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Haploidentical bone marrow transplantation in patients with advanced myelodysplastic syndrome.

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Keywords:	Haploidentical transplant, MDS, higher risk

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Haploidentical bone marrow transplantation in patients with advanced myelodysplastic syndrome.

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Figure 1

Running title: Haploidentical transplant for higher risk MDS

Keywords: Haploidentical transplant, MDS, higher risk

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3 To the Editor
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6 Myelodysplastic syndromes (MDS) are a heterogeneous and complex group of
7 hematopoietic stem cell disorders, primarily found within the elderly
8 population, characterized by ineffective hematopoiesis with a variable risk to
9 progression to acute myeloid leukemia,. Despite innovative drug
10 developments, allogeneic hemopoietic cell transplantation (HCT) is, to date,
11 the only available curative option for myelodysplastic syndrome patients [1,2].
12 Indication and timing of the procedure have been widely discussed in the
13 literature [3-5]. However, HCT is broadly underutilized: older patients' age,
14 age related comorbidities, lack of appropriate donor are factors involved into
15 the limited application of HCT to MDS [6-7]. Over the last decade, the
16 emerging role of reduced-intensity conditioning and the use of alternative
17 donors (i.e. haplotransplant, cord blood transplant) have expanded the
18 eligibility and feasibility of this procedure to several patients and to those who
19 are not eligible for a standard myeloablative conditioning regimen. Because a
20 haploidentical donor is available in most families recent implementation of
21 haploidentical HCT in transplant centers program has offered to many patients
22 the opportunity to undergo this potentially curative approach.
23
24

25 From August 2011 until March 2016, 30 consecutive patients with median age
26 of 60 years (range 43-70) and a median comorbidity index [8] of 3 (range 0-
27 7), underwent T cell replete haplotransplant [9]. All but one presented
28 advanced disease characteristics: 16 very high risk , 8 high risk, 5
29 intermediate, 1 low risk according the revised international prognostic scoring
30 system (r-IPSS)[10].
31
32

33 Median diagnosis-transplant interval was 9.5 months. Fifteen patients had
34 received de-methylating agents before transplant, no complete response was
35 observed. Haplo donors/recipients were typed at the HLA-A, HLA-B,HLA-C,
36 HLA-DRB1 at high resolution level. The donor/recipient pairs exhibited a
37 median of 4 mismatches (range 0 to 4) on the unshared haplotype.
38 Conditioning regimen was assigned on the basis of age and comorbidity index
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3 [8]: ten patients received myeloablative conditioning regimen and 20 a
4 reduced intensity conditioning regimen as previously reported [9].
5

6 All patients received un-manipulated marrow derived hemopoietic cells.
7 Marrow harvest was done as previously described [11]. The median of infused
8 nucleated cell dose was $3.1 \times 10^8/\text{kg}$ (range 1.1-6). Graft versus host
9 prophylaxis was performed by post transplant high doses of cyclophosphamide
10 [9].
11

12 Overall survival, disease free survival rate, non-relapse mortality, acute and
13 chronic graft versus host disease (GvHD) rates were calculated using the
14 method of Kaplan and Meier with relapse and death as competitive events.
15

16
17 The cumulative incidence of grade II-IV acute GvHD was 15%. Chronic GvHD
18 developed in six patients and was extensive in five. Two patients experienced
19 graft failure and were successfully re-transplanted with the same haploidentical
20 donor after non myeloablative-conditioning regimen. Cumulative incidence of
21 non-relapse mortality was 4% and 18% at one and 4 years, respectively. Two
22 patients died in complete remission at 389 (chronic GvHD+ sepsis) and 1123
23 (interstitial pneumonitis) days after transplant, respectively.
24

25 Seven patients relapsed at a median time from transplant of 188 days (range
26 139 - 560 days). Cumulative risk of relapse was 27%. All relapsed patients
27 subsequently died by disease progression despite best supportive care (n=4),
28 salvage therapy with donor lymphocytes infusion (n=1), de-methylating
29 agents and donor lymphocytes infusion (n=1) or acute leukemia like
30 chemotherapy plus de-methylating agent and donor lymphocytes infusion (n=
31 1). At the time of this writing of the 21 surviving patients (all in remission) two
32 are receiving chronic GvHD treatment.
33

34 With a median follow up of 20.5 months (range 4 - 54) the 3 years overall
35 survival and disease free survival were 72% (95% CI 63-81) and 69% (95%
36 CI 60-78), respectively. Figure 1 reports the 3 years overall (a) and disease
37 free survival (b). Relapse remains a major challenge in this setting of patients
38 with extremely poor prognosis despite post transplant treatment therapy. No
39 significant risk factor for death or relapse was identified in our limited
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3 transplant series however mutation analysis was not carried out. A dismal
4 outcome has been recently reported in several research articles according to
5 somatic mutational status [12.13]. A better relapse risk stratification before
6 HCT could help identify subgroups of patients who are more likely to benefit
7 from an adapted conditioning regimen or from early post transplant
8 therapeutic strategies such as preemptive/prophylactic donor lymphocytes
9 infusion and/or hypo-methylating agents.

10 This analysis is hampered by the limited number of patients analyzed and by
11 the usual limitations related to its retrospective nature. However these data,
12 considering very high-risk features of disease in more than 50% of patients
13 and elevated median comorbidity index are encouraging and deserve further
14 studies. A larger prospective trial of haploidentical transplant in higher risk
15 MDS patients fitting with the procedure and lacking an HLA identical donor is
16 warranted.
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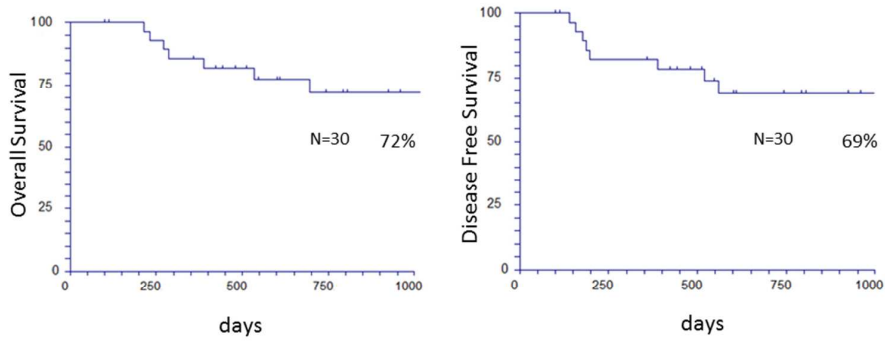
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7 Figure 1: Three years overall (a) and disease free survival (b) of the 30 MDS
8 patients submitted to haploidentical HCT. Because of the limited number of
9 patients in follow up after the third year no survival data have been calculated
10 after these limit despite e single late death (day + 1123) was registered.
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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.

254x190mm (96 x 96 DPI)