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Long-term follow-up of patients with chronic myeloid leukemia having received autologous stem cell transplantation

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Abstract

Prior to introduction of imatinib mesylate, the median survival of chronic myeloid leukemia (CML) patients was approximately 60 months and the standard treatment with interferon-alpha (IFN-α) resulted in major cytogenetic responses of 20-25 %. As an alternative treatment approach besides allogeneic transplantation intensive chemotherapy followed by autologous hematopoietic stem cell transplantation (autoHSCT) was investigated at that time with the rationale of debulking disease burden and mobilisation and transplantation of Philadelphia chromosome-negative (Ph-) stem cells.

In the era of tyrosine kinase inhibitors (TKIs) as state-of-the-art therapy for CML, the concept of autoHSCT has attracted only little interest and long-term follow-up and outcome data after autoHSCT in CML patients is scarce. In this long-term analysis, we report on 21 CML patients, mobilized in early chronic phase (ECP) and transplanted with largely Ph- grafts,

who received IFNα as maintenance therapy. Imatinib mesylate was administered upon cytogenetic relapse or disease progression while on IFN-α. The 10-year survival was 61% and 11 patients (52%) were alive at a median follow-up of 12.5 years (range 0.3 - 13.8) with 8 patients in complete hematologic remission (CHR) and 3 of 8 in major molecular remission (MMR). While all patients in MMR and 2 of 5 patients in CHR received imatinib, it is noteworthy that three patients remaining in CHR only received IFN-α maintenance after autoHSCT.

With the limitations of a small patient population, this is the longest follow-up analysis demonstrating that autoHSCT in CML is very efficient to debulk the disease, restore Ph-negative hematopoiesis and is able to induce major and sustained molecular responses in the majority of patients with substantial long-term survival rates.

Keywords: CML; autologous transplantation; long-term follow up

Introduction

Chronic myeloid leukemia (CML) is characterized by the presence of the Philadelphia chromosome, a reciprocal translocation that results in the BCR-ABL fusion gene (1-3). Deciphering of the BCR-ABL protein as a tyrosine kinase (TK) and the development of several substances, which are able to block BCR-ABL´s increased tyrosine kinase activity, have revolutionized the treatment of CML (4, 5). Currently, Imatinib mesylate is considered standard of care for first-line treatment of chronic phase CML (6, 7).

However, in the 1990´s, before the introduction of TKIs, treatment intensification of CML patients in early chronic phase (ECP) with high-dose chemotherapy (e.g. busulfan, melphalan and cyclophosphamide combined with total body irradiation in some studies) followed by autoHSCT and IFNα maintenance was a promising and intensively investigated treatment regimen (8-14). The strong rationale behind this treatment approach was the concept of debulking the disease burden, mobilization of Ph- hematopoietic stem cells and consecutive transplantation of a largely Ph- autograft.

While some observations pointed to increased remission rates and prolonged survival when autografting was performed in ECP, a meta-analysis of six randomized studies was unable to show a benefit for autoHSCT compared to IFNα-based therapy with regard to event free survival and overall survival (15). Whether there still exists a role for autoHSCT in the current management of CML, e.g. to reverse imatinib resistance or to eliminate clones harbouring BCR-ABL kinase domain mutations remains to be determined (15, 16).

Interestingly, only few long-term data on autografted patients are available (15, 18). Therefore, we report our long-term follow-up analysis on 21 CML patients who were autografted in ECP between 1995 and 1999.

Patients and Methods

Patient selection, mobilization of CD 34^+ stem cells and high-dose chemotherapy with autologous transplantation have been described in detail previously (10, 11). Briefly, after priming with rhG-CSF (5 µg/kg s.c.; Filgrastim, Amgen, Germany), mobilization chemotherapy consisted of idarubicin (8 mg/m^2, day 1-3), cytosine arabinoside (400 mg/m^2, day 1-3) and etoposide (150 mg/m^2, day 1-4). On day 7 after chemotherapy, administration of rhG-CSF (10 µg/kg s.c. daily) in all patients and rhIL-3 (5 µg/kg s.c, Novartis, Germany) in 12 patients was started until stem cell harvest. After apheresis, positive selection for CD 34^+ cells was performed using avidin-immunoaffinity columns (CellPro, Washington, USA) or Isolex magnetic cell separation (Baxter, Unterschleissheim, Germany). High-dose chemotherapy contained busulphan (4 mg/kg day -7 to -4) and cyclophosphamide (60 mg/kg day -1 to -2). After autologous transplantation of a minimum of 1.5 x 10^6 CD 34^+ cells, intravenous rhG-CSF treatment was started on day +3 until neutrophil recovery (> 1.5 x 10^9/l). 20 patients were transplanted in first chronic phase and one patient in accelerated phase with a median time from initial diagnosis of 12 months (**Table 1**). Following platelet regeneration, patients were treated with IFN-α (initially 3 x 3x10^6 units/week; dose reduction to 3 x 1.5x10^6 units/week or less if side effects occurred) until complete cytogenetic/molecular remission, onset of intolerance or progressive disease. If imatinib was started, the inital dose was 400 mg daily. One patient received Nilotinib 2 x 400 mg daily and Dasatinib 2 x 70 mg daily after imatinib failure and one patient received Nilotinib 2 x 400 mg daily upon imatinib failure. Patient's characteristics are provided in **Table 1**.

Overall survival and median follow-up were estimated using the Kaplan-Meier method.

Results

Of 21 CML patients transplanted with an autograft between 1995 and 1999 at our institution, 11 patients were alive at follow-up analysis in 2009. Three patients (one receiving imatinib, one nilotinib and one dasatinib) were in complete hematologic remission (CHR) but without complete regeneration. Five patients (two on imatinib, three on IFNα) were in CHR and three patients were in major molecular remission (MMR) (**Table 2**). It is noteworthy that three patients remaining in CHR only received IFNα maintenance after autoHSCT, while all patients in MMR and 2/5 patients in CHR received imatinib.

Five patients had died after a median of 36 months (range 20-150) due to progressive disease with only one patient having received imatinib (**Table 2**). Three patients had received allogeneic stem cell transplantation (alloHSCT) in complete hematologic remission, chronic or accelerated phase, three, four and nine years after autoHSCT, respectively. Unfortunately, all three died due to infectious complications or graft-versus-host disease following alloHSCT. One patient died two months after autoHSCT in CP due to toxic alveolitis and lung bleeding and one patient died seven years after autoHSCT of undetermined cause.

In our patient cohort, the 10-year survival rate after autologous transplantation was 61% (13/21) and overall survival after a median follow-up of 12.5 years was 52 % (11/21) (**Figure 1**).

Discussion

Due to the impact of TKI in the first-line therapy of CP-CML only few data are available on long-term outcome after autoHSCT in CML patients. However, as some patients have primary or develop secondary resistance to imatinib and other TKIs and are not eligible for alloHSCT, autoHSCT might still be a treatment option in a defined subset of CML patients.

Simonsson et al. showed a median survival of 7.5 years after autoHSCT in the pre-imatinib era (16). However, in a meta-analysis of this and other trials from several groups, a benefit of autoHSCT in the initial treatment of CML as compared to interferon-α (alone or in combination) could not be demonstrated (15). Furthermore, it has to be mentioned that all trials involved in that analysis closed early because of the introduction of imatinib. Of those trials, the German CML III A trial is still ongoing for analysis.

However, intensive chemotherapy for HSC-mobilization followed by autoHSCT of Ph-negative grafts has been shown to be effective in debulking leukemia burden and to induce good cytogenetic and molecular responses maintained by low-dose IFN-a in some patients as demonstrated by our data and others' (10-14). Recently, some very promising studies have shown that mobilization of Ph-negative peripheral blood progenitor cells by G-CSF alone while patients are being treated with imatinib is feasible (19, 20). However, data on successful transplantation of such cells has not been investigated thoroughly, yet (21).

In our study all patients had received mobilization chemotherapy plus filgrastim in order to collect $CD34^+$ stem cells. While in this study CML patients were treated with TKIs several years after autoHSCT, in the era of imatinib and 2nd and 3rd generation TKIs a potential treatment concept would rather consist of initial treatment with TKIs and a stem cell harvest in CCR and/or MMR. In case of TKI-resistance later on in the course of CML, autoHSCT could be one possible treatment option for patients who are ineligible for alloHSCT.

Compared to the median survival in CP-CML of 60 months prior to introduction of imatinib our data on a small cohort of selected patients show substantial overall survival after

treatment with intensive chemotherapy and autologous stem cell transplantation, followed by TKI therapy in the majority of patients. However, the significance of maintenance therapy with IFN-α and that of subsequent therapy with imatinib or another TKI is difficult to interpret (22). The initial debulking by chemotherapy might be of primary importance in this setting.

As the precise role of transplantation of autologous Ph-negative PBPC in the management of CML patients resistant to current first-line therapy with TKIs is still unknown further evaluation in suitably designed clinical trials is warranted.

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Tables

Table 1. Patient characteristics

Patients characteristics	
Male/female	16/5
Age at transplantation (years)	46 (25-58)
Remission status prior to transplantation (19 patients evaluable)	18 CP, 1 AP
Sokal Score prior to transplantation (data of 11 patients evaluable)	0,7 (0,52-1,74)
Time from initial diagnosis until transplantation (months)	12 (5-64)
Time from transplantation until first imatinib treatment (11 patients; years)	7 (4-13)
Follow-up after transplant (years)	12.5 (0.3-13.8)

Values are given as median and range
CP= chronic phase, AP= accelerated phase

Table 2. Time course of 21 CML patients with remission status (where available) from transplantation to last follow-up or death.

	1995	96	97	98	99	2000	01	02	03	04	05	06	07	08	09
1	Tx	▲●			▲			▲	▲	▲	▲		▲	▲	▲ **a**
2		Tx	BC	BC ж											
3	Tx	▲◙	▲◙		CP	CP	CP		▲□		▲	▲	▲□♠	▲□	▲□ **a**
4	Tx	CP			CP	CP	CP	AC♠	▲	▲al.Tx	ж				
5		Tx	▲●	AC	CP	al.Tx	ж								
6		Tx	▲◙			▲		▲	●	▲◙	▲	▲	BC♠	BC ж	
7		Tx	AC		2.Tx	BC ж									
8		Tx	▲●	▲○		▲○	▲◙		▲◙		▲	▲		▲	▲ **a**
9		Tx			CP	♠	CP	▲◙	▲□	▲		▲■	▲	▲	▲□ **a**
10		Tx		CP	AC al.Tx	ж									
11		Tx	▲	▲◙	▲◙	▲■	▲■	▲■	▲■						▲ **a**
12		Tx	▲	▲●	▲	▲●	▲	▲	▲	▲●	▲	▲	▲	▲○	▲♠ **a**
13		Tx	CP	CP	CP	CP	CP	CP♠			CP●	CP●			▲**x** **a**
14		Tx	CP	CP	CP	CP	CP♠	CP	CP	CP	CP	CP	CP ♦♣	CP	▲**x** **a**
15		Tx	▲	▲	▲	CP	CP	CP	CP	▲♠	▲	▲		CP	▲**x**♦ **a**
16		Tx	CP	CP	CP	CP	CP	▲	▲♠	▲	▲	▲	▲	▲□	▲ **a**
17			Tx	ж											
18				Tx	CP	BC ж									
19				Tx	CP	CP	CP	CP	CP	CP	CP	CP	CP	CP	BC ж
20					Tx	CP	▲	CP	CP	CP♠	▲	ж			
21					Tx	▲	▲	▲	▲	▲	▲	▲	▲	▲□♠	▲□ **a**

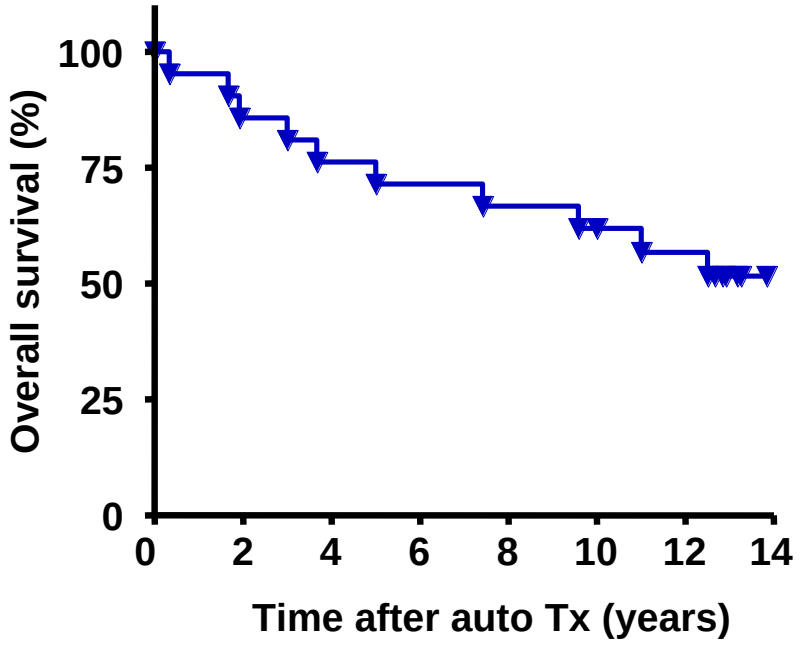
Tx = transplantation; **ж** = death; **a** = alive
▲ = CHR (complete hematologic response)
▲x = CHR without complete regeneration
○ = MCR (minimal cytogenetic remission)
● = PCR (partial cytogenetic remission)
◙ = CCR (complete cytogenetic remission)

□ = MMR (major molecular remission)
■ = CMR (complete molecular remission)
CP = chronic phase
AC = acceleration
BC = blast crisis
al.Tx = allogeneic stem cell transplantation
♠ = Start with Imatinib
♦ = Start with Nilotinib
♣ = Start with Dasatinib

Figure legends

Figure 1. Overall survival of CML patients from time of transplantation using the Kaplan-Meier method.

Figure 1.


Overall survival (%)
100
75
50
25
0
0
2
4
6
8
10
12
14
Time after auto Tx (years)