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Efficacy and safety of autologous peripheral blood stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia

A study protocol for a multicenter exploratory prospective study (Auto-Ph17 study)

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Abstract

Introduction: The prognosis of Philadelphia chromosome positive acute lymphoblastic leukemia (Ph + ALL) has been dramatically improved since the introduction of tyrosine kinase inhibitors (TKIs). Although allogeneic hematopoietic cell transplantation (allo-HCT) is a major treatment option, the role of autologous peripheral blood stem cell transplantation (auto-PBSCT) has been reconsidered, especially in patients who achieved early molecular remission.

Methods and analysis: This is a multicenter exploratory study for Ph + ALL patients aged between 55 and 70 years who achieved complete molecular remission within 3 cycles of chemotherapy. The target sample size is 5, and the registration period is 2 years. The primary endpoint is Day100- mortality after transplantation, and the secondary endpoints are survival, relapse rate, nonrelapse mortality, and adverse events.

This study is divided into 3 phases: peripheral blood stem cell harvest, transplantation, and maintenance. Chemomobilization is performed using a combination of cyclophosphamide (CPM), doxorubicin, vincristine (VCR), and prednisolone (PSL). As a preparative regimen, the LEED regimen is used, which consists of melphalan, CPM, etoposide, and dexamethasone. Twelve cycles of maintenance therapy using a combination of VCR, PSL, and dasatinib are performed.

In association with relapse, the minimal residual disease (MRD) of *BCR-ABL* chimeric gene and T-cell subsets are analyzed both before and after auto-PBSCT.

Ethics and dissemination: The protocol was approved by the institutional review board of Nagoya University Hospital and all the participating hospitals. Written informed consent was obtained from all patients before registration, in accordance with the Declaration of Helsinki. Results of the study will be disseminated via publications in peer-reviewed journals.

Trial registration: Trial registration number UMIN000026445.

Authorship: SN devised the research, secured the funding and drafted this manuscript. IS, YM, SS, MS, TN, KM, YK, AK, MY, MK, HI, SK, MO, TG, ST, MM, HN, and HK advised on the study design and data collection. All authors read and approved the final manuscript.

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Ethics approval Nagoya University Hospital Ethics Committee approved the study (reference: 2016–0532).

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Abbreviations: allo-HCT = allogeneic hematopoietic cell transplantation, auto-PBSCT = autologous peripheral blood stem cell transplantation, CPM = cyclophosphamide, Ph+ALL = Philadelphia chromosome-positive acute lymphoblastic leukemia, PSL = prednisolone, TKIs = tyrosine kinase inhibitors, VCR = vincristine.

Keywords: autologous peripheral blood stem cell transplantation, dasatinib, efficacy, Philadelphia chromosome positive acute lymphoblastic leukemia, safety

1. Introduction

The role of autologous peripheral blood stem cell transplantation (auto-PBSCT) for Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) has changed in the era of tyrosine kinase inhibitors (TKIs), although allogeneic hematopoietic cell transplantation (allo-HCT) is still considered to be an option to cure Ph+ALL.[1–5] In the Cancer and Leukemia Group B (CALGB) 10001 study, overall survival (OS) (median 6.0 years vs not reached) and disease-free survival (DFS) (median 3.5 vs 4.1 years) were similar between patients with a partial or complete molecular response who had undergone autologous transplantation and those who had undergone allo-HCT.[6] In addition, in patients achieving a major molecular response, the outcome was similar between patients who had undergone autologous transplantation and those who had undergone allo-HCT [OS: hazard ratio (HR) 0.94, 95% confidence interval (95% CI) 0.53–1.65, $P=.82$; DFS: HR 0.95, 95% CI 0.51–1.74, $P=.95$] in the study of the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL).[7] Because hematological complete remission (CR) has been achieved in many patients recently,[8,9] monitoring of minimal residual disease (MRD) is important for long-term disease control.[10–15]

Age is one of the most important prognostic factors in patients who underwent allo-HCT, although the outcome of allo-HCT is generally favorable in Japan (http://www.jdchct.or.jp/en/data/slide/2016/). In Ph+ALL patients, an age of 55 years or older has been identified as a risk factor for nonrelapse mortality (NRM) after allo-HCT.[15] On the contrary, the risk of NRM is much lower in auto-PBSCT, and auto-PBSCT has been performed on patients around 70 and up to 75 years old.[16]

In this study, we planned to analyze the safety and efficacy of auto-PBSCT for Ph+ALL patients aged between 55 and 70 years with an early molecular response. In addition, immune recovery after auto-PBSCT is also a subject of interest, especially the function of T cells.

2. Objectives

2.1. Primary

The primary endpoint is Day 100- mortality after transplantation.

2.2. Secondary

The secondary endpoints are as follows:

(1) Day100- molecular and hematological relapse rate;
(2) 1-year molecular and hematological relapse rate;
(3) 3-year molecular and hematological relapse rate;
(4) Day100- OS, DFS, relapse rate, and NRM;
(5) 1-year OS, DFS, relapse rate, and NRM;
(6) 3-year OS, DFS, relapse rate, and NRM;
(7) The proportion of therapy-related mortality;
(8) The proportion of adverse events in each regimen;
(9) Success rate of PBSCH;
(10) Detection of *BCR-ABL* chimeric gene in harvested peripheral blood stem cells by real-time quantitative polymerase chain reaction (RQ-PCR);
(11) Safety of PBSCT (the proportion of engraftment and engraftment failure);
(12) Cumulative dose of dasatinib (DA) during maintenance therapy;
(13) Mutation analysis of the *BCR-ABL* chimeric gene in relapsed patients.

3. Methods and analysis

3.1. Study design

This is a multicenter exploratory study of auto-PBSCT for Ph+ALL. This study is divided into 3 phases: peripheral blood stem cell harvest (PBSCH), transplantation, and maintenance (Fig. 1). Because this is an exploratory study, the target sample size is 5, and the registration period is 2 years. This study was registered in the UMIN Clinical Trials Registry with the identifier UMIN000026445.

3.2. Study setting

Eight hospitals in Aichi Prefecture agreed to take part in this study: Anjo Kosei Hospital, Ichinomiya Municipal Hospital, Konan Kosei Hospital, Toyohashi Municipal Hospital, Nagoya Medical Center, Japanese Red Cross Nagoya Daiichi Hospital, Japanese Red Cross Nagoya Daini Hospital, and Nagoya University Hospital. The protocol was approved by the institutional review board of each hospital (the latest edition ver. 1.1 13/Jun/2017). Written informed consent was obtained from all patients before registration, in accordance with the Declaration of Helsinki.

Patients are registered in this study after the independent review by the Data center in the Center for Advanced Medicine and Clinical Research of Nagoya University Hospital, where the inclusion and exclusion criteria are checked. Independent monitoring will be planned at least annually according to the Japanese clinical trial guideline.

3.3. Participants

The inclusion criteria are as follows:

(1) Acute lymphoblastic leukemia [B-lymphoblastic leukemia/lymphoma of WHO classification (5th edition)].
(2) BCR/ABL positive.
(3) Patients aged between 55 and 70 years.
(4) Newly diagnosed patients.
(5) Complete molecular remission (CMR) within 3 chemotherapy regimens.

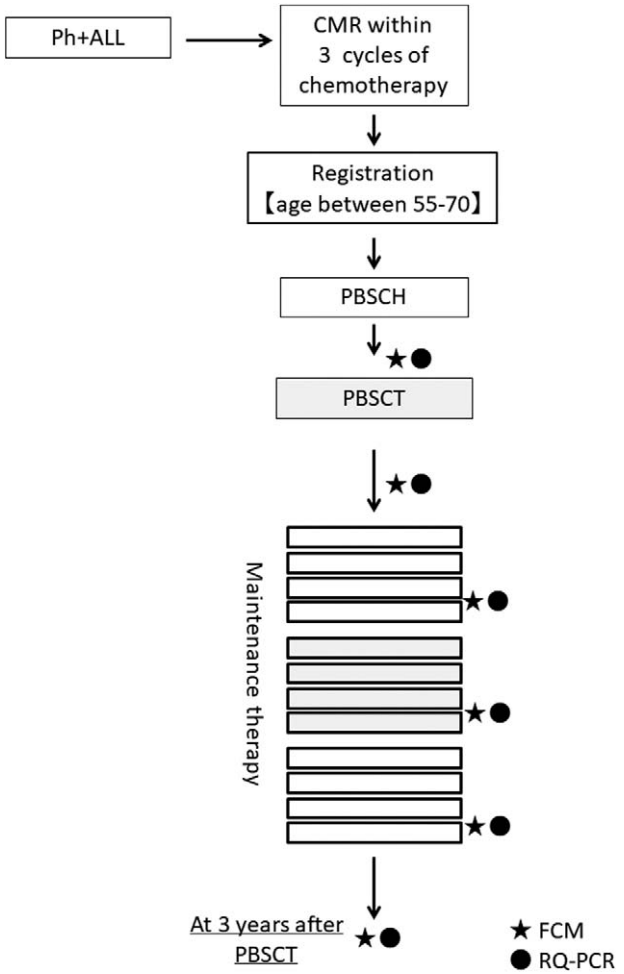

Figure 1. Outline of the Auto-Ph17 study. CMR = complete molecular remission, FCM = flow cytometry, PBSCH = peripheral blood stem cell harvest, PBSCT = peripheral blood stem cell transplantation, Ph + ALL = Philadelphia chromosome-positive acute lymphoblastic leukemia, RQ-PCR = real-time quantitative polymerase chain reaction.

(6) The Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, 2, or 3.
(7) Adequate function of key organs:
  a) Cardiac; No serious abnormal findings on electrocardiogram or echocardiogram.
  b) Hepatic; Serum total bilirubin≦2.0 mg/dL.
  c) Renal; Serum creatinine≦2.0 mg/dL.
  d) Pulmonary; Percutaneous oxygen saturation≧94%
(8) Voluntary written consent is given before enrollment.

CMR is defined by the absence of detectable MRD with a sensitivity of at least 0.01%.[7]

Exclusion criteria are as follows:

1. Heart insufficiency:
  1) Uncontrolled angina or heart failure, or myocardial infarction within 3 months.
  2) Congenital long QT syndrome.
  3) Ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation, Torsades de pointes),
  4) QTc≧481 ms
2. Pulmonary fibrosis, interstitial pneumonitis.

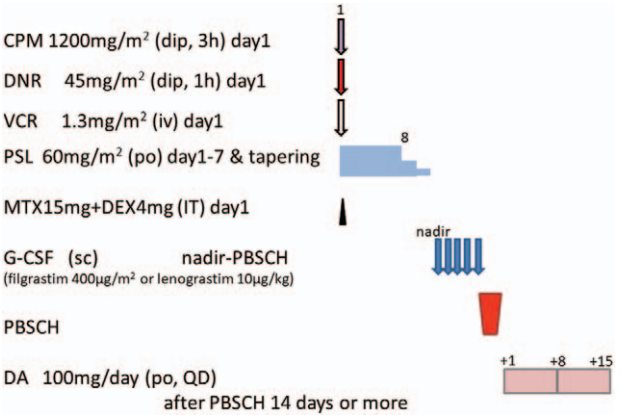

Figure 2. Chemomobilization regimen for peripheral blood stem cell harvest. CPM = cyclophosphamide, DA = dasatinib, DNR = doxorubicin, G-CSF = Granulocyte colony-stimulating factor, IT = intrathecal injection, MTX = methotrexate, PBSCH = peripheral blood stem cell harvest, PSL = prednisolone, VCR = vincristine.

3. Uncontrollable diabetes mellitus:
  1) Fasting blood sugar > 250 mg/dL even with insulin administration.
  2) Hypoglycemic attack twice or more/day due to insulin administration
4. Grade 4 infection.
5. HIV antibody positive.
6. HBs antigen positive.
7. Acquired bleeding diathesis.
8. Psychiatric illness.
9. Active another malignancy.
10. Patients who, in the judgment of the investigator, are inappropriate for entry into this study.

3.4. Study procedures-PBSCH

Chemomobilization is performed for PBSCH: cyclophosphamide (CPM) 1200 mg/m^2 (65 years≧; 750 mg/m^2) on Day 1, doxorubicin 45 mg/m^2 (65 years≧; 40 mg/m^2) on Day 1, vincristine (VCR) 1.3 mg/m^2 (65 years≧; 1 mg/m^2) on Day 1, prednisolone (PSL) 60 mg/m^2 (65 years≧; 40 mg/m^2) on Days 1 to 7, and intrathecal injection of methotrexate 15 mg and dexamethasone (DEX) 4 mg on Day 1 (Fig. 2). Granulocyte colony-stimulating factor (G-CSF) (filgrastim 400 μg/m^2 or lenograstim 10 μg/kg s.c.) is initiated in the neutropenic phase and continued until the end of PBSCH. PBSCH is initiated on the day when the WBC count is around 5×10^9/L. PBSCH is finished when 2×10^6/kg or more CD34+ cells are collected. The second PBSCH is performed when the total corrected CD34+ cells were less than 2×10^6/kg after 3 days of PBSCH.

The second PBSCH is performed using the CHASE regimen, which is used for PBSCH in lymphoma patients[17,18]: CPM 1200 mg/m^2 (65 years≧; 750 mg/m^2) on Day1, cytarabine 2 g/m^2 (60 years≧; 1 g/m^2, 65 years≧; 500 mg/m^2) on Days 2 and 3, etoposide (ETP) 100 mg/m^2 on Days 1 to 3, and DEX 40 mg/body (65 years≧; 20 mg/body) on Days 1 to 3.

DA 100 mg/day is administered for 14 days or longer from the day following the date of last PBSCH.

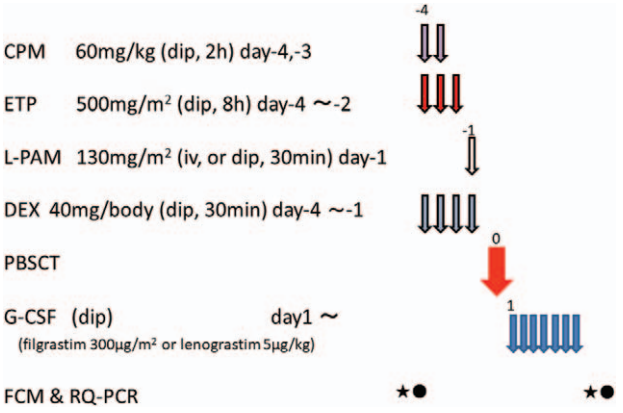

Figure 3. Preparative regimen for peripheral blood stem cell transplantation (the LEED regimen). CPM = cyclophosphamide, DEX = dexamethasone, ETP = etoposide, FCM = flow cytometry, G-CSF = Granulocyte colony-stimulating factor, L-PAM = melphalan, PBSCT = peripheral blood stem cell transplantation, RQ-PCR = real-time quantitative polymerase chain reaction.

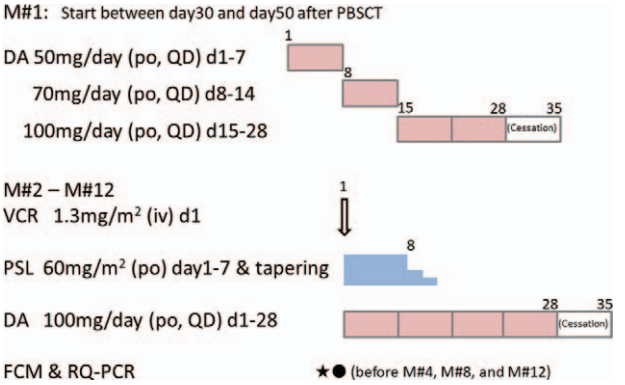

Figure 4. Maintenance regimens. DA = dasatinib, FCM = flow cytometry, PBSCT = peripheral blood stem cell transplantation, PSL = prednisolone, RQ-PCR = real-time quantitative polymerase chain reaction, VCR = vincristine.

3.5. Study procedures-transplantation

The LEED regimen is used as a preparative regimen for autologous PBSCT, which is used for autologous PBSCT in lymphoma patients[17,19]: melphalan 130 mg/m^2 on Day–1, CPM 60 mg/kg on Days –4 and –3, ETP 500 mg/m^2 on Days –4 to –2, and DEX 40 mg/body on Days –4 to –1 (Fig. 3). G-CSF (filgrastim 300 μg/m^2 or lenograstim 5 μg/kg s.c.) is initiated on Day 1 and continues until the WBC counts reach around 5 x 10^9/L.

3.6. Study procedures-maintenance

Maintenance therapy is started between Day 30 and Day 50 after transplantation when the patient can undoubtedly take oral medication. As maintenance course #1, DA is initiated as a dose of 50 mg/day, and increased up to 100 mg/day: 50 mg/day on Days1 to 7, 70 mg/day on Days 8 to 14, 100 mg/day on Days 15 to 28, and then ceased on Days 29 to 35. As maintenance course #2–12, a combination of VCR, PSL, and DA is administered: VCR 1.3 mg/m^2 on Day 1, PSL 60 mg/m^2 on Days 1 to 7, and DA 100 mg/day on Days 1 to 28 every 35 days (Fig. 4).

3.7. Minimal residual disease and tumor immunology

In connection with relapse, MRD using RQ-PCR for detection of *BCR-ABL* chimeric gene and T-cell subsets using flow cytometry, especially FOXP3 + CD25 + CD4 + regulatory T cells (Tregs),[20,21] are analyzed at designated time points: before conditioning for transplantation, Day 30 after transplantation, before maintenance courses #4, #8, and #12, and 3 years after transplantation.

4. Discussion

This is an exploratory study for the safety and efficacy of auto-PBSCT for Ph + ALL. It is generally recognized that autologous transplantation has a higher risk of relapse than allogeneic transplantation due to lack of allogeneic immunity but a much lower risk of NRM. Higher age, especially 55 years or older, was reported to be a significant risk factor for NRM after allogeneic transplantation for Ph + ALL.[15] To minimize the risk of NRM and relapse, this study targets patients aged 55 years or older with CMR.

The chemomobilization regimen for PBSCH varies depending on studies. [22,23] It is common for patients with malignant lymphoma or multiple myeloma to receive high-dose CPM or multidrug chemotherapy and G-CSF. For multidrug chemotherapy, there are several reports using a combination of CPM, anthracycline, and steroids,[24–26] which are commonly used in combination for Ph + ALL. Therefore, in this study, we chose the Japan Adult Leukemia Study Group (JALSG) Ph + ALL213 consolidation C2 regimen for PBSCH, which was one of widely used chemotherapy regimens for Ph + ALL in Japan (UMIN000012173).

There is no specific preparative regimen of auto-PBSCT for Ph + ALL. Previous studies have used preparative regimens for allogeneic transplantation, or auto-PBSCT for malignant lymphoma or multiple myeloma.[6,7] In this study, the LEED regimen is used for the following reasons: The regimen is commonly used for auto-PBSCT of malignant lymphoma in participating hospitals; Each drug used in the LEED regimen is covered by insurance in Japan for acute leukemia; and Etoposide has been a key drug of preparative regimen for ALL.[27–29]

Tregs have received a lot of attention in relation to cancer immunity in recent years. Tregs suppress antitumor immunity and contribute to tumor progression and metastasis.[21,30] On the contrary, in cancer patients, effector cells including CD8 + T cells are primed and expanded to suppress tumors. Therefore, the balance of Tregs and effector T cells will affect the prognosis. In chronic myeloid leukemia patients, it was reported that the number of Tregs was significantly lower in the CMR group than in the No-CMR group.[31] Our hypothesis is that dominant recovery of effector T cells after auto-PBSCT will contribute to long-term relapse-free survival in Ph + ALL patients.

This study can provide a foundation of auto-PBSCT for Ph + ALL. MRD-based strategies would identify patients who could achieve long-term remission without allo-HCT and lead to safer treatment for Ph + ALL.

References

[1] Fielding AK. Current treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2011;2011:231–7.

[2] Mizuta S, Matsuo K, Nishiwaki S, et al. Pretransplant administration of imatinib for allo-HSCT in patients with BCR-ABL-positive acute lymphoblastic leukemia. Blood 2014;123:2325–32.
[3] Zhang FH, Ling YW, Zhai X, et al. The effect of imatinib therapy on the outcome of allogeneic stem cell transplantation in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia. Hematology 2013;18:151–7.
[4] Tanguy-Schmidt A, Rousselot P, Chalandon Y, et al. Long-term follow-up of the imatinib GRAAPH-2003 study in newly diagnosed patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: a GRAALL study. Biol Blood Marrow Transplant 2013;19:150–5.
[5] Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. Lancet Oncol 2012;13:936–45.
[6] Wetzler M, Watson D, Stock W, et al. Autologous transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia achieves outcomes similar to allogeneic transplantation: results of CALGB Study 10001 (Alliance). Haematologica 2014;99:111–5.
[7] Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood 2015;125:3711–9.
[8] Yanada M, Takeuchi J, Sugiura I, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. J Clin Oncol 2006;24:460–6.
[9] Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol 2009;27:5175–81.
[10] Yanada M, Sugiura I, Takeuchi J, et al. Prospective monitoring of BCR-ABL1 transcript levels in patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia undergoing imatinib-combined chemotherapy. Br J Haematol 2008;143:503–10.
[11] Ravandi F, Jorgensen JL, Thomas DA, et al. Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy. Blood 2013;122:1214–21.
[12] Hoelzer D. Monitoring and managing minimal residual disease in acute lymphoblastic leukemia. Am Soc Clin Oncol Educ Book 2013;290–3.
[13] Jeha S, Coustan-Smith E, Pei D, et al. Impact of tyrosine kinase inhibitors on minimal residual disease and outcome in childhood Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer 2014;120:1514–9.
[14] Lee S, Kim DW, Cho BS, et al. Impact of minimal residual disease kinetics during imatinib-based treatment on transplantation outcome in Philadelphia chromosome-positive acute lymphoblastic leukemia. Leukemia 2012;26:2367–74.
[15] Nishiwaki S, Imai K, Mizuta S, et al. Impact of MRD and TKI on allogeneic hematopoietic cell transplantation for Ph + ALL: a study from the adult ALL WG of the JSHCT. Bone Marrow Transplant 2016;51:43–50.
[16] Okamoto S. Current indication for hematopoietic cell transplantation in adults. Hematol Oncol Stem Cell Ther 2017;[Epub ahead of print].
[17] Ogura M, Kagami Y, Taji H, et al. Pilot phase I/II study of new salvage therapy (CHASE) for refractory or relapsed malignant lymphoma. Int J Hematol 2003;77:503–11.
[18] Oki Y, Ogura M, Kato H, et al. Phase II study of a salvage regimen using cyclophosphamide, high-dose cytarabine, dexamethasone, etoposide, and rituximab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. Cancer Sci 2008;99:179–84.
[19] Han LN, Zhou J, Hirose T, et al. Feasibility and efficacy of high-dose melphalan, cyclophosphamide, etoposide, and dexamethasone (LEED) chemotherapy with or without rituximab followed by autologous stem cell transplantation for aggressive and relapsed non-Hodgkin's lymphoma. Int J Hematol 2006;84:174–81.
[20] Sakaguchi S, Sakaguchi N, Asano M, et al. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J Immunol 1995;155:1151–64.
[21] Nishikawa H, Sakaguchi S. Regulatory T cells in cancer immunotherapy. Curr Opin Immunol 2014;27:1–7.
[22] Sheppard D, Bredeson C, Allan D, et al. Systematic review of randomized controlled trials of hematopoietic stem cell mobilization strategies for autologous transplantation for hematologic malignancies. Biol Blood Marrow Transplant 2012;18:1191–203.
[23] Giralt S, Costa L, Schriber J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. Biol Blood Marrow Transplant 2014; 20:295–308.
[24] Takeyama K, Ogura M, Morishima Y, et al. A dose-finding study of glycosylated G-CSF (Lenograstim) combined with CHOP therapy for stem cell mobilization in patients with non-Hodgkin's lymphoma. Jpn J Clin Oncol 2003;33:78–85.
[25] Endo T, Sato N, Mogi Y, et al. Peripheral blood stem cell mobilization following CHOP plus rituximab therapy combined with G-CSF in patients with B-cell non-Hodgkin's lymphoma. Bone Marrow Transplant 2004;33:703–7.
[26] Gettys SC, Gulbis A, Wilhelm K, et al. Modified-CVAD and modified-CBAD compared to high dose cyclophosphamide for peripheral blood stem cell mobilization in patients with multiple myeloma. Eur J Haematol 2017;98:388–92.
[27] Laport GG, Alvarnas JC, Palmer JM, et al. Long-term remission of Philadelphia chromosome-positive acute lymphoblastic leukemia after allogeneic hematopoietic cell transplantation from matched sibling donors: a 20-year experience with the fractionated total body irradiation-etoposide regimen. Blood 2008;112:903–9.
[28] Shigematsu A, Kondo T, Yamamoto S, et al. Excellent outcome of allogeneic hematopoietic stem cell transplantation using a conditioning regimen with medium-dose VP-16, cyclophosphamide and total-body irradiation for adult patients with acute lymphoblastic leukemia. Biol Blood Marrow Transplant 2008;14:568–75.
[29] Shigematsu A, Tanaka J, Suzuki R, et al. Outcome of medium-dose VP-16/CY/TBI superior to CY/TBI as a conditioning regimen for allogeneic stem cell transplantation in adult patients with acute lymphoblastic leukemia. Int J Hematol 2011;94:463–71.
[30] Takeuchi Y, Nishikawa H. Roles of regulatory T cells in cancer immunity. Int Immunol 2016;28:401–9.
[31] Shinohara Y, Takahashi N, Nishiwaki K, et al. A multicenter clinical study evaluating the confirmed complete molecular response rate in imatinib-treated patients with chronic phase chronic myeloid leukemia by using the international scale of real-time quantitative polymerase chain reaction. Haematologica 2013;98:1407–13.