Impact of corticosteroid pretreatment in pediatric patients with newly diagnosed B-lymphoblastic leukemia: a report from the Children's Oncology Group

Blasts from children with acute lymphoblastic leukemia (ALL) are sensitive to corticosteroids as evidenced by the fact that single-agent corticosteroid therapy can induce remission in over 55% of patients.[1] Additionally, 90% of patients with newly diagnosed ALL who receive a prednisone prophase with 7 days of corticosteroid monotherapy and intrathecal methotrexate are designated good responders.[2,3] These observations have prompted concerns that corticosteroid exposure prior to ALL diagnosis could adversely affect prognosis by masking otherwise high-risk features such as an elevated presenting white blood cell count (WBC) or alternatively, by resulting in a partial treatment response and promoting disease resistance.[4] Prior studies demonstrated poor outcomes among patients who received corticosteroid therapy, most commonly prolonged courses for presumed rheumatologic diseases or other conditions, prior to their diagnosis of ALL.[5,6]

For these reasons, children who had received non-emergent or more protracted corticosteroid therapy prior to a diagnosis of ALL were excluded from enrollment on previous legacy Children's Oncology Group (COG) and other consortia ALL therapeutic trials.[7-9] With the initiation of the COG AALL03B1 classification study (NCT00482352),[10] and companion therapeutic trials for National Cancer Institute (NCI) standard risk (SR; AALL0331; NCT00103285)[11,12] and high risk (HR; AALL0232; NCT00075725)[13] B-ALL, patients 1-30 years of age who had been exposed to corticosteroids prior to the diagnosis of ALL were eligible for these protocols but stratified according to the timing and duration of their steroid pre-

Table 1. Patients' characteristics.

	Not Steroid Pretreated N=7542	Steroid Pretreated N=247	*P*
Age			
<10 years	5816 (77.1%)	163 (66.0%)	<0.0001
≥10 years	1726 (22.9%)	84 (34.0%)	
Gender			
Male	4065 (53.9%)	139 (56.3%)	0.46
Female	3477 (46.1%)	108 (43.7%)	
Race			
White	5688 (75.4%)	185 (74.9%)	
African American	474 (6.3%)	19 (7.7%)	0.73
Other*	1380 (18.3%)	43 (17.4%)	
Ethnicity			
Hispanic or Latino	1623 (21.5%)	45 (18.2%)	
Not Hispanic or Latino	5597 (74.2%)	194 (78.6%)	0.30
Unknown	322 (4.3%)	8 (3.2%)	
NCI risk			
Standard risk	4991 (66.2%)	122 (49.4%)	<0.0001
High risk	2551 (33.8%)	125 (50.6%)	
White blood cell count			
<50x10^9/L	6420 (85.1%)	188 (76.1%)	0.0001
≥50x10^9/L	1122 (14.9%)	59 (23.9%)	
MRD day 29 (0.1%)			
<0.1%	6652 (89.3%)	208 (85.6%)	
≥0.1%	800 (10.7%)	35 (14.4%)	0.07
MRD day 29 (0.01%)			
<0.01%	5866 (78.7%)	174 (71.6%)	
≥0.01%	1586 (21.3%)	69 (28.4%)	0.008
Response			
Rapid early responder	6326 (84.9%)	196 (82.4%)	0.29
Slow early responder	1128 (15.1%)	42 (17.6%)	
CNS status			
CNS1	6694 (88.8%)	203 (82.5%)	
CNS2	750 (9.9%)	32 (13.0%)	<0.0001
CNS3	97 (1.3%)	11 (4.5%)	

*Other race includes Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other and unknown. NCI: National Cancer Institute; MRD: minimal residual disease; CNS: central nervous system.

treatment. Patients with T-ALL were treated separately and are not included in this report. Institutional review boards at COG centers approved the studies and informed consent for participation in the study was obtained from patients or their parents/legal guardians.

After enrollment on AALL03B1, patients initiated a common three- or four-drug induction on AALL0331 and AALL0232 based on NCI risk group and corticosteroid pretreatment. At the end of induction, risk assignments were completed on the basis of sentinel cytogenetic alterations and early treatment response assessed by morphology and flow cytometry-based minimal residual disease (MRD).

The duration and timing of corticosteroid exposure and availability of a WBC prior to corticosteroid exposure (pre-steroid complete blood count, CBC) were recorded. Notably, corticosteroid therapy after a diagnosis of ALL was confirmed but prior to the start of systemic protocol chemotherapy was not allowed; pretreatment included only exposures prior to the diagnosis of ALL. The timing of corticosteroid exposure was recorded as within the week (7 days) or month (weeks -4 to -1) preceding diagnosis. The duration of corticosteroid exposure was recorded as <48 h or >48 h; the exact duration of exposure and the corticosteroid formulation used were not collected.

Corticosteroid pretreatment was used to modify treatment assignment (Figure 1). If corticosteroids were administered in the week preceding diagnosis, patients without a pre-steroid CBC and <48 h of exposure were assigned to the HR AALL0232 protocol (and remained eligible for randomization) given the concern that corticosteroid pretreatment could lower the initial WBC and affect NCI risk group determination. Patients with >48 h of corticosteroid exposure in the week preceding diagnosis received augmented therapy designated for slow early responders, as longer corticosteroid exposure in close proximity to diagnosis could affect early treatment response. No treatment changes were made for patients who had been exposed to corticosteroids for <48 h in the week preceding diagnosis with a pre-steroid CBC. Patients who had had corticosteroid pretreatment in the month preceding diagnosis were managed separately. Those with <48 h of exposure had no change in therapy whereas patients with >48 h of exposure were assigned to the HR treatment protocol AALL0232 given concerns that a high WBC could have been masked.

Data current as of June 30, 2016 are used in this report. Event-free survival (EFS) was defined as the time from study entry to first event [induction failure (>25% blasts on day 29 of induction or ≥5% blasts and/or MRD ≥1% on day 43), induction or remission death, relapse or second malignancy] or date of last follow-up for event-free patients. Overall survival (OS) was defined as the time from study entry to death or date of last follow-up. Survival rates were estimated using the Kaplan-Meier method with standard errors as described by Peto *et al.*[14] Survival curves were compared using the log-rank test. Multivariable analysis (Cox proportional hazards model) was used to identify independent prognostic factors. Proportions were compared with the χ^2 test or Fisher exact

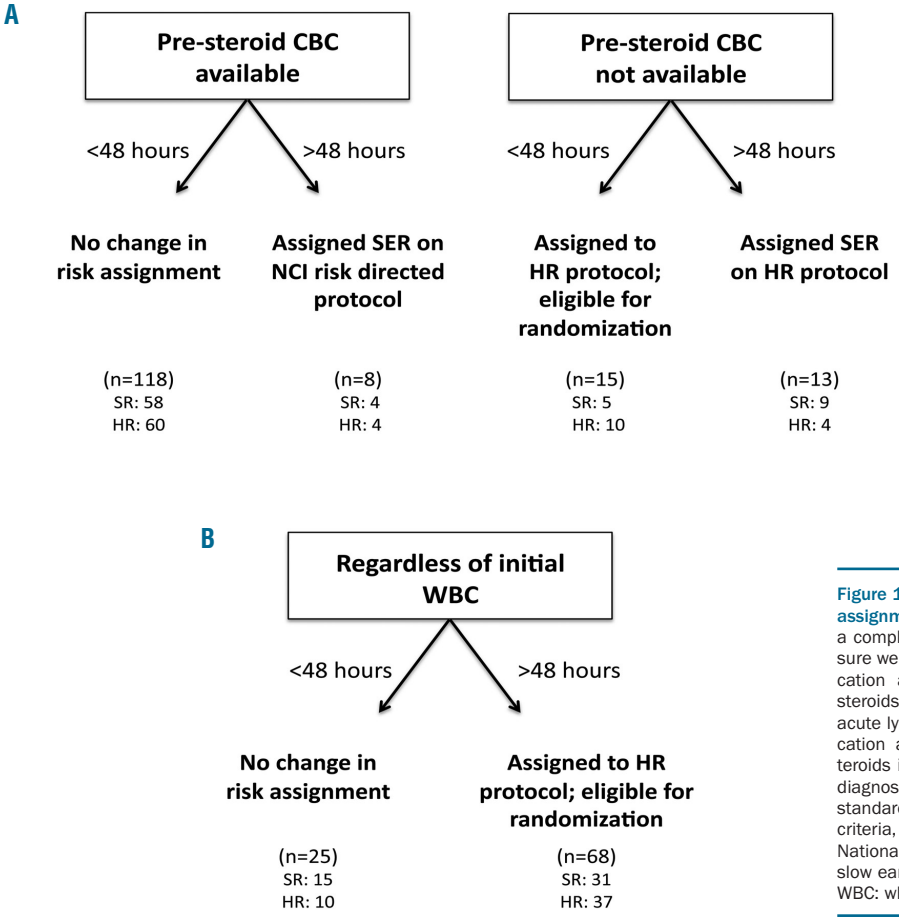

Figure 1. Corticosteroid pretreatment modified risk assignment. Duration, timing and the availability of a complete blood count prior to corticosteroid exposure were used for risk assignment. (A) Risk stratification algorithm for those who received corticosteroids in the week preceding their diagnosis of acute lymphoblastic leukemia (ALL). (B) Risk stratification algorithm for those who received corticosteroids in the month (weeks -4 to -1) preceding the diagnosis of ALL. CBC: complete blood count; SR: standard risk, according to National Cancer Institute criteria, at diagnosis; HR: high risk, according to National Cancer Institute criteria, at diagnosis; SER: slow early responder; NCI: National Cancer Institute; WBC: white blood cell count.

test. A *P*-value less than 0.05 was considered statistically significant for all comparisons. All analyses were performed with SAS® software. All graphics were generated using R (*http://www.R-project.org*, version 3.0.1).

Among the 7,789 patients (SR, AALL0331, n=5,057 and HR, AALL0232, n=2,732) eligible and evaluable from 2003-2011, 247 (3.2%) had received corticosteroids in the 4 weeks prior to their B-ALL diagnosis. Corticosteroid pretreatment had been received by 1.5% (n=77) of the patients on the AALL0331 trial and 6.2% (n=170) on AALL0232. Of the 170 patients enrolled on the HR protocol, 125 were NCI HR based on an initial WBC ≥50x10^9/L (n=59) and/or age ≥10 years (n=66) at presentation and 45 were NCI SR patients assigned to the HR regimen based on corticosteroid pretreatment. The clinical characteristics of the corticosteroid-pretreated patients compared to those who were not pretreated are detailed in Table 1. A significantly higher percentage of corticosteroid-pretreated patients were ≥10 years of age at diagnosis, had a higher presenting WBC (≥ 50x10^9/L) and had central nervous system leukemia.

Induction response rates did not differ significantly among the corticosteroid-pretreated patients (Table 1). In aggregate, 82.4% of SR and HR corticosteroid-pretreated patients were rapid early responders compared to 84.9% of patients who had not received corticosteroid pretreatment (*P*=0.29). While there were no significant differences in the MRD responses using the protocol-specified threshold of 0.1% by flow cytometry, the corticosteroid pretreated SR and HR patients together had higher rates of end-induction MRD positivity using the contemporary threshold of 0.01% compared to patients who had not been pretreated with corticosteroids: MRD ≥0.01% in 28.4% *versus* 21.3%, respectively (*P*=0.008). Induction treatment responses were also separately assessed among SR and HR patients treated on AALL0331 and AALL0232 and no significant differences in end-induction morphological remission rates or MRD responses were observed between the corticosteroid-pretreated and not-pretreated patients (*Online Supplementary Table S1*).

Outcomes were also assessed separately among SR and HR patients treated on AALL0331 and AALL0232. The 5-year EFS rates for SR corticosteroid-pretreated *versus* not-pretreated patients treated on COG AALL0331 were 94.5%±2.8% and 90.0%±0.4% (*P*=0.16), respectively and the corresponding OS rates were 97.2%±2.0% and 96.3%±0.3% (*P*=0.51), respectively. The 5-year EFS rates for HR corticosteroid-pretreated *versus* not-pretreated patients were 76.6%±3.5% and 77.7%±0.9% (*P*=0.57), respectively and the OS rates were 86.4%±2.9% and 87.3%±0.7% (*P*=0.81), respectively (Figure 2). Moreover, in multivariable analysis for EFS including NCI risk group and day 29 MRD, corticosteroid pretreatment was not an adverse prognostic factor (hazard ratio 1.06; *P*=0.70) (*Online Supplementary Table S2*).

Since the majority of corticosteroid-pretreated patients received limited exposure in the week preceding diagnosis after the results of a CBC were known, we also compared the outcomes of the 45 NCI SR patients who were allocated to HR therapy on AALL0232 to the outcomes of non-steroid pretreated patients on AALL0331. The former included 14 patients in whom a pre-steroid CBC was not obtained prior to their exposure in the week preceding diagnosis, and 31 patients who received >48 h of corticosteroids in weeks -4 to -1. No differences in EFS or OS were observed. Five-year EFS and OS rates were 93.3%±4.0% *versus* 90.0%±0.4% (*P*=0.76), and 95.5%±3.3% *versus* 96.3%±0.3% (*P*=0.90), respectively for the corticosteroid-

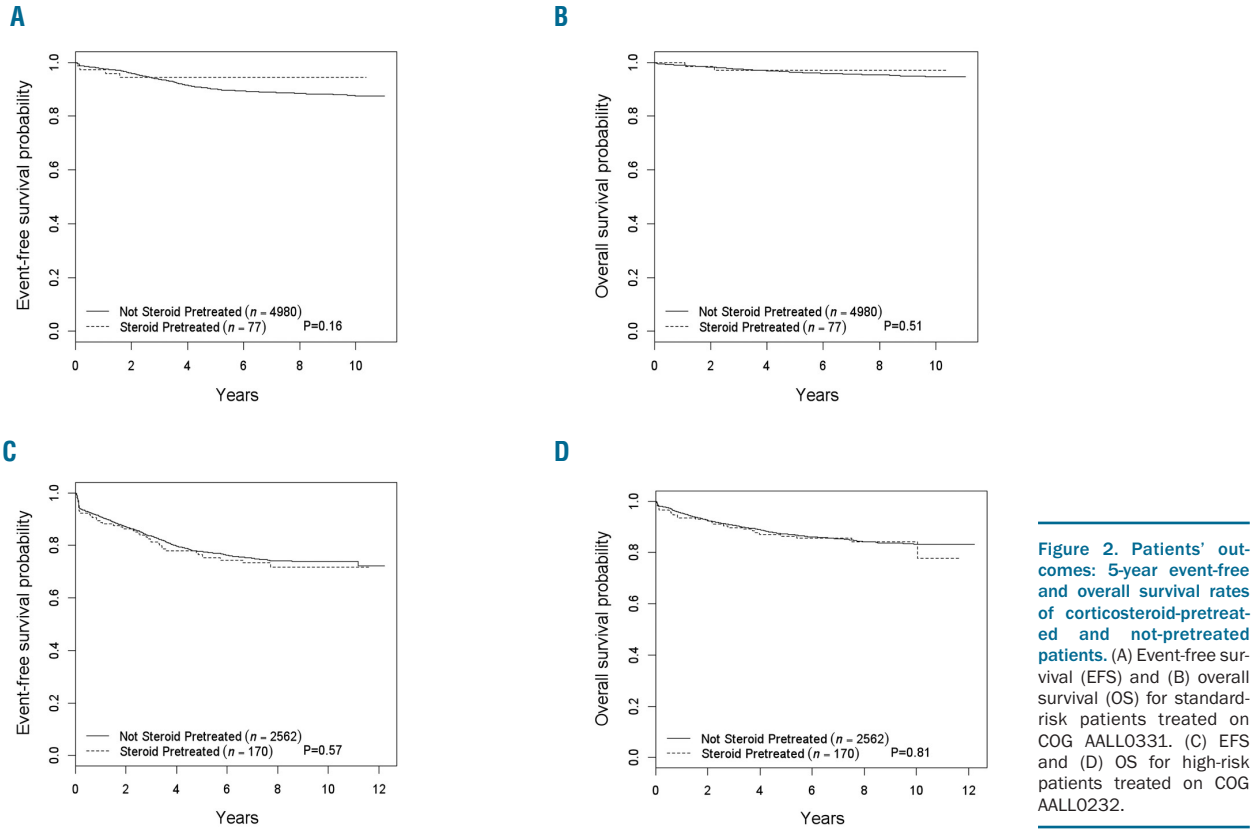

Figure 2. Patients' outcomes: 5-year event-free and overall survival rates of corticosteroid-pretreated and not-pretreated patients. (A) Event-free survival (EFS) and (B) overall survival (OS) for standard-risk patients treated on COG AALL0331. (C) EFS and (D) OS for high-risk patients treated on COG AALL0232.

pretreated *versus* non-steroid-pretreated NCI SR patients (*Online Supplementary Figure S1*).

With the inception of the COG AALL03B1 classification study and companion therapeutic trials, cortico-steroid pretreatment was systematically accounted for in risk assignment algorithms.[15] The majority of children had short exposures with a known pre-steroid CBC and their outcomes were not adversely affected when they received NCI risk-directed therapy, without modification. Corticosteroid pretreatment was more common among patients with high-risk disease features. While the indications for corticosteroid pretreatment were not recorded, perhaps a higher disease burden at presentation and more symptoms prompted a misdiagnosis and treatment intervention before a diagnosis of ALL was recognized. It is difficult to ascertain whether more protracted and chronic exposure could have affected outcomes adversely since the exact duration of cortico-steroid exposure in the month prior to diagnosis, or more remotely, was not recorded. The subset of patients most likely to reflect chronic exposure were the patients who received >48 h of corticosteroids in the month preceding diagnosis. Notably, while this group of patients had nearly identical outcomes to other non-steroid pretreated patients, these outcomes were achieved after receiving HR therapy. Going forward, similarly pretreated patients will therefore continue to be allocated to HR regimens.

In conclusion, with treatment modifications to account for the potential impact of corticosteroid exposure prior to ALL diagnosis on both the presenting WBC and early response to induction therapy, children who had been pretreated with corticosteroids had comparable outcomes to those who had not received prior corticosteroid therapy. Moreover, in a multivariable analysis, cortico-steroid pretreatment did not negatively affect outcomes. These observations support the continued inclusion of patients who have received corticosteroids prior to their diagnosis of ALL on therapeutic studies, with uniform adaptations in risk stratification to account for the potential impact of this exposure.

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Acknowledgments: EAR is a KiDS of NYU Foundation Professor of Pediatrics. MLL is a Benioff Chair of Children's Health and the Deborah and Arthur Ablin Endowed Chair of Pediatric Molecular Oncology. SPH is the Jeffrey E. Perelman Distinguished Chair in the Department of Pediatrics at The Children's Hospital of Philadelphia.

Funding: this work was supported in part by Children's Oncology Group grants U10 CA98543, U10 CA98413, U10 CA180886, and U10 CA180899 as well as St. Baldrick's Foundation.

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doi:10.3324/haematol.2018.215616

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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