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| Complete List of Authors: | Varaldo, Riccardo; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Raiola, Anna Maria; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Di Grazia, Carmen; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Aquino, Sara; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Beltrami, Germana; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Bregante, Stefania; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Cruciani, Fabio; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Dominietto, Alida; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Ghiso, Anna; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Giannoni, Livia; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Gualandi, Francesca; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Ibatici, Adalberto; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Lamparelli, Teresa; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Marani, Carlo; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>van Lindt, Maria; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia<br>Santini, Valeria; University of Florence, Hematology<br>Bacigalupo, Andrea; Università Cattolica Sacro Cuore, Istituto di Ematologia, Fondazione Policlinico Gemelli<br>Angelucci, Emanuele; IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, U.O. Ematologia |
| Keywords: | Haploidentical transplant, MDS, higher risk |

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# Haploidentical bone marrow transplantation in patients with advanced myelodysplastic syndrome.

Varaldo Riccardo[1], Raiola Anna Maria[1], Di Grazia Carmen[1], Aquino Sara[1], Beltrami Germana[1], Bregante Stefania[1], Cruciani Fabio[1], Dominietto Alida[1], Ghiso Anna[1], Giannoni Livia[1] ,Gualandi Francesca[1], Ibatici Adalberto[1], Lamparelli Teresa[1], Marani Carlo[1], Van Lint Maria Teresa[1],Valeria Santini[2,4] Bacigalupo Andrea[3] & Angelucci Emanuele[1,4].

1 U.O. Ematologia *IRCCS Azienda Ospedaliera Universitaria San Martino – IST. Istituto Nazionale per la Ricerca sul Cancro. Genova, Italy*

2 Azienda Ospedaliero-Universitaria Careggi, University of Florence, Firenze, Italy

3. Istituto di Ematologia, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Gemelli Roma, Italy

4 FISM: Fondazione Italiana Sindromi mielodisplastiche

Correspondence: Emanuele Angelucci U.O. Ematologia *IRCCS Azienda Ospedaliera Universitaria San Martino – IST. Istituto Nazionale per la Ricerca sul Cancro. Largo Rosanna Benzi, 10 16132 GENOVA. Italy.*

*Email: emanuele.angelucci@hsanmartino.it*

*Tel +39 010 5553176*

*Fax +39 010 5556789.*

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Figure 1

**Running title**: Haploidentidal transplant for higher risk MDS

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To the Editor

Myelodysplastic syndromes (MDS) are a heterogeneous and complex group of hematopoietic stem cell disorders, primarily found within the elderly population, characterized by ineffective hematopoiesis with a variable risk to progression to acute myeloid leukemia,. Despite innovative drug developments, allogeneic hemopoietic cell transplantation (HCT) is, to date, the only available curative option for myelodysplastic syndrome patients [1,2]. Indication and timing of the procedure have been widely discussed in the literature [3-5]. However, HCT is broadly underutilized: older patients' age, age related comorbidities, lack of appropriate donor are factors involved into the limited application of HCT to MDS [6-7]. Over the last decade, the emerging role of reduced-intensity conditioning and the use of alternative donors (i.e. haplotransplant, cord blood transplant) have expanded the eligibility and feasibility of this procedure to several patients and to those who are not eligible for a standard myeloablative conditioning regimen. Because a haploidentical donor is available in most families recent implementation of haploidentical HCT in transplant centers program has offered to many patients the opportunity to undergo this potentially curative approach.

From August 2011 until March 2016, 30 consecutive patients with median age of 60 years (range 43-70) and a median comorbidity index [8] of 3 (range 0-7), underwent T cell replete haplotransplant [9]. All but one presented advanced disease characteristics: 16 very high risk , 8 high risk, 5 intermediate, 1 low risk according the revised international prognostic scoring system (r-IPSS)[10].

Median diagnosis-transplant interval was 9.5 months. Fifteen patients had received de-methylating agents before transplant, no complete response was observed. Haplo donors/recipients were typed at the HLA-A, HLA-B,HLA-C, HLA-DRB1 at high resolution level. The donor/recipient pairs exhibited a median of 4 mismatches (range 0 to 4) on the unshared haplotype. Conditioning regimen was assigned on the basis of age and comorbidity index

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[8]: ten patients received myeloablative conditioning regimen and 20 a reduced intensity conditioning regimen as previously reported [9].

All patients received un-manipulated marrow derived hemopoietic cells. Marrow harvest was done as previously described [11]. The median of infused nucleated cell dose was 3.1 $x10^8$/kg (range 1.1-6). Graft versus host prophylaxis was performed by post transplant high doses of cyclophosphamide [9].

Overall survival, disease free survival rate, non-relapse mortality, acute and chronic graft versus host disease (GvHD) rates were calculated using the method of Kaplan and Meier with relapse and death as competitive events.

The cumulative incidence of grade II-IV acute GvHD was 15%. Chronic GvHD developed in six patients and was extensive in five. Two patients experienced graft failure and were successfully re-transplanted with the same haploidentical donor after non myeloablative-conditioning regimen. Cumulative incidence of non-relapse mortality was 4% and 18% at one and 4 years, respectively. Two patients died in complete remission at 389 (chronic GvHD+ sepsis) and 1123 (interstitial pneumonitis) days after transplant, respectively.

Seven patients relapsed at a median time from transplant of 188 days (range 139 - 560 days). Cumulative risk of relapse was 27%. All relapsed patients subsequently died by disease progression despite best supportive care (n=4), salvage therapy with donor lymphocytes infusion (n=1), de-methylating agents and donor lymphocytes infusion (n=1) or acute leukemia like chemotherapy plus de-methylating agent and donor lymphocytes infusion (n= 1). At the time of this writing of the 21 surviving patients (all in remission) two are receiving chronic GvHD treatment.

With a median follow up of 20.5 months (range 4 - 54) the 3 years overall survival and disease free survival were 72% (95% CI 63-81) and 69% (95% CI 60-78), respectively. Figure 1 reports the 3 years overall (a) and disease free survival (b). Relapse remains a major challenge in this setting of patients with extremely poor prognosis despite post transplant treatment therapy. No significant risk factor for death or relapse was identified in our limited

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transplant series however mutation analysis was not carried out. A dismal outcome has been recently reported in several research articles according to somatic mutational status [12.13]. A better relapse risk stratification before HCT could help identify subgroups of patients who are more likely to benefit from an adapted conditioning regimen or from early post transplant therapeutic strategies such as preemptive/prophylactic donor lymphocytes infusion and/or hypo-methylating agents.

This analysis is hampered by the limited number of patients analyzed and by the usual limitations related to its retrospective nature. However these data, considering very high-risk features of disease in more than 50% of patients and elevated median comorbidity index are encouraging and deserve further studies. A larger prospective trial of haploidentical transplant in higher risk MDS patients fitting with the procedure and lacking an HLA identical donor is warranted.

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## References


1. Malcovati L, Hellström-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: Recommendations from the European LeukemiaNet. Blood 2013;122(17): 2943–64.
2. Santini V, Alessandrino PE, Angelucci E, et al. Clinical management of myelodysplastic syndromes: Update of SIE, SIES, GITMO practice guidelines. Leuk Res. 2010;34(12):1576–88.
3. Alessandrino EP, Della Porta MG, Malcovati L, et al. Optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndrome. Am J Hematol 2013;88(7):581–88.
4. Della Porta MG, Alessandrino EP, Bacigalupo A, et al. Predictive factors for the outcome of allogeneic transplantation in patients with myelodysplastic syndrome stratified according to the revised International Prognostic Scoring System (IPSS-R). Blood 2014;123(15):2333–42.
5. Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: Delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood 2004;104(2):579–85.
6. El-Jawahri A, Kim HT, Steensma DP, et al. Does quality of life impact the decision to pursue stem cell transplantation for elderly patients with advanced MDS? Bone Marrow Transplant 2016;51(8):1121-26.
7. Mishra A, Anasetti C. Selection of Patients With Myelodysplastic Syndrome for Allogeneic Hematopoietic Stem Cell Transplantation. Clin Lymphoma Myeloma Leuk 2016;16 Suppl:S49-52.
8. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2005;106(8):2912-19.
9. Raiola AM, Dominietto A, Ghiso A, et al. Unmanipulated Haploidentical Bone Marrow Transplantation and Posttransplantation Cyclophosphamide for Hematologic Malignancies after Myeloablative Conditioning. Biol Blood


For Peer Review

Marrow Transplant 2013;19(1):117–22.

10. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120(12):2454–65.
11. Bacigalupo A, Tong J, Podestà M, et al. Bone marrow harvest for marrow transplantation: effect of multiple small (2 ml) or large (20 ml) aspirates. Bone Marrow Transplant. 1992;9(6):467–70.
12. Dalla Porta MG, Galli A, Bacigalupo A et al. Clinical Effects of Driver Somatic Mutations on the Outcomes of Patients With Myelodysplastic Syndromes Treated With Allogeneic Hematopoietic Stem-Cell Transplantation. J Clin Oncol 2016;34(30):3627-37.
13. Lindsley RC, Saber W, Mar BG. Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation. N Engl J Med 2017 ;376(6):536-547.

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Figure legend

Figure 1: Three years overall (a) and disease free survival (b) of the 30 MDS patients submitted to haploidentical HCT. Because of the limited number of patients in follow up after the third year no survival data have been calculated after these limit despite e single late death (day + 1123) was registered.

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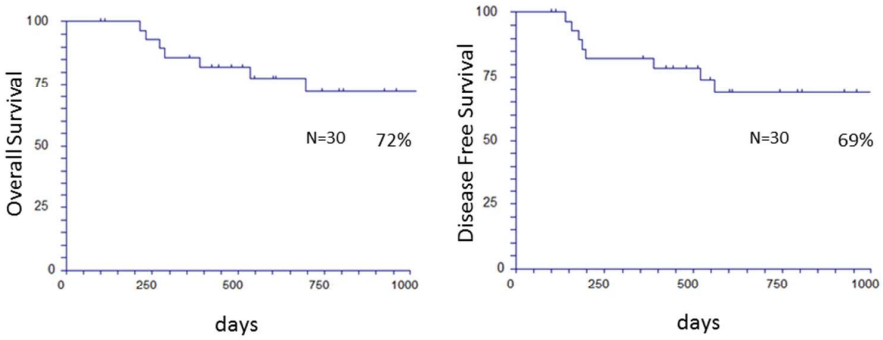


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