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ALLOGENEIC STEM CELL TRANSPLANTATION IN PATIENTS WITH MYELODYSPLASTIC SYNDROME

Outcome Analysis According to the International Prognostic Scoring System

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SUMMARY

We determined the outcome of patients with myelodysplastic syndrome (MDS) and secondary acute myeloid leukemia (sAML) after allogeneic stem cell transplantation according to their international prognostic scoring system (IPSS) risk categories at diagnosis. A total of 11 females and 7 males, with a median age of 45 years, were transplanted. With a median follow-up of 60 months, the 6-year actuarial event-free survival (EFS) for Less Advanced (Low and Intermediate-1 risk IPSS) and Advanced (Intermediate-2 and High risk IPSS) MDS was 71.4% and 43.6%, respectively (p=0.002). We did not observe a difference in EFS depending on cytogenetics at diagnosis (good risk 53.8% Vs intermediate and high risk 53.3%, p=ns), neither on the type of conditioning regimen used (myeloablative 50% Vs reduced intensity 52.2%, p=ns). Our results support that IPSS score at diagnosis may be used to predict EFS in patients with MDS undergoing allogeneic SCT.

Keywords: myelodysplastic syndrome, stem cell transplantation, IPSS

RESUMO

TRANSPLANTE ALOGÉNICO DE CÉLULAS ESTAMINAIS EM DOENTES COM SÍNDROME MIELODISPLÁSICA: Análise de Acordo com o Índice de Prognóstico Internacional

Neste estudo avaliámos o valor preditivo do índice prognóstico internacional (IPSS) na altura do diagnóstico em doentes com síndrome mielodisplásica (SMD) e leucemia mielóide aguda secundária submetidos a transplante alogénico de células estaminais. Foram transplantados um total de 11 mulheres e sete homens, com uma mediana de idades de 45 anos. Com um seguimento mediano de 60 meses, a sobrevivência livre de eventos aos 6 anos nos doentes com doença menos avançada (IPSS Risco Baixo e Intermédio 1) e com doença avançada (IPSS Intermédio 2 e Alto Risco) foi de 71.4% e 43.6%, respectivamente (*p*=0.002). Não observámos diferenças significativas na sobrevivência livre de eventos de acordo com a análise citogenética na altura do

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diagnóstico (risco bom 53,8% VS risco intermédio e alto 53,3%, p=ns) nem com o tipo de regime de condicionamento utilizado (mieloablativo 50% VS intensidade reduzida 52,2%, p=ns). Os nossos resultados demonstram que o IPSS na altura do diagnóstico pode ser utilizado para predizer a sobrevivência livre de eventos em doentes com SMD submetidos a transplante alogénico de células estaminais.

Palavras chave: sindrome mielodisplásica, transplante de células estaminais, IPSS

INTRODUCTION

Stem cell transplantation (SCT) is the only curative treatment for patients with Myelodysplastic syndrome (MDS) and secondary acute myeloid leukemia (sAML)[1]. However, the median age of patients with MDS at the time of diagnosis is above the sixth decade of life and most studies have demonstrated an increment in transplant-related complications with increased age[2]. Now that reduced intensity allogeneic SCT has become widely available, new indications for transplant emerge in patients with MDS, particularly if we can predict their outcome according to prognostic models such as the international prognostic scoring system (IPSS). There is good evidence that patients with advanced MDS should be submitted to allogeneic SCT soon after the diagnosis[3].

The IPSS for MDS is a consensus prognostic risk--based analysis system that classifies MDS pts into 4 risk groups using as variables the cytogenetic profile of the patient, the proportion of bone marrow blasts and the number of peripheral blood cytopenias [4]. The objective of our analysis was to determine the outcome of SCT in patients with MDS and sAML according to their IPSS risk categories at diagnosis, and whether IPSS correlated with relapse and non-relapse mortality post-transplant.

PATIENTS AND METHODS

Between February 1990 and August 2003, 27 patients with primary MDS or sAML to MDS were submitted to SCT at our institution. From this group, we were able to determine the IPSS score at the time of diagnosis in 18 patients. (Table 1). The patients with Low and Intermediate-1 risk IPSS were grouped as Less Advanced MDS and those with Intermediate-2 and High risk IPSS were classified as Advanced MDS. A total of 11 females and 7 males, with a median age of 45 (range, 13 to 59) years, were transplanted. The morphologic characterization according to the French British American (FAB) classification of MDS at the time of transplant, as well as their cytogenetic profile at diagnosis, are depicted in Table I. Eleven patients (61%) had refractory anemia with excess blasts (with or without transformation) or sAML. Thirteen patients (72%) had good risk cytogenetics (10 patients had normal karyotypes, 2 patients had 5q- and 1 patient had 20q-), 4 patients (22%) had intermediate risk cytogenetics (2 patients with +8, 1 patient had t(6;9) and 1 patient presented with 11q- plus 15q+) and 1 patient had poor risk cytogenetics (complex karyotype). According to IPSS, 7 patients were classified as Less Advanced MDS and 11 patients as Advanced MDS (Table I). The median time from diagnosis to transplant was 6.5 months (range, 1.7 to 54.8 months). Six of seven patients with sAML received induction chemotherapy before the transplant. Only 2 of these 6 patients achieved complete remission prior to transplant, while the remaining 4 patients were transplanted with persistent disease. The other patient with sAML underwent SCT without previous treatment. The conditioning regimens consisted of busulfan 16 mg/kg plus cyclophosphamide 120 mg/kg (BuCy) in 8 patients submitted to an HLA-identical related conventional SCT, of fludarabine 150mg/m^2, rabbit ATG 25 mg/kg, prednisolone 2 mg/kg and melphalan 80 to 120 mg/m^2 (Fluda/ATG/Pred/Mel) in 4 patients submitted to an HLA-identical related reduced intensity SCT, of Fluda/ATG/Pred/Mel/Ara-C (with melphalan 140mg/m^2 and Ara-C 2.000 mg/m^2) in 4 patients submitted to a matched unrelated SCT and of Fluda/ATG/Pred/Mel/Thiotepa (fludarabine 200mg/m^2, rabbit ATG 25 mg/kg, prednisolone 2 mg/kg, melphalan 120mg/m^2 and thiotepa 10 mg/kg) in 2 patients submitted to a haploidentical CD34-selected SCT from a related donor. The latter 2 patients received a T-cell depleted peripheral blood progenitor cell graft, while the other 16 patients were transplanted with unmanipulated bone marrow. As prophylaxis for graft versus host disease (GVHD), the patients submitted to a conventional SCT received the combination of cyclosporine A and meth-

Table 1 - *Patient Characteristics and Outcome*

UPN	IPSS [1]	Cytogenetics	FAB Subtype [2]	C. Regimen / Donor	Status / Cause of Death
AL 14	Inter 1	Good	RA	Myeloablative / MR	Alive
AL 33	Inter 2	Good	sAML	Myeloablative / MR	Dead / Relapse
AL 98	Inter 2	Good	sAML	Myeloablative / MR	Dead / Graft Failure
AL 110	Low	Good	RA	Myeloablative / MR	Alive
AL 158	High	Inter	RAEBt	Myeloablative / MR	Alive
AL 159	Inter 2	Good	sAML	Myeloablative / MR	Dead / VOD
AL 170	Inter 2	High	sAML	Haploidentical / MMR	Alive
AL 171	Inter 1	Good	RA	Myeloablative / MR	Dead / GVHD
AL 172	Inter 2	Good	sAML	Haploidentical / MMR	Alive
AL 182	High	Good	RAEBt	Myeloblative / MR	Alive
AL 184	High	Inter	sAML	Reduced Int / MR	Dead / Refractory AML
AL 191	High	Good	sAML	Reduced Int / MR	Dead / Graft Falilure
AL 205	Inter 2	Inter	RAEB	Reduced Int / MR	Dead / Infection
AL226	Low	Good	RA	Reduced Int / MR	Alive
AL 245	High	Inter	RAEB	Reduced Int / MUD	Alive
AL 247	Inter 1	Good	RA	Reduced Int / MR	Dead / Graft Failure
AL 259	Low	Good	RARS	Reduced Int / MUD	Alive
AL 265	Low	Good	RA	Reduced Int / MUD	Alive

[1] IPSS at the time of diagnosis; [2] FAB subtype at the time of transplant

Abbreviations: UPN – unique patient number; AL – allogeneic; Intermed – Intermediate; RA - refractory anemia; RARS - refractory anemia with ring sideroblasts; RAEB – refractory anemia with excess blasts; RAEBt - refractory anemia with excess blasts in transformation; sAML – secondary AML; Int – Intensity; MR - HLA-matched related; MMR – HLA-mismatched related; MUD – HLA-matched unrelated; VOD – hepatic veno-occlusive disease; GVHD – graft versus host disease

otrexate, while those submitted reduced intensity SCT from HLA-matched donors were treated with mycophenolate mofetil plus cyclosporine A. The 2 recipients of CD34--selected T-cell depleted haploidentical grafts did not receive any pharmacologic prophylaxis for GVHD, as described in detail elsewhere[5].

RESULTS AND DISCUSSION

With a median follow-up of 60 months (range, 20 to 180 months), the 6-year actuarial event-free survival (EFS) for the whole group was 53.5% (data not shown). We also analysed the impact of known prognostic factors in MDS in the outcome of our patient population. The log rank statistic test was used in this analysis. The 6-year actuarial EFS for Less Advanced and Advanced MDS according to the IPSS was 71.4% and 43.6%, respectively (p=0.002) (Figure 1). The same degree of significance was attained between the patients with the FAB subtypes refractory anemia and refractory anemia with ringed sideroblasts versus patients refractory anemia with excess blasts and sAML (71.4% Vs 43.6%, *p*=0.002) (data not shown). We did not observe a difference in EFS depending of cytogenetics (good risk 53.8% Vs intermediate and high risk 53.3%, *p*=ns).

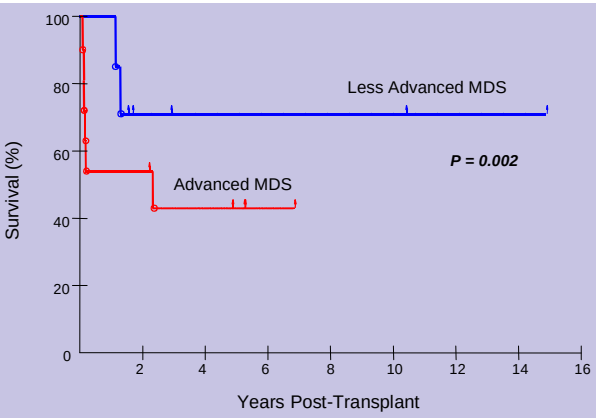

Fig. 1 – *Event Free Survival of patients with Advanced MDS (IPSS Intermediate 2 and High) and Less Advanced MDS (IPSS Low and Intermediate 1)*

In our group of patients, only FAB and IPSS subtypes had an influence on survival. In fact, 6 of the 8 patients that died had sAML (n=5) or RAEB (n=1). No doubt, this strong correlation is due to the high score attributed to bone marrow blast percentage by the IPSS scoring system. Although the IPSS was originally developed to predict survival of patients with MDS not undergoing SCT, it has also been shown to correlate with relapse post-transplant[6]. Even though most of our patients had intermediate 2 or high risk IPSS and 5 patients underwent transplant with active AML, only 2 patients died of relapse/persistent disease. This low incidence of relapse was probably due to the fact that recipients of unrelated grafts developed some form of GVHD and the 2 recipients of haploidentical transplants developed GVHD after an infusion of a limited dose of donor leukocytes[5]. Another 6 patients died of other causes (Table 1): three patients had complications associated with graft failure (they never achieved the engraftment), 1 patient died of hepatic veno--occlusive disease, 1 patient died with severe acute graft versus host disease and 1 patient died of infection. Although it did not achieve statistical significance, there was a trend for increased non-relapse mortality in patients with Intermediate 2 and High risk IPSS in our series. Two of 3 patients without evidence of engraftment had refractory sAML and died before day 30 post-transplant. Even though we considered them as having graft failure, it would be more correct to ascribe these deaths to multiple organ failure associated with no evidence of engraftment until the day of death.

In contrast to other authors, we did not find a relationship between cytogenetics and survival post-transplant[7], which may be related to the low number of patients in our series. It is noteworthy that 5 of 7 patients with sAML at the time of transplant had good cytogenetics at the time of diagnosis and, in fact, 6 of the 8 patients that died had good risk cytogenetics. However, they were classified as having advanced disease by the IPSS scoring system, since the percentage of bone marrow blasts was high. We also examined whether the type of transplant and the conditioning regimen used had any impact on survival. Four of the 8 patients that died received a conventional myeloablative SCT from an HLA-matched family donor, 3 patients were transplanted also from an HLA-matched family donor after a reduced intensity conditioning regimen and 1 patient had received a reduced intensity SCT from an HLA-matched unrelated donor. Therefore, patients submitted to a myeloablative SCT did not have a significantly different EFS at 6 years than the recipients of a reduced intensity conditioning regimens (50% Vs 52.5%, respectively; *p*=ns).

In summary, our results support that IPSS score at diagnosis may be used to predict event-free survival in patients with MDS undergoing allogeneic SCT.

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