

REVIEW

Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma

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There is no standard of care for patients with advanced forms of mycosis fungoides, Sézary syndrome and other less common subtypes of primary cutaneous T-cell lymphoma. Expected median survival for such patients with conventional therapy is only 1–4 years. As a result of such dismal prognosis, alternative strategies based on autologous and allogeneic transplantation have been explored, and a relatively small number of case reports and small series communicated to date have provided evidence for the potential role of haematopoietic transplantation in these patients. High-dose radio-chemotherapy and autologous rescue has been shown to induce complete responses in the majority of patients. Disappointingly though, these responses were very short-lived in nearly all cases. On the contrary, the use of allogeneic transplantation has provided solid evidence for an allogeneic GVL effect in these malignancies. In fact, more than two-thirds of the allogeneic transplant recipients reported in the literature experienced long-term durable remissions of more than 3 years, which would appear superior to the expected median survival for such patients. This review summarizes the experience published to date in this setting and highlights main areas that would merit further investigation.

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Introduction

Primary cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of malignancies, which account for approximately 1–2% of all non-Hodgkin's lymphomas. The most common forms of CTCL are mycosis fungoides (MF) and Sézary syndrome (SS), with an annual incidence of about 3–4 cases per million people.^{1–3} For the majority of patients, the natural history of CTCL remains indolent. Patients normally present with a slow progression from erythematous cutaneous lesions into palpable plaques, then tumours, and subsequently spread to lymph nodes and visceral organs over the course of many years.^{3,4} Clinical management of these patients is therefore primarily dependent on their clinical presentation and disease stage, which has a strong correlation with overall prognosis (Table 1).^{5–11} Treatment options for CTCL comprise a wide range of topical and systemic therapies, including radiotherapy, cutaneous and extracorporeal phototherapy, interferons, topical and systemic chemotherapy, retinoids and rexinoids, monoclonal antibodies, cytokines, and an increasing array of newer biological agents.^{9,12–15} Patients with early-stage MF have an excellent prognosis and should be treated with skin-directed therapy, while patients with more aggressive forms of CTCL normally require systemic therapy.

Despite current systemic therapy, patients with CTCL with adverse prognostic factors, such as those with advanced-stage MF and SS, achieve only short-lived clinical responses. These lead to a recurrent pattern of clinical responses and disease relapse, and often death either from refractory disease or from the complications of multiple lines of therapy. Currently, there is no effective standard of care for patients with advanced-stage CTCL, whose prognosis remains poor, with an expected median survival of only 1–4 years (Table 1).⁹ As a result of such dismal prognosis with conventional therapy, alternative strategies based on autologous and allogeneic haematopoietic stem cell transplantation (HSCT) are being increasingly explored in these patients.¹⁶ Conditioning chemo-radiotherapy combined with either autologous rescue or the antitumour effect from allogeneic grafts has

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Table 1 TNMB staging system for primary CTCL

<i>TNMB classification</i>	<i>ISCL/EORTC Revision¹¹</i>				
<i>Tumour skin stage</i>					
T1	Limited patches/plaques <10% body surface area				
T1a	Only patches				
T1b	Plaques with or without patches				
T2	Patches/plaques ≥10% body surface area				
T2a	Only patches				
T2b	Plaques with or without patches				
T3	One or more tumours (≥1 cm diameter)				
T4	Confluent erythema covering ≥80% body surface area				
<i>Nodal stage</i>					
N0	No peripheral lymph node involvement; biopsy not required				
N1	Clinically abnormal nodes and histology DG 1 or NCI-LN ₀₋₂				
N1a	Clone negative ^a				
N1b	Clone positive ^a				
N2	Clinically abnormal nodes and histology DG 2 or NCI-LN ₃				
N2a	Clone negative ^a				
N2b	Clone positive ^a				
N3	Clinically abnormal nodes and histology DG 3-4 or NCI-LN ₄				
Nx	Clinically abnormal nodes and no histological confirmation				
<i>Metastatic visceral stage</i>					
M0	No visceral disease				
M1	Visceral disease with histological confirmation				
<i>Blood stage</i>					
B0	No circulating Sézary cells (<5% of blood lymphocytes)				
B0a	Clone negative ^a				
B0b	Clone positive ^a				
B1	Low blood tumour burden: ≥5% of lymphocytes are Sézary cells				
B1a	Clone negative ^a				
B1b	Clone positive ^a				
B2	High blood tumour burden: ≥1000/μl Sézary cells and clone positive ^a				
<i>Staging system</i>					
<i>Stage</i>	<i>T</i>	<i>N</i>	<i>M</i>	<i>B</i>	<i>Median survival^b</i>
IA	1	0	0	0-1	Not reached at 32 years
IB	2	0	0	0-1	12.1-12.8 years
IIA	1-2	1-2	0	0-1	10.0 years
IIB	3	0-2	0	0-1	2.9 years
III	4	0-2	0	0-1	
IIIA	4	0-2	0	0	3.6-4.6 years
IIIB	4	0-2	0	1	
IVA ₁	1-4	0-2	0	2	
IVB ₂	1-4	3	0	0-2	13 months
IVB	1-4	0-3	1	0-2	

Abbreviations: DG (Dutch grade) 1 = dermatopathic lymphadenopathy; DG 2 = early involvement with presence of cerebriform nuclei >7.5 μm; DG 3 = partial effacement of lymph node architecture with abundant cerebriform nuclei cells; DG 4 = complete effacement; NCI LN₀ = no atypical lymphocytes; LN₁ = occasional isolated atypical lymphocytes; LN₂ = many atypical lymphocytes or arranged in 3-6 clusters; LN₃ = aggregates of atypical lymphocytes which preserve nodal architecture; LN₄ = partial/complete effacement of nodal architecture by atypical lymphocytes.

^aT-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene.

^bThe classification and staging system have been recently updated to incorporate blood involvement and other new advances. Survival analysis of some of these new subgroups and indicators will be of great value, but for the purpose of this manuscript median survival values are provided according to more classical staging system in place at the time of presentation of the cases discussed.⁹

been shown to be an effective alternative for many haematological malignancies refractory to conventional therapy.

Lymphoma is currently the most frequent indication for performing an HSCT in Europe. In particular, the percentage of allogeneic HSCT for lymphoma has markedly increased over recent years due to the introduction of reduced-intensity conditioning allogeneic HSCT.^{17,18} Despite the broad experience with HSCT in other forms of lymphoma, the experience in CTCL is still limited to a small number of cases and small series reports. This review

focuses on published data on the use of autologous and allogeneic HSCT for CTCL and discusses the most pressing issues.

Autologous HSCT for mycosis fungoides and Sézary syndrome

Conventional single-agent chemotherapy is active against CTCL and, when combined in a number of chemotherapy

regimens, leads to higher levels of response in advanced refractory CTCL. These responses, however, are usually short-lived and do not translate into an improved overall and progression-free survival (reviewed by Whittaker *et al.*,⁹ Pichardo *et al.*,¹² Trautinger *et al.*¹⁴ and Whittaker and Foss¹⁵). Autologous HSCT relies on the potential advantage of the administration of high doses of radiotherapy and/or chemotherapy to maximize the antitumour effect, while overcoming profound myeloablation with the reinfusion of autologous haematopoietic stem cells. In the context of CTCL, the overall experience with autologous HSCT is very limited. From 1986 to date, 20 cases of autologous HSCT in patients with MF/SS have been reported (summarized in Table 2). These were 11 men and 9 women, with a median age of 46 years, ranging from 26 to 67 years, and a diagnosis of MF in 18 cases (stages IIB (10), IVA (5) or IVB (3)), 1 case of MF transformed to a high-grade lymphoma and 1 additional case of SS. Most patients had high-dose chemotherapy only-based conditioning regimens, the most common of which was a combination of casmustine, etoposide and melphalan (BEM; 8). A group of patients were conditioned with the combination of chemotherapy and total body irradiation (5) or total lymphoid

irradiation (1), and a total of nine patients were treated with total skin electron beam therapy immediately prior to transplantation to reduce cutaneous disease burden.

The procedure was safe, with only one transplant-related death, occurring as a result of sepsis on day +15 post transplant. In addition to safety, autologous HSCT was also shown to exert an effective anti-CTCL effect, inducing CR in all but one of the 19 evaluable patients. Discouragingly though, the responses were very short-lived, with reported median progression-free survivals from less than 100 days to about 7 months in one study.^{19–26} The median estimated time to disease progression was only 2.3 months (1–14). One of the limitations of autologous HSCT that may lead to early relapse is the potential reinfusion of malignant cells contaminating the graft. Thus, T-cell depletion to purge the graft from tumour cells prior to autologous HSCT was studied and was found to be feasible and safe.²⁴ Disease relapse did nevertheless occur whether or not T-cell depletion of the graft was performed, and in patients with minimal residual disease-positive as well as -negative grafts. The overall risk of rapid relapse was high in these T-cell-depleted HSCT patients, perhaps by compromising antitumour immunity.²⁵ In this overall experience of

Table 2 Autologous HSCT in patients with mycosis fungoides and Sézary syndrome

Study reference	Age	Sex	Disease—stage/prior therapy lines	Conditioning	SC source	Clinical course	Outcome
Chen ¹⁹	—	M	MF IVB/-	—	BM	CR/relapsed d + 40	Died of PD
Bigler ²⁰	49	F	MF IVB/-	TSEB-Cy-VP16-BCNU	BM	CR/relapse d + 64	Died d + 286
	60	M	MF IIB/-	TSEB-Cy	BM	CR/relapse d + 70	Died d + 1687
	49	M	MF IVA/-	Cy-TBI	BM	PR/progressed d + 93	Died d + 382
	37	F	MF IIB/-	TSEB-Cy-TBI	BM	CR/relapsed d + 96	Died d + 837
	26	F	MF IIB/-	TSEB-TLI-BCNU-VP16-CisPt	BM	CR/no relapse at 1 y	NA
	41	F	MF IVB/-	BCNU-VP16-CisPt	BM	CR/no relapse at 1 y	NA
Sterling ²¹	—	M	SS/-	Cy-TBI	—	CR/relapsed at 3 m	—
Ferrà ²²	32	F	MF tHG-NHL/6 lines	Cy-TBI-VP16-BCNU	PB	CR/relapsed at 2 m treated with IFN, LEB	ANED at 22 m
Olavarria, ²⁴ Russell-Jones ²⁵	47	M	MF IIB/2 lines	TSEB-MEL-TBI	PB CD34+	CR/relapsed at 2 m	Alive with disease
	52	F	MF IVA/5 lines	BEM	PB CD34+	CR/relapsed at 12 m	Alive with disease
	27	M	MF IVA/3 lines	VP16-TBI	PB CD34+	CR/relapsed at 14 m	Alive with disease
	49	F	MF IVA/5 lines	BEM	BM	NA/NA	Died d + 15 (sepsis)
	38	M	MF IVA/3 lines	TSEB-BEM	PB CD34+	CR/relapsed at 9 m	Alive with disease
	67	M	MF IIB/3 lines	TSEB-BEM	PB CD34+	CR/relapsed at 2 m	Died of PD
	42	F	MF IIB/5 lines	BEM	PB CD34+	CR/relapsed at 4 m	Died of PD
	38	M	MF IIB/4 lines	BEM	PB CD34+	CR/not relapsed	ANED at 10 m
57	F	MF IIB/3 lines	TSEB-BEM	PB CD34+	CR/relapsed at 1 m	Died of PD	
Ingen-Housz ²⁶	51	M	MF IIB/3 lines	BEAM	PB	CR/relapsed treated with IL2 and chemo.	ANED at 84 m
Gabriel ²³	45	M	MF IIB/1 line	TSEB-BEM	PB CD34+ and C1H	CR/relapsed d + 64, with progression to IVB	Allogeneic HSCT at 6 m (Table 3)

Abbreviations: ANED = alive with no evidence of disease; BCNU = carmustine; BEAM = BCNU-Etoposide-Citarabine-Melphalan; BEM = BCNU-Etoposide-Melphalan; BM = bone marrow; C1H = campath-1H/alemtuzumab; CisPt = cisplatin; CR = complete response; Cy = cyclophosphamide; d + = day post transplant; F = female; HSCT = hematopoietic stem cell transplantation; M = male; m = months; MEL = melphalan; MF = mycosis fungoides; NA = not available/not applicable; PB = peripheral blood; PB CD34+ = CD34+ -selected progenitors from PB SC; PD = progressive disease; PR = partial response; SC = stem cell; SS = Sézary syndrome; TBI = total body irradiation; tHG-NHL = transformed to high-grade non-Hodgkin's lymphoma; TSEB = total skin electron beam; VP16 = etoposide; y = years; staging as per TNMB system.

autologous HSCT for MF/SS patients, only one patient has remained alive with no evidence of post transplant disease progression. Two additional patients achieved a second CR with conventional treatment following an early relapse post transplant, and remain disease-free at 22 and 84 months. Despite the short progression-free survivals, it would appear as if at least some patients could achieve a better control of their CTCL following relapse after autologous HSCT, which might remain as the only potential benefit from a procedure with no apparent curative potential for these patients.

Allogeneic HSCT for mycosis fungoides and Sézary syndrome

In contrast to autologous HSCT, allogeneic HSCT avoids the risk of tumour contamination of the graft, which is derived from a healthy donor, and can potentially deliver an additional GVL effect. These potential benefits may, however, be offset by the higher morbidity and mortality of the procedure, in particular following standard myeloablative conditioning regimens. The published experience of allogeneic HSCT for advanced forms of MF and SS is also modest, with a total of only 21 patients, 11 men and 10 women, reported from 1994 to date (summarized in Table 3). Fourteen of these patients had advanced MF (stage IIB in 2, stage III in 1, stage IVA in 10, stage IVB in 1), 5 had SS and 2 others had high-grade lymphoma transformed from MF. Patients were very heavily pre-treated, with a median of seven lines of treatment prior to allogeneic HSCT. Sixteen donors were HLA-identical siblings and five were matched unrelated donors.

The first reported case in 1994 demonstrated that a long-term progression-free survival of up to 6 years could be attained in a patient with advanced-stage MF following allogeneic HSCT,²⁷ suggesting that it may be a curative option. Five years later, Burt *et al.*,²⁸ provided the first direct evidence of GVL effect in MF in a 27-year-old female patient with stage IVA, who achieved a CR with a myeloablative sibling allogeneic HSCT. Disease recurrence in this patient, 9 months after transplant, showed clinical and histologic remission in response to withdrawal of immunosuppressive medication and donor lymphocyte infusion. Further experience with myeloablative HSCT has been contributed by several groups. Conditioning consisted primarily of CY and single-dose or fractionated TBI, with additional etoposide in one case and chemotherapy-only BU CY conditioning in another. Out of the 10 patients reported to date, 8 remained alive and with no evidence of disease at a median of 57 months from the time of HSCT. The incidence of acute and chronic GVHD was high. Although one patient died from complications of GVHD, six of the eight patients with sustained remission had ongoing chronic GVHD, thereby providing further evidence supporting a possible GVL effect in CTCL.^{29–33} Although encouraging, these results with myeloablative allogeneic HSCT are restricted to younger patients, with a median age in these reports of 31.5 years (13–46). However, patients with CTCL are normally in their fifties or older, and would not be eligible for allogeneic HSCT following

myeloablative conditioning. With a view to reduce the toxicity associated with myeloablative conditioning and to expand eligibility to patients in an age range where CTCLs are more frequent, reduced-intensity conditioning (RIC) allogeneic HSCT has also been explored in this setting.

The first published data on the feasibility of RIC-HSCT for patients with MF came from a group in Milan that reported three cases of advanced MF in patients aged 60, 51 and 52 years, all of whom engrafted and achieved remission following sibling allogeneic RIC-HSCT.³⁴ Despite viral reactivations and infections, patients tolerated the procedure well, with only one death from a bacterial sepsis on day +73 post transplant. More importantly, the other two patients remained alive with no evidence of disease 18 and 24 months post transplant in association with skin chronic GVHD, providing evidence of a GVL effect against MF in the context of RIC-HSCT. Further experience of RIC-HSCT in CTCL was subsequently reported by Herbert *et al.*³⁵ in two patients with advanced refractory SS and MF and a third case with high-grade transformation of MF. All cases relapsed promptly after transplantation, but subsequently showed evidence of disease response following reduction of immunosuppression and donor lymphocyte infusion. These responses, however, were not sustained despite considerable chronic GVHD. One patient died at 11 months post transplant, with severe pneumonitis complicating progressive chronic GVHD. The authors concluded that to obtain maximum benefit from RIC-HSCT in patients with advanced CTCL, it should be used relatively early in the disease course and at a stage of lower disease bulk. The largest series of allogeneic HSCT in advanced CTCL comes from the City of Hope Comprehensive Cancer Centre.³² In addition to four cases of myeloablative HSCT already discussed above, this study also included one sibling donor and three matched unrelated donor RIC-HSCT, consisting of fludarabine and melphalan. One of the patients died of respiratory syncytial virus infection, while the others remain alive, in CR, and with good performance status despite ongoing chronic GVHD. An additional case of RIC-HSCT has been recently reported by the groups at Hammersmith Hospital and St Thomas' Hospital in London.²³ A 45-year-old man with cytotoxic variant of MF who received an autologous HSCT at tumour stage (IIB) relapsed 2 months after transplant and rapidly progressed to develop visceral pulmonary disease and multiple skin lesions. In this situation, he received a peripheral blood sibling RIC-HSCT with fludarabine, CY and *in vivo* alemtuzumab. Although the pulmonary lesions resolved on day +12, his skin lesions reappeared by day +18. Upon discontinuation of cyclosporine on day +30, the patient developed skin GVHD and all evidence of disease disappeared by day +71. Unfortunately, the patient died in CR on day +265 from progressive multifocal leucoencephalopathy. Finally, a relatively large series of 15 patients treated with RIC-HSCT for advanced MF and SS has been communicated recently in abstract format by the group from Milan.³⁶ The patients were 10 men and 5 women, at a median age of 48 years (38–65), with diagnoses of advanced-stage MF (9) or SS (6), refractory to a median of 3 previous lines of treatment.

Table 3 Allogeneic HSCT in patients with mycosis fungoides and Sézary syndrome

Study reference	Age	Sex	Disease—stage/prior therapy lines	Conditioning	GVHD prophylaxis	Donor	Clinical course	Outcome
Koepfel ²⁷	21	F	MF IVA/7 lines	Cy-TBI	CsA-MTX-CCS-IL2Abs	Sibling	Early CR; then relapse on d + 70 treated with LEB/TSEB/IFN	ANED at 6y/no GVHD
Burt, ²⁸ Guitart ²⁹	27	F	MF IVA/4 lines	Cy-TBI	CsA-CCS	Sibling	Early CR with aGVHD-II; various relapse episodes from 9 m, responsive to STOP IS, DLI and topical treatments	PR at 5y
	36	M	MF IIB/4 lines	Cy-TBI	CsA-CCS	Sibling	Achieved CR; transient grade III aGVHD	ANED at 4.5y/cGVHD
	39	F	MF/SS IVA/5 lines	Cy-VP16-TBI	CsA-CCS-MMF	Sibling	Achieved CR, with grade II GI and skin GVHD	ANED at 15m/cGVHD
Masood ³⁰	37	F	MF IVA/10 lines	Cy-TBI	CsA-MTX	Sibling	Achieved CR on d + 14; skin and GI aGVHD	ANED at 2y/cGVHD
Soligo ³⁴	60	M	MF/SS IVA/7 lines	FLU-mini-TBI	CsA-MMF	Sibling	STOP IS at 2m led to grade III skin aGVHD, which induced CR	ANED at 24m
	51	M	MF/SS IVA/3 lines	CyFLUx2-mini-TBI	CsA-MMF	Sibling	Achieved CR with grade III skin aGVHD on d + 58	ANED at 18m/cGVHD
	52	M	MF IVA/8 lines	CyFLUx2-mini-TBI	CsA-MMF	Sibling	Early CR; grade III skin aGVHD; developed sepsis and miocarditis	Died in CR on d + 73
Herbert ³⁵	38	M	MF III/9 lines	FLU-MEL	CsA	Sibling	CR at d + 32, GVHD-III and relapse; managed with IS and DLI	ANED at 28 m/cGVHD
	51	M	SS/4 lines	FLU-MEL	CsA	Sibling	Early PR; presented aGVHD grades II and III and relapse episodes which required changes in IS and DLI; multiple infections	Died at 11 months from relapse and cGVHD (Pneumonitis)
	48	F	MF tHG-NHL/1 line	FLU-MEL	CsA-MTX	Sibling	Brief CR with MF relapse at 4m which responded to STOP IS New HG-NHL relapse at 6m, treated with salvage chemotherapy	ANED at short FU
Molina ^{31,32}	22	F	SS/6 lines	Cy-FTBI	CsA-MTX-CCS	MUD	Extensive skin cGVHD; KPS 80%	ANED at 108 m/cGVHD
	45	—	MF IVA B0/8 lines	Cy-FTBI	CsA-MTX-CCS	Sibling	Limited skin cGVHD; KPS 100%	ANED at 89 m/cGVHD
	46	M	SS/8 lines	Cy-FTBI	CsA-MMF	Sibling	Extensive skin and oral cGVHD	Died in CR at 16 m
	21	F	SS/7 lines	BU CY	CsA-MMF	Sibling	Limited skin cGVHD; KPS 90%	ANED at 60 m/cGVHD
	59	M	SS/7 lines	FLU-MEL	CsA-MMF	Sibling	Extensive skin cGVHD; KPS 70%	ANED at 53 m/cGVHD
	50	—	MF IVA B1/5 lines	FLU-MEL	CsA-MMF	MUD	Limited liver cGVHD; KPS 90%	ANED at 45 m/cGVHD
	48	—	MF IVA B0/10 lines	FLU-MEL	CsA-MMF-MTX	MUD	Limited skin cGVHD; KPS 90%	ANED at 33 m/cGVHD
35	—	MF IIB B0/12 lines	FLU-MEL	CsA-MMF-MTX	MUD	Died from a RSV infection	Died d + 34	
Carrié ³³	13	M	MF tHG-NHL/2 lines	Cy-TBI	CsA-MTX	MUD	DLI and IFN induced CR of post-HSCT relapse; No GVHD	ANED at 1y
Gabriel ²³	45	M	MF IVB/Post-Auto	Cy-FLU	CsA-C1H	Sibling	Early CR (d + 12); relapsed d + 18; STOP CsA d + 30; CR d + 71 with skin cGVHD; progressive multifocal leucoencephalopathy	Died in CR on d + 256

Abbreviations: ANED = alive with no evidence of disease; BM = bone marrow; BUCY = busulfan-cyclophosphamide; C1H = campath-1H/Alemtuzumab; CCS = corticosteroids; CR = complete response; CsA = cyclosporine A; Cy = cyclophosphamide; d + = day post transplant; DLI = donor lymphocyte infusion; F = female; FLU = fludarabine; FTBI = fractionated TBI; FU = follow-up; GI = gastrointestinal; GVHD = graft versus host disease (acute, aGVHD; chronic, cGVHD); HSCT = hematopoietic stem cell transplantation; IS = immunosuppressive treatment; KPS = Karnofsky performance status; LEB = localized electron beam; M = male; MEL = melphalan; MF = Mycosis Fungoides; mini-TBI = one dose of 200 cGy; MMF = methotrexate; MTX = methotrexate; MUD = matched unrelated donor; PB = peripheral blood; PR = partial response; RSV = respiratory syncytial virus; SC = stem cell; Sib-D, sibling donor; SS = Sézary syndrome; TBI = total body irradiation; tHG-NHL = transformed to high-grade non-Hodgkin's lymphoma; TSEB = total skin electron beam; y, years; staging as per the TNMB system.

The conditioning regimen included low-dose TBI (200 cGy) in all cases, in association with pentostatin alone or with fludarabine and CY for sibling HSCT, and with fludarabine, melphalan and alemtuzumab for unrelated donor HSCT. At a median follow-up of 41 months, five patients had died (two from progressive disease and three from transplant-related mortality) and nine patients remained in CR, with an estimated 5-year progression-free survival probability of 60%. This outcome would appear substantially superior to that expected for such high-risk patients in the absence of transplantation, although the presentation of the full data from this cohort of patients is still awaited.

Unlike the experience with autologous HSCT, published reports of allogeneic transplantation in MF and SS have reproducibly shown durable long-term remissions. Overall outcome results in patients reported to date are encouraging. In addition to a tumour-free graft, there is good evidence of an allogeneic GVL effect in these malignancies. First, long-term durable remissions associate with chronic GVHD, second, disease relapse or progression can be triggered by immunosuppressive treatment, and last and more important, such disease progression subsequently responds to discontinuation of immunosuppressive drugs and to the infusion of donor lymphocytes. Out of the 21 allogeneic HSCT recipients reviewed here, 15 are alive and disease-free at a median post transplant follow-up of more than 3 years. Particularly interesting are the results of RIC-HSCT, the success of which relies primarily on the GVL effect, which appears to be equally efficacious as the conventional myeloablative HSCT to induce durable remissions. In addition, this strategy may allow broader application to older patients or to those with comorbidities. In fact, the median age of patients undergoing RIC-HSCT for MF/SS was 50 years, nearly two decades higher than that of the subgroup of myeloablative HSCT.

HSCT for forms of CTCLs other than mycosis fungoides and Sézary syndrome

Haematopoietic stem cell transplantation has also been used to treat patients with other types of CTCLs less common than MF and SS. Nishio *et al.*, from Hokkaido University, have reported two cases of autologous HSCT for CD30-negative cutaneous large T-cell lymphoma. The first case was a 52-year-old woman with no peripheral lymphadenopathies or bone marrow involvement who achieved CR following six courses of combination chemotherapy. She went on to receive high-dose chemotherapy and an unmanipulated peripheral blood (PB) autologous HSCT, but unfortunately suffered an early relapse 40 days after transplant.³⁷ The second patient was a 60-year-old man with widespread cutaneous tumours and axial and inguinal lymphadenopathies. The patient received four cycles of combination chemotherapy, obtaining a partial remission, and then three further courses in addition to local electron beam irradiation, to attain first CR. Autologous PB progenitors were positively immunoselected to a final CD34+ purity of 98.8%, and infused

following conditioning with ranimustine, carboplatin, etoposide and cyclophosphamide. The procedure was again well tolerated, and in this occasion the patient remained in CR for at least 16 months after HSCT.³⁸

This same group has also reported on two cases of autologous HSCT for subcutaneous panniculitis-like T-cell lymphoma (SPLTCL). The first case was a 20-year-old male patient with aggressive progression of SPLTCL that involved extracutaneous sites, including hepatosplenomegaly, abdominal lymphadenopathies, ascites and pleural effusions.³⁹ The patient received treatment initially with corticosteroids and subsequently with six courses of CHOP-etoposide, achieving a first CR. Then, he received consolidation treatment with an unmanipulated PB autologous HSCT following conditioning with high-dose chemotherapy (ranimustine, carboplatin, etoposide and cyclophosphamide). Overall, the procedure was well tolerated and the patient remained in continuous CR for at least 12 months after HSCT. The second case was a 21-year-old man with SPTCL presenting initially as a localized subcutaneous nodule that responded well to six courses of CHOP chemotherapy and local radiation.⁴⁰ Two years later, the disease relapsed with transformation into leukaemia, and a second CR was obtained with acute lymphoblastic leukaemia-type induction chemotherapy. Following consolidation chemotherapy, the patient received an autologous HSCT with selected CD34+ PB progenitors (97.6% purity) and etoposide, cyclophosphamide and TBI conditioning. An additional case of SPLTCL in a 39-year-old man who received systemic chemotherapy and an autologous HSCT has been described. In this case, however, amputation of the limb primarily involved with the lymphomatous infiltrate to debulk refractory disease was part of the treatment regimen.⁴¹

Allogeneic HSCT has also been described in patients with other forms of CTCL. One of the earliest reports of the use of RIC-HSCT in CTCL described a 22-year-old female patient with a CD30-negative large T-cell lymphoma.⁴² Her disease progressed rapidly despite three lines of single-dose and combination chemotherapy, and then she went on to receive a one class-II antigen HLA-mismatched related allogeneic HSCT from her father within the first year from diagnosis. Despite the young age of the patient, she had a reduced-intensity conditioning consisting of fludarabine, low-dose TBI (200 cGy) and *in vivo* ATG. The patient neither developed GVHD nor experienced signs of disease response up to 6 weeks after HSCT. At this point, immunosuppression was stopped, and a slow disease regression commenced. The patient had no evidence of disease by 6 months after transplant, and remained in CR and with a good performance status at 1 year. More recently, another case of HSCT for SPLTCL in a 15-year-old girl has been reported.⁴³ Following two unsuccessful lines of combination chemotherapy, the patient received salvage therapy with alemtuzumab followed by a myeloablative (etoposide and fractionated TBI) PB HLA-identical sibling HSCT. The patient engrafted, achieved full donor chimerism by day +21 and had no transplant-related complications. At the time of report, the patient had remained well and in CR for 31 months after transplant.

Conclusion

Haematopoietic stem cell transplantation has been increasingly explored in patients with advanced CTCL, in particular in those with SS and MF stages IIB and higher, who are known to have a very poor prognosis with standard systemic therapy. High-dose radio-chemotherapy followed by an autologous HSCT can induce CR in the majority of these patients, but responses are uniformly very short-lived, with a median time to relapse after transplantation of only very few months. Despite these disappointing results, some of the patients who relapsed presented forms of their CTCL that became easier to control with standard therapy than before the autologous HSCT. For a procedure with no curative potential, this may remain the only potential benefit for these patients.

The use of allogeneic HSCT in CTCLs has shown solid evidence of an allogeneic GVL effect. As a matter of fact, more than two-thirds of the patients reported in the literature to have received an allogeneic HSCT for advanced forms of CTCL remained alive and with no evidence of disease at a long median follow-up of more than 3 years, which would appear substantially superior to the median expected disease-free, or even overall survival for such patients. Particularly attractive and worth investigating are the results with RIC-HSCT, which may expand the applicability of this strategy to older patients and those with comorbidities. Many questions remain unanswered. The optimal conditioning regimen and timing of HSCT in the course of the disease are unknown. What the data suggest, though, is that in patients with advanced refractory CTCLs that would be eligible for allogeneic HSCT, the results could be improved further if the procedure was performed earlier in the disease course, before patients get very heavily treated, and at a stage of lower disease bulk, in particular for patients receiving an RIC-HSCT. The high incidence of acute and chronic GVHD, although associated with GVL, has a negative impact on the morbidity and mortality of the procedure and remains open for improvement. In this regard, newer drugs such as alemtuzumab or denileukin difitox that combine a strong prophylactic and therapeutic effect against GVHD with efficacy against CTCL may help controlling the severity of GVHD in allogeneic HSCT recipients for CTCL while contributing to disease control. Overall, allogeneic HSCT is feasible and effective in patients with advanced CTCL, and merits further investigation.

The limited amount of data available so far makes the analysis in this review necessarily broad in scope and leaves many specific questions open for further investigation. The specific outcome of some subgroups of patients, such as those with stage III erythrodermic MF, who have a better overall prognosis within the advanced-stage MF group, or those who have developed a profound immunosuppression as a result of multiple lines of therapy prior to HSCT and would be expected to do worse in terms of risk of infections associated with the HSCT procedure, requires a more detailed analysis than what can be provided here. The role of HSCT for CTCL needs to be ascertained in the context of the numerous biological agents that are becoming available for the treatment of these patients in the past few years, but were not available at the time that many

of the cases reviewed here were reported. These newer therapies may actually play a positive supporting role to the curative potential of HSCT, in particular allogeneic HSCT, in the form of post transplant maintenance therapy. Such analyses merit all further investigation. Registry-based analysis of all cases reported of HSCT for patients with CTCLs, and prospective trials, some of which are already ongoing, will be the only means to find answers to the many questions remaining.

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