



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

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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 $\geq 50 \times 10^9/L$. 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 1 RC and 3 after relapse in ALLIC group. Relapses and other adverse events occurred mostly in patients with WBC $\geq 100 \times 10^9/L$.

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 $\geq 100 \times 10^9/L$ 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

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 $50 \times 10^9/L$ treated in the Department of Pediatric Oncology and Hematology in Krakow. One group

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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 $\geq 50 \times 10^9/L$ 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 $<50 \times 10^9/L$ (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 $\geq 50 \times 10^9/L$, which was at that time our only criterion for high risk ALL patients. Patients with WBC $<50,000 \times 10^9/L$ 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 $\geq 50 \times 10^9/L$ treated with those protocols and being in follow-up for more than 5 years.

Material and Methods

Within the group of 235 children treated according to ALLIC-2002 there were 45 (19.14%) with initial WBC $\geq 50 \times 10^9/L$, among them 23 with initial WBC $\geq 100 \times 10^9/L$. There were 35 boys and 10 girls, aged from 1.4 to 17.5 years (median 7.3 years). The initial WBC ranged from $\geq 50 \times 10^9/L$ to $863 \times 10^9/L$ (median $100.8 \times 10^9/L$). 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 $\geq 50 \times 10^9/L$. 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 $50.6 \times 10^9/L$ to $764 \times 10^9/L$ (median $122 \times 10^9/L$). 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

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

Drugs (mg/m ²)	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 x 74	20 x 63
Mtxith	8/10/12 x 6	8/10/12 x 11	8/10/12 x (13)
ARA-C ith	30/m ² x 6		x 6
Soludacith	15/m ³ x 6		x 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 $\geq 100 000/\mu l$	48 (64.8%)	23 (51.1%)
Relapses		
$\geq 50 000/\mu l$	13	9
$\geq 100 000/\mu l$	11/13	04/9
Deaths		
$\geq 50 000/\mu l$		
Without IRC	3	1
In IRC	1	2
In relapse	12	4
$\geq 100 000/\mu l$		
Without IRC	3	0
In IRC	1	2
In relapse	10	3
Alive (%)	57 (74)- in I CR 1 in II CR after HSCT	33 (45)- in I CR (10 after HSCT) 5 in II CR
5-year EFS	77%	73%
5-year OS	78%	83.60%

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.

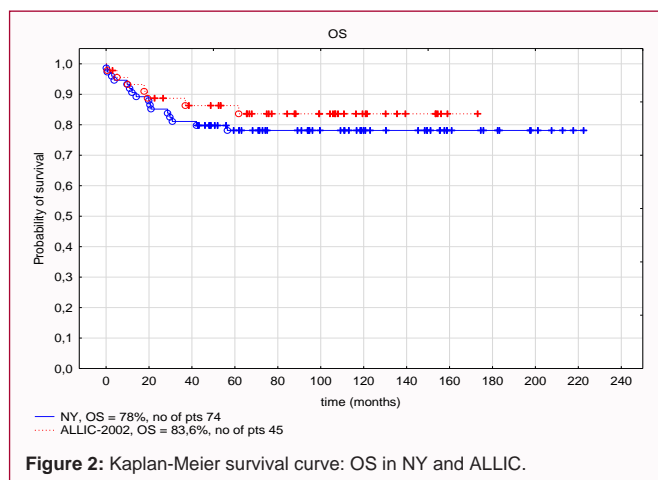
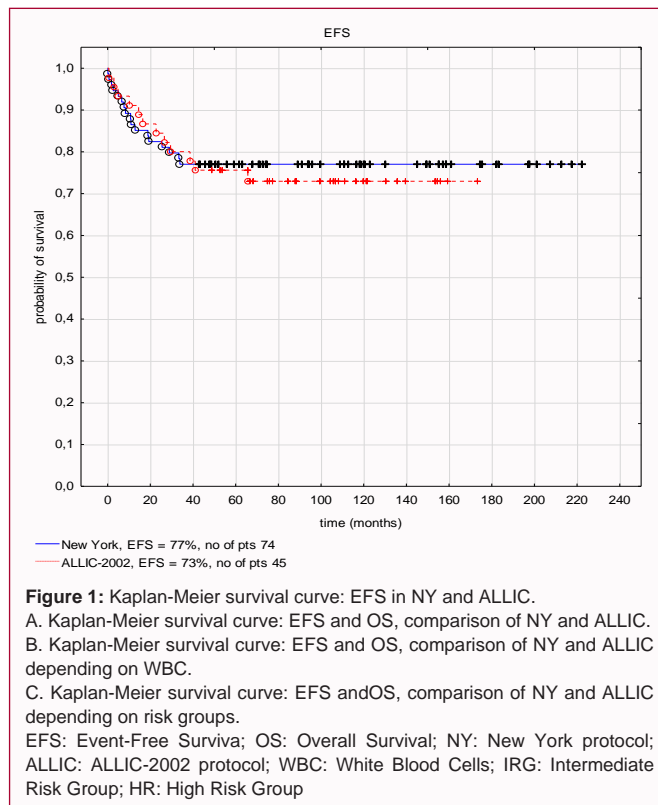
Protocol/Parameter	New York	p (log rank)	ALLIC-2002	p (log rank)
Age (years)				
01-5	86%	0.086	83.90%	0.177
6-18	68.40%		65.40%	
01-9	81.80%	0.59	81.10%	0.078
10-18	75%		53.80%	
Gender				
Male	71.40%	0.189	77.10%	0.316
Female	84.40%		56%	
Initial WBC (/μl)				
50 000-99 999	92.30%	0.1973	73.90%	0.91
≥ 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%	

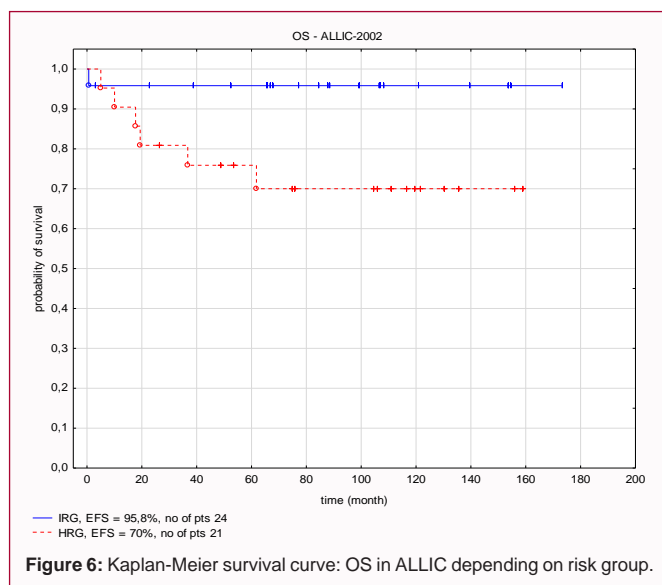
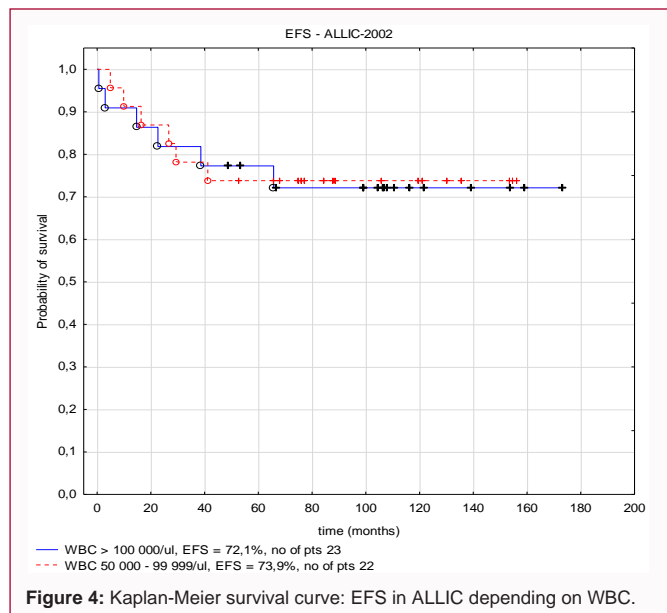
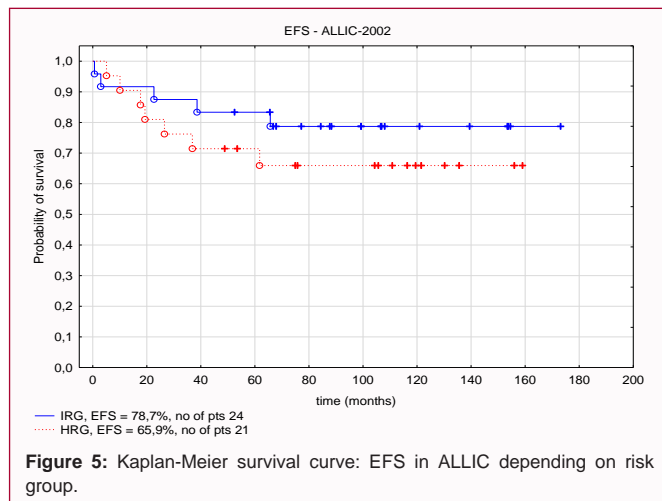
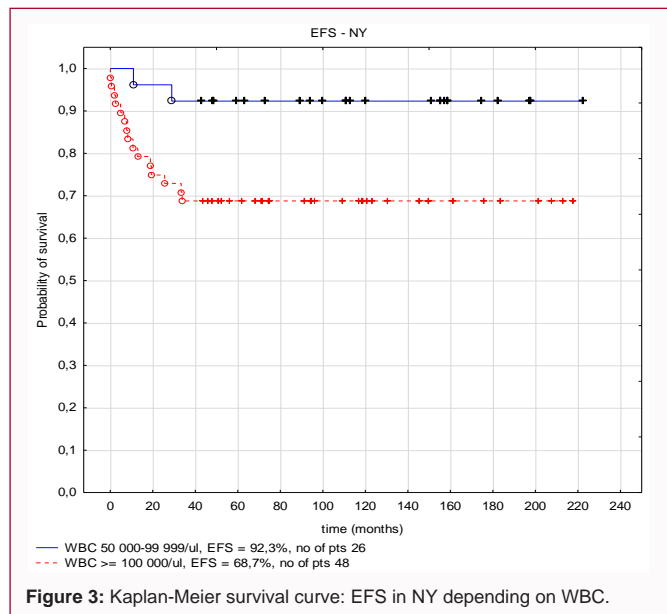
in II CR). Thirty three (73.3%) patients are alive in I CR (including 10 after HSCT). Among 23 patients with initial leukocytosis $\geq 100 \times 10^9/L$: 4 patients relapsed (3 of them died, one remains in I CR) and 2 died in I CR. In the group of 22 patients with WBC lower than $100 \times 10^9/L$ 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 $50 \times 10^9/L$: $836 \times 10^9/L$, median $132 \times 10^9/L$) than in IRG (range $51 \times 10^9/L$: $440 \times 10^9/L$, median $82 \times 10^9/L$). 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 $WBC \geq 100 \times 10^9/L$ (11 patients). Other adverse events (all four deaths without or in I CR) occurred also (exclusively) among patients with initial $WBC \geq 100 \times 10^9/L$. 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



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 CR. There



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 $WBC \geq 50 \times 10^9/L$ 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 $WBC \geq 50 \times 10^9/L$ 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 $\geq 50 \times 10^9/L$, 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 $50 \times 10^9/L$: $100 \times 10^9/L$ and $\geq 100 \times 10^9/L$ 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 than 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 $50 \times 10^9/L$ 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 $>100,000/\mu L$.

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 $>50,000/\mu L$ 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.

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