Reduced intensity stem cell transplantation for advanced soft tissue sarcomas in adults: a retrospective analysis of the European Group for Blood and Marrow Transplantation

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ABSTRACT

We conducted a retrospective analysis on adult patients with advanced soft tissue sarcoma (STS) other than rhabdomyosarcoma who received allogeneic stem cell transplantation and were registered at the EBMT database. The aim of of the study was to assess whether an immune-mediated graft-versus-tumor (GVT) effect could be generated in this disease. Among 26 patients included in the registry, 14 were eligible for this analysis as they had received reduced intensity stem cell transplantation for chemorefractory disease. Two patients died of transplant-related complications and eight of progressive disease; four are alive and experienced long-lasting disease stabilisation following transplant. Our study may suggest that an immune-mediated effect cannot be excluded in some STS.

Keywords: non-myeloablative, allogeneic SCT; soft tissue sarcoma, graft-versus-tumor.

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The investigational application of reduced intensity stem cell transplantation (RST) in patients with refractory non-hematologic cancers proved that a meaningful graft-versus-tumor effect can be generated in patients with renal cell cancer and possibly in those with other solid tumors.[1,2] RST has been proposed as a therapeutic option in patients with advanced soft tissue sarcoma (STS) for two main reasons: i) the poor prognosis of this disease, with a median survival of about 1 year with conventional treatments,[3] ii) the evidence of an immune-mediated effect against sarcoma in experimental animal models of allogeneic transplantation.[4,5] However, only single case reports and small series of patients with STS treated with RST from HLA-matched siblings have been reported. Although some authors have reported some evidence of a graft-versus-sarcoma effect in humans,[6-8] the largest study that has been published so far included nine patients with various histotypes[9] and did not show any evidence of cancer regression after RST. We have retrospectively reviewed, on behalf of the European Group for Blood and Marrow Transplantation (EBMT) solid tumor working party (STWP), the EBMT database providing results from the largest so far published series of patients with STS who had been treated with RST. This series of patients, while including different STS histotypes, is relatively homogeneous as for concerns type of conditioning regimen and tumor status at transplantation. Patients with rhabdomyosarcoma were excluded as this is most frequently a pediatric disease with an extremely different natural history.

Design and Methods

Twenty-six adult patients with STS who underwent allogeneic stem cell transplantation and were registered in the EBMT database were considered. Because of the lack, from a preliminary analysis, of important

Table 1. Patients' characteristics and outcome of transplant.

Patient	Age	Histology	Disease status at BMT	Metastatic sites at BMT	Time from initial diagnosis to BMT (mo.)	Status at BMT	Conditioning treatment	aGVHD (grade)	cGVHD	Best response at BMT	Status at last follow-up
1	47	Clear cell sarcoma	MTS	Lung; Liver	197	PD	Thio-Flu-CTX	No	Absent	PD	Died of PD on Day 77
2	51	Fibrosarcoma	MTS	Lung	41.2	PD	TBI-Flu	Skin (2)	Absent	PD	Died of PD on Day 70
3	23	Synovial sarcoma	MTS	Pleural Involvement	21	PD	Flu-CTX	Liver (4)	NA	NA	Died of GVHD on Day 59
4	46	Schwannoma	Locally advanced	Chest Wall	18.9	PD	Thio-Flu-CTX	Skin; liver (4)	NA	NA	Died of GVHD on Day 50
5	48	Liposarcoma	MTS	Bone; Soft Tissue	58	SD	Flu-CTX	No	Limited	SD	Died of PD on Day 987
6	43	Sarcoma NAS	MTS	Lung; Liver	5.8	PD	Thio-Flu-CTX	No	NA	SD	Died of PD on Day 1078
7	50	Hemangiopericytoma	MTS	Bone; Liver	52.1	PD	Flu-CTX	No	Absent	SD	Alive at Day 446
8	45	GIST	MTS	Liver	7.2	PD	Flu-CTX	Skin; liver; bowel (3)	Limited	SD	Died of PD on Day 854
9	42	Liposarcoma	MTS	Lung; Bone; Soft tissue	27.6	PD	Flu-Melph	Skin (2)	Absent	PD	Died of PD on Day 133
10	22	Synovial sarcoma	MTS	Lung	35.6	SD	Flu-CTX	No	Extensive	SD	Alive at Day 868
11	43	Leiomyosarcoma	Locally advanced		46.6	PD	Flu-CTX	No	Extensive	PD	Died of PD on Day 528
12	43	Unknown	MTS	Lung	19.2	SD	Bu-Flu-ATG	Gut; skin (2)	Absent	PD	Died of PD on Day 114
13	40	Endometrial stromal sarcoma	MTS	Lung; Soft tissue	38.2	PD	Thio-Flu-CTX	No	Absent	SD	Alive at Day 206
14	40	Synovial sarcoma	MTS	Liver; Soft tissue	12.8	PD	Thio-Flu-CTX	Bowel (3-4)	Absent	SD	Alive at Day 196

MTS: metastatic; aGVHD: acute graft-versus-host disease; cGVHD: chronic graft-versus-host disease; PD: progressive disease; SD: stable disease; Thio: thiotepa; Flu: fludarabine; CTX:cyclophosphamide; TBI: total body irradiation 200cGy; GIST: gastointestinal stromal tumor; Melph: melphalan; Bu: busulfan; ATG: anti-thymoglobulin; NA: not applicable.

clinical data, including type of conditioning regimen in several cases, all centers were re-contacted for missing data. Patients with chemosensitive disease at transplantation (n=9) and patients who received myeloablative chemotherapy (n=3), were eventually excluded. This was done in order to limit confounding elements as much as possible (e.g. disease response to drugs included in the conditioning regimen) which could affect the possibility of investigating the existence of a graft-versus-sarcoma effect. Fourteen patients with a complete data set, transplanted in seven European institutions from 2000 to 2005, were analyzed. All patients had metastatic or locally advanced disease, which was bulky (conventionally considered as a tumor mass with a maximum diameter ≥10 cm) in five. The median age was 43 years (range: 22 - 51). The ECOG performance status (PS) was 0-1 in 12 patients, and was not reported for the other two patients. All patients received a fludarabine-based reduced intensity conditioning regimen followed by allogeneic stem cell transplantation from an HLA identical or one antigen-mismatched sibling donor. The patients' relevant characteristics are reported in Table 1. The median time from diagnosis to transplantation was 31.6 months (range: 5.6 to 197 months). Engraftment was achieved in all patients. Not lineage-specific peripheral blood full donor chimerism, was documented in 11 patients and mixed chimerism in 3 patients. Tumor response was reported according to RECIST criteria.

Results and Discussion

After a median follow-up of 201 days from transplant two patients had died of acute graft-versus-host disease (GVHD) for an overall treatment related mortality of 14%. Given the early occurrence of these deaths (at 50 and 59 days post-treatment), these patients were not evaluable for disease response. Overall, acute GVHD was reported in nine out of the 14 patients (64%) and was grade 3-4 in four cases (28%) and grade 2 in 5 cases (36%). Chronic GVHD occurred in 4 out of 9 evaluable patients (44%) and was extensive in two. In this series of heavily pre-treated patients, albeit limited, morbidity and mortality appear to be similar to those reported for patients with hematologic malignancies treated with RST.[10]

After a median follow-up of 326 days, 8 out of 12 patients, evaluable for a disease response, had died of progressive disease (PD, 66%), while four patients remained progression-free at 196, 206, 446 and 868 days after transplant (Table 1). The Kaplan-Meier estimates of progression-free and overall survival (PFS and OS) are

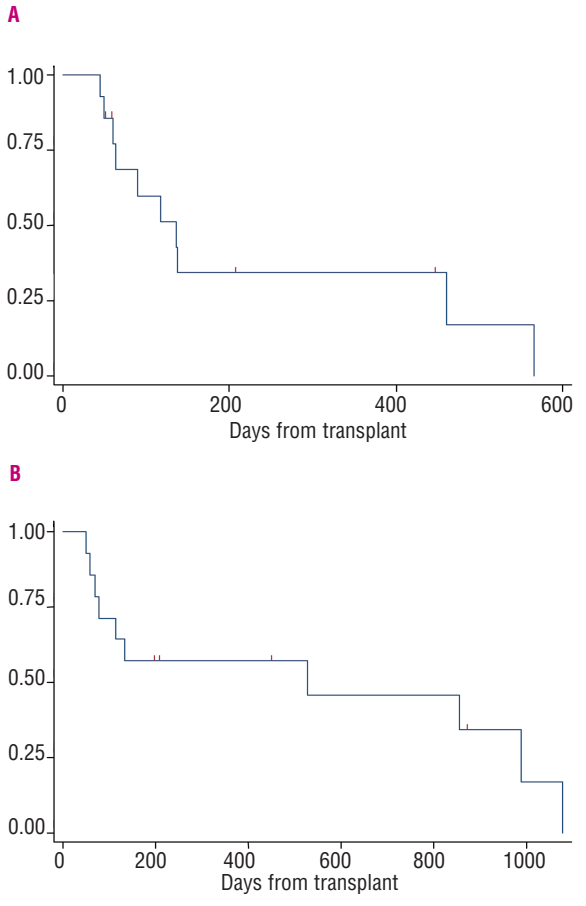

Figure 1. Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) for STS patients treated with RST; red marks represent patients who are progression-free (A) and patients who are still alive (B).

illustrated in Figure 1A and 1B, respectively. The median OS was 326 days (range 50-1078 days), whereas the median PFS was 103 days (range 50-565). The mean time from transplantation to assessment of response was 57 days (range 13-260 days).

No objective responses have been reported suggesting that the postulated graft-versus-sarcoma effect might not occur following RST. However, it is important to note that: i) patients with these characteristics have an extremely poor prognosis and do not have further therapeutic options that have proven to be safe and effective; ii) the presence of chemo-refractory and progressing disease at the time of transplantation is associated with poor outcome even in patients with hematologic malignancies known to be susceptible to a graft-versus-tumor effect; iii) three patients, none of whom had bulky disease at the time of transplantation, obtained a relatively long-lasting disease stabilization after RST. For these reasons we believe that the results presented in this study do not completely rule out the possibility that an immune-mediated effect might have contributed to tumor control in some patients.

A well designed phase II study, enrolling patients with limited tumor burden and slow growing tumors, is required to define the possible role of RST in patients with STS in whom conventional treatments have failed.

Authors' Contributions

SSec and MC contributed equally to re-contacting each center and analyzing the data. The other authors provided data that were missing from the EBMT database.

Conflict of Interest

The authors reported no potential conflicts of interest.

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