RESEARCH ARTICLE
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The Outcome of Modified St. Jude Total XV Protocol in Turkish Children with Newly Diagnosed Acute Lymphoblastic Leukemia: A Single-Center Retrospective Analysis

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Abstract
Objective: This study examines the prognostic factors and outcomes of Turkish children with newly diagnosed acute lymphoblastic leukemia (ALL) who were treated with Modified St. Jude Total XV Protocol, which was modified by adding high-dose methylprednisolone (HDMP) before induction in the original protocol.
Materials and Methods: A cohort of 183 newly diagnosed ALL patients aged 1-18 years received Modified St. Jude Total XV Therapy between January 1, 2008 and January 30, 2016. HDMP was administered for 7 days, with randomized doses at 10 or 20 mg/kg/d, tapered during the subsequent 7 days to 5 and 10 mg/kg/d, followed by 2 mg/kg/d for 2 weeks. Absolute blast count in peripheral blood and minimal residual disease (MRD) in bone marrow were assesses at the end of the initial HDMP treatment (Day 7). MRD in the bone marrow was measured on day 15 and at the end of the induction period. These patients were followed until July 15, 2019.
Results: The five-year event-free (EFS) and overall survival (OAS) rates for all patients were 85.6±2.6% and 89.2±2.3%, respectively. The steroid good responder rate (<1 000/mm3 absolute blast count in peripheral blood on Day 7) was 88%, with 97% of children achieving complete remission post-induction. No significant differences were observed between the two groups in survival rate and infection frequency. EFS and OAS correlated with initial leukocyte count, age 10–18 years at diagnosis, CD20 positivity at diagnosis, and gram-negative bacterial infection during remission induction.
Conclusion: The notable response rates on day 7 and 15, along with encouraging EFS and OAS outcomes with Modified St. Jude Total XV in childhood ALL patients underscore the early and high response effect of HDMP. Short-term HDMP can be initiated at the onset of induction, administered at 10 mg/kg/day for the initial 7 days, aiming to minimize potential side effects.
Keywords: Acute lymphoblastic leukemia, child, survival, prognostic factors

ÖZET
Amaç: Bu çalışmada, akut lenfoblastik lösemi (ALL) tanısı almış ve orjinal protokole indüksiyon fazının öncesine yüksek doz metilprednizolon (YDMP) tedavisi eklenerek modifiye edilmiş Modifiye St, Jude Total XV protokolü ile tedavi edilen çocuk hastalarda sağkalım ve prognostik faktörleri incelemektedir.
Gereç ve Yöntemler: 1 Ocak 2008 ile 30 Ocak 2016 tarihleri arasında 183 yeni tanı almış 1-18 yaş ALL hastasına, Modifiye St. Jude Total XV tedavisi uygulandı. YDMP tedavisi, indüksiyon öncesi 7 gün boyunca, 10 veya 20 mg/kg/gün dozlarında randomize olarak verildi. Takip eden 7 gün, 5 ve 10 mg/kg/gün ve ardından 2

hafta boyunca 2 mg/kg/gün olarak uygulandı. YDMP tedavisinin sonunda (7. Gün), periferik kanda absolü blast sayısı (ABS) ve kemik iliğinde minimal kalıntı hastalık (MKH) ile indüksiyonun 15. gün ve sonunda kemik iliğinde MKH değerlendirildi. Hastaların takibi 15 Temmuz 2019'da sonlandırıldı.
Bulgular: Tüm hastalar için 5 yıllık olaysız (OSK) ve genel sağkalım (GSK) oranları sırasıyla % 85.6±2.6 ve % 89.2±2.3'tü. Steroide iyi yanıt veren (YDMP tedavisi 7. günde periferik kanda ABS <1 000/mm^3) hastaların oranı %88 iken indüksiyon sonunda tam remisyon %97 hastada kaydedildi. İki grup karşılaştırıldığında, sağkalım oranları ve enfeksiyon sıklığında anlamlı farklılık gözlemlenmedi. OSK ve GSK, tanı anındaki lökosit sayısı, tanı yaşının 10-18 olması, tanıda CD20 pozitifliği ve indüksiyon döneminde gram negative bakteriyel enfeksiyon geçirme durumu ile ilişkili bulundu.
Sonuç: Çocukluk çağı ALL hastalarında, Modifiye St. Jude Total XV tedavisi ile, indüksiyon tedavisinin 7. ve 15. gününde gözlemlenen dikkate değer yanıt oranları ve teşvik edici sağkalım sonuçları, YDMP'nin erken ve yüksek tedavi yanıtına katkı sağlayabileceğini vurgulamaktadır. İndüksiyon tedavisinin başlangıcında, kısa süreli, olası yan etkileri de en aza indiremek adına 10 mg/kg/gün dozunda YDMP tedavisi uygulanabilir.

INTRODUCTION

Childhood acute lymphoblastic leukemia (ALL) is the most common cancer in children, with five-year survival rates reaching 85–90% owing to advancements in risk-stratified treatment protocols and supportive care(1). Advances in clinical trials and a deeper understanding of ALL pathobiology enhance precise and effective risk classification, directing intensive treatment to high-risk groups and protecting others from drug-induced toxicities (2-7)

The primary aim in the induction phase is to maximally eradicate lymphoblasts to ensure remission and prevent the development of drug resistance. Glucocorticoids have been the backbone agent in the induction treatment of ALL, used at conventional doses (40–60 mg/m^2/day prednisolone), varying in bioequivalence across different clinical studies (8-11). In our center, high-dose methylprednisolone therapy (HDMP) has been used in patients with ALL before and during remission induction since 1990, following encouraging results in various clinical trials, including with patients with acute myeloid leukemia (AML) and ALL. Corticosteroid-dependent reduction of lymphoblasts in peripheral blood has been shown as a good prognostic marker for survival (12-15).

In this study, we investigate the effect of different HDMP doses in induction on early treatment response and survival in childhood ALL. Our aim is to contribute to a new therapeutic approach for enhancing survival rates and to bolster research on childhood ALL survival in Turkey. To address the efficacy of HDMP and the limited experience with diverse treatment protocols, we conducted a retrospective analysis on patients treated with Modified St. Jude Total XV Therapy at our hospital, one of the leading cancer centers in Turkey.

METHODS

Study population

The medical records of 207 newly diagnosed patients with ALL at Hacettepe University Ihsan Dogramaci Children's Hospital between January 1, 2008 and January 30, 2016 were reviewed. Exclusions comprised patients under one year old (n=8), treatment at another hospital before admission to our center (n=1), protocol changes (n=6) and post-diagnosis transfer to another hospital (n=1). Data on socio-demographic, clinic, laboratory, imaging, and treatment characteristics of the 183 included patients were extracted from the electronic health records and patient files.

Treatment protocol

St. Jude Total Therapy XV was implemented with modifications, including a seven-day HDMP therapy before induction and the omission of upfront high-dose methotrexate (HDMTX) and intrathecal cytarabine. Consequently, Days 19 and 26 of induction corresponded to Days 15 and 22, respectively. The second modification was administration of first dose HDMTX as 2.5 gr/m^2 to all risk groups in consolidation treatment due to unknown methotrexate (MTX) pharmacokinetics. Notably, the original protocol established the safety of excluding cranial radiotherapy (RT) from childhood ALL treatment, and no patient in our study received cranial RT. Additionally, although a minor change, the DNA index was not used in risk classification as it was not assessed at our hospital. Aside from these adjustments, our protocol and treatment response assessment were identical to the original version (16). *(The outlines of remission-induction and the criteria for risk classification are summarized in Supplementary 1).*

Patients were consecutively randomized into Group A (n=65, 36%) or Group B (n=90, 49%), receiving 10 and 20 mg/kg/d HDMP, respectively (max. 1 000 mg/d), for seven days before induction. HDMP doses were tapered to 5 and 10 mg/kg/d, respectively, in the following week. Both groups then received 2 mg/kg/d MP for the subsequent two weeks. A third group, Group C, included patients with a high tumor burden (hyperleukocytosis [>100×10^9/L] and significant organomegaly) who received lower MP doses (<10 mg/kg/d) for the first seven days to forestall acute tumor lysis syndrome (TLS). At the end of the HDMP treatment (on Day 7), the peripheral absolute blast count (ABC) was recorded to assess early treatment response, with

<1x10^9/L in peripheral blood accepted as a good steroid response. Bone marrow (BM) minimal residual disease (MRD) was measured on Day 15 and at the end of induction for all patients, and on Day 22 for those with MRD of 1% or more on Day 15. Poor response was defined as BM MRD >1%, 1%, and 0.01% on Days 15 and 22 and at the end of induction, respectively.

Morphological assessment, cytogenetic analysis (including classical karyotyping, fluorescence in situ hybridization , and/or polymerase chain reaction), and immunophenotyping were performed at diagnosis for all patients. Cerebrospinal fluid (CSF) analysis involved cytocentrifugation and cytological methods to determine central nervous system (CNS) involvement, categorized as CNS-1 (no detectable blast cells), CNS-2 (<5 leukocytes/ mm^3 with blasts and <10 erythrocytes/ mm^3), CNS-3 (≥5 leukocytes/ mm^3 with blasts and <10 erythrocytes/ mm^3) and traumatic status (>10 erythrocytes /μL of CSF with blasts) as per the original protocol. Even if blasts were not observed, we classified patients with erythrocytes in their CSF as traumatic to adhere to the protocol and administered additional triple intratechal treatment.

Immunophenotyping and MRD assessment utilized by flow cytometry (FCM), defining CD positivity as over 20% expression in leukemia blasts within bone marrow samples. Patients were classified as low, standard, or high risk after the remission induction treatment according to the criteria in the original protocol.

Statistical analysis

Chi-Square and Fisher's exact tests were used to compare the differences in the distribution of parameters among patient subgroups. Survival analysis included event-free survival (EFS), measured from diagnosis to first outcome event (treatment failure, death, relapse, secondary malignancy, or treatment discontinuation), and overall survival (OAS), measured from diagnosis to death from any cause or loss of contact. The statistical impact of demographic, clinical, and laboratory characteristics of patients on survival was evaluated via Kaplan-Meier analysis with the log-rank test. Variables with $p<0.10$ in univariate analysis were included in Cox's proportional hazard regression model, using the Enter method to identify the most impactful factors. IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses, with $p<0.05$ considered statistically significant.

RESULTS

Initial characteristics of patients

Table 1 details the clinical and laboratory features of patients. The distribution of risk groups was 49% low, 41% standard, and 10% high risk. CNS involvement (CNS-3) was found at diagnosis in 5% of patients. Among these, a significantly higher proportion had an initial leukocyte count of ≥50x10^9/L and T-cell leukemia compared to those without CNS involvement ($p=0.014$ and $p<0.001$, respectively). Additionally, significantly more patients in the group with a leukocyte count of ≥50x10^9/L at diagnosis had T-cell ALL and CNS-3 status than the group with an initial leukocyte count of <50x10^9/L ($p<0.001$ and $p=0.012$, respectively). Furthermore, hyperdiploidy and t(12;21) (ETV6-RUNX1) were not detected in the patients with initial leukocyte counts of ≥50x10^9/L.

Treatment outcomes

The treatment outcomes of all patients, based on clinical and biological characteristics, were displayed in Table 2. On Day 7 of HDMP, peripheral ABC was assessed in 156 of 183 patients; 137 (88%) of whom were steroid good responders (SGRs). SGR rate was significantly higher (92%) in those receiving HDMP (Groups A and B) compared to Group C (60%), which had a higher rate of T-cell ALL and high-risk patients ($p<0.01$). The MRD-negative rate was 96% on Day 15 and 92% at the end of induction, with 97% achieving complete morphological remission. On the 15th day, MRD >1% was detected in 7 patients, all of whom had MRD values above 0.01% at the end of induction. Additionally, 6 patients who showed steroid response on the 7th day and had MRD <1% on the 15th day had MRD values above 0.01% at the end of induction and were treated as high-risk. Among the13 patients with MRD values above 0.01% at the end of induction, 12 were considered to be in morphological remission, while one patient was evaluated as refractory ALL. Induction failures occurred due to TLS-related death (n=1), refractory leukemia (n=1), and fatal infections, comprising acute respiratory distress syndrome related to pneumonia (n=2), E. coli sepsis (n=1), and Clostridium sepsis (n=1).

During follow-up, 6 patients classified as low risk and one patient classified as standard risk transitioned to the high-risk protocol in the 7th week of maintenance therapy due to the detection of MRD >0.1% in the bone marrow.

Bone marrow transplantation was performed on a total of 9 patients, comprising 7 high-risk patients and 2 standard-risk patients with BM relapse and recurrent isolated CNS relapse. Among these patients, 3 have died. Four out of 7 patients with t(9;22) underwent bone marrow transplantation, and all were alive untill the end of the study period.

Comparison of Groups A and B

There were no significant differences in age, sex, initial leukocyte count, immunophenotype, CNS status at diagnosis, or risk group classification between Group A and B ($p>0.05$). Additionally, the proportions of SGRs on Day 7 and BM FCM-MRD-negative patients on Day 15 and at the end of induction were similar between two groups ($p>0.05$) (Supporting Information).

Survival rates

Excluding one patient who died early in induction due to TLS, the 182 eligible patients (median follow-up 6.6 years) achieved a five-year EFS of 85.6% (95% CI, 83–88.2%) and OAS of 89.2% (95% CI, 86.9–91.5%) (Fig. 1). Groups A and B demonstrated similar survival rates (Group A: EFS 87.6%, OAS 89.4%; Group B: EFS 89.2%, OAS 92.2%), while Group C exhibited significantly lower EFS compared to Groups A and B (p=0.043), though their OAS rates were similar (p=0.435).

Prognostic factors

The age of 10–18 years, an initial leukocyte count of $\geq 50x10^9$/l and t(1;19)(E2A-PBX1) positivity at diagnosis, along with gram-negative bacterial infections during the induction, were significantly associated with poorer EFS and OAS in univariate analysis. Standard-risk and CD20-positive patients had significantly lower EFS and OAS, respectively, compared to low-risk and CD20-negative patients. Trends toward increased survival for SGRs on Day 7 and FCM-MRD-negative patients on Day 15 and at the end of the induction were observed, but not significant (p>0.1).

A Cox regression multivariate analysis, using factors with a p-value <0.1 in univariate analysis, independently associated age 10–18 years, $\geq 50x10^9$/L leukocyte count, and CD20 positivity at diagnosis as adverse predictors of both EFS and OAS. Gram-negative bacterial infection during induction was also an independent predictor of poorer OAS (Table 3).

Infections in remission induction

Infections and microbiological causative agents were evaluated during induction. At least one infection episode, 255 episodes in total, during induction was experienced in 148 patients (81%). The predominant infections were febrile neutropenia (n=115, 45%), pneumonia (n=38, 15%), and central venous catheter/port infections (n=255, 9%). The investigation into the relationship between HDMP dosage and vulnerability to infection found no significant difference between Groups A and B (p>0.05).

DISCUSSION

The five-year EFS of 85.6% and OAS of 89.2% achieved in this study were comparable to St. Jude Total Therapy XV (EFS: 85.6%, OAS: 93.5%), and slightly higher than the recent Surveillance, Epidemiology, and End Results Program data for patients under 15 treated between 2010 and 2017 (72%) and other major studies (9, 10, 17-21). The hallmark of our study is the use of HDMP treatment in pre-induction, likely contributing to our superior survival rates.

Apart from the trials conducted at our institution, the Dana Farber Cancer Institute protocol 91-01 is the only one in the literature for administering a high steroid dose before induction. Similar to our study's findings, high-dose dexamethasone (18 mg/m^2/d, or 150 mg/m^2/d) produced a greater bone marrow response, overcoming drug insensitivity and low glucocorticoid-receptor expression in lymphoblasts compared to prednisolone (40 mg/m^2/d), standard-dose dexamethasone (6 mg/m^2/d) (22).

In our study, we observed a notable early impact of HDMP, with a higher proportion of MRD-negative patients at Day 15 (96%) and the end of induction (92%) compared to counterparts in the St. Jude Total XV protocol (79.9% and 79.6%, respectively), as well as other major collaborative trials(9, 10, 22-24). Moreover, achieving a morphological remission rate of 99% by the end of induction underscores the significant effect of HDMP in swiftly eradicating lymphoblasts during this phase. However, our SGR rate on Day 7 (88%) was akin to protocols using conventional steroid doses (17, 25-27). The group with steroid poor response comprised significantly higher rates of patients with T-cell phenotype, leukocyte count $\geq 50x10^9$/L at diagnosis, CNS-3, and standard as well as high-risk compared to SGRs (respectively, p=0.001, p<0.001, p=0.005, p=0.015, p=0.022). Seventeen out of nineteen steroid poor responders had negative MRD on Day 15 and at the end of induction. This might suggest that observing the efficacy of HDMP by Day 7 might be premature. Furthermore, the possibility of rapid eradication of steroid-resistant lymphoblasts with HDMP and the non-identification of the prognostic impact of MRD on the 15th and 42nd days could be speculated as the advantageous impact on survival of a higher cumulative dose of HDMP in the first two weeks.

In the comparison between patients in Group A (10 mg/kg/day) and Group B (20 mg/kg/day), the difference in early treatment response and survival rates did not achieve statistical significance. While comparing the early efficacy, side effects, and survival influence of HDMP with conventional steroid doses wasn't feasible, the lower EFS in Group C patients (irregular dose), who required lower methylprednisolone doses due to concerns about TLS from hyperleukocytosis, might offer insights into the effectiveness of HDMP treatment.

Expanding our investigation, we explored infections during induction to assess whether HDMP heightened susceptibility. While this study couldn't directly compare infection frequencies between HDMP and conventional steroid doses, a prior study at our center found no difference (28). Infection rates during induction vary widely across studies, ranging from 52% in Jude Total XV to 80% in the Pediatric Oncology Group protocol by Lillian et al. The most common infection, acute neutropenia, and bacterial agents isolated were consistent with those in the original protocol (29, 30). Our relatively high infection rate (81%) might be attributed to factors such as port

placement in all patients (12.5% with port infections), housing leukemia follow-up patients alongside those hospitalized for other conditions due to the absence of a dedicated hematology service at our center during the study, and limited facilities and intermittent construction in our hospital.

The current study revealed age (10–18 years) and leukocyte count ($\geq 50x10^9$/L) at diagnosis, well known prognostic factors, significantly impacted EFS and OAS. The lower survival rates among adolescents lack a definitive explanation, but studies suggest several contributing factors. This age group tends to exhibit fewer favorable prognostic genetic factors, such as hyperdiploidy and t(12;21) (ETV6-RUNX1), while showing higher prevalence of unfavorable ones like *BCR::ABL1* and iAMP21. Additionally, post-induction MRD burden tends to be higher among adolescents, and they experience more treatment-related complications such as pancreatitis, thromboembolism, steroid-induced diabetes mellitus, and osteonecrosis. These disparities may be attributed to age-related changes in drug pharmacokinetics and pharmacodynamics. Alternatively, they could be associated with poorer treatment adherence in adolescent patients compared to younger cohorts (31, 32).

In our study, t(1;19)(E2A-PBX1) emerged as the sole poor genetic prognostic marker. Two of the four patients with this marker died due to sepsis in the maintenance period and BM relapse. While prior studies linked it to poorer outcomes, recent research revealed no impact on outcomes, although it might still be associated with CNS relapse (33). Notably, established indicators like *BCR::ABL1*, KMT2A rearrangement, hypodiploidy, t(12;21) (ETV6-RUNX1), and hyperdiploidy did not significantly affect EFS or OAS in our study, possibly due to the genetic specifics of a small number of patients.

It's intriguing that CD20 positivity emerged as a predictor of adverse events and death in our study. Borowitz et al. found shorter EFS in CD20-positive patients, but later studies suggest that CD20 expression may not affect prognosis (34, 35). Additionally, Ou et al.'s meta-analysis revealed no KMT2A rearrangement, associated with heightened relapse risk, in CD20-positive patients (36). Surprisingly, KMT2A rearrangements were observed in 13% of CD20-positive patients in our study. CD20 expression often signifies poor prognosis in adult ALL, leading to the incorporation of rituximab, a monoclonal antibody targeting CD20, in treatment regimens for adults with B-cell precursor ALL (37). In future studies, the prognostic impact of CD20 positivity, its correlation with other factors, and potential therapeutic options, can be explored in a larger patient cohort.

The St Jude Total Therapy Study XVI achieved the highest five-year survival rate in pediatric ALL (EFS 88.2% [95% CI, 84.9–91.5%] and OAS 94.1% [95% CI, 91.7–96.5%]) so far (38). Despite reduced CNS relapse and increased EFS in St Jude Total Therapy Study XVI, its OAS rate matched that of Total Therapy Study XV. The ALL IC- Berlin-Frankfurt-Munster (BFM) 2002 study, reported 74±1% and 82±1% EFS and OAS, respectively (17). Senay et al. applied the modified St Jude Total XV protocol, using HDMP therapy alongside a multiple chemotherapy regimen during induction, not before, and reported a 5-year EFS and OAS of 78.3% and 80%, respectively (39). Hazar et al. reported 8-year EFS and OAS rates of 63.2% (95% CI 54.4-72.0) and 72% (95% CI 63.6-80.4), respectively, whereas Koçak et al. reported 12-year EFS and OAS of 75.0% and 80.6%, respectively, based on their experience with the ALL-BFM 95 protocol (40, 41). Our promising EFS and OAS rates achieved with the modified St. Jude Total XV in childhood patients with ALL surpass those seen in the protocols conducted by prominent centers in our country and major study groups worldwide (10, 18, 40-42).

CONCLUSION

This manuscript significantly contributes to the literature by revealing favorable survival rates and prognostic factors in a large pediatric ALL population. The high early response in induction using HDMP appears pivotal for treatment success. Notably, pre-induction steroid treatment is not applied in other major protocols, except for the use of conventional dosages in BFM protocols (43). In conclusion, integrating short-term HDMP therapy into protocols as a pre-induction phase seems viable. Our study revealed no significant variance in survival rates between 10 and 20 mg/kg/d HDMP doses. Hence, initiating treatment with the lower dosage during the first week would be more appropriate to reduce potential side effects.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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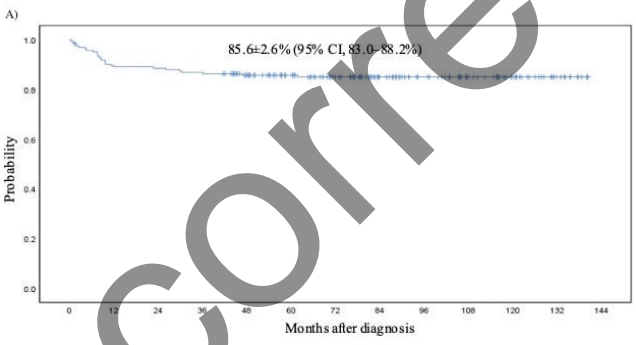
Abbreviation	Meaning
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
EFS	Event-Free Survival
OAS	Overall Survival
HDMP	High-Dose Methylprednisolone
HDMTX	High-Dose Methotrexate
RT	Radiotherapy
BM	Bone Marrow
MRD	Minimal Residual Disease
CSF	Cerebrospinal fluid
CNS	Central Nervous System
FCM	Flow Cytometry
HSCT	Hematopoietic Stem-Cell Transplantation
SGR	Steroid Good Responder
TLS	Tumor Lysis Syndrome
BFM	Berlin-Frankfurt-Munster
CD	Cluster of Differentiation
ABC	Absolute Blast Count



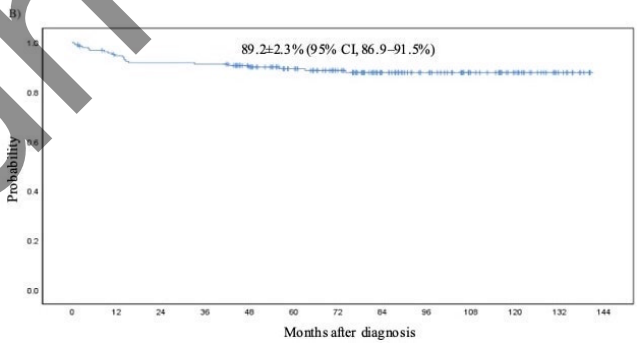


TABLE 1 Presenting Clinical and Biological Patient Features

Characteristics	No. (%) Patients	Mean±SD	Median±SD
Age at diagnosis, yrs		6.7±4.4	5.3 (1–18)
1–10	140 (76)		
>10	43 (24)		
Sex			
Male	108 (59)		
Female	75 (41)		
Complete blood count, at diagnosis			
Hemoglobin (g/dL)		8.6±2.2	8.6 (2.7–17.8)
Leucocyte ($\times 10^9$/L)		45.6±91.3	9.9 (1.3–574.6)
Platelet ($\times 10^9$/L)		114.4±117.6	74.5 (5–703)
Involvement of systems			
Hepatomegaly	158 (86)		
Lymphadenopathy	85 (46)		
Splenomegaly	78 (43)		
Skeletal system involvement	20 (25)		
Skin involvement	2 (1)		
Testicular involvement	1 (0.5)		
CNS status			
CNS-1	118 (65)		
CNS-2	8 (4)		
CNS-3	9 (5)		
Traumatic with blasts	47 (26)		
Cytology			
Hypodiploidy	13/68 (19)		
t(12;21)	12/84 (14)		
Hyperdiploidy	7/68 (10)		
t(9;22)	7/138 (5)		
KMT2A rearrangements	6/48 (12)		
t(1;19)	4/65 (6)		
Trisomy 21	3/163 (2)		

TABLE 2 Treatment Outcome According to Selected Clinical and Biologic Characteristics

Characteristics	No. Patients	5-Year Event-Free Survival % (95% CI)	*p*	5-Year Overall Survival% (95% CI)	*p*
Age at diagnosis, yrs					
1–10	140	89.9	**0.003**	92.6	**0.003**
>10	42	70.8		77.6	
Sex					
Male	107	86.9	0.683	88.7	0.871
Female	75	83.8		90.0	
Leukocyte count ($\times 10^9$/L)					
≥50	34	67.6	**<0.001**	78.9	**0.011**
<50	148	89.7		91.5	
Immunophenotype					
B-lineage	167	85.5	0.643	89.5	0.351
T-lineage	15	86.7		86.7	
CD20 positivity at diagnosis					
Present	68	79.1	0.080	81.9	**0.021**
Absent	110	90.0		93.5	
Genetic abnormality					
Hypodiploidy					
Present	13	83.3	0.748	83.3	0.959
Absent	55	81.8		86.8	
Hyperdiploidy					
Present	7	85.7	0.730	85.7	0.895
Absent	61	81.7		86.2	
BCR::ABL1					
Present	7	100.0	0.283	100.0	0.372
Absent	131	85.3		89.8	
KMT2A rearrangement					
Present	6	83.3	0.862	100.0	0.408
Absent	42	83.3		90.3	

TABLE 3 Independent Risk Factors for Major Adverse Events or Deaths

Major Adverse Events	**No. patients**	**Hazard Ratio (95% CI)**	***p* value**
Age at diagnosis, yrs			
1–10	140	1.0	**0.007**
>10	42	5.012 (1.541–16.302)	
Leukocyte count, ($x10^9$/L)			
≥50	34	5.980 (1.484–24.101)	**0.012**
<50	148	1.0	
CD20 positivity at diagnosis			
Present	68	2.531 (0.997–6.427)	**0.050**
Absent	110	1.0	
Death			
Age at diagnosis, yrs			
1–10	140	1.0	**0.018**
>10	42	6.735 (1.395–32.524)	
Leukocyte count, ($x10^9$/L)			
≥50	34	5.934 (1.397–25.204)	**0.016**
<50	148	1.0	
CD20 positivity at diagnosis			
Present	68	3.786 (1.304–10.993)	**0.014**
Absent	110	1.0	
Infection with gram-negative bacteria during induction			
Present	24	4.449 (1.205–16.428)	**0.025**
Absent	158	1.0	