with respect to OS, NRM, and relapse were
160 analyzed with a log-rank test (Mantel-Cox) by univariate analysis. The multivariate
161 analysis was performed using the potential predicting factors that were significant by
162 univariate analysis with Cox proportional hazards regression models. The calculations
163 were performed with SPSS software version 23.0.

164

165 **RESULTS**

166 To date, the French ProMISe database includes 74,779 autologous transplant and
167 38,860 allogeneic transplant observations from 98 centers in France, Belgium, and
168 Switzerland. We searched the French ProMISe database for all registered patients
169 from January 2006 to December 2016. A total of 47 patients who met the inclusion
170 criteria were included.

171 **Lymphoma and ASCT**

172 The initial neoplasm for eight patients (17.0%) was a Hodgkin Lymphoma, whereas it
173 was a Non-Hodgkin Lymphoma for 37 (78.7%) (Table 1). Fourteen patients (29.8%)
174 received more than two lines of chemotherapy before autologous transplantation
175 (range 0-8). Conditioning consisted in Carmustine – Etoposide – Cytarabine –
176 Melphalan (BEAM) for 80.8% of patients and other regimens for only 19.2%. Thirty-
177 seven patients (78.7%) achieved complete remission. There were no patients with
178 relapsed lymphoma at the time of allo-HSCT, but it is unknown whether there were
179 patients who relapsed or progressed from lymphoma between ASCT and allo-
180 HSCT. There were no patients who relapsed from lymphoma after allo-HSCT.

181

182 **MDS**

183 The median time from ASCT to the diagnosis of t-MDS was 74.4 months (range 2.2-
184 259). Eleven patients (23.5%) had MDS-EB-1, 12 (25.6%) MDS-EB-2, and 22
185 (46.7%) other types of MDS. No diagnostic information was obtained for two patients
186 (4.2%).

187 Cytogenetic data were obtained for 41 patients: 82.9% had at least one cytogenetic
188 abnormality. The most frequent cytogenetic anomalies were on chromosomes 7 (11
189 patients, 23.4%) and 5 (six patients, 12.8%) or both of those (fifteen patients, 31.9%).

190 Among the patients, 23.4% were considered to be at low risk and 59.6% at high-risk.

191 Sixty-eight percent of patients received at least one treatment line before allo-HSCT:
192 16 (34.1%) received hypomethylating agents and 11 (23.4%) AML-like induction
193 treatment. Ten patients (21.3%) achieved complete remission before transplantation
194 and 36 (76.6%) were not in complete remission prior to allo-HSCT.

195

196 **HSCT**

197 The characteristics of the patients at allo-HSCT are shown in Table 2.

198 The median age at allo-HSCT was 58 years (range: 30 - 71 years) and most of the
199 patients were male (78.7%). The median time interval from diagnosis of t-MDS to
200 allogeneic transplantation was 7.9 months (range: 2.5 - 16.8).

201 Peripheral blood stem-cells (PBSC) were the source used for 87.4% of patients.
202 Nineteen patients (40.5%) were transplanted from an HLA-identical sibling donor and
203 17 (36.2%) from a matched unrelated donor. 10 patients (21.2%) had an mismatched
204 unrelated donor including three patients (6.3%) received umbilical cord blood
205 transplantation (one with a double cord). None of them received a haploidentical
206 donor. Myeloablative conditioning (MAC) was used in nine patients (19.1%), four
207 received a combination of busulfan/cyclophosphamide regimen (two BuCy and two
208 CyBu), with conventional doses (12.8 mg/kg busulfan IV, 120 mg/kg
209 cyclophosphamide), three a combination of fludarabine/busulfan with ATG (150
210 mg/m² fludarabine, 12.8 mg/kg busulfan and various doses of ATG between 2.5 mg–5
211 mg/kg), one fludarabine/busulfan without ATG (160 mg/m² fludarabine, 9.6 mg/kg
212 busulfan), and one fludarabine and TBI (120 mg/m² fludarabine, 8 Gy TBI).

213 Thirty-eight patients (80.9%) received reduced intensity conditioning (RIC). 22
214 patients received a combination of fludarabine-busulfan-based RIC with ATG or ALG
215 (100–150 mg/m² fludarabine, 3.2–6.4 mg/kg busulfan, 2.5-5 mg/kg ATG or 5–20
216 mg/kg ALG). 4 patients received fludarabine-busulfan-based RIC without ATG. Eight
217 patients received fludarabine-TBI-based RIC (2Gy–8 Gy) and four patients received
218 sequential FLAMSA-RIC.

219 Eighteen patients (38.3%) received prophylaxis with cyclosporine (CsA) and
220 mycophenolate mofetil (MMF) and 11 (23.4%) cyclosporine and methotrexate
221 (MTX). Twelve patients (25.5%) received only cyclosporine and six (12.8%)
222 received other regimens. The most frequent serological status for cytomegalovirus
223 (CMV) was 29.7% R⁺/D⁺. Thirteen transplants (27.1%) were performed with the
224 combination R⁺/D⁻.

225 Performance status was assessed using the Karnofsky Performance Score (KPS): 29
226 patients (61.8%) had a score of 90-100 before transplantation.

227

228 **Response to allo-HSCT and complications.**

229 The median duration of post-transplant follow-up was 22 months (range 0.7-107) and
230 median survival 6.9 months (95% CI 0-19).

231 Thirty-four patients (72.3%) were in complete response after allo-HSCT and nine
232 patients (19.1%) had a relapse/progression post-transplantation. The response was not
233 evaluated for four patients (8.6%) because of the early death of three and lost to
234 follow-up one of them.

235 Acute GvHD occurred in 20 patients (42.5%), seven (14.8%) had grade I, and 13
236 (27.7%) had a grade requiring treatment (Grade II-IV). Ten patients (21.3%)
237 developed chronic GvHD, of whom four (8.6%) had extensive and six (12.7%)
238 limited involvement At the time of the analysis in August 2017, there were 15
239 relapses or progressions of which 13 died: 12 related to relapse and one could
240 not determine the cause. 11 patients in complete remission died due to
241 transplant complications, mainly infectious. 3 patients had early death due to

242 transplant complications without knowing the response obtained to the
243 transplant. No deaths due to veno-occlusive disease or graft rejection were reported.
244 The causes of death are listed in Table 3.

245

246 **Univariate and Multivariate analysis of patients**

247 OS for all patients was 45% (95% confidence interval 29-60) at first year, 39% (95%
248 CI 24-55) at 2 years and 30% (95% CI 15-45) at 3 years (Table 4 and Figure 1).

249 Univariate analysis found that prior therapy of t-MDS with hypomethylating agents
250 before allo-HSCT ($p=0.02$) and the presence of an HLA mismatch ($p=0.004$) were
251 associated with poorer OS (Table 5). Multivariate analysis showed only a non-
252 statistically significant association with poorer OS for patients receiving a treatment
253 based on hypomethylating agents (HR, 3.55; 95% CI, 0.97 - 12.97; $p=0.06$), and no
254 other clinically significant factors (Table 6).

255 NRM was 35% (95% CI 18–51) at first year, 39% (95% CI 21–56) at 2 years, and
256 44% (95% CI 25–63) at 3 years (Table 4 and Figure 1). Univariate analysis identified
257 gender ($p=0.02$), graft type ($p=0.02$) mismatched unrelated donor type ($p<0.001$) and
258 the presence of an HLA mismatch ($p=0.001$) to be significant risk factors (Figure 2).

259 Multivariate analysis showed an association between the use of a mismatch unrelated
260 donor (MMUD) and shorter survival after transplantation, relative to identical siblings
261 or matched unrelated donors (MUD) (HR, 6.21; 95% CI, 1.63– 23.62; $p=0.007$)

262 The risk of relapse was 35% (95% CI 18–53) at first year, 41% (95% CI 22–61) at 2
263 years and 41% (95% CI 22–61) at 3 years (Table 4 and Figure 1). The type of MDS
264 and presence of marrow blasts ($p=0.008$) were the most significant predictive factor
265 of relapse in univariate analysis, however multivariate analysis did not identify the
266 presence of marrow blasts as a significant factor of relapse.

267 **DISCUSSION**

268 This retrospective study of the SFGM-TC, which examined the experience of allo-
269 HSCT in patients, with t-MDS after an ASCT for lymphoid neoplasm, over 10 years,
270 showed donor mismatch to adversely affect OS. This is the first series published in
271 this specific population. In other studies, such patients account for 7 - 32% of the
272 sample.^{13,14,19-26} Most of the survival data of these studies show results for a mix of
273 patients, including those with t-AML and t-MDS exposed to multiple treatments
274 (chemotherapy and/or radiotherapy, and not necessarily previous ASCT) and various
275 primary diseases (solid organ neoplasms, lymphoid neoplasms, myeloid neoplasms,
276 and congenital anomalies).

277 Although allo-HSCT has been used as a curative therapeutic modality for eligible
278 patients, data published by several groups have shown poor long-term survival.<sup>13,14,19-
279 ²¹ In our series, the median overall survival was 6.9 months with OS at first and third
280 year of 45 and 30%, respectively. The high NRM and relapse rates at three years
281 (44% and 41%, respectively) were similar to those previously reported by other
282 studies, consistent with the poor prognosis of these patients.</sup>

283 Relapse or progression of t-MDS was the main cause of mortality (44.4%) in our
284 study. Patients with MDS-EB-1 and MDS-EB-2 had a higher risk of relapse by
285 univariate analysis. The association of these aggressive variants of myelodysplasia
286 with higher relapse rates has been described in other studies on patients with various
287 primary diseases. It is not known whether treating t-MDS before transplantation can
288 decrease the risk of relapse or whether maintenance treatment should be started after
289 transplant to prevent relapse. In our study, the only type of pre-transplant treatment
290 associated with improved survival was AML-like therapy even if they had not

291 achieved CR before transplantation, in univariate analysis ($p= 0.02$). The multivariate
292 analysis shows a non-statistically significant association of hypomethylating agents
293 before transplantation with a poorer OS (HR 3.55, 95% CI 0.97-12.97, $p=0.06$)
294 regardless of the response they obtained with this treatment before transplantation, in
295 contrast to patients with *de novo* MDS and poor risk cytogenetics, who normally
296 benefit from this approach.²⁸ Our results are not valued for the sample size and the
297 retrospective analysis. Prospective studies are necessary to determine the benefit of a
298 type of treatment before transplantation²⁷ A retrospective analysis that included more
299 patients with t-AML than t-MDS, reports relapse rates of 42% and 44% at 5 and 10
300 years with OS of 38% and 24% respectively, when AML-like chemotherapy is used
301 before transplantation.²⁵

302 No patient in our study received post-transplant maintenance therapy. The use of
303 maintenance therapy, with low doses of azacytidine after allo-HSCT²⁸ and
304 azacytidine²⁹ or decitabine with infusion of donor lymphocytes³⁰, has been published
305 recently and may be worth considering. Targeted therapies, directed against mutated
306 oncogenes, such as IDH-1, IDH-2, or FLT-3 genomic alterations, may improve the
307 outcome of specific subsets of patients in the future.

308 Infections and GVHD were the main cause of non relapse mortality.

309 In our series there were 27 deaths, 12 were due to relapse, 8 due to infections and 3
310 due to GVHD. The few deaths due to GVHD show the intensity of the
311 immunosuppressive prophylaxis used, limiting the graft-versus-tumor effect,
312 increasing the possibility of relapse and the appearance of infections. Multiple
313 schemes and doses used in conditioning and immunosuppressive prophylaxis, testing
314 the usual drugs, have not allowed to identify whether one scheme is superior to

315 another. A significant factor to improve survival was the absence of a mismatch by
316 using either HLA identical-sibling or matched unrelated donors, as previously
317 reported.¹⁴ A prospective study of the SFGM-TC reported better OS (37% vs 15%,
318 p=0.02) of patients with high-risk MDS who had identical HLA donors *versus* those
319 who did not.³¹ In our series, there was a lower frequency of NRM in patients with
320 10/10 donors than 9/10 donors (HR, 6.21, 95% CI, 1.63-23.62, p=0.007), although
321 was not significant in OS by multivariate analysis. NRM associated with
322 mismatched HLA donors could be improved with new prophylactic strategies to
323 counter GvHD, such as post-transplant cyclophosphamide (PT-Cy). Reports over the
324 last years on a small number of patients with *de novo* MDS/AML and t-MN who
325 underwent allo-HSCT show similar results for HLA identical-sibling, MUD, or
326 haploidentical donors.³² A recent retrospective series of EBMT in patients with MDS
327 who underwent haploidentical transplants reported better OS for patients treated with
328 PT-Cy than those who were not (OS at three years of 38% vs 28%), but with high
329 NRM (41% vs 55%).³³ This modality may be an acceptable option, although the risk
330 of relapse remains high and variations in the dose of PT-Cy have even been tested in
331 high-risk patients with refractory MDS/AML.³⁴ Indeed, older patients were recently
332 reported to have OS of 42%, and a relapse rate of 24% at two years.³⁵ Strategies to
333 improve progression-free survival and decrease NRM using PT-Cy have been
334 implemented. The ALTERGREF trial (NCT03250546), currently in the inclusion
335 phase, will evaluate the effect of PT-Cy for prevention of GvHD in haploidentical and
336 HLA-9/10 mismatched unrelated donors transplant.

337 The proportion of patients with high risk cytogenetic has been previously reported to
338 be 17 - 49%.^{13,14,23,24} In our study, 68% (32 patients) had adverse cytogenetic

339 alterations, especially abnormalities in chromosomes 5 and 7. However, the results
340 were probably not significant for the few patients in the other risk categories.

341 The best time to perform the transplant is unknown. It is possible that rapid
342 transplantation could reduce the risk of t-MDS/t-AML-related deterioration.²⁵
343 Although a higher frequency of NRM is possible if the transplant is performed
344 beyond six months (50% vs 12.5%, p=0.03) caused by toxicity and infections due to
345 multiple chemotherapy cycles²³, we found no difference in OS or NRM. Although
346 the median age of 58 years is higher than for other large related series and 60% of
347 patients had a KPS \geq 90, these factors did not play a significant role in survival, as in
348 other series.^{12-14,20,23,25}

349 Our data also do not support that factors related to the primary disease and its
350 treatment can influence survival. Interestingly, no veno-occlusive disease was
351 observed in this population having received a previous autologous transplantation.

352 A retrospective report of EBMT found better results in the period between 1998 and
353 2006 than for transplants performed before 1998 (40% vs 29%, p=0.02).¹³ We found
354 no differences between the periods of 2006-2010 and 2011-2016, probably because
355 support care has not changed as much in the last 10 years as during the transition from
356 the 80's to 90's.

357 Treatment options are still limited for patients who are not candidates for allo-HSCT.
358 Other therapeutic strategies have been tested using azacitidine or clofarabine
359 associated with chemotherapy with encouraging results.^{36,37}

360 The limitations of our study include the collection of retrospective data and the
361 absence of a historical group for comparisons. Patient selection may have varied

362 between centers. The small number of patients and the low incidence of secondary
363 myelodysplasia makes it difficult to perform a prospective study.

364 In summary, although the number of patients in this study was small, the results
365 suggest that patients receiving an ASCT for a lymphoid neoplasm who develop t-
366 MDS have short OS after allo-HSCT, with few long-time survivors. The use of
367 MMUD donors with standard GvHD prophylaxis should be avoided in such
368 indications for allo-HSCT. Studies that attempt to determine whether the
369 implementation of Cy post transplantation would improve these outcomes with
370 mismatched donors are still ongoing. It remains necessary to explore more
371 alternatives and transplant strategies in this critical population.

372

373 **AUTHOR CONTRIBUTIONS**

374 EG and DJA designed the study, analyzed the data, and wrote the paper. All authors
375 provided patient data, approved the study design, critically reviewed the manuscript
376 and approved the final draft.

377

378 **ACKNOWLEDGEMENTS**

379 The authors thank Nicole Raus and Réda Chebel from the SFGM-TC for data
380 collection and management, and all the data managers of the participating centers for
381 providing supplementary data.

382

383 **CONFLICT OF INTEREST**

384 The authors declare no conflict of interest.

385

386

387 **REFERENCES**

388

389 1. Appelbaum F, Herzig G, Ziegler J, et al. Successful engraftment of
390 cryopreserved autologous bone marrow in patients with malignant lymphoma.
391 *Blood*. 1978; 52: 85-95.

392

393 2. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with
394 autologous bone marrow transplantation in relapsed and resistant Hodgkin's
395 disease: results of a BNLI randomised trial. *Lancet*. 1993; 341: 1051-1054.

396

397 3. Philip T, Gulielmi C, Hagenbeek A, et al. Autologous bone marrow
398 transplantation as compared with salvage chemotherapy in relapses of
399 chemotherapy- sensitive non- Hodgkin's Lymphoma. *N Engl J Med*. 1995;
400 333: 1540-1545.

401

402 4. Stone R. Myelodysplastic Syndrome after autologous transplantation for
403 lymphoma: The price of progress? *Blood*. 1994; 83: 3437-3440.

404

405 5. Howe R, Micallef INM, Inwards DJ, et al. Secondary myelodysplastic
406 syndrome and acute myelogenous leukemia are significant complications
407 following autologous stem cell transplantation for lymphoma. *Bone Marrow*
408 *Transplant*. 2003; 32: 317-324.

409

410 6. Gyan E, Foussard C, Bertrand P, et al. High-dose therapy followed by
411 autologous purged stem cell transplantation and doxorubicin-based

- 412 chemotherapy in patients with advanced follicular lymphoma: a randomized
413 multicenter study by the GOELAMS with final results after a median follow-
414 up of 9 years. *Blood*. 2009; 113: 995-1001.
- 415
- 416 7. Akhtari M, Bhatt VR, Tandra PK, et al. Therapy-related myeloid neoplasms
417 after autologous hematopoietic stem cell transplantation in lymphoma patients.
418 *Cancer Biology & Therapy*. 2013; 14: 1077-1088.
- 419
- 420 8. Pedersen-Bjergaard J, Andersen MK, Christiansen D. Therapy-related acute
421 myeloid leukemia and myelodysplasia after high-dose chemotherapy and
422 autologous stem cell transplantation. *Blood*. 2000; 95: 3273-3279.
- 423
- 424 9. Smith SM, Le Beau MM, Huo D, et al. Clinical-cytogenetic associations in
425 306 patients with therapy-related myelodysplasia and myeloid leukemia: the
426 University of Chicago series. *Blood*. 2003; 102: 43-52.
- 427
- 428 10. Armand P, Kim H, De Angelo DJ, et al. Impact of cytogenetics on outcome of
429 de novo and therapy-related AML and MDS after allogeneic transplantation.
430 *Biol Blood Marrow Transplant*. 2007; 13: 655-664.
- 431
- 432 11. Yoshizato T, Nannya Y, Atsuta Y, et al. Genetic abnormalities in
433 myelodysplasia and secondary acute myeloid leukemia: impact on outcome of
434 stem cell transplantation. *Blood*. 2017; 129: 2347-2358.
- 435
- 436 12. Chang CK, Storer BE, Scott BL, et al. Hematopoietic cell transplantation in

437 patients with myelodysplastic syndrome or acute myeloid leukemia arising
438 from myelodysplastic syndrome: similar outcomes in patients with de novo
439 disease and disease following prior therapy or antecedent hematologic
440 disorders. *Blood*. 2007; 110: 1379-1387.

441

442 13. Kröger N, Brand R, Van Biezen A, et al. Risk factors for therapy-related
443 myelodysplastic syndrome and acute myeloid leukemia treated with allogeneic
444 stem cell transplantation. *Haematologica*. 2009; 94: 542-549.

445

446 14. Litzow MR, Tarima S, Pérez WS, et al. Allogeneic transplantation for therapy-
447 related myelodysplastic syndrome and acute myeloid leukemia. *Blood*. 2010;
448 115: 1850-1857.

449

450 15. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health
451 Organization classification of myeloid neoplasms and acute leukemia. *Blood*.
452 2016; 127: 2391-2405.

453

454 16. Greenberg P, Cox C, Le Beau MM, et al. International scoring system for
455 evaluating prognosis in Myelodysplastic Syndromes. *Blood*. 1997; 89: 2079-
456 2088.

457

458 17. Cheson B, Greenberg P, Bennett J, et al. Clinical application and proposal for
459 modification of the International Working Group (IWG) response criteria in
460 myelodysplasia. *Blood*. 2006; 108: 419-425

461

- 462 18. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for
463 grading acute graft-versus-host disease: retrospective comparison with
464 Glucksberg grade. *Br J Haematol.* 1997; 97: 855–864.
465
- 466 19. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the Intensity of Conditioning
467 Regimens: Working Definitions. *Biol Blood Marrow Transplant.* 2009; 15:
468 1628-1633.
469
- 470 20. Ballen KK, Gilliland DG, Guinan EC, et al. Bone marrow transplantation for
471 therapy-related myelodysplasia: comparison with primary myelodysplasia.
472 *Bone Marrow Transplant.* 1997; 20: 737–743.
473
- 474 21. Yakoub-Agha I, De La Salmonière P, Ribaud P, et al. Allogeneic Bone
475 Marrow Transplantation for Therapy- Related Myelodysplastic Syndrome and
476 Acute Myeloid Leukemia: A Long-Term Study of 70 Patients—Report of the
477 French Society of Bone Marrow Transplantation. *J Clin Oncol.* 2000; 18:
478 963-971.
- 479 22. Witherspoon RP, Deeg J, Storer B, et al. Hematopoietic Stem-Cell
480 Transplantation for Treatment- Related Leukemia or Myelodysplasia. *J*
481 *Clinical Oncol.* 2001; 19: 2134-2141.
482
- 483 23. Yokoyama H, Mori SI, Kobayashi Y, et al. Hematopoietic stem cell
484 transplantation for therapy-related myelodysplastic syndrome and acute
485 leukemia: a single-center analysis of 47 patients. *Int J Hematol.* 2010; 92:
486 334–341.

487

488 24. Spina F, Alessandrino PE, Milani R, et al. Allogeneic stem cell transplantation
489 in therapy-related acute myeloid leukemia and myelodysplastic syndromes:
490 impact of patient characteristics and timing of transplant. *Leuk Lymphoma*.
491 2012; 53: 96–102.

492

493 25. Alam N, Atenafu EG, Kuruvilla J, et al. Outcomes of patients with therapy-
494 related AML/myelodysplastic syndrome (t-AML/MDS) following
495 hematopoietic cell transplantation. *Bone Marrow Transplant*. 2015; 50: 1180–
496 1186.

497

498 26. Finke J, Schmoor C, Bertz H, et al. Long-term follow-up of therapy-related
499 myelodysplasia and AML patients treated with allogeneic hematopoietic cell
500 transplantation. *Bone Marrow Transplant*. 2016; 51: 771–777.

501

502 27. Metafuni E, Chiusolo P, Laurenti L, et al. Allogeneic Hematopoietic Stem
503 Cell Transplantation In Therapy-Related Myeloid Neoplasms (t-MN) of the
504 Adult: Monocentric Observational Study and Review of the Literature.
505 *Mediterr J Hematol Infect Dis*. 2018; **10** :1-12.

506

507 28. Malcovati L, Hellström-Lindberg E, Bowen D, et al. Diagnosis and treatment
508 of primary myelodysplastic syndromes in adults: Recommendations from the
509 European LeukemiaNet. *Blood*. 2013, 122: 2943-2964.

510

511 29. De Lima M, Giralt S, Thall PF, et al. Maintenance therapy with low-dose

512 azacitidine after allogeneic hematopoietic stem cell transplantation for
513 relapsed AML or MDS: a dose and schedule finding study. *Cancer*. 2010; 116:
514 5420-5431.

515

516 30. Steinmann J, Bertz H, Wäsch R, et al. 5-Azacytidine and DLI can induce long-
517 term remissions in AML patients relapsed after allograft. *Bone Marrow*
518 *Transplant*. 2015; 50: 690–695.

519

520 31. Schroeder T, Rautenberg C, Krüger W, et al. Treatment of relapsed AML and
521 MDS after allogeneic stem cell transplantation with decitabine and DLI—a
522 retrospective multicenter analysis on behalf of the German Cooperative
523 Transplant Study Group. *Ann Hematol*. 2018; 97: 335-342.

524

525 32. Robin M, Porcher R, Adès L, et al. HLA-matched allogeneic stem cell
526 transplantation improves outcome of higher risk myelodysplastic syndrome A
527 prospective study on behalf of SFGM-TC and GFM. *Leukemia*. 2015; 29:
528 1496 – 1501.

529

530 33. Di Stasi A, Milton DR, Poon LM, et al. Similar transplantation outcomes for
531 acute myeloid Leukemia and myelodysplastic syndrome patients with
532 haploidentical versus 10/10 human leukocyte antigen- matched unrelated and
533 related donors. *Biol Blood Marrow Transplant*. 2014; 20:1975 – 1981.

534

535 34. Robin M, Porcher R, Ciceri F, et al. Haploidentical transplant in patients with
536 myelodysplastic syndrome. *Blood*. advances 2017; 1:1876 – 1883.

537

538 35. Nakamae H, Koh H, Katayama T, et al. HLA haploidentical peripheral blood
539 stem cell transplantation using reduced dose of posttransplantation
540 cyclophosphamide for poor-prognosis or refractory leukemia and
541 myelodysplastic syndrome. *Exp Hematol*. 2015; 43: 921–929.

542

543 36. Ciurea SO, Shah MV, Saliba RM, et al. Haploidentical transplantation for
544 older patients with acute myeloid leukemia and myelodysplastic syndrome.
545 *Biol Blood Marrow Transplant*. 2018; 24:1232-1236.

546

547 37. Ballya C, Thépota S, Quesnela B, et al. Azacitidine in the treatment of therapy
548 related myelodysplastic syndrome and acute myeloid leukemia (tMDS/AML):
549 A report on 54 patients by the Groupe Francophone des Myelodysplasies
550 (GFM). *Leuk Res*. 2013; **37**: 637– 640.

551

552 38. Jabbour E, Faderl S, Sasaki K, et al. Phase 2 Study of Low-Dose Clofarabine
553 Plus Cytarabine for patients with higher risk Myelodysplastic Syndrome who
554 have relapsed or are refractory to hypomethylating agents. *Cancer*. 2016; 1-9.