Summary: We describe 16 leukapheresis (LK) procedures performed in 7 children with different types of leukemia and hyperleukocytosis. We also provide an analysis of previously published experiences of pediatric LK. Median age and body weight of patients were 12.3 years (range, 0.2 to 16.7 y) and 49 kg (range, 5 to 61 kg). Immediate pre-first-LK median white blood cell count was 478 × 10^9/L (108 × 10^9/L to 988 × 10^9/L). All cytoreduction were performed on Cobe Spectra cell separator. Sixty-eight percent of procedures were performed with peripheral veins. Extracorporeal line had been primed with red blood cell for 31% of LK. The median decrease in white blood cell count after each LK was 33% (0% to 69%), and overall decrease after completion of LK procedures was 62% (11% to 94%). Only minor clinical adverse events and no metabolic complication were attributable to LK. No more clinical symptom of hyperleukocytosis was observed after completion of LK procedures. Our findings are consistent with reported results in other pediatric series: LK is a well-tolerated procedure that can be safely performed with an experienced pediatric team even on the smallest children.

Key Words: leukapheresis, hyperleukocytosis, leukostasis, leukemia, children

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At diagnosis time, 5% to 25% of children with acute leukemia present with hyperleukocytosis, arbitrarily defined as a white blood cell (WBC) count >100 × 10^9/L and often associated with increased morbidity and mortality.1,2 Leukostasis is one of the predominant manifestations of hyperleukocytosis: high leukocytes level leads to vascular obstruction and tissue hypoxia. It results from 2 mechanisms: the overcrowding of leukemic blasts in the microcirculation increasing blood viscosity and the adhesive interactions between blasts and endothelium.3 Leukostasis is a medical emergency because it can lead to organ damages and it is associated with increased mortality (up to 40% in adult patients).4 Although leukostasis can affect any organ system, symptoms usually arise from involvement of pulmonary and cerebral microvasculature leading to respiratory distress and neurological and ophthalmological disorders.3 Because of risk of organ damage, therapy must be started quickly to decrease the WBC count. However, early chemotherapy can worsen lysis syndrome in first place despite supportive care (aggressive hydration, rasburicase). Therefore, leukapheresis (LK) (apheresis stems from the Greek to take away or remove) which consists in the withdrawal of whole blood from the body, WBC being then concentrated and removed from the blood and the other constituents being infused back into the patient, allows reducing mechanically the peripheral WBC count and to decrease or prevent leukostasis symptoms, limiting tumor lysis syndrome or disseminated intravascular coagulation. Because of relatively rare occurrence of major hyperleukocytosis in pediatric patients and because of potential apheresis problems which are specific to children (vascular access, flow rate difficulties, and metabolic or hemodynamic problems due to high proportion of patient’s total blood volume extracted from the intravascular circuit), pediatric LK reports are anecdotal2,5–8 and most of reports about LK in hyperleukocytosis concern adult patients.9,10 Here, we report our monocentric experience in LK on children to analyze efficiency and tolerance of the method in pediatric population. We also provide an analysis of previously published experiences of pediatric LK.

MATERIALS AND METHODS

Patients
All patients with leukemia younger than 18 years who underwent LK in Clermont-Ferrand University Hospital Pediatric Department between March 2000 and March 2013 were included in analysis.

LK
All LK procedures were conducted by 2 experienced pediatric nurses and a pediatrician in a LK room installed in the pediatric ward. We used a Cobe Spectra separator (Gambro BCT Inc., Lakewood, CO), under manual control of the standard MNC program (Program 4.7). Minimal hemoglobin (Hb) values before starting LK and transfusion or red blood cell (RBC) priming were according to previously published algorithm.11 Briefly, the priming of the extracorporeal line with 150 mL of irradiated, CytoMega-loVirus negative, RBC was reserved for patients with blood volume of <1 L and/or a Hb level of <100 g/L, but the decision to prime or not was made on a case by case basis, the child’s general condition and the anticipated duration of procedure being of importance. Platelets transfusion was considered when the preapheresis platelets count was
C2
109/L. Citrate glucose formula A (ACD-A) was used as anticoagulant, at a ratio of between 1:12 and 1:15. To prevent hypocalcemia, 0.5 g/10 kg of calcium gluconate was systematically administered 12 hours and 1 hour before LK starts and every 60 minutes during collection (orally or in bolus intravenous dose). Hypothermia was prevented in all patients with woolen blankets and hot-water bottles. Body temperature and diuresis were carefully monitored. As in most patients, a central line was not yet inserted for chemotherapy, peripheral access (18- or 22-G intravenous catheter with wings and injection port; Surflo-W, Terumo, Leuven, Belgium) was privileged. Local anesthesia with lidocaine-prilocaine (5% EMLA cream; Astra, Paris, France) was systematically used for peripheral venous access, together with inhalation of equimolar mixture of nitrous oxide and oxygen (Entonox; Astra Medical, Toulouse, France). A temporary femoral or jugular catheter was used if it was deemed impossible to ensure adequate blood flow with peripheral veins. The femoral/jugular catheter was not removed until the last LK and continuous infusion of heparin solution was used to prevent occlusion of the line. At the start of the procedure the blood flow rate used was 1 mL/kg/min and was subsequently gradually adjusted (manual control) to the maximum rate tolerated. The rate of blood withdrawal that was maintained for the longest duration per LK was considered the procedure flow rate. Complications related to LK were assessed up to 2 hours post-LK with clinical examination and full blood count (1 h post-LK).

RESULTS

Patients

Seven children with newly diagnosed different types of leukemia were concerned, 3 acute lymphoblastic leukemias, 1 acute myeloblastic leukemia, 1 chronic myelomonocytic leukemia, and 2 chronic myelogenous leukemias. Median age, body weight, and blood volume of the patients were 12.3 years (range, 0.2 to 16.7 y), 49 kg (range, 5 to 61 kg), and 3083 mL (range, 836 to 3799 mL), respectively. At the time of diagnosis, 4 patients (57%) suffered from symptoms imputable to hyperleukocytosis (dyspnea, priapism, papilledema, and headache). Immediate pre-first-LK median WBC, platelet count, and Hb level were 478\times 10^9/L (range, 108 to 2000\times 10^9/L to 988 \times 10^9/L), 75 \times 10^9/L (range, 14 \times 10^9/L to

![FIGURE 1. Peripheral blood WBC count during course of leukapheresis in 3 patients with acute lymphoblastic leukemia and hyperleukocytosis. LK indicates leukapheresis; WBC, white blood cells.](image-url)
<table>
<thead>
<tr>
<th>References</th>
<th>No. of Patients</th>
<th>Age (y)/Weight (kg)</th>
<th>Diagnosis</th>
<th>Device</th>
<th>Vascular Access</th>
<th>Blood Volumes Processed /LK</th>
<th>No. LK</th>
<th>WBC (10^9/L)*</th>
<th>Before LK</th>
<th>After LK</th>
<th>Author’s Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haase et al¹</td>
<td>2</td>
<td>14/531 5/57</td>
<td>AML</td>
<td>Cobe Spectra</td>
<td>Sheldon</td>
<td>1 patient’s BV 2.3 patient’s BV</td>
<td>4</td>
<td>302</td>
<td>527</td>
<td>102</td>
<td>LK together with conservative management and specific oncological therapy may contribute to rapid leukocyte reduction with acceptable risk. There were no procedure-related adverse events. Symptoms due to hyperleukocytosis markedly improved after cytoreduction.</td>
</tr>
<tr>
<td>Woloskie et al²</td>
<td>8</td>
<td>0.08/4.5</td>
<td>ALL</td>
<td>Cobe Spectra</td>
<td>8 Fr Quinton jugular</td>
<td>1</td>
<td>551</td>
<td>116</td>
<td>140</td>
<td>LK can be safely performed on even the smallest children with forethought, planning, and a multidisciplinary effort (in a neonatal intensive care unit)</td>
<td></td>
</tr>
<tr>
<td>Bubala et al³</td>
<td>2</td>
<td>15/— 17/—</td>
<td>CML</td>
<td>—</td>
<td>—</td>
<td>3250 mL 4600mL</td>
<td>4</td>
<td>366</td>
<td>353</td>
<td>180</td>
<td>Rapid cytoreduction, no clinical complications</td>
</tr>
<tr>
<td>Veljković et al⁴</td>
<td>2</td>
<td>16/— 17/—</td>
<td>CML</td>
<td>Cobe Spectra</td>
<td>pv</td>
<td>1 patient’s BV</td>
<td>3</td>
<td>320</td>
<td>435</td>
<td>100</td>
<td>LK is safe and effective (a single LK can reduce the WBC count by 30%-60%) therapeutic option for patients with: WBC count of &gt; 300 x 10^9/L or leukostasis (confusion, visual disturbances, hearing disturbances, respiratory symptoms, priapism). Discontinue the LK when the WBC is &lt; 50 x 10^9/L-100 x 10^9/L and clinical manifestations are resolved.</td>
</tr>
<tr>
<td>Lowe et al⁵</td>
<td>68</td>
<td>—</td>
<td>ALL</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>416 (202-1512)</td>
<td>WBC reduction: 244 (37-1342)</td>
<td>500 (108-980)</td>
<td>198 (39-445)</td>
<td>LK may be reserved for patients with extremely high leukocyte counts (&gt;400 x 10^9/L) and patients who have leukostasis-related complications at presentation</td>
</tr>
<tr>
<td>This study</td>
<td>7</td>
<td>12.3 (0.2-16.7)/49 (5-61)</td>
<td>AML</td>
<td>Cobe Spectra</td>
<td>pv or F 1.7 patient’s BV (1-2.5)</td>
<td>2 (1-6)</td>
<td>416 (202-1512)</td>
<td>WBC reduction: 244 (37-1342)</td>
<td>500 (108-980)</td>
<td>198 (39-445)</td>
<td></td>
</tr>
</tbody>
</table>

*Before the 1st and after the last LK.

AML indicates acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; BV, blood volume; CML, chronic myelogenous leukemia; F, femoral line; FR, French; HB, hemoglobin; LK, leukapheresis; pv, peripheral vein; WBC, white blood cells.
whereas Veljković et al\(^7\) propose to use LK in patients with WBC count of $>300 \times 10^9$/L. In our experience, LK is discussed for all patients with WBC count of $>100 \times 10^9$/L for preventing complications of stasis. One to 4 LK procedures per patient are performed in published reports, however, there is no universally accepted criterion as to a discontinuation of the LK. Generally, the aim is a marked reduction of leukocytes, to a “safe” count of $<100 \times 10^9$/L. We agree with Veljković et al\(^7\) recommendation to discontinue LK when the total cell count is $<50–100 \times 10^9$/L and clinical manifestations are resolved.

In our study, as in Lowe et al\(^8\)'s experience, chemotherapy was delayed (no more than 24 h) in children who had LK as compared with those who did not need cytoreduction.

LK procedures are more difficult in very young and small (≤15 kg) children due to the technical requirements of blood cell separators that had been designed for application in adults. However, the ability of Cobe Spectra and more recently of Optia separator to pediatric LK is confirmed.\(^2,7,8\) Woloskie et al\(^8\) showed that these devices allow safe LK even in the smallest patients (≤8 kg).

Because of the small calibers of peripheral veins, central venous access is systematically used by some authors.\(^2,5,8\) This remains a valuable option in very young children. However, as Veljković et al\(^7\), we recommend to use peripheral veins whenever possible.

Here, after each of the 16 LK, the median decrease in WBC count was 33%. The achieved reduction in leukocyte counts is consistent with reported results in other pediatric series (20% to 50%).

Tolerance is a crucial issue in a pediatric context. Most authors agree that LK is well tolerated, with minimal acute side effects, even in children with a body weight as low as 4.5 kg.\(^8\) Given that the main LK-related difficulties encountered in the smallest patients (vascular access and metabolic or hemodynamic problems) are strongly dependent on the experience of the care team, we stress the importance of having a dedicated pediatric environment with an experienced team specifically dedicated to pediatric care, and we recommended to carry out LK in neonatal intensive care unit with reinforced experienced collection team.

In summary, although LK has restricted indications and seems to be obsolete, it is an effective and helpful technique of cytoreduction that we must not forget, especially in some circumstances such as clinical leukostasis or high blood viscosity associated with severe anemia. In children diagnosed with hyperleukocytic leukemia, LK for cytoreduction is a well-tolerated procedure that can be safely performed with an experienced pediatric team even in the smallest children. Although there is consensus that in children with leukostasis-related complications LK may be useful on preventing serious complications, there are no universally accepted criteria as to the WBC count that would initiate leukocyte depletion in children without clinical symptoms of leukostasis (Table 2).

**REFERENCES**


