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Hematopoietic progenitor cell collection in patients with chronic myelogenous leukemia in complete cytogenetic remission after imatinib mesylate therapy

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Abstract

The introduction of BCR–ABL tyrosine kinase inhibitors such as imatinib has changed the treatment of chronic myelogenous leukemia (CML). More than 75% of patients achieve complete cytogenetic remission (CCR) after treatment with imatinib, which provides an opportunity to collect minimally involved hematopoietic progenitor stem cell (HPC) products. In order to assess the feasibility of HPC collection in patients with CML, we prospectively enrolled 24 patients who achieved CCR on therapy with imatinib. Two patients could not undergo HPC collection because of coagulopathy. A CD34+ cell yield of $2.0 \times 10^6/\text{kg}$ body weight was obtained in 16/22 (73%) patients. Patients who stopped imatinib for at least 3 weeks prior to HPC collection had significantly higher CD34+ cell yields (median: $6.52 \times 10^6/\text{kg}$ body weight) when compared with patients who continued imatinib through the collection (median: $3.74 \times 10^6/\text{kg}$ body weight). Mobilization with granulocyte colony-stimulating factor (G-CSF) did not increase the levels of BCR–ABL transcript. With a mean follow-up of 46 months, all patients but one were in CCR. In conclusion, a significant number of CD34+ cells can be safely collected in patients with CML who are on imatinib therapy, but CD34+ cell yields improve when imatinib is temporarily withheld.

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Keywords

CML; imatinib; hematopoietic progenitor cell

Introduction

Chronic myelogenous leukemia (CML) accounts for approximately 15% of cases of leukemia in adults [1]. The majority (85%) of patients present in the chronic phase at the time of diagnosis, when the disease can be readily controlled with oral tyrosine kinase inhibitors, e.g. imatinib [1]. Allogeneic hematopoietic cell transplant (HCT) remains the only curative option for patients with CML, but is associated with a high rate of treatment-related mortality and morbidity [2]. Additionally, a significant number of patients with CML are not eligible for allogeneic HCT because of factors such as age, comorbidity, or lack of a matching donor.

Autologous HCT, on the other hand, has the potential benefits of lower treatment-related mortality, high engraftment rate, and avoidance of graft-versus-host disease (GVHD) [3,4]. However, one of the major concerns with autologous HCT is contamination of the hematopoietic progenitor cell (HPC) product with clonogenic tumor cells [5]. In order to overcome this problem, a number of strategies including *in vitro* culture [6], collection of stem cells upon recovery from intensive chemotherapy [7], or selection by differences in cell surface antigen expression [8] have been employed. More recent studies have shown a high rate of collection of BCR-ABL mRNA-negative stem cells after filgrastim-induced mobilization in patients treated with imatinib [9,10].

The high rate of complete cytogenetic remission (CCR) in patients treated with imatinib provides an opportunity to collect minimally involved HPC products. In this prospective study we determined the feasibility of harvesting HPCs in patients with CML in first chronic phase who had achieved CCR following imatinib therapy.

Materials and methods

Patient eligibility

Patients were eligible if they had CML in complete hematologic and cytogenetic remission after imatinib therapy. Complete hematologic remission was defined as: white blood cell count $<10 \times 10^9/L$ with $<5\%$ basophils and no immature granulocytes on differential; platelet count $<450 \times 10^9/L$; and spleen non-palpable. Complete cytogenetic remission was defined as 0% Philadelphia (Ph)-positive metaphases in at least 20 evaluable metaphases [11,12]. Other inclusion criteria were: Zubrod performance status 2, serum creatinine <1.8 mg/dL, serum bilirubin <1.5 mg/dL, serum alanine aminotransferase (ALT) <3 times the upper limit of normal, and patients with a human leukocyte antigen (HLA)-identical sibling who refused allogeneic HCT. The study was approved by the institutional review board of the M. D. Anderson Cancer Center, and informed written consent was documented for all patients.

Stem cell mobilization and apheresis

Peripheral blood stem cells were collected after mobilization with 10 µg/kg body weight filgrastim (granulocyte colony-stimulating factor [G-CSF], Neupogen; Amgen, Inc., Thousand Oaks, CA) per day. Peripheral blood CD34⁺ cell counts were monitored by flow cytometry. Phycoerythrin (PE)-conjugated anti-CD34 and fluorescein isothiocyanate (FITC)-conjugated anti-CD45 monoclonal antibodies were supplied by BD Biosciences (Becton Dickinson, San Jose, CA). CD34⁺ cells were gated, analyzed, and reported as a percentage of white cells. Leukapheresis was started when the peripheral blood CD34⁺ cell count was 10/µL, and was performed using the COBE Spectra cell separator (COBE BCT, Inc., Lakewood, CO). Three times the estimated blood volume was processed during each collection. Anticoagulant citrate dextrose solution (ACD-A) was used as anticoagulant. Samples from leukapheresis products were collected to determine the number of CD34⁺ cells prior to freezing. Yields of collected stem cells were calculated per kilogram body weight.

Bone marrow (BM) was aspirated from the posterior iliac crest using standard techniques, under general anesthesia, with a target of at least 1×10^8 nucleated cells/kg of patient weight [13]. HPC-marrow (M) products were cryopreserved in 10% dimethylsulfoxide (DMSO), and HPC-apheresis (A) products were cryopreserved in 5% DMSO. All products were stored in vapor phase liquid nitrogen at -180°C , using standard cell therapy laboratory procedures. The option of peripheral blood versus BM harvest was discussed with the patients. The study favored BM harvest, given the significantly more experience available with this approach in CML.

Quantitative real-time polymerase chain reaction for BCR–ABL transcripts

Quantitative real-time polymerase chain reaction (RQ-PCR) analysis for the BCR–ABL fusion transcript was performed on total RNA extracted by the TRIzol method (Invitrogen, Carlsbad, CA), followed by reverse transcription with Superscript RT (Invitrogen) and PCR with TaqMan primers (Applied Biosystems, Foster City, CA) for transcripts e1a2, e13a2, e14a2, and total ABL1 transcripts in a single tube reaction, as previously described [14]. The assay had a 5-log quantitative range (demonstrated by dilution series included on every run), with copy number determined by absolute quantitation using DNA standards, and results expressed as the ratio of BCR–ABL to [BCR–ABL + ABL] levels. Major molecular response (MMR) was defined as a BCR–ABL ratio of 0.05%, based on the average levels of newly diagnosed samples in this assay, with complete molecular response (undetectable transcript) representing a 4.5–5-log reduction from average baseline levels.

Statistical analysis

Summary statistics of CD34⁺ cells, mononuclear cells (MNCs), and total nucleated cells (TNCs) were provided in the form of mean, median, and range. Values for CD34⁺ cells, MNCs, and TNCs were transformed to the logarithmic scale for all statistical analyses. Comparisons of CD34⁺ cells and TNCs between different patient groups were carried out using the analysis of variance (ANOVA) method. All tests were two-sided, and *p*-values of 0.05 or less were considered statistically significant. Pearson's correlation test was used to

estimate the correlation coefficient between age, imatinib duration, and CD34+ cell count. Statistical analysis was carried out using SAS version 9 (SAS Institute, Cary, NC).

Results

Patient and disease characteristics

Twenty-four patients were accrued between May 2003 and March 2006. Patient and disease characteristics are summarized in Table I. At the time of collection, all patients were negative for the BCR–ABL translocation by fluorescence *in situ* hybridization (FISH) analysis except one, who had 6% FISH-positive cells, but had diploid cytogenetics on standard analysis. An additional patient had trisomy 8 on conventional cytogenetic analysis. Four patients (16%) were in complete molecular remission (negative for BCR–ABL mRNA by RQ-PCR), while 18 (75%) patients showed residual BCR–ABL transcript at the time of harvest (median BCR–ABL/[BCR–ABL + ABL] percentage was 0.04, range: 0.003–10.79) (Table II).

Median BCR–ABL fusion transcript level measured by RQ-PCR was 0.04 prior to, and 0.03 after HPC collection, which was not significantly different ($p = 0.53$). This was also true for the patients who underwent G-CSF mobilization ($p = 0.52$), with nearly all patients showing less than 2–3-fold variation in pre- and post-mobilization BCR–ABL/[BCR–ABL + ABL] percentage, which is within the methodological variation of the RQ-PCR assay.

Peripheral blood stem cell collection and BM harvesting

Three patients who underwent BM harvest did not achieve the TNC goal of $1 \times 10^8/\text{kg}$ and CD34+ cell goal of $0.5 \times 10^6/\text{kg}$. Two of these patients subsequently underwent successful HPC collection by apheresis. The median post-processing storage volume for HPC-M products was 300 mL (range: 235–300). All but one patient who underwent apheresis ($n = 7$) achieved the CD34+ cell goal of $2 \times 10^6/\text{kg}$. No difference was seen in collected TNC or CD34+ cell number in patients who did or did not stop imatinib prior to HPC collection ($p > 0.1$). However, patients who stopped imatinib for at least 3 weeks ($n = 5$) prior to HPC collection had a significantly higher CD34+ cell yield (median: $6.52 \times 10^6/\text{kg}$, range: 4.76 – $10.08 \times 10^6/\text{kg}$) when compared with patients who did not stop imatinib or stopped imatinib for less than 3 weeks ($n = 16$) (median: $2.09 \times 10^6/\text{kg}$, range: 0.84 – $6.11 \times 10^6/\text{kg}$) ($p = 0.002$). Age was not significantly correlated with CD34+ cell yield (correlation coefficient $r = 0.22$, $p = 0.33$). Similarly, duration of imatinib therapy did not significantly correlate with CD34+ cell yield ($r = 0.22$, $p = 0.33$). Moreover, the dose of imatinib did not affect CD34+ cell yield. Overall, the median CD34+ cell collection was $3.74 \times 10^6/\text{kg}$ (range: 0.84 – $10.08 \times 10^6/\text{kg}$) and the median TNC collection was $3.15 \times 10^8/\text{kg}$ (range: 1.48 – $24.98 \times 10^8/\text{kg}$). The median MNC collection for HPC-A products ($n = 7$) was $11.91 \times 10^8/\text{kg}$ (range: 6.44 – $15.42 \times 10^8/\text{kg}$). Key findings are summarized in Table III.

The mean follow-up was 46 months (range: 4–70). During this period, one patient underwent allogeneic HCT from an HLA-matched related donor after developing accelerated phase CML. Another patient underwent autologous HCT 5 months after marrow collection, due to cytogenetic relapse and lack of a matching donor. This patient achieved

neutrophil engraftment on day 9 post-transplant and platelet engraftment on day 10 post-transplant. (Neutrophil engraftment was defined to have occurred on the first of 3 consecutive days that the absolute neutrophil count exceeded $0.5 \times 10^9/\text{L}$ of blood. Platelet count recovery was defined as having occurred on the day that the platelet count exceeded $20 \times 10^9/\text{L}$ of blood, independent of platelet transfusions.) Both patients were in CCR, and continued to take imatinib at the time of last follow-up. All other patients were also on imatinib, and all except one were in CCR at the time of last follow-up.

Discussion

Imatinib is considered first-line therapy for patients with CML who present in the chronic phase. Therapy with imatinib can be complicated by the development of resistance [15], and drug discontinuation is usually followed by disease recurrence [16]. Many patients who experience disease progression during imatinib therapy will respond to other tyrosine kinase inhibitors, but a significant minority will not. Allogeneic HCT is an important salvage option, but is associated with GVHD and higher risk of transplant-related mortality.

Several single-center and retrospective trials have shown that autologous HCT for CML could prolong survival [17]. However, since the advent of tyrosine kinase inhibitors such as imatinib, the number of autologous HCTs for CML has declined [18]. According to the European Group for Blood and Marrow Transplantation (EBMT), it remains considered as developmental [19]. In theory, autologous HCT can be used in patients with CML to restore susceptibility to imatinib; eliminate the Ph-positive clone with BCR–ABL mutation; and reduce disease bulk before or after imatinib [17]. Several authors have previously shown that an adequate number of Ph-negative stem cells can be collected in patients with CML who have been treated with interferon- α [20–25]. More recent studies have looked at the feasibility of Ph-negative stem cell collection in patients treated with imatinib [9,10,26–28]. A recent report showed that $>2 \times 10^6$ CD34+ cells/kg were harvested after filgrastim mobilization in a patient with CML who had received treatment with imatinib and nilotinib [29]. We therefore conducted this prospective study to evaluate the feasibility of HPC collection in patients on imatinib therapy achieving CCR. Although we favored BM harvesting, eight patients underwent apheresis, based on patient preference, inability to undergo BM harvest due to medical conditions, or after failure of adequate collection with BM harvest.

Our results also show that adequate CD34+ cell yield ($2.0 \times 10^6/\text{kg}$) was achieved in 73% of all patients who underwent collection. This observation is in accordance with the previous results of Kreuzer *et al.* [9] and Perseghin *et al.* [27], who used G-CSF for mobilization of peripheral blood stem cells. In our study, the majority of patients (64%) underwent BM harvest. The median CD34+ cell count in these patients was $2.1 \times 10^6/\text{kg}$. Although the use of G-CSF for mobilization in patients with CML has not been associated with adverse outcomes, it is worth noting that adequate numbers of CD34+ cells can be collected from BM harvests in patients on imatinib therapy. Furthermore, for two patients, in whom there was failure to collect a sufficient number of HPCs at initial BM harvest, successful mobilization and collection of HPCs by apheresis was later possible.

It has been previously suggested that therapy with imatinib can affect CD34+ cell yield. In an earlier study by Drummond *et al.* [28], in which imatinib therapy remained uninterrupted in all patients in the study, target CD34+ cell yield was achieved in only 40% of patients. Conversely, studies by Hui *et al.* [26] and Perseghin *et al.* [27] showed that interruption of imatinib therapy led to a significant increase in CD34+ cell yield. Although target CD34+ cell yield was achieved in 89% and 72% of patients in studies by Gordon *et al.* [10] and Kreuzer *et al.* [9], respectively, without any interruption of imatinib therapy, we noticed a significant increase in the yield of CD34+ cells in patients who discontinued imatinib for 3 weeks prior to collection, suggesting that withholding imatinib for a brief period of time may be a reasonable strategy in patients who are unable to undergo collection of a sufficient number of HPCs while on imatinib. Such intervention does not appear to adversely affect disease control. Although a multivariate analysis to assess other factors impacting HPC collection could not be performed due to limited sample size, our results support the view that the collection of HPCs in patients with CML can be reversibly affected by imatinib therapy.

At present, it is not clear which patients with CML achieving CCR with imatinib should undergo HPC collection (if any). It also remains to be seen whether universal collection is cost-effective, or a risk-adapted approach is needed. Further research may identify subsets of patients with CML who may benefit from pre-emptive HPC collection in a cost-effective manner [30].

In conclusion, we have demonstrated the feasibility of collection of adequate numbers of CD34+ stem cells in patients who achieve CCR on imatinib therapy. Accrual to this study was very slow, and only one autologous transplant was performed. The development of newer tyrosine kinase inhibitors continues to change the management of this disease, and it remains to be proven that autologous HCT will ever have a role in the management of CML. Further studies are also needed to evaluate the engraftment potential of HPCs collected in these patients.

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Table I

Patient and disease characteristics.

Characteristic	Value
Total number of patients enrolled (<i>n</i>)	24
Sex (female/male)	15/9
Mean age, years (range)	42.5 (25–62)
Method of collection (<i>n</i>)	
BM harvest	14
Apheresis	6
BM harvest followed by apheresis *	2
Did not undergo collection †	2
Median duration of imatinib therapy, months (range)	29.5 (11–57)
Median time from diagnosis to collection, months (range)	32.5 (13–134)
Median time to CCR, months (range)	13.5 (4–39)
Prior treatment (<i>n</i>)	
IFN-α	1
IFN-α + Ara-C	6
IFN-α + Ara-C + hydroxyurea	1
IFN-α + Ara-C + homoharringtonine	1

* Two patients did not yield sufficient numbers of stem cells with BM harvest and subsequently underwent apheresis.

† Did not undergo collection due to coagulopathy.

BM, bone marrow; CCR, complete cytogenetic remission; IFN-α, interferon-α; Ara-C, cytarabine.

Table II
Patient characteristics and hematopoietic progenitor cell yields in patients with chronic myelogenous leukemia who achieved complete cytogenetic remission after imatinib therapy.

Patient number	Age (years)	Sex	CML		Duration of imatinib prior to HPC collection (months)	Duration of CCR prior to HPC collection (months)	Total number of prior therapies	Method of HPC collection	Number of aphereses	Preparative regimen	CD34+ yield (× 10 ⁶ /kg bw)	TNC yield (× 10 ⁸ /kg bw)	BCR-ABL mRNA		BCR-ABL mRNA RQ-PCR prior to HPC collection	BCR-ABL mRNA RQ-PCR after HPC collection	Duration of follow-up (months)	Current outcome	Comments
			duration prior to HPC collection (months)	duration prior to HPC collection (months)															
1	46	M	35	30	15	2	2	PBSC	5	G-CSF	4.736	24.976	0.0138	1.04	0.0138	1.04	70	MR	Allogeneic HCT; trisomy 8
2	46	F	36	32	14	1	1	BM/PBSC	2	None/ G-CSF	4.757	9.609	0.03	0.03	0.03	0.03	45	MR	
3	42	F	22	18	2	1	1	BM		None	2.045	1.61	0.1858	0.834	0.1858	0.834	59	CCR	
4	30	F	69	41	30	2	2	BM		None	0.994	1.482	0.524	1.11	0.524	1.11	58	CCR	
5	30	F	30	30	10	1	1	BM		None	1.23	2.46	0.1776	NA	0.1776	NA	24	CCR	
6	54	F	13	11	1	1	1	BM		None	2.106	2.7	0	0	0	0	59	MR	
7	53	F	57	31	36	2	2	BM		None	0.843	2.056	0	0.0051	0	0.0051	53	MR	
8	27	M	72	46	37	2	2	BM		None	5.367	3.155	10.7952	25.53	10.7952	25.53	55	CCR	Autologous HCT; 6% FISH-positive cells [*]
9	59	F	56	35	43	2	2	BM		None	4.377	3.474	0.0275	0.054	0.0275	0.054	58	CCR	
10	45	F	24	23	16	1	1	NA		None	NA	NA	NA	NA	NA	NA	NA	CCR	Coagulopathy; not collected
11	58	F	27	22	14	1	1	PBSC	3	G-CSF	1.359	14.58	0.0693	0.0796	0.0693	0.0796	55	MR	
12	51	M	56	22	34	2	2	BM		None	3.744	3.6	0	0	0	0	12	MR	
13	29	M	30	29	2	1	1	BM		None	3.863	2.384	0.0446	0.02	0.0446	0.02	4	CCR	
14	25	M	25	23	18	1	1	BM		None	2.075	3.055	0.0032	0.02	0.0032	0.02	52	CCR	
15	39	M	55	43	43	2	2	BM		None	2.7	2.73	0	0	0	0	48	MR	
16	51	F	43	43	34	1	1	BM		None	NA	NA	0.058	0.003	0.058	0.003	53	MR	Failed to collect any cells
17	29	M	17	16	9	1	1	BM/PBSC	2	None/ G-CSF	6.942	11.679	0.15	0.1	0.15	0.1	47	MR	
18	30	F	19	19	5	1	1	BM		None	2.058	2.572	0.23	0.02	0.23	0.02	49	CCR	
19	51	F	134	53	98	2	2	NA		None	NA	NA	NA	NA	NA	NA	NA	MR	Coagulopathy; not collected
20	62	F	29	28	21	1	1	PBSC	3	G-CSF	6.107	16.584	0.04	0	0.04	0	44	MR	
21	47	F	52	36	28	2	2	PBSC	2	G-CSF	5.903	6.838	0.02	0.01	0.02	0.01	46	MR	

Patient number	Age (years)	Sex	CML duration prior to HPC collection (months)	Duration of imatinib prior to HPC collection (months)	Duration of CCR prior to HPC collection (months)	Total number of prior therapies	Method of HPC collection	Number of aphereses	Preparative regimen	CD34+ yield ($\times 10^6$ /kg bw)	TNC yield ($\times 10^8$ /kg bw)	BCR-ABL mRNA RQ-PCR		Duration of follow-up (months)	Current outcome	Comments
												prior to HPC collection	after HPC collection			
22	55	F	17	16	13	1	PBSC	3	G-CSF	6.517	18.276	0.06	0.09	43	CCR	
23	44	M	59	57	51	1	PBSC	2	G-CSF	10.075	13.167	0.04	0.05	32	CCR	
24	27	M	27	26	14	1	BM		None	1.052	1.785	0.62	0.53	41	CCR	

* Positive for BCR-ABL translocation.

PBSC, peripheral blood stem cells; BM, bone marrow; G-CSF, granulocyte colony-stimulating factor; NA, not available; RQ-PCR, quantitative real-time polymerase chain reaction; CCR, complete cytogenetic remission; MR, molecular remission; HPC, hematopoietic progenitor cell; bw, body weight; HCT, hematopoietic cell transplant; FISH, fluorescence in situ hybridization.

Table III

Results of TNC and CD34+ cell collection.

Total patient number (<i>n</i> = 21)*	Median CD34+ cell number ($\times 10^6$) (range)	Median TNC number ($\times 10^8$) (range)
Sex (<i>n</i>)		
Male (9)	3.86 (1.05–10.08)	3.16 (1.79–24.98)
Female (12)	2.08 (0.84–6.52)	3.09 (1.48–18.28)
<i>p</i> -Value [†]	0.21	0.88
Imatinib held (<i>n</i>)		
Yes (12)	3.42 (0.84–10.08)	8.22 (1.48–18.28)
No (9)	3.74 (1.23–5.37)	2.73 (1.61–24.98)
<i>p</i> -Value	0.9	0.18
Imatinib held for 3 weeks (<i>n</i>)		
Yes (5)	6.52 (4.76–10.08)	11.68 (6.84–18.28)
No (16)	2.09 (0.84–6.11)	2.72 (1.48–24.98)
<i>p</i> -Value	0.002	0.009
Source of stem cells (<i>n</i>)		
PBSCs (8) [‡]	6.01 (1.36–10.08)	13.87 (6.84–24.98)
BM (13)	2.08 (0.84–5.37)	2.57 (1.48–3.6)

* One patient who underwent BM harvest failed to collect any cells and was not included in analysis. Two patients did not undergo collection due to coagulopathy.

[†] *p*-Values based on ANOVA on the logarithmic scale.

[‡] Includes patients who failed BM harvest but subsequently underwent apheresis (*n* = 2).

TNC, total nucleated cell; PBSC, peripheral blood stem cell; BM, bone marrow.