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Collection of Philadelphia-negative stem cells using recombinant human granulocyte colony-stimulating factor in chronic myeloid leukemia patients treated with α-interferon

JUAN-CARLOS HERNÁNDEZ-BOLUDA,* ENRIC CARRERAS,* FRANCISCO CERVANTES,* PEDRO MARÍN,° EDUARDO ARELLANO-RODRIGO,* MONTSERRAT ROVIRA,* FRANCESC SOLÉ,# ELISABET LLOVERAS,# BLANCA ESPINET,# AGUSTÍN OCEJO,* EMILI MONTSERRAT*

*BMT Unit, Institute of Hematology and Oncology, Department of Hematology; °Blood Bank, Hospital Clínic, IDIBAPS; #Cytology Laboratory, Hospital del Mar, Barcelona, Spain

Correspondence: Dr. Enric Carreras, MD, BMT Unit, Hematology Department, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain.
Phone/Fax: international +34.9.32275428.
E-mail: carreras@clinic.ub.es

Background and Objectives. Autologous stem cell transplantation is a therapeutic option for chronic myeloid leukemia (CML) patients who are not candidates for allogeneic transplant. To reduce the risk of post-autografting disease recurrence, different strategies of stem cell selection have been attempted. The results of using recombinant human granulocyte colony-stimulating factor (rHuG-CSF) for harvesting hematopoietic progenitors in CML patients treated with interferon-α (IFN) are reported.

Design and Methods. Twenty-one CML patients who received IFN for a median of 21 (8-68) months were mobilized with rHuG-CSF (10 μg/kg/day). Twelve were in complete (CCR) or major (MCR) cytogenetic response. Complete success was considered a sufficient harvest (> 1×10^6/kg $CD34^+$ cells/kg) without Philadelphia $(Ph)^+$ metaphases in at least one apheresis; a partial success was a sufficient harvest with 1-35% Ph^+ cells.

Results. A total of 78 aphereses were performed. No patient had major side-effects. The median number (range) of mononuclear and $CD34^+$ cells obtained was, respectively, 8.6×10^8/kg (0.9-22.6) and 3.3×10^6/kg (0.4-26.3) per patient. A sufficient cell yield was collected in all but three patients. A complete/partial success was achieved in seven CCR/MCR patients (63%) and in three (33%) with other responses. Four patients underwent successful autografting using the stem cells obtained after rHuG-CSF mobilization.

Interpretation and Conclusions. Mobilization of IFN-treated patients using rHuG-CSF is safe and provides a significant proportion of Ph–negative progenitors in CML patients in complete or major cytogenetic response.

Key words: chronic myeloid leukemia, interferon, mobilization, rHuG-CSF, autografting.

To date, allogeneic stem cell transplantation is the only therapy with the potential to cure patients with chronic myeloid leukemia (CML).[1] However, since less than 30 percent of patients are candidates for allogeneic transplantation because of lack of a donor or age limitations, alternative therapies are required. The rationale for the use of autologous stem cell transplantation (ASCT) is the coexistence of normal hematopoietic progenitors with their malignant counterparts in the marrow and blood of CML patients, such that these progenitor cells are temporarily able to restore a Ph-negative hematopoiesis following autograft.[2]

Evidence of the role of Ph^+ cells contaminating the graft in the recurrence of CML after autologous transplantation[3] has led to the development of different strategies to improve stem cell selection. *In vitro* purging techniques[4] have resulted in significant decreases in the proportion of Ph^+ cells in the inoculum. *In vivo* purging is an alternative approach to obtaining Ph-negative cells. In this context, interferon-α (IFN) is able to induce 20-30% major cytogenetic responses in the early chronic phase of CML.[5,6] However, given the difficulties in collecting a sufficient number of progenitors for autografting in IFN-treated patients, the use of recombinant human granulocyte colony-stimulating factor (rHuG-CSF) for stem cell mobi-

Table 1. Main clinicohematologic characteristics at time of mobilization with rHuG-CSF in 21 Ph-positive CML patients treated with IFN.

	Median (range)	*No. of patients*
Age, yrs.	43 (16-61)	
Sex (M/F)		14/7
Previous treatment		
Busulfan		1
Hydroxyurea		18
Busulfan and hydroxyurea		1
ABMT*		1
Response to IFN		
Complete cytogenetic response		5
Major cytogenetic response		7
Minor cytogenetic response		3
Minimal cytogenetic response		2
Hematologic response only		4
Time lapse diagnosis-harvest, months	36 (13-102)	
WBC count, $\times 10^9$/L	3.8 (2-8.9)	
Platelet count, $\times 10^9$/L	126 (86-899)	

**Autologous bone marrow transplantation.*

lization has recently been evaluated.[7-11]

The aim of the present study is to provide further information on the use of rHuG-CSF in harvesting hematopoietic progenitor cells in CML patients treated with IFN.

Design and Methods

Patients

From January 1995 to November 1999, 21 patients diagnosed with chronic phase Ph+ CML and treated with IFN were enrolled in the present study. Their main clinicohematologic characteristics and previous therapies are shown in Table 1. At the time of study entry, all patients were receiving IFN and had been on this treatment for a median time of 21 months (range, 8-68); in two cases IFN treatment was associated with intermittent subcutaneous low-dose cytarabine. Disease status was evaluated within the month prior to mobilization by means of physical examination, complete blood counts, and bone marrow cytogenetic analysis.

Mobilization procedure

rHuG-CSF was given at a dose of 10 μg/kg/day s.c. for six consecutive days unless the WBC count increased up to 70×10^9/L or significant side-effects appeared. Prior to 1997, the policy was to discontinue IFN administration either 14 days earlier (n = 8) or the day before (n = 2) starting rHuG-CSF. From 1997, IFN was maintained during the mobilization (n = 11). Apheresis sessions were started on day 3 (until 1997) or 4 (thereafter) of rHuG-CSF administration and performed with a Fenwald CS3000-plus blood-cell separator (Baxter, Deerfield, Ill, USA) for four consecutive days; 10 liters of blood were processed daily, at flow rates of 50-60 mL/min using antecubital veins. To evaluate the results, a complete success was considered when the sum of the patient's collections reached the target cell dose (> 1×10^6 CD34+ cells/kg)[12,13] without detectable Ph+ metaphases, whereas a partial success was considered when the target cell dose was collected but with 1-35% Ph+ cells; other situations were regarded as a failure. In the latter cases, an additional harvest was considered using rHuG-CSF at a dose of 24 μg/kg/day s.c. three months later, while the patient had discontinued IFN treatment. Successful harvests were cryopreserved in DMSO without further manipulation.

Cytogenetic studies

Prior to mobilization, cytogenetic studies were carried out on both the patients' marrow and each of the apheresis products. Conventional G-banding analysis was performed on a minimum of 10 metaphases using short (24h) cultures without addition of mitogens. Complete cytogenetic response (CCR) was defined as no detectable Ph-positive marrow metaphases, major cytogenetic response (MCR) as 1-34% Ph+ metaphases, minor cytogenetic response (mCR) as 35-64% Ph+ metaphases, minimal cytogenetic response as 65-99% Ph+ metaphases, and hematologic response as normalization of the blood cell counts without a decrease in the Ph+ marrow cells.[5] Fluorescence *in situ* hybridization (FISH) studies for the BCR-ABL rearrangement were carried out on interphase cells using the LSI bcr spectrum green/abl spectrum orange probe (Vysis, Downers Grove, USA). The technique was performed as described in the proceedings supplied by the manufacturer, with a total of 100 evaluable interphase nuclei being analyzed per sample. In order to rule out false-positive cases due to the coincidental co-localization of the two signals, at least 10 interphase nuclei showing the BCR-ABL fusion gene were required to consider a result as positive.[14]

Statistical methods

Correlations were studied by the Spearman rank and Mann-Whitney rank sum tests. Fisher's exact probability test and Student's t-test were used to compare categorical and continuous variables, respectively. *p* values were considered statistically significant if < 0.05. All computations were performed using Statistica software (Statsoft Inc., Tulsa, OK, USA).

Table 2. Data on previous treatment and total cell yield of the harvest.

Pat. #	Prior treat.* (mos.)	IFN ther. (mos.)	IFN during mobilization	No. of aphereses	MNC° (10^9/kg)	CD34+ (10^6/kg)
1	HU (1)	46	maintained	4	17	2.5
2	HU (1)	36	maintained	4	19.6	3.9
3	BU/HU (22/36)	27	maintained	4	7.3	1.3
4#	HU (6)	20	maintained	2	6	0.4
5	HU (7)	12	maintained	4	7.5	3.9
6	HU (6)	23	maintained	3	4.6	0.6
7	HU (6)	21	maintained	4	9.5	1.9
8	HU (6)	18	maintained	4	13.5	1.8
9	HU (60)	50	maintained	4	7.5	1.1
10	HU (1)	11	maintained	4	0.9	0.7
11	HU (48)	37	maintained	4	6.2	4.7
12	BU (1)	25	stopped one d. before	4	11.4	3.4
13	HU (24)	28	stopped one d. before	4	22.6	7.1
14	HU (1)	15	stopped 14 d. before	4	8.1	9.8
15	ABMT	21	stopped 14 d. before	4	11.6	26.3
16	HU (11)	8	stopped 14 d. before	4	9.8	13.6
17	HU (9)	17	stopped 14 d. before	4	6.6	1.1
18	HU (1)	12	stopped 14 d. before	4	12.3	3.3
19	HU (1)	68	stopped 14 d. before	4	10.8	15
20	HU (1)	11	stopped 14 d. before	1	3.2	2
21	HU (1)	32	stopped 14 d. before	4	8.6	10.6
Median (range)		21 (8-68)		4 (1-4)	8.6 (0.9-22.6)	3.3 (0.426.3)

**HU: hydroxyurea, BU: busulfan, ABMT: autologous bone marrow transplantation; °MNC: mononucleated cells; #this patient was successfully mobilized three months later.*

Results

Mobilization and harvest

The apheresis procedures were well tolerated, except in a patient in whom rHuG-CSF had to be discontinued due to severe bone pain; in two additional cases rHuG-CSF was also prematurely stopped because of high WBC counts (> 70×10^9/L). Overall, a total of 78 aphereses were performed, with a median of four procedures per patient (range 1-4). Fewer than 4 aphereses were carried out in 3 patients at the physician's discretion; this decision was made following collection of a sufficient cell yield with a single apheresis (n = 1) or, conversely, in view of very poor initial collections (n = 2). As shown in Table 2, the median total number of mononuclear cells (MNC) and CD34+ cells of the harvest were 8.6×10^8/kg (range, 0.9-22.6) and 3.3×10^6/kg (range, 0.4-26.3) per patient, respectively. A sufficient number of progenitors (> 1×10^6/kg CD34+ cells) was collected in all but 3 patients; in one of these patients an adequate cell dose was achieved following a second mobilization three months later.

Table 3. Cell yield of successive aphereses.

	Apheresis #1 (n = 21)	Apheresis #2 (n = 20)	Apheresis #3 (n = 19)	Apheresis #4 (n = 18)
MNC ($\times 10^8$/kg)*	3.2 (1.4-5.4)	2.7 (1.4-5.9)	2.1 (0.9-6.1)	2.0 (0.7-5.7)
CD34+ cells ($\times 10^6$/kg)*	0.7 (0.1-4.3)	0.7 (0.1-12.8)	0.7 (0.2-6)	0.65 (0.1-5.2)
Sufficient cell yield°	7/21	15/21	17/21	18/21

**Median (range); °cumulative no. of patients reaching > 1×10^6/kg CD34+ cells/ total no. of patients.*

Table 4. Cytogenetic studies of the patients' bone marrow (BM) and apheresis products.#

Pt. No.	% Ph+ metaph. BM pre-harvest	Aphereses (no.)	% Ph+ #1 G-banding/ FISH	% Ph+ #2 G-banding/ FISH	% Ph+ #3 G-banding/ FISH	% Ph+ #4 G-banding/ FISH
1	0	4	0/16	0/12	0/7	0/5
4	0	2	–/19	0/8	–	–
5	0	4	33/26	0/15	0/21	0/28
13	0	4	6/13	5/21	0/16	3/16
8	0	4	–/17	-/8	–	––
7	3	4	0/19	0/18	0/12	0/9
2	20	4	33/–	-/9	–	–
3	20	4	12/–	20/-	20/-	–
6	20	3	52/–	100/-	50/-	–
12	29	4	62/17	35/21	8/20	0/21
11	29	4	100/–	79/–	70/-	68/-
10	30	4	0/14	0/6	0/12	0/-
18	53	4	50/–	0/–	5/–	0/20
17	58	4	52/26	30/27	18/20	–
9	65	4	88/–	71/––	72/–	66/-
14	92	4	92/–	90/–	92/–	95/-
16	95	4	47/58	–/48	29/53	–/56
15	100	4	100/76	100/78	100/87	–
19	100	4	70/85	62/83	100/–	–/83
20	100	1	69/77	–	–	–
21	100	4	100/–	100/–	–	–
Median (range)	29 (0-100)	4 (1-4)	52/19 (0-100) (13-85)	30/18 (0-100) (6-83)	18/20 (0-100) (7-87)	0/20.5 (0-95) (5-83)

Data on the cell yield obtained in the successive aphereses are presented in Table 3. The proportion of patients reaching the cumulative target CD34+ cell dose was 33%, 71%, 81%, and 86% after apheresis #1, #2, #3, and #4, respectively. No significant difference was observed between the cell yield (MNC and CD34+ cells) obtained in each of the 4 aphereses. With regard to the factors influencing CD34+ cell harvest, a significantly higher

harvest was obtained in patients who discontinued IFN prior to the mobilization as compared to the remaining ones (median $CD34^+$ cells 8.4×10^6/kg, range: 1.1-26.3 vs. 1.8×10^6/kg, range: 0.4-4.7, respectively; $p = 0.006$).

Cytogenetic studies

Conventional cytogenetic studies were informative in 62 of the 78 aphereses (Table 4). FISH studies were carried out on 43 of the 78 apheresis products, with a total of 36 samples being assessed by both methods. The median number of metaphases and interphase nuclei analyzed were 14 (range, 10-73) and 100 (range, 50-100) per sample, respectively. Before mobilization, the median percentage of Ph^+ metaphases in the patients' bone marrow was 29% (range, 0-100), while it was 52% (range, 0-100), 30% (range, 0-100), 18% (range, 0-100) and 0% (range, 0-95) in apheresis #1, #2, #3 and #4, respectively. The median percentage of Ph^+ metaphases per apheresis in CCR/MCR patients was 1.5 (range, 0-100) vs 70.5 (range, 0-100) in the remaining situations ($p < 0.001$). No detectable Ph^+ cells were observed in 20 of 62 (32%) collections. However, in 13 of 18 such cases (72%), residual (> 10%) BCR-ABL positive cells (range, 12-28) were detected by FISH analysis.

Final assessment

Adequate information was available for all but one patient who had insufficient metaphases for analysis in all apheresis samples (#8). A completely or partially successful collection was achieved in 7 patients (63%) who were in CCR/MCR prior to mobilization and in only 3 (33%) with other pre-harvest cytogenetic responses (p = NS). Actually, patient #8, considered *not evaluable*, could be considered to have had a partially successful mobilization if the results obtained by FISH analysis of his apheresis products are used for evaluation. In only 2 cases (#6 and #11) was the degree of cytogenetic response in the harvest worse than the one observed in the bone marrow. Four patients (#2, #3, #8, and #12) were subsequently autografted using the stem cells from the harvest obtained with rHuG-CSF mobilization.

Discussion

Early studies showed that cytogenetic responses could be obtained with ASCT using unmanipulated autologous marrow or blood stem cell progenitors harvested in chronic-phase CML.[15,16] Moreover, autografted patients, particularly those attaining a cytogenetic response, survived longer than age-matched controls treated with conventional chemotherapy.[16] It was, therefore, postulated that the survival benefit could be ascribed to a delay in the blast crisis appearance, due to a reduction in the leukemic cell burden at risk of clonal transformation or to a proliferative disadvantage of the malignant stem cells after transplantation. However, post-transplant cytogenetic responses were always transient, which could be due to a failure to eradicate the disease by the conditioning regimen, to the presence of residual Ph^+ cells in the inoculum or both. In this regard, the contribution of Ph^+ cells contaminating the inoculum in post-transplant recurrence has been clearly established.[3]

Since intensification of the pre-transplant conditioning regimen is limited by its toxicity, most attempts to improve ASCT results have focused on strategies to eliminate the Ph^+ stem cell content of the graft. In this sense, several *in vitro* purging methods have been developed,[4] but their efficacy in obtaining Ph-negative products has not translated into a clear clinical benefit. The observation that a proportion of normal metaphases can be seen in CML patients treated with intensive chemotherapy after marrow aplasia recovery provided the rationale for developing *in vivo* selection methods.[17] One such strategy involves collection of Ph-negative progenitors from the peripheral blood early in the recovery phase after combination chemotherapy.[18,19] However, this approach has the disadvantage of needing the patient to be admitted to hospital and the potential risks derived from the treatment-induced aplasia.

Recently, several groups have explored the possibility of collecting stem cell progenitors in IFN-treated chronic-phase CML patients. Archimbaud *et al.*[7] reported their experience on stem cell mobilization using G-CSF in 30 CML patients with various degrees of response to IFN. The procedure was well tolerated, a sufficient stem cell harvest was obtained in most cases, and a significant proportion of Ph-negative cells was collected in patients with good pre-harvest response to IFN. These observations were confirmed in recent studies by the above[11] and other investigators.[8-10] The results in the present study are in keeping with the aforementioned studies. Firstly, the mobilization using rHuG-CSF was safe and could be performed on an outpatient basis, with no patient having major side-effects. Secondly, the same degree of cytogenetic response was seen following the procedure. Moreover, in the majority of cases a cell yield sufficient for autografting could be collected, irrespective of the duration of previous IFN treatment. Actually, all patients treated with IFN for more than

3 years reached the target cell dose. The effect on the harvest of maintaining or stopping IFN treatment during mobilization could not be properly assessed in the present study, due to baseline differences between the two groups of patients analyzed. Thus, all but 2 patients who discontinued IFN prior to mobilization were poor cytogenetic responders to IFN in whom the harvest was performed to obtain a back-up product prior to unrelated marrow transplantation, whereas those maintained on IFN during mobilization were good responders in whom the cryopreservation was performed to obtain a Ph-negative cell back-up which could be used for autografting in case of disease progression. Nevertheless, our current policy is to maintain IFN during mobilization, since it did not preclude a sufficient harvest in most cases.

As far as cytogenetic assessment is concerned, as previously described using similar mobilization protocols,[7,9] a decrease in the percentage of contaminating Ph+ cells was observed in successive aphereses. Consequently, if the number of apheresis procedures is decided on the basis of the sequential cell dose yield, a one-day delay in the initiation of the aphereses would seem reasonable to optimize the harvest of Ph-negative cells. In contrast, the first collections after early hemopoietic recovery are reported to be the least contaminated by Ph+ cells in mobilization strategies based on chemotherapy.[13,18] A possible explanation for such a discrepancy could be that the Ph+ progenitors may be more sensitive to chemotherapy and therefore take longer to regenerate than the normal progenitors. On the other hand, the high rate of completely Ph-negative apheresis products (32%) observed in our series is noteworthy. As expected, a strong correlation between the cytogenetic status of the pre-harvest marrow and the apheresis products was found. Thus, in nearly half of the patients with pre-harvest CCR/MCR a completely Ph-negative collection was obtained, whereas the results were worse in the remaining cases. Nevertheless, even in the latter group some patients in whom the amount of residual Ph+ metaphases in the apheresis samples decreased to less than 35% were observed.

The mechanisms responsible for the preferential collection of Ph-negative progenitors are unclear. IFN can enhance the adhesion of CML progenitors to the marrow stroma while sparing the adhesion of normal progenitors.[20] Alternatively, a preferential stimulation of the residual Ph-negative cells by rHuG-CSF has been suggested,[21] and such an effect has been reported in patients treated with G-CSF for CML relapse after allogeneic transplantation.[22]

In summary, mobilization of IFN-treated CML patients using rHuG-CSF is a feasible and safe strategy for obtaining Ph-negative progenitors for autotransplant purposes. This approach allows a substantial proportion of completely Ph-negative apheresis products to be obtained in patients with a good pre-harvest response to IFN.

Contributions and Acknowledgments

JC-HB analyzed the data and wrote the paper. EC designed the protocol. FC was responsible for the clinical management of the patients and collaborated in writing the paper. PM performed the mobilization procedures and stem cell cryopreservation. E-AR, MR and AO collaborated in the clinical management of the patients. FS, EL and BE performed the cytogenetic studies and EM gave some ideas for the production of the paper and contributed to the final writing.

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Disclosures

Conflict of interest: none.

Redundant publications: no overlapping with previous papers.

References

1. Sawyers CL. Chronic myeloid leukemia. N Engl J Med 1999; 340:1330-40.
2. Bhatia R, Verfaillie CM, Miller JS, McGlave PB. Autologous transplantation therapy for chronic myelogenous leukemia. Blood 1997; 89:2623-34.
3. Deisseroth AB, Zu Z, Claxton D, Hanania EG, Fu S, Ellerson D, et al. Genetic marking shows that Ph+ cells present in autologous transplants of chronic myelogenous leukemia (CML) contribute to relapse after autologous bone marrow in CML. Blood 1994; 83:3068-76.
4. Carlo-Stella C, Mangoni L, Piovani G, Almici C, Garau D, Caramatti C, et al. In vitro marrow purging in chronic myelogenous leukemia: effect of mafosfamide and recombinant granulocyte-macrophage colony-stimulating factor. Bone Marrow Transplant 1991; 8:265-73.
5. Anonymous. Interferon a-2a compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. The Italian Cooperative Study Group on Chronic Myeloid Leukemia. N Engl J Med 1994; 330:820-5.
6. Guilhot F, Chastang C, Michallet M, Guerci A, Harousseau JL, Maloisel F, et al. Interferon a-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. French Chronic Myeloid Leukemia Study Group. N Engl J Med 1997; 337:223-9.
7. Archimbaud E, Michallet M, Philip I, Charrin C, Clapisson

G, Belhabri A, et al. Granulocyte colony-stimulating factor given in addition to interferon-α to mobilize peripheral blood stem cells for autologous transplantation in chronic myeloid leukaemia. Br J Haematol 1997; 99:678-84.
8. Reiffers J, Taylor K, Gluckman E, Gorin NC, Mahon FX, Miclea JM, et al. Collection of Ph-negative progenitor cells with granulocyte-colony stimulating factor in patients with chronic myeloid leukaemia who respond to recombinant a-interferon. Br J Haematol 1998; 102: 639-46.
9. Russo D, Martinelli G, Montefusco V, Amabile M, Rosti G, Marin L. Collection of Ph-negative progenitor cells from Ph+ CML patients in complete cytogenetic remission after long-term interferon-α therapy. Haematologica 1999; 84:953-5.
10. Olavarria E, Parker S, Craddock C, Philpott N, Tiniakou M, Chase A, et al. Collection of Ph-negative progenitor cells from interferon responsive patients with chronic myeloid leukemia: effect of granulocyte-colony-stimulating factor mobilization. Haematologica 2000; 85:647-52.
11. Michallet M, Thiebaut A, Philip I, Charrin C, Vigouroux C, Thomas X, et al. Late autologous transplantation in chronic myelogenous leukemia with peripheral blood progenitor cells mobilized by G-CSF and interferon-α. Leukemia 2000; 14:2064-9.
12. Johnson RJ, Owen RG, Child JA, Morgan GJ, Barnard DL, Dickinson H, et al. Mobilization of Philadelphia-negative peripheral blood mononuclear cells in chronic myeloid leukaemia using hydroxyurea and G-CSF (filgrastim). Br J Haematol 1996; 93:863-8.
13. McBride NC, Cavenagh JD, Newland AC, Lillington DM, Murrell C, Kelsey SM. Autologous transplantation with Philadelphia-negative progenitor cells for patients with chronic myeloid leukaemia (CML) failing to attain a cytogenetic response to a interferon. Bone Marrow Transplant 2000; 26:1165-72.
14. Sinclair PB, Green AR, Grace C, Nacheva EP. Improved sensitivity of BCR-ABL detection: a triple-probe three-color fluorescence in situ hybridization system. Blood 1997; 90: 1395-402.
15. Reiffers J, Goldman J, Meloni G, Cahn JY, Gratwohl A. Autologous stem cell transplantation in chronic myelogenous leukemia: a retrospective analysis of the European Group for Bone Marrow Transplantation. Bone Marrow Transplant 1994; 14:407-10.
16. McGlave PB, De Fabritiis P, Deisseroth A, Goldman J, Barnett M, Reiffers J, et al. Autologous transplants for chronic myelogenous leukaemia: results from eight transplant groups. Lancet 1994; 343:1486-8.
17. Goto T, Nishikori M, Arlin Z. Growth characteristics of leukemia and normal hematopoietic cells in Ph1+ chronic myelogenous leukemia in vivo and in vitro and effects of intensive treatment with the L15 protocol. Blood 1982; 59: 793-808.
18. Chalmers EA, Franklin IM, Kelsey SM, Newland AC, Clark RE, Sproul AM, et al. Treatment of chronic myeloid leukaemia in first chronic phase with idarubicin and cytarabine: mobilization of Philadelphia-negative peripheral blood stem cells. Br J Haematol 1997; 96:627-34.
19. Carella AM, Lerma E, Corsetti MT, Dejana A, Basta P, Vassallo F, et al. Autografting with Philadelphia chromosome-negative mobilized hematopoietic progenitor cells in chronic myelogenous leukemia. Blood 1999; 93:1534-9.
20. Bhatia R, Wayner EA, McGlave PB, Verfaillie CM. Interferon a restores normal adhesion of chronic myelogenous leukemia hematopoietic progenitors to bone marrow stroma by correcting impaired β1 integrin receptor function. J Clin Invest 1994; 94:384-91.
21. Bedi A, Griffin CA, Barber JP, Vala MS, Hawkins AL, Sharkis SJ, et al. Growth factor-mediated terminal differentiation of chronic myeloid leukemia. Cancer Res 1994; 54:5535-8.
22. Giralt S, Escudier S, Kantarjian H, Deisseroth A, Freireich EJ, Andersson BS, et al. Preliminary results of treatment with filgrastim for relapse of leukemia and myelodysplasia after allogeneic bone marrow transplantation. N Engl J Med 1993; 329:757-61.

Peer Review Outcomes

What is already known on this topic

IFN induces cytogenetic remissions in a minority of patients with CML. Philadelphia-negative PBSC can be harvested from IFN responders.

What this study adds

Confirmation of the role of IFN as in vivo purging agent. Feasibility of autologous SCT using such cells.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Prof. Eduardo Olavarria, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Prof. Olavarria and the Editors. Manuscript received July 30, 2001; accepted November 14, 2001.

Potential implications for clinical practice

Development of new strategies combining IFN with tyrosine kinase inhibitors to achieve long-term cytogenetic remissions in CML.

Eduardo Olavarria, Associate Editor