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Collection of Ph-negative progenitor cells from interferon responsive patients with chronic myeloid leukemia: effect of granulocyte-colony-stimulating factor mobilization

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ABSTRACT

Background and Objectives. **The observation that patients with chronic myeloid leukemia (CML) may relapse following stem cell transplantation because of Philadelphia positive cells contaminating the graft have led to a variety of strategies to reduce this contamination. This study investigate the feasibility of collective, Ph-re cells from patients with CML in chronic phase.**

Design and Methods. **A total of 18 patients with chronic myeloid leukemia in chronic phase who had responded to varying degrees to treatment with interferon-α (IFN) were subjected to mobilization with granulocyte colony-stimulating factors and peripheral blood progenitor cell collection. Nine patients were in complete cytogenetic remission (CCR) and nine were partial responders. IFN was stopped 2 to 4 weeks before the procedure. G-CSF was given by subcutaneous injection once daily at a dose of 10 µg/kg.**

Results. **Five patients underwent one collection procedure only, 10 underwent two procedures and 3 patients had three collections. The median number of nucleated cells (NC) per patient collected was 10.2×10^8/kg (4.4-19.7) and the median number of $CD34^+$ cells was 2.5×10^6/kg (0.4-9.4). Analyzable cytogenetic data were available for 26/34 (76%) leukapheresis procedures. The median percentage of Ph- negative metaphases for patients in CCR was 100% (73-100). Patients not in CCR had a higher level of Ph^- positive cells in their collections (median 23%, range 0-79%, p=0.01). Of the nine patients in CCR, 8 had at least one apheresis from which progenitor cells were 100% Ph^- negative; conversely, patients not in CCR had detectable Ph positive cells in every collection. Four patients have undergone autologous stem cell transplantation.**

Interpretation and Conclusions. **It was possible to collect sufficient Ph negative progenitor cells from patients in CCR but collections from other patients contained significant numbers of Ph-positive cells.**

Key words: chronic myeloid leukemia, Ph-negative, stem cells, autografting

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Chronic myeloid leukemia (CML) is characterized by the presence of a chromosomal marker, the Ph- chromosome in all cells of the clone.[1] Allogeneic stem cell transplantation (SCT) is the only potentially curative therapy for CML but is applicable only in a minority of patients: those who are under the age of 60 years and have an HLA compatible donor.2

Recombinant interferon-α (IFN) can induce complete hematologic responses in 70-80% of patients and complete or major cytogenetic responses in 25 to 30% of patients.[3,27] The addition of cytarabine (Ara-C) to IFN can increase the major cytogenetic response rate to 40%.[4] However, despite prolonged survival, most patients who respond to IFN remain positive, as detectably by polymerase chain reaction (PCR), for the BCR-ABL transcript.[3]

Therefore, the majority of patients with CML do not benefit from allogeneic SCT or IFN therapy. For this group of patients different strategies have been developed, including intensive chemotherapy and autologous SCT.[5-8] Previous studies have indicated that autologous SCT should be performed in chronic phase as results for patients in advanced phase are very poor.[7,9] The observation that relapse can occur, in part, due to the presence of Ph- positive cells contaminating the graft[10] has led to a variety of strategies to obtain a Ph- negative graft. *In vitro* techniques, such as culture of the stem cells with cyclophosphamide,[11] interferon,[12] anti-sense oligonucleotides,[13] immunologic selection[14] or long-term cultures[15] have been applied but without clear benefit.

A novel strategy consists in the collection of stem cells after mobilizing chemotherapy with or without G-CSF.[16-19] The Genoa group has demonstrated promising results in patients with early chronic phase disease, with the proportion of patients achieving a Ph- negative collection reaching almost 100%. Patients subsequently autografted achieved complete or major cytogenetic remission in 84% of cases.[20]

Granulocyte colony-stimulating factor mobilizes peripheral blood progenitor cells (PBPC) in patients with malignancies and in healthy donors.[21,22] Since IFN can induce cytogenetic responses in CML patients, it could therefore be considered as another form of *in vivo* purging. Ph- negative bone marrow harvests have been obtained from IFN responders[23] but the number of progenitor cells was very low. Two French groups[24,25] have explored the possibility of

Table 1. Clinical characteristics of 18 patients undergoing G-CSF mobilization.

	Median or Number	*Range or %*
Age at diagnosis	38.5 years	25.0-55.2
Sex (M/F)	9/9	50/50
Previous treatment		
Busulphan	3	17
Hydroxyurea	18	100
Ara-C	2	11
Autografting	2	11
Response to IFN		
Complete remission	9	50
Major response	2	11
Partial response	5	28
Minima response	2	11
Duration of IFN therapy	17 months	3-35
Interval diagnosis-harvest	25 months	7-42

collecting PBPC from IFN responsive CML patients after G-CSF mobilization. The study reported here evaluates the feasibility of harvesting PBPC from CML patients with a variety of degrees of cytogenetic response to IFN or any other therapy (from minimal to complete) and their use in autologous SCT at the time of disease progression. PBPC were collected after G-CSF priming.

Design and methods

Patients

A total of eighteen patients with CML in chronic phase were entered into this study. They had received treatment with IFN for a median of 17 months (3-35). Their median age was 38.5 years (25-55.2). Nine were male and nine female. CML had been diagnosed a median of 25 months (7-42) prior to entering the study. Previous treatments included busulfan, hydroxyurea, Ara-C and autologous SCT (Tables 1 and 4).

At the time of entering the study, all patients were in complete hematologic remission (or with slightly decreased peripheral blood counts). Nine (50%) patients were in complete cytogenetic remission (CCR) defined by the absence of Ph- positive metaphases in the bone marrow by conventional cytogenetics. Two patients (11%) were in major cytogenetic response (MCR) defined by >65% of Ph- negative metaphases. Five (28%) patients had between 35% and 65% of Ph- negative metaphases (partial response, PR) and two (11%) patients had less than 35% Ph- negative metaphases (minimal cytogenetic response, mCR).

All patients were receiving IFN at the time of entering the study. One patient underwent a second PBPC collection at a time when she was partially Ph- negative (10%) following autologous SCT. One patient was in second chronic phase following chemotherapy for lymphoblastic transformation. In addition, two patients had been treated with subcutaneous Ara-C concurrently with IFN. The median dose of IFN at time of entry was 30 MU per week (3-42) and the highest IFN dose had ranged between 15 and 63 MU per week.

Mobilization procedure

IFN therapy was discontinued for 2-4 weeks before commencing G-CSF mobilization. G-CSF (Lenograstim, Chugai-Rhône-Poulenc or Filgrastim, Amgen) was administered subcutaneously once daily at a dose of 10 µg/kg until the leukapheresis was completed. Peripheral blood stem cell harvests were performed with a Cobe Spectra cell separator. The target cell dose was 10×10^8 nucleated cells (NC)/kg or alternatively 1.5×10^6 $CD34^+$ cells/kg.

The decision to commence leukapheresis depended upon the white cell count (WCC) on day 4 and/or day 5 ($>15\times10^9$/L). Although some patients were monitored by peripheral blood $CD34^+$ cell counts, this did not influence the decision to proceed to leukapheresis. PBPC collections started on day 4 in twelve patients and on day 5 for the remaining six patients.

Apheresis products were cryopreserved in 10% DMSO and autologous plasma using a controlled-rate freezer and stored in liquid nitrogen. Each daily collection was assessed for total nucleated cell count, $CD34^+$ cells and cytogenetics.

A collection was deemed to be *successful* if the sum of each patient's collections was greater than the target cell dose and there was no evidence of the Ph-chromosome in the cytogenetics assay. A collection was regarded as *sufficient* if more than the target cell dose was collected but there was any degree of contamination by Ph- positive metaphases. A collection was *inadequate* if less than the target cell dose was achieved irrespective of the results of the cytogenetic analysis.

Autografting procedure

Patients proceeded to autologous SCT when their disease progressed. Cytoreduction was achieved with busulfan alone as previously described.[8] Interferon therapy was resumed at low dosages upon normalization of blood count after SCT.

Results

Mobilization and harvest procedures

A total of 34 leukapheresis procedures were analyzed in this study. Five patients underwent just one leukapheresis. Ten patients needed two collections and three patients required three collections to obtain sufficient PBPC. Therapy was well tolerated with no cases of grade 2 or greater WHO toxicity. The most common side effect was bone pain (63% of patients). All patients regained identical hematologic control after stopping G-CSF and re-starting IFN.

Median yields for NC and $CD34^+$ cells are summarized in Table 2. The median NC per patient was 10.2×10^8/kg (4.4-19.7) and the median $CD34^+$ cell dose per patient was 2.5×10^6/kg (0.4-9.4). NC and CD34+ yields in the first apheresis were equivalent

Table 2. Stem cell yield and number of leucapheresis of 18 patients undergoing G-CSF mobilisation.

	Median or Number	*Range or %*
Number of leukapheresis		
One	5	28
Two	10	56
Three	3	16
Median NC/kg per patient	10.2×10^8	4.4-19.7
Median CD34+/kg per patient	2.5×10^6	0.4-9.4
Target cell dose*		
$>10\times10^6$ NC/kg	13	72
$>1.5\times10^6$ CD34+/kg	10	56
Failed	2	11

Table 3. Cytogenetics analysis: Leucapheresis evaluation.

% of Ph⁻	*CCR patients (n=9) 18 apheresis*	*Non CCR patients (n=9) 16 apheresis*	*Total (n=18) 34 apheresis*
100%	9 (50%)	0 (0%)	9 (26%)
36-99%	3 (17%)	4 (25%)	7 (21%)
0-35%	0 (0%)	10 (63%)	10 (29%)
Failed	6 (33%)	2 (12%)	8 (24%)

Table 4 (a). Treatment details and characteristics of individual collections of 9 patients undergoing G-CSF mobilisation in complete cytogenetic remission.

UPN	*Duration of IFN*	*Other Treatment*	*Apheresis No.*	*MNC x 10^8/kg*	*CD34 x 10^6/kg*	*% Ph negative*	*No. Metaphases*
1	15 months	HU	1	8.5	0.17	Failed	na
			2	6.8	0.33	100	10
2	18 months	HU	1	6.69	1.81	100	10
3	22 months	HU	1	3.91	0.39	Failed	na
			2	4.8	0.91	100	10
4	14 months	HU	1	5.82	4.05	Failed	na
			2	2.84	2.67	100	14
5	35 months	HU, BU	1	4.56	0.96	96	52
			2	5.04	1.59	100	38
6	12 months	HU	1	6.03	na	Failed	na
			2	7.3	na	100	30
7	17 months	HU	1	3.33	na	97	28
			2	2.33	na	Failed	na
			3	3.65	na	100	24
8	27 months	HU, PQT	1	3.18	na	100	10
			2	3.6	na	Failed	na
			3	3.14	na	73	26
9	20 months	HU	1	7.1	2.06	100	20

Table 4 (b). Treatment details and characteristics of individual collections of 9 patients undergoing G-CSF mobilisation in partial cytogenetic remission.

UPN	*Duration of IFN*	*Other Treatment*	*% Ph negative at harvest*	*Apheresis no.*	*MNC x 108/kg*	*CD34 x 106/kg*	*% Ph negative*	*No. Metaphases*
10	10 months	HU, Autograft	7%	1	8.29	5.3	0	30
				2	8.11	4.06	5	20
11	3 months	HU, Ara-C Autograft	10%	1	6.5	0.36	20	20
				2	4.28	0.39	0	20
				3	5.53	0.66	5	20
12	28 months	HU, Ara-C	44%	1	6.84	0.47	30	28
				2	12.89	2.06	65	20
13	6 months	HU	48%	1	14.1	11.8	60	20
14	14 months	HU, BU	51%	1	4.43	0.47	78	27
15	12 months	HU	53%	1	4.9	na	23	22
				2	5.3	na	Failed	na
16	24 months	HU, BU	57%	1	10.6	3.06	16	25
				2	7.12	5.23	33	15
17	17 months	HU	70%	1	7.7	0.62	Failed	na
				2	7.7	1.13	71	14
18	18 months	HU	73%	1	8.2	2.51	93	30

UPN: Unique Patient Number. IFN: Interferon alpha. Hu: Hydroxyurea. BU: Busulfan. PQT: Poly-Chemo-Therapy, Vincristine, Daunorubicin, Prednisolone, Adriamycin, and Cyclophosphamide.

compared with apheresis numbers 2 (10 patients) and 3 (3 patients).

The median WCC on the first day of apheresis was 27.7×10^9/L (14.3-57.8). There was a correlation between WCC and NC but not with $CD34^+$ count on each apheresis (data not shown). The proportion of patients reaching cumulative target cell dose with one, two or three apheresis showed that 44% achieved the target after a single leukapheresis although three of these patients proceeded to a second collection. Three patients (17%) needed three collections.

Overall, all but two patients achieved the scheduled target cell dose (Table 2). Thirteen patients mobilized more than 10×10^8 NC/kg, and six of these patients also had more than 1.5×10^6 $CD34^+$ cells/kg. Four additional patients had more than $1.5\times10^6CD34^+$ cells/kg despite a lower NC yield. Of the two patients with inadequate yield, one refused to have further collections. There were no differences in the NC or $CD34^+$ yield between patients in CCR and not in CCR.

Cytogenetic analysis

Of the 34 leukaphereses performed, cytogenetic analysis was available in 26 cases (Tables 3 and 4). In eight cases the cytogenetic study failed or yielded too few metaphases. All eighteen patients had at least one successful cytogenetic test performed on one collection. The median number of metaphases analyzed per apheresis was 20 (10-52). Details of individual leukapheresis yields and proportion of Philadelphia negative metaphases on each collection are shown in Table 4.

The median percentage of Ph- negative metaphases was 79% (0-100). The median percentage of Ph- negative metaphases for patients in CCR was 100% (73-100). In contrast, patients not in CCR had a higher Ph- positive contamination (median 23%, range 0-79%), which was statistically significant (p=0.01). A total of 9 leukaphereses from eight patients (all of them in CCR) were 100% Ph- negative. Only 3 leucaphereses from CCR patients were found to have Ph- positive contamination (3%, 4% and 27).

Patient evaluation

In order to evaluate the efficacy of G-CSF mobilization we divided the patients into CCR and non-CCR groups (Figure 1). Of the nine patients in CCR, eight had at least one apheresis that was 100% Ph- negative. In four of these patients a *successful* collection was obtained (see *Design and Methods* section for definitions); in another four the collection was *sufficient* but not enough Ph- negative cells could be harvested, and one patient failed to mobilize an adequate number of PBPC. However, on six occasions the cytogenetic analysis failed, including in two patients who may have achieved a successful collection.

Of the nine patients with a less than complete cytogenetic response, eight had sufficient PBPC collected and only one patient had an inadequate collection. Not unexpectedly, none of these patients achieved a successful collection. An increase in the percentage of Ph- negative cells was found in 4 (45%) patients, although no patient improved the degree of cytogenetic response (MCR, PR and mCR) when compared to the previous bone marrow assessment.

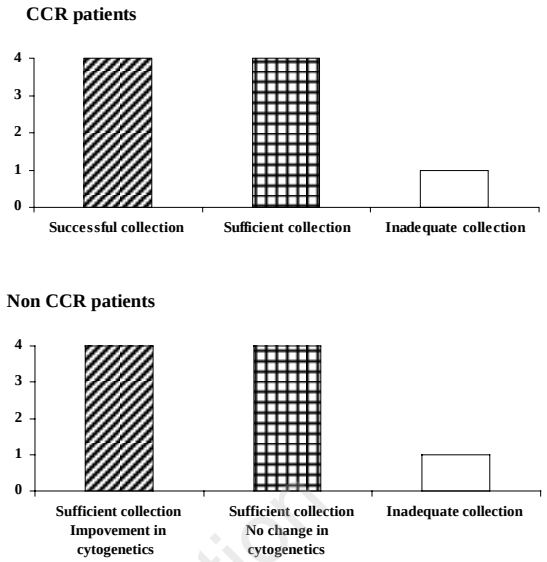

Figure 1. ***Successful collection:*** **cumulative Ph- negative cell dose > 10×10^8 NC/kg and/or > 1.5×10^6 $CD34^+$/kg.** ***Sufficient collection:*** **Cumulative stem cell dose > 10×10^8 NC/kg and/or > 1.5×10^6 $CD34^+$/kg but Ph- negative cells < 10×10^8 NC/kg and < 1.5×10^6 $CD34^+$/kg.** ***Inadequate collection:*** **Cumulative stem cell dose < 10×10^8 NC/kg and < 1.5×10^6 CD34+/kg, independent of cytogenetics.**

Autografting

Four patients have undergone autologous SCT using the material collected after G-CSF mobilisation. In three patients the indication for SCT was progression at the chromosomal level while in the remaining patient the reason was consolidation of second chronic phase after lymphoid blastic transformation.

Neutrophil (>0.5×10^9/L) and platelet (>50×10^9/L) engraftment occurred at a median of 17.5 days (12-25) and 25 days (14-120+), respectively. One patient had not engrafted platelets by day +120. The cells in this patient were collected in second chronic phase after 2 courses of chemotherapy for lymphoblastic transformation. Cytogenetic responses following autologous SCT varied from 100% Ph- negative to 100% Ph- positive and correlated with Ph- status of the collection. One patient has undergone unrelated donor allogeneic SCT. The three remaining patients continue in second chronic phase.

Discussion

This study confirms the feasibility of obtaining Ph-negative progenitors from patients with CML and various degrees of cytogenetic response to IFN using G-CSF mobilization. In addition, G-CSF can mobilize PBPC from patients who achieve cytogenetic

response after other treatment modalities such as autologous SCT and combination chemotherapy. G-CSF was well tolerated and produced no effect on the Ph- positive clone since the same level of cytogenetic response persisted after the procedure in all patients.

This procedure may produce better results than bone marrow harvesting since IFN-related marrow hypoplasia greatly impairs the collection of stem cells, even when IFN has been discontinued for several weeks.[23]

One of the goals of the study was to assess the possibility of preferentially mobilizing Ph- negative stem cells from patients with partial cytogenetic response. It is accepted that growth factor can stimulate proliferation equally in both normal and CML progenitor cells. However, some patients who relapse after allogeneic SCT may achieve remission after G-CSF and this has been attributed to a preferential effect of G-CSF on Ph- negative cells.[26] We have shown that in the majority of patients with CCR, complete Ph- negative collections can be obtained. Approximately half of the patients with partial cytogenetic remission had a relative increase in the percentage of Ph- negative cells collected as compared with the bone marrow assessment prior to the mobilization. However, in no patient was the category of cytogenetic response changed.

Interferon was stopped at least 2 weeks before G-CSF mobilisation in order to minimize any potential deleterious effect on the mobilization. No disease progression was observed during this discontinuation of IFN. The median WCC at the time of the first leukapheresis (4-5 days of G-CSF) was comparable to the WCC reported in healthy donors and patients with solid tumors. In fact, the WCC and stem cell yields were similar to those reported by other groups in patients with CML who continued on IFN.[24,25] Few patients needed to proceed to a second or third collection and no patient underwent more than 3 aphereses.

It was relatively easy to collect sufficient Ph- negative cells from patients in CCR. However, this group of patients may benefit less from this approach since their disease would be likely to have a benign prognosis. It is the group of patients with partial response to IFN who would benefit most from the collection of partially negative PBPC. Such patients could be autografted with this material in the case of disease progression (which will inevitably occur in the short-medium term) or in order to improve cytogenetic response. Carella *et al.* in Genoa have pioneered the use of Ph- negative progenitor cells collected after high dose chemotherapy in patients with CML.[16,17,20] Best results have been obtained in patients in early chronic phase. In a similar way IFN could be considered an alternative method of *in vivo* purging, but with overall less toxicity.

IFN can result in some degree of cytogenetic response in more than 50% of patients[27] and, according to our study and other observations, it is possible to collect Ph- negative stem cells from the majority of these patients. A substantial number of patients with CML can, therefore, be autografted with Ph-negative material. Recent reports have shown that there is a correlation between the percentage of Ph-negative cells in the graft and the degree of cytogenetic response after autologous SCT.[16,20,28] However, the ability of such transplants to reconstitute mainly Ph- negative hemopoiesis long-term needs to be investigated. The advent of new drugs (such as Novartis STI-571) may increase the proportion of patients from whom Ph- negative PBPC could be collected.

In our study, four patients have been autografted with the material collected after G-CSF mobilization. No major problems with engraftment were seen. Cytogenetic outcome correlated with the cytogenetic status of the PBPC collection, as previously described.[24,28] However, more patients, longer follow-up and perhaps additional measures such as post-SCT immunomodulation are needed to establish the role of autologous SCT with Ph- negative PBPC in the management of CML.

Potential implications for clinical practice

All patients achieving any degree of cytogenetic response to IFN or other therapy should be considered for PBPC harvesting. This parallels the recommendation made some time ago by this institution that all CML patients should have PBPC collected at diagnosis.

Contribution and Acknowledgments

EO is the main contributor to this paper and the leading investigator for this study. All other authors have contributed to the design of the trial, the interpretation of data, the revision of the maniscript and final approval. EO, EK, NP and JG have been responsible for the editorial work. The authors are grateful to the members of the stem cell lab and the haematology day care unit for their work in dealing with patients and leucapheresis procedures.

Disclosures

Conflict of interest: none

Redundant publications: no substantial overlapping with previous papers.

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