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The Role of Leukapheresis in the Current Management of Hyperleukocytosis in Newly Diagnosed Childhood Acute Lymphoblastic Leukemia

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Abstract

Background—Hyperleukocytosis in children with acute lymphoblastic leukemia (ALL) has been associated with early morbidity and mortality. The use of leukapheresis in these children treated with contemporary therapy remains controversial.

Procedure—We analyzed clinical data from patients enrolled onto frontline protocols for ALL (Total Therapy XV and XVI) between 2003 and 2014. We documented adverse events within the first 14 days in patients with a white blood cell (WBC) count $\geq 200 \times 10^9/L$ and reviewed their management.

Results—Fifty-three (7.8%) of 678 consecutive pediatric patients with newly diagnosed ALL presented with hyperleukocytosis (median WBC count $393 \times 10^9/L$; range, 200 to 1,014). Two deaths in patient without initial hyperleukocytosis occurred within the first two weeks from diagnosis secondary to bacterial sepsis. A total of 21 (40%) patients with ALL and hyperleukocytosis developed grade 3 or 4 adverse events regardless of the use of leukapheresis ($p > 0.99$ and $p = 0.19$). Sixteen of 53 (30%) patients with ALL received low-dose chemotherapy for leukocytoreduction initially. One third of patients received urate oxidase, and none of the patients with hyperleukocytosis required hemodialysis.

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Conflict of Interest

The authors have no conflict of interest.

Conclusions—The early morbidity and mortality commonly associated with hyperleukocytosis in children with newly diagnosed ALL can be avoided with contemporary supportive care and conservative management possibly obviating the need for costly and potentially dangerous leukapheresis.

Keywords

ALL; molecular diagnosis & therapy; Oncology; general; Leukemias; acute

Introduction

Hyperleukocytosis is an oncologic emergency that can lead to early morbidity and mortality among children with acute lymphoblastic leukemia (ALL). Hyperleukocytosis is generally defined as a white blood cell (WBC) count ≥ 100 or $200 \times 10^9/L$ and is associated with young age, T-cell ALL subtype, and rearrangements of *KMT2A* or *BCR-ABL* [1–3]. Approximately 10% to 20% of children with newly diagnosed acute leukemia present with hyperleukocytosis and are at risk for leukostasis manifesting as acute respiratory distress syndrome (ARDS), intracranial hemorrhage, stroke, and acute kidney injury [2, 4]. Although hyperleukocytosis is more common in children with ALL than those with acute myeloid leukemia (AML) at diagnosis, hyperviscosity and leukostasis occur at a lower WBC count and account for high rates of clinical symptoms and death among patients with AML [5–10].

Leukapheresis has historically been used for leukoreduction in leukemia patients with hyperleukocytosis. However, there are no clinical guidelines for its application. Randomized controlled trials are also lacking to prove efficacy of leukapheresis in reducing morbidity and mortality in this population [3, 11–13]. Patients typically need leukapheresis more than once to effectively reduce the leukemia cell burden. Additionally, leukapheresis may be limited by its timely availability, necessity for central venous access, and potentially can cause other adverse effects and lead to delay in initiation of chemotherapy [4, 7, 14, 15]. Finally, many patients receive concomitant chemotherapy such as hydroxyurea or low-dose cytarabine, making it difficult to assess the effect of leukapheresis alone. The St. Jude Children's Research Hospital (SJCRH) experience with the use of leukapheresis in patients with acute leukemias treated prior to 2003 was previously published^{2, 4} but advances in supportive care may have influenced the optimal management of hyperleukocytosis in patients treated on contemporary protocols. In this study, we summarize the clinical complications, management, and outcomes of pediatric patients with newly diagnosed ALL and hyperleukocytosis treated in the current era.

Methods

Patients

The present study includes patients enrolled on SJCRH frontline ALL protocols Total Therapy XV and Total Therapy XVI between September 2003 and September 2014. Patient and disease characteristics at presentation including age, gender, leukemia subtype, central nervous system (CNS) status, WBC, hemoglobin, platelet count, lactate dehydrogenase (LDH), uric acid, creatinine, potassium, calcium, phosphorous, prothrombin time (PT),

activated partial thromboplastin time (aPTT), and international normalized ratio (INR) at the time of diagnosis were extracted from the electronic medical records. Delay of protocol-based chemotherapy among patients with hyperleukocytosis was calculated using the time point of arrival to our institution and the administration of day 1 daunorubicin. The studies were approved by the Institutional Review Board. Informed consent was obtained from parents or guardians and assent from patients as appropriate at the time of diagnosis.

Leukapheresis and Cyto reduction with Chemotherapy

The decision about whether and when to use leukapheresis was made on a case-by-case basis by the pediatric oncologist on service in consultation with the intensive care unit physician and the director of the blood bank. Indications for leukapheresis were extracted from the chart. Patients had access to expedited leukapheresis 24 hours per day and 7 days per week. Chemotherapy for cyto reduction was optional and per the discretion of the treating physician using prednisolone with or without vincristine.

Adverse Events and Use of Leukapheresis

Among patients with hyperleukocytosis, defined here as a WBC count $200 \times 10^9/L$, the use of leukapheresis was recorded, and adverse events occurring during the first 14 days after diagnosis reviewed [2, 4, 7]. Grade 3 or 4 hemorrhagic, neurologic, renal, and respiratory complications were the toxicities of interest, prospectively captured as per Common Terminology Criteria for Adverse Events (version 2.0 and 3.0), and included in the analysis.. Tumor lysis syndrome was defined as the presence of two or more of the following metabolic derangements within 3 days prior or 7 days after the initiation of leukemia-directed therapy: hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia (laboratory tumor lysis syndrome). The presence of laboratory tumor lysis syndrome and an increased creatinine level, seizures, cardiac dysrhythmia, or death was defined as clinical tumor lysis syndrome [16].

Statistics

Continuous variables were compared using the Wilcoxon rank-sum test (two subgroups) or the Kruskal-Wallis test (more than two subgroups). Comparison of categorical variables between subgroups was performed using the Chi-square test or Fisher's exact test. Analyses were performed with SAS version 9.3 and R version 3.1.0.

Results

Patient Characteristics

Demographic and disease characteristics are summarized in Table 1. A total of 678 patients with ALL (248 enrolled on Total Therapy XV, 430 on Total Therapy XVI) were included in this analysis. The 53 (7.8 %) patients with hyperleukocytosis were more likely to be younger than 1 or older than 9 years of age ($p=0.0003$), male ($p=0.0336$), and to have T lineage immunophenotype ($p<0.0001$), CNS involvement ($p<0.0001$), elevated LDH ($p<0.0001$) and elevated uric acid ($p<0.0001$).

Early Adverse Events and Management

Two deaths secondary to *Bacillus cereus* sepsis and subsequent cardio-respiratory arrest were observed and confirmed by autopsy within the first two weeks after diagnosis of leukemia. Both cases did not present with hyperleukocytosis at diagnosis. A total of 111/678 (16%) patients with ALL developed grade 3 or 4 adverse events of interest in the first two weeks from diagnosis. These adverse events were more common among patients with hyperleukocytosis than those without ($p<0.0001$). Patients with ALL and hyperleukocytosis were more likely to develop hemorrhagic/vascular ($p<0.0001$), neurologic ($p<0.0001$), renal ($p<0.0001$), or respiratory ($p<0.0001$) complications (Table 2).

Eleven of 53 (21%) patients with ALL developed clinical ($n=4$) or laboratory tumor lysis syndrome ($n=7$). Approximately one third of patients received urate oxidase per the discretion of the treating physician. When stratified by protocol, 57 of the 248 (23%) patients enrolled on Total Therapy XV and 174 of the 430 (41%; $p<0.0001$) patients enrolled on Total Therapy XVI received urate oxidase.

Nine of 53 (17%) patients with ALL and hyperleukocytosis underwent leukapheresis (Table 3), but the occurrence of adverse events did not differ significantly between patients who did, or did not, receive leukapheresis (Table 4). Complications from hyperleukocytosis prior to leukapheresis were present in one patient with ALL (pulmonary hyperviscosity). The main indication for leukapheresis among patients with ALL was anticipated renal or metabolic complications ($n=6$). Most common complications following leukapheresis included hypocalcemia ($n=4$), thrombosis ($n=1$), bleeding ($n=2$), and catheter malfunction ($n=1$). The average time to initiation of protocol-based chemotherapy was 25 hours (SD 20; range, 1 to 63 hours) among patients with hyperleukocytosis who underwent leukapheresis without prior or concomitant cytoreduction with chemotherapy. Four patients had both cytoreduction with chemotherapy and leukapheresis. The last patient who underwent leukapheresis at our institution was in 2009. Sixteen of 53 (30%) patients with ALL had leukoreduction with low-dose chemotherapy alone. Among this group, we saw four patients with preceding renal ($n=1$), pulmonary ($n=2$), and vascular complications ($n=1$). The average time to protocol based chemotherapy was 64 hours (SD 21; range 34 to 100 hours) in patients that had undergone cytoreduction. There was a larger average reduction of WBC count after cytoreduction compared to leukapheresis (75% vs. 53%; $p=0.0431$; Figure 1). Among patients with hyperleukocytosis, there was no significant difference in the mean age at diagnosis, WBC count, or frequency of early adverse events comparing patients that underwent cytoreduction with leukapheresis alone, chemotherapy alone, or a combination of both.

Discussion

In this study, we found that the use of leukapheresis was of no clinical benefit for children with acute lymphoblastic leukemia that presented with a WBC count $\geq 200 \times 10^9/L$ and related adverse events.

While leukapheresis has been historically used for leukoreduction to avoid complications from leukostasis and metabolic complications, there is no clear data to show a benefit of using this procedure [4, 8, 17, 18]. Since 2009, we have exclusively used low-dose chemotherapy for leukoreduction prior to initiation of protocol-based chemotherapy when warranted. The results of this study, in conjunction with prior data, demonstrate that the frequency of early adverse events secondary to hyperleukocytosis was not improved by the use of leukapheresis. In fact, recent studies have noted leukapheresis-related complications in as many as 85% of procedures in patients with either ALL or AML. These complications were predominantly comprised neurological and respiratory problems [13]. Seven of our 9 (78%) patients that underwent leukapheresis experienced procedure related complications such as hypocalcemia, catheter malfunction, coagulopathy, and catheter related thrombosis. While some of these complications were managed in the short-term, others such as catheter related thrombi required prolonged anti-coagulation, adding more complexity to the care of these patients and potential long term morbidity. We found no difference in the frequency of early adverse events comparing patients that underwent leukapheresis, cytoreduction with chemotherapy, or a combination of both. In terms of effectiveness of lowering the WBC count, the use of cytoreduction appeared superior to leukapheresis although it needs to be mentioned that it involved repeated doses of steroids over a longer period of time than leukapheresis. Therefore, we believe that leukapheresis may only be a perceived need but in fact not necessary in patients with ALL and hyperleukocytosis. In contrast to this population, there are studies that have demonstrated a trend towards decreased early death rates in the AML population using leukapheresis. For example, Creutzig *et al.* recently recommended the use of leukapheresis in patients with a WBC count $>200 \times 10^9/L$ and with FAB M4/M5 to prevent bleeding/leukostasis. However, as the authors state themselves, more evidence is needed in light of the lack of randomized controlled trials and other circumstantial variables that may complicate the interpretation of published studies [19].

The clinical complications from hyperleukocytosis are caused by the increased blood viscosity and decreased deformability of individual leukemia cells that lead to leukostasis in the microvasculature and small vessel occlusion. Therefore, transfusion with packed red blood cells is generally delayed in patients with hyperleukocytosis to avoid precipitation of leukostasis [5, 6]. The larger size of lymphoblasts compared to normal blood cells predispose patients with hyperleukocytosis to develop leukostasis [5, 6]. Hence, it is not surprising that children with acute leukemia and hyperleukocytosis have a higher incidence of early adverse events, including death [2–4, 7, 10].

In our cohort, 2/678 (0.3%) patients died from infection during the first 14 days of induction. Neither patient presented with hyperleukocytosis. We demonstrate that meticulous modern supportive care and rapid diagnosis and initiation of appropriate chemotherapy can eliminate deaths related to complications of hyperleukocytosis. This improvement may be due to the prompt availability of platelet transfusion for thrombocytopenia, delayed packed red blood cell transfusion until resolution of hyperleukocytosis, early initiation of low-dose cytoreductive chemotherapy, and careful management of tumor lysis syndrome.

Historically, about 20% of patients with high-risk leukemia and acute kidney injury during induction therapy underwent hemodialysis [20]. In this study, two patients required

hemodialysis but neither of them presented with hyperleukocytosis. One of the two patients arrived at SJCRH with significant electrolyte imbalance from tumor lysis syndrome and underwent hemodialysis on day -1. The other patient developed renal failure on day 2 of induction therapy, secondary to tumor lysis syndrome. Neither of them underwent leukapheresis. We attribute this low rate of hemodialysis to excellent supportive care and liberal use of urate oxidase, which is highly effective to prevent urate nephropathy and acute kidney injury [21].

Previous reports have demonstrated controversial results regarding delay of chemotherapy and leukapheresis [4, 18]. The average time to start of protocol-based therapy was shorter in patients that underwent leukapheresis compared to cytoreduction which is not surprising because in our experience, cytoreduction commonly requires more than one dose to lower the WBC effectively and there is a perceived reduction of urgency to start induction, given that the patient is already receiving a therapeutic intervention.

Lastly, the differences in complications among the studied sub-groups of patients, or the lack thereof, need to be interpreted cautiously given the relatively small number of patients and events.

In summary, we systematically present the clinical complications, management, and outcomes of a contemporary pediatric cohort of newly diagnosed patients with ALL that presented with hyperleukocytosis. Our results show no early deaths related to hyperleukocytosis among these patients and suggest that leukapheresis may not be necessary to reduce the occurrence of early adverse events in this population.

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Abbreviations

ALL	Acute lymphoblastic leukemia
aPTT	activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
CNS	Central nervous system
INR	International normalized ratio
LDH	Lactate dehydrogenase
PT	Prothrombin time
SJCRH	St. Jude Children's Research Hospital
WBC	White blood cell

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Figure 1.
Decline of WBC count after use of leukapheresis (solid line) and cytoreduction (dashed line)
in patients with ALL

TABLE I

Presenting characteristics of patients with acute lymphoblastic leukemia with and without hyperleukocytosis

Characteristics	WBC × 10 ⁹ /L at Diagnosis		
	All (%) n=678	<200 (%) n=625	200 (%) n=53
Age [years]			
Mean (SD)	7.1 (4.9)	7.0 (4.9)	8.2 (5.0)
Median (range)	5.5 (0.2–18.9)	5.3 (0.2–18.9)	7.8 (0.3–18.7)
Gender			
Male	379 (56)	342 (55)	37 (70)
Female	299 (44)	283 (45)	16 (30)
Lineage			
B cell	567 (84)	549 (88)	18 (34)
T cell	111 (16)	76 (12)	35 (66)
BCR-ABL status			
Present	15 (2)	13 (2)	2 (4)
Protocol			
Total XV	248 (37)	231 (37)	17 (32)
Total XVI	430 (63)	394 (63)	36 (68)
Urate oxidase			
Yes	231 (34)	199 (32)	32 (60)
No	447 (66)	426 (68)	21 (40)
Laboratory values		Median (range)	
Hematology			
WBC count [×10 ⁹ /L]	12.8 (0.2–1,014)	11 (0.2–200)	338 (200–1,014)
Hemoglobin [g/dL]	8.0 (0.8–17.3)	7.9 (0.8–17.3)	8.6 (3.4–13.8)
Platelets [×10 ⁹ /L]	50 (0–902)	52 (0–902)	32 (5–243)
Chemistry			
Potassium [mmol/L]	4.1 (2.3–8.9)	4.1 (2.6–8.9)	4.2 (2.3–7.4)
Calcium [mg/dL]	9.4 (4.0–16.3)	9.40 (6.6–16.3)	9.2 (4.5–10.5)
Phosphorous [mg/dL]	4.8 (1.7–11.3)	4.8 (1.9–11.3)	4.2 (1.7–6.3)
Creatinine [mg/dL]	0.4 (0.1–2.3)	0.4 (0.2–2.3)	0.5 (0.1–1.2)
LDH [units/L]	753 (103–23,564)	681 (103–23,564)	3,985 (360–20,132)
Uric acid [mg/dL]	4.9 (1.0–27.3)	4.7 (1.0–27.3)	9.3 (3.3–16.1)

Characteristics	WBC $\times 10^9/L$ at Diagnosis		
	All (%) n=678	<200 (%) n=625	200 (%) n=53
Coagulation			
INR	1.1 (0.7–3.1)	1.1 (0.7–3.1)	1.4 (1.0–3.1)
aPTT [sec]	30.8 (19.2–79.8)	30.8 (19.2–79.8)	30.9 (21.8–49.8)
PT [sec]	14.1 (10.4–32.3)	13.9 (10.4–25.8)	16.9 (12.7–32.3)

aPTT – partial thromboplastin time; CNS – central nervous system involvement; 1=no blasts, 2=1–4blasts, 3 blasts; INR – international normalized ratio; PT – prothrombin time; WBC – white blood cells

TABLE II

Comparison of pertinent complications among patients with acute leukemia who presented with and without hyperleukocytosis at diagnosis

Acute lymphoblastic leukemia				
Toxicity (grade 3 and 4)	WBC × 10 ⁹ /L at Diagnosis			P value
	All (%) n=678	<200 (%) n=625	≥200 (%) n=53	
Any				
Yes	111 (16)	90 (14)	21 (40)	<0.0001
No	567 (84)	535 (86)	32 (60)	
Hemorrhagic/vascular				
Yes	6 (1)	5 (1)	1 (2)	<0.0001
No	672 (99)	620 (99)	52 (98)	
Neurologic				
Yes	18 (3)	15 (2)	3 (6)	<0.0001
No	660 (97)	610 (98)	50 (94)	
Renal				
Yes	47 (7)	38 (6)	9 (17)	<0.0001
No	631 (93)	587 (94)	44 (83)	
Respiratory				
Yes	51 (8)	41 (7)	10 (19)	<0.0001
No	627 (92)	584 (93)	43 (81)	

WBC – white blood cells

TABLE III

Clinical characterization of patients who underwent leukapheresis at the time of diagnosis

Study	Age	Sex	WBC [×10 ⁶]	HGB [g/dL]	PLT [×10 ⁶]	Lineage/ FAB	Mediastinal mass	Laboratory abnormalities	Urate oxidase	AEs from hyperleukocytosis			Leukapheresis			Hours until chemotherapy	Status
										Prior to leukapheresis	After leukapheresis	Number of leukapheresis procedures	Indication besides leukocytosis	Complications			
Acute lymphoblastic leukemia																	
TOT XV	5.6	M	1,014	7.5	39	T	No	Uric acid 10, INR 2.1	Yes	-	-	NA	Risk for renal dysfunction	Hypocalcemia	63	Expired	
TOT XV	11.7	M	392	11.4	6	T	Yes	Uric acid 14	No	-	-	1	Risk for renal dysfunction	Hypocalcemia	10	Alive	
TOT XV	6.3	M	357	10.8	52	T	No	Uric acid 11, INR 1.9	No	-	-	1	Risk for renal dysfunction	Bleeding at catheter site	15	Alive	
TOT XV	1.2	F	656	6.8	33	T	Yes	Uric acid 10	No	-	-	2	Risk for renal dysfunction	Hypocalcemia, bleeding	24	Relapsed, salvaged, alive	
TOT XV	5.4	F	657	11.7	142	T	Yes	K 6.2, Uric acid 10, aPTT 38, INR 1.5	No	-	-	2	Risk for renal dysfunction	Hypocalcemia	26	SCT, alive	
TOT XV	8.0	M	315	13.3	243	T	No	Uric acid 10, PT 20, aPTT 38, INR 1.7	Yes	Pulmonary	-	1	Risk for renal dysfunction	None	15	Alive	
TOT XVI	8.5	F	346	4.9	56	ETP	No	-	No	-	-	1	-	None	50	BMT, alive	
TOT XVI	1.8	M	225	7.3	16	B	No	Uric acid 5	No	-	Pulmonary	1	-	Manual pheresis (patient size)	1	Alive	
TOT XVI	0.5	M	412	7.7	37	B	No	-	No	-	Thrombosis	2	-	Catheter related thrombus, difficult access	26	Alive	

aPTT – partial thromboplastin time; CNS – central nervous system involvement; |=no blasts, 2=1–4 blasts, 3 blasts; Cr – creatinine; FAB – French American British classification; HGB – hemoglobin; INR – international normalized ratio; K – potassium; Phos – phosphorous; PT – prothrombin time;WBC – white blood cells

TABLE IV

Comparison of pertinent complications among patients that presented with hyperleukocytosis who did or did not undergo leukapheresis

Acute lymphoblastic leukemia				
Characteristics	Leukapheresis			
	All (%) n=53	Yes (%) n=9	No (%) n=44	P value
Any				
Yes	21 (40)	3 (33)	18 (41)	NS
No	32 (60)	6 (67)	26 (59)	
Hemorrhagic/vascular				
Yes	1 (2)	1 (11)	0 (0)	NS
No	52 (98)	8 (89)	44 (100)	
Renal				
Yes	9 (17)	0 (0)	9 (20)	NS
No	44 (83)	9 (100)	35 (80)	
Respiratory				
Yes	10 (19)	2 (22)	8 (18)	NS
No	43 (81)	7 (78)	36 (82)	
Neurologic				
Yes	3 (6)	0 (0)	3 (7)	NS
No	50 (94)	9 (100)	41 (93)	

NS – not significant