Bone Marrow Transplantation (2008) 41, 239–244

www.nature.com/bmt

ORIGINAL ARTICLE

Blood stem cell mobilization and collection in patients with chronic lymphocytic leukaemia: a nationwide analysis

E Jantunen[1], M Itälä[2], T Siitonen[3], T Kuittinen[1], J Heiskanen[4], E Koivunen[5], E Juvonen[4], R Silvennoinen[5], T Nousiainen[1], P Koistinen[3], L Volin[4] and K Remes[2]

[1]*Department of Medicine, Kuopio University Hospital, Kuopio, Finland;* [2]*Department of Medicine, Turku University Central Hospital, Turku, Finland;* [3]*Department of Medicine, Oulu University Hospital, Oulu, Finland;* [4]*Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland and* [5]*Department of Medicine, Tampere University Hospital, Tampere, Finland*

Some reports suggest that blood stem cell mobilization is difficult in a proportion of patients with CLL. We evaluated this issue in a large cohort of CLL patients. One hundred and twenty-eight patients with CLL underwent blood stem cell mobilization during 1995–2005 in Finland. Ninety-five percent of the patients had received fludarabine. The most common mobilization regimen was intermediate-dose CY plus G-CSF (90 patients, 70%). At least 2×10^6/kg CD34$^+$ cells were collected after the first mobilization attempt in 83 patients (65%), whereas 45 patients (35%) failed to reach this collection target. No differences were observed between these patient groups with regard to age, time from the diagnosis to mobilization, number of previous treatment lines, number of fludarabine courses, time from the last fludarabine-containing chemotherapy to mobilization, disease status or degree of marrow infiltration. Patients who failed collection had platelets $<100 \times 10^9$/l more commonly at the time of mobilization (30 vs 4%, $P<0.001$). A significant proportion of patients with CLL were difficult to mobilize. Adequate marrow function including platelet counts $>100 \times 10^9$/l seem to be important factors in terms of successful blood stem cell collection.

Bone Marrow Transplantation (2008) **41,** 239–244; doi:10.1038/sj.bmt.1705897; published online 29 October 2007
Keywords: chronic lymphocytic leukaemia; stem cell mobilization; cyclophosphamide; mobilization failure

Introduction

CLL is a common chronic lymphoproliferative disorder characterized by clonal proliferation of B lymphocytes in blood, bone marrow, lymph nodes and spleen. The disease course is highly variable depending on well-defined prognostic factors including clinical stage, cytogenetic findings[1] and mutational status of immunoglobulin genes.[2]

Although CLL is, in most cases, highly sensitive to alkylating agents and nucleoside analogues alone[3] or combined with CY,[4] these treatments are not curative. Combinations of alemtuzumab[5] or rituximab[6] with chemotherapy have shown promising response rates, but long-term follow-up data are still needed. Despite improvements in the therapy of CLL, more intensive approaches, including autologous stem cell transplantation,[7–10] might be considered in a proportion of patients.

Some previous studies indicate that blood stem cell mobilization might be difficult in a proportion of patients with CLL.[8,11,12] Although extensive pre-treatment may jeopardize success of mobilization, it is noteworthy that a significant proportion of patients failed in this mobilization after first-line therapy.[8,12] To characterize mobilization issues in a larger cohort of patients with CLL, a nationwide retrospective analysis was undertaken.

Patients and methods

A questionnaire was sent to all five university hospitals in Finland with regard to mobilization and collection of blood stem cells in patients with CLL in 1995–2005. In addition to gender and age, time from diagnosis to mobilization, previous therapy for CLL, number of fludarabine-containing courses, disease status at mobilization, and marrow infiltration and blood cell counts just prior to mobilization were also requested. Disease status (response to previous treatment) was assessed according to the National Cancer Institute criteria.[13] For procedural factors, mobilization regimen used, peak blood CD34$^+$ cell counts after mobilization (B-CD34$^+$ peak), time from mobilization to B-CD34$^+$ peak, number of apheresis, yield of the first apheresis, total yield of CD34$^+$ cells and selection of the graft were collected. Also, re-mobilization and its success were asked for. Successful mobilization was defined as collection of $\geqslant 2 \times 10^6$/kg CD34$^+$ positive cells after a mobilization course (maximum four aphereses). All other mobilization outcomes (no apheresis due to low B-CD34$^+$ counts or collection of $<2 \times 10^6$/kg CD34$^+$ cells after a

Correspondence: Dr E Jantunen, Department of Medicine, Kuopio University Hospital, PO Box 1777, Kuopio 70211, Finland.
E-mail: esa.jantunen@kuh.fi
Received 26 June 2007; revised 21 August 2007; accepted 7 September 2007; published online 29 October 2007

Table 1 Characteristics of 128 CLL patients who received blood stem cell mobilization in Finland 1995–2005

Gender	
Female	42 (33%)
Male	86 (67%)
Age, median (range)	57 (37–69)
Time from dx to mobilization (months), median (range)	26 (3–220)
No. of previous regimens	
1 Regimen	88 (69%)
2 Regimens	21 (16%)
>2 Regimens	19 (15%)
No. of patients with FLU therapy	122 (95%)
No. of courses with FLU, median (range)	4 (0–10)
Time from the last FLU-containing chemotherapy to mobilization (months), median (range)	2 (1–28)
Time from last chemotherapy to mobilization <2 months, no. of patients	33 (26%)
Disease status at mobilization[a]	
CR	42 (33%)
PR	77 (60%)
NR	9 (7%)
BM infiltration (%) prior to mobilization, median (range)	10 (0–90)
Platelet count at mobilization ($\times 10^9$/l) median (range)	155 (40–404)
Mobilization regimen	
CY4 + G-CSF	90 (70%)
CY2 + G-CSF	31 (24%)
G-CSF alone	5 (4%)
Other	2 (2%)

Abbreviations: CY2 = cyclophosphamide 2 g/m^2; CY4 = cyclophosphamide 4 g/m^2; dx = diagnosis; FLU = fludarabine; NR = non-responder.
[a]According to the NCI criteria.[13]

single mobilization attempt) were regarded as failures. Data on engraftment were also requested in patients who received high-dose therapy.

During the study time period, 128 patients with CLL received mobilization therapy and were admitted for blood stem cell apheresis. Characteristics of these patients are presented in Table 1. The number of mobilized patients ranged from 12 to 39 per centre during the study period.

Statistical analysis

All analyses were preformed using SPSS 11.0 for Windows (SPSS, Chicago, IL, USA). For comparison of patients who successfully showed mobilization and those who failed the first mobilization attempt, the means were compared by using Mann–Whitney *U*-test. χ^2-test was used to compare nominal data between these patient groups. *P*-values <0.05 were considered statistically significant. For parameters significant by univariate analysis, a multivariate analysis using logistic regression was applied.

Results

Success of mobilization and collections

Blood stem cell mobilization and collection were successful in 83 patients (65%), whereas 45 patients (35%) experienced mobilization failure according to the definition used. In fact, in 39 patients (30%), collections were not started at all due to low B-CD34$^+$ counts. The percentage of patients who failed in the first mobilization and collection ranged from 17 to 43% per centre.

The median peak number of blood CD34$^+$ cells measured after mobilization was 30×10^6/l (0–287). The median number of collections in 89 patients was 2 (range: 1–4). The median number of CD34$^+$ cells collected was 5.4×10^6/kg (range: 0.5–32.7). The yield of the first apheresis was $\geqslant 2 \times 10^6$/kg CD34$^+$ cells in 52 patients (40% of all patients; 63% of patients with successful collections). CD34$^+$ cell selection was performed in 47 cases.

Factors predicting mobilization failure

Characteristics of patients with successful collection and those who failed to mobilize are presented in Table 2. Age, gender, time from diagnosis to mobilization, disease status, number of previous treatment regimens (1 vs $\geqslant 2$) or time interval from the last chemotherapy cycle to mobilization were not statistically significant in univariate analysis. Patients who failed in mobilization had received more fludarabine-containing cycles (4 vs 3), but the difference did not reach statistical significance. Of 36 patients treated only with a combination of fludarabine plus CY (FC), successful collection after the first mobilization occurred in 20 patients (56%). The success rate was 81% in 36 patients treated only with fludarabine prior to mobilization.

Mobilization success was comparable between patients who received CY 4 g/m^2 plus G-CSF and those who received CY 2 g/m^2 + G-CSF (69 vs 61%). Of note, only one out of five patients mobilized with G-CSF alone achieved the minimum collection target.

Patients who failed in mobilization had significantly lower platelet counts just prior to mobilization (146 vs 162×10^9/l, $P = 0.019$) and had platelets $<100 \times 10^9$/l more commonly just prior to mobilization (30 vs 4%, $P<0.001$). Poor mobilizers had significantly lower peak B-CD34$^+$ counts (8 vs 43×10^6/l, $P<0.001$), and the peak appeared later after the start of mobilization (13 vs 11 days, $P = 0.019$). However, in multivariate analysis, no factors were found to be associated with mobilization failure.

Outcome of re-mobilization

In 14 out of 45 patients (31%) who failed in the initial blood stem cell mobilization, a re-mobilization attempt was performed (Table 3). More than 2×10^6/kg CD34$^+$ cells were collected after the second mobilization in six patients (43%), and altogether seven patients had grafts containing at least 2×10^6/kg CD34$^+$ cells when apheresis products of these two mobilizations were combined. Notably, all five patients mobilized with cytarabine-containing regimens were collected successfully.

Engraftment after high-dose therapy

Altogether, 80 patients received high-dose therapy with blood stem cell support. All evaluable patients were engrafted successfully. The medians to reach neutrophils $>0.5 \times 10^9$/l and platelets $>20 \times 10^9$/l were 11 (9–19) and 13 days (8–25), respectively.

Table 2 Patient and mobilization characteristics in patients with successful blood stem cell mobilization and those who failed mobilization

	Successful mobilization (N = *83*)	*Mobilization failure* (N = *45*)	P-*value*
Gender			
Female	28 (34%)	14 (31%)	NS
Male	55 (66%)	31 (69%)	
Age, median (range)	57 (39–69)	56 (38–67)	NS
Time from dx to mobilization, months, median (range)	25 (3–220)	29 (4–142)	NS
No. of regimens prior to mobilization			
1	59 (70%)	29 (64%)	NS
⩾2	25 (30%)	16 (35%)	
No. of FLU courses before mobilization, median (range)	3 (0–8)	4 (0–10)	NS
Rituximab use	9 (11%)	6 (13%)	NS
Alemtuzumab use	3 (4%)	3 (7%)	NS
Time from last FLU-containing chemotherapy to mobilization (months) median (range)	2 (1–28)	2 (1–10)	NS
Platelet count at mobilization ($\times 10^9$/l), median (range)	162 (73–404)	146 (40–268)	0.019
Platelet count $<100\times10^9$/l at mobilization	3/83 (4%)	12/40 (30%)	<0.001
BM infiltration (%) at mobilization median (range)	10 (0–70)	15 (0–90)	NS
Disease status at mobilization			
CR	25 (30%)	17 (38%)	NS
PR	54 (65%)	24 (53%)	
NR	4 (5%)	4 (9%)	
Mobilization regimen			
CY4 + G-CSF	61 (75%)	29 (64%)	NS
CY2 + G-CSF	20 (23%)	11 (24%)	
G-CSF	1 (1%)	4 (9%)	
Other	1 (1%)	1 (2%)	
Peak B-CD34$^+$ counts after mobilization ($\times 10^6$/l), median (range)	43 (11–287)	8 (0–25)	<0.001
Time to peak B-CD34$^+$ count (days), median (range)	11 (5–20)	13 (5–27)	0.019
No. of CD34$^+$ cells collected	5.8 (2.0–32.7)	1.2 (0.5–1.9)[a]	<0.001

Abbreviations: CT = chemotherapy; CY2 = cyclophosphamide 2 g/m^2; CY4 = cyclophosphamide 4 g/m^2; dx = diagnosis; FLU = fludarabine; NR = non-responder.
[a]Apheresis performed in six patients.

Discussion

In this large retrospective multicentre series of CLL patients, a large number of patients failed to reach the minimum collection target after blood stem cell mobilization. Further, premobilization factors were of limited importance in predicting mobilization failure. These facts underscore the problems of blood stem cell mobilization and collection in patients with CLL.

Previous studies have indicated that a significant proportion of patients with CLL are difficult to mobilize.[8,11,12] Tournilhac *et al*.[12] used G-CSF mobilization after combination of fludarabine and CY (FC) and found successful collections after the first mobilization attempt in only 16% of the patients. In our experience of 36 patients who had received only FC therapy prior to mobilization, the success rate with identical definition was as high as 56%; all except one patient mobilized with CY + G-CSF. This suggests that CY-based regimens are more effective than G-CSF alone in terms of blood stem cell mobilization in this patient group. In the Medical Research Council (MRC) trial, patients received fludarabine alone followed by blood stem cell mobilization with CY 2 g/m^2 plus G-CSF in responding patients.[8] The success rate was 69%. In our analysis of patients treated with only fludarabine prior to mobilization, the success rate was as high as 81% (29/36 patients). This is about the same figure (14/17, 82%) as was found by the Italian investigators with CY4 + G-CSF mobilization after fludarabine monotherapy.[14]

No clear differences were observed in our retrospective analysis with regard to successful collection between patients mobilized with CY4 + G-CSF and those mobilized with CY2 + G-CSF. On the other hand, only one out of five patients mobilized with G-CSF alone reached the collection target in this series. Interestingly, cytarabine appeared to be efficient in re-mobilization in this series (success in 5/5 patients) as well in a previous series by Montillo *et al*.[15] (success in 13/14). Further, a recent French trial suggested a higher success rate after DHAP (dexamethasone–cytarabine–cisplatinum) when compared to mobilization with G-CSF alone in fludarabine-treated CLL patients.[16] Cytarabine-containing regimens are thus worth trying in CLL patients either as the first mobilization or for re-mobilization.

Some previous studies suggest that fludarabine therapy may be detrimental in terms of mobilization capacity in patients with lymphoproliferative diseases.[17–19] In our analysis, the patients who failed blood stem cell collection had received more fludarabine-containing cycles than had patients with successful collections, although the difference was not statistically significant. As suggested by earlier studies, longer time from the last chemotherapy to mobilization may be associated with better mobilization outcome.[20,21] The time interval from previous chemotherapy to mobilization was at least 2 months in 74% of the patients in our analysis, but a longer waiting time might have improved collection success in at least some patients.

Platelet counts were lower in patients who failed to achieve the minimum collection target. This is in line with previous findings.[21] However, the platelet count was $>100\times10^9$/l in 70% of the patients who failed in the initial collection, making this factor of limited practical value. On the other hand, if a platelet count is $<100\times10^9$/l at the start of mobilization therapy, the chances of successful mobilization are minimal. Waiting a few extra months may be worthwhile, if clinically feasible.

Based on this survey as well as previous studies[8,11,12,14,15,20–22] (Table 4), patients with CLL are more difficult to mobilize than many other haematological patient groups. Previous treatments have been variable, as have the mobilization regimens used preventing more detailed conclusions, but success rates for collections have been in the order of 60–70% in most studies. This contrasts

Table 3 Remobilization in 14 patients with CLL who fail to achieve collection of $> 2 \times 10^6$/kg CD34$^+$ cells after the first mobilization attempt

Gender/age	*I mobilization*			*II mobilization*				
	Mobilization regimen	*Maximum B-CD34$^+$ cells ($\times 10^6$/l)*	*Apheresis yield, $\times 10^6$/kg (no. of collections)*	*Time from previous mobilization (months)*	*Mobilization regimen*	*Maximum B-CD34$^+$ cells ($\times 10^6$/l)*	*Aphaeresis yield, $\times 10^6$/kg (no. of collections)*	*$\geqslant 2 \times 10^6$/kg collected (I+II mobilization)*
F/58	CY4+G	11	0 (0)	52	ESHAP+G	23	4.1 (2)	Yes
M/63	CY4+G	16	1.1 (1)	3	ESHAP+G	24	5.6 (2)	Yes
N/52	G	14	0 (0)	1	ESHAP+G	179	18.2 (1)	Yes
M/43	CY4+G	5	0 (0)	14	CY4+G	16	0 (0)	No
M/52	CY4+G	0	0 (0)	2	CY4+G+A	0	0 (0)	No
M/55	CY4+G	4	0 (0)	6	CY2+G	3	0 (0)	No
M/44	CY4+G	4	0 (0)	11	CY2+G	6	0 (0)	No
M/55	CY4+G	10	0 (0)	6	CY2+G	10	0 (0)	No
M/60	d-BEAM+G	17	1.2 (1)	1	AraC+G	75	6.6 (1)	Yes
M/53	CY2+G	5	0 (0)	3	AraC+G	39	5.9 (2)	Yes
M/46	CY4+G	15	0.8 (1)	1	CY2+G	15	1.4 (2)	Yes
F/62	CY2+G	7	0 (0)	3	G	14	1.8 (4)	No
M/37	G	11	0 (0)	1	CY4+G	28	5.9 (3)	Yes
M/42	CY4+G	25	1.9 (3)	4	G	5	0 (0)	No

Abbreviations: F = female; M = male; A = amifostine; CY2 = cyclophosphamide 2 g/m^2; CY4 = cyclophosphmide 4 g/m^2; d-BEAM = dexamethasone–carmustine–etoposide–cytosine arabinoside–melphalan; ESHAP = etoposide–methylprednisolone–cytosine arabinoside–cisplatinum; G = granulocyte colony-stimulating factor.

Table 4 Summary of published studies on blood stem cell mobilization and collection in patients with CLL

References	*No. of patients*	*Previous treatment*	*Mobilization regimen*	*Target collection ($\times 10^6$/kg)*	*Successful collection*
Itälä *et al.*[11]	8	Variable	CY4+G-CSF	5	5 (63%)
Scime *et al.*[14]	17	F	CY4+G-CSF	2	14 (82%)
Sutton *et al.*[22]	12	ESHAP	CY120 mg/kg+G-CSF or G-CSF alone	2	8 (67%)
Michallet *et al.*[20]	29	Variable	CY+G-CSF 14 CT+G-CSF 7 G-CSF 8	2	13/24 (54%)[a]
Montillo *et al.*[15]	14	F-CAM	G-CSF AraC	2.5	2/10 (20%) 13/14 (93%)[b]
Tournilhac *et al.*[12]	36	FC	G-CSF	2	6 (16%) 12 (32%)[c]
Lysak *et al.*[21]	56	F	CY3+G-CSF	2	23 (41%)
Milligan *et al.*[8]	88	F	CY2+G-CSF	2	59 (67%)
Present study	128	Variable, F in 95%	CY4+G-CSF 89 CY2+G-CSF 31 G-CSF 5	2	83 (65%) 90 (70%)[c]

Abbreviations: CAM = alemtuzumab; CT = combination chemotherapy; ESHAP = etoposide–methylprednisolone–cytosine arabinoside–cisplatinum; F = fludarabine; FC = fludarabine plus cyclophosphamide.
[a]Only patients with CD34$^+$ cells measured from the collection yield.
[b]Remobilization in eight patients, first mobilization in six patients.
[c]Including remobilization(s).

with multiple myeloma where successful collections can be performed in more than 90% of patients.[23–25] In patients with non-Hodgkin's lymphoma, success rates of 80–90% have been reported by several investigators.[26–30] The reasons for poorer mobilization in patients with CLL are poorly understood. Heavy marrow infiltration causing long-term changes in the microenvironment may be a potential explanation. Another reason might be the more prolonged action of myelosuppressive agents used to treat CLL before stem cell collection. Fludarabine might not be the most detrimental as such, but its combination with CY may impose long-term harmful effects on blood stem cell mobilization in a subset of patients.

The role of autologous stem cell transplantation in patients with CLL is, at present, uncertain due to the absence of published randomized studies as well as developments in conventional therapy. Patients who might be candidates for allogeneic stem cell transplantation but who lack a suitable donor might be considered for autologous stem cell transplantation. This applies to fludarabine-refractory patients or to those who relapse early after first line therapy.[31,32] In these cases, early prognostic evaluation is important, and the possibility of blood stem cell mobilization and collection should be considered after first-line therapy to optimize both collection success and graft quality.

To conclude, a significant proportion of patients with CLL are difficult to mobilize. CY-based regimens may be more effective than growth factors alone. Prediction of mobilization failure is problematic although thrombocytopenia may serve as an important warning sign. In view of the relatively high mobilization failure rate with current regimens, studies using a combination of filgrastim and AMD3100, a selective CXR4 agonist,[33,34] might also be of interest in CLL patients.

Acknowledgements

This study was supported by a grant from the Blood Disease Research Foundation and EVO funding by Kuopio University Hospital.

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