Outcome of Pediatric Acute Lymphoblastic Leukemia: Sixty Years of Progress

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Abstract. *Background: A retrospective analysis was performed to investigate the survival outcomes in pediatric acute lymphoblastic leukemia (ALL) based on time period. We hypothesized that improvement has been obtained with the time-dependent therapeutic era and rise in the gross domestic product (GDP) and Human Development Index (HDI). Materials and Methods: Data from 710 children who were treated for ALL between 1958 and 2018 at a single pediatric center were analyzed for probability of 5-year overall survival (pOS), event-free survival (pEFS) and relapse risk (pRR). Time periods were defined by the treatment protocols used in seven consecutive therapeutic eras. Results: Over the 60-year period analyzed, pOS increased from 1.2% to 90.7%, pEFS from 1.2% to 86.6%, and pRR decreased from 98.8% to 9.9% for patients treated in the past decade. Risk of mortality for patients who received chemotherapy and hematopoietic cell transplant was reduced to 9.9% in the recent era, however, no statistically significant survival difference was found between patients treated with stem cell transplant and those not. Conclusion: The therapeutic era, related to improved GDP and HDI, was a statistically significant predictor of increased OS from ALL.*

Poland has a population of 38 million inhabitants, and every year, about 200-220 children (age <18 years) are diagnosed

with acute lymphoblastic leukemia (ALL), the most frequent pediatric malignancy. History of the treatment of childhood ALL has become a paradigm for cancer cure (1). Clinical trials on ALL have successfully evolved over more than five decades in Europe, Asia and North America, and have contributed to the current cure rate of about 90% in childhood ALL in resource-rich countries (2). Few data are available on the progress of results of therapy in childhood ALL in less economically developed countries, especially when compared to the 1960s (3), an important aspect considering the number of Eastern European countries, including Poland, which underwent multi-aspect national transformation in the early 1990s.

In this study, we present results of therapy of 710 children diagnosed with ALL over a period of 60 years at a single center in Poland. We hypothesized that improvement in outcome might be related to the therapeutic era and rise in the gross domestic product (GDP) and Human Development Index (HDI).

Patients and Methods

Design of the study. All patients diagnosed and treated for ALL at a single pediatric center were included in retrospective analysis of outcomes of treatment, with respect to the therapeutic era, defined by time period when specific antileukemic treatment protocols were applied. The probability of 5-year overall survival (pOS) of children with ALL was also analyzed according to the changes in macroeconomic indicators GDP and HDI (4, 5) in Poland.

Patients. Between 1958 and 2018, a total of 710 patients aged under 18 years were diagnosed with ALL and treated at the Department of Pediatric Hematology and Oncology (Department of Pediatrics up to 1997) in Bydgoszcz, Poland. The follow-up was completed by mid 2019. The diagnosis of ALL was based on morphology of bone marrow, peripheral blood, and cerebrospinal fluid smears with the May–Grunwald–Giemsa method, and cytochemical analyses, employing the French–American–British classification. Immunophenotyping was performed from 1989 with the use of panels of monoclonal antibodies stained by immunohistochemical methods, followed by flow cytometry.

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Therapeutic protocols. With respect to time period and therapeutic protocols ('therapeutic era') used, patients were divided into seven groups according to therapy at time of diagnosis: Group I, 1958-1972: various therapies, 215 patients; group II, 1976-1983: St Jude Children's Research Hospital protocols V-VII (6, 7), 56 patients; group III, 1983-1988: Berlin-Frankfurt-Munster ALL-BFM 76/79 protocols (8), 33 patients; group IV, 1988-1995: Nordic Society for Pediatric Hematology and Oncology (NOPHO) ALL-86 protocol (9), 81 patients; group V, 1995-2002: ALL-BFM-90 (10, 11) (96 patients), and New York I/II protocols (12), 19 patients; group VI, 2002-2010: Intercontinental Cooperative ALL-IC-2002 protocol (13), 115 patients; and group VII, 2010-2018: ALL-IC-2009 protocol (13), 95 patients. Except for group I, for all other time periods, international treatment protocols were used. During the past two decades, some patients with high-risk disease and those with relapse qualified for hematopoietic cell transplantation (HCT) (14).

Statistical methods. The primary endpoint was the probability of OS. This variable, as well as probability of event-free survival (pEFS) and risk of relapse (RR) were calculated with the Kaplan-Meier method, and compared by log-rank test. An 'event' was defined as relapse or death. After adjusting for different risk groups within the protocols, the Cox regression model was used to calculate treatment outcomes for the seven therapeutic eras analyzed, and hazard ratios (HR) were calculated, with 95% confidence interval (95% CI). SPSS 25 (IBM, Armonk, NY, USA) statistical package was used.

Results

Overall outcomes. Over the 60-year period analyzed, pOS increased from 1.2% to 90.7% ($p<0.0001$), pEFS from 1.2% to 86.6% ($p<0.0001$), and pRR decreased from 98.8% to 9.9% ($p<0.0001$) for patients treated in the past decade (Figure 1).

Outcome in different time periods. In group I, complete remission (CR1) was achieved by 111/215 children, with a mean duration of 7 months. Mean OS was 0.8 years (95% CI=0.7-1.0 years), and probability of 5-year OS was 0.012 ± 0.008 . In group II, CR1 was achieved by 51/56 patients. Mean OS was 6.4 years (95% CI=3.4-9.3 years), however, relapse occurred in 41 cases, and only four children remained alive in long-term continuous CR1. In group III, CR1 was observed in 30/33 (90.9%) children. Mean OS was 13.7 years (95% CI=9.5-17.9 years). Twelve relapses occurred in this group, with only one patient surviving after relapse; the number of deaths in the analyzed group was 17, thus 16 patients stayed in long-term remission. In group IV, CR1 was achieved in 71/81 children. Mean OS was 12.8 years (95% CI=10.6-15 years), and 41 patients stayed in long-term remission, including four patients in CR2. In group V, 103/106 (97.2%) children achieved CR. Mean OS was 11.2 years (95% CI=10.1-12.4). Relapse of disease occurred in 21 (19.8%) patients, 30 patients died, and 76 patients stayed in long-term CR. In group VI, CR was

Figure 1. Treatment outcomes for children with acute lymphoblastic leukemia treated between 1958 and 2018.

achieved by 113/115 (98.3%) patients. Mean OS was 7.4 years (95% CI=6.8-7.8 years). Relapses occurred in 27 (23.5%) children, deaths occurred in 26 (22.6%), thus 87 patients stayed in long-term CR. In group VII, CR was achieved by 93/95 (97.9%) patients. Mean OS was 4.1 years (95% CI=2.7-6.5 years). Relapses occurred in nine (9.5%) children, deaths occurred in eight (8.4%), thus 87 patients stayed in long-term CR.

With respect to macroeconomic indicators, OS increased over time, corresponding to the growth of GDP of Poland (Figure 2).

Risk of treatment failure. After adjusting for different risk groups within the protocols, a Cox regression model was used to calculate treatment outcomes for the seven therapeutic eras

Figure 2. Overall survival (OS) and gross domestic product (GDP) for children with acute lymphoblastic leukemia in Poland. Primary axis: GDP (continuous line) provided in billions of international dollars as purchasing power parity, a way of measuring economic variables in different countries so that irrelevant exchange rate variations do not distort comparisons (1980-2014, https://en.wikipedia.org/wiki/Economy_of_Poland). Secondary axis: Probability of OS (black bars) of children with acute lymphoblastic leukemia.

Table I. Results of 5-year overall survival (pOS), event-free survival (pEFS) and relapse risk (pRR), with hazard ratio (HR) of death, event and relapse.

Therapeutic era	5-Year pOS			5-Year pEFS			5-Year pRR		
	Probability	HR (95% CI)	p-Value	Probability	HR (95% CI)	p-Value	Probability	HR (95% CI)	p-Value
2011-2018	0.907±0.034	1		0.866±0.041	1		0.099±0.036	1	
2002-2011	0.791±0.038	2.2 (1.0-4.8)	0.053	0.711±0.042	2.1 (1.1-4.1)	0.022	0.207±0.039	1.9 (0.9-4.1)	0.091
1995-2002	0.779±0.043	2.4 (1.1-5.3)	0.026	0.684±0.107	2.2 (1.1-4.2)	0.016	0.194±0.044	1.5 (0.7-3.4)	0.281
1988-1995	0.580±0.055	4.9 (2.7-10)	<0.0001	0.519±0.056	3.8 (2.0-7.3)	<0.0001	0.338±0.069	2.9 (1.4-6.4)	0.006
1983-1988	0.545±0.087	5.9 (2.5-13)	<0.0001	0.532±0.088	4.2 (2.0-8.9)	<0.0001	0.390±0.092	4.0 (1.7-9.6)	0.002
1976-1983	0.196±0.053	12.7 (6.0-27)	<0.0001	0.074±0.034	13.4 (7.1-25)	<0.0001	0.888±0.049	15.9 (7.7-32)	<0.0001
1958-1972	0.012±0.080	30.8 (15-62)	<0.0001	0.012±0.080	18.5 (10.3-33)	<0.0001	0.988±0.008	29.9 (15.2-58)	<0.0001

CI: Confidence interval.

analyzed. Univariate analysis performed with respect to therapeutic era indicated that HRs for death, RR and risk of an event (relapse or death) decreased 30.8-, 24.5-, and 18.5-fold, respectively, over the period analyzed (Table I).

Transplant outcome. From 2003, patients with relapse were also treated with HCT. Relative to patients who were treated with chemotherapy only, the risk of mortality for patients who received both chemotherapy and HCT was reduced to 9.9% in the most recent era. However, no statistically significant difference in survival was found between patients with relapse treated with HCT and those not [5-year pOS after HCT was 0.54 vs. 0.30 after chemotherapy only ($p=0.24$) (data not shown)].

Discussion

Over the analyzed 60-year period, a steady improvement in the cure rate was observed in children with ALL admitted to our center. When compared to outcomes obtained in the USA (6, 7, 12, 15), Germany (8, 10, 11) and Scandinavian countries (9), OS results of patients treated at our center were lower by about 15-20% up until 1995, however, although still worse afterward, the difference was no more than 10%. The long-term survival rate increased from 1.2% in the 1960s to 90% in the current era.

Lower treatment outcomes in our center, as compared to reports from American and German studies of 1975-1995, may have resulted from limited access to chemotherapeutic

agents and insufficient access to adequate supportive therapy (16). Diagnosis of ALL might also have been delayed before 1990 because of limited diagnostic capabilities. Nevertheless, with the improvement of Poland's economical situation from the last decade of the 20th century, the outcomes of ALL have improved, and with the use of recent international protocols, the results are comparable to those of international groups (13). Still, we did not find any improvement to be associated with HCT, as was also observed in adolescent and young adults by others (17), although significant progress is being observed at our and other centers both in transplant and chemotherapy care (14, 18).

Despite Poland having one of the lowest values for GDP and HDI in Europe (5), Polish centers are able to strictly follow international protocols for children with ALL nowadays, and the results are even better, with 5-year EFS of 86.6%, 5-year OS of 90.7%, and RR 9.9%. These results, with mean survival of 4.1 years, are better than the final results of the intercontinental trial ALL-IC-2002 which reached 5-year OS of 82%, EFS of 74%, and relapse rate of 19% (13).

In conclusion, lower GDP and HDI before 1990 affected all Polish pediatric hemato-oncology centers, including ours. However, current cooperation and participation of Polish centers within large international and intercontinental cooperative trials (ALL IC-2002 and ALL IC-2009) resulted in a cure rate of 90% and has created opportunities for even better future survival of pediatric patients with ALL with the use of modern treatment modalities, such as targeted or chimeric antigen receptor T-cell therapy (19, 20).

Conflicts of Interest

The Authors have no conflicts of interest to disclose in regard to this study.

Authors' Contributions

ED, MP: Concept/design, data collection, data analysis/interpretation, writing article; MŁ, HŻ, AM, MK, BKR, KC, RD, AK, MPR: data collection, data analysis/interpretation, approval of article; JS: concept/design, data analysis/interpretation, critical revision of article, approval of article

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