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Successful mobilization of hematopoietic peripheral blood progenitor cells with paclitaxel-based chemotherapy as initial or salvage regimen in patients with hematologic malignancies

Autologous hematopoietic progenitor cell transplantation is a standard of care in several hematologic diseases, but many patients are unable to mobilize a sufficient number of cells for transplantation. Paclitaxel is a plant alkaloid effective against ovarian and breast cancers, and has also been proven active in multiple myeloma and non-Hodgkin´s lymphoma, among other human neoplasms.[1,2] We and others have described the efficacy of paclitaxel-based chemotherapy in mobilizing large amounts of hematopoietic progenitors in patients with ovarian or breast cancer.[3-5] However, data on the use of paclitaxel and rhG-CSF for hematopoietic cell mobilization in patients with hematologic malignancies is scarce; only recently McKibbin *et al*. have described this schedule in 26 patients after failure of a prior mobilization regimen.[6] To further determine the potential clinical utility of paclitaxel with rhG-CSF for hematopoietic progenitor mobilization in patients with non-solid tumors, we investigated: (i) the mobilizing ability and toxicity of this schedule as initial treatment, or as salvage therapy in patients who failed a mobilization attempt with rhG-CSF, and (ii) the efficacy and tolerability of cyclophosphamide (Cy), given in combination with paclitaxel and rhG-CSF after mobilization failure with filgrastim alone.

Between January 1999 and January 2008, 75 patients with a primary diagnosis of a hematologic malignancy who were scheduled for autologous transplant received paclitaxel in the mobilization schedule (Table 1). The time elapsed from the last treatment was at least three weeks. All patients gave informed consent.

Group A included 19 patients with risk factors for failure to achieve successful mobilization, representing 12% out of a total 156 first-line mobilizations with rhG-CSF during the same study period. Most patients displayed coexistence of various factors associated with poor mobilization success (Table 1). Patients received paclitaxel 170 mg/m^2 i.v. by continuous infusion for 24 hours (day 1) followed by 8 µg/kg s.c rhG-CSF (P-G) daily until the last apheresis.[4] Thirty-three patients received the same

Table 1. Patients' characteristics.

Patients' characteristics	*Group A* P-G (n=19)*	*Group B P-G (n=33)*	*Group C P-Cy-G (n=23)*	*p*
Age, years (median, range)	47, 15-67	52, 19-66	57, 31-69	0.0146
Males (%)	8 (42%)	19 (58%)	11 (48%)	0.5367
Diagnosis				
Acute leukemia	4 (21%)	10 (30%)	1 (4%)	0.0017
Lymphoma	9 (47%)	16 (48%)	7 (30%)	
Multiple myeloma	6 (32%)	7 (21%)	14 (61%)	
CLL	0	0	1 (4%)	
Disease status				0.0512
Complete remission	10 (53%)	24 (73%)	8 (35%)	
Partial remission	7 (37%)	8 (24%)	13 (57%)	
Progression	2 (10%)	1 (3%)	2 (9%)	
Median time (weeks) from last chemotherapy cycle	17	10	10	0.4610
Patients with previous radiotherapy	3 (16%)	3 (9%)	5 (22%)	0.4201

*Group A, patients treated with paclitaxel-rhG-CSF (P-G) as first line therapy; group B and group C, patients treated with paclitaxel-rhG-CSF (P-G) or paclitaxel-cyclophosphamide-rhG-CSF (P-Cy-G) respectively, after failure of mobilization with rhG-CSF. p values are calculated with the Kruskal-Wallis test. *Group A patients: 15 patients presented with myelodysplastic features and/or hypocellular bone marrow; 6 had been treated with fludarabine, platinum or melphalan, 6 revealed poor hematologic recovery from previous cycles, with intervals to achieve neutrophils >1×10^9/L and/or platelets >50×10^9/L greater than four weeks, and 2 of them had bone marrow involvement by tumor. CLL: chronic lymphocytic leukemia.*

Table 2. Parameters of peripheral blood progenitor cell mobilization in 60 patients (acute leukemias excluded) treated with paclitaxel-rhG-CSF (P-G) either as first line therapy –group A-, or salvage therapy –group B-, or with paclitaxel-cyclophosphamide-rhG-CSF (P-Cy-G).

	Day of first apheresis (Day 1)	*Day 1 WBC $\times 10^9$/L*	*Day 1 peripheral blood CD34$^+$/μL*	*Day 1 CD34$^+$/kg yield ($\times 10^6$/kg)*	*Total CD34$^+$/kg yield ($\times 10^6$/kg)*	*Aphereses performed*	*% in Day 1 with >2$\times 10^6$ CD34$^+$ kg*
P-G	9 (6-12)	13.7 (2.6-23.5)	44 (4-201)	2.0 (0.2-10.6)	2.4 (0.2-10.6)	1 (1-5)	53%
Group A (n=15)	9 (7-12)	13.3 (3.8-21.4)	40 (12-103)	1.2 (0.5-10.6)	2.3 (1.4-10.6)	2 (1-5)	47%
Group B (n=23)	9 (6-10)	14.7 (2.6-23.5)	44 (4-201)	2.23 (0.2-9.3)	2.5 (0.2-9.3)	1 (1-3)	56%
P-Cy-G (n=22)	14 (9-19)*	15.7 (3.2-24.7)	41 (4-389)	2.6 (0.6-11.4)	3.2 (1.2-11.4)	1 (1-25)	68%

**p<0.05 between groups (Kruskal-Wallis test). Values are expressed as median (range).*

schedule as above as a second mobilization attempt (group B). Group C included 23 patients who were treated with a protocol containing paclitaxel as above, followed 24 hrs. later by Cy 4 g/m^2 i.v. as a one hour infusion. On the third day, rhG-CSF was started s.c. at a dose of 8 µg/kg each day until the completion of leukapheresis (P-Cy-G).[4] For patients in both B and C groups, paclitaxel containing schedules were administered after a first failed mobilization attempt with s.c rhG-CSF (10 µg/Kg), that had induced maximal CD34$^+$ cells in peripheral blood <7/µL (P-Cy-G) or 7-14/µL (P-G).

Peripheral blood counts, and CD34$^+$ cell concentrations were assessed on days 5, 7, and daily afterwards, and in each apheresis product. CD34$^+$ cell evaluations were performed as previously described.[4] Leukapheresis procedures were initiated when total white blood cell count exceeded 5-10$\times 10^9$/L, or when peripheral blood CD34$^+$ cells were >15/µL. Daily leukaphereses were executed using a COBE Spectra (COBE BCT, Lakewood, CO, USA) blood cell separator, by processing 3 total blood volumes daily, until a target number of 2$\times 10^6$/CD34$^+$/kg recipient body weight was achieved.

The analysis of both paclitaxel containing schedules (P-G and P-Cy-G) showed that patients in the P-G group met the criteria to start leukapheresis earlier (median day 9, range 6-23) than those patients receiving P-Cy-G (median day 14, range 9-19; p=0.0001), resulting in higher rhG-CSF costs in the latter group (€1086 *vs.* €1520, p=0.0006).

When excluding the 15 patients diagnosed with acute leukemia, as it has been previously established that these patients mobilize poorly,[7] and to avoid skewed data between groups, the ability to mobilize was similar in patients receiving P-G and P-Cy-G in terms of peak peripheral blood CD34$^+$ cells (50.0 *vs.* 49.5/µL respectively; p=0.4452), and yields of CD34$^+$ cells in the first apheresis (2.0 *vs.* 2.6$\times 10^6$/Kg respectively; p=0.2070). The use of paclitaxel resulted in 83% of patients achieving the minimum threshold number of CD34 >2$\times 10^6$/Kg (73% in group A, 91% in group B, and 81% in group C, p=0.7550). Thus, the use of paclitaxel-based regimens allowed successful mobilization in 86% of patients that had failed previous mobilization with rhG-CSF (Table 2).

The use of paclitaxel containing schemes was less efficient in the setting of acute leukemia, with an overall success rate of 44%. Age, disease status, time elapsed after last chemotherapy, and previous radiotherapy did not correlate with the mobilization outcome (p>0.05). The mobilization therapy was generally well tolerated, with grades III and IV neutropenia or thrombopenia significantly lower in P-G than in P-Cy-G patients (p=0.0002, and p=0.0121 respectively). Thus, the median duration of neutrophils <1$\times 10^9$/L was 1 day (range 0-3), and 6 days (range 4-12) respectively; p=0.0003, while that of platelet counts below 50$\times 10^9$/L was 0 days (range 0-3) and 4 days (range 0-16) respectively; p=0.0215. Only 12% of patients had clinical infection (8% *vs.* 22% in P-G *vs.* P-Cy-G respectively; p=0.0864), and no differences were observed between regimens in terms of fever (6% *vs.* 17%; p=0.1130), nor in number of patients requiring RBC, or platelet transfusion (p>0.05). No procedure-related deaths occurred.

A significant proportion of patients receiving standard mobilization for the purpose of autologous transplantation fail to mobilize bone marrow cells into the periphery. Currently, AMD3100 is the most promising mobilizing agent under investigation, but this CXCR4 antagonist is restricted to clinical studies. Additionally, pre-clinical and clinical studies show that acute myeloid leukemia, and chronic lymphocytic leukemia cells may be mobilized by AMD3100 via CXCR4 inhibition,[8-10] thus limiting the use of this agent in patients with certain hematologic malignancies. Our findings show that paclitaxel is effective in mobilization of PBSC in patients with hematologic malignancies, not only as salvage therapy,[6] but also in patients with adverse prognostic factors for mobilization. The overall mobilization success rate was 75%, being lower in acute leukemia (44%) than in other hematologic malignancies (83%). The addition of Cy to this regimen did not increase the collection yield, whereas it aggravated the injurious effect of chemotherapy on bone marrow. Since rhG-CSF in the first days of mobilization is likely to be not relevant, a delayed rhG-CSF administration might be considered as a strategy to reduce mobilization costs in P-Cy-G patients.[11]

In conclusion, our data show that mobilization of CD34$^+$ cells using paclitaxel is an effective, safe, and predictable strategy that allows efficient mobilization in patients with hematologic malignancies as first or second line priming schedule in poor mobilizers.

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Sex-specific patterns and trends in the incidence of hematologic malignancies in 0-24 year olds from Northern England, 1968-2005

Sex-specific patterns and trends in the incidence of childhood cancer have consistently been demonstrated,[1] and can provide insights into pathogenesis. Unfortunately often only pooled results have been given. Potentially this may have masked sex-specific temporal trends, especially over a prolonged time period.

A previous study from the Northern Region of England examined the incidence of leukemias and lymphomas diagnosed in cases aged 0–24 years during the period 1968–1995.[2] This analysis found an overall increase in the incidence in the area. Similar increases have been found in other studies from the UK and elsewhere.[1]

The aim of the present study was to update the previous analyzes from the Northern Region and to determine whether there were sex-specific trends in incidence. We analysed all hematologic malignancies diagnosed in cases aged 0–24 years who were resident in the Northern Region during the period 1968 – 2005. Analyses were made separately for boys and girls (aged 0-14) and adolescent/young adult males and females (aged 15-24).

Case details were extracted from the specialist Northern Region Young Persons' Malignant Disease Registry (NRYPMDR). All cases of cancer within the region occurring in residents aged less than 25 years are reported to the registry. Data are carefully cross-checked with regional and national cancer registries at regular intervals. This guarantees that information is very accurate and complete. The overall completeness of ascertainment for cases aged 0-24 years has been estimated to be more than 98%.[2] The International Classification of Diseases for Oncology (ICDO-2) was used for coding morphology and primary site of diagnosis.[3] Cases were grouped using the International Classification of Childhood Cancer (ICCC).[4]

The NRYPMDR is exempted (under Section 60 of the UK Health and Social Care Act 2001) from the need to obtain patient consent for recording and analysis of data.

Age-standardized rates (ASRs) and 95% confidence intervals (CIs) were calculated based on a standard world population.[5] Rates were calculated for the entire study period (1968–2005) and for three shorter time periods (1968–1980, 1981–1993, 1994–2005). Temporal trends in annual ASRs were analyzed using linear regression. Statistical significance was taken as $p<0.05$.

Full results are given in Tables 1 and 2. For both sexes lymphoid leukemia predominates in the younger age-group whilst Hodgkin's lymphoma (HL) predominates in the older age-group. There is a striking surplus of male over female cases of childhood lymphoma. This excess is less marked in the adolescent/young adult age group. There was an overall statistically significant increase in the incidence of hematologic malignancies in boys (0.6% per annum, 95% CI: 0.1% to 1.2%) and an overall significant decrease in adolescent/young adult males (-1.0% per annum, 95% CI: -1.9% to -0.1%). However, these overall trends obscure the pattern of changes in incidence in specific diagnostic groups. For the leukemias there was a marginally significant increase for boys (0.5% per annum, 95% CI: -0.1% to 1.2%), which was driven by childhood peak cases (1-4 years). There was no evidence for any significant temporal changes for older males or for females of any age. In contrast, for lymphomas there was a significant upward trend for childhood cases of lymphoma in girls (3.5% per annum, 95% CI: 1.3% to 5.6%), due to a marked increase in the incidence of HL. A significant downward trend in the incidence of adolescent/young adult cases of lymphoma in males (-1.4% per annum, 95% CI: -2.5% to -0.3%) was due to a decrease in the incidence of HL (-1.8% per annum, 95% CI: -3.0% to -0.5%).

Increases in the incidence of childhood leukemia have been previously reported from the UK, Europe and the USA, which were especially marked for childhood peak cases.[6] The present study has shown that the upward trend was confined to males diagnosed with lymphoid leukemia at ages 1-4 years. Current epidemiological evidence suggests a role for infections in etiology,[6] possibly in combination with other environmental agents.[1] The male-specific increase in the incidence of lymphoid leukemia in the Northern Region is consistent with greater susceptibility of boys to an etiological agent.

Higher risk of childhood leukemia has been associated