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MINIREVIEWS

Treatment of mycosis fungoides, in the era of stem cell transplantation

Pusem Patir, Filiz Vural

Pusem Patir, Filiz Vural, Department of Hematology, Ege University Hospital, Bornova, 35100 Izmir, Turkey

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Correspondence to: Filiz Vural, MD, Department of Hematology, Ege University Hospital, Kazimdirik district, Bornova, 35100 Izmir, Turkey. fivural@yahoo.com
Telephone: +90-532-5468368
Fax: +90-232-3903530

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Abstract

Mycosis fungoides and Sèzary syndrome are the most common subtypes of cutaneous T-cell lymphomas. Even though, in early-stage disease, Mycosis fungoides commonly has a more indolent course, disease will progress in about 20% of such patients. About 30% of patients have been reported to develop advanced-stage disease and, at present, there is no cure for the disease. A number of systemic approaches have been used for advanced-stage mycosis fungoides (IIB-IV) and transformed disease. Aggressive approaches seem to be warranted in such patients. The scope of this review is the stem cell transplantation in mycosis fungoides and its leukemic variant, Sèzary syndrome.

Key words: Mycosis fungoides; Sèzary syndrome; Stem cell transplantation

Core tip: Some cutaneous T-cell lymphoma patients progress to advanced-stage disease or leukaemic stages. To date, there is no cure for those cases. In the last few years, several publications reported durable responses in some patients following allogeneic hematopoietic stem cell transplantation. Our aim is to define outcomes after hematopoietic stem cell transplantation for mycosis fungoides and Sèzary syndrome.

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INTRODUCTION

Cutaneous T-cell lymphomas (CTCL) are amongst a group of malignancies of T-lymphocytes which primarily involves the skin. Mycosis fungoides (MF) and Sèzary syndrome (SS) are the most common subtypes of CTCL[1]. Based on the TNM classification, MF has four clinical stages, which has been translated further into early-stage and advanced-stage disease. Patients are considered to have "limited-stage" or "advanced-stage" disease if they have stage IA, stage IB, or stage IIA

Table 1 Summary of studies on auto hematopoietic stem cell transplantation and allo hematopoietic stem cell transplantation in patients with mycosis fungoides and Sèzary syndrome

Ref.	Year	Study location	Cases	Feature of study
AutoHSCT				
Bigler *et al*[11]	1991	United States	6	The first publication containing patient series with autoHSCT
Olavarria *et al*[9]	2001	United Kingdom	9	The analysis of autoHSCT with harvested cells post-T-cell depletion
Duarte *et al*[10]	2008	Spain	20	The use of auto and alloHSCT were summarized in this review
AlloHSCT				
Duvic *et al*[14]	2010	United States	19	The safety and efficacy of total skin electron beam with alloHSCT
Duarte *et al*[12]	2010	EBMT	60	The first large multicenter analysis of alloHSCT
Schlaak *et al*[15]	2012	Germany	-	To compare the efficacy and safety of conventional therapies with alloHSCT
de Masson *et al*[16]	2014	France	37	The largest multicenter analysis of alloHSCT for transformed MF
Duarte *et al*[13]	2014	EBMT	60	Updated with a prolonged median follow-up of 7 yr
Lechowicz *et al*[17]	2014	United States United Kingdom Australia	129	The largest reported descriptive cohort of patients receiving alloHSCT

HSCT: Hematopoietic stem cell transplantation; MF: Mycosis fungoides.

disease and stage ⅡB, stage Ⅲ, or stage Ⅳ, respectively. Even though, in early-stage disease, MF commonly has a more indolent course, disease will progress in about 20% of such patients[2]. About 30% of patients have been reported to develop advanced-stage disease and, at present, there is no cure for the disease[3]. In terms of outcome, the most significant predictor appears to be clinical stage of the disease.

In most of advanced stage CTCL cases, short-term clinical responses can be achieved with the use of various therapies, with a median survival time of 2.9 years. Patients with SS, on the other hand, have shorter median survival, approximately 13 mo[2,4,5]. A number of systemic approaches have been used for advanced-stage MF (ⅡB-Ⅳ) and transformed disease. These approaches include the use of retinoids, histone deacetylase inhibitors, interferon-α, bexarotene, the fusion toxin denileukin diftitox, extracorporeal photopheresis and chemotherapy without or in conjunction with stem cell transplantation. Despite of the limited data, the outcome is very poor in younger patients who have advanced-stage MF and are refractory to or relapsed after treatment with IFN-α, bexarotene, or histone deacetylase inhibitors. Aggressive approaches seem to be warranted in such patients[6]. The scope of this review is the stem cell transplantation in MF and its leukemic variant, SS.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Overview

Hematopoietic stem cell transplantation (HSCT) is a procedure in which hematopoietic progenitor cells obtained from bone marrow or peripheral or umbilical cord blood, either autologous or allogeneic, is administered to the recipient with the aim of recomposing the bone marrow. It has been shown that conditioning regimen composed of chemotherapy and/or radiotherapy combined with either autologous or allogeneic grafts was an efficient salvage treatment for a number of hematological malignancies that are unresponsive to conventional therapies. The most common indication for an HSCT in Europe is lymphomas. There has been an increase in the rate of allogeneic HSCT (alloHSCT) for lymphoma in recent years, largely owing to the introduction of reduced-intensity conditioning (RIC) alloHSCT[7,8]. RIC is a procedure to reduce the tumor size prior to the transplant to refrain from standard regimes of high-dose therapy. RIC appears to be as effective as standard conditioning regimens but with significantly less toxicity. Even though we have sufficient experience with HSCT in other types of lymphoma, there is only a handful of cases and series available with regard to CTCL (Table 1).

Autologous HSCT for mycosis fungoides and Sèzary syndrome

Results with autologous HSCT (autoHSCT) did not particularly meet the expectations[9,10]. As a matter of fact, autoHSCT is rarely, if ever, used for MF or SS. Bigler *et al*[11] published the first paper on the advanced-stage MF and autoHSCT in 1991 and reported the outcome of six patients after autoHSCT. Later, in 2001, Olavarria *et al*[9] published the analysis of autoHSCT with harvested cells post-T-cell depletion of nine patients with advanced-stage MF. Their data showed that complete clinical remission had been achieved in all patients and the median duration to achieve complete remission was 7 mo. However, the authors have reported that some of the cutaneous diseases relapsed, albeit in a less aggressive form. In 2008, the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation analyzed data of twenty patients with advanced MF/SS who received an autoHSCT since 1986 retrospectively. They calculated that the median estimated time to disease progression was only 2.3 mo[11]. Unfortunately, high-dose chemotherapy with

autoHSCT showed only short-lived responses.

Allogeneic HSCT for mycosis fungoides and Sèzary syndrome

AlloHSCT may be considered for patients with advanced disease (≥ stage ⅡB) whose disease fails to respond to all primary therapy options or who do not experience durable responses with any primary or salvage therapies.

The first large multicenter analysis of alloHSCT for advanced-stage MF came from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation in 2010 that reported sixty patients with MF and SS. Data showed that, estimated overall survival (OR) in patients with advanced-stage MF/SS at 1 year and 3 years were 66% and 54%, respectively. In MF/SS patients, disease status, donor type and type of conditioning regimen have been identified as the main determinants of the outcome of alloHSCT, with the disease status having the highest impact across all outcomes. An earlier phase of the disease time course independently predicted both lower relapse/progression and higher progression free survival and overall survival. Neither the differences in outcomes between MF and SS patients or between TNM stages were significant. RIC protocols appeared to lower the risk of non-relapse mortality (NRM) below to that associated with myeloablative conditioning (MAC) without apparently increasing the risk of relapse/progression. RIC alloHSCT continued to offer a better OS than MAC alloHSCT. AlloHSCTs from matched HLA-identical related donors had a better outcome than alloHSCTs from matched unrelated donors. There are only 15 cases in a series on matched unrelated donor in MF/SS, which makes our experience very limited. It is possible that the outcome would be better as our experience builds up[12]. This original series were reanalyzed by the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation in 2014. New analyses revealed that OS at 5 and 7 years were 46% and 44%, respectively while PFS at 5 and 7 years were 32% and 30%, respectively, confirming that patients with advanced-stage MF or SS indeed benefited from alloHSCT. Data also showed that 27 patients (45%) had relapse or progression at a median of 3.8 mo after HSCT, indicating that disease relapse and progression comprised the main causes of post-transplant failure. It is worth noting that 8 of these 27 patients were alive at a median of 8 years after HSCT. This finding suggests that donor lymphocyte infusions (DLI) and/or other salvage therapies were very beneficial in rescuing some patients. At last follow-up visit, 27 patients were alive, and 26 of them were in CR. Seven year NRM was 22%, with the latest NRM occurring 14 mo after HSCT. Moreover, the risk of NRM is slightly higher if the patient has a poor performance score at HSCT (Karnofsky < 70) and the risk of relapse or progression is higher in patients who receive T-cell depletion. However, none of these alters survival significantly[13].

Duvic *et al*[14] reported the results of their prospective study on 19 patients with advanced stage MF who underwent total skin electron beam irradiation, followed by alloHSCT with conditioning with fludarabine and melphalan. The authors calculated the 2-year OS and PFS and reported them as 79% and 53%, respectively. The authors also reported that was the main cause of failure of treatment among their patients who had advanced phase disease was progressive disease.

Further, Schlaak *et al*[15] planned to compare in patients with advanced primary cutaneous T-cell lymphomas the efficacy and safety of conventional therapies with alloHSCT. Unfortunately, an updated literature search in January 2013 did not reveal any randomised controlled trials. Therefore, the authors of this study could not come up with a validated conclusion or propose recommendations for clinical practice.

A retrospective multicenter analyses has been carried out by de Masson *et al*[16] in 37 patients who had advanced stage CTCL and treated with alloHSCT. These patients included 20 cases (54%) with transformed MF. Best to our knowledge, this study is the largest multicenter retrospective analysis of alloHSCT for transformed MF. Therefore, the estimated 2-year OS rate of 57% in this study indicates that alloHSCT is suitable in advanced stage primary CTCL, including transformed MF. Nineteen (51%) patients experienced progression, which translates into 56% 2-year cumulative incidence of progression. The relapse rate was higher than other studies which could be explained by the fact that most of our patients had transformed MF, which is associated with a higher risk of relapse.

Lechowicz *et al*[17] conducted a study on the outcomes of alloHSCT in MF/SS, using the data gathered from 129 subjects who presented in 2014 to the Center for International Blood and Marrow Transplant Research. To our knowledge, this analysis is the largest descriptive study on patients who received alloHSCT for MF/SS. However, due to the fact that 39% of the patients had stage Ⅳ MF/SS, this cohort represents the minority of patients with MF/SS with very aggressive disease. The result of that study confirms that alloHSCT is useful, delivering acceptable NRM (19%-28%) in MF/SS patients and that patients benefit from the treatment.

CONCLUSION

Based on the publications with limited evidence, HSCT has the potential to increase response in advanced-stage MF and the results are especially consistent and promising for alloHSCT. However, autoHSCT is not devoid of any disadvantages, one of which is the possibility of an early relaps. This may be due reinfusing the malignant cells, which contaminate the graft. Hence, T-cell depletion to get the graft free from tumor cells before autoHSCT is a feasible and safe option[9]. Insufficient results achieved by autoHSCT means that alloHSCT should be listed as the treatment option for

advanced-stage MF. In contrast to autoHSCT, alloHSCT, which is obtained from a healthy donor, avoids the risk of tumor contamination of the graft and more importantly, has the potential to provide a ground for adoptive immunotherapy, leading to "graft-versus tumor-effect" (GVT)[18]. Based on previous reports, alloHSCT in advanced-stage MF appears to be superior to autoHSCT but relapse remains the major cause of mortality[9-11]. Even though relapse is not uncommon, the course of the disease varies and some relapse with more indolent disease than others. It is obviously easier to manage relaps with indolent disease by non-chemotherapeutic agents. Duarte *et al*[10] argued that DLI was beneficial in achieving complete remission after alloHSCT even if the patients had advanced-stage MF relapses and that this was an indication of the presence of GVT effect[10]. Even though high grade graft-versus-host disease (GvHD) following alloHSCT is one of the greatest challenges for a clinician, low grade GvHD is a desired situation as a positive relationship has been found between disease-free survival and low grade GvHD. Therefore especially low grade skin GvHD, which often involves the skin in MF might increase the effectiveness of alloHSCT in MF[19].

Limited number of studies in this area calls for caution while interpreting the results and implementing the findings in planning the treatment. To date, we have not been able to accumulate sufficient data from randomized controlled trials, which would otherwise clearly demonstrate the efficacy of alloHSCT in advanced-stage MF. We need more research, especially, prospective studies to enhance our knowledgebase in newer therapeutic modalities and establish a protocol on when to use alloHSCT.

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