Role of autotransplantation in the treatment of acute promyelocytic leukemia patients in remission : Fukuoka BMT Group observations and a literature review

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Role of autotransplantation in the treatment of

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Fukuoka BMT Group Observations and a literature review

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Summary

We retrospectively analyzed the outcomes of 26 patients with acute promyelocytic leukemia (APL) in the first or second complete remission (CR), who underwent autologous peripheral blood stem cell transplantation (auto-PBSCT) between 1992 and 2008. All patients received all-trans retinoic acid (ATRA)-based induction therapy. After two courses of consolidation chemotherapy, upfront auto-PBSCT was performed in 20 patients in the first CR (CR1). Five patients had a high white blood cell count of more than 10×10^9/L (high-risk), while 15 patients had a count of less than 10×10^9/L (low-risk) at initial presentation. In addition, six patients, who were considered as low-risk patients at presentation, had a relapse after three cycles of consolidation and 2 years of maintenance therapy, but gained the molecular remission after re-induction and consolidation, and underwent auto-PBSCT in the second CR (CR2). In 26 recipients, engraftment was rapid and no transplant-related mortality was documented. All 20 patients autotransplanted in CR1 were still in CR at a median of 133 months (73 – 193 months), and six patients who underwent auto-PBSCT in CR2 were also still in CR at a median of 41 months (2 – 187 months) without maintenance therapy. PML/RARα chimeric mRNA was undetectable in PBSC or bone marrow samples examined before auto-PBSCT. Despite a small number of cases studied, our retrospective observations suggest that auto-PBSCT may be an effective treatment option to continue durable CR in the treatment of high-risk APL. We review previous reports and discuss the role of autotransplantation in the treatment of APL patients in CR.

Introduction

Combination therapy with upfront all-trans retinoic acid (ATRA) and anthracycline-based chemotherapy for induction and consolidation, as well as ATRA-based maintenance, has dramatically improved the outcomes of patients with acute promyelocytic leukemia (APL) (1, 2). This treatment strategy is currently the standard of care for newly diagnosed APL patients. However, relapse occurs in about 20% of patients receiving ATRA and chemotherapy, and is still a major obstacle to cure for APL patients(3-6). A recent multivariate analysis revealed that APL patients with a white blood cell (WBC) count of more than 10×10^9/L at initial presentation have a significantly increased relapse risk and poorer survival (1, 3, 7). New strategies include risk-adapted therapies to intensify the use of anthracyclines and/or cytarabine (CA) in either induction or consolidation for high-risk APL patients (1, 8, 9).

Autologous hematopoietic stem cell transplantation (HSCT) has been widely used to consolidate remission in patients with acute myelogenous leukemia (10, 11). Since new risk-adapted treatment strategies combined with upfront ATRA have provided higher cure rates, HSCT might not always be necessary for APL patients who are in the first complete molecular remission at the end of consolidation (12). Therefore, the role of HSCT in the front-line APL therapy has changed during recent years. In this paper, we use historical data to report the long-term safety and therapeutic efficacy of myeloablative therapy followed by autologous peripheral blood stem cell transplantation (auto-PBSCT) in 20 APL patients in the first complete remission (CR1) and six patients in the second CR (CR2). We discuss the role of auto-HSCT for APL patients based on our observations and previously reported literatures.

Materials and Methods

Patient Characteristics

Between April 1992 and November 2008, 26 APL patients, who were treated with myeloablative conditioning followed by auto-PBSCT in remission, were enrolled in this study at six institutions of the Fukuoka Blood & Marrow Transplant Group (FBMTG). All patients were diagnosed as APL morphologically according to the French-American-British classification. The diagnosis was also confirmed by the presence of t(15; 17)(q22; q21) by karyotypic analysis and/or detection of the PML/RARα transcript by reverse transcription polymerase chain reaction (RT-PCR).

Clinical characteristics of these patients are listed in Table 1. The patients comprised 14 males and 12 females with a median age of 45 years (16-68 years). Of these 26 patients, 20 received upfront auto-PBSCT in CR1 between April 1992 and November 2002. Five of these 20 patients had a WBC count of more than 10×10^9/L, and were considered as high-risk patinets (1, 3, 7), and six patients showed additional karyotypic abnormalities with t(15;17) at presentation (Table 1). In contrast, after August 1993 according to the policy of each institution, APL patients in molecular CR1 after consolidation are no longer always indicated for upfront auto-PBSCT. Consequently, six patients received auto-PBSCT in CR2 during the period up to November 2008, although all of these six patients had a WBC count of less than 10×10^9/L at presentation but had a relapse of APL after cessation of maintenance therapy for CR1. This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Chemotherapy and Collection of Peripheral Blood Stem Cells (PBSCs)

Remission induction therapy for 23 patients consisted of ATRA 45 mg/m^2 and anthracyclines including daunorubicin (DNR) or idarubicin (IDA). The remaining three patients were treated with ATRA alone at the same dosage because their WBC count at

presentation was less than 0.5 x 10^9/L. Consolidation chemotherapy consisted of cytosine

arabinocide (CA) 500 mg/m^2 every 12 h for 6 days (intermediate-dose CA) combined with

mitoxantrone 7 mg/m^2 for 3 days in the first course and etoposide 100 mg/m^2 for 5 days in the

second course (10, 13).

In 20 patients who were assigned to receive upfront auto-PBSCT in CR1,

autologous PBSCs were collected during the hematopoietic recovery phase after the second

course of consolidation followed by granulocyte-colony stimulating factor (G-CSF,

filgrastim; Kyowa Hakko Kirin, Japan). Collected and unmanipulated PBSC were

cryopreserved until transplantation. The remaining six patients after the second consolidation

chemotherapy, were treated with an additional course of intermediate-dose CA combined with

DNR 25mg/m^2 for 4 days, followed by treatment with ATRA, and low-dose methotrexate and

mercaptopurine as maintenance therapy as described by Sanz et al (1). Thereafter, these six

patients, who had a WBC count of less than 10 x 10^9/L at presentation and were considered as

low-risk patients, had a relapse of leukemia at a median of 22 months (8 – 54 months) after

diagnosis. Three patients showed molecular relapse, which was detected by RT-PCR, while

the remaining three patients showed hematologic relapse. Three patients received re-induction

cytotoxic chemotherapy without arsenic trioxide (ATO), and the remaining three patients

received ATO 0.15 mg/m^2 with or without IDA. All six patients achieved molecular CR2

after one course of re-induction chemotherapy. Autologous PBSCs were collected after an

additional two or three course of consolidation chemotherapy in these patients.

Auto-PBSCT

The pre-transplant conditioning regimen for all patients consisted of busulfan 4

mg/kg on days -8 to -5, etoposide 20 mg/kg on days -4 and -3, and CA 3 g/m^2 every 12 hours

on days -3 and -2 (BEA regimen) (10, 13). Busulfan was administered orally in four devided

doses daily in all patients. We did not study the pharmachokinetics of oral busulfan nor adjust

to a targeting dose. Concurrently, G-CSF was administered to prime residual leukemic cells at a dose of 5 μg/kg on day -14 to -6, 10 μg/kg on days -5 to -4 in combination with continuous infusion of CA 100 mg/m^2 on day -12 to -6. Cryopreserved PBSCs were rapidly thawed in a 37 ℃ water bath and infused on day 0.

RT-PCR analysis

Nested RT-PCR analysis of PML/RARa chimeric mRNA was performed to detect minimal residual disease (MRD) with sensitivity threshold between 10^{-6} and 10^{-7} in PBSC samples in 15 of 20 patients who underwent auto-PBSCT in CR1, and bone marrow samples in all six patients just before auto-PBSCT in CR2 as described previously (14).

Results

Auto-PBSCT in CR1

Twenty patients received upfront high-dose chemotherapy (G-SCF-combined BEA regimen) with auto-PBSCT during CR1 after a median of 6 months (5-13 months) from the initial diagnosis. A median dose of 7.1 x 10^6 CD34$^+$ cells/kg was transplanted. No engraftment failure was observed. The median days to reach a granulocyte count above 0.5 x 10^9/L, a platelet count above 20 x 10^9/L, and independence from platelet transfusion was 15 days (range, 13 – 24 days), 11 days (range, 8 – 210 days) and 11 days (range, 6 – 191 days), respectively. No treatment-related deaths were observed after auto-PBSCT. Grade 1-2 stomatitis and diarrhea occurred in most recipients; however, significant adverse events, which were graded in accordance with National Cancer Institute Common Toxicity Criteria (version 2.0), above grade 3 were not observed.

At a median follow-up time of 133 months (73 – 193 months), all of twenty patients were continuing CR1 without maintenance therapy. Nested RT-PCR analysis was performed to test contamination of the infused PBSCs with APL cells. PML/RARα chimeric mRNA was

undetectable in PBSCs samples obtained from all 15 patients. After auto-PBSCT (median follow-up time, 43 months), MRD could not be detected in bone marrow samples from any of these patients.

Auto-PBSCT in CR2

Six patients, who had relapse but achieved CR2 after re-induction chemotherapy, were assigned to receive auto-PBSCT. RT-PCR analyses of BM samples obtained from all six patients before auto-PBSCT were negative for MRD. They received G-SCF-combined BEA regimen followed by auto-PBSCT after a median of 26 months (12 – 61 months) from the initial diagnosis. A median dose of $6.1x10^6$ CD34$^+$ cells/kg was transplanted. Engraftment was documented in all six patients. The median days to reach a granulocyte count above 0.5 x 10^9/L, a platelet count above 20 x 10^9/L, and independence from platelet transfusion was 11 days (range, 9 – 12 days), 14 days (range, 11 – 15 days) and 11 days (range, 8 – 15 days), respectively. No treatment-related deaths and no significant adverse events above grade 3 were documented. No significant difference was observed in hematopoietic recovery or adverse effect between 20 and six patients in CR1 and CR2, respectively after auto-PBSCT. All six patients who received transplantation in CR2 remained in CR at a median follow-up time of 41 months (2 – 187 months) without maintenance therapy.

Discussion

The European Cooperative Group for Blood and Marrow Transplantation (EBMT) group conducted a survey on APL patients who underwent HSCT between 1993 and 2003 in Europe (15). In their analysis of 625 APL patients, the number of auto-HSCT has decreased progressively for patients in CR1 since 1998, whereas that for patients in CR2 has remained stable. The emergence of a new risk-adapted treatment strategy combining ATRA and ATO has dramatically changed the role of auto-HSCT in the treatment of APL in CR1 and CR2. In

contrast, allogeneic HSCT should be considered for patients with persistent MRD or without hematologic remission if an HLA-matched donor is available (12).

G-CSF can stimulate the proliferation of myeloid leukemic cells because most express receptors for G-CSF, and increased susceptibility of leukemic cells to cell-cycle-specific agent CA. Moreover, recent evidences have shown that G-CSF can mobilize hematopoietic stem cells from bone marrow niche by disruption of adhesion molecules such as CXCR4/SDF1 and VCAM1/VLA4 (Papayannopoulou T. Blood 2004). In this context, G-CSF can also mobilize leukemic stem cells into circulation from bone marrow niche, resulting in the increased susceptibility to chemotherapeutic agents. Clinical studies support a potential role to reduce leukemic relapse after auto-HSCT and allo-HSCT (Takamatsu Y et al. Bone Marrow Transplant 1994; Takahashi S et al. Bone Marrow transplant 1994; Gondo H et al. Bone Marrow Translant 1997; Tomonari A et al. Eur J Haematol. 2006).

Auto-HSCT in CR1

Large multicenter studies have shown that treatment regimens combining upfront ATRA and chemotherapy have provided high cure rates (2-7). In addition, multivariate analyses have revealed that the most important factor predicting relapse is a WBC count of more than 10×10^9/L at initial presentation (1, 3, 7). Therefore, many investigators have tried to classify the risk for each patient and modulate the regimen to intensify the use of anthracyclines and/or CA in either induction or consolidation therapy for high-risk patients (1, 9). A joint analysis by the Spanish cooperative group "Programa para el Estudio de la Terapéutica en Hemopatía Maligna" (PETHEMA) and the European "French-Belgian-Swiss APL" group compared the outcomes of PETHEMA LPA99 and European APL 2000 trials, and demonstrated that addition of high-dose of CA in consolidation has benefited high-risk patients (5). Thereafter, through the combined analysis of APL93 and APL2000 trials, the European APL group confirmed a dramatically improved outcome of APL patients with high

WBC counts when treated with escalating dose of CA in APL2000 trial: between these two trials, CR rate increased from 89% to 93%, and the 5-year cumulative incidence of relapse decreased from 40% to 9.5% in patients with high WBC counts (between 10 - 50 x 10^9/L). In patients with very high WBC counts of more than 50 x 10^9/L, the CR rate increased from 82% to 91%, and 5-year cumulative incidence of relapse decreased from 59% to 24% (9). These results showed that upfront ATRA combined with intensified consolidation with high-dose CA has potential benefits for high-risk APL patients. Therefore, in terms of the intensification of chemotherapy, theoretically auto-PBSCT would be the best therapy to maximize the antileukemia effect as well as to minimize transplant-related mortality (TRM) by rapid engraftment, especially for high-risk patients, if TRM can be reduced as much as possible. In our study, upfront auto-PBSCT was performed in 20 APL patients in CR1 after consolidation, which included five high-risk patients. Engraftment was rapid, and TRM was not documented. All of these patients continued in CR for more than 10-years without maintenance therapy, indicating that leukemia-free survival (LFS) at 10-years was 100%. All infused PBSCs were negative for MRD in good-risk and high-risk patients who were examined. Thus, high-dose chemotherapy followed by auto-PBSCT as well as deep CR status, reflecting negative MRD in PBSCs, would have benefited our patients, as several reports indicated that molecular CR would be an important factor for patients autotransplanted in CR2. In contrast, according to the multicenter retrospective survey from the EBMT group, LFS at 5-years was approximately 70% in 149 APL patients in CR1 receiving auto-HSCT, indicating that the results in APL patients autotransplanted in CR1 were not better than those in patients given ATRA-combining risk-adapted chemotherapy (5). In addition, a long-term follow-up study with a median of 10-years of follow-up (APL 93 trial) recently revealed the benefits of prolonged maintenance with ATRA plus chemotherapy for high-risk patients with initial WBC counts of more than 5 x 10^9/L (16). In these high-risk patients, cumulative incidence of relapse declined from 68.4% with no maintenance to 20.6% with combined ATRA and

chemotherapy maintenance. Based on these results, auto-HSCT is not routinely recommended for APL patients in CR1 (12, 17), although there has been no randomized trial to compare outcomes among APL patients in CR1 receiving upfront auto-HSCT versus ATRA-combining risk-adapted chemotherapy for induction, consolidation, and maintenance (15, 18-21).

Auto-HSCT in CR2

For APL patients who had relapse after ATRA-containing regimens, ATO is presently regarded as the best treatment option; 2-year overall survival (OS) was reported to be approximately between 50% – 60% after repeated cycles of ATO combined with chemotherapy in relapsed APL patients achieving CR2 (22, 23). The consolidation strategy after ATO-induced CR2 generally consists of HSCT, and the choice of transplant modality is mainly based on PCR status. Allo-HSCT is restrictively chosen for patients failing to achieve molecular CR2, since allo-HSCT offers greater antileukemic activity because of its graft-versus-leukemia effect but obviously involves a greater risk of TRM (23). Auto-HSCT was recently considered to be one of the most useful options for consolidation in relapsed APL patients (12, 15, 17, 23).

In a report of the EBMT group, 195 APL patients in CR2 autotransplanted between 1993 and 2003 were enrolled in the survey; the 5-year estimate of leukemia free survival was 51% (15). Although no data were available on re-induction and consolidation chemotherapy, or on PCR status of the graft and/or recipients before transplant, the results demonstrated that a large population of patients in CR2 achieved long-term OS after auto-HSCT. De Botton also discussed the benefit of auto-HSCT in 50 APL patients who relapsed after ATRA-containing treatment in 2004. The relapse-free survival at 7-years was 79.4 % with a TRM of 6% after auto-HSCT (24). They analyzed MRD status in 30 available cases. PCR before auto-HSCT was positive in PBSCs in two cases and negative in 28 cases. One out of two cases

autografted with a positive PCR assessment relapsed, and only three out of 28 cases (11%) autografted with negative PCR also relapsed (24). In the patients autografted with negative PCR, relapse-free survival at 7-years increased to 87.3 %, indicating that auto-HSCT would be effective for the treatment of relapsed APL if performed in molecular CR2; this was consistent with previous reports (25-27) (Table 2).

Thomas et al reported their experience using ATO as re-induction therapy for 28 relapsed APL patients. Nine of 24 patients achieving molecular CR underwent auto-HSCT, and all of them continued in CR2 (2-year leukemia-free survival and OS rates of 100%) (28). In our study, six patients had a relapse of APL after cessation of maintenance therapy although all six patients were considered as low-risk patients; three patients were treated with chemotherapy as re-induction for relapsed APL before the era of ATO, while the remaining three underwent ATO-containing chemotherapy. All six patients gained molecular CR2 after one course of re-induction chemotherapy, and PBSCs were collected after the subsequent chemotherapy. Six patients received auto-HSCT in CR2, and were continued in CR without maintenance at a median of 41 months (2 – 187 months). Furthermore, Thirugnanam et al recently showed that, following remission induction with an ATO-based regimen in relapsed APL patients, consolidation with auto-HSCT was associated with a significantly superior clinical outcome compared with ATO-based maintenance; EFS at 5-years was 83.3% in patients who underwent auto-HSCT versus 34.4% in those who did not (29). In addition, since recent evidence has revealed that ATO treatments comprising at least two cycles can result in molecular CR in nearly 80% of relapsed APL patients (23), auto-HSCT may become more beneficial for APL patients in molecular CR2 receiving ATO treatment.

Future Perspective

Recently, Lee *et al* reported the importance of serial measurement of MRD by PCR analysis during therapy in 70 newly diagnosed APL patients (30). According to their

prospective study, MRD after upfront ATRA and anthracycline-based induction chemotherapy was detectable in half of the patients and was undetectable in the remaining half. All patients negative for PCR after induction had a favorable clinical course thereafter, without relapse. In contrast, after the first consolidation, MRD was still detectable exclusively in about 30% of the patients positive for PCR after induction, who were highly susceptible to subsequent hematologic relapses despite additional consolidation (30). Therefore, patients who remain PCR-positive after the first consolidation may be candidates requiring further ATO-containing treatment followed by HSCT: auto-HSCT has a strong ant-APL activity and potent roles in the treatment of APL particularly in molecular CR, while allogeneic HSCT would be recommended for patients who fail to gain molecular CR. Large prospective studies and careful follow-ups with serial quantification of MRD would be needed to assess the value of an individualized, response-oriented treatment strategy and the role of HSCT in the treatment of APL patients.

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Table 1. Comparison between CR1 and CR2

	CR1 (n = 20)	CR2 (n = 6)
Age	45(16-68)	45.5(37-50)
Sex (M / F)	12/8	2/4
WBC at Diagnosis		
$>10 \times 10^9$/L	5	0
$\leqq 10 \times 10^9$/L	15	6
Additional chromosomal abnormality		
Yes	6	1
No	14	5
Months from diagnosis to auto-PBSCT	6 (5-13)	25.5 (12-61)
Months from auto-PBSCT to present	133(37-193)	41 (2-187)
Infused CD34+ cells ($\times 10^6$cells/kg)	7.1(1.03-20.2)	6.1(0.5-11.2)

Table 2 Autotransplantation Results in APL

Author (Publication)	N	Age (Median)	Disease Status at Transplant	Source of autotransplantation	Pretransplant BM PCR	Graft PCR	%TRM	Outocome %DFS/ %EFS/ %RFS/ %LFS(Interval) Median Survival Median Duraion of CR
Mandelli et al (1994)	187	30	CR1: 129 CR2: 58	BM	NA	NA	CR1: 18 CR2: 23	CR1: 42 ± 4 (7-yr LFS) CR2: 22 ± 8 (4-yr LFS)
Meloni et al (1997)	15	38	CR2: 15	BM	Negative 8 Positive 7	NA	0	Median Duraion of CR PCR positive*: 5 months PCR negative**: 28.5 months
Ferrant et al (1997)	36	NA	CR1: 36	BM	NA	NA	NA	70 (3-years LFS) 83 (3-years OS)
Roman et al (1997)	10	47	CR1: 8 CR2: 1 PR: 1	BM 4 PB 6	Negative 2	NA	0	Median Survival: 41 months
Lo Coco et al (1997)	8	40	CR2: 8	BM	Negative 8	NA	0	Median Duraion of CR: 11 months
Ottaviani et al (1998)	16	30	CR1: 13 PR: 1 CR2: 1 CR3: 1	BM	Negative 12 Posirtive 3	NA	0	Median Survival CR1: 55 months CR2: 16 months
Thomas et al (2000)	22	NA	CR2: 22	BM 5 PB 17	Negative 9 Positive 1	Negative 2 positive 4	9	77 (3-years DFS)
Ferrara et al (2004)	6	38	CR2: 6	BM or PB	Negative 6	Negative 6	0	Median Duraion of CR: 36 months
de Botton et al (2005)	50	45	CR2: 50	BM 43 PB 7	Negative 28 Positive 2	Negative 20 Positive 2	6	79.4 (7-years RFS) 60.6 (7-years EFS)
Sanz et al (2007)	344	50(CR1) 38(CR2)	CR1: 149 CR2: 195	CR1: BM 92, PB 57 CR2: BM 91, PB 104	NA	NA	CR1: 10 CR2: 16	CR1: 70 (5-years LFS) CR2: 51 (5-years LFS)
Thirugnanam et al (2009)	14	33	CR2: 12 CR3: 2	PB	Negative 14	NA	0	83.33±15.21 (5-years EFS)
Kamimura et al (present study)	26	45	CR1: 20 CR2: 6	PB	CR2: Nevative 6	CR1: Negative 15	0	100% 11-years LFS(CR1) 100% 3-years LFS(CR2)

abbribiations

CR; complete remission,   CR1; first complete remission,   CR2; second complete remission,   PR; partial response,   PBSC; peripheral blood stem cell,   BM; bone marrow,

LFS; leukemia-free survival,   OS; Overall survival,   DFS; disease free survival,   EFS; event free survival,   TRM; treatment-related mortality,   NA, not available

*PCR positive; pretransplant BM PCR positive

**PCR negative; pretransplant BM PCR negative