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A Meta-analysis of Patients Receiving Allogeneic or Autologous Hematopoietic Stem Cell Transplant in Mycosis Fungoides and Sézary Syndrome

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The survival outlook in advanced mycosis fungoides (MF) is poor. Autologous and allogeneic stem cell transplants (SCT) have been shown, in small case series and case reports, to have the potential for long-term remission or to alter disease course. Allogeneic SCT is thought to have a curative potential secondary to a graft-versus-lymphoma (GVL) effect. A patient-level meta-analysis was performed to compare the outcome of allogeneic versus autologous SCT in patients with MF/Sézary syndrome (SS) using 39 cases from the literature. There were a total of 20 allogeneic and 19 autologous transplant cases. The gender, age, and stage distribution was similar between the transplant groups. The allogeneic group received significantly more systemic therapies prior to transplant ($P < .0005$) and had longer follow-up after transplant. Overall survival (OS) results showed a more favorable outcome of patients who received allogeneic SCT ($P = .027$). Event-free survival (EFS) demonstrated a more durable response in patients who received allogeneic SCT ($P = .002$). In the allogeneic group, the majority (70%) of patients experienced persistent graft-versus-host disease (GVHD), mostly with mild to moderate severity, and 2 of 4 deaths were related to GVHD. Meanwhile, the majority of the deaths (8 of 10) in the autologous group were because of progressive disease. These results support the belief that allogeneic SCT offers a better survival and disease-free outcome versus autologous SCT in MF/SS, likely because of a GVL effect.

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INTRODUCTION

Mycosis fungoides (MF) and Sézary syndrome (SS) belong to a group of cutaneous T cell lymphomas (CTCL) characterized by a proliferation of $CD4^+/CLA^+/CCR4^+/CD7^-/CD26^-$ T cells in the skin. MF usually presents with patch and plaque lesions, but in advanced stages may progress to skin tumors with greater risk for lymph node and visceral organ involvement [1]. SS is the erythrodermic or leukemic form of MF with circulating malignant T cells in the peripheral blood and often portends a poorer prognosis [2].

Although it is the most common primary lymphoma of the skin, MF is rare and usually indolent. Conventional treatments include topical nitrogen mustard, topical high potency steroids, electron beam radiotherapy, and phototherapy [3,4]. These treatments usually produce complete or partial remission. For mild MF disease—up to stage IIA—prognosis is generally good. Patients with stage IA disease have similar overall survival (OS) compared to others of the same age, gender, and race, and median survival is 11 years for patients with stage IB-IIA MF [5].

A subset of patients have advanced MF or SS, which is heralded by the presence of skin tumors or erythroderma at presentation. Other unfavorable prognostic factors include large cell transformation on histologic examination, and development of extracutaneous disease. In these patients, prognosis is poor with 5-year survival for stage IIB/III and stage IV

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MF of 47% and 27%, and 15-year survival of 15% and 10%, respectively [5]. The management of advanced MF includes chemotherapy, photopheresis, radiotherapy, interferon-α, retinoids like bexarotene, as well as targeted therapies such as monoclonal antibodies and denileukin diftitox. These treatments are only expected to be palliative with limited-duration remissions [3,6].

There is hope that stem cell transplants (SCT) have the potential to provide prolonged remissions or possible cure of advanced MF/SS. The collective experience in allogeneic and autologous transplant is limited but optimistic, especially for allogeneic SCT. A proposed gravt-versus-leukemia (GVL) effect is thought to be responsible for higher effectiveness of allogeneic transplants [7]. However, there have been no controlled prospective studies to date, and the literature thus far consists of case reports, small case series, and reviews [8].

PATIENTS AND METHODS

Data Collection and Patient Selection

This retrospective meta-analysis was based on data obtained from several sources. A PubMed search was performed, using the phrases "mycosis fungoides"/"Sézary syndrome"/"cutaneous T cell lymphoma" and "stem cell transplant," to include data from previously reported cases and case series of MF/SS patients. Patients with $CD4^+$ predominant MF or SS who received peripheral blood or bone marrow-derived SCTs were included in the study. Papers needed to be written in English and published prior to March 2008 for study inclusion. In total, 9 papers on allogeneic SCTs in MF/SS and 7 papers on autologous SCTs were reviewed, and all were used in the data analysis. Staging was based on TNM and B classification of MF/SS described by the Committee on Staging and Classification of MF/SS in 1979 [9]. Although there are revised staging recommendations by the International Society for Cutaneous Lymphomas, the publications from which these patients were gathered were written prior to the recent guidelines [10].

Information regarding patient age, gender, stage at diagnosis, stage at progression, previous treatments, type of SCT, inductive therapy, preparation/conditioning therapy, use of total-body irradiation (TBI) or total skin electron beam (TSEB) therapy, remission/relapse, graft-versus-host disease (GVHD), infection, mortality, time of transplant, and last follow-up were obtained from published reports. Authors were contacted by e-mail or phone for additional information where the literature was not clear. Complete remission (CR) was defined as resolution of skin, lymph node, viscera, or blood involvement (if applicable) clinically, histologically, radiographically, or molecularly, within 60 days of transplant. GVHD was categorized as acute (occurring <100 days from transplant) or chronic, and presence at last follow-up was noted. If acute, the affected area was noted, if possible, and if chronic, it was described as limited or extensive. Although the terminology has undergone debate and change, the reports described GVHD in those terms.

Statistical Analysis

Event-free survival (EFS), OS, and relapse curves were created from the date of transplant until the date of last follow-up or an event, and calculated by the method of Kaplan and Meier [11]. Both log-rank and Cox models were used for analysis. Competing risk models were created with tests described by Gray [12]. Two-tailed, independent samples *t*-tests were used to compare means. Analyses were performed with R version 2.2.0 and SPSS version 15.0 [13]. Disease progression, relapse, and death from any cause defined events for EFS.

Table 1. Patient Characteristics

		Allogeneic	Autologous
Total No. pts		20	19
Age (years)	median	42	47
	range	(21-59)	(20-67)
Gender	male	9	10
	female	11	9
Clinical stage (NCI 1979) at transplant	IB	1	1
	IIB	3	9
	IIIA	1 (SS)	0
	IVA	15 (5 SS)	5
	IVB	0	4
Median No. prior therapies	Skin-directed	2	2
	Systemic*	4.5	1
Total follow-up time (months)	median	38	21
	range	(1-108)	(0.5-84)
Follow-up time of surviving patients (months)	median	45	22
	range	(15-108)	(10-84)

*Significant ($P < .05$) differences are marked.

Table 2. Overview of the Literature with Transplant Regimens

Reference	Age/Gender	Stage at Transplant	Conditioning Regimen	Myelo-ablative?	Radiation?	Type of Transplant	Disease relapse	Remission at Last f/u	Outcome @ Last f/u	GVHD at Last f/u?
Molina et al., 1999, 2005 [24, 27]	22F	SS/IVA	CyP 60mg/kg x 2D	Y	Y; TBI	Allo; MUD BMT	N	Y	alive @ 108 mo	Y; extensive skin
	45	IIB	CyP 60mg/kg x 2D	Y	Y; TBI	Allo; sibling matched BMT	N	Y	alive @ 89 mo	Y; limited skin
	46	SS/IVA	CyP 60mg/kg x 2D	Y	Y; TBI and TSEB	Allo; sibling matched PBSCT	N	Y	died @ 16 mo from GVHD complications	Y; extensive skin, oral
	21F	SS/IVA	busulfan 16mg/kg, CyP 60mg/kg x 2D	Y	N	Allo; sibling matched PBSCT	N	Y	alive @ 60 mo	Y; limited skin
	59	SS/IIIA	Flu, 25mg/m^2 x 5D then Mel 140mg/m^2 x 1D	N	N	Allo; sibling matched PBSCT	N	Y	alive @ 53 mo	Y; extensive skin
	50	IVA	Flu, 25mg/m^2 x 5D then Mel 140mg/m^2 x 1D	N	N	Allo; MUD BMT	N	Y	alive @ 45 mo	Y; limited skin
	48	IVA	Flu, 25mg/m^2 x 5D then Mel 140mg/m^2 x 1D	N	N	Allo; MUD BMT	N	Y	alive @ 33 mo	Y; limited skin
	35	IIB	Flu, 25mg/m^2 x 5D then Mel 140mg/m^2 x 1D	N	N	Allo; MUD PBSCT	N	Y	died @ 1.1 mo from RSV	N
Guitart et al., 2002 [14]	36M	IIB	CyP 120mg/kg with mesna	Y	Y; TBI	Allo; sibling matched BMT	N	Y	alive @ 54 mo	N
	39F	SS/IVA	CyP 120mg/kg with mesna, etopisode 30mg/kg	Y	Y; TBI	Allo; sibling matched BMT	N	Y	alive @15 mo	N
Burt et al., 2000 [28]	27F	IVA	CyP 200mg/kg	Y	Y; TBI	Allo; sibling matched BMT + CD34 PBSC	Y @ 9 mo and 5 yrs	N	alive s/p 1 DLI @ 60 mo	Y; limited skin
Masood et al., 2002[29]	37F	IVA	CyP 120mg/kg x 2 doses	Y	Y; TBI and TSEB	Allo; sibling matched BMT + CD34 PBSC	N	Y	alive @ 24 mo	Y; mild gut
Soligo et al., 2003 [30]	56M	IVA	Flu 30mg/m^2 x 3D	N	Y; TBI	Allo; sibling matched BMT + CD34 PBSC	N	Y	alive @ 24 mo	N
	47M	IVA	2 cycles: Flu, 30mg/m^2 x 3D + CyP 300mg/kg x 3D	N	Y; TBI	Allo; sibling matched BMT + CD34 PBSC	N	Y	alive @ 18 mo	Y; limited skin
	37M	IVA	2 cycles: Flu 30mg/m^2 x 3D + CyP 300mg/kg x 3D	N	Y; TBI	Allo; sibling matched BMT + CD34 PBSC	N	Y	died @ 2.4 mo of sepsis, myocarditis	Y; grade II cut aGVHD
Koeppl et al., 1994 [31]	29F	IVA	CyP 60mg/kg x 2D	Y	Y; TBI	Allo; sibling matched BMT	Y @ 70D and 4 yrs	Y	alive @ 72 mo	Y; limited skin

Herbert et al., 2004 [6], (personal electronic mail communication 2008)	35M	IIB	Flu, 25mg/m^2 x 5D then Mel 140mg/m^2 x 1D	N	N	Allo; sibling matched BMT + CD3	Y @ 4mo, 13mo, 24mo	N	alive s/p 4 DLIs @ 95* mo	Y; extensive skin
	49M	SS, IVA	Flu, 25mg/m^2 x 5D then Mel 140mg/m^2 x 1D	N	N	Allo; sibling matched BMT + CD3	Y @ D43 and 4mo	N	died s/p 1 DLI @ 11 mo of GVHD complications	Y; extensive skin
	48F	IVA	Flu, 25mg/m^2 x 5D then Mel 140mg/m^2 x 1D	N	N	Allo; sibling matched PBSCT	Y @ 4 and 6mo	Y	alive @ 17* mo	Y; limited skin
Introcaso et al., 2008 [32]	53F	IVA	Flu, 25mg/m^2, CyP 350mg/m^2	N	Y; TBI	Allo; sibling matched SCT	N	Y	alive @ 43 mo	Y; limited skin
Ferra et al., 1999 [33]	38F	IVB	CyP, 1500mg/m^2 x 2D, carmustine 300mg/m^2, etoposide 200mg/m^2 x 3D	NA	Y; TBI	Auto: PBSCT	Y @ 2mo	N	alive @ 22 mo	NA
Sterling et al., 1995 [34]	48M	IIB	CyP 60mg/kg x 2, prednisone	NA	Y; TBI and local rad to lower leg	Auto: BMT	Y @ 3mo	N	died @ 15 mo of PNA	NA
Olavarria, Russell-Jones et al., 2001 [35], [36]	47M	IIB	melphalan 140mg/m^2	NA	Y; TBI and TSEB	Auto: PBSCT	Y @ 2mo	N	alive @ 38 mo	NA
	52F	IVA	BCNU 450mg/m^2 x 1D, etoposide 500mg/m^2 x 4D, Mel 140mg/m^2 x 1D	NA	N	Auto: PBSCT	Y @ 12mo	N	alive @ 26 mo	NA
	27M	IVA	etoposide 50mg/kg	NA	Y; TBI	Auto: PBSCT	Y @ 14mo	N	alive @ 30 mo	NA
	49F	IVA	BCNU 450mg/m^2 x 1D, etoposide 500mg/m^2 x 4D, Mel 140mg/m^2 x 1D	NA	N	Auto: BMT	NA	N	died @ 0.5 mo of septicemia	NA
	38M	IVA	BCNU 450mg/m^2 x 1D, etoposide 500mg/m^2 x 4D, Mel 140mg/m^2 x 1D	NA	Y; TSEB	Auto: PBSCT	Y @ 9mo	N	alive @ 21 mo	NA
	67M	IIB	BCNU 450mg/m^2 x 1D, etoposide 500mg/m^2 x 4D, Mel 140mg/m^2 x 1D	NA	Y; TSEB	Auto: PBSCT	Y @ 2mo	N	died @ 11 mo of dz	NA
	42F	IIB	BCNU 450mg/m^2 x 1D, etoposide 500mg/m^2 x 4D, Mel 140mg/m^2 x 1D	NA	N	Auto: PBSCT	Y @ 4mo	N	died @ 8 mo of dz	NA
	38M	IIB	BCNU 450mg/m^2 x 1D, etoposide 500mg/m^2 x 4D, Mel 140mg/m^2 x 1D	NA	N	Auto: PBSCT	N	Y	alive @ 10 mo	NA
	57F	IIB	BCNU 450mg/m^2 x 1D, etoposide 500mg/m^2 x 4D, Mel 140mg/m^2 x 1D	NA	Y; TSEB	Auto: PBSCT	Y @ 1mo	N	died @ 3 mo of dz	NA
Bigler et al., 1991 [37]	49F	IVB	CyP 40mg/kg x 4D, etoposide 200mg/m^2 x 3D, BCNU 300mg/m^2 x 1D	NA	Y; TSEB	Auto: BMT	Y @ D64	N	died @ 9.4 mo of dz	NA
	60M	IIB		NA	Y; TBI and TSEB	Auto: BMT	Y @ D70	N	died @ 55.5 mo of dz	NA
	49M	IVA	CyP 60mg/kg x 2D	NA	Y; TBI	Auto: BMT	Y @ D93	N	died @ 12.6 mo of dz	NA
	37F	IIB	CyP 50mg/kg x 4D	NA	Y; TBI and TSEB	Auto: BMT	Y @ D96	N	died @ 27.5 mo of dz	NA
	26F	IIB	BCNU 200mg/m^2 x 3D, etoposide 800mg/m^2 x 3D, cisplatin 40mg/m^2 x 5D	NA	Y; local rad to mantle and spleen, TSEB	Auto: BMT	N	Y	alive @ 22 mo	NA
	41F	IVB	BCNU 200mg/m^2 x 3D, etoposide 800mg/m^2 x 3D, cisplatin 40mg/m^2 x 5D	NA	Y; local rad to CNS	Auto: BMT	N	Y	alive @ 21 mo	NA

(*Continued*)

Table 2. (*Continued*)

Reference	Age/Gender	Stage at Transplant	Conditioning Regimen	Myeloablative?	Radiation?	Type of Transplant	Disease relapse	Remission at Last f/u	Outcome @ Last f/u	GVHD at Last f/u?
Chen et al., 1986 [38]	40M	IVB		NA	Y; TBI	Auto: BMT	Y @ D42	N	died @ 3.7 mo of dz	NA
Ingen-Housz-Oro et al., 2004 [39]	51M	IB	BCNU, etoposide, aracytine, Mel	NA	N	Auto: PBSCT	Y @ 2.5mo	Y	alive @ 84 mo	NA

My indicates myeloablative; NMy, nonmyeloablative; N, no; Y, yes; CyP, cyclophosphamide; BMT, bone marrow transplant; PBSCT, peripheral blood stem cell transplant; PBSC, peripheral blood stem cells; SS, Sézary syndrome; Gy, Gray; F, female; M, male; D, days; Flu, fludarabine; Mel, melphalan; Allo, allogeneic; Auto, autologous; NA, not applicable; @, at; mo, months; yrs, years; cut, cutaneous; aGVHD, acute graft-versus-host disease; TBI, total-body irradiation; f/u, follow-up; TSEB, total skin electron beam radiotherapy; BCNU, carmustine; rad, radiation; dz, disease; MUD, matched unrelated donor; s/p, status post; DLI, donor lymphocyte infusions.
*Information obtained via author correspondence.

RESULTS

The clinical characteristics of the allogeneic and autologous SCT groups were similar (Table 1). There were 39 patients total: 20 patients in the allogeneic group, 19 in the autologous with similar gender and age demographics (P, age = .236). Patients with advanced disease, that is, stages IIB and IVA MF, were represented in both groups, with more stage IVA patients in the allogeneic group (15 versus 5). Meanwhile, 6 patients in the allogeneic group and 1 patient in the autologous transplant group had SS. Allogeneic patients had longer follow-up times from transplant. The median number of total therapies prior to SCT was 6.5 in the allogeneic groups (range: 3-12) and 3 (range: 0-8; $P < .0005$) in the autologous group. When divided into skin-directed versus systemic therapies, the number of skin-directed therapies was similar between the 2 groups, whereas the allogeneic transplant group received significantly more systemic therapies prior to SCT ($P < .0005$). Thirteen patients in the autologous and 12 in allogeneic group received TBI or electron beam therapy in addition to chemotherapy in their preparatory regimens (Table 2). Nine patients in the allogeneic group received myeloablative preparative regimens, whereas the remainder received reduced-intensity (nonablative) protocols. In the allogeneic group, stem cells were obtained from the bone marrow or peripheral blood of matched siblings or matched unrelated donors.

The Kaplan-Meier estimates demonstrate significantly superior OS in the allogeneic transplant group with P-value = .027 (Figure 1). OS rates at 1 and 5 years (with 95% confidence intervals [CI]) were 68% (46%-90%) and 23% (0%-58%) in the autologous group, and 85% (69%-100%) and 80% (62%-98%), respectively, in the allogeneic group. EFS was also significantly better in patients receiving an allogeneic versus an autologous transplant (P = .002; Figure 2). EFS rates at 1 and 5 years (with 95% CIs) were 20% (1%-39%) and 0, respectively, in the autologous group. In the allogeneic group, 1-year EFS was 65% (44%-86%) and was 60% (37%-82%) at 5 years.

Overall, 4 patients in the allogeneic and 10 in the autologous SCT group died in follow-up. Two of the allogeneic deaths were secondary to infection shortly after transplant. The remaining allogeneic transplant recipients died from GVHD complications, although 1 of those patients had residual MF disease at the time of death. In contrast, of the 10 deaths in the autologous group, 8 were of disease, 1 was of infection in a patient with relapsed disease following transplant, and the remaining patient died of infection shortly after transplant.

Disease relapse accounted for the large difference in EFS and mortality between the groups. The cumulative incidence of cancer death was significantly

higher after autologous transplant than allogeneic transplant (Figure 3, test statistic 10.2 on 1 degree of freedom, $P = .0014$ by the competing risk test), whereas there was no significant difference between the groups on noncancer deaths (test statistic = 0.90, $P = .35$).

The total number of events was small, rendering multivariate analysis unreliable and of low power. Nevertheless, we performed a number of multivariate analyses to check for confounding variables by age, gender, and stage, to see if the results could be accounted for by imbalances in those factors. Age alone had a nonsignificant effect on mortality (each year of age multiplied the hazard of death by 1.04, $P = .058$ by the deviance test in the Cox model) as well as on the event hazard (factor of 1.03 per year, $P = .17$). After adjusting for age, the treatment group effect was slightly mitigated. Unadjusted hazards ratio (HR) for treatment group effect on mortality was 3.5, adjusted HR was 2.9, *P*-value for adjusted effect .061; for events the corresponding HR was 3.6 unadjusted, 3.8 adjusted, *P*-value for adjusted effect .003. In the multivariate competing risk regression analysis, cancer death was increased significantly by both age ($P = .022$) and treatment type ($P = .03$), whereas noncancer death was not associated with either age ($P = .89$) or treatment type ($P = .36$). Thus, age did not appear to confound the effects of treatment type.

The analysis of confounding by gender was complicated by missing data on gender in 6 patients. However, gender by itself had no significant effect on OS or EFS and adjustment for it did not appreciably change either the significance or size of the treatment group effect on either mortality or events.

As we started analyzing the possibility of confounding by stage, we observed a difference in the distribution of stage between the 2 treatment groups, with a preponderance of IVA in allogeneic transplant and of IIB in autologous transplant. Of note, in stage IVA, 3/15 allogeneic patients died versus 2/5 in the autologous group, and in stage IIB the death rates were 1/3 for allogeneic and 6/9 for autologous. The raw death rates were higher in the autologous group in both stages. Other stages were so sparse they could not be compared to the treatment groups within the other stages. Within the subgroup of 20 IVA patients and 12 IIB patients, the mortality HR for IIB versus IVA was 1.6, $P = .084$, and the adjusted HR for autologous treatment was 2.7 ($P = .17$), indicating some attenuation of effect but not strong confounding. In summary, the results are that stage has no impact, and the effect of transplant type is unchanged after adjustment.

In patients who relapsed and died, the median time to death was 9.3 months, and of the 5 allogeneic patients who relapsed only 1 died, compared to 9 of 15 relapsed autologous patients ($P = .15$). Of the 5 relapses in the allogeneic group, 2 occurred in the myeloablative group and 3 in the nonmyeloablative group. In 3 of the 5 allogeneic recurrences (1 myeloablative, 2 nonmyeloablative), donor lymphocyte infusions were used with some success [6,14].

The incidence of GVHD was high and nearly equal in the myeloablative and nonmyeloablative allogeneic transplant groups. Six of 9 (67%) patients in the myeloablative group and 9 of 11 (81%) patients in the nonmyeloablative group experienced acute GVHD (aGVHD), ranging from grades I-III and with conjunctival, skin, oral and gastrointestinal (GI) manifestations. Seven and 8 patients in the myeloablative and nonmyeloablative sets, respectively, experienced chronic GVHD (cGVHD). Ninety percent of the allogeneic SCT patients experienced aGVHD or cGVHD; however, GVHD was only present in 70% of patients in the final follow-up. In both transplant groups, there were approximately equal numbers of patients with limited or extensive cGVHD. As previously mentioned, 2 of the 4 allogeneic deaths were attributed to GVHD complications. None of the patients in the autologous SCT group experienced GVHD.

DISCUSSION

Currently, there are a lack of therapies that will achieve long-term remissions or cures in patients with advanced stage MF or SS. Primary and salvage treatments for advanced stages of MF include total skin electron beam therapy, oral bexarotene, photopheresis, interferons, denileukin diftitox, alemtuzumab, and chemotherapeutic agents, many of which were tried and failed in the patients included in our meta-analysis [3,4]. Newer therapies have emerged, such as histone deacetylase inhibitors including

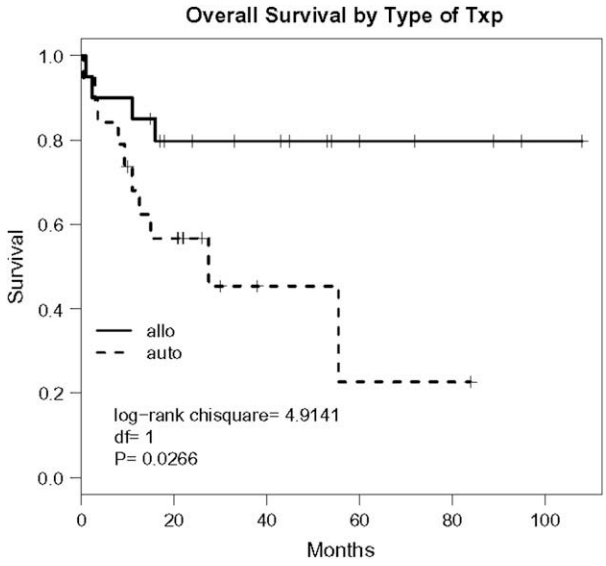

Figure 1. OS of patients with MF receiving an allogeneic transplant (allo) or an autologous transplant (auto), $P = .027$.

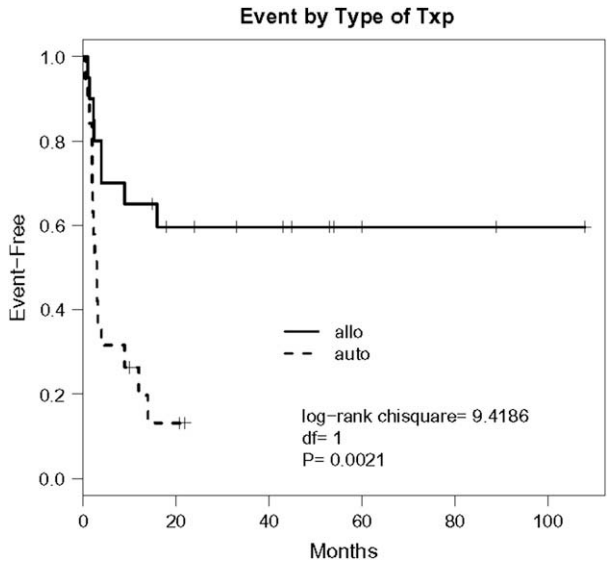

Figure 2. EFS of patients with MF receiving an allogeneic transplant (allo) or an autologous transplant (auto), $P = .0021$.

vorinostat, which was FDA-approved in 2006 for CTCL [15]. The efficacy and optimal role of these therapies as monotherapy, synergistic combinations, or adjuvants are still being developed. Several promising novel or improved therapies are currently undergoing clinical trials. Of the available therapies, hematopoietic SCT may have curative potential; however, currently no large trials exist. This report represents the first meta-analysis of allogeneic and autologous SCTs in MF and SS, the major types of CTCL.

Our univariate and multivariate analysis showed a statistically significantly improvement in relapse, OS and EFS in allogeneic versus autologous SCTs in MF/SS. Patients undergoing autologous SCT rely only on the cytoreductive preparatory regimens prior to stem cell rescue for treatment effect. In some of our study patients, autologous SCT was unable to produce a complete remission, and autologous SCT deaths were usually secondary to disease progression.

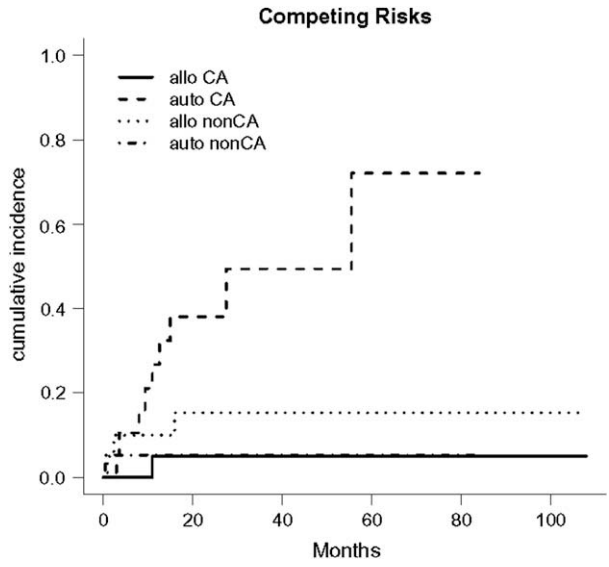

Figure 3. Estimated cumulative incidences of cancer (CA) and noncancer (nonCA) mortality in allogeneic (allo) and (auto) autologous transplant groups.

The decreased relapse rate and increased OS and EFS in the allogeneic SCT may be consistent with the theorized GVL/tumor effect. The graft-versus-tumor effect was noted by Weiden et al. [16], when his group described significantly decreased relapse rate in leukemia patients with GVHD following allogeneic SCT. Subsequent studies of the GVHD/GVL effect after allogeneic SCT for leukemia and lymphoma have substantiated a decreased relapse rate and increased OS and EFS with cGVHD [17,18]. It is the GVL effect that is thought to be responsible for producing cancer remission following nonmyeloablative regimens [19]. Although the association between GVHD and decreased relapse rates is felt to be indicative of GVL, data suggests there may be methods to separate the GVL and GVHD reactions. Possible approaches include using specific preparative regimens [20], choice of immunosuppressive agents, or other manipulations of specific regulatory and suppressor cell populations [21-23]. The morbidity of allogeneic SCT for MF/SS and other malignancies may be lessened in the future if these methods can be perfected to allow the skewing of the immune system in the GVL direction.

Allogeneic SCTs are traditionally associated with higher risk of morbidity and mortality; however, in this study, the number of deaths within the first year was actually greater in the autologous group. Deaths within the first year in patients who received an autologous transplant were largely secondary to progressive disease (5 out of 6). In the allogeneic group, 3 of the 4 recorded deaths occurred in the first year and were secondary to infection (2) or complications of GVHD (1). Overall there was a 20% transplant-related mortality rate in allogeneic patients, which is comparable to published data for other diseases.

In general, the conditions under which a candidate may be approved for a myeloablative allogeneic SCT are limited to patients under the age of 60. Unfortunately, MF tends to occur at an average age of 60 years, which, until recently, may have decreased the availability of allogeneic transplant to these patients [24]. However, the use of reduced-intensity regimens (RICs) should allow more MF patients, including patients in their seventies, the opportunity to proceed to an allogeneic transplant. There was not enough data to perform meaningful comparisons between myeloablative and RICs; however, the frequency of GVHD was similar between the 2 types of preparatory regimens in this patient population. TBI and TSEB have been associated with an increased risk of GVHD, perhaps through

injury of thymic epithelial cells or the GI tract [25,26]. In our study, a greater percentage of patients who did not receive TBI therapy had GVHD at last follow-up (6 of 8 patients who did not receive TBI versus 8 of 12 patients who did). In contrast, the percentage of patients with GVHD at last follow-up was higher in patients who received electron beam therapy at some point in their MF/SS therapy (7 or 8 patients who received TSEB versus 7 of 12 patients who did not). However, the statistical significance was not determined because of the small sample size.

With new advances in transplantation and the data presented here, hematopoietic SCT for advanced MF should be considered in patients who have refractory disease or short-lived responses with standard therapies. In this meta-analysis, allogeneic SCT was associated with statistically superior clinical outcomes compared to autologous SCT, which supports a potentially significant GVL effect in MF and SS. It is unclear whether donor leukocyte infusions at the time of relapse or in the case of persistent disease following transplant may also have an impact on disease outcome. The encouraging results from this study further validate the selection of allogeneic over autologous hematopoietic SCT in the management of advanced MF or SS [4], and support the need for further investigation of optimal strategies for allogeneic hematopoietic HSCT in MF and SS.

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