original article

# Improved outcome for children with acute lymphoblastic leukemia after risk-adjusted intensive therapy: a single-institution experience

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**BACKGROUND AND OBJECTIVE:** Because of the need for more comprehensive information on the least toxic and most effective forms of therapy for children with acute lymphoblastic leukemia (ALL), we reviewed our experience in the treatment of children with ALL at King Faisal Specialist Hospital and Research Centre (KFSH&RC) and King Fahad National Center for Children's Cancer and Research (KFNCCC&R) over a period of 18 years with a focus on patient characteristics and outcome.

**METHODS:** During the period of 1981 to 1998, records of children with ALL were retrospectively reviewed with respect to clinical presentation, laboratory findings, risk factors, stratification, therapy and outcome. The protocols used in treatment included 4 local protocols (KFSH 81, 84, 87 and 90), and subsequently, Children's Cancer Group (CCG) protocols, and these were grouped as Era 1 (1981-1992) and Era 2 (1993-1998).

**RESULTS:** Of 509 children with ALL treated during this period, 316 were treated using local protocols and 193 using CCG protocols. Drugs used in Era 1 included a 4-drug induction using etoposid (VP-16) instead of L-asparaginase. Consolidation was based on high dose methotrexate (MTX) 1g/m$^2$ and maintenance was based on oral mercaptopurine (6-MP) and MTX with periodic pulses using intravenous teniposide (VM-26), Ara-C, L-asparaginase, adriamycin, prednisone, VP-16 and cyclophosphamide. International protocols were introduced in Era 2, which was also marked by intensification of early treatment, a wider selection of cytoreductive agents, and the alternating use of non-cross-resistant pairs of drugs during the post-remission period. The end-of-induction remission rate improved from 90% in Era 1 to 95% in Era 2, which was of borderline statistical significance ($P$=.049). The 5-year event-free survival (EFS) improved from 30.6% in Era 1 to 64.2% in Era 2 ($P$<.001). Improvement in outcome was achieved without any significant increase in morbidity or mortality, due to improvement in both systemic therapy and supportive care. The most important independent prognostic factors were intensity of therapy, poor risk category assignment and CNS disease at diagnosis.

**CONCLUSION:** Outcome in children with ALL has improved because of intensification of treatment protocols and better supportive care.

Childhood acute lymphoblastic leukemia (ALL) has served as a model for cancer treatment for over five decades. With more precise diagnostic criteria and risk stratification, more effective therapy administered in controlled clinical trials, and better supportive care, the outlook for children with ALL has improved dramatically.[1] Today, approximately 80% of children treated for this disease in developed countries will enjoy long-term disease free survival and, in most instances, will be cured.[2] Although the benefits of intensive therapy are clear, its appropriateness for all groups of patients remains in question. This is especially so in

view of its potential morbidity and mortality.[3-5]

To meet the need for more comprehensive information about the least toxic and most effective forms of therapy for children with ALL, we reviewed data on about 500 patients enrolled in consecutive clinical studies conducted from 1981 through 1998 at King Faisal Specialist Hospital and Research Centre (KFSH&RC) and King Fahad National Center for Children's Cancer and Research (KFNCCC&R), which is part of KFSH&RC. Our study addressed questions that are important for planning future treatment and that are best answered with follow-up information collected over many years. For example, have rates of cure improved progressively since the development of effective antileukemic therapy, and if so, was this at the expense of more morbidity and mortality?

## METHODS

From 1 January 1981 through 31 December 1998, 509 consecutive patients in all risk categories who were 14.5 years of age or less and who had ALL were enrolled in treatment studies at KFSH&RC and KFNCCC&R. The diagnosis was based on morphologic evaluation of Wright's stained smears of bone marrow and negative staining for myeloperoxidase (<3 percent positive blasts), immunophenotyping and cytogenetics. Immunophenotyping was not available until 1985 and cytogenetic data were not available for almost half of the patients either due to unavailability of the technique or the inability to perform the test. The institutional review board approved treatment protocols and informed consent was obtained for all patients. Definitions of remission, failure of induction, relapse, and meningeal leukemia have been reported elsewhere.[6,7]

The KFSH&RC therapy program for childhood ALL spanned two eras (Table 1). The first era (1981 to 1992) was characterized by the sequential introduction of protocols designed at KFSH&RC. They were labeled as KFSH 81, 84, 87, and 90 (the numbers reflect the years the protocols were introduced). KFSH&RC 1981 had 2 arms, standard and high risk, which used prophylactic CNS radiation therapy in both arms. However, in view of the significantly inferior outcome in both arms, the decision was to abandon stratification and prophylactic CNS therapy for subsequent protocols (84, 87 and 90). Radiation therapy subsequently was reserved for patients with CNS relapse. Etoposide (VP-16) was used during induction instead of L-asparaginase and induction lasted 6 weeks with cyclophosphamide used on days 28 and 35. There was periodic intensification

**Table 1.** Description of the treatment eras.

| Era and number of patients | Protocols | Number of patients per protocol | Notes on therapy |
|---|---|---|---|
| Era 1 (1981-1992), (n=316) | ALL KFSH&RC 81-Standard | 60 | - 81 SR and HR used RT. Later, on protocol 84, RT was reserved for CNS relapsed patients, VP-16 was used during induction instead of L-asparaginase and induction lasted 6 weeks with cyclophosphamide used on day 28, 35.<br>- There was periodic intensifications at 4 and 8 months of first year maintenance and re-induction at the end of first year.<br>- Second year maintenance was based mainly on oral medications with intensification at the end of second year with VP-16/cyclophosphamide.<br>- Maintenance lasted 2 years regardless of gender.<br>- Stratification was abandoned after the 81 protocol. |
| | 81-High risk | 25 | |
| | 84 | 79 | |
| | 87 | 84 | |
| | 90 | 68 | |
| Era 2 (1993-1998), (n=193) | CCG 1881b | 41 | - International protocols were used (starting with CCG-1800 series protocols) which were marked by the intensification of early treatment for all patients, a wider selection of cytoreductive agents, and the alternating use of non-cross resistant pairs of drugs during the post remission period.<br>- Stratification was based on WBC count, age, clinical tumor burden and cytogenetics. Mature B-cell ALL was excluded. There was no separate protocol for T-cell ALL. |
| | CCG 1891b | 63 | |
| | CCG 1882a | 66 | |
| | CCG 1882b | 23 | |

SR=standard risk, HR=high risk, RT=radiation therapy

at 4 months of the first year using teniposide (VM-26) and cytarabine (Ara-C) and at 8 months using L-asparaginase and cytarabine and re-induction at the end of the first year. Second year maintenance was based mainly on the oral medications mercaptopurine (6-MP) and methotrexate (MTX) with intensification at the end of second year with VP-16/cyclophosphamide. Maintenance lasted 2 years regardless of gender.

The second era (January 1993 to December 1998), when international protocols were introduced (starting with the CCG-1800 series protocol), was marked by the intensification of early treatment for all patients, a wider selection of cytoreductive agents, and the alternating use of non-cross-resistant pairs of drugs during the post-remission period. In addition, there was use of cranio-spinal irradiation to treat newly diagnosed patients with CNS disease. Remission retrieval therapy in Era 1 relied on the same agents that were given during initial treatment. In subsequent years, patients were enrolled on different strategies of retrieval therapy, including bone marrow transplantation. All patients identified since 1988 as mature B-cell ALL (positive surface immunoglobulin) were treated on separate protocols. There were very few infants treated on the CCG 1883 protocol and they were excluded from this analysis.

Physicians at KFSH&RC and KFNCCC&R followed all patients who finished their protocols successfully. Since 1998, patients who survived for two or more years after the completion of treatment were seen in the After Completion of Therapy Clinic at KFNCCC&R. The purpose of these visits was to monitor patient health and to provide medical care for late adverse effects, such as retarded growth, thyroid dysfunction, learning disability, infertility, second cancers, and neurological and psychosocial problems.

Overall survival (OS), event-free survival (EFS) and disease-free survival (DFS) were computed by the method of Kaplan and Meier.[8] The log-rank test was used to compare survival curves. EFS is defined as complete remission in a surviving patient without relapse at any site and without the development of life-threatening second cancers (such as a brain tumor). Patients who survived without leukemia for at least 3 years after the cessation of therapy were classified as long-term survivors. All analyses were based on records that were up-to-date through April 2005.

## RESULTS

The presenting features of the patients enrolled in these treatment studies are shown in Table 2. For the 509 patients, the mean age was 5.27 years, the median age was 4.27 years, and the age range was 0.2-14.5 years.

**Table 2.** Presenting characteristics of children treated for acute lymphoblastic leukemia.

| Characteristics | Era 1 (n=316) | Era 2 (n=193) | *P* value |
|---|---|---|---|
| **Age (years)** | | | |
| ≤1 | 9 (2.8) | 4 (2.1) | |
| >1-<10 | 265 (83.9) | 168 (87.0) | NS |
| ≥10 | 42 (13.3) | 21 (10.9) | |
| Male | 196 (62) | 114 (59.1) | NS |
| **Symptoms** | | | |
| Fever | 208 (65.8) | 145 (75.1) | .034 |
| Bone or joint pain | 70 (22.2) | 79 (40.9) | <.001 |
| Bleeding | 132 (41.8) | 68 (35.2) | |
| Lymphadenopathy | 197 (62.3) | 135 (69.9) | |
| Hepatomegaly | 196 (62.0) | 114 (59.1) | NS |
| Splenomegaly | 166 (52.5) | 110 (57.0) | |
| Testicular swelling | 13 (4.1) | 2 (1.0) | |
| CNS leukemia | 36 (11.4) | 34 (17.5) | |
| **WBC (×10⁹/L)** | | | |
| <10 | 150 (47.5) | 102 (52.8) | |
| 10-24.9 | 67 (21.2) | 39 (20.2) | |
| 25-49.9 | 24 (7.6) | 17 (8.8) | NS |
| 50-99.9 | 25 (7.9) | 14 (7.3) | |
| ≥100 | 49 (15.5) | 18 (9.3) | |
| **Hemoglobin (g/L)** | | | |
| <50 | 10 (3.2) | 18 (9.3) | NS |
| 50-99.9 | 194 (61.4) | 126 (65.3) | <.001 |
| ≥100 | 108 (34.2) | 44 (22.8) | <.001 |
| **Platelets (×10⁹/L)** | | | |
| <20 | 74 (23.4) | 43 (22.3) | .004 |
| 20-49.9 | 95 (30.1) | 62 (32.1) | .011 |
| 50-99.9 | 62 (19.6) | 46 (23.8) | |
| ≥100 | 80 (25.3) | 41 (21.2) | <.001 |

Data are number and percentage of patients.

The presenting features of the patients enrolled in Era 1 versus Era 2 were similar except for fever and bone or joint pain, which were more common among patients of Era 2. Hemoglobin and platelet levels probably reflect transfusion practice rather than true values. Altogether, 85.1% of patients were older than 1 year of age but younger than 10 years, and 78.4% had a leukocyte count

**Table 3.** Characteristics of leukemia blasts.

| Feature | Era 1 (n=316) | Era 2 (n=193) | *P* value |
|---|---|---|---|
| **FAB** | | | |
| L1 | 261 (82.6) | 131 (67.9) | .003 |
| L2 | 38 (12.0) | 43 (22.3) | |
| L3 | 5 (1.6) | 1 (0.5) | |
| Undetermined | 12 (3.8) | 18 (9.3) | |
| **Immunophenotyping** | | | |
| Precursor B | 93 (29.4) | 156 (80.8) | <.001 |
| B | 6 (1.9) | 3 (1.6) | |
| T | 20 (6.3) | 25 (13.0) | |
| Undetermined | 197 (62.4) | 9 (4.6) | |
| **DNA Index** | | | |
| <1.16 | 2 (0.6) | 57 (29.5) | <.001 |
| ≥1.16 | - | 29 (15.0) | |
| Undetermined | 314 (99.4) | 107 (55.5) | |
| **Cytogenetic studies** | | | |
| Normal | 58 (18.4) | 58 (30.1) | <.001 |
| Abnormal | 37 (11.7) | 64 (33.2) | |
| Undetermines | 221 (69.9) | 71 (36.8) | |
| Karyotype | | | |
| Hyperdiploid >51 | 5 (13.5) | 21 (32.8) | .042 |
| Diploid | 2 (5.4) | 0 (0.0) | |
| Hypodiploid | 2 (5.4) | 5 (7.8) | |
| **Chromosomal translocation** | | | |
| t(1;19) / E2A-PBX1 | 1 (2.7) | 2 (3.1) | NS |
| t(9;22) / BCR-ABL | 3 (8.1) | 1 (1.6) | |
| t(4;11) MLL-AF4 | - | 2 (3.1) | |
| Others | 24 (64.9) | 33 (51.6) | |

Data are number and percentage of patients.

below 50 000 per cubic millimeter. There were a higher proportion of boys, which is consistent with findings in other large cohorts of children with ALL. Table 3 shows characteristics of the leukemic blasts. There were more patients with French-American-British (FAB) morphology type L2 in Era 2. Most of the patients had precursor B-cell ALL. The percentage of T-cell ALL was within the range reported in industrialized countries and reported earlier for the KFSH&RC.[9-11] In Era 1, most patients did not have a DNA index or cytogenetic determination.

*Event-free survival*

Five-year EFS improved significantly from Era 1 to Era 2 (30.6% vs. 64.2 %) (Figure 1) (*P*=≤.001). The vast majority of patients treated in Era 1 either relapsed or had other adverse events within 2 years after diagnosis. In Era 1, with the introduction of more effective therapy coupled with better supportive care, the 5-year EFS increased from 16.8% to 35.4% (Figure 2). In Era 2, further improvement in therapy, use of cranial and cranio-spinal irradiation for selected patients, and use of prophylaxis against *Pneumocystis carinii* pneumonia in addition to assignment to risk categories based on more reliable assays (immunophenotyping, DNA index and cytogenetics) collectively increased the 5-year EFS to 64.2%. Surprisingly, the 5-year EFS for CCG 1881 (good risk) was not better than CCG 1891 (intermediate risk) (Figure 3). There was no significant difference between 1882a and 1882b protocols (Figure 4). Patients with CNS disease at diagnosis fared significantly worse than patients with non-CNS disease. The impressive improvement in 5-year EFS in Era 2 (64.2% compared to 30.6% for Era 1) was not at the expense of more toxicity, either early (Figure 5) or late.

*Patterns of treatment failure*

The end-of-induction remission rate improved from 90% (Era 1) to 95% (Era 2) (*P*<.049). Changes in treatment within the therapy program influenced the pattern as well as the frequency of treatment failure (Table 4). Advances in prophylaxis therapy for meningeal leukemia led to a decrease in the rate of isolated meningeal relapse from 11.1% to 3.1% (*P*=.27) and from 6.0% to 1.0% (*P*=.46) for combined relapses (hematological and meningeal). Hematological relapse decreased from 30.7% to 11.4% (*P*=.013), a reflection of a significant improvement in effective treatment and supportive care. The incidence of testicular relapse decreased from 2.8% to 1.0% with a better control of systemic leukemia. Two important forms of toxicity, death due to infections and hemorrhage, accounted for 7.3% and 6.7% of the loss of patients in Era 1 and Era 2, respectively. Death due to leukemia decreased from 29.1% to 9.3% (*P*=≤.001).

*Post-treatment failure and long-term survival*

The effectiveness of leukemia therapy is ultimately gauged by the proportion of patients who remain well after the cessation of treatment. Table 5 shows the shift from relapse on therapy to relapse after completion

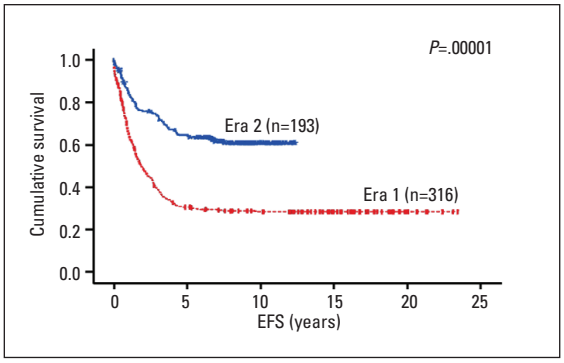


**Figure 1.** Event-free survival in Era 1 and Era 2.

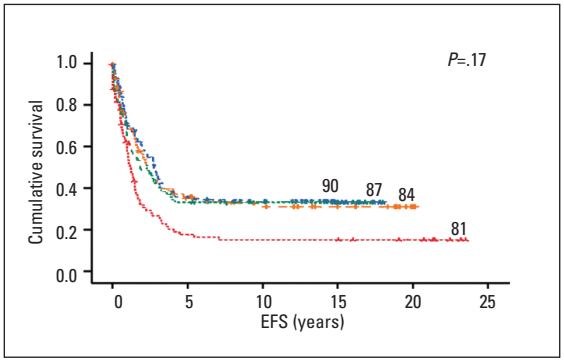


**Figure 2.** Event-free survival in Era 1 by protocol.

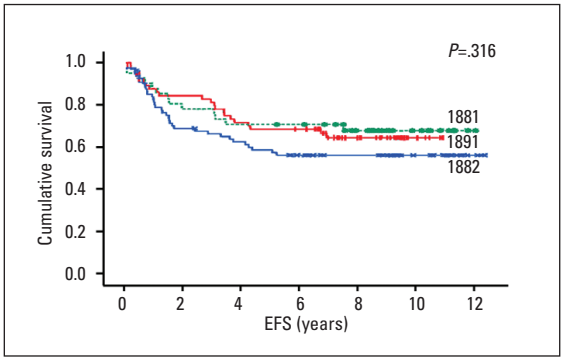


**Figure 3.** Event-free survival in Era 2 by protocol.

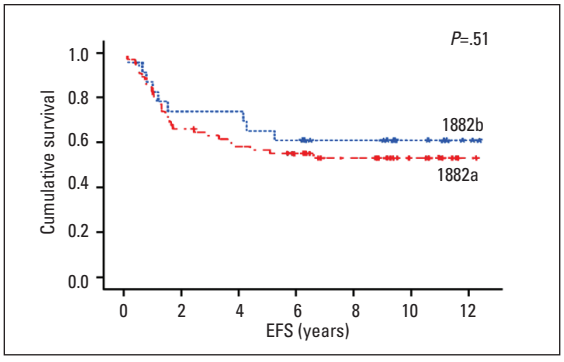


**Figure 4.** Event-free survival with CCG 1882 protocol per arm.

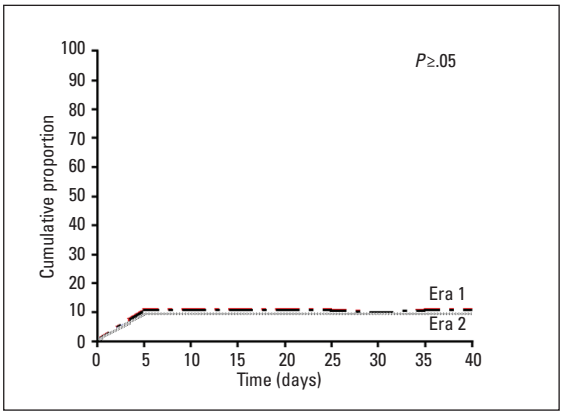


**Figure 5.** Treatment-related mortality in Era 1 and Era 2.

**Table 4.** Sites of relapse.

| Era | Era 1 | Era 2 | *P* value |
|---|---|---|---|
| All patients | 316 (62.1) | 193 (37.9) | |
| Median follow-up (years) | 3.36 | 7.39 | - |
| Induction failure | 35 (11.1) | 10 (5.2) | .023 |
| Patient with relapse | | | |
| Bone marrow (BM) | 97 (30.7) | 22 (11.4) | .013 |
| CNS | 35 (11.1) | 6 (3.1) | NS |
| BM + CNS | 19 (6.0) | 2 (1.0) | |
| Testes | 9 (2.8) | 2 (1.0) | |
| BM + testes | 11 (3.5) | 2 (1.0) | |
| Patients who died | | | |
| Leukemia | 100 (31.6) | 18 (9.3) | <.001 |
| Others | 26 (8.2) | 15 (7.8) | NS |

Data are number and percentage of patients unless noted otherwise.

**Table 5.** Time of relapse in relation to therapy.

| Era | Era 1 | Era 2 | *P* value |
|---|---|---|---|
| All patients | 316 (62.1) | 193 (37.9) | - |
| Relapsed on therapy | 124 (39.2) | 28 (14.5) | <.001 |
| Relapse off therapy | 58 (18.4) | 7 (3.6) | <.001 |

Data are number and percentage of patients.

of therapy, which was highly significant. The median follow-up for Era 1 was only 3.36 years due to death or loss to follow-up of patients early in the course of their treatment and follow-up. The median follow-up for Era 2 was 7.39 years. The median follow-up for the whole group was 6.33 years.

*Delayed effects of therapy*

Children are referred to the After Completion Of Therapy Clinic after 2 years of therapy. The majority of these children are leading normal lives without obvious health problems. Malignant solid tumors have not been diagnosed. One child had a recurrent benign meningioma that required multiple resections. Data for secondary hematological malignancies, specific abnormalities of growth and neuro-psychological functions will be the subject of a separate retrospective analysis.

## DISCUSSION

This study demonstrates continued improvement in treatment outcomes during two consecutive eras of clinical trials of treatment for childhood ALL. We attribute these gains to a series of modifications of treatment, including better systemic control with intensification of early treatment for all patients and better CNS preventive and therapeutic modalities, i.e. more intensive intrathecal therapy, cranial prophylaxis and craniospinal irradiation. Additional factors, such as improvements in antimicrobial therapy and advances in intensive care, contributed to the more favorable outcome by allowing the use of more intensive therapy without any significant change in the number of deaths due to infections and toxic causes, and by shortening interruptions of chemotherapy.

Cure of leukemia should mean permanent recovery from the disease, a definition difficult to apply to patients like ours who did not have specific biology-based re-evaluation studies, especially for minimal residual disease (MRD). In the absence of such data, a continuous complete remission as long as 5 years strongly suggests cure. The results of the St. Jude Children's Research Hospital (SJCRH) study indicated that a patient's risk of treatment failure becomes negligible (less than 1%) after three or four years of EFS after the cessation of therapy or perhaps after 2 years in low-risk patients.[12] Late relapses may evolve from slow-responding sub-clones as in t(12;21)-positive ALL, reflecting the persistence of a preleukemic clone.[13] In view of the very high hematological as well as CNS relapses in our patients treated on KFSH&RC protocol 1981, the decision was made to abandon stratification.[7] This was similar to the SJCRH experience where, beginning in 1984, they treated all patients, regardless of their risk status, with intensified therapy.

The limited outcome of protocols KFSH 81, 84, 87 and 90 coupled with the addition of more staff and better supportive care made it possible to move to far more intensive protocols like the CCG 1800 series. The impressive improvement in EFS in Era 2 5-year EFS (64.2% compared to the 30.6% for Era 1) was not at the expense of more toxicity. This 5-year EFS of Era 2 lags behind the reported EFS of the same protocols used in North America but not by very much (64.2% vs 75%).[14,15] This difference in outcome reflects differences in availability of resources, compliance, and possibly the biology of the blast and host.

Risk-adapted therapy tailors treatment based on the predicted risk of relapse, augmenting therapy for patients whose tumors require this approach, while avoiding the more toxic effects of augmented treatment in children who can be cured with treatment of standard intensity. Treatment outcome depends not only on the treatment applied, but also on the biology of the tumor and the host. The same factors should be used for later refinements based on initial response and several biological features.[16]

Age and WBC count continue to be the two most important and readily available prognostic factors.[17,18] The National Cancer Institute/Rome criteria are based on these two factors.[19] WBC, a reflection of tumor burden, correlates with other features such as hepatosplenomegaly and mediastinal mass. The Berlin-Frankfurt-Munster (BFM) Cooperative Clinical Trials Consortium incorporates peripheral blast count and liver and spleen size into a single variable that can be used in risk-based classification. The distribution of our 509 patients by age, WBC and organomegaly are similar to figures from the developed countries, which underscores the importance of biology-based assays to delineate differences in the biology of ALL in different countries and even within the same country. Due to the poor outcome of patients treated on protocol KFSH 81, stratification based on clinical factors was abandoned for the rest of Era 1. Clinical factors were not sufficient to reliably stratify patients, and biologic factors, e.g. DNA index and molecular genetics were not available. However, stratification was possible in Era 2 using a combination of both factors. More patients in Era 2 were high risk based on biologic factors like the DNA index. The higher percentage of patients 10 years or older in developed countries reflects the pediatric age cut of 18 years versus 14 years in Saudi Arabia. Adolescents with ALL fare better on pediatric ALL protocols rather than adult ones and should be included

in intensive pediatric protocols. The design of new trials for the treatment of young adults with ALL should inspired by pediatric protocols.[20] Gender and immunophenotyping are other features consistently associated with outcome. The gender of our patients was similar to other reported studies with a male predominance at 60.9%.

Most of the patients in Era 1 did not undergo immunophenotyping. In contrast, in Era 2 only 4.6% did not have lineage determined. The distribution of T-cells was within the range reported in industrialized countries. T-cell immunophenotyping has been associated with inferior EFS rates, which may be related to association with unfavorable features or a selective response to chemotherapeutic agents and hence a decreased response to therapy.[21]

The presence of CNS disease at diagnosis is also an adverse prognostic factor. The presence of blasts on the cytospin in the absence of elevated cerebrospinal fluid (CSF) WBC (so called "CNS 2" status or a traumatic lumbar puncture, defined as a red blood cell count (RBC) >10 uL with blasts (TLP+) is also associated with a poorer outcome.[22,23] Our patients with CNS disease at diagnosis fared worse than patients without CNS disease. However, advances in prophylactic therapy for meningeal leukemia led to a decrease in the rate of isolated meningeal relapse from 11.1% to 3.1% and from 6% to 1% for combined hematological and meningeal relapse. CNS leukemia is the subject of another retrospective analysis. CNS leukemia at diagnosis was an important independent prognostic factor in a multivariate analysis (Figures 6, 7).

Evidence suggests that the adverse prognostic significance of CNS status might be overcome with additional intrathecal chemotherapy, and the more recent use of the dexamethasone regimen might also be beneficial in this regard.[23,24] Fewer patients are currently receiving cranial irradiation and in the context of effective systemic chemotherapy, a radiation dose of 12 Gy, rather than the conventional dose of 18 Gy appears to provide adequate protection against CNS leukemia, even in patients at high risk.[25] It is desirable to avoid cranio-spinal irradiation for most ALL patients.

Hyperdiploid ALL has a very good outcome attributed to the favorable prognostic impact of triple trisomies (chromosome 4, 10, 17).[26,27] In contrast, hypodiploid blasts are a negative prognostic feature.[28] Hyperdiploidy in Era 2 patients was reported in 25 patients representing 25.7% of patients who had abnormal cytogenetic studies, a percentage similar to reports from industrialized countries.

DNA index was not available for most Era 1 patients; only 2 patients had it tested. In Era 2, about half the patients had their DNA index reported, and 57 patients (29.5%) had a DNA index <1.16 and 29 (15%) had a DNA index ≥1.16. There was no significant difference in survival, which may be related to the smaller number of patients tested or the effect of other prognostic factors (Figure 8).

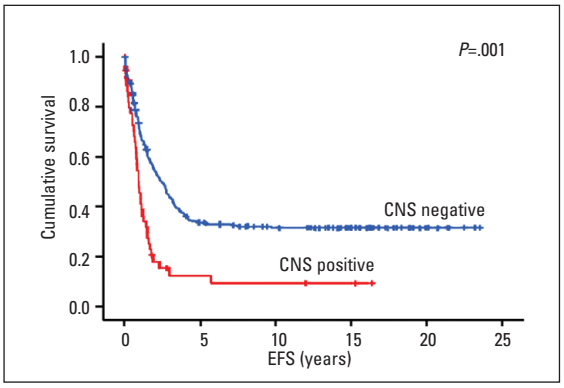


**Figure 6.** Event-free survival in Era 1 according to CNS status.

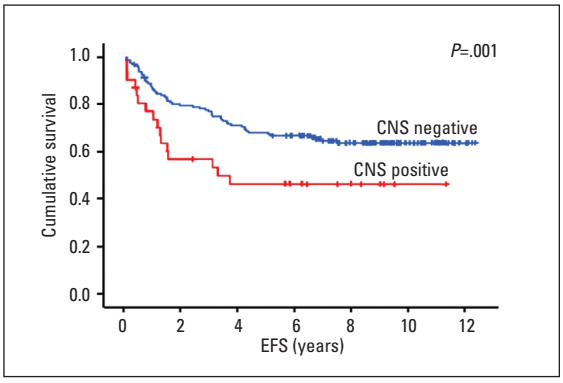


**Figure 7.** Event-free survival in Era 2 according to CNS status.

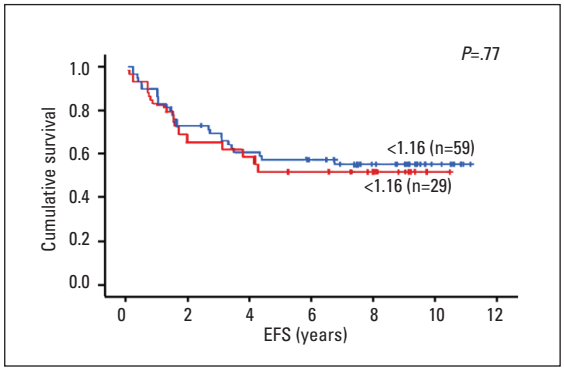


**Figure 8.** Event-free survival according to DNA index status.

Almost one-third of ALL blasts show chromosomal translocations in the absence of changes in chromosome number. The most common is t(12;21) (p13;q22), which is recognized in up to 25% of precursor-B ALL patients. The other translocations include t(1,19) (q23;q13), t(4,11) (q21;q23), and t(9;22)(q34;q11), which have been reviewed extensively elsewhere.[1,2,29] Translocation (12;21) was not reported during this study period because only conventional cytogenetics was available. Therefore, as a cryptic translocation, it was missed. Currently t(12;21) is tested using molecular studies, such as fluorescent in situ hybridization (FISH). t(1;19), t(9;22), and t(4;11) were reported in 4%, 4%, 2% of patients, respectively, which is similar to reports in industrialized countries. The percentage of abnormalities in ploidy or translocations precludes accurate evaluation of their impact on survival.

Early response to therapy is one of the most useful predictors of outcome.[30-33] Our study did not address this issue, but we are currently collecting data on the rate of disappearance of peripheral blasts and on day 14 bone marrow. The MRD assay is a powerful technique to assess early response.[34-36] MRD was not used to stratify our patients, but we are currently measuring MRD in our patients as a research tool. We are planning to proceed to use it as an important factor of stratification in the near future.

The surprisingly inferior outcome in our good-risk patients treated on CCG 1881 Protocol (Figure 3) may be due to the admixing of standard-risk and high-risk patients, reflecting gaps in the traditional stratification system using conventional prognostic factors. This underscores the need for more precise prognostic factors providing deeper insight into the biology of both the blasts and the host. Such factors include gene expression profiling,[37-39] MRD assays and pharmacogenomics.[40,41] Gene expression profiling can provide important information that not only helps to classify ALL, but may also predict response to drugs and toxicities. Profiling can also identify novel therapeutic targets. MRD is becoming the most important prognostic factor because it reflects the genetics of the lymphoblast, the pharmacodynamics and pharmacogenetics of the host. Pharmacogenetic studies are important to individualize doses, because the same dose of either methotrexate on mercaptopurine is associated with different levels in the host and a variable outcome.

In conclusion, the introduction of intensive therapy in the setting of improving supportive care is feasible in developing countries and does result in significant improvement in patient outcome. Good results can be achieved within a local infrastructure. A prospective study within a larger regional study group (Middle East Childhood Cancer Alliance) is already underway to obtain more reliable data about the causes of treatment failure, thus laying the foundation for further progress. New biology-based assays will help achieve a better stratification and therefore better tailoring of therapy. The ultimate aim is to cure all patients with minimal or no toxicities at all. That may be achieved with a better understanding and more effective use of target therapy. There are already ongoing studies to test the efficacy of imatinib mesylate in cases with BCR-ABL fusion and a study is planned for patients with MLL-rearranged leukemia using a FMS-like tyrosine kinase-3 (FLT-3) inhibitor.[1]

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