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Long-term treatment results of Polish pediatric and adolescent patients enrolled in the ALL IC-BFM 2002 trial

To the Editor:

In 2002, the Polish Pediatric Leukemia/Lymphoma Study Group joined the ALL IC-BFM 2002 trial, which was intended for countries with inadequate skills and resources for PCR-based MRD monitoring.1 On the basis of the pioneering findings of the BFM group regarding measurement of early response to prednisone in peripheral blood on day eight and percentage of bone marrow blasts on day 15, all the patients could be stratified in risk groups by accessible and inexpensive methods. Considering inequalities in resources and facilities among the participating countries, it seems justified to us to report on the treatment results of this trial in patients with ALL treated in 14 Polish pediatric oncohematology center.

Between November 2002 and November 2011, 1872 children aged 1-17 with newly diagnosed ALL were consecutively enrolled in the ALL IC-BFM 2002 protocol according to a registered trial at ClinicalTrials.gov (NCT00764907). Infants younger than 12 months were excluded. The patients were diagnosed according to cytomorphic criteria (more than 25% lymphoblasts present in bone marrow), immunophenotyping (EGIL criteria) and cytogenetic and FISH/molecular genetics examination of bone marrow specimens. A central review on the national level of morphologic, flow cytometric and genetic results was required. The prognostic factors of ALL IC-BFM 2002 included: age, white blood cell count (WBC) at diagnosis, response to prednisone at day 8, results of bone marrow evaluation on day 15 or 33 of the therapy and, finally, the presence of BCR/ABL1 and KMT2A/AF1 specific genetic aberrations. At diagnosis, the patients were stratified into three groups: standard, intermediate, and high-risk groups. Risk group definitions and treatment plan are presented in the paper by Stacy et al.2 OS and EFS curves were estimated according to Kaplan-Meier with Greenwood Standard Error (SE), and compared using a two-tailed log-rank test. Cumulative incidence (CI) curves for the events were estimated according to risk groups, and were compared using the Gray test. All statistical calculations were performed using STATISTICA13. The study was approved by the local institutional review board and a written informed consent from the guardians was a prerequisite.

A total of 1872 patients (56.6% males and 43.4% females) were treated under the ALL IC-BFM 2002 Protocol. A median follow up time for the entire group was 6.4 years (Q1 = 4.32, Q3 = 8.53). The median age at diagnosis was 5.3 years, ranging from more than 1 to 17 years of age. Most children (55%) were in the age range 1 to <6 years, while the group aged 6 to <10 years accounts for 19% of the cohort, 10 to <15 years was 17%, and those older than 15 years constitute 9%. For WBC counts at diagnosis below 20×10⁹/l was revealed in 64.3% of the children while in 10.1% WBC was more than 100×10⁹/l. CNS status 1 in 88%, 2-7% and 5% showed signs of CNS involvement. Mediastinal involvement from the leukemic process was found in 7.8%, testicular involvement was shown in 20 boys (1.9%). The immunophenotype in most children was revealed as preB cell lineage (89%) and T cell lineage was shown in 11%. The conventional cytogenetic analysis was performed in all subjects with newly diagnosed ALL. Chromosome preparations of BM cells were informative for analysis in 1056 (56.4%) patients. Chromosome aberrations were revealed in 523 (27.9%) cases. Hypodiploidy was presented in 22 (2.1%) patients. Investigations in fusion genes BCR/ABL1, KMT2A/AF1 were required under the ALL IC-BFM 2002 protocol as primary and obligatory tests. The t (9;22)(q34;q11.2) translocation that produced the fusion gene BCR/ABL1 was detected in 65 (3.5%) pediatric patients. The rearrangements of KMT2A were presented in...
42 (2.2%) children and in five children the KMT2A/AFF1 fusion gene was confirmed.

According to risk stratification, 32.6% of the children were qualified for a standard-risk group (SR), 48.1% were qualified as intermediate-risk (IR), and 19.3% as high-risk (HR). After 7 days of steroid therapy, 10.9% of patients were assessed as prednisone poor responders. Bone marrow on day 15 M1 (<5% blasts) was revealed in 68.6%, on M2 (5% to <25% blasts) in 19.7%, and on M3 (≥25% blasts) in 9.9% patients. Complete remission (CR1) of the disease on day 33 was achieved in 96% of the patients, while 65 patients (4%) achieved CR1 between days 52-96, and were classified as late responders and they were stratified to the HR group. Five children did not achieve CR1 by day 96 (before first HR2 block) and they continued therapy on individual decisions.

A total of 268 (14.3%) deaths were noted in the entire group, including 30 (11.2%) deaths in the SR group, 116 (43.2%) in IR, and 122 (45.5%) deaths in HR. Given the size of the risk groups, the death rate observed in the SR group was 4.77%, 13.47% in IR, and 32.87% in the HR group. When patients who underwent BMT are excluded, the death rate in the HR group is as high as 39.3%. Cumulative death risk in the SR group at 5 years was estimated at 4.4%, 14.2% in the IR group, and 37.3% in HR (Figure S1). In 36 cases, deaths happened during the induction therapy, before CR1 was achieved, and the estimated death rate at induction was 1.92% (0.82% for the SR group, 2.23% for IR, and 3.04% for the HR group). A total of 81 deaths were noted at the CR1 phase (death rate of 4.55%, with 1.19% in SR, 3.26% in IR, and 13.77% in the HR group). Deaths related to relapse were noted in 106 children.

The incidence of death at CR was significantly higher in children aged ≥10 years vs younger children (9.3% vs 2.6%; P < .001) and in T-ALL vs BCP-ALL (9% vs 3.5%; P < .001). But, differences were not found between girls and boys (4.0% vs 4.5%; P = .7). The main causes of deaths are presented in Table S1.

Overall survival (OS) for 1872 children with ALL treated under the ALL IC-BFM 2002 protocol in Poland was 86% after 5 years, whereas the EFS rate was 79%. The EFS for the SR group (n = 608) was 90%, 80% for IR (n = 899), and 62% for HR (n = 361) at 5 years, and at 10 years EFS was 88%, 79%, and 59%, respectively (Figure 1). Relapses occurred in 275 children (14.7%), of which 51 cases occurred in the SR group (8.4% of the patients who were stratified for the SR group), 147 cases in IR (16.4%), and 77 in HR (21.2%). Cumulative relapse risk for the SR group was 8% (SE 1.1), whereas the IR and
HR groups showed 16.5% (SE 1.2) and 25.9% (SE 2.0) respectively (Figure S2).

Treatments using standardized regimens or protocols have led to unprecedented improvements in survival of children with cancer, but most published regimens are based on therapies developed and delivered in high-income countries. The ALL IC-BFM 2002 trial was designed to be conducted in countries with inadequate skills and resources for PCR-based MRD monitoring enabling, however, the stratification and treatment of children with ALL according to a BFM-based backbone protocol. The EFS in our cohort at 5 years is estimated to be as high as 79%, and OS of 86% at 5 years. These results are clearly comparable to treatment outcomes presented by several major study groups or institutions, since over the last two decades the world’s leading leukemia groups have achieved 5-year OS rates of approximately 90% with 2% to 3% deaths resulting from toxicity in childhood ALL.

A major concern regarding BFM-type chemotherapy for less experienced groups with limited resources was the potential risk of excessive therapy related mortality (TRM). Indeed, we observed a 4.55% rate of deaths upon CR, ranging from 1.19% in the SR to 13.77% in the HR patients. Several study groups from countries with high health expenditures have reported that 2-5% of children with ALL die from other causes than relapse, and 1-2% of patients die during the induction phase.

Our study demonstrates a death rate for both induction before CR1 (1.92%) and during the CR1 phase (4.55%). This may result from the long duration of the analysis and a change in the standards of supportive therapy. The major leading causes of death, similar to other reports, were sepsis, progressive ALL and SCT-related complications. Infections, both bacterial and fungal, resulted in 24.3% of deaths in our cohort. In comparison, Möricke et al. have reported 69% cases of death as infection-related. The risk of life-threatening infection increased during the induction phase.

The cumulative incidence of relapse in our patients after 5 years for the whole cohort was 15% (SE 0.8), while the individual risk groups showed 8% (SE 1.1) for SR, 16.5% (SE 1.2) for IR, and 25.9% (SE 2.0) for HR. These results are nearly identical with those obtained by the ALL BFM95 study: 16.2% overall (SR-7.8%, SE 1.0; MR-16.8%, SE 2.0) for HR. These results are nearly identical with those obtained by the ALL BFM95 study: 16.2% overall (SR-7.8%, SE 1.0; MR-16.8%, SE 1.2, and HR-38.6%, SE 3.6).

In conclusion, ALL IC-BFM 2002 proved as a highly effective protocol for treatment of children with ALL in Polish pediatric oncohematology centers. The design of the study allowed us to achieve outcomes comparable to those reported by study groups in several countries with high health-related expenditures. The study based on inexpensive and accessible stratification criteria was highly successful.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS


ETHICS STATEMENT

The ethics committee of Medical University of Lublin, Poland. The committee’s reference number: KE-0254/178/2002.


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SUPPORTING INFORMATION

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