

Hematopoietic stem cell transplantation in advanced cutaneous T-cell lymphoma

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Short title: Stem cell transplantation in CTCL

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Abstract

We retrospectively reviewed data pertaining to 5 patients with cutaneous T-cell lymphoma (CTCL) who had received hematopoietic stem cell transplantation (HSCT) between 2004 and 2015 at Kurume University Hospital, along with their clinical data until March, 2016. For patients with advanced CTCL eligible for HSCT, autologous HSCT was performed when they responded well to chemotherapy, and allogeneic HSCT was selected for patients with advanced mycosis fungoides (MF)/Sézary syndrome (SS) and CTCL other than MF/SS with poor chemosensitivity. Two patients (primary cutaneous anaplastic large cell lymphoma, and primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma) who responded well to chemotherapy received autologous HSCT: one patient was alive in partial remission and the other died due to therapy-related acute myeloid leukemia without disease relapse. In the remaining 3 patients with MF or SS, allogeneic HSCT was performed. Although 1 patient with MF died due to disease progression, the remaining 2 patients were alive in complete remission. Although there were 2 deaths in this study, the outcomes were considered satisfactory.

Keywords: allogeneic, autologous, cutaneous T-cell lymphoma, donor lymphocyte infusions, hematopoietic stem cell transplantation

Introduction

Cutaneous T-cell lymphoma (CTCL) is a relatively rare disease. The reported age-adjusted incidence of CTCL is 6.4 per 1,000,000 persons; and the incidence rate was highest between the ages of 70 and 79 years.¹ Approximately half of all patients with CTCL are diagnosed with mycosis fungoides (MF).² Although most patients with CTCL have an indolent disease course, some patients with MF, Sézary syndrome (SS), or other subtypes of CTCL (particularly CTCL with aggressive clinical behavior) exhibit poor prognosis.²

Hematopoietic stem cell transplantation (HSCT) has been used to treat lymphoma and leukemia. For the past 3 decades, HSCT has expanded rapidly through constant technological evolution.³ Autologous transplantation does not lead to graft versus host disease (GVHD) and is associated with lower treatment-related mortality as compared to that associated with allogeneic transplantation. Thus, autologous transplantation can be used in older patients.⁴ Although toxicity of preparative regimen and GVHD are potential drawbacks of allogeneic transplantation, graft versus tumor effects contribute to lower relapse rates with allogeneic transplantation than with autologous transplantation.⁴ Donor lymphocyte infusions (DLI), infusion of lymphocytes obtained from the donor of an allogeneic HSCT, is used to prevent rejection and to treat post-transplant relapse.⁵

Although advanced CTCL is expected to be well managed with HSCT, no clinical trials

have been conducted owing to the rarity of the condition. However, several retrospective studies on HSCT in patients with advanced CTCL have been conducted; nonetheless, most of these studies included only MF and SS.^{6, 7}

At our university hospital, for patients with advanced CTCL eligible for HSCT, autologous HSCT is selected when they respond well to chemotherapy, while allogeneic HSCT is selected for patients with advanced MF/SS and CTCL other than MF/SS who show poor chemosensitivity. We retrospectively evaluated data from 5 patients with advanced CTCL, who underwent autologous or allogeneic HSCT. Autologous HSCT was performed as a salvage or a consolidation therapy.

Patients and Methods

We retrospectively reviewed data pertaining to all patients with CTCL who had received HSCT at Kurume University Hospital between 2004 and 2015. A case report for patient 2 has already been published.⁸ The study was approved by the review board of Kurume University School of Medicine.

The following clinical data were collected for all patients until March 2016: age, sex, diagnosis, disease stage and Eastern Cooperative Oncology Group Performance-Status at initial diagnosis as well as that before transplantation, previous treatment, duration between

initial diagnosis and transplantation, type of transplantation, source of stem cells, and conditioning regimens. The following post-transplantation data were also collected: GVHD prophylaxis, presence or absence of GVHD, and outcomes.

Results

Clinical features before transplantation

Table 1 summarizes the clinical features before transplantation. Five patients (3 females and 2 males) were enrolled in this study. Median age at diagnosis was 39 years. Two patients had MF and the other 3 had primary cutaneous anaplastic large cell lymphoma (PCALCL; n = 1), primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (PCAETCL; n = 1), and SS (n = 1).

The patient with PCALCL (patient 1) had only skin lesions at diagnosis,⁹ which later progressed to lymph node and bone involvement. The patient with PCAETCL (patient 2) had no other organ involvement except for skin.⁹ Because skin lesions of the patient with PCALCL (patient 1) were only small nodules and the number of nodules was always less than 5, tumor resection was performed as one of the treatment options.

In the patient with PCALCL (patient 1), all lesions including those of skin, lymph nodes, and bone responded well to chemotherapy; however, less than 10% of lesions did not resolve,

and complete remission (CR) was not achieved before transplantation. In the patient with PCAETCL (patient 2), CR was achieved before transplantation.

The median duration between diagnosis and transplantation was 25 months.

Types of transplantation

Table 2 summarizes the types of transplantation that were determined based on their chemosensitivity and diagnosis. Patients with PCALCL or PCAETCL (patients 1 and 2) were treated with autologous peripheral blood stem cell transplantation owing to the good response to chemotherapy, whereas patients with MF or SS (patients 3–5) were treated with allogeneic HSCT owing to their specific diagnosis.

Reduced intensity conditioning regimen was administered to 1 patient (patient 3), and myeloablative conditioning regimen was administered in the other 2 patients selected for allogeneic HSCT.

GVHD prophylaxis was administered. Although 2 out of 3 patients developed acute GVHD, none died due to acute GVHD.

Outcomes

Table 2 summarizes the treatment outcomes. All patients achieved CR after

transplantation. The patient with MF (patient 5) could not sleep before transplantation because of severe pruritus of skin lesions that did not resolve despite various treatments for pruritus. However, the stubborn pruritus disappeared once the patient achieved CR (Fig. 1).

Relapse occurred in 3 patients (patients 1, 3, and 4). In the patient with PCALCL (patient 1), skin lesions recurred 36 months after transplantation, but which were surgically resected and the patient is alive. Patient 3 (MF) experienced relapse in the skin and lymph nodes 10 months after transplantation; the patient died 30 months after transplantation due to disease progression. Patient 4 (SS) experienced relapse in the skin and peripheral blood 6 months after transplantation. Despite cessation of immunosuppression therapy, expecting graft versus tumor effects, SS relapsed and progressed gradually. However, eventually, CR was achieved with DLI performed 13 months after transplantation; thereafter, CR was maintained without GVHD for 6 years. Although the patient with PCAETCL (patient 2) did not experience relapse, therapy-related acute myeloid leukemia (AML) developed 35 months after transplantation; the patient died of AML.⁸

Discussion

To date, 9 patients with PCALCL have been reported to receive HSCT.^{6, 7, 10} In a 21-year-old female patient, CR was achieved with anti-CD30 monoclonal antibody

administered more than 1 year after relapse of PCALCL following autologous HSCT.¹⁰ In patient 1 of the present study, although PCALCL recurred 36 months after transplantation, the aggressive behavior of PCALCL returned to an indolent disease course, which allowed tumor resection without any complications. Taken together, autologous HSCT can potentially eradicate aggressive components of PCALCL.

To date, only 8 patients with PCAETCL have been reported to receive HSCT.^{6, 8, 11, 12} Of these, 4 underwent allogeneic HSCT: 2 were alive in CR, whereas the other 2 died due to disease progression. Three patients underwent autologous HSCT: 2 patients achieved CR followed by disease relapse, and 1 died due to disease progression. One patient relapsed after showing a favorable response to autologous HSCT, and additional treatment with lenalidomide was not effective, resulting in receiving palliative treatment. Patient 2 from our study achieved CR but died due to therapy-related AML. In total, 5 of these died after HSCT. Considering that CR was maintained in 2 patients treated with allogeneic HSCT, allogeneic HSCT may be preferable over autologous HSCT in patients with PCAETCL. However, our patient 2 who was treated with autologous HSCT did not experience relapse of PCAETCL for 46 months after transplant, until his death due to secondary AML. The relative role of allogeneic and autologous HSCT for the treatment of PCAETCL is yet to be elucidated.

In patient 4, DLI was effective in resolution of the relapse of SS, and achievement of CR.

The reported response rates of DLI for relapse in lymphomas after allogeneic HSCT has ranged from 42% to 85%.¹³ This rate tended to be high in patients with indolent lymphomas and low in those with advanced lymphomas, which suggests that low tumor burden and slowly-growing malignancies may be essential conditions for favorable response to DLI.¹³ Patient 4 in our study satisfied these conditions. To date, 6 patients with MF/SS have been reported to undergo DLI after allogeneic HSCT.^{6, 14, 15} Of these, 3 patients achieved CR,^{6, 14} 2 obtained PR,¹⁵ and 1 died of the disease after DLI.¹⁵ DLI seems to be effective in the treatment of post-transplant relapse of MF/SS.

Our report suggests that HSCT is a viable treatment option for advanced CTCL.

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Legends

Figure 1 Clinical manifestation of patient 5. Patient 5 with mycosis fungoides exhibited markedly pruritic plaques and nodules all over the body before treatment (a, b). All lesions resolved with disappearance of pruritus after allogeneic HSCT (c, d).

Table 1. Clinical features before transplantation

Patient	Sex	Age at diagnosis (years)	Diagnosis	TNM classification (stage) at diagnosis	PS at diagnosis	Previous treatment	TNM classification (stage) before transplantation	PS before transplantation	Duration between diagnosis and transplantation (months)
1	F	39	PCALCL	T1aN0M0	0	EBI, CHOP, CHASE, ESHAP, IFN- α , IFN- γ , Tumor resection	T2aN1M1	0	78
2	M	38	PCAETCL	T3bN0M0	0	CHOP, CHASE, IFN- γ , Etoposide	CR	0	7
3	F	39	MF	T3N2M0B0 (IIB)	0	PUVA, EBI, CHOP, CHASE, IFN- γ	T3N2M0B0 (IIB)	0	25
4	M	54	SS	T4N0M0B2 (IVA1)	0	CHOP, Etoposide, CHASE	T4N0M0B2 (IVA1)	1	15
5	F	58	MF	T1N0M0B0 (IA)	0	NB-UVB, CHOP, Gemcitabine, Prednisolone	T3N3M0B0 (IVA2)	1	86

PCALCL: primary cutaneous anaplastic large cell lymphoma, PCAETCL: primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, MF: mycosis fungoides, SS: Sézary syndrome, EBM: electron beam irradiation, CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone, CHASE: cyclophosphamide, cytosine arabinoside, etoposide, dexamethasone, ESHAP: etoposide, cisplatin, cytarabine, methylprednisolone, IFN: interferon, PUVA: psoralen plus ultraviolet A, NB-UVB: narrowband-ultraviolet B, CR: complete remission, PS: Performance-Status

Table 2. Types of transplantation and outcome

Patient	Diagnosis	Type of transplantation	Conditioning regimen	GVHD		Response	Treatment after	Outcome
				prophylaxis	Acute GVHD	(duration after transplantation)	transplantation (Response)	
1	PCALCL	Autologous-PBSCT 8.37 x 10 ⁶ /kg CD34+ cells	MCEC	-	-	CR (36m) → Relapse	Tumor resection (PR)	Alive in PR (58m)
2	PCAETCL	Autologous-PBSCT 8.37 x 10 ⁶ /kg CD34+ cells	MCEC	-	-	CR	-	Died due to therapy-related AML (46m)
3	MF	Allogeneic-HSCT Unrelated male, HLA identical 7.33 x 10 ⁹ /kg Nucleated cells, 1.56 x 10 ⁸ /kg CD34+ cells	Cyclophosphamide, TBI	Tacrolimus, Methotrexate	Erythema (Grade2)	CR (10m) → Relapse	Localized irradiation, Vorinostat (NR)	Died due to disease progression (30m)
4	SS	Allogeneic-HSCT Unrelated female, HLA identical 24.15 x 10 ⁹ /kg Nucleated cells, 3.1 x 10 ⁸ /kg CD34+ cells	Fludarabine, Busulfan, TBI	Tacrolimus, Methotrexate	None	CR (6m) → Relapse	Donor lymphocyte infusions (CR)	Alive in CR (73m)
5	MF	Allogeneic-HSCT Umbilical cord blood, HLA non-identical (2 locus unmatched) 2.86 x 10 ⁷ /kg Nucleated cells, 10.89 x 10 ⁵ /kg CD34+ cells	Fludarabine, Busulfan, TBI	Tacrolimus, Methotrexate	Diarrhea (Grade1), Oral mucositis (Grade3)	CR	-	Alive in CR (23m)

PCALCL: primary cutaneous anaplastic large cell lymphoma, PCAETCL: primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, MF: mycosis fungoides, SS: Sézary syndrome, PBSCT: peripheral blood stem cell transplantation, HSCT: hematopoietic stem cell transplantation, HLA: human leukocyte antigen, MCEC: ranimustine, carboplatin, etoposide, cyclophosphamide, TBI: total body irradiation, GVHD: graft-versus-host disease, CR: complete remission, PR: partial remission, NR: no response, AML: acute myeloid leukemia, m: months

