Clinics in Oncology

Research Article
Published: 14 Dec, 2020

# Extended Follow-Up of Children with High-Risk Acute Lymphoblastic Leukemia Treated with American and European Protocols - A Clash of Different Ideas

*Kinga Kwiecinska[1,2], Zakrzewska Zuzanna[1,2], Wojciech Strojny[2], Magdalena Cwiklinska[1,3], Walentyna Balwierz[1,2] and Szymon Skoczen[1,2]**

[1]Department of Pediatric Oncology and Hematology, Jagiellonian University Medical College, Poland

[2]University Children Hospital, Poland

## Abstract

**Purpose:** To assess long-term outcomes in children with high risk ALL treated according to American and European protocols.

**Methods:** A group of 74 children treated with New York like protocols was compared to a group of 45 children treated according to ALLIC-2002. All studied patients had initial WBC ≥ 50 × $10^9$/L. NY consisted of very intensive, repeated multidrug cycles administered over the period of 3 years, whereas ALLIC provided intensive multidrug chemotherapy for 7 months in IRG and 9 months in HRG, followed by maintenance therapy applied for up to two years of treatment.

**Results:** After more than 5 years of follow-up 57 (77%) of NY and 33 (73%) of ALLIC patients are alive in first complete remission. There were 13 (17.6%) and 9 (20%) relapses as well as 16 (9.4%) and 7 (15.6%) deaths respectively. Five-year EFS and OS in NY were 77%/78% and in ALLIC 73%/83.6% respectively. HSCT after relapse was performed in 1 patient from NY. There were 13 HSCT performed in I RC and 3 after relapse in ALLIC group. Relapses and other adverse events occurred mostly in patients with WBC ≥ 100 × $10^9$/L.

**Conclusion:** Generally, the achieved results were satisfactory and comparable to those observed in other centers at that time. OS in the NY patients was inferior mainly due to lack of effective HSCT procedures commonly available for ALLIC patients. Despite higher intensity of NY we did not observe more fatal events not related to the relapse; however the frequency of late side effects in NY treated patients was probably higher. The criterion of initial leukocytosis WBC ≥ 100 × $10^9$/L still indicates children with high risk of relapse and death, although modern risk criteria (mainly MRD and genetic evaluation) are much better for adequate risk stratification.

**Keywords: Acute lymphoblastic leukemia; Risk factors; Stratification; Leukocytosis**

OPEN ACCESS

***Correspondence:***
*Szymon Skoczen, Department of Oncology and Hematology, Institute of Pediatrics, Jagiellonian University Medical College, Wielicka St. 265, 30-663 Krakow, Poland, E-mail: szymon.skoczen@uj.edu.pl*

**Received Date**: *27 Oct 2020*
**Accepted Date**: *10 Dec 2020*
**Published Date**: *14 Dec 2020*

***Citation:***
*Kwiecinska K, Zuzanna Z, Strojny W, Cwiklinska M, Balwierz W, Skoczen S. Extended Follow-Up of Children with High-Risk Acute Lymphoblastic Leukemia Treated with American and European Protocols - A Clash of Different Ideas. Clin Oncol. 2020; 5: 1759.*



## Abbreviations

ALL: Acute Lymphoblastic Leukemia; ALLIC: ALLIC-2002 protocol; BFM: Berlin Frankfurt Munster Study Group; BM: Bone Marrow; BM M1: Blast Cells <5% in Bone Marrow; BM M2: Blast Cells 5: 25% in Bone Marrow; BM M3: Blast Cells >25% in Bone Marrow; CCG: Children's Cancer Group; CNS-1: Central Nervous System free of Leukemia; CNS-2: Central Nervous System free of Leukemia, contaminated with blood; CNS-3: Involvement of Central Nervous System in Leukemic Disease; CR: Complete Remission; EFS: Event Free Survival; Gy: Gray; HR: High Risk; HRG: High-Risk Group; HSCT: Hematopoietic Stem Cell Transplantation; IR: Intermediate Risk; IRG: Intermediate Risk Group; MRD: Minimal Residual Disease; NY: New York protocol; OS: Overall Survival; WBC: White Blood Cells

## Introduction

One of the most important factors influencing the efficacy of the treatment of Acute Lymphoblastic Leukemia (ALL) patients is adjusting the intensity of therapy to risk criteria. The risk criteria have been changed within the time between the first attempts of treatment of ALL patients and nowadays.

We compared the outcome of two groups of patients with ALL and initial leukocytosis over 50 × $10^9$/L treated in the Department of Pediatric Oncology and Hematology in Krakow. One group

was treated according to New York-like protocols (1988-2003), the other with ALLIC-2002 protocol (2003-2012). The historical treatment results in ALL with initial WBC WBC ≥ 50 × $10^9$/L on protocols used between 1981 and 1986 in the centers of Polish Pediatric Leukemia/Lymphoma Study Group were significantly lower than in children with WBC <50 × $10^9$/L (33% *vs.* 60%) [1]. Therefore, in 1988 we introduced modified New York protocol (NY) dedicated for those children, first implemented in CCG/USA by Steinherz et al. [2]. The inclusion criterion was pediatric ALL with initial leukocytosis WBC ≥ 50 × $10^9$/L, which was at that time our only criterion for high risk ALL patients. Patients with WBC <50,000 × $10^9$/L at diagnosis were treated according to less intensive BFM protocol. In 2003 we stopped recruiting to the New York protocol and started ALLIC-2002 established by BFM-group (ALLIC) for all the ALL patients. Instead of the single risk group criterion of initial WBC for HR patients the multiple criteria were introduced to the risk stratification. The criteria for high risk group were: genetic abnormalities (t 9;22 and 4;11), poor prednisone response, initially IR patients with BM M3 in day 15, BM M2 or M3 in 33 day, blast cells in mediastinal tumor or in testicles after 33 day of treatment [3,4]. The last patient recruited to ALLIC was diagnosed on Dec 22nd, 2012. The idea of NY was very intensive chemotherapy from the very beginning to the end of 3-years lasting treatment, whereas ALLIC provided 7-days steroids prophase followed by intensive multidrug i.v. chemotherapy during induction of remission, consolidation and reinduction (which altogether lasted 7 months in IRG and 9 months in HRG) and for the rest of the two-year treatment period less intensive maintenance therapy had been used (mercaptopurine and methotrexate given orally). Cranial irradiation was given for all NY patients (18 Gy as prophylaxis and 24 Gy in CNS positive patients), whereas only the selected group of ALLIC patients underwent this procedure (12 Gy for selected CNS 1/2 patients, 18 Gy for all CNS 3 patients). The details concerning intensity of treatment are provided in Table 1. The aim of our study was to compare the treatment results among children with initial WBC ≥ 50 × $10^9$/L treated with those protocols and being in follow-up for more than 5 years.

**Table 1:** Cumulative doses of drugs used in New York and ALLIC-2002 protocols.

| Drugs (mg/m²) | New York | ALLIC-2002-IRG | ALLIC-2002-HRG |
|---|---|---|---|
| prednisone | 20 220 | 1680 | 1680 |
| dexamethasone | | 210 | 810 |
| VCR | 70.5 | 12 | 18 |
| DNR | | 120 | 120 |
| DOXO | 540 | 120 | 120 |
| L-ASPA | 1 200 000 | 80 000 | 380 000 |
| CY | 18 000 | 3 000 | 5 000 |
| ARA-C | 4560 | 1800 | 9 800 |
| 6-MP | | 3080 + 25 900 | 1740 + 22050 |
| 6-TG | 20 340 | 840 | 840 |
| Mtxi.v. | 4400 | 8000 (BCP), 20 000(T) | 20 000 |
| VDS | | | 12 |
| IFO | | | 8 000 |
| VP-16 | | | 1 000 |
| Mtxp.o. | | 20 × 74 | 20 × 63 |
| Mtxith | 8/10/12 × 6 | 8/10/12 × 11 | 8/10/12 × (13) |
| ARA-C ith | 30/m² × 6 | | × 6 |
| Soludacith | 15/m³ × 6 | | × 6 |

RT 18 Gy 12 Gy (selected pts)/18 Gy 12 Gy or HSCT/18 Gy

**Table 2:** Characteristic of NY and ALLIC patients.

| Protocol/Results | New York | ALLIC-2002 |
|---|---|---|
| Patients number | 74 | 45 |
| Gender- male/female | 42/32 | 35/10 |
| Age (median) years | 1.4-17.5 (7.3) | 1.7-18.6 (5.3) |
| Initial WBC (median)/µl | 50.000-863.000 (100.81) | 50.600-764.000 (122) |
| WBC ≥ 100 000/µl | 48 (64.8%) | 23 (51.1%) |
| Relapses | | |
| ≥ 50 000/µl | 13 | 9 |
| ≥ 100 000/µl | 11/13 | 04/9 |
| **Deaths** | | |
| ≥ 50 000/µl | | |
| Without IRC | 3 | 1 |
| In IRC | 1 | 2 |
| In relapse | 12 | 4 |
| ≥ 100 000/µl | | |
| Without IRC | 3 | 0 |
| In IRC | 1 | 2 |
| In relapse | 10 | 3 |
| Alive (%) | 57 (74)- in I CR | 33 (45)- in I CR (10 after HSCT) |
| | 1 in II CR after HSCT | 5 in II CR |
| 5-year EFS | 77% | 73% |
| 5-year OS | 78% | 83.60% |

## Material and Methods

Within the group of 235 children treated according to ALLIC-2002 there were 45 (19.14%) with initial WBC ≥ 50 × $10^9$/L, among them 23 with initial WBC ≥ 100 × $10^9$/L. There were 35 boys and 10 girls, aged from 1.4 to 17.5 years (median 7.3 years). The initial WBC ranged from ≥ 50 × $10^9$/L to 863 × $10^9$/L (median 100.8 × $10^9$/L). We compared these results with those obtained from 22.06.1988 to 10.03.2003 according to modified New York protocols for children with ALL and WBC at diagnosis ≥ 50 x $10^9$/L. The NY group consisted of 74 patients, 42 boys and 32 girls, aged 1.7 to 18.6 (median 5.3) years, with; WBC at diagnosis ranged from 50.6 × $10^9$/L to 764 × $10^9$/L (median 122 × $10^9$/L). The characteristic of studied groups is presented in Table 2.

### Statistical analysis

Overall Survival (OS) and Event Free Survival (EFS) were calculated using the Kaplan-Meier method. OS was defined as the time from diagnosis to death from any cause; patients alive or lost to follow-up were censored at the date they were last known alive. EFS was defined as the time from diagnosis to disease progression, relapse or death from any cause. Patients who were alive without disease progression or relapse were censored at the time they last were seen alive and event-free. For comparisons of Kaplan-Meier curves we used the log-rank test. All statistical analysis were performed using STATISTICA 13 software.

## Results

In the ALLIC (45 patients) 1 died without achieving remission, 2 died in I CR due to sepsis, 9 patients relapsed: (4 died, 5 are alive

**Table 3:** Results of analysis of influence of selected parameters on EFS.

| Protocol/Parameter | New York | p (log rank) | ALLIC-2002 | p (log rank) |
|---|---|---|---|---|
| Age (years) | | | | |
| 01-5 | 86% | 0.086 | 83.90% | 0.177 |
| 6-18 | 68.40% | | 65.40% | |
| 01-9 | 81.80% | 0.59 | 81.10% | 0.078 |
| 10-18 | 75% | | 53.80% | |
| Gender | | | | |
| Male | 71.40% | 0.189 | 77.10% | 0.316 |
| Female | 84.40% | | 56% | |
| Initial WBC (/µl) | | | | |
| 50 000-99 999 | 92.30% | 0.1973 | 73.90% | 0.91 |
| ≥ 100 000 | 68.70% | | 72.10% | |
| Immunophenotype | | | | |
| BCP-ALL | 76.90% | 0.606 | 64.60% | 0.181 |
| T-ALL | 82.70% | | 84.20% | |
| Risk group (ALLIC) | | | | |
| IRG | | | 78.70% | 0.34 |
| HRG | | | 65.90% | |

**Table 4:** Results of analysis of influence of selected parameters on OS.

| Protocol/Parameter | ALLIC-2002 | p (log rank) |
|---|---|---|
| Risk group (ALLIC) | | |
| IRG | 95.80% | P=0.03257 |
| HRG | 70% | |

in II CR). Thirty three (73.3%) patients are alive in I CR (including 10 after HSCT). Among 23 patients with initial leukocytosis ≥ 100 × $10^9$/L: 4 patients relapsed (3 of them died, one remains in I CR) and 2 died in I CR. In the group of 22 patients with WBC lower than 100 × $10^9$/L we observed 5 relapses (one patient died) and 1 death without I CR. According to the protocol risk criteria 24 patients (20 boys and 4 girls) were assigned to IRG, and 21 (15 boys and 6 girls) to HRG. We observed higher WBC in HRG (range 50 × $10^9$/L: 836 × $10^9$/L, median 132 × $10^9$/L) than in IRG (range 51 × $10^9$/L: 440 × $10^9$/L, median 82 × 109/L). Among 24 patients assigned to IRG one boy died without achieving I CR, 4 patients (2 girls and 2 boys) experienced relapse. All relapsed children live in II CR. Within 21 HRG patients there were 2 deaths in I CR and 5 relapses (4 boys and 1 girl); only one relapsed patient lives in II CR, the remaining 4 died due to progression of the disease. We observed significantly better treatment results in IRG patients compared to HRG, with EFS 78.7% and 65,9% (p=0.342) and OS 95.8% and 70% (p=0.34), respectively.

Analyzing the results obtained between Jun 22nd, 1988 and Mar 10th, 2003 using modified New York protocols we observed the following: Out of 74 NY patients 3 died without I CR, 1 died in I CR, and 13 relapsed. Only 1 relapsed patient lives in II CR after HSCT, the remaining 12 died due to progression of the disease. The majority of patients are alive: 57 (77%) in I CR, 1 in II CR. Relapses occurred mostly in patients with WBC ≥ 100 × $10^9$/L (11 patients). Other adverse events (all four deaths without or in I CR) occurred also (exclusively) among patients with initial WBC ≥ 100 × $10^9$/L. We assessed EFS and OS in ALLIC and NY patients as well as the influence of WBC, age, gender and immunophenotype on EFS in both groups (Figures 1-4). We also compared the EFS and OS in ALLIC patients assigned to

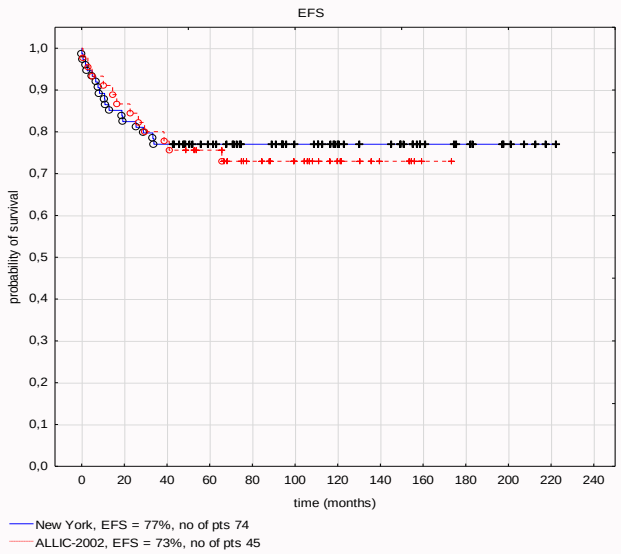


**Figure 1:** Kaplan-Meier survival curve: EFS in NY and ALLIC.
A. Kaplan-Meier survival curve: EFS and OS, comparison of NY and ALLIC.
B. Kaplan-Meier survival curve: EFS and OS, comparison of NY and ALLIC depending on WBC.
C. Kaplan-Meier survival curve: EFS andOS, comparison of NY and ALLIC depending on risk groups.
EFS: Event-Free Surviva; OS: Overall Survival; NY: New York protocol; ALLIC: ALLIC-2002 protocol; WBC: White Blood Cells; IRG: Intermediate Risk Group; HR: High Risk Group

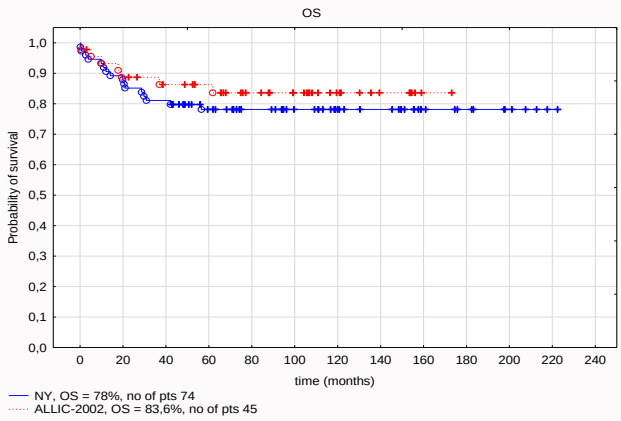


**Figure 2:** Kaplan-Meier survival curve: OS in NY and ALLIC.

IRG and HRG. The results are presented in Table 3 and on Kaplan-Meier survival curves (Figure 1). We found the differences between compared groups (especially regarding initial WBC and different risk groups in ALLIC) (Figure 5 and 6), but no significance was found with the use of log rank test, due to limited number of patients. No significant influence of age, gender, WBC, immunophenotype on EFS was found in either group with the use of log rank test. The only significant difference was found in OS between IRG and HRG ALLIC patients (0.958 and 70%, respectively, p=0.03257).

There were no significant differences in the results of treatment between two studied groups of patients. In the first period (on New York protocols) only 1 patient had HSCT performed after relapse. In the later period HSCT was performed in I CR in 13 patients (12 boys and 1 girl). Only 3 out of 13 patients experienced relapse: 2 of them died, 1 live in II CR. Three out of 9 patients who experienced relapse had subsequent HSCT: One of them died, 2 are alive in II RC. There

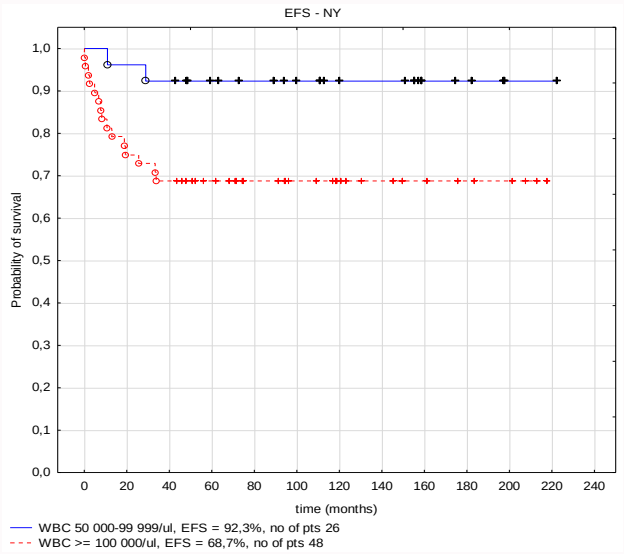


**Figure 3:** Kaplan-Meier survival curve: EFS in NY depending on WBC.

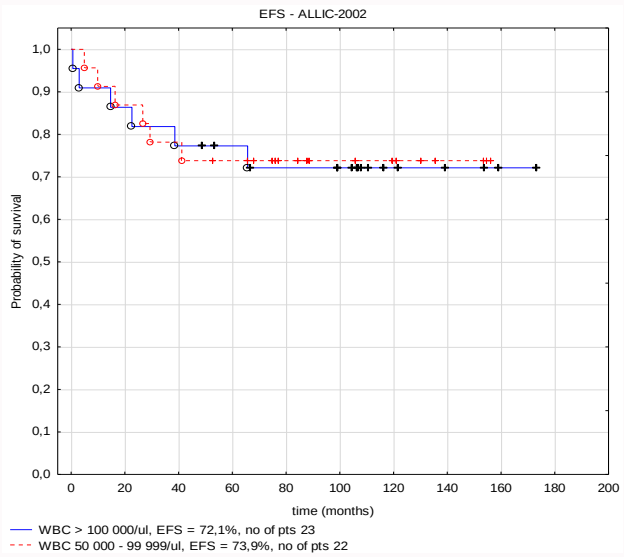


**Figure 4:** Kaplan-Meier survival curve: EFS in ALLIC depending on WBC.

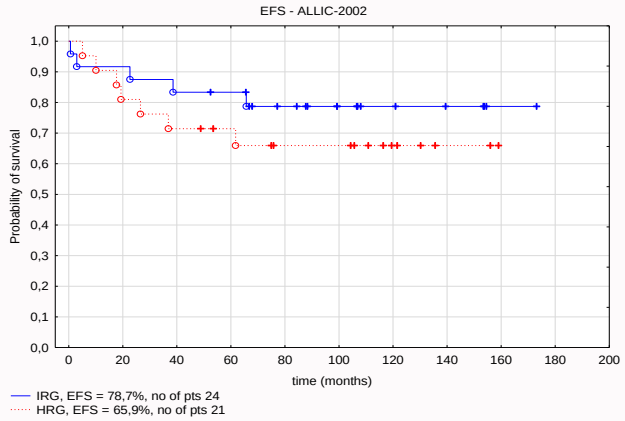


**Figure 5:** Kaplan-Meier survival curve: EFS in ALLIC depending on risk group.

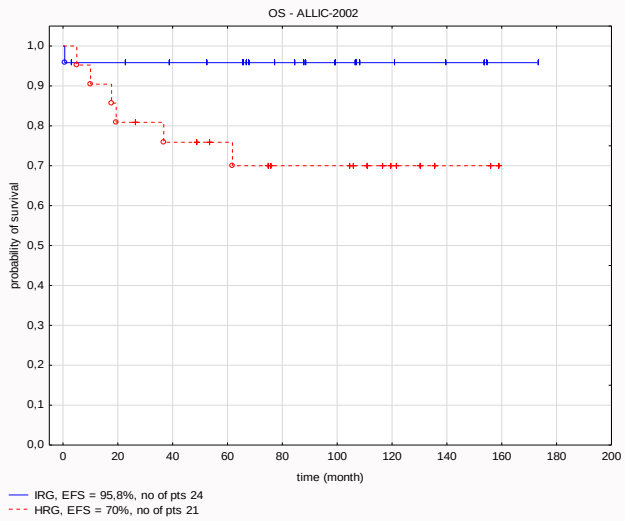


**Figure 6:** Kaplan-Meier survival curve: OS in ALLIC depending on risk group.

were no significant differences among New York and ALLIC-2002 patients regarding event free survival. Five-year EFS in New York group was 77% *vs.* 73% in ALLIC-2002 group (p=0.75). However, we noticed higher 5-year OS in ALLIC-2002 group when compared to New York (83.6% and 78%, respectively, p=0.462), which was the effect of successful HSCT procedures performed in relapsed patients in the later period of treatment.

## Discussion

In late 80-s forced by dismal treatment results in children with initial WBC ≥ 50 × $10^9$/L on BFM protocols another approach was urgently needed. In 1987 the Steinhertz group reported 5-year EFS reaching 70% in such group of patients. It was the time of tendency to intensification of treatment protocols. The idea of maintaining of high intensity for 3 years in very high risk according to that time stratification was very promising. Necessity to cure as much children as possible seemed to be more important than late effects we were not fully aware of. It was kind of courage to introduce high dose chemo in children with high WBC and often bulky disease. Since 2003 the BFM: Based protocol came back for high risk children as the results were comparable and the awareness of late-effects was common. Stratification of ALLIC was based on adjustment of risk group to response to therapy and genetic abnormalities. Therefore patients with WBC ≥ 50 × $10^9$/L not necessarily were assigned to HRG.

New York protocol, being much more intensive than ALLIC-2002, was conducted in an earlier period, when the quality of supportive care was inferior. Also, diagnostic procedures at that time were rather limited: The microscopic assessment and immunophenotyping, without wide genotyping and MRD assessment. The only risk criterion was initial WBC [5]. Generally, the achieved results were satisfactory with 5-year EFS 77%, comparable to those observed in other centers [6-8]. In the NY patients 5-year OS was inferior to the results obtained in ALLIC, mainly due to effective HSCT procedures provided for selected HR ALLIC patients. Very intensive NY was beneficial at that time for some patients who most probably would experience relapse and died with less intensive protocol. However, there were also children who could have been cured with less intensive therapy if more sophisticated risk criteria, mainly MRD and genetic evaluation, would have been available [9-12]. The results of ALLIC confirmed it, because we could observe significant differences

among treatment results in IRG and HRG, regarding our selected patients with initial WBC ≥ 50 × $10^9$/L, with EFS 78.7% and 65.9% (p=0.34), and OS 95.8% and 70% (p=0.03257), respectively. The differences among patients with initial WBC 50 × $10^9$/L: 100 × $10^9$/L and ≥ 100 × $10^9$/L on ALLIC were less pronounced (EFS 73.9% and 72.1%, respectively, p=0.91). Despite higher intensity of NY we did not observe more fatal events not related to the relapse, compared to ALLIC-2002 group (3/45 *vs.* 4/74), however the frequency of late side effects in NY treated patients was probably higher.

In studied groups we obtained better EFS on NY then on ALLIC. One can only speculate that results on NY would have been even better if HSCT and modern supportive treatment had been available at that time. On the other hand survival curves for NY patients will be probably decreased within the time due to late effects in highly pretreated cohort.

Therefore, despite a good outcome we are aware of the fact that very intensive chemotherapy conducted for a long period of time, as in NY protocol, has to be associated with high prevalence of severe and long lasting side effects, increasing within the time, in many patients [13]. Doubtfully, survivors treated with NY should be strictly follow-up for the entire life. Unfortunately the adult health service is not aware of survivors care and insufficient what makes their future uncertain.

## Conclusions

The criterion of WBC 50 × $10^9$/L stratifying children with ALL to HRG was useful in the late eighties of the last century.

The results of NY were comparable to ALLIC.

HSCT improved survival in children with WBC >100,000/μl.

Health consequences in heavily pretreated children are and will be high.

Modern ALL stratification decreases treatment intensity and future late effects of therapy [14].

In late 80s, American protocol strategy for children with ALL and with WBC >50,000/μl was beneficial from the point of view of cure rates comparing to European protocols.

## Acknowledgment

KK, SS designed and performed research, analyzed and interpreted data, and wrote the manuscript. ZZ, MC performed research, analyzed and interpreted data. WS analyzed and interpreted data and critically reviewed the manuscript. WB conducted the clinical protocols and interpreted data.

The datasets used and analyzed during the current study are available from the corresponding author on a reasonable request.

The study was approved by the Ethics Committee of the Jagiellonian University and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

## References

1. Armata J, Cyklis R, Balwierz W, Pekacki A. Curability of acute lymphoblastic leukemia in children treated in years 1975-1984. Nowotwory. 41(4):234-238. (in Polish).
2. Steinherz PG, Gaynon PS, Breneman JC, Cherlow JM, Grossman NJ, Kersey JH, et al. Cytoreduction and prognosis in acute lymphoblastic leukemia--the importance of early marrow response: Report from the Childrens Cancer Group. J Clin Oncol. 1996;14(2):389-98.
3. Stary J, Zimmermann M, Campbell M, Castillo L, Dibar E, Donska S, et al. Intensive chemotherapy for childhood acute lymphoblastic leukemia: Results of the randomized intercontinental trial ALL IC-BFM 2002. J Clin Oncol. 2014;32(3):174-84.
4. Fronkova E, Mejstrikova E, Avigad S, Chik KW, Castillo L, Manor S, et al. Minimal residual disease (MRD) analysis in the non-MRD-based ALL IC-BFM 2002 protocol for childhood ALL: Is it possible to avoid MRD testing? Leukemia. 2008;22(5):989-97.
5. Balwierz W, Moryl-Bujakowska A, Skoczen S, Pawinska K, Balcerska A, Ploszynska A, et al. Improvement of treatment results in children with high risk Acute Lymphoblastic Leukemia (ALL) treated with modified "New York" protocols between 1987 and 2002. Przegladlekarski. 2003;60:13-6. (In Polish).
6. Schrappe M, Reiter A, Zimmermann M, Harbott J, Ludwig WD, Henze G, et al. Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995. Berlin-Frankfurt-Münster. Leukemia. 2000;14(12):2205-22.
7. Nachman J, Sather HN, Cherlow JM, Sensel MG, Gaynon PS, Lukens JN, et al. Response of children with high-risk acute lymphoblastic leukemia treated with and without cranial irradiation: A report from the children's cancer group. J Clin Oncol. 1998;16(3):920-30.
8. Pui CH, Boyett JM, Rivera GK, Hancock ML, Sandlund JT, Ribeiro RC, et al. Long-term results of total therapy studies 11, 12 and 13A for childhood acute lymphoblastic leukemia at St Jude children's research hospital. Leukemia. 2000;14(12):2286-94.
9. Borowitz MJ, Devidas M, Hunger SP, Bowman WP, Carroll AJ, Carroll WL, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: A children's oncology group study. Blood. 2008;111(12):5477-85.
10. Schultz KR, Pullen DJ, Sather HN, Shuster JJ, Devidas M, Borowitz MJ, et al. Risk- and response-based classification of childhood B-precursor acute lymphoblastic leukemia: A combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). Blood. 2007;109(3):926-35.
11. Conter V, Bartram CR, Valsecchi MG, Schrauder A, Panzer-Grümayer R, Möricke A, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: Results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood. 2010;115(16):3206-14.
12. Szczepański T, Harrison CJ, van Dongen JJM. Genetic aberrations in paediatric acute leukaemias and implications for management of patients. Lancet Oncol. 2010;11(9):880-9.
13. Yeh JM, Ward ZJ, Chaudhry A, Liu Q, Yasui Y, Armstrong GT, et al. Life expectancy of adult survivors of childhood cancer over 3 decades. JAMA Oncol. 2020;6(3):350-7.
14. Coustan-Smith E, Sancho J, Hancock ML, Boyett JM, Behm FG, Raimondi SC, et al. Clinical importance of minimal residual disease in childhood acute lymphoblastic leukemia. Blood. 2000;96(8):2691-6.