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Prediction of mobilisation failure in patients with non-Hodgkin's lymphoma

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Summary:

Factors affecting progenitor cell mobilisation in patients with non-Hodgkin's lymphoma (NHL) are incompletely understood. We have analysed factors predicting mobilisation failure in 97 consecutive patients with NHL (59 males, 38 females; median age 49 years) who received mobilisation with intermediate-dose CY (4 g/m^2) followed by G-CSF. The histology included large cell B ($N=50$), mantle cell ($N=16$), follicular ($N=16$) and other NHL ($N=15$). The disease status was 1CR/PR/primary refractory in 66 patients and >1 CR/PR in 31 patients. The minimum criterion for successful mobilisation was the collection of $\geqslant 1.5\times10^6$/kg CD34$^+$ cells. In all, 18 patients (19%) failed to reach this threshold. In univariate analysis, premobilisation factors associated with mobilisation failure included BM involvement at the time of diagnosis ($P=0.001$) or prior to mobilisation ($P=0.001$) and low platelet count just prior to mobilisation ($P=0.001$). In multivariate analysis, only BM involvement at diagnosis ($P=0.004$) and platelet count just prior to mobilisation ($P=0.01$) were associated with mobilisation failure. A mathematical model based on these two factors and presented in the form of a receiver operating characteristics curve showed a sensitivity of 0.71 and a specificity of 0.77 in the prediction of mobilisation failure. Patients at a high risk of mobilisation failure may benefit from novel approaches.

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Autologous PBPCs are increasingly used to support high-dose therapy (HDT) in various diseases.[1,2] The advantage of this approach over the use of marrow stem cells is more rapid engraftment with reduced toxicity and lower costs.[3,4] Currently, non-Hodgkin's lymphoma (NHL) is the leading indication for HDT supported by autologous PBPC rescue.[1,2]

Progenitor cell mobilisation is an essential part of HDT protocols. For NHL patients, no optimal mobilisation regimen exists.[5,6] CY combined with G-CSF is a widely used regimen in various haematological malignancies including NHL.[7–10]

According to previous studies, 10–30% of patients with NHL are difficult to mobilise or fail progenitor cell mobilisation.[11–14] Differences in the proportion of patients who fail mobilisation obviously depend on differences in patient characteristics as well as on definitions for mobilisation failure. There is a paucity of data concerning factors predicting mobilisation failure in patients with NHL, because many studies have also included patients with other diseases. Moreover, most previous studies have accepted patients with variable mobilisation regimens.

Identification of patients who are difficult to mobilise is important both clinically and for optimising resource utilisation. We have therefore analysed predictive factors for mobilisation failure in a cohort of 97 adult NHL patients mobilised with intermediate-dose CY plus G-CSF.

Patients and methods

Patients

Between January 1995 and March 2001, 97 adult NHL patients underwent PBPC mobilisation with intermediate-dose CY (4 g/m^2) and G-CSF followed by progenitor cell aphaeresis in our haematological unit. The patient characteristics are presented in Table 1.

All patient records including pathological, radiological and laboratory data were evaluated using a special formula. Premobilisation factors including age, gender, lymphoma subtype,[15] Ann Arbor stage, time from diagnosis to mobilisation, number of previous chemotherapy cycles and BM involvement were noticed. Previous chemotherapy regimens given to the patients are presented in Table 2. In addition, several postmobilisation factors including neutropenic fever, need for supportive care, blood count nadirs and peak blood CD34$^+$ (B-CD34$^+$) counts were taken into account for each patient.

Mobilisation and collection of PBPCs

All patients were admitted to hospital on day (d) −1, and intravenous hydration was started. The day of CY infusion was defined as d 0. CY (4 g/m^2) was infused during 90 min.

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Table 1 Characteristics of 97 NHL patients mobilised with CY 4 g/m^2 plus G-CSF

Characteristic	*No. of patients*
Sex (male/female)	59/38
Age (years), median (range)	49 (16–70)
Histology (REAL)	
Large cell B	50
Mantle cell	16
Follicular	16
Others	15
BM involvement at diagnosis	38
BM involvement prior to mobilisation	17
Ann Arbor III–IV	75
B symptoms	34
IPI at diagnosis	
0–1	34
2	29
3	26
4–5	8
Previous CHT cycles, median (range)	8 (3–23)
Prior radiotherapy	12
Time (months) from diagnosis to mobilisation, median (range)	7 (3–120)
Disease status prior to mobilisation	
1 CR/PR/primary refractory	66
>1CR/PR	31

REAL = Revised European–American classification of Lymphoid neoplasms;[15] IPI = International Prognostic Index; CHT = chemotherapy.

Table 2 Chemotherapy regimens preceding progenitor cell mobilisation in 97 NHL patients. Only regimens given to at least two patients are included

Regimen	*No. of patients*
CHOP ± HD-MTX/Bleo-CHOP	74
DHAP	18
MACOP-B	14
MIME	10
M-BACOD	7
Chlorambusil	6
ESHAP	6
FND	5
BFM	4
IMVP-16	4
DICE	3
Fludarabine	2
MINE	2
MOPP-ABV	2
Hyper-CVAD	2

CHOP = cyclophosphamide–doxorubisin–vincristine–prednisolone; HD-MTX = high-dose methotrexate; Bleo = bleomycin; DHAP = dexamethasone–cytosine arabinoside–cisplatin; MACOP-B = methotrexate–doxorubisin–cyclophosphamide–vincristine–prednisolone–bleomycin; MIME = mitoquazon–ifosfamide–methotrexate–etoposide; M-BACOD = methotrexate–bleomycin–doxorubisin–cyclophosphamide–vincristine–dexamethasone; ESHAP = etoposide–methylprednisolone–cytosine arabinoside–cisplatin; FND = fludarabine–mitoxantrone–dexamethasone; BFM = Berlin–Frankfurt–Munster protocol; IMVP-16 = ifosfamide–methotrexate–etoposide; DICE = dexamethasone–ifosfamide–cisplatin–etoposide; MINE = mitoquazon–ifosfamide–mitoxantrone–etoposode; MOPP-ABV = metchlorethamine–vincristine–procarbatzine–prednisolone–doxorubicin–bleomycin–vinblastine; Hyper-CVAD = MD Anderson protocol for mantle cell lymphoma.

Mesna (sodium-2-mercapto-ethane sulphonate) 1600 mg/m^2 was given intravenously 30 min before starting the CY infusion and 3 and 6 h after the CY infusion. G-CSF (filgrastim 5 μg/kg/day, 88 patients; lenograstim 263 μg/day, nine patients) was started 48 h after the CY infusion. G-CSF was continued until the end of aphaereses or until mobilisation failure was evident.

The patients were admitted to the ward for progenitor cell aphaeresis on d + 8, unless neutropenic fever or need for supportive care was noticed earlier. Daily complete blood counts were obtained starting on d + 8. B-CD34$^+$ cell count was measured for the first time on d + 9 provided that blood leukocyte count was $>0.5\times10^9$/l. Aphaeresis was started routinely if the morning B-CD34$^+$ count was $>20\times10^6$/l. Aphaeresis was begun in many patients with B-CD34$^+$ cell count between 5 and 20×10^6/l and raising WBC counts. The aim was to collect $>2\times10^6$/kg CD34$^+$ cells ($>5\times10^6$/kg if CD34$^+$ selection was intended). The minimum criterion for successful mobilisation was the collection of $\geqslant1.5\times10^6$/kg CD34$^+$ cells after a single mobilisation. The collections were discontinued after reaching the collection target. In case of poor mobilisation (B-CD34$^+$ counts $<20\times10^6$/l), a collection of at least 1.5×10^6/kg was considered sufficient provided that at least two collections had already been performed or in case of decreasing B-CD34$^+$ counts. All other mobilisation outcomes were regarded as failures. Aphaereses were performed with a Cobe Spectra cell separator (Cobe Laboratories Ltd, Gloucester, UK). For each aphaeresis, 10–151 of blood were processed within 3–4 h. Central venous catheters (Vascath^R) were used for the progenitor cell aphaeresis in more than 90% of the patients.

Measurement of CD34$^+$ cells and cryopreservation of the aphaeresis product

After the mobilisation, the peripheral blood CD34$^+$ cells were analysed by flow cytometry using a class III monoclonal antibody (either HBCA2, Becton Dickinson or 581, Coulter Immunotech) and the ISHAGE gating procedure. The aphaeresis product was analysed for CD34$^+$ cells with the same methodology, cryopreserved within 24 h in 10% DMSO and stored at −150°C.

Supportive care

In the case of neutropenic fever ($\geqslant$38°C) after mobilisation, at least two blood cultures were taken followed by the initiation of broad-spectrum antibiotics. Platelet transfusions were given when the platelet count was $<20\times10^6$/l. Before the insertion of a central venous aphaeresis catheter, the platelet count had to be $>40\times10^6$/l. RBC concentrates were given to keep the Hb level >80 g/l.

Statistical analysis

All calculations were performed with SPSS for Windows Release 11.0 (SPSS Inc., Chicago, IL, USA). The statistical significance of single pre- and postmobilisation factors in univariate analysis was investigated using the χ^2 for independence for categorical variables and the

Mann–Whitney *U*-test for continuous variables. A *P*-value <0.05 was considered statistically significant.

To investigate the relationship between the significant parameters in univariate analysis and the mobilisation failure, a multivariate analysis using logistic regression was applied. The covariates were selected with the stepwise method.

To predict the mobilisation failure for each NHL patient, we used the following equation

$$\text{Probability}\,(\mathbf{P}) = 1/(1+\exp(-Z))$$

where $Z = b_0 + b_1X_1 + b_2X_2 + \cdots + bpXp$. X_1, $X_2,\ldots,X_k$ are covariates and b_0, $b_1,\ldots,b_k$ are their estimated coefficients.

The receiver operating characteristics (ROC) curve of the predictive mathematical model was built by plotting sensitivity against 1-specificity for different probability values. The coordinates of the ROC curve were used to evaluate empirically the best threshold value for a continuous variable in the mathematical model.

Results

In all, 79 patients (81%) were successful mobilisers, whereas 18 patients (19%) experienced a mobilisation failure by the definition used. The median number of aphaereses per patient was 1 (range 0–4). The median number of CD34$^+$ cells collected per first aphaeresis was 2.7×10^6/kg (0.1–19.4).

Premobilisation factors associated with mobilisation failure (Table 3)

BM involvement at the time of diagnosis ($P=0.001$) or prior to mobilisation ($P=0.001$) was associated with mobilisation failure in univariate analysis. In addition, a low platelet count just prior to mobilisation also predicted failure ($P=0.001$), as did a low WBC count ($P=0.038$) and a low ANC count ($P=0.035$).

Postmobilisation factors associated with mobilisation failure (Table 4)

Several postmobilisation factors were associated with mobilisation failure in univariate analyses: a low WBC nadir ($P<0.001$), low platelet nadir ($P<0.001$), neutropenic fever ($P=0.001$) and need for platelet transfusions ($P<0.001$). A longer time to reach peak B-CD34$^+$ count ($P<0.001$) and a lower peak B-CD34$^+$ count after mobilisation ($P<0.001$) were also statistically significant.

Multivariate analysis and predictive mathematical model (Figure 1, Table 5)

In multivariate analysis, only two premobilisation factors retained their independent statistical significance in predicting mobilisation failure: BM involvement at the time of diagnosis ($P=0.004$) and platelet count just prior to mobilisation ($P=0.01$).

Table 3 Premobilisation factors associated with progenitor cell mobilisation in 97 NHL patients in univariate analysis

Factor	*Successful mobilisation (N=79)*	*Mobilisation failure (N=18)*	*P-value*
Age (years)	48 (16–70)	54 (31–64)	NS
Gender (male/female)	50/29	9/9	NS
Histology (REAL)			
Large cell B	40	10	NS
Follicular	15	1	NS
Mantle cell	12	4	NS
Others	12	3	NS
IPI at dg	2 (0–5)	2 (0–5)	NS
BM involvement at dg, no. of patients	25	13	0.001
BM involvement at mo, no. of patients	9	8	0.001
Use of fludarabine, no. of patients	4	3	NS
Months with exposure to CHT prior to mo	6 (2–47)	7 (3–15)	NS
Disease status at mo			
1 CR/PR/refractory	53	13	NS
>1 CR/PR	26	5	NS
WBC count prior to mo ($\times10^9$/l)	5.4 (2.1–17.9)	3.6 (1.7–23)	0.038
ANC count prior to mo ($\times10^9$/l)	3.0 (0.3–9.1)	1.9 (0.4–21.8)	0.035
Platelet count prior to mo ($\times10^9$/l)	252 (49–696)	158 (37–422)	0.001
Months from last CHT to mo	1 (1–34)	1 (1–2)	NS
No. of prior CHT cycles	8 (3–23)	8 (4–18)	NS
Prior radiotherapy, no. of patients	8 (10%)	4 (22%)	NS

Values are medians (range within parenthesis) unless otherwise indicated. NS = nonsignificant; IPI = International Prognostic Index; CHT = chemotherapy; mo = mobilisation; dg = diagnosis; REAL = Revised European–American classification of Lymphoid neoplasms.[15]

Table 4 Postmobilisation factors associated with progenitor cell mobilisation in 97 NHL patients in univariate analysis

Factor	*Successful mobilisation (N=79)*	*Mobilisation failure (N=18)*	*P-value*
WBC count nadir ($\times10^9$/l)	0.5 (0.1–7.4)	0.2 (0.1–0.7)	<0.001
Platelet count nadir ($\times10^9$/l)	48 (7–265)	12 (1–63)	<0.001
Days WBC count $<1.0\times10^9$/l	2 (0–8)	3 (2–9)	<0.001
Days platelet count $<50\times10^9$/l	1 (0–11)	6 (0–14)	<0.001
Neutropenic fever after mo, no. of patients	31 (39%)	15 (83%)	0.001
Platelet transfusions, units	0 (0–26)	12 (0–48)	<0.001
Days from mo to first aphaeresis	10 (8–16)	12 (10–14)	0.049
Days from mo to peak B-CD34$^+$	10 (9–16)	12 (11–14)	<0.001
Peak B-CD34$^+$ after mo ($\times10^6$/l)	33 (2–251)	1 (0.2–12)	<0.001
In-hospital days during progenitor cell aphaeresis	4 (2–22)	8 (5–14)	<0.001

mo = mobilisation.
Values are medians (range within parenthesis) unless otherwise indicated.

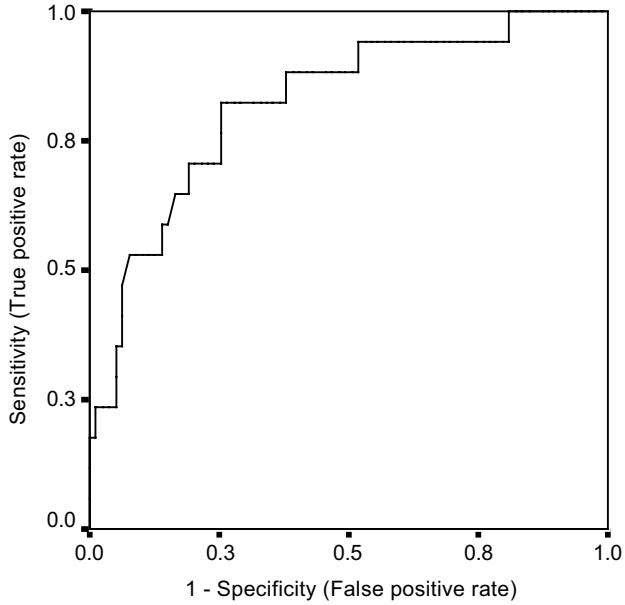

Figure 1 ROC curve shows sensitivity (true-positive value) and 1-specificity (false-positive rate) of the mathematical model to predict the mobilisation failure for each non-Hodgkin's lymphoma patient. Area under the curve = 0.82; 95% CI = 0.71–0.93.

Table 5 Risk of mobilisation failure according to the mathematical model

BM involvement at diagnosis	*Platelet count just prior to mobilisation (× 10⁹/l)*	*Risk of failure (%)*
+	100	61
+	150	55
+	200	39
−	100	19
−	150	13
−	200	9

In the mathematical model, X_1 = BM involvement at diagnosis (if yes = 1; if not = 2) and X_2 = platelet count just prior to mobilisation, $Z = 3.215 + (-1.870)X_1 + (-0.009)X_2$. The probability of the mobilisation failure (**P**) can be calculated with the equation $\mathbf{P} = 1/(1 + \exp^{-(3.215-1.870X_1-0.009X_2)})$.

The area under the ROC curve (Figure 1) built on the mathematical model was 0.82 (CI 95%: 0.71–0.93). The best detected threshold value for a continuous variable (platelet count just prior to mobilisation) to predict mobilisation failure was a platelet count 190×10^9/l with sensitivity = 0.71 (CI 95%: 0.49–0.92), specificity = 0.77 (CI 95%: 0.68–0.86), the positive predictive value = 0.40 (CI 95%: 0.22–0.57) and the negative predictive value = 0.92 (CI 95%: 0.86–0.99).

Based on the mathematical model, we have calculated the risk of mobilisation failure in patients with or without BM involvement and with a given platelet count just prior to mobilisation to give practical examples to clinicians (Table 5).

Engraftment after HDT

All except two successful mobilisers proceeded to HDT supported by autologous PBPC rescue. The conditioning regimen was either BEAC ($N = 44$) or BEAM ($N = 33$). Three patients experienced an early death, but all other patients showed engraftment. The medians to reach ANC $> 0.5 \times 10^9$/l and unsupported platelets $> 20 \times 10^9$/l were 9 (range 7–22) and 12 (range 8–44) days after the progenitor cell infusion, respectively.

Discussion

A significant proportion of NHL patients are still difficult to mobilise. Factors predicting poor mobilisation are incompletely understood. An apparent reason for these difficulties might be the fact that previous studies have been heterogeneous concerning diagnosis, prior therapy and mobilisation regimen used. Our analysis is based on a relatively large patient cohort of a single disease entity mobilised with a single regimen. In univariate analysis, the most important premobilisation factors associated with mobilisation failure were BM involvement at the time of diagnosis or prior to mobilisation and lower platelet counts just prior to the mobilisation. Of postmobilisation factors, low platelet and WBC count nadirs and low peak B-CD34$^+$ counts were predictive of mobilisation failure in univariate analysis. In multivariate analysis only two factors, BM involvement at diagnosis and platelet count just prior to mobilisation, retained their predictive value. Based on these two factors, a mathematical model for the prediction of mobilisation failure in patients with NHL was constructed.

Our finding that 19% of patients failed to mobilise an adequate number of progenitor cells to proceed to HDT is in line with other studies.[11,12,14] We have used a collection of $\geqslant 1.5 \times 10^6$/kg CD34$^+$ cells as a minimum criterion for successful mobilisation. Many studies have established that the ideal PBPC CD34$^+$ cell dose for rapid sustained engraftment is $> 5 \times 10^6$/kg, while the minimum safe progenitor cell dose to proceed to HDT is about 1×10^6/kg.[11,16,17] Our minimum criterion for successful mobilisation seems to be valid since all evaluable patients showed engraftment after HDT with PBPC support.

In univariate analysis, BM involvement was an important factor affecting progenitor cell mobilisation in patients with NHL and retained its predictive value also in multivariate analysis. BM involvement at diagnosis or prior to mobilisation has been found to be an important factor in NHL patients mobilised with G-CSF alone.[14] Apparently, marrow infiltration by malignant cells affects the microenvironment, thereby making effective mobilisation more difficult.

A low platelet count just prior to mobilisation was an important predictive factor for mobilisation failure in our study. To the best of our knowledge, this finding has not been reported earlier in patients with NHL. Lower platelet counts may be due to poor marrow reserves or due to a prolonged action of previous myelosuppressive therapy. Although no difference was observed in the time interval

between the last chemotherapy and mobilisation between patients who were successful mobilisers *vs* those who failed the mobilisation, it is well possible that patients with lower platelet counts had not yet fully recovered from the previous chemotherapy. The importance of the time interval from chemotherapy to the mobilisation has been stressed especially in patients with low-grade NHL[18] and in patients treated with more intensive chemotherapy.[19]

Of interest, the number of previous chemotherapy cycles was not predictive for mobilisation failure in this analysis. This suggests that in addition to quantity also the quality of previous chemotherapy might be an important issue with regard to an adequate stem cell pool. Drake *et al*[20] have proposed a scoring system for previous chemotherapy predicting progenitor cell mobilisation in patients with haematological malignancies. The scoring method was subsequently validated by another group.[21] In another study performed by our team in patients with NHL, we tried to apply this scoring system but found it applicable only in 27% of the patients.[22] Therefore, we established an improved scoring system by adding several drugs not used in the original scoring. Although the improved scoring was applicable in 93% of our patients with NHL, it was also of limited value in predicting progenitor cell mobilisation.[22]

Our mathematical model derived from the results of multivariate analysis showed a reasonable sensitivity. However, the area under the ROC curve (82%) suggests that many other, yet unidentified, factors might be of importance. In addition to unknown factors affecting progenitor cell mobilisation, interindividual differences may also be operating in lymphoma patients mobilised with chemotherapy plus G-CSF, in analogy with healthy progenitor cell donors mobilised with G-CSF alone.[6,23] Vantelon *et al*[24] recently proposed a model based on the number of moderately or highly myelotoxic chemotherapeutic regimens. Their model had relatively good predictive value with a success rate of 80% in patients with low scores and below 20% in patients with high scores.

To conclude, we have identified two premobilisation factors predicting the mobilisation failure in patients with NHL mobilised with intermediate-dose CY plus G-CSF. NHL patients who have BM infiltration at diagnosis and subnormal platelet counts just prior to mobilisation are at significant risk of mobilisation failure. These high-risk patients may benefit from the initiation of aphaeresis at lower B-CD34$^+$counts, because it is unlikely that very high counts will ensue. Patients with adverse premobilisation factors might also be candidates for prospective studies using novel mobilisation regimens to improve progenitor cell mobilisation,[25–27] and to make this treatment option more cost-effective and time saving.

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