Original Article

Therapeutic Leukapheresis in Hyperleukocytic Leukaemias—The Experience of a Tertiary Institution in Singapore

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Abstract

Introduction: Hyperleukocytic leukaemias are associated with early mortality due to respiratory or neurological complications. They result from endothelial damage secondary to leukostasis. Leukapheresis, which aims to lower the white blood cell (WBC) count, has been used in certain patients to reduce the threat from leukostasis. However, there are very few published clinical investigations on the most appropriate use of leukapheresis in hyperleukocytosis. Materials and Methods: We performed a retrospective analysis of 14 patients with hyperleukocytic leukaemia who presented to our institution and underwent therapeutic leukapheresis. We compare their clinical and biological characteristics and investigate the impact of leukapheresis on early mortality and long-term prognosis. Results: The median presenting WBC count was 439 x 10^3/mm^3. Although patients with acute myeloid leukaemia (AML) had the lowest median presenting WBC counts, they constituted the largest group of patients with symptomatic hyperleukocytosis. Leukapheresis was highly effective, with the mean absolute and percentage reduction in WBC after each cycle being 126 x 10^3/mm^3 and 31.9% respectively. Four patients with AML died within 2 weeks of presentation despite prompt and effective leukapheresis. Conclusion: The interaction between the leukaemic cells and the vascular environment, a mechanism that none of the current therapies directly address, is probably more important in causing leukostasis than the absolute cell count itself.

Ann Acad Med Singapore 2005;34:229-34

Key words: Apheresis, Cytoreduction, Hyperleukocytosis, Leukocytoreduction

Introduction

Hyperleukocytic leukaemia is conventionally defined as leukaemia with an initial white blood cell (WBC) count or blast count greater than 100,000/mm^3.[1] It has a dramatic clinical presentation and represents a very challenging therapeutic problem due to the high early mortality. The many early complications and deaths are directly attributed to hyperleukocytosis and its resultant microcirculatory dysfunction, a phenomenon known as leukostasis,[2,3] where the sludging of leukaemic blasts in capillary vessels and their adhesive interactions give rise to deleterious effects. Symptoms may arise from the involvement of any organ system, but intraparenchymal brain haemorrhage and respiratory failure account for the majority of deaths. The rapid destruction of leukaemic cells in response to chemotherapy also causes metabolic disturbances (tumour lysis syndrome).

This has led to the notion that prompt leukocytoreduction is imperative in preventing the high incidence of hyperleukocytic leukaemia-related complications and early deaths. As such, leukapheresis has been widely used following anecdotal case reports describing striking clinical improvements with prompt leukocytoreduction by leukapheresis.[4-8] Although introduced more than 20 years ago,[9] there are still no convincing data that leukapheresis is essential in the immediate treatment of hyperleukocytic leukaemia and the effectiveness of this technique remains in question. Besides, it is an invasive procedure, requiring experienced personnel to establish a central vascular access. With the inherent risks of the procedure, additional costs and the lack of data supporting its course, routine leukapheresis cannot be justified and clinicians tend to pursue a more conventional approach in children and asymptomatic patients.

It is recognised that hyperleukocytosis is an unfavourable prognostic factor where higher risk of relapse and shorter survival rates are commonly seen.[3,10-12] Studies on the impact of leukapheresis on overall mortality are limited,

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but generally concur that it does not improve long-term survival.[13-15] The impact on early mortality however, is controversial. One study reported that leukapheresis managed to reduce 2-week mortality,[13] while another showed that despite efficient leukapheresis, early survival was not improved.[14] Herein, we perform a retrospective analysis of patients presenting with hyperleukocytic leukaemia to our institution from 1998 to 2003 and assess their clinical outcomes and early mortality rate after early leukapheresis.

Materials and Methods

In our institution, there is no standing protocol where leukapheresis should be adhered to for new cases of hyperleukocytic leukaemia. Decisions on leukapheresis are very much based on the discretion of the attending physician and usually, symptomatology and extremes of leukocytosis (WBC counts of more than 100,000/mm^3) are the main deciding factors. However, patients have to be haemodynamically stable before leukapheresis can be instituted. In this retrospective study, we examined the clinical and biological characteristics, and the treatment outcomes, including complete remission rate, early mortality and overall survival, of 14 adult patients with hyperleukocytic leukaemia who underwent leukapheresis in our institution during the period of November 1998 to June 2003. These patients were identified from the "leukapheresis log" for the review period and respective case documents were traced and studied in detail. Diagnoses of their respective leukaemias were established on the basis of morphological and standard cytochemical examination of bone marrow smears. Two patients with acute myeloid leukaemia (AML) were unfit for bone marrow studies and had their diagnoses confirmed on flow cytometry and smears of the peripheral blood.

Patients eligible for therapeutic leukapheresis were identified at the outset when they presented with symptomatic hyperleukocytosis. A 12.5F pheresible catheter was inserted into the subclavian vein by the attending haematologist or the interventional radiologist under radiological guidance if there was a concomitant thrombocytopenia or coagulopathy. Leukapheresis using discontinuous-flow automate instruments (Haemonetics MCS+ LN 9000) was commenced once correct placement of the pheresible catheter was confirmed from chest radiography.

Each procedure was generally completed within 3 hours when 1 calculated total blood volume of the patient would have been pheresed. Overall, leukapheresis was performed daily until there was a significant reduction in the WBC count or until there was sufficient improvement in the patient's clinical status, allowing initiation of induction chemotherapy. Prior to the first leukapheresis cycle, hydroxyurea at doses of 1g to 3 g was started immediately for all patients except for the patient with chronic lymphocytic leukaemia (CLL). All patients also received supportive measures like aggressive intravenous hydration with sodium bicarbonate and oral allopurinol so as to prevent or minimise tumour lysis syndrome. Decision to discontinue leukapheresis again was based very much on the discretion of the individual physician. Generally, it was not based on WBC counts falling below a certain level, but a downward trend in WBC counts with resolution of symptoms of leukostasis.

Results

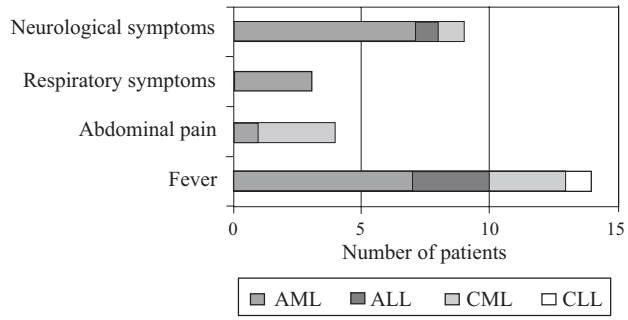
There were 14 cases: 7 acute myeloid leukaemias, 3 acute lymphoblastic leukaemias (ALL), 3 chronic myeloid leukaemia (CML) and 1 chronic lymphocytic leukaemia (CLL). The characteristics of patients at presentation are summarised in Table 1. The median age of the patients was 23.5 years old (range, 15 to 74 years). There were 9 males and 5 females. The median presenting WBC count was 439 x $10^3/mm^3$ (range, 175 x$10^3/mm^3$ to 950 x $10^3/mm^3$). WBC counts causing symptoms were much higher in the lymphocytic leukaemias than the myelocytic ones. As such, there were more cases of AML and CML than ALL and CLL who underwent leukapheresis. It is also remarkable that although patients with AML had the lowest median presenting WBC counts, they constituted the largest group of patients with symptomatic hyperleukocytosis. The blast counts in the acute leukaemias generally paralleled the WBC counts.

A review of their symptomatology (Fig. 1) showed that all patients had fever and 9 patients presented with neurological symptoms, of which 3 patients had concomitant pulmonary manifestations as well. A common presenting complaint amongst patients with chronic myeloid leukaemia was abdominal pain due to congestive hepatosplenomegaly.

Table 1. Patients' Characteristics at Diagnosis

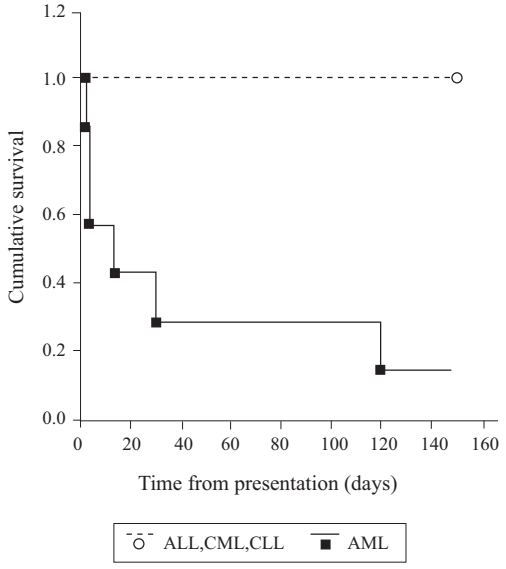
Age (y)	23.5* (15-74)†
Gender (males/females)	9/5
Diagnosis:	
Acute myeloid leukaemia	7
Acute lymphoblastic leukaemia	3
Chronic myeloid leukaemia	3
Chronic lymphocytic leukaemia	1
Presenting white blood cell count (x$10^3/mm^3$):	439* (175-950)†
Acute myeloid leukaemia	303*
Acute lymphoblastic leukaemia	634*
Chronic myeloid leukaemia	510*
Chronic lymphocytic leukaemia	950*

* median value; † range of values



AML: acute myeloid leukaemia; ALL: acute lymphoblastic leukaemia; CML: chronic myeloid leukaemia; CLL: chronic lymphocytic leukaemia

Fig. 1. Presenting symptoms.



AML: acute myeloid leukaemia; ALL: acute lymphoblastic leukaemia; CML: chronic myeloid leukaemia; CLL: chronic lymphocytic leukaemia

Fig. 2. Kaplan-Meier plots of survival in patients with hyperleukocytosis after leukapheresis.

Leukostasis-defining symptoms involving the respiratory or central nervous systems were more commonly seen in acute than chronic leukaemias.

The mean number of cycles of leukapheresis required by each patient was 1.78 (range, 1 to 3). Overall, 25 leukapheresis cycles were performed among the 14 patients. The mean absolute and percentage reduction in WBC after each cycle were 126,000 x10^3/mm^3 (range, 80 x 10^3/mm^3 to 339.5 x 10^3/mm^3) and 31.9% (range, 8.4% to 65.8%) respectively. The median absolute WBC counts after leukapheresis was 175.5 x10^3/mm^3. In subgroup analysis, the mean absolute reduction per cycle of leukapheresis for AML, ALL, CML and CLL were 95.1 x 10^3/mm^3, 183.3 x 10^3/mm^3, 156.3 x 10^3/mm^3, and 80 x 10^3/mm^3 respectively, while the mean percentage reduction per cycle were 32.4%, 38.0%, 32.3% and 8.4% respectively (Table 2). This represents comparable efficacy of leukocytoreduction by

Table 2. Efficacy and Response to Leukapheresis

Underwent leukapheresis	
Once	5
Twice	7
Thrice	2
Mean absolute (x 10^3/mm^3)/Percentage (%) reduction in WBC per cycle of leukapheresis:	
AML	95.1/32.4
ALL	183.3/38
CML	156.3/32.3
CLL	80/8.4

AML: acute myeloid leukaemia; ALL: acute lymphoblastic leukaemia; CML: chronic myeloid leukaemia; CLL: chronic lymphocytic leukaemia

leukapheresis for AML, ALL and CML, where more than 30% reductions in WBC were achieved. As there was only 1 patient in the CLL subgroup, the low yield seen after leukapheresis may not be conclusive. Leukapheresis was generally well tolerated. There was only 1 patient who developed hypotension after the procedure and it was easily reversible with intravenous fluids.

All but 4 patients demonstrated significant symptomatic improvements. These 4 patients with AML died from leukostasis-related problems before induction chemotherapy could be started despite prompt and effective leukapheresis. Three died within the first week of presentation and 1 in the second week. Severe pulmonary and neurological manifestations were more prominent amongst the early mortalities. Reasons for early mortality included intracranial haemorrhage and pulmonary haemorrhage. There was no early mortality amongst patients in the other subgroups. Patients who died during the first 2 weeks tended to be older. Two AML and all 3 ALL patients managed to achieve complete remission (CR) after induction chemotherapy. CR was defined using the Cancer and Leukaemia Group B criteria, i.e., less than 5% blasts in the bone marrow aspirates with the evidence of maturation of cell lines and the restoration of peripheral blood counts.[16] However, all but 1 patient with ALL relapsed 6 months after achieving CR (the clinical outcomes of the individual patients are tabulated, together with their presenting characteristics, in Table 3).

Discussion

In AML, the frequency of hyperleukocytosis ranges from 5% to 13% in adults.[3,11,12] Although hyperleukocytosis is often reported to be associated with monocytic or myelomonocytic subtypes of AML,[17,18] this was not seen in our study. Four out of 7 AML patients and 1 out of the 3 ALL patients had normal chromosomal profiles (Table 3). Rearrangements involving chromosome11q23, which are commonly reported in acute hyperleukocytic leukaemia,[19,20]

Table 3. Presenting Clinical Characteristics and Outcomes after Leukapheresis

Patient	Presenting WBC counts (x 10^3/mm^3)	Age at diagnosis (y)	Diagnosis and subtype	Cytogenetics profile	Respiratory manifestation	Neurological manifestation	Relapse at 6 months after CR	Mortality (days after leukapheresis)
1	491	20	AML Mo	t(11,20)(p13,q11)	No	Yes	Yes	120
2	253	74	AML*	t(9,11)(p22,q23)	No	Yes	NA	3
3	175	16	AML M1	Normal	Yes	Yes	NA	2
4	305	57	AML M1	Normal	Yes	Yes	NA	14
5	242	66	AML M1	Normal	Yes	Yes	NA	30
6	386	56	AML *	Not done	No	Yes	NA	3
7	316	15	AML M1	Normal	No	Yes	Yes	alive at 12 months
8	750	21	ALL L1	t(4,11)(q21,q23)	No	Yes	Yes	200
9	635	26	ALL L2	t(9,22)(q34,q11)	No	No	Yes	alive at 12 months
10	219	21	ALL L1	Normal	No	No	No	alive at 12 months
11	616	19	CML	t(9,22)(q34,q11)	No	No	NA	alive at 12 months; in chronic phase
12	560	42	CML	t(9,22)(q34,q11)	No	No	NA	alive at 12 months; in chronic phase
13	510	16	CML	t(9,22)(q34,q11)	No	Yes	NA	alive at 12 months in chronic phase
14	950	70	CLL	del(6)(q23),+12	No	No	NA	342 (of unrelated cause)

AML: acute myeloid leukaemia; ALL: acute lymphoblastic leukaemia; CML: chronic myeloid leukaemia; CLL: chronic lymphocytic leukaemia; CR: complete remission; NA: not applicable; WBC: white blood count

* Subtyping not possible

were seen in 2 of the acute leukaemias. The Philadelphia chromosome, t(9,22)(q34;q11), another commonly reported cytogenetic abnormality in hyperleukocytic ALL, was found in 1 patient.

There was a higher incidence of leukostasis among patients with AML than ALL despite their lower presenting WBC counts. This could partly be explained by the fact that leukaemic myeloblasts tend to have a larger mean cell volume than leukaemic lymphoblasts and hence it takes more lymphoblasts to reach a critical leukocrit, and to increase whole-blood viscosity.[21] There are now several indications that leukaemic blast-endothelial cell interactions responsible for vascular disruption and bleeding may be triggered by locally released chemo-attractant factors, which ultimately determine the distribution and severity of the damage. [22, 23] Hence, the adhesion molecules displayed by the leukaemic blasts and their chemotactic response to cytokines in the vascular microenvironment are probably more significant in causing leukostasis than the absolute cell count itself. This leads to the hypothesis that blocking the interactions between these molecules and their receptors may prevent microvascular damages.[24,25] Evidently, future therapies for leukostasis will rely on adhesion molecule-blocking antibodies and until this materialises, early mortality among AML patients with hyperleukocytosis will continue to be high.

In our study, all patients with acute leukaemia who did not succumb to early mortality, and went on to receive induction chemotherapy, were able to achieve a complete remission. This contrasts with the study by Dutcher et al,[3] whereby patients with hyperleukocytosis had a lower complete remission rate and required more cycles of induction chemotherapy. The duration of remission in our patients, however, was short. The prognostic value of hyperleukocytosis in both paediatric and adult ALL has been well-established,[26,27] but the prognostic significance of hyperleukocytosis in AML has not been consistently confirmed. Our study, however, shows that hyperleukocytic AML is associated with poor short- and long-term prognoses. In ALL, the short-term prognosis is remarkably better.

Among the patients with CML, leukapheresis resulted in a marked improvement in their symptoms. They tended to run their usual course after leukapheresis. For that matter, most CML patients present with WBC counts of more than 100,000/mm^3 and they tend to tolerate hyperleukocytosis much better than patients with acute leukaemias due to the sequestration of cells in the liver and spleen as well as the fact that the cells are mostly differentiated myeloid cells.

The presence of respiratory distress and neurological symptoms in AML patients is ominous, and few of these patients survived regardless of how prompt and efficient

leukapheresis was. In the 14 patients we described, 2 clinical characteristics associated with early death were common: age and respiratory distress. Amongst the patients who succumbed to early mortality, clinical deterioration and death occurred after the blast counts had been significantly reduced either by leukapheresis or by chemotherapy, suggesting that while leukocytoreduction may be an important initial step in the management of leukostasis, additional measures are needed to prevent leukostasis-induced deaths. Until these additional measures are identified, the standard immediate treatment of acute hyperleukocytic leukaemias remains that of supportive care, where prompt leukocytoreduction by leukapheresis may still play a role.[28]

The disadvantages of leukapheresis are that it requires the placement of large central venous catheters, which may not always be immediately available and it may worsen the thrombocytopenia as a significant number of platelets are often removed with the WBCs by this procedure. If it is not well orchestrated, it may actually delay the initiation of appropriate supportive care and definitive chemotherapy. The optimal timing of leukapheresis and its use in symptomatic patients with WBC counts of less than 100,000/mm^3 remain highly controversial. It is also unclear whether leukapheresis should be used in patients with hyperleukocytosis but no clinical signs of leukostasis.

In our experience, leukapheresis appears to be a non-toxic and efficient method of leukocytoreduction in patients with hyperleukocytic leukaemia. A single efficient cycle of leukapheresis will usually decrease the TWC count by a mean of 31.9% in a few hours. Early deaths are generally due to fatal intracerebral haemorrhages following intravascular leukostasis with subsequent vessel rupture, or to respiratory distress related to pulmonary leukostasis. Early and effective leukocytoreduction may be helpful in preventing complications secondary to hyperviscosity.

Despite the proven leukocytoreductive capability, we still see a high early mortality rate in hyperleukocytic AML. On the other hand, there is no way for us to determine if the survivors are alive as a result of leukapheresis. Leukapheresis should be used with a clear understanding that early deaths and leukostasis may occur even after WBC counts have been significantly reduced. The use of leukapheresis in chronic leukaemias is even more controversial because of its low incidence of leukostasis and its low risk of early mortality. The prophylactic or therapeutic use of drugs targeting the leukocyte-endothelium interface remains to be investigated.

Conclusion

Reflecting uncertainties exemplified by existing studies, our practice has been to perform leukapheresis at the doctor's discretion. Our results suggest that while leukapheresis is of some short-term value in patients with hyperleukocytic leukaemia, it does not improve overall survival. There has been very little improvement in the management of leukostasis in acute leukaemias in the last 20 to 30 years. Leukapheresis, if available, can be performed, but without delaying the supportive treatment with hydration, allopurinol, and hydroxyurea. Evidence-based guidelines as to when to start, how long to perform and when to stop leukapheresis are not available. Ideally, a large randomised prospective trial testing leukapheresis versus not using leukapheresis in patients with hyperleukocytic leukaemia would help answer the above uncertainties. However, such a study is probably ethically unacceptable. Whether the above data justify the use of leukapheresis in the absence of evidence from a randomised trial is doubtful, but it seems likely that any long-term benefit to be derived from this procedure must await further advances in anti-leukaemia therapy. The identification of the adhesion molecules, soluble cytokines and chemotactic ligand-receptor pairs mediating the endothelial damage in acute hyperleukocytic leukaemias should be a priority if better outcomes are desired.

Acknowledgements

The authors would like to thank the nursing staff of the Aphersis Unit, Haematology Centre, Singapore General Hospital.

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