Acute lymphoblastic leukemia in children: correlation of musculoskeletal manifestations and immunophenotypes

Eran Maman · David M. Steinberg · Batia Stark ·
Shai Izraeli · Shlomo Wientroub

Received: 14 January 2007 / Accepted: 18 January 2007 / Published online: 23 February 2007
© EPOS 2007

Abstract

Purpose Studies on musculoskeletal manifestations (MSM) of childhood acute lymphoblastic leukemia (ALL) have yielded variable findings with regard to their clinical impact. We investigated the significance for differential diagnosis, treatment and outcome of musculoskeletal complaints as presenting symptoms of ALL, and their correlation with leukemia immunophenotypes, for which data is lacking.

Methods Data on 783 children in the national study for childhood ALL between 1984 and 2003 were reviewed retrospectively. Statistical analysis examined possible relationships between MSM at the time of diagnosis and demographic and clinical data, biological features of leukemia (peripheral blood counts, immunophenotype and main cytogenetic aberration), response to initial prednisone treatment, and outcome.

Results Of 765 children with data on orthopaedic complaints, 240 presented with MSM (31.4%). Among these children, B cell precursor (BCP) was much more common (209/576, 36.3%) than T cell ALL (25/176, 14.2%). Patients with MSM had lower white blood cell counts (WBC) (median of 9 vs. $20 \times 10^9/L$, $P < 0.001$) and percentage of blast cells in the peripheral blood at diagnosis compared to those without (median of 27 vs. 53%, $P < 0.001$). Hepatomegaly and splenomegaly were less common in MSM group (67 vs. 53% < 3 cm, $P < 0.001$, and 63 vs. 50% < 3 cm, $P < 0.001$, respectively). Poor response to initial treatment with prednisone was recorded in 7.1% of patients with MSM versus 11.5% of those without ($P = 0.086$). The analysis revealed no independent effect of MSM on event-free survival (EFS), after correcting for differences in EFS related to immunophenotype or initial WBC.

Conclusions MSM occur mostly in children with BCP ALL who present with less involvement of extramedullary organs, low peripheral blood blasts and white blood cells counts. These findings highlight the importance of including ALL in the differential diagnosis of MSM even in the presence of an apparently normal peripheral blood count. Our study also suggests that MSM are caused by leukemic cells with enhanced biological propensity to remain relatively confined within the intramedullary bone-marrow space.

E. Maman (✉) · S. Wientroub
Department of Pediatric Orthopaedics,
Dana Children's Hospital,
Tel Aviv Sourasky Medical Center and Sackler
Faculty of Medicine, Tel Aviv University,
6 Weizmann Street, Tel Aviv 62439, Israel
e-mail: eemaman@gmail.com

D. M. Steinberg
Department of Statistics and Operations Research,
Tel Aviv University, Tel Aviv, Israel

B. Stark
Pediatric Hematology Oncology Center, Schneider
Children's Medical Center, Petach-Tikva, Israel

S. Izraeli
Pediatric Hemato-Oncology, Safra Children's Hospital,
Sheba Medical Center, Tel Aviv University, Tel Aviv, Israel

Keywords Acute lymphoblastic leukemia ·
B cell precursor · Leukemia, T cell ·
Immunophenotypes · Musculoskeletal symptoms ·
Differential diagnosis

Introduction

Musculoskeletal manifestations (MSM) associated with acute lymphoblastic leukemia (ALL) in children are common findings with a prevalence estimated between 11.6 and 50% [1–4]. The most common MSM are localized or diffuse bone pain, limp, arthritis, myalgia, failure to use an extremity, as well as other complaints mimicking orthopedic conditions such as osteomyelitis [5–7]. In addition, the affected individuals present an increased risk for fractures [2, 6, 8].

Of note that, during the course of the disease, between 70 and 90% of patients with ALL are reported to show abnormal skeletal findings on radiographs such as osteopenia, cortical lucencies, metaphyseal bands or combinations thereof [9–11]. Pathological changes in bone with subsequent skeletal morbidity are caused by the leukemic cells as well as by the chemotherapeutic agents and glucocorticoids used in leukemia treatment [2, 8, 12, 13].

The prognostic implications of the musculoskeletal expressions of malignancy in children with ALL have remained unclear. On one hand, some authors have suggested that patients with clinically severe MSM have a better prognosis [14, 15], whereas others found either a strong association between radiologically documented severe bone involvement and poor prognosis [16], or no relation at all [17]. On the other hand, the musculoskeletal symptoms can be so prominent or even the only presenting sign that sometimes the diagnosis of leukemia is delayed, and established only after subsequent detailed hematological workup [18, 19]. According to some reports, the presence of normal peripheral blood differential counts on routine laboratory tests, as well as the co-occurrence of commonly associated systemic symptoms such as fever, malaise, anemia, breathing problems or rash may contribute to a delay in diagnosis of the underlying malignancy [18, 20]. Based on non-specific systemic and musculoskeletal complaints, the differential diagnosis is often complex and should take into account a wide range of pathologies such as juvenile rheumatoid arthritis, reactive arthritis, rheumatic fever, osteomyelitis or aplastic anemia [4, 18, 21, 22].

Considering the currently limited data on the distribution of MSM among the ALL subtypes, we studied whether there is an association between musculoskeletal symptoms at the time of diagnosis and specific leukemia phenotypes, and are attempted to investigate further the prognostic implications of MSM at presentation for pediatric patients with ALL in the context of modern intensive treatment.

Patients, methods and study design

From 1984 to 2003, 783 children were enrolled in the Israeli national studies (INS) for childhood ALL (INS 84 1984–1989, 134 pts; INS 89/98, 1989–2003; 649 pts). Informed consent was obtained from the parents or guardians for each patient prior to the child's inclusion in ALL studies. The treatment in INS 89/98 was based on the modified Berlin–Frankfurt–Munster 86/90/95 protocols for ALL [23]. An important change in treatment during this period was the substitution of extended triple intrathecal therapy for preventive cranial radiation to ensure safety of the central nervous system [24].

We conducted a thorough retrospective search into the records of all patients in the INS databases. For the subsequent analyses, we retrieved the data on musculoskeletal manifestations at the time of diagnosis, as well as the demographic and clinical data, biological features of leukemia (peripheral blood counts, immunophenotype, and main cytogenetic aberration), patients' response to initial prednisone treatment, and outcome. Information on duration of symptoms was not included in the data analysis because it was incomplete.

Musculoskeletal manifestations were defined as subjective complaints of bone pain, arthralgia and back pain, clinical findings at physical examinations (arthritis, tendonitis, suspected osteomyelitis), or a limp, refusal to walk or to use the upper extremities. To avoid duplication, the major or most prominent symptom was counted for children who presented with more than one complaint such as both bone and joint problems (16 patients). In an attempt to elucidate their biological significance, the patients presenting with MSM were compared to patients without these symptoms on variables regarding leukemia characteristics, early response to treatment and outcome.

Statistical analysis

Using SPSS version 12.0 (SPSS Inc.), we performed chi-square tests, *t* tests and Wilcoxon tests to examine possible relationships between the presence of musculoskeletal complaints and medical and demographic variables. The Mantel–Haenszel test was applied to control for confounding variables in some of the analyses for possible relationships. In addition, logistic regression analysis was carried out to perform multivariate analysis of these variables. Kaplan–Meier curves, the log–rank test and the Cox regression model were used to assess the relevance of MSM as a prognostic factor for event-free survival (EFS); events in-

cluded relapses, second malignancies and death from any cause. All the tests and summary statistics took into account all patients with complete data on the particular variables included in that analysis. Some analyses excluded patients in categories with very small numbers of subjects (e.g., comparisons by immunophenotype are limited to B cell precursor and T cell).

The sample size achieved 80% power, for a 5% two-sided test, for differences of 0.27 standard deviations for continuous outcomes and an absolute difference of 0.13 for dichotomous outcomes. For analyses that were restricted to the two most recent national studies, the corresponding differences are 0.30 standard deviations and 0.15 absolute difference, respectively. For analyses restricted to B cell (T cell) patients, the corresponding differences are 0.27 and 0.14, respectively, for B cell, and 1.31 and 0.66, respectively, for T cell.

Results

Data on MSM were available for 765 out of 783 children with ALL, of whom 240 patients (31.4%) reported orthopedic complaints upon diagnosis. Bone-related complaints were the most frequent MSM complaints with 124 out of 765 children (16.2%), followed by joint involvement in 72 patients (9.4%). Thirty-seven patients (4.8 %) were found to have walking complaints and seven children (0.9%) had other MSM findings. The MSM subgroups did not differ with respect to any of the medical, demographic or outcome variables (data not shown).

The most outstanding finding is the high frequency of orthopaedic complaints among the children with B cell precursor (BCP) leukaemia, 209 patients out of 576 (36.3%), compared to only 25 out of 176 children with T cell leukemia (14.2%) ($P < 0.0001$). The remaining 13 patients did not have sufficient immunophenotypic data for classification. High-quality cytogenetic data were available only for the latest 312 patients in the INS-98 series, and the examination of the 237 children with B cell lineage leukemia in that study showed no relationships between MSM and major ALL cytogenetic aberrations. Among the patients with MSM we also found smaller liver and spleen sizes ($P < 0.001$), lower WBC ($P < 0.001$), lower peripheral blast percentage ($P < 0.001$), higher haemoglobin (Hb) levels ($P < 0.001$) and higher platelet counts ($P = 0.006$) (Table 1). Some of these differences, most notably the lower WBC count and less hepatosplenomegaly in the MSM group remained significant even after adjustment to the immunophenotype (Tables 2, 3).

Table 1 Leukemia characteristics and outcome of patients with MSM compared to the group without MSM (765 patients)

Parameter	MSM (positive) (240 pts) (%)	MSM (negative) (525 pts) (%)	P value
Origin			
Jew	80	74	0.096
Non-Jew	20	26	
Gender			
Female	42	41	0.93
Male	58	59	
Age (years)			
<1	0	4	0.001
≥1	100	96	
1–10	74	74	0.9
10–15	19	18	
≥15	7	8	
Liver (cm)			
<3	67	53	0.001
≥3	33	47	
Spleen (cm)			
<3	63	50	0.001
≥3	37	50	
WBC ($\times 10^9/L$)			
<20	76	50	0.001
20–100	20	33	
≥100	4	17	
Blast (%)			
<20	41	28	0.001
20–70	37	32	
>70	22	40	
Hb (g%)			
<7	29	49	0.001
7–9	42	33	
9	29	18	
PLT ($\times 10^9/L$)			
<50	36	46	0.006
50–100	23	24	
>100	41	30	
Cell lineage			
B	89	71	0.001
T	11	29	
Prednisone response ^a			
Poor	7	12	0.086
Good	93	88	
EFS (5 years)	75.8 ± 3.0	71.5 ± 2.1	0.038

MSM Musculoskeletal manifestations, *pts* patients, WBC white blood cells, Hb hemoglobin, PLT platelets, EFS event-free survival

^a Limited to eligible patients enrolled in protocols INS 89/98 (total 614 pts)

The early response to prednisone (Table 1) and event-free survival (EFS) were slightly better for patients with MSM (Fig. 1). The five-year EFS for patients with MSM was 75.8% (95% CI 69.8–81.8%) and for patients without MSM was 71.5% (95% CI 67.3–75.7%). However, much of these differences in outcome can be accounted for by the low proportion of T cell leukemia in the MSM group (Tables 2, 3) and the differences in initial WBC. No significant

Table 2 B-lineage leukemia characteristics and outcome of patients with MSM compared to the group without MSM (576 patients)

Parameter	MSM (positive) (209 pts) (%)	MSM (negative) (367 pts) (%)	<i>P</i> value
Origin			
Jew	80	76	0.26
Non-Jew	20	24	
Gender			
Female	42	47	0.27
Male	58	53	
Age (years)			
<1	0	5	0.001
≥1	100	95	
1–10	77	80	0.61
10–15	17	14	
≥15	6	6	
Liver (cm)			
<3	65	55	0.015
≥3	35	45	
Spleen (cm)			
<3	62	54	0.059
≥3	38	46	
WBC (×10 ⁹ /L)			
<20	78	61	0.001
20–100	20	31	
≥100	2	8	
Blast (%)			
<20	40	31	0.018
20–70	38	36	
>70	22	33	
Hb (g%)			
<7	30	55	0.001
7–9	43	33	
9	27	12	
PLT (×10 ⁹ /L)			
<50	36	50	0.002
50–100	25	24	
>100	39	26	
Phenotype			
Calla –	5	5	0.89
Calla +	95	95	
Cytogenetics ^a			
Hyperdiploid	20	21	0.99
TEL/AML1	10	14	0.50
<i>t</i> (9;22)	3.8	3.8	
<i>t</i> (4;11)	1.3	4.5	
Prednisone response ^b			
Poor	5.5	5.5	0.995
Good	94.5	94.5	
EFS (5 years)	76.6 ± 3.2	75.5 ± 2.4	0.328

MSM Musculoskeletal manifestations, *pts* patients, *WBC* white blood cells, *Hb* hemoglobin, *PLT* platelets, *t* chromosomal translocation, *EFS* event-free survival

^a Only INS 98 pts, with cytogenetic data [157 pts MSM(+), 80 pts MSM(–)]

^b Limited to eligible patients enrolled in protocols INS 89/98

relationship of MSM to EFS is found after using the Cox regression model to adjust for either immunophenotype (estimated hazard ratio of 0.81, 95% CI

Table 3 T cell leukemia characteristics and outcome of patients with MSM compared to the group without MSM (176 patients)

Parameter	MSM (positive) (25 pts) (%)	MSM (negative) (151 pts) (%)	<i>P</i> value
Origin			
Jew	80	70	0.28
Non-Jew	20	30	
Gender			
Female	44	26	0.074
Male	56	74	
Age (years)			
<1	0	1	0.563
≥1	100	99	
1–10	58	59	0.993
10–15	29	29	
≥15	13	12	
Liver (cm)			
<3	76	47	0.008
≥3	24	53	
Spleen (cm)			
<3	71	40	0.005
≥3	29	60	
Mediastinal mass			
No	62	36	0.093
Yes	38	64	
WBC (×10 ⁹ /L)			
<20	56	22	0.002
20–100	28	37	
≥100	16	40	
Blast (%)			
<20	44	21	0.002
20–70	36	22	
>70	20	57	
Hb (g%)			
<7	23	25	0.80
7–9	29	36	
9	47	39	
PLT (×10 ⁹ /L)			
<50	37	39	0.43
50–100	12	22	
>100	50	38	
Phenotype			
CD1 –	84	85	0.92
CD1 +	16	15	
Prednisone response ^a			
Poor	14	22	0.41
Good	86	78	
EFS (5 years)	68.2 ± 10.0	62.8 ± 4.1	0.315

MSM Musculoskeletal manifestations, *pts* patients, *WBC* white blood cells, *Hb* hemoglobin, *PLT* platelets, *EFS* event-free survival

^a Limited to eligible patients enrolled in protocols INS 89/98

0.58–1.12, *P* = 0.19) or initial WBC (estimated hazard ratio 0.88, 95% CI 0.64–1.22, *P* = 0.44).

Discussion

Our research is the first to assess the significance of musculoskeletal symptoms of leukemic origin for

Fig. 1 Kaplan–Meier event-free survival curves for children with (*upper curve*) and those without (*lower curve*) orthopaedic complaints at presentation. The low proportion of T cell leukemia and in the MSM group and the differences in initial WBC between the groups can account for the differences in outcome

pediatric ALL patients by using summarized data from a prospectively conducted multicenter treatment protocol. The large database served as well as a national registry of all ALL diagnosed pediatric patients in Israel, and made possible a much more precise estimate of the proportion of affected children presenting with MSM (31.4% of 765 children). Furthermore, it allowed us to investigate the largest pediatric population for which both MSM data and immunophenotype analysis were available.

Of all childhood malignancies, excluding musculoskeletal tumors, acute lymphoblastic leukemia is the most frequently associated with musculoskeletal symptoms at presentation [19]. Several clinical and laboratory features at diagnosis were found to have prognostic value for the children with ALL, and have been grouped in risk-stratified clusters for treatment purposes. Beside the classical NCI consensus age and WBC count criteria, the outcome-focused groupings may include, according to various treatment protocols, involvement of central nervous system and liver, spleen, gender, race, as well as the biological makeup of leukemic cells and the early response to treatment [12, 22, 23, 25, 26]. The prognostic value of some of these outcome determinants was shown to weigh differently for B-precursor and T cell leukemia [26].

Our study investigated the hypothesis that the presentation of ALL with musculoskeletal complaints might be more common in patients in whom the leukemia has a slower progression with a tendency to affect primarily the intramedullary space and structures, such as BCP ALL. Musculoskeletal manifestations of leukemic origin can be regarded, therefore, as the overt expression of an intramedullary pattern of leukemic cells infiltration, which becomes obvious at a relatively early stage. Unlike the T cell ALL, which most proba-

bly stems from the thymus and only subsequently spreads to the bone marrow, the BCP ALL starts in the bone marrow itself. This distinction in origin may constitute a biological explanation for our finding a much higher frequency of MSM among the patients with B-precursor than in those with T cell ALL, in which the involvement of other internal structures (CNS, hepatosplenomegaly or mediastinal mass) is more likely to be found [12, 26, 27]. It seems, therefore, that the clinical picture of ALL at presentation reflects an intramedullary or extramedullary pattern of infiltration of leukemic cells. Our findings strongly suggest that MSM are likely to occur in leukemias with a greater biological affinity to bone marrow and consequently, with a tendency to affect primarily the adjacent structures and the intramedullary space.

MSM at diagnosis among the children with BCP ALL were associated with more-favorable laboratory findings, of which the most significant is a lower peripheral blast count. In addition, our results confirmed previous reports that small liver and spleen, and lower WBC are common findings in patients with MSM, regardless of cell lineage [18, 20].

Our study highlights the importance of including ALL in the differential diagnosis of MSM even in the presence of an apparently normal routine automated complete blood counts (CBC). It is thus recommended to obtain a differential WBC count in any child with vague or prolonged and unexplained musculoskeletal symptoms. Specifically we suggest the performance and examination of a Giemsa stained smear from any cellular joint aspiration in children. “Soft” signs in the WBC, for example mild thrombocytopenia, should also alert the orthopedist to the possibility of bone marrow infiltration by leukemia or other tumor. Most importantly, it is highly recommended to consider bone

marrow examination before commencement of steroids or other drugs (e.g. methotrexate) that may further occult a missed or incipient intramedullary leukemia.

Acknowledgments This study was partially funded by the Israel Cancer Association and The Goldberg Family Chair in Pediatric Surgery, Sackler Faculty of Medicine, Tel Aviv University—Incumbent: Prof. Shlomo Wientroub. The commitment of the principal investigators in The Israeli National Childhood ALL Study Group has been greatly appreciated: Dina Attias, M.D., Bnai Zion Medical Center, Haifa; Gali Avrahami, M.D., and Batia Stark, M.D., Schnieder Children's Medical Center, Petah Tiqva; Ami Ballin, M.D., Edith Wolfson Medical Center, Holon; Bella Bielora, M.D., and Shai Izraeli, M.D., Chaim Sheba Medical Center, Tel Hashomer; Yoav Burstein, M.D., Dana Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv; Ronit Elhasid, M.D., Rambam Medical Center, Haifa; Gabriel Herzog, M.D., Ha'Emek Medical Center, Afula; Yosef Kapelushnik, M.D., Soroka Medical Center, Beer Sheva; Hagit Miskin, M.D., Shaare Zedek Medical Center, Jerusalem; Dalia Sthoeger, M.D., Kaplan Medical Center, Rehovot; Michael Weintraub, M.D., Hadassah University Hospital, Jerusalem. We thank Galli Pen and Dina Kugel for maintaining the INS database, and Irina Opincariu for editing the manuscript.

References

1. D'Astous J, Corrigan M, Wiley J (1984) The musculo-skeletal manifestations of acute lymphatic leukemia in childhood. *Orthop Trans* 8:460
2. Gallagher DJ, Phillips DJ, Heinrich SD (1996) Orthopedic manifestations of acute pediatric leukemia. *Orthop Clin North Am* 27:635–644
3. Heinrich SD, Gallagher D, Warrior R, Phelan K, George VT, MacEwen GD (1994) The prognostic significance of the skeletal manifestations of acute lymphoblastic leukemia of childhood. *J Pediatr Orthop* 14:105–111
4. Tuten HR, Gabos PG, Kumar SJ, Harter GD (1998) The limping child: a manifestation of acute leukemia. *J Pediatr Orthop* 18:625–629
5. Marsh WL Jr, Bylund DJ, Heath VC, Anderson MJ (1986) Osteoarticular and pulmonary manifestations of acute leukemia. Case report and review of the literature. *Cancer* 57:385–390
6. Rogalsky RJ, Black GB, Reed MH (1986) Orthopaedic manifestations of leukemia in children. *J Bone Joint Surg Am* 68:494–501
7. Silverstein MN, Kelly PJ (1963) Leukemia with osteoarticular symptoms and signs. *Ann Int Med* 59:637–645
8. Davies JH, Evans BAJ, Jenney MEM, Gregory JW (2005) Skeletal morbidity in childhood acute lymphoblastic leukaemia. *Clin Endocrinol* 63:1–9
9. Kushner DC, Weinstein HJ, Kirkpatrick JA (1980) The radiologic diagnosis of leukemia and lymphoma in children. *Semin Roentgenol* 15:316–334
10. Parker BR, Marglin S, Castellino RA (1980) Skeletal manifestations of leukemia, Hodgkin disease, and non-Hodgkin lymphoma. *Semin Roentgenol* 15:302–315
11. Simmons CR, Harle TS, Singleton EB (1968) The osseous manifestations of leukemia in children. *Radiol Clin North Am* 6:115–130
12. Chan KW (2002) Acute lymphoblastic leukemia. *Curr Probl Pediatr Adolesc Health Care* 32:40–49
13. Mandel K, Atkinson S, Barr RD, Pencharz P (2004) Skeletal morbidity in childhood acute lymphoblastic leukemia. *J Clin Oncol* 22:1215–1221
14. Kai T, Ishii E, Matsuzaki A, Okamura J, Ikuno Y, Tasaka E, Ueda K (1996) Clinical and prognostic implications of bone lesions in childhood leukemia at diagnosis. *Leuk Lymphoma* 23:119–123
15. Muller HL, Horwitz AE, Kuhl J (1998) Acute lymphoblastic leukemia with severe skeletal involvement: a subset of childhood leukemia with a good prognosis. *Pediatr Hematol Oncol* 15:121–133
16. Masera G, Carnelli V, Ferrari M, Recchia M, Bellini F (1977) Prognostic significance of radiological bone involvement in childhood acute lymphoblastic leukaemia. *Arch Dis Child* 52:530–533
17. Hann IM, Gupta S, Palmer MK, et al (1979) The prognostic significance of radiological and symptomatic bone involvement in childhood acute lymphoblastic leukaemia. *Med Pediatr Oncol* 6:51–55
18. Jonsson OG, Sartain P, Ducore JM, Buchanan GR (1990) Bone pain as an initial symptom of childhood acute lymphoblastic leukemia: association with nearly normal hematologic indexes. *J Pediatr* 117:233–237
19. Trapani S, Grisolia F, Simonini G, Calabri GB, Falcini F (2000) Incidence of occult cancer in children presenting with musculoskeletal symptoms: a 10-year survey in a pediatric rheumatology unit. *Semin Arthritis Rheum* 29:348–359
20. Kobayashi D, Satsuma S, Kamegaya M, Haga N, Shimomura S, Fujii T, Yoshiya S (2005) Musculoskeletal conditions of acute leukaemia and malignant lymphoma in children. *J Pediatr Orthop B* 14:156–161
21. Costello PB, Brecher ML, Starr JJ, Freeman AI, Green FA (1983) A prospective analysis of the frequency, course, and possible prognostic significance of the joint manifestations of childhood leukemia. *J Rheumatol* 10:753–757
22. Redaelli A, Laskin BL, Stephens JM, Botteman MF, Pashos CL (2005) A systematic literature review of the clinical and epidemiological burden of acute lymphoblastic leukaemia (ALL). *Eur J Cancer Care* 14:53–62
23. Schrappe M, Reiter A, Zimmermann M, Harbott J, Ludwig W-D, Henze G, Gadner H, Odenwald E, Riehm H (2000) Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995: Berlin-Frankfurt-Munster. *Leukemia* 14:2205–2222
24. Stark B, Sharon R, Rechavi G, Attias D, Ballin A, Cividalli G, Burstein Y, Sthoeger D, Abramov A, Zaizov R (2000) Effective preventive central nervous system therapy with extended triple intrathecal therapy and the modified ALL-BFM 86 chemotherapy program in an enlarged non-high risk group of children and adolescents with non-B cell acute lymphoblastic leukemia: the Israel National Study report. *Cancer* 88:205–216
25. Maloney KW, Shuster JJ, Murphy S, Pullen J, Camitta BA (2000) Long-term results of treatment studies for childhood acute lymphoblastic leukemia: pediatric oncology group studies from 1986–1994. *Leukemia* 14:2276–2285
26. Pullen J, Shuster JJ, Link M, Borowitz M, Amylon M, Carroll AJ, Land V, Look AT, McIntyre B, Camitta B (1999) Significance of commonly used prognostic factors differs for children with T cell acute lymphocytic leukemia (ALL) as compared to those with B-precursor ALL: a pediatric oncology group (POG) study. *Leukemia* 13:1696–1707
27. Garand R, Vannier JP, Bene MC, Faure GC, Bernard A (1989) Correlations between acute lymphoid leukemia (ALL) immunophenotype and clinical and laboratory data at presentation: a study of 350 patients. *Cancer* 64:1437–1446