Review Article

Peripheral T-cell Lymphomas: Updates in Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

Objective: Peripheral T-cell lymphomas (PTCLs) confer dismal prognosis and no consensus has been established on the role of allogeneic hematopoietic stem cell transplantation (allo-HSCT) due to its rarity and heterogeneity. The purpose was to review key points of allo-HSCT for PTCLs, including indication, times of transplantation, conditioning regimen, graft versus host disease prophylaxis, and treatment of relapse.

Data Sources: A comprehensive search in PubMed and Cochrane up to February 28, 2018, with the keywords "Peripheral", "T", "Lymphoma", and "Transplantation" was done.

Study Selection: Relevant articles including HSCT for PTCLs were carefully reviewed.

Results: Promising data have been reported from advances in transplant technology and more and more PTCLs patients with poor prognosis could benefit from allo-HSCT.

Conclusion: Allo-HSCT is a useful choice for patients with refractory/relapsed PTCLs or high-risk new diagnosed PTCLs.

Key words: Allogeneic; Hematopoietic Stem Cell Transplantation; Peripheral T-cell Lymphoma; Survival

Introduction

Incidence rate of peripheral T-cell lymphomas (PTCLs) is obviously higher in Southeast Asia than North America and Europe, and approximately 20–25% of non-Hodgkin's lymphomas (NHLs) belong to matured T-cell or natural killer (NK) cell lineage in China.[1,2] PTCLs are highly heterogeneous and generally present with aggressive clinical features. Anaplastic lymphoma kinase (ALK)-positive or negative anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AITL), PTCL not-otherwise-specified (PTCL-NOS), and extranodal NK/T-cell lymphoma (ENKL) occupied more than 90% of PTCLs. Except for ALK-positive ALCL, other PTCLs usually had a poor prognosis with 5-year overall survival (OS) rates of <40% because of resistance to conventional chemotherapy and autologous hematopoietic stem cell transplantation (auto-HSCT).[3] Recently, the Swedish Lymphoma Registry reported clinical outcomes in real-word according to 755 patients diagnosed as PTCLs between 2000 and 2009.[4] Although the addition of etoposide to first-line chemotherapy with CHOP regimen and auto-HSCT as up-front consolidation in patients with durable complete remission (CR) or partial remission (PR) improved response and survival, the 5-year OS and progression-free survival (PFS) were only 34.1% and 25.7%, respectively. The main cause of death for 452 patients was disease related ($n = 338$). Prognostic index of T-cell lymphoma (PIT) 2 and higher was considered as high risk and related with a worse prognosis. Fifty-two patients died of treatment-related cause and 62 patients died of treatment unrelated causes.

How to improve the clinical outcomes of PTCLs is an arduous task because of reportedly low PTCL survival rates. Allogeneic HSCT (allo-HSCT) has a curative potential for patients with PTCLs, which is partly mediated by graft versus lymphoma (GVL) effects. For individuals with

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refractory/relapsed PTCLs, allo-HSCT can achieve with higher response rate and more long-term disease-free survivals than auto-HSCT. Allo-HSCT was considered as a promising choice for patients with refractory/relapsed PTCLs.[5] Outcomes of PTCLs after allo-HSCT varied with histologic subtype, lymphoma remission status, chemosensitivity, and conditioning regimen at the time of transplantation. The two major obstacles of allo-HSCT were transplantation-related mortality (TRM) and relapse. As compared with auto-HSCT in patients with PTCLs, benefits of allo-HSCT were partially offset by transplantation-related toxicity, especially graft-versus-host disease (GVHD), organ function failure, and infection. Published data regarding allo-HSCT for PTCLs are limited. At the same time, excessive worry about morbidity and mortality associated with allo-HSCT had further limited its use in newly diagnosed patients with poor prognosis PTCLs at some degrees. As we know, with improvements in supportive care and modified transplantation procedure in the past two decades, the risk of transplantation-related complications associated with allo-HSCT had greatly decreased and expanded the eligibility of allo-HSCT candidates.

Difference of Clinical Outcomes between Autologous Hematopoietic Stem Cell Transplantation and Allogeneic Hematopoietic Stem Cell Transplantation

Auto-HSCT is a standard up-front consolidation for systemic PTCLs in the past. From 2001 to 2007, Nordic Lymphoma Group had completed a large prospective study to evaluate the efficacy of auto-HSCT as an up-front strategy in untreated systemic PTCLs who achieved sustained CR/PR after conventional chemotherapy.[6] A total of 160 patients with confirmed newly diagnosed systemic PTCLs enrolled from 24 centers and only ninety patients were finally treated with auto-HSCT because of 4 cases without evaluable response, 25 cases with primary refractory disease, and 41 cases with progressed disease or stem cell mobilization failure. After a median follow-up of 60.5 months, cumulative of OS and PFS at 5-year after auto-HSCT was 51% and 44%, respectively. From this large population prospective multicenter research which aimed at up-front auto-HSCT in PTCLs patients, we also can see that 43.75% (70/160) of patients did not undergo auto-HSCT in the end because of refractory/relapsed disease or other reasons and more than half patients eventually relapsed after auto-HSCT. Notably, another large multicentric retrospective study recently reported that newly diagnosed PTCLs patients with complete or partial response after induction did not get survival advantage from auto-HSCT as up-front consolidation.[7] For those newly diagnosed PTCLs with durable CR or PR after induction chemotherapy, 5-year PFS and OS among patients using auto-HSCT as first-line consolidation were 46.3% (95% confidence interval [*CI*]: 34.1–57.6%) and 59.2% (95% *CI*: 46.1–70.1%), respectively. However, PTCL patients who failed to achieve durable CR/PR or with a high score of international prognosis index (IPI) or PIT exhibited a dismal prognosis after auto-HSCT.[8] Although many centers still recommended auto-HSCT for PTCL patients with refractory/relapsed disease, clinical outcomes are very poor because majority of cases will die of lymphoma in the end. For refractory or relapsed PTCL patients with auto-HSCT as salvage measures, 2-year PFS and OS were only 21% and 42%, respectively.[9]

In the early years, allo-HSCT in PTCLs was often recommended as a rescue option for patients who have failed after auto-HSCT. Compared to auto-HSCT, benefits of allo-HSCT include avoiding lymphoma cell contamination of the graft, potential GVL effects, and the possibility of donor lymphocyte infusion (DLI) in the event of recurrent disease. The direct and definitive evidence of GVL effects had been proven from the association between DLI and response in relapsed PTCLs patients after allo-HSCT.[10] Mamez *et al*. further confirmed GVL effects in a PTCL patient with indirect evidence.[11] After cyclosporine was withdrawn because of disease progression after +100 days of allo-HSCT, the lesion of lymphoma disappeared in +180 days of allo-HSCT, and this patient achieved persistent CR following withdraw of immune suppression for 33-month posttransplantation.[11]

Of interest, several studies reported that patients with PTCLs had superior survival than patients with diffuse large B-cell lymphoma and lymphomas originating from T-cells may be a good model for GVL effects. Different studies reported various clinical outcomes of patients with mixed subtype PTCLs or only unique subtype experienced allo-HSCT for primary refractory/relapsed disease. Dodero *et al.* reported an encouraging long-term outcome of 52 patients treated with allo-HSCT for relapsed PTCLs (27/52 patients with relapsed disease after auto-HSCT).[10] At 67 months of median follow-up, cumulative OS and PFS at 5-year was 50% and 40%, respectively. Twenty patients with refractory or early relapsed ALCL received allo-HSCT and PFS at 3 years after allo-HSCT was 75% ± 10%.[12] Forty-five patients registered in the European Group for Blood and Marrow Transplantation with AITL were treated with allo-HSCT, and the clinical outcome is encouraging. The cumulative rate of 3-year OS and PFS rates was 64% and 53%, respectively.[13] Some studies about allo-HSCT for PTCLs showed a nonsignificant trend with better outcome in the population with AILT.[10] Twelve patients with advanced and refractory ENKL lymphoma, nasal type (ENKL) had undergone allo-HSCT, and seven cases were alive in sustained remission with a median follow-up of 13 months.[14] Only one case died of TRM during follow-up.[14] It is interesting to further clarify which subtype of PTCLs could be more susceptible to donor-derived immune cells.

Besides as a useful choice for refractory/relapsed PTCLs patients, some centers already explored the allo-HSCT as a

frontline treatment for more and more patients with high-risk PTCLs and the results were promising.[15,16] Loirat *et al*. reported that 29 of 49 newly diagnosed PTCL patients proceeded up-front allo-HSCT.[17] The 2-year PFS rate for transplanted patients was 65.5% and the 2-year PFS rate of patients who did not experience allo-HSCT was <30%. TRM at 1 year after allo-HSCT was only 8.2%.

To date, there are few prospective randomized studies to direct compare allo-HSCT and auto-HSCT in patients with PTCLs. While auto-HSCT is a well-established treatment for PTCLs, lymphoma progression or relapse after auto-HSCT is common and managing patients after recurrence is very difficult. Allo-HSCT not only has the potential advantage of a tumor-free graft but also has immune-mediated GVL effects. It is generally assumed that allo-HSCT is both more effective and more toxic than auto-HSCT. Actually, there is a significantly lower incidence of relapse after allo-HSCT. However, this benefit is also partially offset by an increased rate of TRM. Smith *et al*. retrospectively compared the clinical outcomes between auto-HSCT and allo-HSCT in PTCLs.[18] This study, enrolled 126 allo-HSCT and 115 auto-HSCT patients form north of America, was a large population-based report for PTCL patients undergoing HCT. Three-year PFS of allo-HSCT and auto-HSCT was 36% and 47%, respectively ($P > 0.05$). Although there had no difference in survival between allo-HSCT and auto-HSCT, patients' status in allo-HSCT at transplantation was markedly inferior to that in auto-HSCT. Compared with allo-HSCT patients, auto-HSCT patients were more likely in first CR ($P = 0.001$), and with chemosensitive disease ($P < 0.001$), and fewer lines of pretreatment ($P < 0.001$). Similarly, Kim *et al.* compared the results between auto-HSCT and allo-HSCT in patients with PTCLs.[19] Clinical data of 231 PTCL patients from 52 Japanese and 8 Korean centers were analyzed in this research. In this study, 135 patients were treated with auto-HSCT and 96 patients were treated with allo-HSCT. Five-year OS for patients in CR1/PR1 after auto-HSCT and allo-HSCT was 62% and 69%, respectively. Five-year OS rates of primary refractory disease in the auto-SCT group and allo-SCT group were 45% and 10%, respectively.[19] Because most patients in auto-HSCT group had more sensitive diseases and deeper response than allo-HSCT group. It is clear that patients with refractory/relapsed PTCLs are not easy to be cured with auto-HSCT, conventional chemotherapy, and new drug. Therefore, allo-HSCT is superior to auto-HSCT in some degrees. Those studies indicated that allo-HSCT can improve the prognosis of patients with advanced PTCLs. However, it must be remembered that there are no available randomized data to directly compare the clinical outcomes of auto-HSCT and allo-HSCT, and most of those studies were retrospective analyses of small sample and heterogeneous baseline characteristics of patients. When we think about the allo-HSCT can provide tumor-free grafts and the opportunity for GVL immune responses, we also should see that allo-HSCT accompanied with the increased risk of TRM primarily due to GVHD, infections, and organ failure.

Indication and Timing of Allogeneic Hematopoietic Stem Cell Transplantation

There has been a dispute on the indication and timing of allo-HSCT in PTCL patients for decades. Who and when will benefit from allo-HSCT are key issues in daily clinical practice. National Comprehensive Cancer Network (NCCN) guidelines recommend that if patients with primary refractory or relapsed PTCL-NOS, ALK-negative ALCL, AITL, or enteropathy-associated T-cell lymphoma had intention to transplantation, allo-HSCT should be considered. For Stage I–II nasal ENKL or Stage IV nasal ENKL or any stage extranasal ENKL patients with radiochemotherapy-resistant disease, allo-HSCT should be considered if the patients want to transplantation.

Allo-HSCT may be preferable for PTCL patients who had failed to achieve a CR after first-line chemotherapy, high-risk relapsed disease to second-line chemotherapy, multiple relapsed disease, relapsed/progression disease after auto-HSCT, persistent bone marrow involvement, or inadequate hematopoietic stem cells harvest for auto-HSCT. Prognosis of patients with advanced-stage ENKL or localized ENKL at diagnosis but refractory to prior radiochemotherapy is extremely poor, and the median survival is only several months.[20,21] As we know, higher IPI or PIT score for PTCLs was associated with poor survival rates. For newly diagnosed PTCL patients who had advanced disease with high risk of relapse (PIT score 2 or higher), long-term survival rates of auto-HSCT are very low, and allo-HSCT should be individualized.

Disease status at transplantation is a key factor for disease progression and survival after allo-HSCT. Jacobsen *et al.* from the Dana Farber group reported that allo-HSCT is more successful for patients with nodal T-cell lymphoma other than those with extranodal disease.[22] Patients, with large tumor burden and heavily pretreated refractory lymphoma, usually had inadequately controlled lymphoma and high transplant-related mortality after allo-HSCT. Patients with active disease before allo-HSCT had an increased rate of recurrence compared with patients in remission.[23] Chemosensitivity at the time of transplantation is also one of the most important factors which is associated with disease progression and survival after allo-HSCT. Both chemoresistance at transplantation or prior local radiotherapy was related to a significantly worse survival and this may be associated with the fact that patients with a history of radiotherapy often had refractory and more advanced disease at transplantation.[24] GVL effects generally require weeks to months to develop after allo-HSCT and often correlate with reconstitution of immunity. In patients with progressive/refractory PTCLs, there is little time to exploit potentially beneficial GVL effects.

As auto-HSCT is an effective strategy for PTCL patients in CR at transplantation, and allo-HSCT is a powerful approach for relapsed lymphoma after auto-HSCT.[23] Many medical centers and physicians often reserve allo-HSCT

as a salvaged measure for relapsed PTCL patients after auto-HSCT. In fact, only a minority of patients relapsing after auto-HSCT can actually undergo allo-HSCT. Even if patients with relapsed PTCLs after auto-HSCT have the chance to experience allo-HSCT, the clinical outcomes are still very poor. The data of 263 patients with allo-HSCT from the center for international blood and marrow transplant research (CIBMTR) confirmed that prior auto-HSCT was the most significant risk factor for TRM after allo-HSCT, and 3-year TRM was also as high as 44% even with reduced-intensity conditioning (RIC) regimen.[25]

Different studies showed that performance status was also related to TRM and patients with lower Karnofsky performance scores (KPS) (<80%) before allo-HSCT had 2-fold increased TRM than patients with normal KPS (100%).[23] The history of heavy pretreatment before transplantation is a risk for TRM because most patients would have lower KPS accompanied with more chemotherapies.

Most PTCL patients who had refractory or relapsed lymphoma usually lost the chance of allo-HSCT because of the failure of salvage therapies for relapse, early death after relapse, ineligible performance status for allotransplant, or physician/patient choices. For patients with relapsed/refractory PTCL, the median time between initial diagnosis and relapse/progression was only 6.7 months.[4] The survival of patients with refractory/relapsed disease was very dismal. Median OS for patients (n = 143) with primary refractory PTCLs was only 2.5 months.[4] Median OS and PFS after first relapse/progression was only 5.5 months and 3.1 months, respectively.[26] For a patient who fit to allo-HSCT, transplantation should be carried out in time because majority of high-risk PTCLs often relapsed rapidly. Once lymphoma recurs, performance status will become worse after heavy treatment and the disease status tends to be difficult to achieve complete control even the patient still has a chance for allo-HSCT.

Conditionning Regimens for Allogeneic Hematopoietic Stem Cell Transplantation

Conditioning regimen is a very important factor for disease progression and survival after allo-HSCT. Conditioning regimen has at least three main roles, including helping engraftment of donor cells, killing tumor cells, and controlling disease to allow time for GVL activity. Keeping balance between conditioning intensity and TRM is the key point for PTCL during allo-HSCT. Ideal regimen is associated with an excellent antilymphoma effect and low transplant-related mortality. Different conditioning regimens have been used in allo-HSCT for patients with PTCLs. Conditioning regimens were divided into routine myeloablative conditioning (MAC) and RIC regimens by established consensus criteria.[27]

The antilymphoma effects of a conditioning regimen mainly depend on the constitution and the intensity. It is postulated that MAC is more effective in eradicating lymphoma than RIC. However, compared with RIC, the increased intensity of MAC did not significantly impact OS and PFS after allo-HSCT.[13,18,19] So far, it means we cannot further promote the effect of eradicating lymphoma by endless increasing intensity of conditioning regimen when the intensity of conditioning has increased to a certain degree, and this is why the relapse rate is high after auto-HSCT even under MAC. For patients with prior heavily chemotherapy or older age, the excessively increased dose of regimen is one of the most significant risk factors for transplant-related mortality. RIC allows older and sicker patients to undergo allo-HSCT owing to decrease of regimen-related toxicity. The tolerability of RIC makes it an attractive preparative regimen for allo-HSCT, but the reduced dose or omission of cyclophosphamide, busulfan, and total body irradiation (TBI) raised concerns regarding the immunosuppressive and tumor-ablative potency. Notably, a single-center study of 52 patients with T-cell lymphoma showed that RIC regimens had a seven-fold increased risk of relapse compared with MAC regimens.[22] In general, antilymphoma activity of RIC regimens is weaker than MAC regimens, and RIC is associated with a higher risk of relapse and lower TRM.

The combination of carmustine, etoposide, cytarabine, and melphalan (BEAM) is the most established preparative regimen for lymphoma in the setting of auto-HSCT. Although BEAM is an effective and little toxicity for auto-HSCT, it's tolerance and feasibility as a RIC for allo-HSCT has not been established. Except for lymphoma cell clearance, preclinical studies suggested that melphalan has immunosuppressive activity. Recently, fludarabine melphalan is more commonly utilized as a RIC in allo-HSCT for lymphoma. Corradini *et al.* reported 17 patients with PTCLs using a fludarabine, cyclophosphamide, and thiotepa as RIC regimen.[28] Estimated 3-year cumulative PFS and OS rates were 64% and 81%, respectively, and the 2-year cumulative non-relapse mortality rate was only 6%.[28] Although this result is specially encouraging, the limited patients and heterogeneity of lymphomas make it very difficult to evaluate the role of the intensity in conditioning regimen. CBV is another common preparative regimen for auto-HSCT and was reported as a safe and an effective RIC for allo-HSCT in patients with NHL.[29] Many studies reported that the TRM in the setting of RIC was range from 20% to 44%.[25]

TRM of allo-HSCT is more associated with GVHD and infection than with toxicities from conditioning regimen. With improvements in supportive care, TRM with MAC has fallen from >10% to <5% and widely carried out in Europe for advanced lymphoma. MAC regimens were increasingly used in patients with PTCLs recently. TBI has been used as the backbone of conditioning regimen for allogeneic transplantation because of its strong anti-lymphoma activity and long immunosuppressive effects. The combination of TBI and high-dose cyclophosphamide is the most common conditioning regimen for NHL in the allo-HSCT setting. Kiss *et al.* reported their single institution outcomes of allo-HSCT

patients with NHL receiving the combination of busulfan and cyclophosphamide (Bu/cy) as the preparative regimen.[30] Regimen of Bu/cy not only showed an acceptable toxicity but also achieved favorable outcomes particularly in younger patients. Freytes *et al.* analyzed 114 NHL patients underwent allo-HSCT from 1990 to 1999 according to the IBMTR and the Autologous Blood and Marrow Transplant Registry.[23] Compared with patients with NHL who underwent TBI conditioning allo-HSCT, patients who received non-TBI had a 3-fold increased rate of disease progression.[23] At the same time, patients with non-TBI conditioning had a 2.5-fold increased rate of transplantation failure compared with TBI conditioning group. This was similar to the results from CIBMTR that the use of TBI as a part of conditioning significantly improved PFS.[25] TBI containing regimen was eligible for high-risk PTCLs because of efficacy and acceptable toxicity. Twenty patients with high-risk ALCL relapses or refractory were treated by allo-HSCT with TBI-based regimen and the probability of 3-year even-free survival after allo-HSCT was 75% ± 10%.[12] There need more clinical data to confirm this superiority of TBI in patients with PTCL. Although TBI-based regimen is frequently chosen because lymphoma cells are sensitive to irradiation. We still should keep in mind about long-term complications of TBI including mucositis, cataracts, myelodysplasia, acute leukemia, endocrine insufficiencies, and child development disorders. Patients with mediastinal radiation before allo-HSCT are not been eligible for TBI because TBI may cause interstitial pneumonitis.

When we chose a conditioning regimen, we should consider the treatment-related toxicity as same as antilymphoma activity. Choose MAC or RIC for PTCL patients who fit for allo-HSCT should depend on the balance between risk of relapse and TRM evaluation. The recognition about allo-HSCT in PTCLs was based on that patients can benefit from immunologic GVL effects rather than unlimitedly dose-intensified chemotherapy. Kanakry *et al*. from Johns Hopkins Hospital reported the outcomes of 44 consecutive allo-HSCT for PTCL including 18 RIC haploidentical (haplo) allo-HSCT. The cumulative incidence of relapse at 1-year was 38% and 34% for MAC HLA-identical and RIC haplo allo-HSCT, respectively.[31] In general, MAC is the dominant way to allo-HSCT in young and fit patients. RIC is more suitable for patients with medical comorbidities or older patients including heavily pretreated patients.

Prophlaxis of Graft versus Host Disease

The GVHD prophylaxis consists of based cyclosporine/tacrolimus and short-time methotrexate. This combination was usually administered to all of the allo-HSCT recipients. Mycophenolate mofetil (MMF) had been added to more and more constitution of GVHD prophylaxis. Anti-thymocyte globulin (ATG) was one of the important drugs as intensified GVHD prophylaxis for alternative donor HSCT including unrelated donor or haploidentical-related donor. Trough target level of cyclosporine was 150–400 ng/ml and was quantified usually once a week. MMF levels were not measured and often used 15 mg/kg twice a day. The exact dosage of ATG administered is not clear, and the usual dose in clinical practice is 2.5 $mg \cdot kg^{-1} \cdot d^{-1}$ rabbit ATG on days from −5 to −1. If there is absent of GVHD after allo-HSCT, cyclosporine was often tapered about 6 months for matched sibling donor HSCT and 9 months for alternative donor HSCT.

Sirolimus (rapamycin), an antineoplastic agent with immunosuppression, has reduced the incidence of acute but not of chronic GVHD. van Besien had analyzed 190 lymphoma patients who underwent allo-HSCT from Dana-Farber/Harvard Cancer Center retrospectively.[29] They found that the adding sirolimus to GVHD prophylaxis significantly improved OS after transplantation. For all patients who received sirolimus for GVHD prophylaxis on the base of calcineurin inhibitor, sirolimus was administered orally 12 mg on day 3, followed by 4 mg daily (trough concentrations between 3 and 12 ng/ml). There had no significant impact on the cumulative incidence of acute GVHD after the adding of sirolimus in the GVHD prophylaxis regimen, and patients who received sirolimus or not had a similar incidence of TRM. However, patients who received sirolimus had a significantly lower incidence of disease relapse/progression than those who did not receive sirolimus in RIC allo-HSCT. Three-year cumulative incidence of relapse/progression was 42% in the sirolimus group compared with 74% in the no sirolimus group ($P < 0.001$). Three-year OS rate in the sirolimus group and the no-sirolimus group was 63% and 41%, respectively ($P = 0.007$). These encouraging outcomes were partly associated with the activity of mammalian target of rapamycin inhibitors for lymphoma.

On one hand, some studies showed that patients with chronic GVHD had a lower incidence of disease relapse/progression after allo-HSCT. Compared to other NHL histologies, especially aggressive B-NHL, PTCL can achieve markedly protective effect from chronic GVHD on PFS.[32] On the other hand, chronic GVHD is the most severe long-term complication and a major risk factor for late death after allo-HSCT. Severe GVHD had a deleterious effect on OS. The cumulative incidence of chronic GVHD is between 30% and 60% in most series, and chronic GVHD incidence is dependent on different risks such as age, donor, and stem source. In Japan, there has a tendency to select tacrolimus rather than cyclosporine for GVHD prophylaxis, and the cumulative incidence of chronic GVHD was higher in NHL patients with tacrolimus plus methotrexate than in those with cyclosporine plus methotrexate for GVHD prophylaxis.[24] Many research reported that chronic GVHD significantly reduced by GVHD prophylaxis accompanied with ATG.[33] However, some studies showed *in vivo* T-cell depletion with ATG increased lymphoma recurrence rate and early opportunistic virus infection.

GVHD is the major complication of allo-HSCT. Although GVHD is beneficial to prevent relapse, both severe acute and

chronic GVHD can result in substantial morbidity. Chronic GVHD can last for several months to several years, and extensive chronic GVHD is the major risk of life quality in long-term survivors after allo-HSCT. How to keep balance between effective GVHD prophylaxis and maintaining GVL effect in allo-HSCT setting is important.

Treatment Principle for Relapse after Allogeneic Hematopoietic Stem Cell Transplantation

Although compared with auto-HSCT patients, relapse or progression rates are lower in patients after allo-HSCT. Relapse of PTCL is still the primary cause of treatment failure after allo-HSCT. PTCLs recurrence of 20–60% is reported in different groups, depending on histologic subtypes, prior therapies, chemosensitivity, and disease status. How to manage those patients with relapsed or progressed PTCLs after allo-HSCT is a key problem for clinical practice.

There have no standard guidelines for the salvage therapy of post-allograft relapse. Salvage approaches to deal with relapse/progression for PTCL after allo-HSCT are limited including immunosuppression withdrawal, DLI, chemotherapy, radiation, immunotherapy (such as interleukin-2, interferon-α, and programmed cell death protein-L1 antibody), second allo-HSCT, and some clinical trials. Usually, reduction of immunosuppressive agents was the first step and then utilizes DLI and/or systemic chemotherapy. Although second allogeneic HSCT is an alternative choice, TRM is very high and long-term survival is very poor.

The data from University of Minnesota showed that withdrawal of immunosuppression alone induced CR in 4 of the 13 PTCL patients who relapsed after allo-HSCT.[34] Although there had no reliable data about biological characteristics of the disease on relapse after allogeneic stem cell transplant such as T-cell or NK-cell origin. Patients with T/NK cell lymphoma had more tendency to achieve CR with reduction of immunosuppression alone than other lymphoma histological subtypes such as indolent B-cell lymphoma and highly aggressive lymphoma Burkitt's lymphoma. Horstmann *et al.* reported that 17 patients with T-cell lymphoma underwent the second allo-HSCT and 5-year cumulative PFS after second allo-HSCT was 27%.[35] Chemosensitivity at the second allo-HSCT and interval between the two allo-HSCT (longer than 12 months or not) are significant risk factors for OS and PFS. This study provides first document for T-cell lymphoma that a second allo-HSCT can achieve long-term survival in a substantial fraction of patients with relapsed disease after first allo-HSCT.

Conclusion and Future

For patients with relapsed/refractory or high-risk PTCLs, allo-HSCT has been documented to lead to long-term remissions. However, there still has no confirmed benefit of allo-HSCT over autologous approach because the decreased risk of relapse compared to auto-HSCT was partially offset by higher TRM after allo-HSCT. Further multicenter prospective studies are required to demonstrate the timing of allo-HSCT, the choice of conditioning regimen, the intensity of posttransplantation immunosuppression, treatment of complication, and procedure for relapse.

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Conflicts of interest

There are no conflicts of interest.

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异体造血干细胞移植治疗外周T细胞淋巴瘤的进展

摘要

目的：外周T细胞淋巴瘤 (PTCLs) 预后极差，且由于PTCLs发病率相对较低和异质性较强，目前尚无有关自体或异体造血干细胞移植治疗PTCLs的共识。本文旨在对异体造血干细胞治疗PTCLs的适应症、移植时机、预处理方案、移植物抗宿主病的预防和移植后复发处理等几个关键方面进行综述。

资料来源：对PubMed和Cochrane数据库中2018年2月28日以前的文章应用关键词“外周”、“T”、“淋巴瘤”和“移植”进行综合检索。

研究选择：对检索到的包含造血干细胞移植治疗外周T细胞淋巴瘤的相关文献进行详细回顾和综述。

结果：随着造血干细胞移植技术的进步，异体造血干细胞移植在PTCLs治疗中取得了令人振奋结果，越来越多预后不良的PTCLs患者可能受益于异体造血干细胞移植。

结论：异体造血干细胞移植是初治高危和复发/难治PTCLs的有效治疗措施。