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Original Research Article

Title

Allogeneic hematopoietic stem cell transplantation following reduced-intensity conditioning
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A running head

RIC-HSCT for MF/SS

Keywords

Mycosis fungoides, Sezary syndrome, Allogeneic hematopoietic stem cell transplantation,
Reduced intensity conditioning, Graft-versus-lymphoma effect

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Abstract

Advanced-stage mycosis fungoides and Sezary syndrome (MF/SS) have a poor prognosis. Allogeneic hematopoietic stem cell transplantation (HSCT), particularly using a reduced intensity conditioning (RIC) regimen, is a promising treatment for advanced-stage MF/SS. We performed RIC-HSCT in 9 patients with advanced MF/SS. With a median follow-up period of 954 days after HSCT, the estimated 3-year overall survival was 85.7% (95% confidence interval, 33.4 to 97.9%) with no non-relapse mortality. Five patients relapsed after RIC-HSCT; however, in 4 patients whose relapse was detected only from the skin, persistent CR was achieved in 1 patient and the disease was manageable in other 3 patients by the tapering of immunosuppressants and donor lymphocyte infusion, suggesting that graft-versus-lymphoma effect and “down-staging” effect from advanced-stage to early-stage by HSCT improve the prognosis of advanced-stage MF/SS. These results suggest that RIC-HSCT is an effective treatment for advanced MF/SS.

Introduction

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL), and Sezary syndrome (SS) is a variant type of MF that is characterized by generalized erythema and leukemic change. Early stage (under stage IIA) MF/SS patients have good prognosis with a median survival over 10 years. Treatments for early-stage disease include ultraviolet therapy, topical steroid treatment, and localized radiotherapy. In contrast, patients with advanced disease have poor prognosis with 5-year overall survival (OS) rates of 40 - 50% in stage IIB/III and 10-30% in stage IV despite intensive chemotherapies. [1,2] Allogeneic hematopoietic stem cell transplantation (HSCT), [3-9] particularly following a reduced-intensity conditioning (RIC) regimen, [7,10-12] is a promising strategy for treatment of advanced-stage MF/SS.

In this study, we retrospectively analyzed the outcomes of RIC-HSCT for advanced-stage MF/SS and found that MF/SS appears to be susceptible to graft-versus-lymphoma (GVL) effects.

Materials and methods

Patients

We studied outcomes in a consecutive series of 9 patients with MF/SS who underwent HSCT with RIC regimens between 2004 and 2012 in Hokkaido University Hospital. The study was performed in accordance with institutional ethical guidelines, including the World Medical Association Declaration of Helsinki, and all patients gave informed consent. A diagnosis of MF/SS was made by clinical and immunohistopathological features according to the criteria of the WHO classification (2001) or the revised WHO classification (2008). Staging of the disease was performed according to the criteria of the ISCL / EORTC. [13] Large cell transformation was defined as the presence of more than 25% of large cells in biopsied samples. [14-16]

Transplantation procedures

All of the patients were treated with a RIC regimen. Graft-versus-host disease (GVHD) prophylaxis consisted of the combination of a calcineurin inhibitor (CI) and short-term

methotrexate (sMTX). Granulocyte colony-stimulating factor was administered from day 5 until neutrophil engraftment. The prophylactic regimen for infection included levofloxacin, an antifungal agent (fluconazole, itraconazole or micafungin), and acyclovir.

Definitions

Treatment response was evaluated according to the Consensus WHO criteria for MF/SS.

[17] Relapse was diagnosed on the basis of histopathological findings in the skin lesions or F-18 fluorodeoxyglucose positron emission tomography findings. The day of neutrophil engraftment was defined as the first of 3 days with absolute neutrophil count $>0.5 \times 10^9/l$.

Acute GVHD (aGVHD) was graded according to the consensus criteria. Chronic GVHD (cGVHD) was graded by the criteria of National Institutes of Health consensus development project. [18]

Statistical analysis

Probabilities of OS, progression-free survival (PFS) and after HSCT were estimated using

Kaplan-Meier estimates. Statistical analyses were performed with EZR, which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). [19]

Results

Patients' characteristics

The median age of the patients was 42 years, ranging from 22 to 57 years. Seven patients had MF and two had SS. Eight of those 9 patients had large cell transformation. All patients had advanced disease (stage IIB: n=2, IIIB: n=1, IVA2: n=5, and IVB: n=1). The median interval from disease onset to HSCT was 12 years, ranging from 3 to 23 years. All of the patients received at least 4 lines of treatments prior to HSCT. Disease status at transplant was CR in only one patient and PR in 8 patients. All PR patients had cutaneous disease and four of them had involvement of other lesions including the lymph nodes and peripheral blood (Table 1).

Transplant characteristics

Types of HSCT were bone marrow transplantation in 6 patients, peripheral blood stem cell transplantation in 3 patients, and cord blood transplantation in one patient (Table 2). Six patients underwent transplantation from unrelated donors (8/8 HLA- A, -B, -C, -DR match in 2 patients, 1-locus HLA-mismatch in 3 patients and 2-locus HLA-mismatch in 1 patient) and 3 patients underwent transplantation from HLA-identical sibling donors. Conditioning regimens were as follows: fludarabine (Flu) + busulfan (BU) $\pm$ 2-6 Gy of total body irradiation (TBI) in 6 patients, Flu + melphalan + 2-4 Gy TBI in 2 patients, and Flu + melphalan + anti-thymocyte globulin in one patient. GVHD prophylaxis was tacrolimus (Tac) and sMTX (n=5) or cyclosporine + sMTX (n=4).

Engraftment and GVHD

All patients tolerated the conditioning regimen and achieved neutrophil engraftment (median: 14 days, range: 12 to 22 days). Acute GVHD developed in 8 patients (grade 2: n=7, grade 4: n=1). All of the patients had stage 2 to 4 cutaneous GVHD. Chronic GVHD developed in 7 patients (mild: n=1, moderate: n=2, severe: n=4).

Relapse and GVL effects

Eight patients who underwent transplantation at PR attained CR after HSCT. However, relapse occurred early after HSCT in 5 patients (55.6%) at a median of 45 days and range of 32 to 84 days after HSCT. All of the relapse patients had taken CI at the time of relapse and CI was rapidly tapered off, followed by donor lymphocyte infusion (DLI) in 2 patients. With these immunomodulations, GVHD developed and CR was achieved again in 4 (80%) of the 5 patients. However, one patient remained in CR at a follow-up of 962 days, while the disease recurred in the remaining 3 patients (Supplemental Figure). Detail clinical courses of disease status, GVHD and immunomodulations were shown in Figure 1. The clinical courses of two representative cases are shown in the following.

Case 6

A 57-year-old patient was diagnosed 23 years ago as having MF from the skin biopsy specimen. After the treatment of topical corticosteroid, radiation therapy and combination

chemotherapies for the progression to advanced-stage (Stage IVB), he underwent HSCT following an RIC regimen consisting of Flu, BU and 4 Gy of TBI from an HLA-identical sibling donor. Soon after neutrophil engraftment, the patient developed extensive and infiltrative erythema (Figure 2A). Histological analysis of the skin on day 45 after HSCT showed band-like infiltration of CD3⁺/CD4⁺ T cells in the upper dermis with epidermotropism, indicating disease relapse (Figure 2B-D). Since the skin lesions gradually progressed, immunosuppressants were tapered off on day 134. On day 168, skin and mucosal lesions including oral erosion and ocular hyperemia had developed (Figure 2E) and the cutaneous MF lesions had spontaneously disappeared. A skin biopsy on day 218 showed necrotic keratinocytes, melanophages and vacuolar change in the epidermal-dermal junction (Figure 2F), indicating GVHD. Administration of 1 mg/kg of prednisolone improved GVHD and the patient has since remained in CR.

Case 8

A 43-year-old patient was diagnosed 3 years ago as having MF with advanced-stage

(Stage IIB) from the skin biopsy specimen. After the treatment of topical corticosteroid, Psoralen ultraviolet A, electron beam, radiation therapy and MTX, he underwent HSCT using an RIC regimen consisting of Flu, MEL and ATG from an HLA 2-locus-mismatched unrelated donor. No aGVHD developed. On day 70 after HSCT, infiltrative erythema appeared on the lower abdomen, and a skin biopsy on day 84 showed monotonous infiltration of CD3⁺/CD4⁺ T cells, indicating disease relapse (Figure 3A-D). After the immunosuppressant (Tac) had been tapered off, grade II aGVHD (skin stage 3) developed, followed by an improvement of cutaneous MF lesions. Focal nodular lesions recurred in the left trunk on day 241. The patient received vorinostat followed by DLI on days 290 and 308. On day 325, the patient developed Stevens-Johnson syndrome-type severe GVHD in the skin (Figure 3E-G) that was histologically proven (Figure 3H). Intensive immunosuppression was initiated with pulse methylprednisolone, Tac, and mycophenolate mofetil, resulting in improvement of GVHD and resolution of the cutaneous MF lesions. Cutaneous MF lesions recurred again on day 441, and the patient is currently being treated with modulation of immunosuppressants and vorinostat as of day 427.

Outcome

With a median follow-up period of 954 days (range: 413 to 2992 days) after HSCT, the estimated 3-year OS was 85.7% (95% confidence interval, 33.4 to 97.9%) (Figure 4A) and the estimated 3-year PFS was 44.4% (Figure 4B). There was no non-relapse mortality (NRM). One patient died on day 738 due to underlying disease, 5 patients, including one patient achieved CR by immunomodulation, are alive in CR, and the remaining 3 patients are alive with disease being treated by the immunomodulations, DLI, localized radiotherapy, vorinostat, or MTX (Supplemental Figure).

Discussion

Our study suggests that RIC-HSCT is a promising strategy for the treatment of advanced MF/SS; 3-year OS was 85.7% without NRM. Duarte *et al.* reported that the 3-year OS rate in 60 patients with advanced MF/SS who underwent allogeneic HSCT was 54% and that an RIC regimen improved transplant outcome due to less NRM than that in the case of a

myeloablative conditioning (MAC) regimen (3-year OS: 63% vs 29%, 2-year NRM: 49% vs 14%). [7] In another retrospective large-scale study by de Masson A *et al.*, 2-year OS was 56% and 3-year PFS was 31%, and the type of conditioning regimen (RIC versus MAC) had no significant impact on transplant-related mortality. [9]

The excellent outcome in our study is likely due to less NRM than that in other studies. HSCT for MF/SS is often complicated with severe bacterial infection due to disruption of the skin barrier by the skin lesions of MF/SS. [20-22] In our study, such severe infection events were not observed. All of our patients received RIC regimens, in which the severity of cytopenia is mild and the risk of severe infection is reduced compared to those in MAC regimens.

In addition, disease could be managed relatively easily after relapse following HSCT by the immunomodulations. Early relapse of MF was observed in 5 patients; however, in 4 patients whose relapse was detected only from the skin, persistent CR was achieved in 1 patient and the disease was manageable in other 3 patients by the treatment of immunomodulations, including the tapering of immunosuppressants and DLI, suggesting

that GVL effect and “down-staging effect” from advanced-stage to early-stage by HSCT improve the prognosis of advanced-stage MF/SS. Such a GVL effect against MF/SS mediated by the tapering of immunosuppressants and DLI has been reported previously. [7,8,23-25] A strong GVL effect against MF/SS has also been suggested in a study in which allogeneic HSCT was compared with autologous HSCT. Wu *et al.* performed meta-analysis of data for 39 patients with MF/SS who underwent allogeneic or autologous HSCT. [5] Both OS and event-free survival (EFS) in patients who underwent allogeneic HSCT were significantly higher than those in patients who underwent autologous HSCT (5-year OS: 23% vs 80%, 5-year EFS: 0% vs 60%). Skin is the main tissue affected in both MF/SS and GVHD. Alloreactive donor T cells that have infiltrated into the skin to cause GVHD may also attack MF/SS cells mostly present in the skin, leading to a potent GVL effect. However, development of severe GVHD severely affects quality of life and survival of patients. Actually in our study, high incidence of both acute and chronic GVHD was observed, and most of them developed after the tapering of immunosuppressants or DLI. Fortunately, there was no NRM, nevertheless control of both MF/SS and GVHD is often difficult.

Relapse rate was high after HSCT in our study. This may be due to the use of an RIC regimen and a higher proportion of non-CR patients than those in other studies. It should be noted that all disease relapses occurred within 100 days after HSCT in our study. These results urge us to develop novel strategies to prevent relapse after RIC-HSCT without causing severe GVHD. Histone deacetylase inhibitors such as vorinostat are effective for CTCL. [26-28] Interestingly, a recent study suggested that vorinostat prevented GVHD when given in conjunction with standard GVHD prophylaxis. [29] These results suggest that prophylactic use of vorinostat may be a promising strategy to control GVHD and prevent relapse of MF/SS at the same time. We are conducting a phase I study of posttransplant vorinostat therapy for prevention of early relapse after HSCT for MF/SS.

Our study has several limitations that should be considered when reviewing the results, including the use of a retrospective design and inclusion of a small number of patients. Nevertheless, due to the rarity of the diseases, our data provide useful information on the use of HSCT in patients with MF/SS. RIC-HSCT is an effective treatment option for advanced-stage MF/SS. Further studies are needed to improve the outcome, particularly to

prevent relapse of MS/SS after HSCT.

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Figure legends

Figure 1. Clinical courses of disease status, GVHD and immunomodulation therapy

Gray bar indicates the immunosuppressants including calcineurin inhibitors and/or steroids.

White circle indicates complete remission, gray circle indicates partial remission, and black circle indicates relapse or disease progression.

Figure 2. Clinical course of patient 6 after HSCT

The patient had infiltrative erythema on the whole body after HSCT (A). HE staining showed band-like atypical lymphocytic infiltration in the upper dermal layer with a collection of epidermal atypical lymphocytes forming a Pautrier microabscess (B. 40x). Immunohistochemical staining for CD3 (C. 40x) and CD4 (D, 40x). Cutaneous GVHD after the tapering of immunosuppressants (E). Hematoxylin-eosin staining showed necrotic keratinocytes and vacuolar change of the basal cell layer and subepidermal blistering (F. 40x).

Figure 3. Clinical course of patient 8 after HSCT

The patient showed a focal nodular lesion of the left trunk in the period of the 1st relapse after HSCT (A). HE staining showed epidermotropic atypical lymphocytic infiltration with invasion of the superficial dermis (B. 40x). Immunohistochemical staining for CD3 (C. 40x) and CD4 (D,40x). Stevens-Johnson syndrome-type aGVHD including ocular hyperemia (E), oral mucositis (F) and erythema on the whole body surface (G). Hematoxylin-eosin staining

showed necrotic keratinocytes in epidermis and vacuolar change in the epidermal-dermal junction (H. 40x).

Figure 4. Kaplan-Meier plots of OS (A) and PFS (B) after HSCT for MF/SS.

Supplemental Figure. Summary chart for the clinical course and treatment outcome of patients in this study

Disease status at transplant was CR in 1 patient and PR in 8 patients. At 1 month after HSCT, all of the 8 patients transplanted at PR had attained CR, but relapse occurred in 5 patients. Of these 5 patients, 1 patient died due to underlying disease, 1 patient is alive in CR achieved by immunomodulation, and the remaining 3 patients are alive with disease.

Gray parts indicate disease status at the last follow-up.

Figure 1.

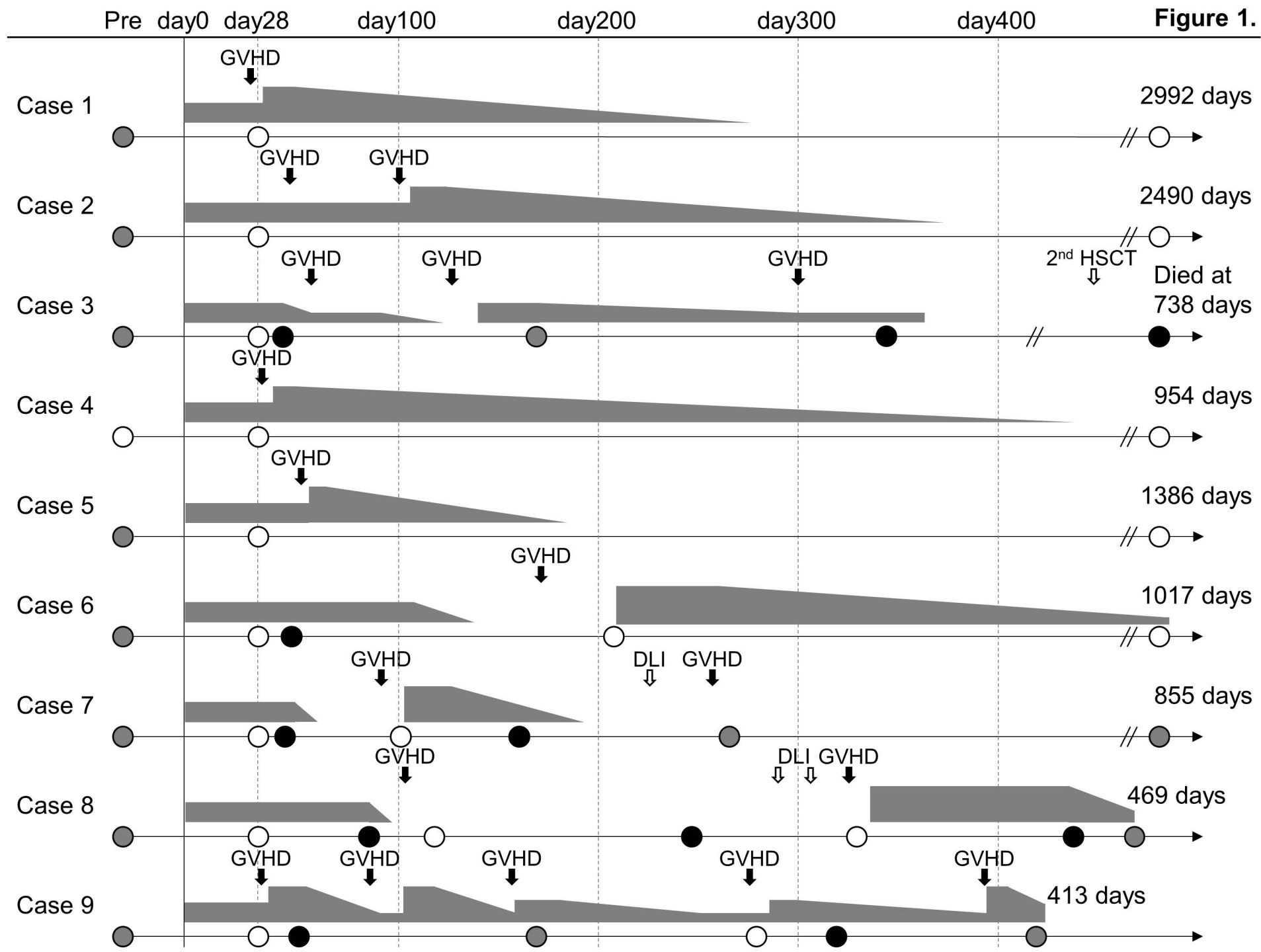


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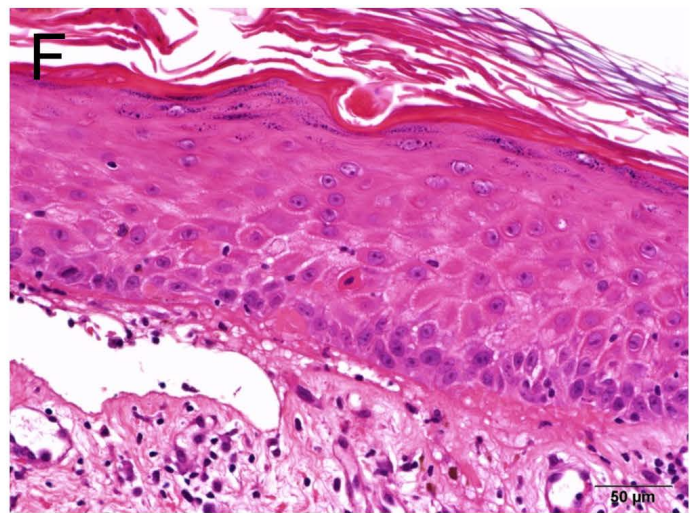
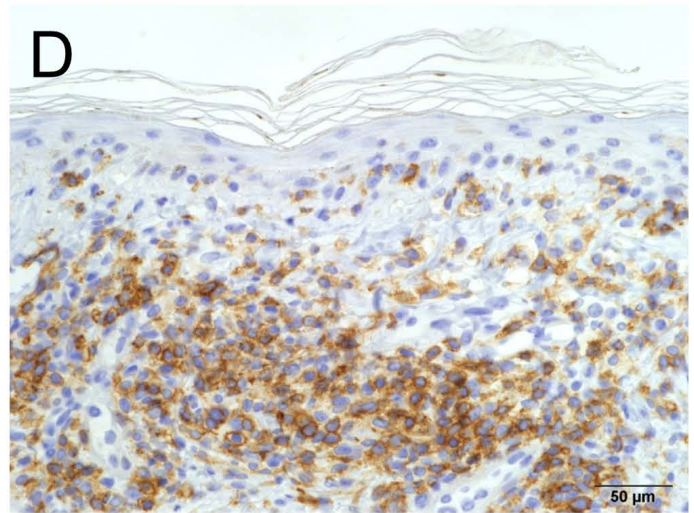
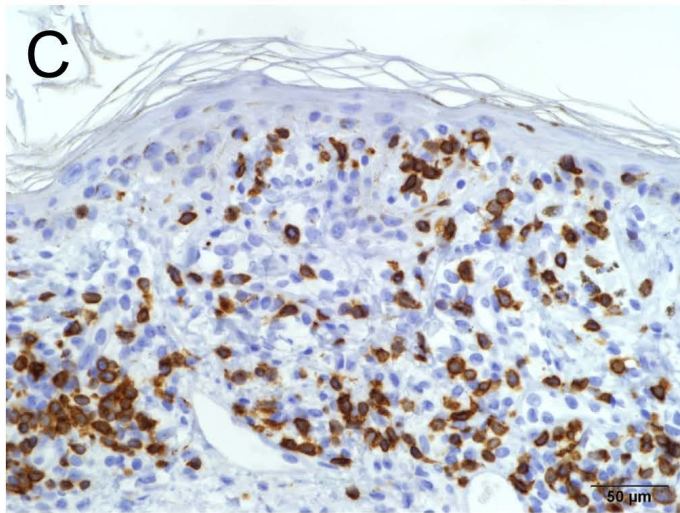
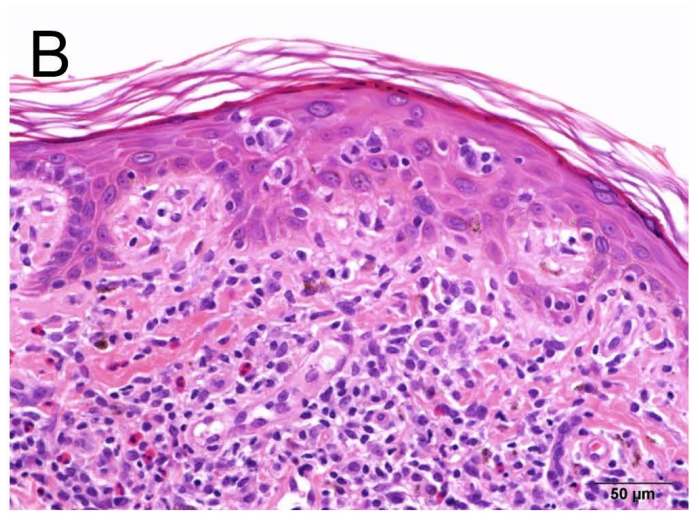


Figure 3.

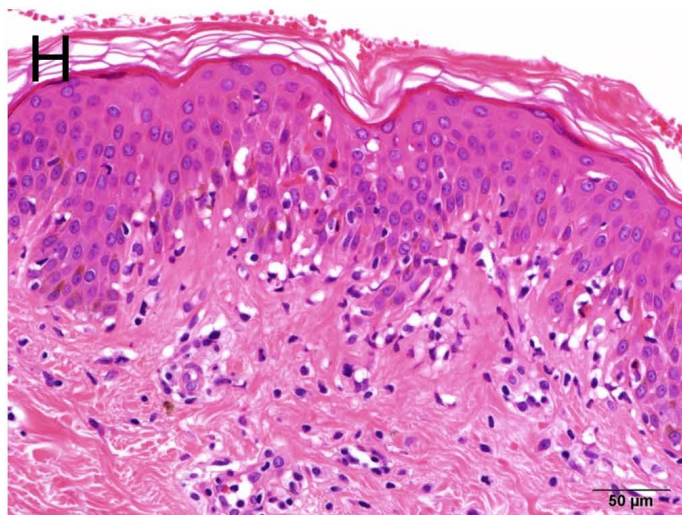
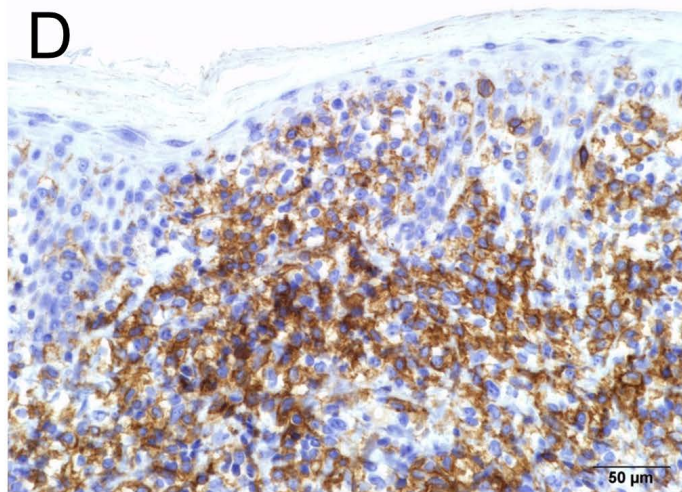
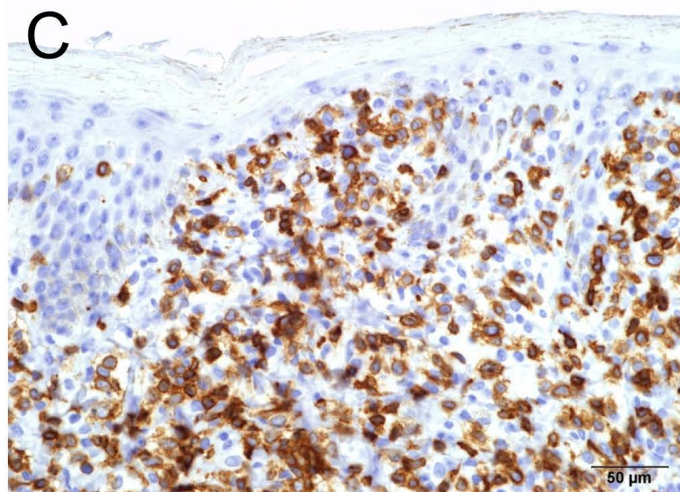
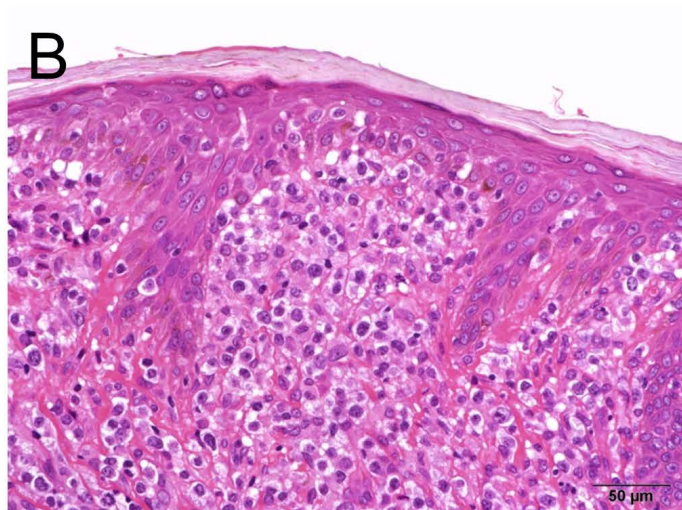


Figure 4.

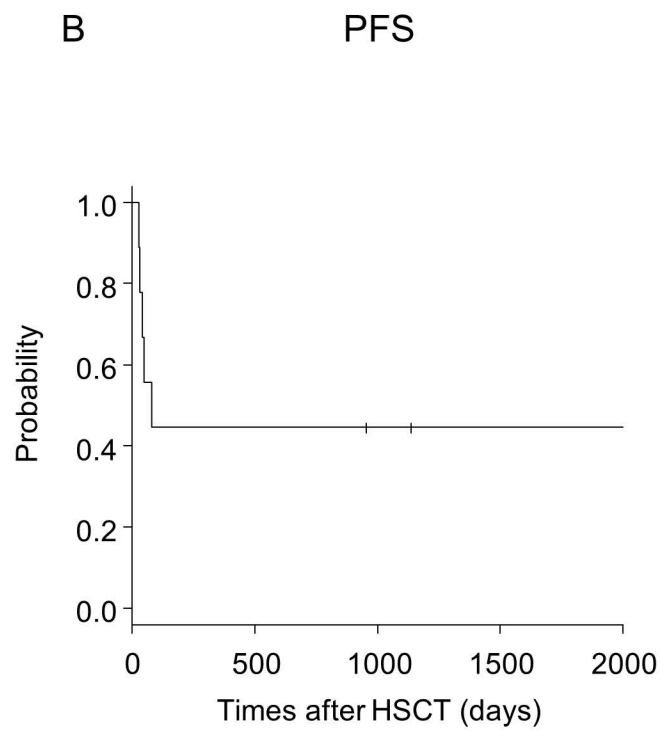
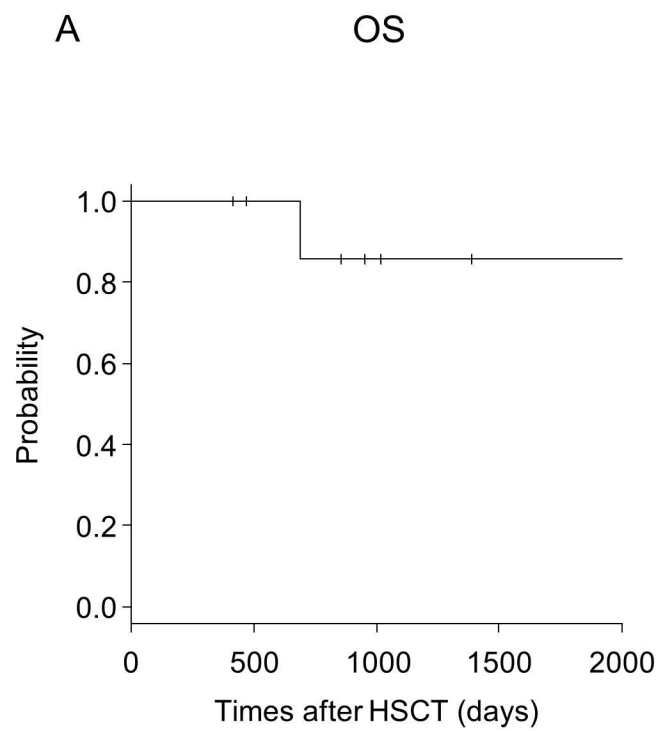


Table 1 Patient characteristics

Patient	Age / Sex	Desease	Disease onset to HSCT (years)	Clinical stage	Disease status at HSCT	Lesions at HSCT	Large cell Transformation	Number of prior treatment regimens
1	22 / M	SS	6	IVA2 / T2N3M0B1	PR	Skin, Lymph node	+	4
2	41 / M	SS	20	IIIB / T4N1M0B1	PR	Skin, peripheral blood	-	4
3	40 / F	MF	7	IVA2 / T3N3M0B0	PR	Skin	+	5
4	55 / F	MF	8	IVA2 / T3N3M0B0	CR	No	+	4
5	45 / M	MF	12	IVA2 / T2N3M0B0	PR	Skin, Lymph node	+	4
6	57 / M	MF	23	IVB / T4N2M1B0	PR	Skin, Lymph node	-	6
7	34 / F	MF	13	IIB / T3N2M0B0	PR	Skin	+	4
8	43 / M	MF	3	IIB / T3N0M0B0	PR	Skin	+	5
9	42 / F	MF	14	IVA2 / T2N3M0B0	PR	Skin	+	4

Abbreviations: HSCT; allogeneic hematopoietic stem cell transplantation, M; male, F; female, SS; sezary syndrome, MF; mycosis fungoides, PR; partial response, CR; complete response.

Table 2 Transplant characteristics and outcomes

Patient	HSCT	Conditioning	Acute GVHD (Grade / Skin stage)	Chronic GVHD (Total / Skin score)	Relapse / lesion	Intervention after relapse, Outcome
1	U-BMT	Flu+Mel+TBI 2Gy	II / 3	Moderate / 2	No	Alive at day 2992 in CR
2	CBT	Flu+BU+TBI 4Gy	II / 3	Severe / 3	No	Alive at day 2889 in CR
3	R-BMT	Flu+BU	III / 2	Mild / 0	day 30 / Subcutaneous tissue, Skin, Lymph node	Chemotherapy, 2nd allo-HSCT and DLI, Died of disease progression at day 738
4	R-PBSCT	Flu+BU+TBI 6Gy	II / 3	No	No	Alive at day 954 in CR
5	U-BMT	Flu+BU+TBI 4Gy	II / 3	No	No	Alive at day 1386 in CR
6	R-PBSCT	Flu+BU+TBI 4Gy	II / 3	Severe / 3	day 45 / Skin	Discontinuation of Tac, Alive at day 1017 in CR
7	U-BMT	Flu+BU+TBI 4Gy	II / 3	Moderate / 1	day 32 / Skin	DLI, EB, PUVA, vorinostat and MTX, Alive at day 855 in PR
8	U-BMT	Flu+Mel+ATG	No	Severe / 3	day 84 / Skin	Reduction of Tac and steroid, DLI and vorinostat, Alive at day 469 in PR
9	U-BMT	Flu+Mel+TBI 4Gy	IV / 4	Severe / 3	day 53 / skin	Reduction of steroid or Tac, Alive at day 413 in PR

Abbreviations: HSCT; allogeneic hematopoietic stem cell transplantation, GVHD; graft-versus-host disease, U-BMT; unrelated bone marrow transplantation, CBT; cord blood transplantation, R-BMT; related bone marrow transplantation, R-PBSCT; related peripheral blood stem cell transplantation, Flu; fludarabine, Mel; melphalan, TBI; total body irradiation, BU; busulfan, ATG; antithymocyte globulin, CR; complete response, DLI; donor lymphocyte infusion, Tac; tacrolimus, EB; electron beam, PUVA; Psoralen ultraviolet A, MTX; methotrexate, PR; partial response.