Management of hyperleukocytosis in pediatric acute myeloid leukemia using immediate chemotherapy without leukapheresis: results from the NOPHO-DBH AML 2012 protocol

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Abstract

Hyperleukocytosis in pediatric acute myeloid leukemia (AML) is associated with severe complications and an inferior outcome. We report results on patients with hyperleukocytosis included in the NOPHO-DBH AML 2012 study. We recommended immediate initiation of full-dose chemotherapy (etoposide monotherapy for 5 days as part of the first course), avoiding leukapheresis and prephase chemotherapy. Of 714 patients included in the NOPHO-DBH AML 2012 study, 122 (17.1%) had hyperleukocytosis, and 111 were treated according to the recommendations with etoposide upfront without preceding leukapheresis or prephase chemotherapy. The first dose was applied the same day as the AML diagnosis or the day after in 94%. Etoposide was administered via peripheral veins in 37% of patients without major complications. After initiation of etoposide the white blood cell counts on days 2-5 were 69%, 36%, 17% and 8%, respectively, of the pre-treatment level. On day 3, 81% of patients had a white blood cell count <100 x10^9/L. Five-year event-free and overall survival rates for all patients with hyperleukocytosis were 52.9% (95% confidence interval [95% CI]: 44.4-63.0) and 74.1% (95% CI: 66.4-82.6), compared to 64.9% (95% CI: 60.9-69.1) and 78.9% (95% CI: 75.4-82.4) for patients without hyperleukocytosis (P<0.001 for event-free survival, P=0.1 overall survival). Six-week early mortality was 4.1% for all patients with hyperleukocytosis (2.7% for the 111 patients treated with etoposide upfront). We conclude that management of hyperleukocytosis in pediatric AML with immediate etoposide monotherapy without leukapheresis or prephase chemotherapy is feasible, safe and effective. The reduction

in white blood cell count during the first days is comparable to the reported results of leukapheresis, and outcomes seem at least equivalent to therapies including leukapheresis. Based on our results, we advocate abandoning leukapheresis for hyperleukocytosis in pediatric AML. Instead, it is crucial to start induction chemotherapy as early as possible.

Introduction

Hyperleukocytosis is commonly, but arbitrarily, defined as a white blood cell (WBC) count above 100x10^9/L.[1] In pediatric acute myeloid leukemia (AML), hyperleukocytosis carries an increased risk of early morbidity and mortality, mainly due to the effects of leukostasis (infarction, pulmonary involvement) and bleeding,[2,3] whereas tumor lysis syndrome is less frequent than in acute lymphoid leukemia.[4]

There has been an ongoing debate regarding the benefit, in both adults and children, of cytoreductive measures such as prephase chemotherapy and leukapheresis or exchange transfusion preceding the initiation of full AML therapy.[5-8] The technical feasibility and safety of leukapheresis has been confirmed in various studies, but several authors have questioned its clinical benefit. Still, many authors advocate leukapheresis in situations complicated by severe leukostasis.[9-11] Others have discussed possible drawbacks of leukapheresis, particularly that of delaying full AML therapy, and have advocated immediate AML chemotherapy.[12,13] After evaluation of the existing literature and analysis of the Nordic Society of Pediatric Hematology and Oncology (NOPHO) experiences,[14] the NOPHO-DBH consortium issued recommendations on the management of hyperleukocytosis as an appendix to the NOPHO-DBH 2012 protocol.[15] Since we considered the benefit of leukapheresis/exchange transfusion as uncertain, we instead recommended immediate initiation of the first course of induction (which starts with 5 days of monotherapy with etoposide), as soon as the AML diagnosis was established, avoiding both prephase chemotherapy and leukapheresis/exchange transfusion. Our hypothesis was that immediate chemotherapy would be at least as effective and safe as initial therapy with leukapheresis or exchange transfusion. The aim of the present paper is to report the results of this rather uncommon approach.

Methods

Definitions

Hyperleukocytosis was defined as a highest WBC count before therapy of ≥100x10^9/L. Early death is defined differently in various studies, so we decided to report on early death both within 2 weeks and within 6 weeks of diagnosis. To categorize WBC response to etoposide therapy, we arbitrarily used the term slow responder for a patient whose WBC count was still >100x10^9/L on day 3, before the third dose of etoposide.

Patients and therapy

The study includes patients enrolled in the NOPHO-DBH AML 2012 protocol, diagnosed between March 1, 2013 and September 30, 2021 from the NOPHO-DBH-SHIP consortium. This consists of the Nordic countries (Sweden, Denmark, Finland, Norway, Iceland), the Baltic countries (Lithuania, Estonia, Latvia), Belgium, the Netherlands, Hong Kong, Israel, Spain and (after conclusion of this study) Portugal. Ethical committees of each country approved the protocol and all parents/participants provided informed consent. Eligibility criteria were age under 18 years and *de novo* AML, excluding patients with Down syndrome, myelodysplastic syndrome, acute promyelocytic leukemia, secondary AML and (appropriate only for patients without hyperleukocytosis) isolated chloromas without recurring AML-related fusion genes.

Patients with hyperleukocytosis were identified in the study database, and relevant data extracted. In addition, questionnaires were sent to the treating hospitals, asking for more detailed information about patients with hyperleukocytosis. Questions included WBC count on days 1-6 of therapy, use of peripheral lines for chemotherapy, date of AML diagnosis and initiation of hydration, time point of first etoposide dose, modifications of etoposide dose, use of leukapheresis/exchange transfusion and prephase chemotherapy, as well as questions on treatment in an Intensive Care Unit, ventilator therapy, and complications of hyperleukocytosis and/or therapy. We received completed questionnaires for all of the 122 included patients with hyperleukocytosis.

Treatment of acute myeloid leukemia and management of hyperleukocytosis

All patients were treated according to the NOPHO-DBH AML 2012 protocol, registered at the European Medical Agency (EUDract 2012-002934-35) and at *www.clinicaltrials.gov* (NCT01828489), with two randomized questions in the first and second induction courses.[16] The first AML course was either MEC (mitoxantrone, etoposide, cytarabine; standard arm), or DxEC (liposomal daunorubicin, etoposide, cytarabine; experimental arm). The MEC course stems from the Japanese AML-99 protocol.[17] Both MEC and DxEC commenced with 5 days of etoposide monotherapy (150 mg/m^2 as a 2-hour infusion daily) and continued with an anthracycline (mitoxantrone or daunorubicin) and cytarabine from day 6. From November 2017 all patients received MEC because daunorubicin became unavailable. Guidelines related to the protocol included recommendations on the management of hyperleukocytosis. In addition to hydration, cautious use of red blood cell transfusions,

but liberal use of platelet transfusions, and administration of rasburicase were encouraged. The first etoposide dose (as part of course 1) was to be started immediately after the AML diagnosis had been confirmed. Etoposide could be administered via peripheral venous lines if insertion of a central venous line was considered too risky. Use of prephase chemotherapy and leukapheresis/exchange transfusion was discouraged regardless of WBC count and complications.

Statistics

The statistical analysis was performed using IBM SPSS statistics version 28 or R version 4.0.3 (R Foundation, Vienna, Austria). The χ^2 test was used to compare the frequency of events. Continuous data were compared using the Student *t* test or Mann-Whitney U test, as appropriate. The probability of overall survival was calculated using the Kaplan-Meier method. Overall survival was defined as time elapsed between date of diagnosis and death. Event-free survival was defined as time from diagnosis until death, resistant disease, relapse or second malignant neoplasm. Cumulative incidence of relapse was calculated using time from diagnosis until relapse with all other events as competing events. Treatment-related mortality was defined as all deaths, with relapse, resistant disease and second malignant neoplasm as competing events. Ninety-five percent confidence intervals (95% CI) for survival curves were calculated according to the method of Link.[18] Cumulative incidence of relapse and transplant-related mortality were calculated using competing risks data analysis according to Fine and Gray.[19] Estimates of event-free and overall survival, cumulative incidence of relapse and transplant-related mortality are given at 5 years. All living patients were censored at the time of last follow up but not later than August 31, 2022. The log-rank test was used to compare survival of subgroups. Cox proportional hazards models were used to estimate univariate and multivariate hazard ratios (HR) for survival outcomes. All tests were two-sided and *P* values <0.05 were considered statistically significant.

Results

Patients

One hundred twenty-two of the 714 (17%) per-protocol

Table 1. Characteristics and outcome of 714 patients included in the study, divided according to whether they did or did not have hyperleukocytosis.

	Hyperleukocytosis N=122	Non-hyperleukocytosis N=592	*P*
Male sex, N (%)	63 (52)	301 (51)	0.87
Age, N (%)			0.71
<2 years	33 (27)	133 (22)	
2-9 years	42 (34)	210 (36)	
10-14 years	33 (27)	168 (28)	
15-18 years	14 (12)	81 (14)	
CNS involvement, N (%)	22/119 (19)	75/587 (13)	0.10
Extramedullary tumor, N (%)	20/113 (18)	62/584 (11)	0.03
Genetic subgroups, N (%)			
RUNX1::RUNX1T1	2 (1.7)	91 (15)	<0.001
CBFB::MYH11	13 (11)	54 (9.1)	0.58
KMT2A::MLLT3	14 (12)	63 (11)	0.76
KMT2A other	28 (23)	72 (12)	0.002
FLT3-ITD no *NPM1*	25 (21)	48 (8.1)	<0.001
FLT3-ITD with *NPM1*	7 (5.8)	11 (1.9)	0.01
NPM1 no *FLT3*-ITD	4 (3.3)	22 (3.7)	0.83
Other aberrations	28 (23)	231 (39)	<0.001
Outcomes			
Early death (6 weeks), N (%)	5 (4.1)	13 (2.2)	0.06
Complete remission, N (%)	100 (82)	552 (93)	<0.001
Resistant disease, N (%)	14 (12)	23 (3.9)	<0.001
TRM at 5 years, % (95% CI)	7.4 (3.6-12.9)	5.9 (4.2-8.1)	0.47
CIR at 5 years, % (95% CI)	28 (19.4-36.1)	25 (21.2-28.6)	0.32
EFS at 5 years, % (95% CI)	53 (44.4-63.0)	65 (60.9-69.1)	<0.001
OS at 5 years, % (95% CI)	74 (66.4-82.6)	79 (75.4-82.6)	0.10

CNS: central nervous system; ITD: internal tandem duplication; TRM: transplant-related mortality; 95% CI: 95% confidence interval; CIR: cumulative incidence of relapse; EFS: event-free survival; OS: overall survival.

patients had hyperleukocytosis. They did not differ from patients without hyperleukocytosis in terms of age, sex or central nervous system involvement, but they did have a higher proportion of extramedullary tumors (18% *vs.* 11%) (Table 1). They had a significantly lower frequency of *RUNX1::RUNX1T1* fusions (2% *vs.* 15%), and a higher proportion of *KMT2A* rearrangements (*KMT2A::MLLT3* excluded) (23% *vs.* 12%) and *FLT3*-internal tandem duplication (ITD) without *NPM1* mutation (21% *vs.* 8%).

Patients with hyperleukocytosis: white cell counts, time intervals, tumor lysis prophylaxis

The median of the highest WBC counts in patients with hyperleukocytosis was 211x10^9/L (range, 101-880x10^9/L). Sixty-nine patients (57%) had WBC >200x10^9/L (Table 2). A definite diagnosis of AML was established at the latest 1 day after admission in 111/118 cases (94%, information missing for 4 patients). Hydration was started on the day of admission or before admission, at the referring institution, in 77 of 88 re-

Table 2. Clinical and biological characteristics, complications and outcome for all 122 hyperleukoctosis patients combined and split according to whether they received etoposide monotherapy upfront or commenced therapy with prephase chemotherapy and/or leukapheresis.

	All HL patients N=122	Etoposide upfront N=111	PCT and/or LA* N=11	*P*
Male sex, N (%)	63 (52)	56 (51)	7 (64)	0.53
Age in years Mean ± SD Median (range)	 7.1±0.5 7.0 (0-17)	 7.3±0.5 7.0 (0-17)	 4.8±2.0 0 (0-17)	0.35
Highest WBC count before therapy, x 10^9/L Mean ± SD Median (range)	 236±11 211 (101-880)	 228±11 210 (101-880)	 313±32 329 (145-481)	0.02
WBC >200 x 10^9/L, N (%)	69 (57)	60 (54)	9 (81)	0.08
CNS involvement, N (%)	20/109 (18)	18/100 (18)	2/9 (22)	0.89
French-American-British type, N (%) M0/M1/M2 M4 M5	 26/100 (26) 24/100 (24) 49/199 (50)	 24/89 (27) 20/89 (23) 45/89 (51)	 2/11 (18) 4/11 (36) 4/10 (40)	0.57
Genetic subgroup, N (%) *RUNX1::RUNXT1* *CBFB::MYH11* *KMT2A::MLLT3* *KMT2A*-other *FLT3*-ITD no *NPM1* Other aberrations	 0/117 (0) 14/117 (12) 11/113 (10) 28/114 (25) 33/120 (28) 35/103 (34)	 0/106 (0) 14/107 (13) 11/103 (11) 25/105 (24) 30/108 (28) 31/88 (35)	 0/11 (0) 0/10 (0) 0/10 (0) 3/9 (33) 3/12 (25) 3/8 (38)	 - 0.004 0.21 0.09 0.81 0.77
Therapy, complications and early death rate Interval from diagnosis to 1st dose of etoposide in days Mean ± SD Median (range) Care in Intensive Care Unit, N (%) Mechanical ventilation, N (%) CNS hemorrhage and/or infarction, N (%) Bleeding outside CNS, N (%) Thromboembolic event, N (%) Disseminated intravascular coagulation, N (%) Tumor lysis syndrome, N (%) Cardiac complications, N (%) Infection grade 3 or 4 CTCAE, N (%) No complications, N (%) Early death <2 weeks, N (%) Early death <6 weeks, N (%)	 0.5±0.06 0 (0-3) 45/120 (38) 19/120 (17) 5/121 (4.1) 8/120 (6.7) 11/121 (9.1) 6/115 (5.2) 20/121 (17) 9/120 (7.5) 50/120 (42) 65/120 (54) 3 (2.5) 5 (4.1)	 0.4±0.06 0 (0-3) 34/109 (31) 15/109 (14) 4/110 (3.6) 7/109 (6.4) 9/109 (8.3) 6/108 (5.6) 16/109 (15) 7/109 (6.4) 45/110 (41) 63/109 (58) 2 (1.8) 3 (2.7)	 0.9±0.18 1 (0-3) 11 (100) 4 (36) 1 (9.1) 1 (9.1) 1 (9.1) 0/8 (0) 3 (33) 2 (18) 5/10 (50) 2 (18) 1 (9.1) 2 (18)	 0.05 - - <0.001 0.07 0.32 0.55 0.63 0.49 0.24 0.06 0.58 0.01 0.25 0.06

*One patient underwent both leukapheresis and exchange transfusion. HL: hyperleukocytosis; PCT: prephase chemotherapy; LA: leukapheresis; SD: standard deviation; WBC: white blood cell count; CNS: central nervous system; ITD: internal tandem duplication; CNS: central nervous system: CTCAE: Common Terminology Criteria for Adverse Events.

ported cases (88%). In ten cases hydration was commenced the day after (11%), and in one case after 2 days. Hydration alone - in patients not treated with leukapheresis and/or prephase chemotherapy - resulted in a mean WBC drop from 228.6±11x10^9/L (highest value) to 192.9±11 x 10^9/L (value at the start of etoposide treatment). Rasburicase alone was used as tumor lysis prophylaxis or therapy in 70 cases (63%), allopurinol alone was used in 18 (16%), both drugs in 19 patients (17%), and in four patients neither allopurinol nor rasburicase was used (11/122 not reported).

Prephase chemotherapy, leukapheresis and exchange transfusion

Contrary to the recommendations, 11/122 patients (9%) were treated with prephase chemotherapy and/or leukapheresis/exchange transfusion (Figure 1, Table 2). Eight of 113 patients (7%, missing information for 9 patients) received prephase chemotherapy, in some cases before the AML diagnosis had been confirmed. This consisted of typical AML pretreatment (low-dose cytarabine ± thioguanine) in three patients, steroids in three patients, and all-*trans* retinoic acid/dexamethasone in one patient misdiagnosed as having acute promyelocytic leukemia; the prephase chemotherapy was not specified in one case. Leukapheresis was performed in six of 119 patients (5%, information missing for 3 patients). In two patients, two procedures were done. The only exchange transfusion was performed in a patient who also underwent leukapheresis. The time interval from leukapheresis to the first dose of etoposide was -2 days in one patient (i.e., etoposide was started before leukapheresis), 1 day in three patients, and 2 days in two patients. The median of the highest WBC in the six leukapheresis patients was 320x10^9/L compared to 210x10^9/L in patients not treated with leukapheresis (P=0.16). All six patients were admitted to the Intensive Care Unit.

Etoposide therapy, peripheral venous access

In 94% of 111 patients who received etoposide upfront, the first dose was administered the same day or the day after the AML diagnosis had been confirmed (101/107 patients, missing information for 4 cases). The duration of the infusion was 2 hours in 96% of cases, and was 3 or 4 hours in the remaining five cases. The dose of etoposide was modified in two of 111 patients who received the drug upfront (aborted after the second dose in 1 patient; dose reduced to 90% due to tumor lysis syndrome in the other patient). Etoposide was administered through a peripheral venous line in 43 of 115 reported cases (37%). The peripheral line was used for 1 day in eight patients, for 2-4 days in 14 patients, and for 5 days in 13 patients (missing data for 8 patients). In one patient treated for 5 days, the etoposide infusion was complicated by extravasation, which was treated with local hyaluronidase leaving no later sequelae. One patient had a superficial thrombophlebitis. No other complications were reported.

Response to etoposide monotherapy

The 111 patients who received etoposide monotherapy upfront were included in the following analyses. In one of these patients, etoposide treatment was aborted after two doses due to increasing WBC count, and he proceeded to leukapheresis. This patient is included on an intention-to-treat basis. Table 2 displays the characteristics of the etoposide-treated patients compared to the 11 patients who underwent leukapheresis or prephase chemotherapy as their initial therapy. The latter patients had significantly higher WBC counts.

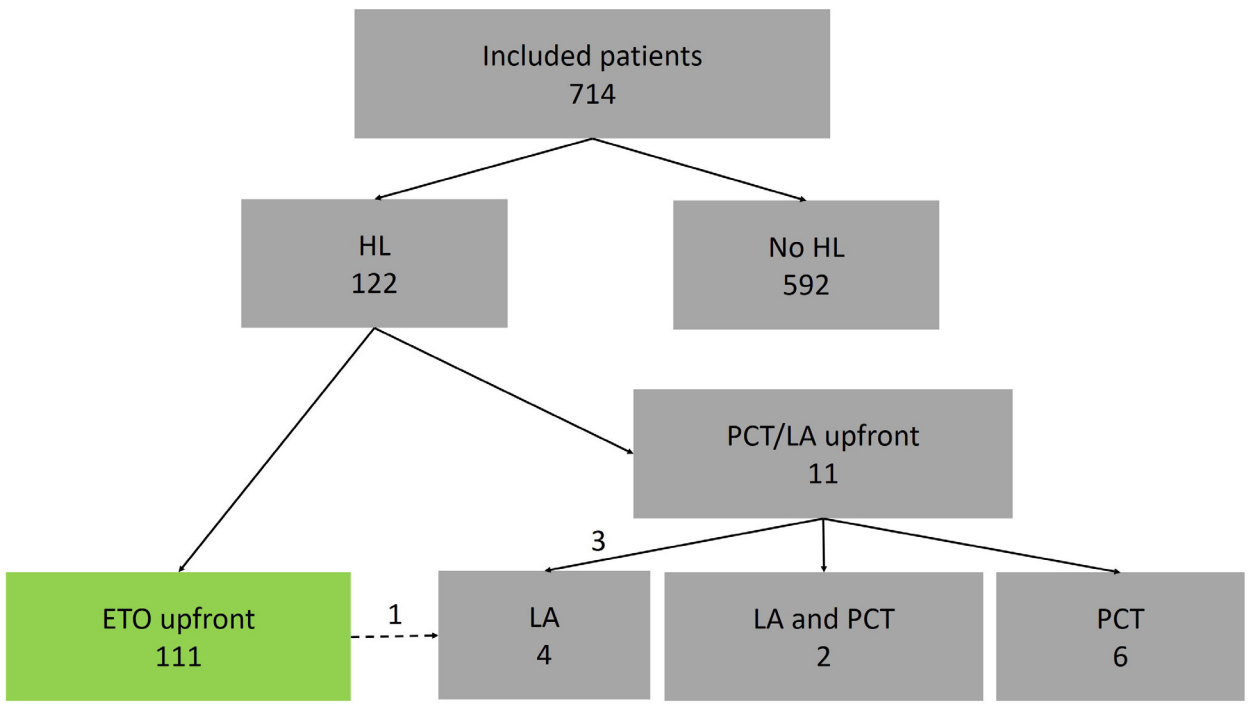

Figure 1. Initial management of the 714 patients included in the study. Green color indicates patients treated according to the recommendations with upfront etoposide. One of these underwent leukapheresis on day 4 because of a poor response to etoposide. In one patient who underwent leukapheresis, exchange transfusion was also performed. HL: hyperleukocytosis; PCT: prephase chemotherapy; LA: leukapheresis; ETO: etoposide.

After starting etoposide treatment, the numbers of WBC remaining on days 2-5 were 69%, 36%, 17% and 8%, respectively, of the pre-treatment level, i.e. a reduction of 50% per day from day 2 (Figure 2A). It is important to note that the interval between starting etoposide and WBC value day 2 (mean 16 hours) is shorter than the intervals between WBC counts on the other days (mean 24 hours), which may explain the smaller reduction in WBC between days 1 and 2. On day 3 (after 2 doses of etoposide), 89/110 patients (81%) had a WBC count below 100x10^9/L and 84/106 (80%) had less than 50% of the WBC on day 1.

Figure 2B displays WBC curves for all 111 etoposide-treated patients during the first 5 days of their therapy. According to our definition (WBC >100x10^9/L on day 3, i.e. after 2 doses of etoposide), we identified 21 slow responders. Compared to good responders, these slow responders had significantly higher WBC counts (mean 324x10^9/L *vs.* 169x10^9/L; *P*<0.001), more frequently had *FLT3*-ITD (10/20 [50.0%] *vs*. 20/88 [22.7%]; *P*=0.04) and less frequently had French-American-British (FAB) type M4/M5 leukemia (8/17 [47%] *vs*. 57/72 [79%]; *P*=0.007) (the denominators are different because of missing data). Importantly, in all slow responders but one the WBC had dropped on day 3 (in 12/21 to <67% of the value before etoposide) and continued to decrease in the following days. On day 6, after five doses of etoposide, 19 of the 21 slow responders had a WBC count <50x10^9/L.

Complications

The complications that occurred in the study patients are shown in Table 2. The most feared complications of hyperleukocytosis are pulmonary leukostasis and cerebral hemorrhage and/or infarction. Nearly half of all patients with hyperleukocytosis required supplemental oxygen, and 17% required mechanical ventilation, which usually reflects severe pulmonary leukostasis. Although only reaching borderline significance, the proportion of patients with hyperleukocytosis requiring mechanical ventilation was higher in those with FAB M4/M5 (15/72, 21%) than in those in the other FAB groups (1/25, 4%; *P*=0.06). Central nervous system hemorrhage and/or infarction was seen in 5% of the patients. Tumor lysis syndrome occurred in 17% of the patients, of whom one needed hemodialysis. Other complications were bleeds outside the central nervous system (7%), cardiac complications (8%) and thromboembolic events (9%). Cardiac complications included reduced ventricular function (N=3), pericardial effusion (N=2), tachycardia (N=2), pulmonary hypertension, and chloroma on a tricuspid valve. Thromboembolic events included pulmonary thrombosis (N=2), thromboses in vena porta (N=2), inferior vena cava (N=2), and femoral vein as well as some minor central venous line-related thromboses. Disseminated intravascular coagulation occurred in 5.6% of patients treated with etoposide upfront, but in none of the 11 patients who underwent leukapheresis/prephase chemotherapy. This may reflect a selection bias, since ongoing disseminated intravascular coagulation could be a relative contraindication to leukapheresis. Sixty-five of 120 patients (54.2%) had no registered complications (supplemental oxygen was not counted as a complication).

Outcomes

The 5-year event-free survival rate was lower for patients with hyperleukocytosis (52.9% [95% CI 44.4-63.0]) than for patients without hyperleukocytosis (64.9% [95% CI:

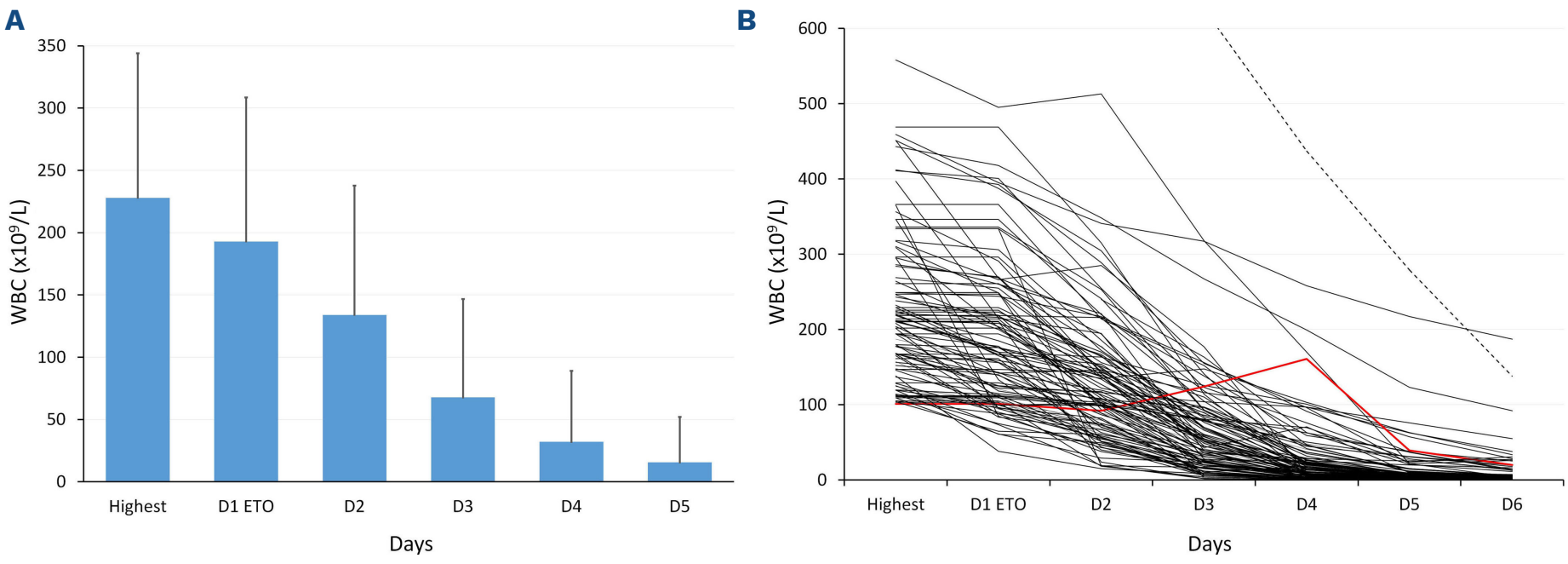

Figure 2. White blood cell counts before and during etoposide monotherapy in 111 pediatric patients with acute myeloid leukemia and hyperleukocytosis. (A) Average and standard deviation of white blood cell count (WBC). Related to WBC on day 1, the percentages of remaining WBC on days 2-5 were 69%, 36%, 17% and 8%, respectively. (B) WBC for each of the 111 patients. Dotted line: patient with a highest WBC of 880x10^9/L, for the sake of readability only part of the curve is displayed (not shown: day 1, WBC 862x10^9/L; day 2, WBC 818x10^9/L; day 3, WBC 626x10^9/L). Red line: non-responding patient who underwent leukapheresis on day 4 (patient 4 in Table 3). Highest: highest WBC before therapy. D1 ETO: WBC on day of first etoposide dose. The last WBC value before the etoposide infusion was reported. D2-D6: WBC 1 to 5 days after the first dose of etoposide.

60.9-69.1], *P*<.001; HR=1.64 [95% CI: 1.23-2.20]), due to a higher frequency of resistant disease in the patients with hyperleukocytosis (14/122 *vs*. 23/592; *P*<0.001) (Figure 3A). Multivariate Cox regression, adjusting for main cytogenetic subgroups (Table 1), showed that hyperleukocytosis remained an independent adverse factor (HR=1.55 [95% CI: 1.14-2.10]; *P*=0.005). There was no significant difference in 5-year cumulative incidence of relapse (27.5% [95% CI: 19.4-36.1] *vs*. 24.8 [95% CI: 21.2-28.6]; *P*=0.32) or 5-year transplant-related mortality (7.4% [95% CI: 3.6-12.9] *vs*. 5.9% [95% CI: 4.2-8.1]; *P*=0.47). Overall survival at 5 years was 74.1% (95% CI: 66.4-82.6) in patients with hyperleukocytosis compared to 78.9% (95% CI: 75.4-82.6) in patients without hyperleukocytosis (*P*=0.1, HR=1.38 [95% CI: 0.93-2.06]) (Figure 3B). Including genetic subgroups in the multivariate Cox regression showed a hazard ratio of 1.22 (95% CI: 0.83-1.88; *P*=0.28) for hyperleukocytosis.

Compared to the group without hyperleukocytosis, patients with hyperleukocytosis had a trend to higher 6-week early death rate (5/122, 4.1% *vs*. 13/592, 2.2%; *P*=0.06). Details on the five patients who died early are shown in Table 3. Three out of 122 patients with hyperleukocytosis (2.5%) died within 2 weeks. Of 69 patients with a WBC >200 x10^9/L, 14 patients died, but only three during the first 6 weeks. Three of 111 patients treated with etoposide upfront died within 6 weeks (3%), compared to 2/11 (18%) in the group exposed to prephase chemotherapy/leukapheresis (*P*=0.06) (Table 2).

Discussion

We report on 122 pediatric AML patients with hyperleukocytosis treated on the NOPHO-DBH AML 2012 protocol. The immediate start of full-dose etoposide monotherapy, without prephase chemotherapy or invasive procedures regardless of WBC count and FAB type, was feasible and effective. A reduction of WBC to <100x10^9/L was obtained after two doses of etoposide in 82% of patients. The overall survival rate was 74.1%, which was not significantly different from that of patients without hyperleukocytosis. Slow responders significantly more often had *FLT3*-ITD mutations and a significantly lower proportion of them had FAB type M4/M5. Early mortality within 6 weeks of diagnosis was low (4.1% for all, 1.8% for patients receiving etoposide upfront without prephase chemotherapy or leukapheresis), and reported complications were similar to those in previous studies.

The high number of patients in this study, the adherence to the recommended management of patients with hyperleukocytosis and the detailed documentation of early treatment and WBC counts allowed a thorough evaluation of the effectiveness of 5 days of upfront etoposide monotherapy which was part of the first chemotherapy course. Only 9% of patients received prephase chemotherapy and/or leukapheresis. However, because of the small number of these patients and a selection bias (they had significantly higher WBC counts), it is not possible to make a meaningful comparison with patients treated with upfront etoposide chemotherapy.

There is an ongoing debate on the benefit of leukapheresis in both adult and pediatric AML. Most authors agree that the technical aspects of leukapheresis are well established, and that the procedure can be performed safely in both adults and children/adolescents.[7,13,20-25] Controversies exist regarding the clinical benefit of leukapheresis as an initial therapeutic measure. The main argument against leukapheresis is that a beneficial effect on early clinical outcomes has not been shown in clinical trials[7,8,10,11] and

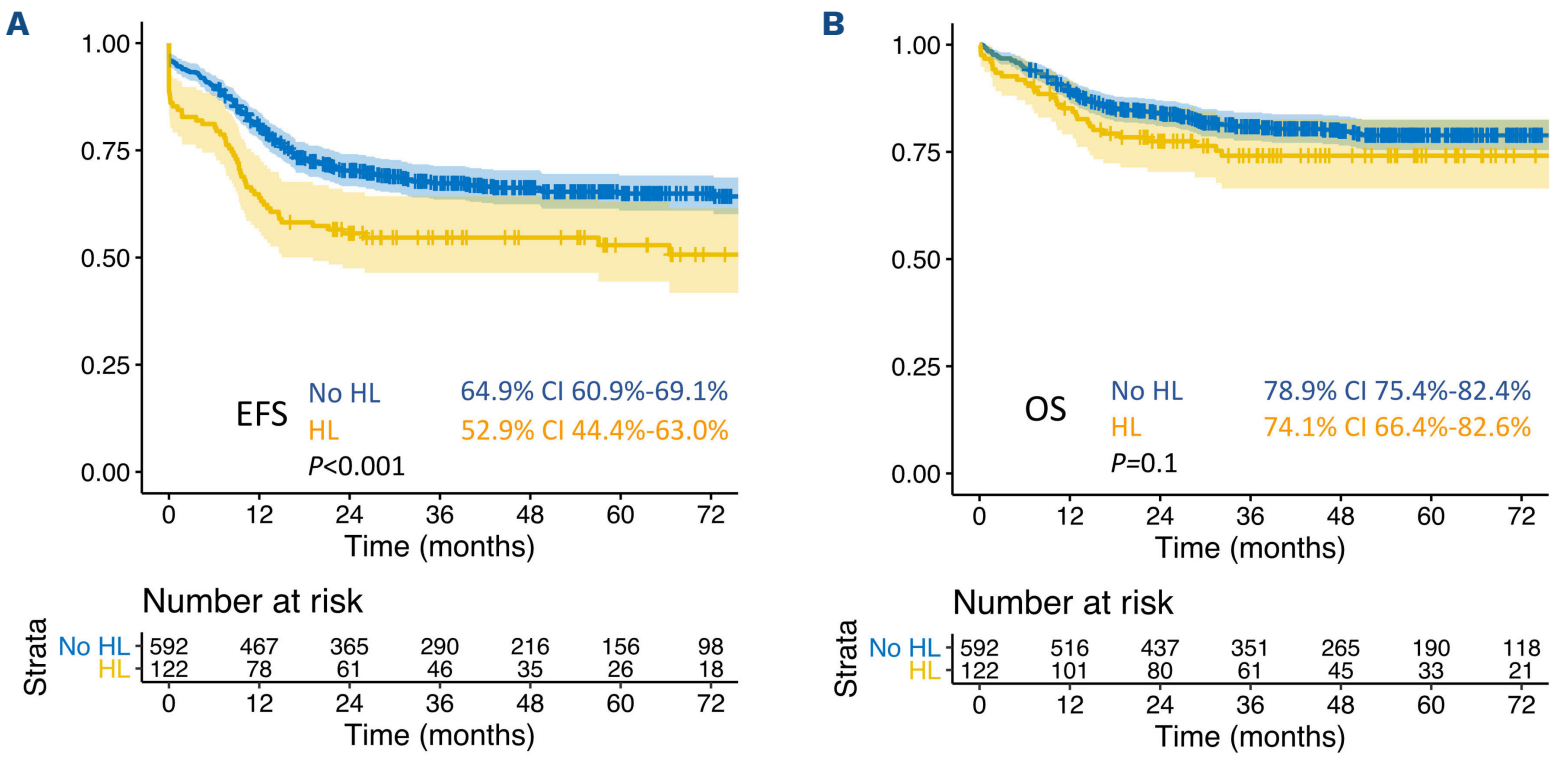

Figure 3. Comparisons of the outcomes of patients with (N=122) and without (N=592) hyperleukocytosis. (A) Event-free survival. (B) Overall survival. EFS: event-free survival; HL: hyperleukocytosis; CI: 95% confidence interval; OS: overall survival.

that long-term prognosis is not improved.[26-28] Other arguments against the procedure include the requirement of a central venous catheter, the decrease in the number of platelets with the procedure, the rapid rebound of blasts after leukapheresis, a possible delay before starting full-dose chemotherapy, costs, and the fact that the procedure is not available everywhere.[29,30]

Presently, most authors discourage routine use of leukapheresis in adult AML patients with hyperleukocytosis, but recommend the procedure in selected cases with manifest leukostasis.[10,26,27,31,32] The picture is not so clear in pediatric AML, perhaps due to smaller numbers of patients in studies on hyperleukocytosis. A recent population-based study from the USA showed that leukapheresis is still widely used in pediatric leukemias, albeit with decreased frequency over recent years.[33] The Berlin-Frankfurt-Münster (BFM) group has seen a trend towards reduced early death following leukapheresis in selected cases, and has recommended leukapheresis/exchange transfusion in patients with a WBC count above 200x10^9/L and in patients with a WBC count between 100-200x10^9/L and FAB M4/M5 type leukemia.[6] Following these recommendations, 102/115 patients (88%) in our study would have been candidates for leukapheresis. The largest study on hyperleukocytosis so far suggested that leukapheresis did not reduce induction mortality, but data on leukapheresis were available only for a subgroup of patients (89/256), of whom 18% underwent leukapheresis.[8] A recent study from St. Jude on 49 children diagnosed between 1997 and 2017 reported no advantage for leukapheresis (N=16) compared to cytoreduction with low-dose cytarabine (N=18) or upfront protocol chemotherapy (N=14).[34] A single, small pediatric study reported good results using immediate chemotherapy without invasive cytoreductive measures.[12]

In our trial, the use of leukapheresis/exchange transfusion was discouraged regardless of WBC count and pre-existing complications. We found that immediate initiation of full-dose chemotherapy (in our case etoposide monotherapy for the first 5 days) had a comparable effect on WBC as that of leukapheresis/exchange transfusion in the majority of patients, including those with very high WBC counts. After 1 and 2 days of therapy (1 and 2 etoposide doses), WBC numbers were reduced to 68% and 33% of the value before therapy. These are numbers comparable to those achieved with leukapheresis. In leukemias with hyperleukocytosis, a single leukapheresis can reduce the WBC count by 30-60%.[35] In adult AML, one study reported that in 40% of cases leukapheresis did not reduce WBC counts signifi-

Table 3. Early deaths (during the first 6 weeks after diagnosis).

	Sex/age in years	WBC x 10^9/L	Prephase chemo-therapy	LA	DTD	Comments
Patient 1	F/0	164	Low dose cytarabine, thioguanine	No	4	Never started etoposide. Died of sepsis.
Patient 2	M/5	397	No	No	3	Rapid response to etoposide. Died of brain hemorrhage.
Patient 3*	M/0	232	No	No	45	Infant, diagnosed 2 weeks after birth. Tumor lysis syndrome. Rapid response to etoposide. Secondary fever with elevated C-reactive protein. Systemic fungal infection with *Trichosporon asahii*. In spite of antifungal treatment gradual hepatic failure, and multiorgan failure.
Patient 4	F/9	101	No	Yes	7	Upfront etoposide. After second dose, increasing WBC from 92 to 124x10^9/L and deteriorating clinical condition. Etoposide therapy aborted and LA performed the day after, resulting in a WBC drop from 161 to 39x10^9/L. Died of multiorgan failure.
Patient 5	M/17	350	No	Yes	20	LA on the day of admission (and diagnosis of acute myeloid leukemia). The following day, WBC was 215x10^9/L and etoposide therapy was commenced. Died of sepsis.

*Patient 3 was included in the early death group since the secondary complications leading to death started well before the end of week 6. WBC: white blood cell count; LA: leukapheresis; DTD: days to death (from diagnosis); F: female; M: male.

cantly, while 60% achieved a WBC count of <100x10^9/L.[36] Others reported WBC decreases of 50%[37] and even 71%.[21] Three pediatric studies reported a median decrease after leukapheresis of 60%,[22] an overall decrease after one or several leukaphereses of 60%,[23] a mean 50.7% reduction after a single leukapheresis procedure and an additional 17.1% reduction after a second therapeutic leukocytapheresis procedure.[25] However, the numbers of patients in the pediatric studies were small; the three mentioned studies included a total of 41 pediatric patients (14 of whom had acute lymphoid leukemia).

The 20% slow responders to etoposide monotherapy significantly more often had *FLT3*-ITD and/or non-M4/M5 FAB types. FAB M4/M5 is known to be associated with a higher risk of leukostasis, and we observed a trend towards more frequent need of mechanical ventilation in FAB M4/M5 patients than in patients with other FAB types. Our findings support the concept that immediate chemotherapy may be as good as or better than leukapheresis even in M4/M5 leukemias with complications due to leukostasis.

One of the 111 patients in our study receiving etoposide as initial therapy was a non-responder, with increasing WBC counts after two doses of etoposide. This patient proceeded to leukapheresis on day 4 but died some days later. Alternatives to leukapheresis would have been to introduce an anthracycline earlier or even just to continue etoposide. However, it is impossible to conclude whether a different approach could have improved the patient's outcome.

We studied the use of 5 days of etoposide monotherapy to reduce initial WBC counts, since this was the first part of our first induction course. It can be assumed that a different induction chemotherapy may have resulted in a similar reduction in WBC during the first days. However, an important advantage of etoposide monotherapy is its very convenient administration as a 2-hour infusion once daily, which facilitates the immediate start of chemotherapy. Placing a central venous line is not necessary, since the drug can be administered via peripheral venous access and the risk of severe damage due to extravasation is low. In our study, more than one third of the patients received at least part of their etoposide treatment via peripheral venous access, the only complication being one case of extravasation, which left no sequelae.

We discouraged the use of prephase chemotherapy such as low-dose cytarabine. Accordingly, only a few patients received such treatment. Three of eight patients received acute lymphoid leukemia-directed therapy (steroids) since the leukemia was initially misinterpreted as acute lymphoid leukemia. In a recent review on hyperleukocytosis in acute and chronic leukemias it was stated that "it is increasingly important to administer 'bridging' (non-definitive) chemotherapy to mitigate the risk of leukostasis while awaiting the detailed leukemia characterization required for a definitive treatment plan".[9] In our experience, non-definitive chemotherapy is rarely necessary. In over 90% of our patients, a definitive diagnosis could be established within 1 day of admission. Nonetheless, in leukemias for which the diagnosis cannot be timely established, treatment with a combination of etoposide and steroids seems reasonable in urgent cases.

Our 6-week early mortality of 4.1% for all patients with hyperleukocytosis, and 1.8% for patients receiving etoposide upfront without prephase chemotherapy or leukapheresis/exchange transfusion compares favorably to rates in previous studies. Death occurred within 2 weeks in 2.4% of all patients and 1.8% of those receiving etoposide upfront. Only one of 70 patients with a WBC count >200 x10^9/L died within the first 2 weeks. A previous NOPHO study reported an early death rate of 30% in patients with WBC >200x10^9/L.[14] In a BFM study, 2-week early mortality from bleeding and/or leukostasis was 1.8% in 1,251 pediatric patients with AML. Patients with a WBC count >100x10^9/L had an early death rate of 2.3%. Patients with a WBC count >200x10^9/L had a rate of 14.3%, and if they had a FAB type M4/M5, the early death rate was 20%.[6] In nine consecutive St. Jude AML studies from 1963 to 2002, the early death rate in patients with hyperleukocytosis fell from 22.9% in the first period before 1983, to only 2.8% in the later period.[38] In their most recent study, no early deaths (from diagnosis to 2 weeks after the initiation of protocol therapy) occurred in 49 patients with hyperleukocytosis.[34] Sung *et al*. reported an induction death rate of 1.3% for patients with WBC counts <100x10^9/L, and rates of 3.4%, 1.5%, 8.0% and 10.5% for those with WBC counts of 100-200x10^9/L, 200-300x10^9/L, 300-400x10^9/L, and >400x10^9/L, respectively.[8] In all the cited studies, leukapheresis and/or exchange transfusion was performed in a proportion of patients (13.4%-37%).

We conclude that management of hyperleukocytosis in pediatric AML with immediate chemotherapy without invasive cytoreduction is feasible, safe and results in a rapid reduction of WBC. Patients with hyperleukocytosis had lower event-free survival due to a higher rate of resistant disease, but their overall survival was excellent compared to that of patients managed with other protocols using leukapheresis/exchange transfusion as part of their therapy. Ideally, a very large randomized trial would be needed to provide a final answer on the possible benefit of leukapheresis. However, it seems unlikely that such a study will ever be conducted, given the rarity of the condition, the urgency for decision-making, and physician preferences.[10] In the light of this, and based on our results, we advocate abandoning leukapheresis in hyperleukocytosis in pediatric AML. Instead, it is crucial to start induction chemotherapy as early as possible.

Disclosures

No conflicts of interest to disclose.

Contributions

BZ, JA, HH, and GK designed the research study. BZ, NAC, DC, BDM, JMFN, HH, KJ, KLJ-D, GK, ZK, OGJ, BL, MM-K, JP,

RP, CJP, KS, and JA obtained patients' consent and provided clinical information. BZ, UNN, AT, and JA analyzed the results. BZ and JA wrote the paper. All authors commented on and approved the manuscript.

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Data-sharing statement

Requests for access to data used in this article for research purposes can be made to the senior author.

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