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REVIEW ARTICLE

Haematopoietic Stem Cell Transplantation for Lymphoma

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ABSTRACT

Recent advances in chemotherapy and chemoimmunotherapy have improved the outcomes of many lymphoma patients. However, patients with relapsed or refractory disease continue to have poor outcomes. Studies show that intensive chemotherapy followed by autologous haematopoietic stem cell transplantation improves survival and is the standard of care for relapsed Hodgkin's lymphoma, diffuse large B-cell lymphoma, and follicular lymphoma. Upfront autologous haematopoietic stem cell transplantation in first remission is considered the standard of care for mantle cell lymphoma, an aggressive disease with poor outcomes. Allogeneic haematopoietic stem cell transplantation, with a reduced intensity conditioning regimen if necessary, may be considered for the management of patients with refractory disease who relapse after autologous haematopoietic stem cell transplantation. Given the increased risk of mortality and morbidity associated with haematopoietic stem cell transplantation, it is important to perform the procedure at the appropriate time and select patients who are most likely to benefit from the procedure based on factors such as age, disease status, chemosensitivity, disease grade, histological subtype, and disease stage at diagnosis.

Key Words: *Hematopoietic stem cell transplantation; Lymphoma, non-Hodgkin; Transplantation, autologous*

中文摘要

淋巴瘤的血幹細胞移植

李國維

化療及免疫化學療法新近的發展可以改善很多淋巴瘤患者的治療結果。可是復發或頑固性腫瘤患者仍然有較差的治療結果。研究結果顯示高劑量化療及隨後的自體血幹細胞移植可改善病人存活率，亦順理成章成為復發性霍奇金淋巴瘤、瀰漫大B細胞淋巴瘤、及濾泡性淋巴瘤的標準療法。套細胞淋巴瘤屬於較難治療的淋巴瘤，結果往往較差，於首次緩解時進行前期自體血幹細胞移植被視為標準療法。對於已接受自體血幹細胞移植但仍出現復發性病情的頑固性腫瘤患者來說，可考慮異體血幹細胞移植（必要時可用減低劑量療方）。由於血幹細胞移植可能會增加患病及死亡風險，醫生必須要為病人選擇合適的治療時間，並考慮病人的年齡、疾病狀態、藥敏、疾病等級、病理組織分類及疾病診斷時的分期，以確保病人得到最大的治療效益。

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INTRODUCTION

In the past few decades, there has been substantial progress in the treatment of Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) with effective combinations of chemotherapeutic and immunological agents.[1,2] However, managing patients who relapse after or are refractory to first-line treatment, and have advanced disease with poor prognostic factors continues to be a challenge. Studies have shown that this group of patients, if sensitive to chemotherapy and radiotherapy, demonstrate improved survival when treated with intensive chemotherapy followed by autologous haematopoietic stem cell transplantation (auto-HSCT).[3-5] Regrettably, relapse or disease progression is common after auto-HSCT, and the prognosis remains poor.[6-8] Selected lymphoma patients from this category may benefit from allogeneic HSCT (allo-HSCT).[9]

FACTORS AFFECTING THE OUTCOME OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION

HSCT refers to a procedure in which haematopoietic stem cells of any donor type and any source (bone marrow, peripheral blood, or cord blood) are given to a recipient to partially or completely repopulate and replace the haematopoietic system.[10] Both auto- and allo-HSCT are associated with an increased risk of mortality and morbidity due to the procedure. For example, auto-HSCT may lead to organ toxicity due to high-dose chemotherapy (HDT) and radiation prior to the procedure, and is associated with an increased risk of infection due to prolonged pancytopenia.[11] Allo-HSCT may cause opportunistic infections and severe graft-versus-host disease (GVHD) involving the skin, liver, and / or gut even when the patient and donor are human leukocyte antigen (HLA)–identical siblings.[1] Thus, it is important to select patients who are most likely to benefit from HSCT based on factors such as age, timing of transplant, histological subtype, disease stage at diagnosis, chemosensitivity, presence of comorbidities, disease grade, and disease status.

For example, in one study among HL patients, male sex, minimal disease, and history of complete remission (CR) just before relapse that led to HSCT were identified as favourable factors for event-free survival (EFS).[11]

Age is one of the most important determinants of the outcomes of both auto- and allo-HSCT, results being significantly better in younger patients and children than adults.[10] However, patients older than 50 years who are physically fit with minimal comorbidities may also benefit from the procedure without incurring a high risk of toxicity.[11]

Appropriate timing of HSCT is also an important factor that determines the outcome of the procedure. For instance, performing allo-HSCT in early first relapse or second remission of NHL is associated with considerably better results than performing the procedure later in the disease course.[1]

The presence of bulky disease pretransplant is an independent predictor of poor prognosis for both HL and NHL patients. Thus, it is advisable to treat prospective HSCT patients until they are as close to being in remission as possible. Post-transplant radiotherapy may be employed to further improve the prognosis.[11]

Chemosensitivity of the disease is essential for auto-HSCT. It has been shown that chemotherapy responsiveness is associated with decreased rate of disease progression and increased rates of progression-free survival (PFS) and overall survival (OS).[9]

ROLE OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN COMMON LYMPHOMAS

Given the large number of lymphoma subtypes, the following discussion is limited to a few common subtypes, namely HL, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL), in which the role of HSCT is better defined.

Hodgkin's Lymphoma

HL is a highly curable disease with most patients presenting with localised disease and responding favourably to chemotherapy and radiotherapy.[12,13] However, patients with relapsed or refractory disease have poor outcomes and second-line chemotherapy followed by auto-HSCT is the standard of care for these patients, based on evidence from numerous randomised controlled trials.[13]

In one study, patients with relapsed HL were randomised to HDT with dexamethasone and carmustine, etoposide, cytarabine, and melphalan (Dexa-BEAM) and either two further courses of Dexa-BEAM or high-dose BEAM and auto-HSCT. After a median follow-up of 39 months, freedom from treatment failure was significantly better for patients

given BEAM-HSCT (55%) than those given Dexa-BEAM (34%; 95% confidence interval [CI], -39.87 to -2.13; p = 0.019), although OS did not differ in the two treatment groups.[14]

Refractory HL includes patients with disease progression during frontline therapy or within 90 days of completing frontline therapy, and patients failing to achieve a partial response (PR) to initial therapy. A study showed that the outcomes of patients with chemosensitive refractory HL improved significantly with HDT followed by auto-HSCT. At a median follow-up of 10 years after conventional-dose cytoreductive chemotherapy followed by HDT and auto-HSCT, the EFS, PFS, and OS rates were 45%, 49%, and 48%, respectively. Notably, chemosensitivity to standard-dose second-line chemotherapy (SDSC) predicted a better survival, with responding patients having an EFS, PFS, and OS of 60%, 62%, and 66%, respectively, versus 19%, 23%, and 17%, respectively, in poor responders to SDSC (p<0.001).[15]

Patients who relapse after auto-HSCT or are truly refractory to first-line therapy are considered for experimental approaches such as allo-HSCT, which is associated with clinically beneficial immune-mediated graft-versus-tumour effect and lower relapse rates than auto-HSCT. However, conventional or myeloablative allo-HSCT is also associated with extremely high rates of nonrelapse mortality (NRM).[16] Thus, there is a trend towards using reduced-intensity conditioning (RIC) allo-HSCT, particularly in patients considered poor candidates for myeloablative allo-HSCT (such as older patients). In one study among patients with refractory or relapsed HL who underwent allo-HSCT after either a myeloablative or an RIC protocol, NRM was significantly decreased in the RIC group (hazard ratio [HR] = 2.9; 95% CI, 1.6-5.0; p<0.001). In addition, the RIC group demonstrated better OS (HR = 2.1; 95% CI, 1.3-33; p=0.04) and a trend for better PFS (HR = 1.5; 95% CI, 1.0-2.4; p=0.07) versus the myeloablative group. Improved PFS was an attribute of chronic GVHD associated with a significantly decreased frequency of relapse.[16]

Diffuse Large B-cell Lymphoma

Patients with intermediate- or high-grade NHL who relapse after initial therapy have a poor prognosis. The landmark Parma trial showed that treatment of patients with chemosensitive relapsed DLBCL with HDT and auto-HSCT was associated with higher EFS and OS than conventional chemotherapy, and established the procedure as the standard of care for this group of patients.[3] At a median follow-up of 63 months, response rates, EFS, and OS were 84%, 46%, and 53% after bone marrow transplantation versus 44%, 12%, and 32% after chemotherapy without transplantation, respectively (p = 0.001 for EFS; p = 0.038 for OS).[3]

Approximately 30 to 50% of patients with diffuse aggressive DLBCL do not achieve CR with initial chemotherapy (i.e. are refractory) and need salvage therapy. Data show that these patients may benefit from HDT plus auto-HSCT, provided the disease is chemosensitive and patients have factors favouring HSCT. In one study, 44% of DLBCL patients (n = 184) achieved CR or CR with residual imaging abnormalities of unknown significance after auto-HSCT. The probabilities of PFS and OS at 5 years after transplantation were 31% (95% CI, 24-38%) and 37% (95% CI, 30-45%), respectively. Multivariate analysis showed that patients — who remained chemotherapy-sensitive, had good performance status, were younger than 55 years, had received only one or two prior chemotherapy regimens, and had received either pre- or post-transplant irradiation — were most likely to benefit from the treatment.[4]

It has been demonstrated that more than 50% of DLBCL patients identified as 'high-risk' by the age-adjusted International Prognostic Index (IPI) fail to achieve CR with standard induction therapy and have a poor prognosis.[17] Data from 13 randomised trials that compared upfront HDT and auto-HSCT versus additional doses of conventional chemotherapy in patients with aggressive DLBCL found that auto-HSCT was associated with improved disease-free survival and OS rates in only four studies; there was no difference in outcomes in the other nine studies. However, these studies were conducted in the pre-rituximab era and the results may not be applicable to current practice.[18] A recent study in advanced-stage high-intermediate and high IPI diffuse aggressive DLBCL patients showed that early auto-HSCT improved PFS for responders, including those induced with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with or without rituximab (CHOP±R). The two-year PFS rates in patients receiving CHOP±R followed by auto-HSCT and only CHOP±R were 69% and 56%, respectively (HR = 1.7; 95% CI, 1.2-2.5; p=0.005); two-year OS rates were not significantly different between the two treatment groups (74% and 71% respectively;

HR = 1.2; 95% CI, 0.8-1.9; p=0.32).[19] These data strongly favour the use of HDT with auto-HSCT as a component of first-line therapy to improve the outcomes of DLBCL patients with intermediate- and high-risk disease in the rituximab era.[18]

Auto-HSCT is less effective in DLBCL patients with chemoresistant relapse, probably due to the lack of graft-versus-lymphoma (GVL) effect and reinfusion of malignant cells from the peripheral blood used for transplantation. Allo-HSCT, employing bone marrow as the stem cell source and having the advantage of a GVL effect, is considered a potential therapeutic option for DLBCL patients who relapse after auto-HSCT. However, there is concern that acute or chronic GVHD and opportunistic infections leading to high treatment-related mortality (TRM) rates may offset the benefits associated with this procedure.[5]

Follicular Lymphoma

Although FL has an indolent disease course, relapse is common in patients with extensive disease who are difficult to cure and have a median survival of only 4.5 years after disease recurrence.[20] Data show that HDT followed by auto-HSCT is effective and can result in longstanding remissions, particularly when performed early in the disease.[21-23] The randomised European CUP trial also showed that HDT followed by auto-HSCT translated into improved PFS (HR = 0.3; 95% CI, 0.2-0.6) and OS (HR = 0.4; 95% CI, 0.2-0.9) compared with additional chemotherapy in patients with relapsed follicular NHL.[20]

According to the 2009 European Society for Medical Oncology (ESMO) clinical recommendations, relapsed FL can also be managed with rituximab maintenance therapy (due to its favourable safety profile, efficacy to prolong PFS and strong tendency towards improved OS), and radioimmunotherapy for consolidation after induction therapy.[24]

Although incorporation of rituximab in the strategy of auto-HSCT improves the duration of remission in relapsed FL, this is not curative and it does not alter the risk of death related to secondary myelodysplasia and other malignancies. It is believed that non-myeloablative allo-HSCT may be the only potentially curative treatment for relapsed FL.[25] A phase II study by the Cancer and Leukemia Group B showed that allo-HSCT following RIC conditioning was safe and effective in chemosensitive patients with recurrent low-grade B-cell malignancies. The six-month and three-month TRM rates were 2.4% and 9.0%, respectively, and three-year EFS and OS rates were 75% and 81%, respectively.[26] In another study, allo-HSCT for relapsed chemosensitive FL after non-myeloablative conditioning with fludarabine, cyclophosphamide and rituximab was associated with a six-year PFS and OS of 83% and 85%, respectively.[25]

Mantle Cell Lymphoma

MCL is characterised by a rapidly progressive course and poor clinical outcome. It is also considered incurable with conventional chemotherapy. A recent therapeutic approach for improving the prognosis of MCL involves intensive consolidation with HDT followed by auto-HSCT. In a randomised trial by the European MCL Network, patients with advanced MCL after achieving PR or CR by CHOP-like induction therapy were assigned to consolidation with myeloablative radiochemotherapy followed by auto-HSCT or α-interferon maintenance (IFNα) therapy. Patients in the HSCT arm showed a significantly longer PFS of 39 months versus 17 months in the IFNα arm (p=0.0108). The three-year OS was 83% after HSCT versus 77% in the IFN group (p=0.18).[27] In the second Nordic MCL trial, intensive chemoimmunotherapy including high-dose cytarabine and rituximab plus auto-HSCT resulted in OS and CR of 96% and 54%, respectively. The six-year OS, EFS, and PFS were 70%, 56%, and 66%, respectively, with no relapses occurring after five years.[28] Due to the potentially curative impact of this therapeutic approach, auto-HSCT in first remission after a rituximab-based induction therapy is accepted as standard therapy of MCL.[27]

For MCL patients with relapsed and refractory disease, allo-HSCT with the RIC protocol is a reasonable option leading to long-term disease-free survival. Analysis of the long-term outcome of a risk-adapted transplantation strategy for MCL in 121 patients who underwent HSCT showed that the six-year PFS and OS with RIC allo-HSCT were 46% and 53%, respectively. Notably, TRM rates were 0% at 3 months and 9% at 1 year.[29]

2006 EUROPEAN GROUP FOR BLOOD AND MARROW TRANSPLANTATION RECOMMENDATIONS FOR HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN LYMPHOMA

The Accreditation Subcommittee of the European Group for Blood and Marrow Transplantation (EBMT)

regularly publishes special reports on the existing HSCT practices for haematological diseases in Europe based on the EBMT registry data and expert opinion. The 2006 EBMT recommendations for HSCT in common lymphomas are presented below.[10]

Hodgkin's Lymphoma

Auto-HSCT is the standard therapy for relapsed HL, but not for patients in first CR, including those with poor prognostic factors at diagnosis. Patients with disease refractory to first-line therapy but sensitive to salvage therapy may benefit from auto-HSCT. Patients with truly primary refractory disease or chemorefractory relapse do not experience long-term benefits with auto-HSCT; however, the procedure may be considered to be an initial debulking therapy to be followed by allo-HSCT as consolidation therapy (Table).[10]

Diffuse Large B-cell Lymphoma

Auto-HSCT is the standard approach for patients with relapsed aggressive DLBCL. First-line auto-HSCT may only be considered in patients with unfavourable prognostic factors at diagnosis. Patients who relapse after auto-HSCT can receive RIC allo-HSCT with an HLA-matched donor. Auto-HSCT is not an option for refractory patients (Table).[10]

Follicular Lymphoma

Auto-HSCT is not the first-line therapy for FL but may have a role in some high-risk subgroups. Auto-HSCT is the standard of care for managing early relapsed FL. Allo-HSCT using an RIC protocol can be considered for patients relapsing after auto-HSCT (Table).[10]

Mantle Cell Lymphoma

Considering the inherent poor prognosis of MCL, early intensification with auto-HSCT should be considered for MCL patients. Debulking with auto-HSCT followed by allo-HSCT using a RIC protocol may be considered as a developmental approach (Table).[10]

LOCAL EXPERIENCE IN HAEMATOPOIETIC STEM CELL TRANSPLANTATION FOR LYMPHOMA

By 2009,148 auto-HSCT procedures have been performed for the treatment of NHL at the Queen Mary Hospital, Hong Kong. More than 90% of the patients had high-grade lymphomas such as DLBCL, lymphoblastic lymphoma (LL) or Burkitt's lymphoma. First CR (CR1) transplants were performed in 24 patients with high-grade lymphoma who were marrow negative and showed good OS (up to 84% at 10 years). The majority of cases were referred for relapse and these demonstrated OS rates of 50 to 60% at 10 years. In the initial period, refractory cases were also treated but these had very poor survival and such cases are no longer treated with auto-HSCT.

A total of 73 patients had allo-HSCT procedures during the same period, the majority of whom were young (median age, 41 years) with high-grade lymphomas including DLBCL, LL and MCL. The source of haematopoietic stem cells was HLA-matched siblings for 61 cases; 10 cases had unrelated donors, and 2 had related donors. Upfront allo-HSCT (direct allo) was performed in 61 patients with poor prognosis due to marrow involvement, as they were unlikely to benefit

Table. 2006 EBMT recommendations for HSCT in common lymphomas.[10]

Disease	Disease status	Auto-HSCT*	Allo-HSCT*
Hodgkin's lymphoma	CR1	GNR	GNR
	Chemosensitive relapse; ≥CR2	S	D
	Refractory	CO	D
Diffuse lymphocytic B-cell lymphoma	CR1 (high IPI)	CO	GNR
	Chemosensitive relapse; ≥CR2	S	D
	Refractory	GNR	D
Follicular lymphoma	CR1 (high IPI)	CO	GNR
	Chemosensitive relapse; ≥CR2	S	CO
	Refractory	D	D
Mantle cell lymphoma	CR1	S	D
	Chemosensitive relapse; ≥CR2	S	D
	Refractory	GNR	D

Abbreviations: EBMT = European Group for Blood and Marrow Transplantation; HSCT = haematopoietic stem cell transplantation; CR1, 2 = first, second complete remission; IPI = International Prognostic Index; auto-HSCT = autologous HSCT; allo-HSCT = allogeneic HSCT.

* GNR = generally not recommended; S = standard of care, generally indicated in suitable patients; CO = clinical option, can be carried out after careful assessment of risks and benefits; D = developmental, further trials are needed.

from auto-HSCT; only 12 patients were relapses after auto-HSCT (auto-allo). All patients, except one, received myeloablative conditioning therapy. OS rates at five years after direct allo and auto-allo were 58% and 45%, respectively.

CONCLUSION

Recent advances in chemotherapy and chemoimmunotherapy have improved the outcomes of many lymphoma patients. However, patients with relapsed or refractory disease continue to do poorly. Intensive chemotherapy followed by auto-HSCT improves survival and is the standard of care for relapsed HL, DLBCL, and FL. Upfront auto-HSCT in first remission is the standard of care for MCL, an aggressive disease with poor outcomes. Allo-HSCT with a RIC protocol may be considered for managing patients with refractory disease or those who relapse after auto-HSCT. Given the increased risk of mortality and morbidity associated with HSCT, it is important to select patients who are most likely to benefit from the procedure based on factors such as age, disease status, chemosensitivity, disease grade, histological subtype, and disease stage at diagnosis. Choosing appropriate timing for the procedure is also important, as HSCT performed early in the disease course have demonstrably better outcomes than those performed later.

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