Therapeutic leukapheresis: 9-year experience in a University Hospital

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Background. Hyperleucocytosis is associated with higher morbidity and mortality related to possible development of leucostasis, tumour lysis syndrome and/or disseminated intravascular coagulation. There is insufficient evidence of the need for leukocytapheresis during early treatment of hyperleucocytosis, and its efficiency remains controversial, although leucoreduction is a measure that can prevent adverse events and death. The aim of this study was to analyse the safety and effectiveness of therapeutic leukocytapheresis and its influence on early mortality in our case series, adjusted to independent mortality risk factors described in the literature.

Materials and methods. This was a retrospective review (June 2003-June 2012) of procedures carried out for the treatment of hyperleucocytosis at the Haematology and Haemotherapy Service of Miguel Servet University Hospital. The patients' data and technical information were prospectively registered for each leukocytapheresis session.

Results. Thirteen patients underwent a total of 27 leukocytapheresis procedures. After an average of two sessions, a statistically significant drop in the initial leucocyte counts was observed ($p<0.01$), as well as a relevant drop in lactate dehydrogenase levels. The only analytical value statistically related to early mortality in univariate analysis was initial creatinine level greater than 1.2 mg/dL ($p=0.012$, OR=2.5).

Discussion. Despite the small size and limited homogeneity of our case series, we can conclude that leukocytapheresis is a safe and effective therapeutic measure for leucoreduction in haematological pathologies of any lineage, particularly in patients without acute myeloid leukaemia. Patients with acute myeloid leukaemia had worse outcomes within 6 months of having finished leukocytapheresis sessions, as well as in terms of mean global survival and mean time of mortality. However, global mortality rates were similar in patients with or without acute myeloid leukaemia.

Keyword: hyperleucocytosis, leukocytapheresis, leucoreduction, leucostasis.

Introduction

Hyperleucocytosis is arbitrarily defined as a leucocyte count greater than 100×10^9/L, and typically appears in some haematological neoplasms[1]. Hyperleucocytosis implies higher rates of morbidity and mortality related to the possible development of leucostasis, tumour lysis syndrome and/or disseminated intravascular coagulation[2]. The number of leucocytes necessary for leucostasis changes with each pathology, owing to, among other factors, different morphological, molecular and plasticity characteristics of the blast cells[1], as well as the capacity of endothelial cell to release cytokines. In acute myeloid leukaemia (AML), leucostasis appears at leucocyte counts above 100×10^9/L, and severe symptoms appear above 400×10^9/L in acute lymphoblastic leukaemia; however, symptoms do not appear in chronic lymphoid leukaemia until the leucocyte count exceeds 500×10^9/L-$1{,}000\times10^9$/L[1,2].

Hyperleucocytosis mainly affects the central nervous system and respiratory system. There may be gastrointestinal symptoms, but these are less frequent[1,3]. Leucoreduction is a measure to prevent adverse events and death caused by hyperleucocytosis, since it influences cell differentiation in the bone marrow by increasing the proportion of blast cells in S-phase, a fact that translates into increased efficiency of certain antineoplastic agents such as cytarabine and methotrexate[1].

Although the technical foundations for performing leukocytapheresis (LCP) were laid more than 20 years ago, there is insufficient evidence about its use in the early treatment of leukaemia with hyperleucocytosis[4]. In addition, the efficiency of LCP remains controversial[4]. The invasive and risky nature of this technique, the need for experienced staff and, in some cases, central venous access, as well as the additional costs and limited scientific evidence proving its effectiveness with regards to global long-term survival are reasons why some centres prefer more conventional treatment in asymptomatic and paediatric patients[4-6].

However, the clinical guidelines for therapeutic apheresis of the American Society for Apheresis (ASFA)[2] support the routine implementation of LCP in cases of hyperleucocytosis secondary to acute myeloid leukaemia (AML) with signs of leucostasis (ASFA indication level I, evidence level 1B), whereas the evidence for efficacy of prophylactic LCP use in acute lymphoblastic leukaemia is controversial (indication level III, evidence level 2C). The Spanish Apheresis Group (*Grupo Español de Aféresis,* GEA), Spanish Society of Blood Transfusion (*Sociedad Española de Transfusión Sanguínea*, SETS) and Spanish Society of Haematology and Haemotherapy (*Sociedad Española de Hematología y Hemoterapia,* SEHH) recommend LCP in cases of hyperleucocytosis with leucostasis in their document, "Urgent indications for therapeutic apheresis".

Non-randomised and prospective studies have examined the benefits of LCP in patients with hyperleucocytosis. There are many published retrospective analyses proving that LCP, combined with chemotherapy, reduces early mortality without influencing the long-term prognosis[4,7-9], although the short-term benefit was not found in some other studies[10-12].

The aim of this study was to analyse the safety and effectiveness of therapeutic LCP as a leucoreduction strategy and its influence on early mortality in our case series, adjusted to the independent mortality risk factors described in the literature.

Materials and methods

We retrospectively reviewed LCP procedures carried out over a period of 9 years (June 2003 to June 2012) for the treatment of hyperleucocytosis at the Haematology and Haemotherapy service of a level IV 1,200-bed hospital, a reference centre for related allogeneic haematopoietic stem cell transplantation. Data were obtained from patients' clinical histories and electronic medical records (Intranet, Modulab, Netbank, Izasa®, Zaragoza, Spain). Data were registered prospectively at each LCP session in the transfusion unit, to ensure that there was no loss of data. In our centre, we considered starting LCP in patients with a leucocyte count greater than 100×10^9/L, or at development of symptoms of leucostasis.

Demographic, clinical, analytical and technical variables were reviewed. Tumour lysis syndrome was defined on the basis of the following criteria: hyperkalaemia, hyperuricaemia, hyperphosphataemia, hypocalcaemia and uraemia[13]. Early mortality was defined as death within the first 14 days after diagnosis.

Procedure

To perform LCP according to our centre's protocol, all patients required a central catheter for blood extraction and return, and a peripheral venous access for fluid replacement and administration of medications. The COBE® Spectra™ LRS (Barcelona, Spain) continuous flow system was used. The collection speed is calculated by the system's programme using its configuration for leucoreduction, taking into account the data introduced for each patient (leucocyte count, weight and size). The volume that is normally processed is 1.5-2 blood volumes in adults and 3-3.5 volumes in children. The anticoagulant used is acid-citrate-dextrose solution A (ACD-A), and the blood/anticoagulant ratio ranges between 13:1 and 15:1. At the beginning of each session, two 10-mL vials of 10% intravenous calcium gluconate are administered prophylactically, by continuous infusion. In the case of symptomatic hypocalcaemia, another 10-mL vial is administered orally. In cases in which volume replacement is required, this is achieved with Human Albumin Grifols® 5% (Barcelona, Spain).

Statistical methods

We performed descriptive analyses of all variables, determining the frequencies and percentages for qualitative variables and measures of central tendency (average±standard deviation) for quantitative variables. Relationships between quantitative variables and categorical and quantitative variables were determined by applying the Student's *t*-test. Mortality rates were obtained by means of Kaplan-Meier curves. P values less than 0.05 were considered statistically significant. We used SPSS version 18 software (IBM, Zaragoza, Spain) for the statistical analyses.

Results

During the 9 years reviewed, LCP procedures were performed on 13 patients, with an average age of 53 years (range, 7-80 years) (Table I). The most frequent diagnosis was acute leukaemia: of the nine patients (69.2%) with this condition, six had *de novo* leukaemia, two had secondary leukaemia and one had AML in first relapse after haematopoietic stem cell transplantation. The remaining pathologies were two cases of chronic myelomonocytic leukaemia, one case of myelofibrosis and one case of T-cell prolymphocytic leukaemia. Poor-prognosis cytogenetic features were present in three of the 13 patients.

With respect to clinical manifestations among symptomatic patients, the most frequent symptoms were respiratory (46.2%), as shown in Table I. There was only one case of tumour lysis syndrome after the LCP procedure. This coincided with the beginning of chemotherapy in a patient with persistent leucocytosis, despite 60% leucoreduction achieved by LCP. We observed more symptoms (mainly respiratory) at disease debut, as well as tumour lysis syndrome, in patients without AML, despite the fact that most of AML cases were of the monocytic (M4 or M5) type.

Table I - Clinical and analytical characteristics of patients, by diagnosis.

Pt	Age/ gender	Diagnosis	Clinical features	Leucocytes before LCP ($\times 10^9$/L)	Leucocytes after LCP ($\times 10^9$/L)	HU	CT schema	Disease state within 6 months after LCP	Time of death (days after LCP)
1	49/W	CT- related AML (M4)	F	240.9	47.8	No	ICE	MRD	Alive
2	44/M	1st relapse after allogeneic HSCT for AML (M4)	No	263.9	54.6	Yes (before LCP)	ICE	2nd Relapse	368
3	64/M	AML (M4)	F	117.4	84.3	No	ICE	Deceased	10
4	61/M	AML (M4)	No	179	72.6	No	ICE	Deceased	77
5	29/W	AML (M4)	No	136	50.1	No	ICE	PR	163
6	7/W	AML (M5)	D	264.2	113.7	No	AIE SHOP-AML/2007	Deceased	56
7	18/W	T-cell ALL	R	390	47.8	Yes (after LCP)	PETHEMA 2003/AR	CR	Alive
8	51/M	Type 1 CMML	R, D, TLS	412	275	Yes	No	Deceased	8
9	59/M	Biphenotypic and bilineal AL	TLS with CT	200	112	No	ICE	CR	725
10	77/M	T-cell prolymphocytic leukaemia	R	394.9	123	No	COP	PR	1306
11	64/M	Type 1 CMML	R and D	198.9	155.8	Yes	No	AML (M4) progression	360
12	53/M	MF after ET	F and R	136.9	57.5	No	MP	Deceased	99
13	80/W	Ambiguous lineage leukaemia after ET and PV	R and TLS	323.5	44.2	Yes (before LCP)	No	Deceased	1

Pt: patient; M: man; W: woman; CT: chemotherapy; HU: hydroxyurea; LCP: leukocytapheresis; AML: acute myeloid leukaemia; ALL: acute lymphoblastic leukaemia; CMML: chronic myelomonocytic leukaemia; HSCT: haematopoietic stem cell transplantation; MF: myelofibrosis; ET: essential thrombocytosis; PV: polycythemia vera. R: respiratory; F: fever; D: digestive; TLS: tumour lysis syndrome; PETHEMA 2003/AR: 2003 High Risk ALL protocol, Spanish Programme for the Study and Treatment of Malignant Haemopathologies, ICE: idarubicin, cytarabine, etoposide; COP: cyclophosphamide, vincristine, prednisone; MP: melphalan, prednisone; AIE: cytarabine, idarubicin, etoposide; SHOP-AML/2007: 2007 AML treatment protocol, Leukaemia Working Group of the Spanish Paediatric Haematology and Oncology Society. CR: complete remission; MRD: minimal residual disease; PR: partial remission.

The mean initial leucocyte count was 240.2 (±120.4)×10^9/L, which reduced to 95.2 (±65)×10^9/L at completion of all LCP sessions. A statistically significant global drop in initial leucocyte counts was observed ($p<0.01$, 95% CI 80.1-209.8) after an average of two LCP sessions; the average decrease was 145 (±107.3)×10^9/L (60.4% with respect to the initial counts), as shown in Figure 1. There were no relevant variations in creatinine levels (before LCP: 1.28±0.7 mg/dL; after LCP: 1.27±0.8 mg/dL). However, a substantial drop of 51.8% in lactate dehydrogenase (LDH) levels was seen (1,142.7±550 U/L *vs* 609.6±534.2 U/L), as shown in Figure 2. No important differences in leucoreduction rate were observed when comparing diagnosis, age or disease state within 6 months of ending LCP.

Patients without AML had higher initial leucocyte counts and haemoglobin, haematocrit and creatinine values, but lower initial LDH levels. AML patients had greater reductions in LDH (62.35% *vs* 33.38%), but decreases in leucocyte count were similar in both groups (64.78% in AML patients and 61.85% in the remaining patients). Declines in initial leucocyte counts were statistically significant in both groups ($p=0.005$ for AML patients and $p=0.004$ for other cases) (Table II).

Five (38.5%) patients were transfused before beginning LCP, and 11 patients were transfused during the LCP procedure (6 required red blood cell transfusions, 2 platelet transfusions and 2 both red blood cell and platelet transfusions). Haemoglobin values fell an average of 0.5 g/dL, haematocrit decreased by 1.8% and platelet counts dropped an average of 86×10^9/L.

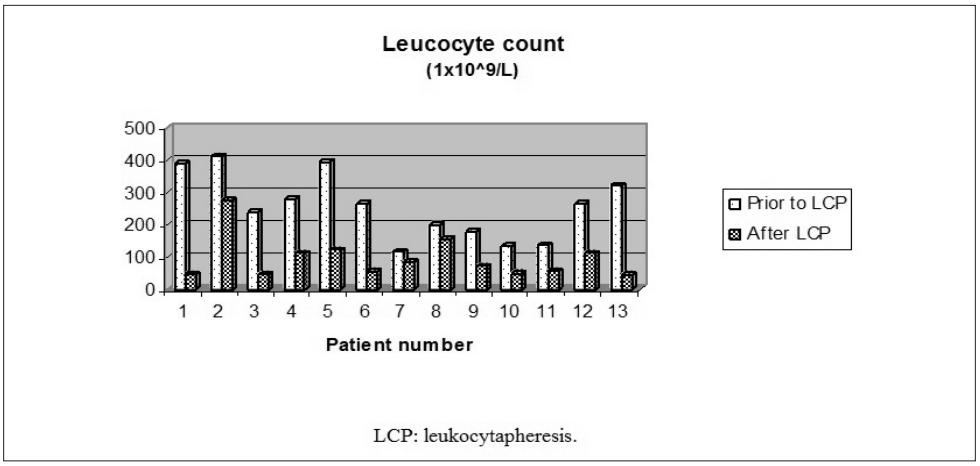

Figure 1 - Leucocyte count prior to and after leucocytapheresis.

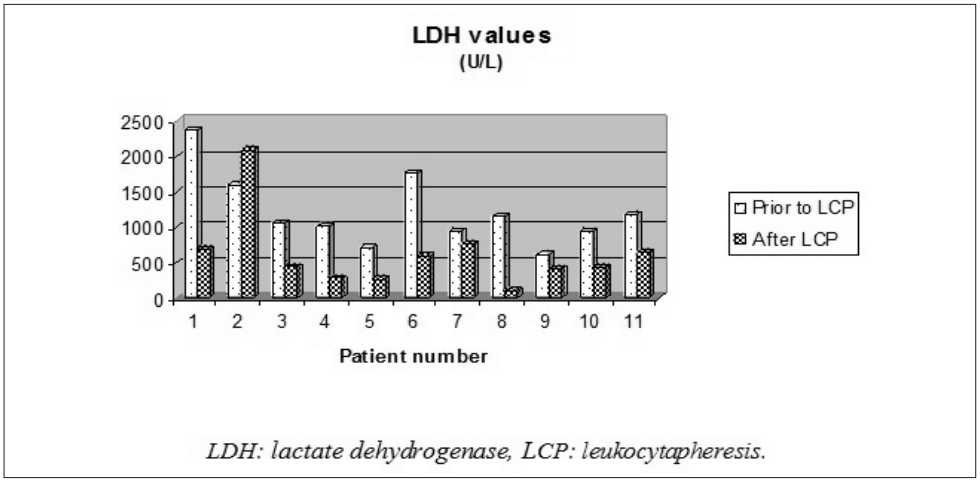

Figure 2 - LDH levels prior to and after leucocytapheresis.

Regarding independent risk factors for early mortality (dyspnoea, initial creatinine greater than 1.2 mg/dL and initial LDH levels greater than 1,000 U/L)[5], no patients presented these three factors concurrently. The only analytical parameter statistically related to early mortality in the case series in univariate analysis was an initial creatinine level greater than 1.2 mg/dL (p=0.012, OR=2.5, 95% CI 0.855-7.3) (Tables I and III). Despite the fact that patients without AML had neoplasms with worse prognosis and more risk factors for mortality (Table II), they had better outcomes within 6 months after having finished the LCP sessions, and a longer time to death. However, global mortality rates were similar for both groups (83.3% for AML patients, and 85.7% for the remaining patients).

Before beginning LCP, two patients received hydroxyurea therapy, with an average dose of 2 g/day (1-3 g/day). Nine patients (69.2%) received induction chemotherapy (Table I). Rasburicase was administered to three patients in the case series before the start of chemotherapy.

Apheresis techniques

Each patient underwent an average of two (range, 1-4) LCP sessions. Average body weight in the case series was 63 kg (range, 28-84.5 kg). In each session, 1.5 (range, 1.5-2) whole blood volumes were processed, equivalent to 4,095 mL (range, 1,820-5,492.5 mL), and the average replacement volume was 951 mL (range, 441-1,912.3 mL). Most patients (61.5%) began LCP between 24-48 hours after diagnosis, with the mean being 1.92±1.3 days (range, <24 hours-5 days). Patients without AML required two or more LCP sessions, whereas AML patients received one or more sessions.

Twenty-seven LCP sessions were performed during the period reviewed. Technique-related adverse events were observed in seven sessions (25.9%). The most frequent adverse event was hypotension (2 sessions), with the remainder including dizziness, bradycardia, perioral paraesthesia, and problems with catheter flow and return pressure. None of these events was severe, but on one occasion (hypotension) the session was cancelled at the

Table II - Results in patients with AML *vs* patients with other haematological neoplasms.

	AML	Other diseases
Patients (n)	6	7
Age (years)	46.5 (7-65)	59 (18-80)
Gender (n, M/W)	3 M / 3 F	5 M / 2 F
Diagnosis (n)	*De novo:* 4 Secondary to CT: 1 Relapse: 1	*De novo:* 3 Progression: 2 Chronic: 2
*Current status**	Alive: 1 Deceased: 5	Alive: 1 Deceased: 6
Symptoms at disease onset (n)	Asymptomatic: 3 Fever: 2 Abdominal pain:1	Asymptomatic: 1 Respiratory: 4 Respiratory and abdominal pain: 1 Fever and respiratory: 1
Tumour lysis syndrome (n)	None	3
Initial WBC count (×10⁹/L)	200.2±65.1	305.3±105.8
WBC count after LCP (×10⁹L)	70.5±25.5	116.5±81.8
Initial LDH levels (U/L)	1,155.4±411.5	1,133.7±664.4
LDH levels after LCP (U/L)	435±213.7	755.2±691.7
Decrease in WBC count (×10⁹/L)	129.7±67.2	188.8±111.7
Decrease in LDH levels (U/L)	720.4±397.9	510.7±716.3
Risks factors (n):		
Over 60 years old	2	3
Start of LCP 48 h after diagnosis	2	2
Poor prognosis pathologies	1	3
Poor prognosis cytogenetics	2	1
Initial WBC count ≥300×10⁹/L	0	4
Initial LDH level ≥1,000 U/L	4	3
Initial creatinine above 1.2 mg/dL	1	4
Presence of dyspnoea	0	5
No HU therapy before LCP	5	3
*Disease state within 6 months after LCP**	Deceased: 3 Second relapse: 1 PR: 1 MRD: 1	Deceased: 3 CR: 2 PR: 1 Progression: 1
*Time of death***	77 (10-368)	229.5 (1-1,306)
Mean global survival (months)	14.8±6.3	20.8±8.3

AML: acute myeloid leukaemia; M: man, W: woman, CT: chemotherapy, WBC: white blood cells, LDH: lactate dehydrogenase to the caption. HU: hydroxyurea, LCP: leukocytapheresis, PR: partial response, MRD: minimal residual disease.
* Status at the end of follow up; ** Median days after LCP.

request of the patient, despite recovery of blood pressure. No predominance of adverse effects was seen according to gender, pathology or age range. Technique-related adverse events were more common in AML patients (n=4, 66.7% *vs* n=1, 14.3% in the other patients).

The mean follow-up time of the patients was 45.2±30.7 months (range, 4.2-109.9), with a global mortality rate of 11 (84.6%) patients by the end of the study. Most deaths were of infectious origin (53.8%): septic shock in four patients and pneumonia in three. The remaining causes of death were: pulmonary leucostasis (n=1; according to the death report, despite normalised leucocyte count after LCP, 48 hours before death), fulminant liver failure of multifactorial origin (n=1), brain haemorrhage (n=1) and second relapse of AML after haemopoietic stem cell transplanation (HSCT) (n=1). The mean survival of the whole series was 18.3±6.3 months. Early mortality rates were higher in patients without AML (28.6% *vs* 16.6% for AML), but mean global survival was higher in these latter patients (20.8±8.3 months *vs* 14.8±6.3 months for patients with AML) (Table II).

Discussion

In terms of diagnoses, clinical presentation of leucostasis and causes of death, the characteristics of our case series are similar to those of other published studies[4,5,7-12,14-16]. However, the low frequency of neurological[8,10,11,14,15] or haemorrhagic[7,16] symptoms secondary to leucostasis in our patients is noteworthy. This might be due to the promptness of LCP completion by our team. No important adverse events related to the technique were observed, despite the fact that we were mostly treating patients with serious disorders.

It is, however, important to clarify that insertion of a central catheter and use of a two- or three-lumen catheter may not be necessary for LCP done at other centres, if the patient has appropriate peripheral venous access. This is because one or two LCP processes are normally carried out, and the flows used are low. At our centre, we implant such devices because our patients will need chemotherapy to ensure effectiveness of the procedure.

The global survival of the AML patients in our series (14.8 months) was longer than that in other studies[5,7,8] (6.5 months, 10.5 months and 10 days, respectively), with no important differences observed with respect to age, diagnosis or risk factors among these patients and ours. However, it is important to clarify that none of the AML patients in our series had tumour lysis syndrome. The chemotherapy schema, analytical values and technical characteristics of our case series are similar to those published by other centres[4-8,14].

We did not find statistically significant differences in early mortality rates and mortality within 6 months,

Table II - Mortality rates adjusted to risk factors.

Studied risk factors	Mortality within 2 weeks			Mortality within 6 months		
	Living	Deceased	p-value	Living	Deceased	p-value
Older than 60 years	3	2 (40%)	0.252	0	5 (100%)	0.224
Beginning LCP 48 h after diagnosis	2	2 (50%)	0.913	1	3 (75%)	0.522
Pathologies with poor prognosis*	4	0 (0%)	0.913	1	3 (75%)	0.522
Cytogenetics with poor prognosis**	2	1 (33.3%)	0.279	0	3 (100%)	0.4
Initial leucocyte count above 300×10^9/L	2	2 (50%)	0.125	1	3 (75%)	0.522
Initial LDH level above 1,000 U/L	5	2 (28.6%)	0.735	2	5 (71.4%)	0.190
Initial creatinine level above 1.2 mg/dL	2	3 (60%)	0.012	0	5 (100%)	0.224
Presence of dyspnoea	3	2 (40%)	0.835	1	4 (80%)	0.715
No hydroxyurea before LCP	7	1 (12.5%)	0.252	3	5 (62.5%)	0.429

LCP: leukocytapheresis. LDH: lactate dehydrogenase.
*Pathologies with poor prognosis were defined as: relapsed disease or chronic disease transformed into acute disease or prolymphocytic leukaemia.
**Cytogenetics with poor prognosis was defined as: complex karyotype, FTL3-ITD AML.

with respect to age, pathology, cytogenetics, presence of dyspnoea, leucocyte count, LDH level, hydroxyurea use or time interval between diagnosis and the start of LCP sessions.

The early mortality rate in our case series (23%) is similar to those published by Tan *et al.*[4] (28%) and Bug *et al.*[7] (25%). But early mortality in our AML cases was lower (28.57%) than the rates published by Chang *et al.*[10] and De Santis *et al.*[9] (33% and 46%, respectively). Early LCP completion did not prove to be either a prognostic factor or a response predictor. The effect of cytoreductive chemotherapy prior to LCP could not be properly assessed, because it was received by only two of the patients in our case series. Factors found to be predictive of early mortality in other case series were not statistically significant in univariate analysis in our series, except for initial creatinine levels, which could have been influenced by our small sample size. However, in three of the five patients who received hydroxyurea therapy, the survival rate was over 360 days, which may be attributable to synergy between LCP, hydroxyurea and chemotherapy, although establishing the influence of each of these factors on the survival rate is beyond the scope of this article.

When comparing results in patients with AML *vs* those with other haematological malignancies, we can conclude that the former had worse outcomes within 6 months after having finished LCP sessions, as well as in terms of mean global survival and mean time of mortality.

We cannot estimate the incidence of hyperleucocytosis at our centre because this is not registered systematically. However, the approximate frequency is at least one case per year. A limitation of our service is that all LCP sessions must be carried out on weekdays because there is a lack of experienced staff available for urgent procedures. The small number of cases in our centre does not justify the creation of such a team. However, two important aspects must be taken into account. Firstly, all the cases in which therapeutic apheresis techniques (plasma replacement and cytapheresis) are indicated, and secondly, the possibility of major deterioration in the patient's condition or decreased possibility of treatment response, if these procedures are delayed. These points are examined further in the document mentioned above, "Urgent indications for therapeutic apheresis" by GEA, SEHH and SETS.

Despite the small size and limited homogeneity of our case series, our results lead us to conclude that LCP is a safe and effective therapeutic method of leucoreduction in haematological pathologies of any lineage, particularly in patients without AML. In most cases, after an average of two sessions, significant decreases in leucocyte count and LDH level are achieved. The reduction of LDH can be interpreted as a consequence of reduction in tumour burden and/or tumour lysis syndrome. A multicentre, randomised trial is needed to confirm our conclusions.

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Conflicts of interest

The authors declare that they have no conflicts of interest regarding this article.

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