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, TN, KM, YK, AK, MK, HI, SK, MO, TG, ST, MM, HH, and HK advised on the study design and data collection. All authors read and approved the final manuscript.

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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 autologous hematopoietic cell transplantation (allo-HCT) is still considered an option to cure Ph+ALL. 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. 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. In patients with an age of 55 years or older, 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.

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.
(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 $\leq 2.0 \text{mg/dL}$.
   c) Renal; Serum creatinine $\leq 2.0 \text{mg/dL}$.
   d) Pulmonary; Percutaneous oxygen saturation $\geq 94\%$.

(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 $\geq 481 \text{ms}$

2. Pulmonary fibrosis, interstitial pneumonitis.

3. Uncontrollable diabetes mellitus:
   1) Fasting blood sugar $> 250 \text{mg/dL}$ 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

Chemo mobilization is performed for PBSCH: cyclophosphamide (CPM) 1200 mg/m$^2$ (65 years $\geq$; 750 mg/m$^2$) on Day 1, doxorubicin 45 mg/m$^2$ (65 years $\geq$; 40 mg/m$^2$) on Day 1, vincristine (VCR) 1.3 mg/m$^2$ (65 years $\geq$; 1 mg/m$^2$) on Day 1, prednisolone (PSL) 60 mg/m$^2$ (65 years $\geq$; 40 mg/m$^2$) on Days 1 to 7, and intrathecal injection of methotrexate (MTX) 4 mg on Day 1 (Fig. 2). Granulocyte colony-stimulating factor (G-CSF) 400 $\mu$g/m$^2$ or lenograstim 10 $\mu$g/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 $5 \times 10^9$/L. PBSCH is finished when $2 \times 10^9$/kg or more CD34$^+$ cells are collected. The second PBSCH is performed when the total corrected CD34$^+$ cells were less than $2 \times 10^6$/kg after 3 days of PBSCH.

DA 100 mg/day (po, QD) after PBSCH 14 days or more

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.
transplantation has a higher risk of relapse than allogeneic PBSCT for Ph+ALL. It is generally recognized that autologous transplantation due to lack of allogeneic immunity but a much reported to be a significant risk factor for NRM after allogeneic transplantation for Ph+ALL. 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. 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, 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.

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. 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.

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. 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. 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.

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