Outcome of adult patients with acute lymphoblastic leukaemia receiving the MRC UKALL XII protocol: a tertiary care centre experience

Shaikh M U, Ali N, Adil S N, Khurshid M

ABSTRACT

Introduction: Acute lymphoblastic leukaemia (ALL) is a heterogeneous group of lymphoid neoplasm resulting from the proliferation of malignant lymphoid cells. We aimed to study the outcome of adult patients with ALL receiving the Medical Research Council UKALL XII protocol.

Methods: This was a retrospective study conducted at Aga Khan University Hospital from January 2001 to December 2008. The medical records of all adult patients were reviewed and analysed for clinical, morphological and immunological features at presentation and impact on treatment outcomes. Multivariate analysis and survival studies were performed using Kaplan-Meier statistics.

Results: The total number of patients was 54, with a male to female ratio of 3.4:1 and a median age of 28 years. Common presenting symptoms were fever (n is 49) and bleeding (n is 14). 38 patients had haemoglobin less than 10 gms/dl, 21 had white blood cell (WBC) count of 50 × 10E9/L or more, and 35 had lactate dehyrogenase more than 1,000 IU. Morphologically, FAB-L2 was the commonest subtype, with 38 patients with B-ALL and eight with T-ALL. Multivariate analysis showed that age above 30 years, male gender, WBC count above 50 × 10E9/L and T-ALL subtype were independent risk factors for poor survival. 46 (85 percent) patients achieved complete remission. The median survival was 12.3 months. At the end of five years, 16 patients were alive, two were alive with disease and 14 were in complete remission.

Conclusion: Overall survival and relapse rates in our study were comparable to those reported internationally.

Keywords: acute lymphoblastic leukaemia, adults, MRC UKALL XII protocol, Philadelphia chromosome, treatment outcome

Singapore Med J 2011;52(5):370-374

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is a heterogeneous group of lymphoid neoplasm resulting from monoclonal proliferation of malignant lymphoid cells in the blood, bone marrow and other organs.[1] Currently, due to intensive chemotherapy regimens, the outcome of adult ALL has improved markedly. The complete response rates now are more than 80%[2] and the long-term survival rate is 30%–45%.[3] In the past five decades, the outcome of childhood ALL has evolved from a median survival of two months at the time of diagnosis[4] to a long-term survival rate of 80%.[5] The better results seen among the childhood population as compared to adults with ALL have been attributed to a number of prognostic factors.

White blood cell (WBC) count at presentation is an important risk factor reported in almost every study done on adult ALL.[6] The widely used cut-offs for B and T lineage are 30 × 10^9/L and 100 × 10^9/L, respectively.[7] The presence of a Philadelphia chromosome is the most important cytogenetic abnormality in ALL. It is present in 20%–30% of patients and indicates a grave prognosis with standard chemotherapy.[8] Male gender has been reported to be an independent prognostic risk factor, with male patients faring worse than female patients, the most probable reason being relapse at sanctuary sites, e.g. the testes.[9] Finally, response to initial treatment has been regarded as the most significant risk factor, as data suggests that the inability to achieve clearance at Day 10 correlates with a worse outcome. However, this data has mainly been published in childhood ALL series.[10]

There are a number of studies on the outcomes of adults diagnosed with ALL in the literature. However, such information is sparse from our part of the world. This study was designed to describe the survival

Department of Pathology and Microbiology, Aga Khan University and Hospital, PO Box 3500, Stadium Road 74800, Karachi, Pakistan

Shaikh MU, MBBS, FCPS
Associate Professor

Ali N, MBBS, FCPS
Instructor

Adil SN, MBBS, FCPS
Associate Professor

Khurshid M, MBBS, FRCP, FCPS
Professor

Correspondence to:
Dr Natasha Ali
Tel: (92) 21 4861548
Fax: (92) 21 4934294
Email: natasha.ali@aku.edu

Table I. Laboratory parameters (n = 54).

Parameter	No. (%)	Mean ± SD (range)
Haemoglobin < 10 gm/dl	14 (28.6)	8.6 ± 2 (4.5–14.2)
Total leucocyte count ≥ 50 × 10^9/L	21 (43.8)	95 ± 140 (0.9–720)
Platelets ≤ 10 × 10^9/L	3 (6.3)	44.5 ± 38 (4–245)
Lactate dehydrogenase ≥ 1,000 IU/L	35 (77)	5,173 ± 9,464 (3,554–3,768)
Uric acid ≥ 8 mg/dl	6 (17.9)	6.3 ± 3 (2–16)

Table II. Leukaemia characteristics (n = 54).

Characteristic	No. (%)
Morphology	
L1	4 (7.4)
L2	50 (92.5)
Immunophenotyping*	
B-ALL	38 (82.6)
T-ALL	8 (17.4)
Cytogenetics	
Normal	27 (50.0)
t9;22	8 (15.0)
Complex	11 (20.3)

* Data is missing for 8 patients.

outcomes of adult patients with ALL in the Pakistani population.

METHODS

This was a retrospective study conducted at Aga Khan University Hospital in adult patients aged > 15 years between January 2001 and December 2008. The medical records of all patients (using the International Classification of Disease 9th edition) (ICD-9), were reviewed through an in-house questionnaire. Consecutive patients diagnosed as ALL subtype L1 and L2 according to the French-American-British (FAB) classification were included in the study, while those diagnosed as ALL L3 were excluded from the study. Data of all included patients was analysed with respect to their clinical presentation, morphological and immunopathological features and treatment outcomes.

Flow cytometry was performed on FACScan (Becton Dickinson, Miami Lakes, FL, USA). The following monoclonal antibodies were used: T-lineage-associated antigens CD3, CD5, CD7; B-lineage antigens CD19, CD20, CD79a, CD22; and antigens TdT and CD10. Conventional cytogenetic analysis and BCR-ABL translocation by fluorescent *in situ* hybridisation were performed in all patients. Pre-treatment investigations included complete blood count, blood chemistry, including liver and renal function tests, lactate dehyrogenase (LDH), uric acid and serum electrolytes.

Patients were treated using the Medical Research Council United Kingdom ALL (MRC UKALL) XII protocol, which consisted of induction therapy divided in two phases. Phase 1 consisted of the following: daunorubicin 60 mg/m^2 (intravenous [IV]) on Days 1, 8, 15 and 22; vincristine 1.4 mg/m^2 (IV) on Days 1, 8, 15 and 22; L-asparaginase 10,000 IU (IV or intramuscular) on Days 17–28; prednisone 60 mg/m^2 (oral) in divided doses on Days 1–28; and methotrexate 12.5 mg (intrathecal) on Day 15. Patients then went on to Phase 2 of induction, which consisted of the following: cyclophosphamide 650 mg/m^2 (IV) on Days 1, 15 and 29; cytarabine 75 mg/m^2 (IV) on Days 1–4, 8–11, 15–18 and 22–25; 6-mercaptopurine 60 mg/m^2 (oral) on Days 1–28; and methotrexate 12.5 mg (intrathecal). Patients were evaluated for response at the end of each of the two phases of induction. Those who achieved complete remission proceeded to intensification and post-remission consolidation.

Patients undergoing intensification therapy received three cycles of high-dose methotrexate 3 g/m^2 administered intravenously on Days 1, 8 and 22, followed by L-asparaginase 10,000 IU on Days 2, 9 and 23, and standard leucovorin rescue. In the consolidation phase, patients received central nervous system prophylaxis 2,400 cGy cranial irradiation and intrathecal cytarabine 50 mg weekly for a period of four weeks. In addition, intrathecal cytarabine 50 mg was administered on four occasions three months apart during the maintenance therapy. Maintenance therapy consisted of vincristine 1.4 mg/m^2 (IV) every three months, prednisone 60 mg/m^2 (oral) for five days every three months, 6-mercaptopurine 75 mg/m^2 (oral) a day, and methotrexate 20 mg/m^2 (oral or IV) once a week. The therapy was continued for a total of 2.5 years from the start of intensification therapy.[11]

Data was collected on a computerised database and analysed using the Statistical Package for the Social Sciences version 16.0.1 (SPSS Inc, Chicago, IL, USA). Data was presented as mean/median values and percentages. Kaplan-Meier curves were used to calculate survival outcomes and Cox-proportional hazard model for multivariate analysis.

RESULTS

During the study period, 54 (42 male and 12 female) patients were admitted with a diagnosis of ALL. The median age of the patients was 28 (range 16–53) years, of which 28 (52%) were ≤ 30 years of age. The common presenting symptoms were fever (n = 49, 82%) and bleeding (n = 14, 25.5%). 42 (79.0%) patients had anaemia, and 35.2% and 18.5% of patients had enlarged lymph nodes and liver, respectively. Poor prognostic factors other than male gender, according to the Luken's criteria,[12] were white cell count ≥ 50 × 10^9/L (n = 21, 43.8%). 63.0% (n = 34) of patients had splenomegaly, 77.0% (n = 35) had LDH ≥ 1,000 IU/L and 92.5% (n = 50) were diagnosed with L2 FAB subtype. Immunophenotyping by flow cytometry revealed 38 patients with B-ALL phenotype; in these patients, the mean WBC count was 69 ± 92.7 (range 0.9–450) × 10^9/L. T-ALL was present in eight patients and their mean WBC count was 82 ± 107 (range 2.4–331) × 10^9/L. Normal chromosomal analysis was present in 27 (50.0%) patients, while 20.3% had complex cytogenetic abnormalities. Philadelphia chromosome positivity was seen in eight patients. One patient each had hyperdiploidy and polysomy 9 cytogenetic abnormalities. Details of the laboratory parameters are shown in Tables I and II.

All 54 patients received treatment and were evaluated for response. Overall, 46 (85.0%) patients went into complete remission. The median time taken to achieve complete remission was 30 (range 20–43) days. Four patients died during induction chemotherapy; the primary cause of death was tumour lysis syndrome (n = 2) and primary induction failure due to progressive disease (n = 2). Four patients discontinued treatment after receiving a few days of induction therapy and moved to other hospitals due to financial reasons.

After a median follow-up period of 18.7 months, 24 (44.4%) patients suffered a relapse with systemic disease and died, whereas 16 (30.0%) were alive. Of these, two were alive with disease and 14 (26.0%) were in complete remission at the end of the study period (Fig. 1). Multivariate analysis showed that age > 30 years, male gender, WBC count ≥ 50 × 10^9/L, haemoglobin < 10 gm/dl and complex cytogenetics were independent risk factors for poor outcome (Fig. 2). The median survival was 12.7 months and disease-free survival was 6.2 months (Figs. 3 & 4).

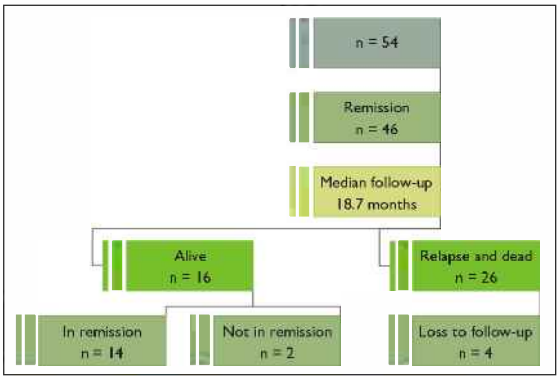

Fig. 1 Outcome of patients with acute lymphoblastic leukaemia

DISCUSSION

In 2008, 44,000 new cases of leukaemia were diagnosed in the West, out of which 42% were acute leukaemia; of these, childhood ALL made up 72%.[13] The incidence of childhood ALL in Pakistan was 32%.[14] Many reports have suggested that adolescents and young adults with ALL have a better outcome when they are treated with paediatric protocols, with survival ranging from 65% to 69%.[15] However, the duration of remission has been disappointingly short.[16] We present a seven-year analysis in the adult population based on 54 patients diagnosed with ALL.

This retrospective analysis focused on three important prognostic factors that influence the survival of ALL, including age > 30 years, male gender and increased WBC count, as well as two rather new prognostic factors – immunophenotyping and cytogenetic analysis. These risk factors have already been established as indicators of poor outcome,[17] and our study confirms their relevance to our population as well. Age is probably the most important prognostic factor. Multiple groups have quoted that overall survival continuously decreases with increasing age, from 34% to 57% for patients < 30 years to 15% to 17% for those > 50 years.[18] The median age of our patients was 24 years. However, the median survival of patients aged > 30 years was 6.8 months, thus reflecting the survival disadvantage.

WBC cell count at diagnosis (≥ 50 × 10^9/L) is associated with an increased risk of relapse.[19] Approximately 33% (n = 18) of our patients with B-ALL had a WBC count > 30 × 10^9/L, whereas 3.7% of those with T-ALL had a WBC count > 100^9L. Although 85% of patients achieved complete remission during induction, 44% relapsed during or after the completion of treatment. Furthermore, increased WBC count is also associated with a risk of complications during induction,[20] as seen in 11% of our patients. Gender is known to be an independent predictive factor for complete remission,[21] and there was a definite male preponderance in our study, similar to that reported in

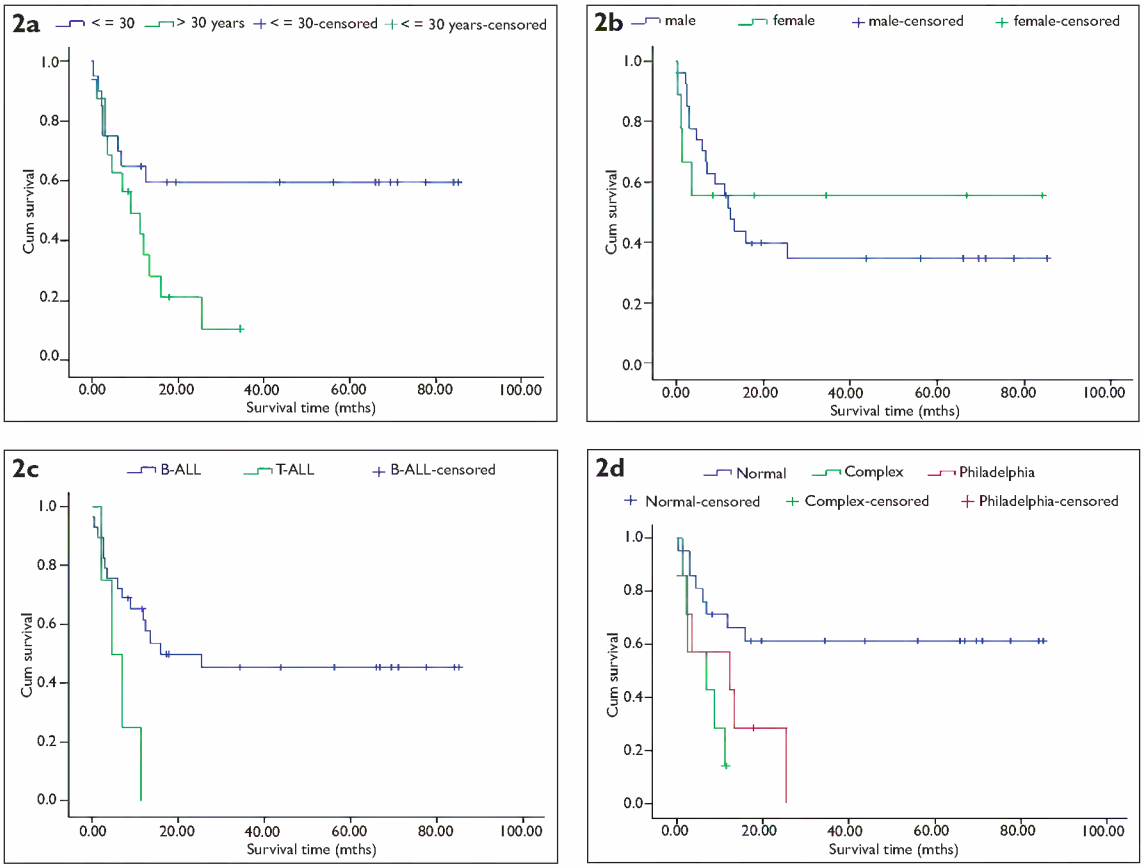

Fig. 2 Correlation of prognostic factors: (a) age; (b) gender; (c) immunophenotype; and (d) cytogenetics with outcome.

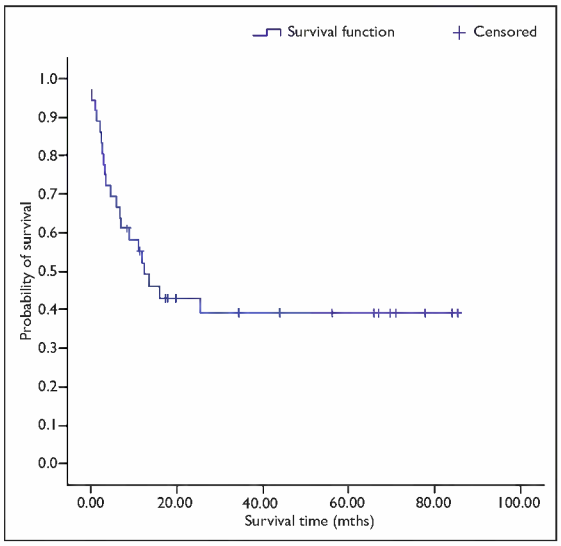

Fig. 3 Kaplan-Meier plots of overall survival.

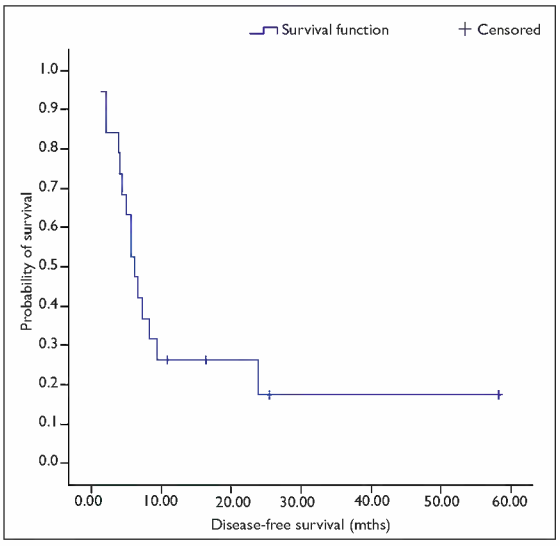

Fig. 4 Kaplan-Meier plots of disease-free survival.

the Western literature.[22] Male gender has been reported to have inferior outcomes,[23] which was also the case in our study.

Complete immunologic characterisation at diagnosis is required to identify subtypes with different presentations and prognosis. Immunophenotyping by flow cytometry has long been considered a critical part of diagnostic evaluation in patients with ALL. Many groups have confirmed the superior outcome of T-lineage ALL as compared to B-lineage ALL.[24] This is in sharp contrast to our study, where patients in the B-ALL subgroup did fairly well. This could be due to

the higher number of patients with B-ALL as compared to T-ALL. Furthermore, only two patients with T-ALL had a WBC count > 100×10^9/L, thereby improving the overall outcome.

Philadelphia chromosome positivity, with an overall incidence of 20%–40% in adults, has an extremely poor prognosis.[25] Its incidence rises to 50% in patients aged ≥ 50 years.[26] Eight patients in our study had 9;22 translocation (Philadelphia chromosome), out which one was alive till the last follow-up. The debate on whether young adults or adolescents should be treated with paediatric protocols remains.[27] The overall and median survival rates are not inevitably lower when these patients are treated with adult protocols, as shown in our study. However, when compared with children below ten years of age, the outcomes are poorer, mainly due to the increased risk of relapse.

We conclude that three risk factors that still influence survival outcomes in adult lymphoblastic leukaemia are age > 30 years, male gender and WBC count > 50×10^9/L. Immnophenotyping and cytogenetic analysis are required for complete characterisation and prognosis. These five factors would help physicians to stratify patients into low- and high-risk groups. The median survival in our study was 12.7 months and disease-free survival was 6.2 months.

REFERENCES

1. Faderl S, Jeha S, Kantarjian H. The biology and therapy of adult acute lymphoblastic leukaemia. Cancer 2003; 98:1337-54.
2. Durrant IJ, Richards SM, Prentic SG et al. The Medical Research Council trials in acute lymphoblastic leukaemia. Hematol Oncol Clin North Am 2000; 14:1327-52.
3. Larson RA. Recent clinical trials in acute lymphoblastic leukaemia by the Cancer and Leukemia Group B. Hematol Oncol Clin North Am 2000;14:1367-79.
4. Farber S, Diamond LK. Temporal remissions in acute leukaemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid. N Engl J Med 1948; 238:787-93.
5. Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukaemia: results of Dana-Farber Consortium Protocol 91-01. Blood 2001; 97:1211-8.
6. Hoelzer D, Thiel E, Loffler H, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukaemia in adults. Blood 1988;71:123-31
7. Hunault M, Harrouseau JL, Delain M, et al. Better outcome of adult acute lymphoblastic leukaemia after early genoidentical allogeneic bone marrow transplantation (BMT) than after late high-dose therapy and autologous BMT: a GOELAMS trial. Blood 2004; 104:3028-37.
8. Westbrook CA, Hooberman AL, Spino C, et al. Clinical significance of the BCR-ABL fusion gene in adult acute lymphoblastic leukaemia. A Cancer and Leukaemia Group B study (8762). Blood 1992; 80:2983-90.
9. Pui CH, Boyett JM, Relling MV, et al. Sex differences in prognosis for children with acute lymphoblastic leukaemia. J Clin Oncol 1999; 17:818-24.
10. Miller DR, Coccia PF, Bleyer WA, et al. Early response to induction therapy as a predictor of disease-free survival and late recurrence of childhood acute lymphoblastic leukaemia: a report from the Children's Cancer Study Group. J Clin Oncol 1989; 7:1807-15.
11. Rowe JM, Buck G, Burnett AK, et al. Induction therapy for adults with acute lymphoblastic leukaemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood 2005; 106:3760-7.
12. Lukens NJ. Acute lymphoblastic leukaemia. Wintrobe's clinical Hematology. Pennsylvania: Lea and Feibiger 1992, pp. 1892-19.
13. Stat bite: Estimated new leukaemia cases in 2008. J Natl Cancer Inst 2008; 16:100:531.
14. Yasmeen N, Ashraf S. Childhood acute lymphoblastic leukaemia; epidemiology and clinicopathological features. J Pak Med Assoc 2009; 59:150-3.
15. Takeuchi J, Kyo T, Naito K, et al. Induction therapy by frequent administration of doxorubicin with four other drugs, followed by intensive consolidation and maintenance therapy for adult acute lymphoblastic leukaemia: the JALSG-ALL93 study. Leukaemia 2002; 16:1259-66.
16. Hoelzer D. Acute lymphoblastic leukaemia--Progress in children, less in adults. N Engl J Med 1993; 329:1343-4.
17. Annino L, Vegna ML, Camera A, et al. Treatment of adult acute lymphoblastic leukaemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. Blood 2002; 99:863-71.
18. Gökbuget N, Hoelzer D. Treatment of adult acute lymphoblastic leukaemia. Hematology Am Soc Hematol Educ Program 2006:133-41.
19. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (Hyper–CVAD), a dose intensive regimen, in adult acute lymphoblastic leukaemia. Cancer 2004; 101:2788-801.
20. Arteaga-Ortiz L, Buitrón-Santiago N, Rosas-López A, et al. [Acute lymphoblastic leukaemia: experience in adult patients treated with hyperCVAD and 0195 Protocol, at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Cohort 2003-2007.] Rev Invest Clin 2008; 60:459-69. Spanish.
21. Shuster JJ, Wacker P, Pullen J, et al. Prognostic significance of sex in childhood B-precursor acute lymphoblastic leukaemia: a Pediatric Oncology Group Study. J Clin Oncol 1998; 16:2854-63.
22. Sather HN, Miller D, Nesbit M, et al. Difference in prognosis for boys and girls with acute lymphoblastic leukaemia. Lancet 1981; 1:739-44.
23. Chessells JM, Richards SM, Bailey CC, et al. Gender and treatment outcome in childhood lymphoblastic leukaemia: report from the MRC UKALL trials. Br J Haematol 1995; 89:364-72.
24. Gökbuget N, Arnold R, Buechner Th, et al. Intensification of induction and consolidation improves only subgroups of adult ALL: Analysis of 1200 patients in GMALL study 05/93. Blood 2001; 98:802a.
25. Gleißner B, Gokbuget N, Bartram CR, et al. Leading prognostic relevance of the BCR-ABL translocation in adult acute B-lineage lymphoblastic leukaemia: a prospective study of the German Multicenter Trial Group and confirmed polymerase chain reaction analysis. Blood 2002; 99:1536-43.
26. Larson RA. Management of acute lymphoblastic leukaemia in older patients. Semin Hematol 2006; 43:126-33.
27. Schiffer CA. Differences in outcome in adolescents with acute lymphoblastic leukaemia: a consequence of better regimens? Better doctors? Both? J Clin Oncol 2003; 21:760-1.