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ORIGINAL ARTICLE

# Long-term outcome of a pediatric-inspired regimen used for adults aged 18–50 years with newly diagnosed acute lymphoblastic leukemia

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On the basis of the data suggesting that adolescents and young adult patients with acute lymphoblastic leukemia (ALL) have improved outcomes when treated on pediatric protocols, we assessed the feasibility of treating adult patients aged 18–50 years with ALL with the DFCI Pediatric ALL Consortium regimen utilizing a 30-week course of pharmacokinetically dose-adjusted *E. coli* L-asparaginase during consolidation. Between 2002 and 2008, 92 eligible patients aged 18–50 years were enrolled at 13 participating centers. Seventy-eight patients (85%) achieved a complete remission (CR) after 1 month of intensive induction therapy. With a median follow-up of 4.5 years, the 4-year disease-free survival (DFS) for the patients achieving a CR was 69% (95% confidence interval (CI) 56–78%) and the 4-year overall survival (OS) for all eligible patients was 67% (95% CI 56–76%). The 4-year DFS for the 64 patients who achieved a CR and were Philadelphia chromosome negative (Ph – ) was 71% (95% CI 58–81%), and for all 74 Ph – patients the 4-year OS was 70% (95% CI 58–79%). We conclude that a pediatric-like treatment strategy for young adults with *de novo* ALL is feasible, associated with tolerable toxicity, and results in improved outcomes compared with historical regimens in young adult patients with ALL.

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## INTRODUCTION

Over the past two decades, the outcomes for children with acute lymphoblastic leukemia (ALL) have significantly improved with modifications of risk-stratified multi-agent, multi-phase chemotherapy and central nervous system (CNS) prophylaxis. Today, patients 1–18 years old who are diagnosed with ALL can expect complete remission (CR) rates that exceed 95% and long-term event-free survival (EFS) that exceeds 80%.[1–5] In contrast, outcomes for adults diagnosed with ALL remain poor. Contemporaneous trials using adult ALL regimens result in long-term survival rates of $<$50%,[6–8] but these differences in response rates and outcome cannot be explained by differences in leukemia biology alone.

Stock *et al.*[9] reported that adolescents and young adults 16–21 years old, who were eligible for either a pediatric or an adult ALL regimen, had markedly improved outcomes if they received the pediatric regimen. Similar findings were apparent when comparing outcomes from young populations in France, the Netherlands and the United Kingdom treated with childhood versus adult regimens.[10–13]

Recognition of the likely role of the treatment regimen in improved outcomes in adolescents and young adult patients treated with pediatric regimens led us to initiate a clinical trial to determine whether an intensive pediatric ALL chemotherapy protocol for children $<$18 years old would be tolerable for 18–50-year-old adults and would result in improved outcomes. Therefore, we initiated a multi-center clinical trial for young adults with ALL and found that the pediatric-inspired regimen was well tolerated and produced encouraging results compared with historical adult ALL regimens.

## MATERIALS AND METHODS

### Study design and patient population

Patients were eligible for protocol entry if they had newly diagnosed ALL (excluding mature B-cell ALL) and were at least 18 years old. Initially, there was no upper age limit for eligibility; the protocol was amended after the first eight patients were enrolled to limit the age range from $>$18 to 50 years and to exclude patients with presumed secondary ALL. Eligible patients had a Zubrod performance status of 2 or less, and exclusion criteria included pregnancy, active psychiatric illness, uncontrolled active infection, prior history of pancreatitis, cerebrovascular accident or hemorrhage or evidence of infection with HIV. There were no specific exclusions based on hepatic or renal function.

A total of 100 patients were enrolled between June 2002 and February 2008 from 13 institutions. The study was conducted according to the Declaration of Helsinki and its amendments. Before study entry, all patients signed an informed consent document approved by the Institutional Review Board at each institution.

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## Therapy

Details of the treatment regimen are summarized in Table 1. Steroid therapy consisted of prednisone during the induction phase and dexamethasone thereafter (that is, during intensification and continuation phases). Patients with persistent leukemia at the end of the first month of treatment were removed from the protocol and given alternative therapy at the discretion of the treating physician. During induction, high-dose methotrexate was administered as a 1-h infusion, whereas leucovorin (200 mg/m$^2$ intravenously) was given 36 h later and was continued at a dose of 24 mg/m$^2$ intravenously or orally every 6 h until the serum methotrexate level was $<1$ μM. The cumulative doxorubicin dose was capped at 300 mg/m$^2$.

*E. coli* asparaginase was given intramuscular (IM) once a week for 30 weeks at a starting dose of 12 500 IU/m$^2$. Subsequent doses were adjusted as indicated in Table 2 to maintain the nadir serum asparaginase activity (NSAA) between 0.100 and 0.140 IU/ml. This range was considered to be therapeutic based upon previously reported pharmacokinetic and pharmacodynamic studies, and was selected with the aim of avoiding excessively high or low NSAA.[14–19] Serum samples were obtained just before administering the second and fourth doses of asparaginase and then every 3 weeks thereafter. Asparaginase activity was determined in real-time using a validated biochemical assay with a 0.025-IU/ml lower limit of quantitation by a central laboratory, as previously described.[20] These results were then used to adjust the dose given 2 weeks after obtaining the sample. Samples had to be obtained 7 days after the prior dose to be considered evaluable. The minimum and maximum asparaginase dose that could be given was 6000 and 25 000 IU/m$^2$, respectively. Patients with extremely low NSAA in serial samples despite dose adjustments were switched to an alternative asparaginase preparation (either polyethylene glycol (PEG)-asparaginase or *Erwinia*-derived asparaginase, as described below) for suspected silent allergy. Asparaginase activity was measured in samples from patients receiving both PEG asparaginase and *Erwinia* asparaginase, although no dose adjustments were made after switching from *Escherichia coli* asparaginase to another preparation of the enzyme.

During the intensification and continuation phases, doses of methotrexate and 6-mercaptopurine were adjusted to maintain absolute phagocyte nadirs of 0.500–0.750 $\times 10^9$/l and were reduced for transaminitis or mucositis. The dexamethasone dose was reduced when starting the continuation phase. Therapy for all patients was stopped after 2 years of continuous CR.

Allogeneic stem cell transplantation was not mandated but encouraged for all patients with high-risk cytogenetic features, such as the Philadelphia chromosome or translocations involving the MLL gene on 11q23. The protocol was amended in September 2006 to add imatinib at a dose of 600 mg daily to all patients who were Philadelphia chromosome positive.

Dexamethasone was permanently discontinued in the setting of symptomatic, radiographically confirmed osteonecrosis. Administration of asparaginase was held until the resolution of mild/moderate pancreatitis or deep venous thrombosis and was permanently discontinued after severe pancreatitis (signs and symptoms $>72$ h, see definitions below). Patients who experienced allergic reactions to *E. coli* asparaginase (of any severity, including local reactions) were switched to IM PEG asparaginase (2000 IU/m$^2$/dose) administered every 2 weeks. Patients who reacted to PEG asparaginase were switched to IM *Erwinia* asparaginase (25 000 IU/m$^2$/dose twice weekly).[20] Asparaginase was permanently discontinued after allergy to all available preparations.

## Immunophenotype and cytogenetics

Bone marrow cells from diagnostic aspirates were examined for cell surface antigens using standard indirect immunofluorescence assays, and were cultured for standard G-banded metaphase cytogenetic analyses. Molecular analysis with real-time PCR allowed for the detection of *BCR-ABL*.

## Statistical methods

The primary end point of this study was the proportion of patients who completed 30 weeks of asparaginase treatment. *A priori*, it was determined that the treatment would be considered 'feasible' if the one-sided lower bound of the 90% exact binomial confidence interval (CI) for feasibility (that is, the proportion of patients in whom it was feasible to administer this regimen for $\geqslant 30$ weeks) was 60% or higher, taking into account patients who were removed from the study to undergo allogeneic stem cell transplantation.

**Table 1.** Therapy on DFCI Adult ALL Consortium Protocol 01–175

| *Time Frame* | *Treatment* |
|---|---|
| Induction 4 Weeks | Vincristine 2 mg weekly, days 1, 8, 15 and 22<br>Prednisone 40 mg/m$^2$/day, days 1–28<br>Doxorubicin 30 mg/m$^2$/dose, days 1and 2<br>Methotrexate 4 g/m$^2$ (8–24 h after doxorubicin) with leucovorin rescue on day 3<br>*E coli* L-asparaginase 25 000 IU/m$^2$ IM × 1 dose, day 5<br>IT cytarabine 50 mg, day 0[a] (prior to initiation of systemic therapy)<br>IT methotrexate/cytarabine/hydrocortisone,[b] days 15 and 29 |
| CNS therapy 3 Weeks | Vincristine 2 mg × 1 dose<br>6-mercaptopurine (6-MP) 50 mg/m$^2$/day orally, × 14 consecutive days<br>Doxorubicin 30 mg/m$^2$ × 1 dose<br>IT methotrexate/cytarabine twice weekly × 4 doses<br>Cranial radiation[c] |
| Intensification 30 Weeks | *Every 3-week cycles:*<br>Vincristine 2 mg, day 1<br>Dexamethasone 18 mg/m$^2$/day b.i.d., orally, days 1–5<br>Doxorubicin 30 mg/m$^2$, day 1 of each cycle to a (cumulative dose 300 mg/m$^2$)<br>6-MP 50 mg/m$^2$/day orally × 14 consecutive days<br>*E. coli* asparaginase<br>*Individualized dosing*: 12 500 IU/m$^2$/dose (starting dose)[d]<br>Methotrexate 30 mg/m$^2$ i.v. or IM weekly, 1 day after asparaginase (no weekly methotrexate until doxorubicin completed).<br>IT methotrexate/cytarabine/hydrocortisone at start of a cycle<br>IT therapy consisting of methotrexate/cytarabine at start of a cycle every 18 weeks |
| Continuation 74 weeks | *Every 3-week cycles:*<br>Same as intensification except no asparaginase and dexamethasone dose reduced to 6 mg/m$^2$/day |

Abbreviations: ALL, acute lymphoblastic leukemia; CSF, cerebrospinal fluid; CNS, central nervous system; IM, intramuscular; IT, intrathecal. [a]Patients with CNS leukemia at diagnosis (CNS-2 and CNS-3) received twice weekly doses of IT cytarabine until CSF was clear of blast cells on three consecutive examinations. [b]IT methotrexate 12 mg; cytarabine 40 mg; hydrocortisone 50 mg. [c]Patients received cranial radiation 1800 cGy delivered as 180 cGy fractions daily for 10 days. The dose was 24 Gy for patients with CNS-2 or CNS-3, regardless of CNS signs or symptoms. [d]Asparaginase dose adjustments based on nadir serum asparaginase activity measurements.

**Table 2.** Individualized asparaginase dose adjustments based on nadir serum asparaginase levels on the adult DFCI ALL Consortium Protocol

| *NSAA (IU/ml)* | *Change in subsequent asparaginase doses* |
|---|---|
| $<0.025$ | Increase by 80%[a] from most recent dose |
| 0.025 to $<0.05$ | Increase by 60% |
| 0.05 to $<0.08$ | Increase by 40% |
| 0.08 to $<0.1$ | Increase by 20% |
| 0.1 to $<0.14$ | No change |
| 0.14 to $<0.20$ | Decrease by 20% |
| $>0.20$ | Decrease by 40% |

Abbreviations: ALL, acute lymphoblastic leukemia; NSAA, nadir serum asparaginase activity. [a]Percentage change from most recent dose. Starting dose 12 500 IU/m$^2$. Minimum dose 6000 IU/m$^2$. Maximum dose 25 000 IU/m$^2$.

Outcome events were death during induction therapy, failure to achieve CR at the end of the 4-week induction phase, death during remission and relapse. EFS was defined as the time from study registration to the first outcome event among all patients. Disease-free survival (DFS) was defined as the time from CR to relapse or death, and only patients who achieved a CR were included in the calculation. Overall survival (OS) was defined as the time from study registration to the time of death from any cause for all patients. Patients not experiencing an outcome event were censored at the date of last follow-up. Patients who went off treatment for a stem cell transplant in CR were not censored at the date of transplant, because transplantation was the recommended treatment strategy for patients with high-risk cytogenetic abnormalities. EFS, DFS and OS were estimated using the Kaplan–Meier method, and the Greenwood formula was used to construct 95% CI. Univariate analyses of the differences in EFS, DFS and OS were conducted with log-rank tests.

The Common Terminology Criteria for Adverse Events (CTCAE) version 2.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcmanual_v4_10-4-99.pdf) was used for coding toxicities. Toxicity data reflect all submitted data, regardless of patient exclusion from other analyses.

### Response assessment and definition of CNS status

Hematologic response was defined by standard criteria.[21] The status of the cerebrospinal fluid (CSF) was defined as follows: CNS-1, no blast cells in cytospin, regardless of CSF cell count; CNS-2, fewer than five white blood cells on CSF cell count, with blasts on cytospin; CNS-3, five or more white blood cells on CSF cell count, with blasts on cytospin.

## RESULTS

### Patient characteristics

Between August 2002 and February 2008, 100 patients (ages 18–50 years; median 28) were enrolled (see Figure 1). Eight patients were deemed ineligible and are excluded from further analysis: two patients were removed from study prior to receiving any chemotherapy, as they were found to have bilineage leukemia and received alternative therapy; four patients were enrolled early in the study prior to the protocol amendment excluding patients with secondary ALL and age $>50$ years; and two patients were ineligible due to a diagnosis of Burkitt's lymphoma. Patient demographics are shown in Table 3. Eighty-eight percent of patients were white and 94% non-Hispanic. Cytogenetic results were available for 88 of the 92 eligible patients. Eighteen patients (20%) were Philadelphia chromosome positive (Ph+); 8 (9%) had 11q23 (*MLL*) translocations; 13 (14%) were hyperdiploid ($>46$ chromosomes: 9 with 47–50 chromosomes and 4 with $>50$ chromosomes); 3 (3%) had hypodiploidy ($<45$ chromosomes); 4 (4%) had 45 chromosomes and 60 (65%) were diploid. Sixty-six patients (71%) had a Zubrod performance status of 0–1 at diagnosis.

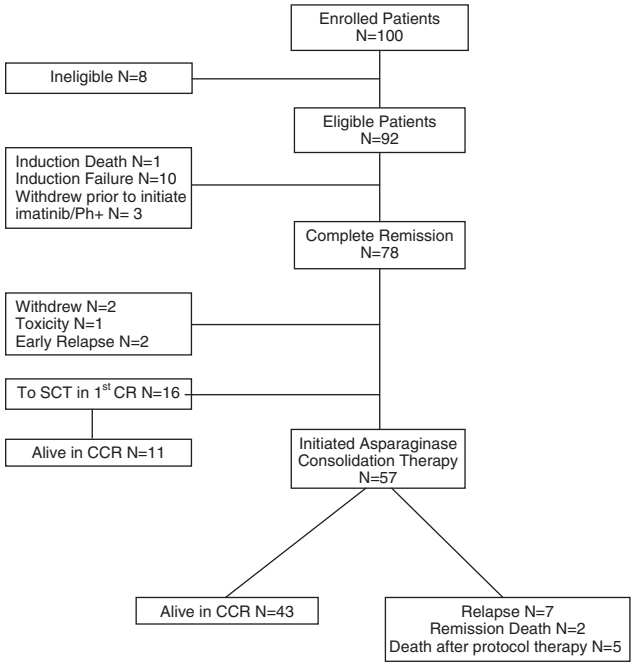


**Figure 1.** DFCI ALL Consortium Protocol flow diagram. One hundred patients with newly diagnosed ALL were enrolled. Ninety-two patients were considered eligible, of whom 78 (85%) achieved a complete remission within 1 month. Fifty-seven were evaluable for the asparaginase feasibility end point. All 92 patients were evaluable for analysis of EFS and OS.

### Overall outcomes

Of the 92 eligible patients, 78 (85%) (90% exact CI: 77–91%) achieved a CR at the end of the 4 weeks of induction therapy. One patient died during induction due to sepsis, 10 patients (11%) had refractory disease at the end of induction (induction failure) and 3 Ph+ patients withdrew from protocol therapy to initiate imatinib prior to achieving a CR. Sixteen of 18 (89%) patients with a T-cell immunophenotype achieved a CR, as did 62 of 74 patients (84%) with a pre-B-cell disease.

Of the 78 patients who achieved CR, 16 underwent an allogeneic stem cell transplant during first remission: 11 were Ph+, 2 patients had a t(4;11) translocation, 1 patient had trisomy 8 and a t(9;12) translocation, 1 patient had a 9q34 translocation and 1 patient had no cytogenetics available. Eleven of the 16 (69%) patients who underwent transplant remain in first CR (CR1).

Of the remaining 62 patients who achieved a CR and did not undergo transplantation in CR1, 5 patients withdrew or never initiated intensification therapy due to transfer of care ($n=1$), bone marrow relapse ($n=2$), infection ($n=1$) or withdrawal of consent ($n=1$). Fifty-seven patients continued with intensification therapy with L-asparaginase. Forty-three of the 57 patients remain in CR1. Seven patients suffered a relapse (five bone marrow alone, one CNS alone and one CNS/optical), two patients died in remission due to pancreatitis or hepatic insufficiency and five deaths occurred while receiving off-protocol therapy.

With a median follow-up of 4.5 years (95% CI 4.1–5.0 years), the 4-year DFS for the 78 patients achieving a CR and OS for all 92 eligible patients was 69% (95% CI 56–78%) and 67% (95% CI 56–76%), respectively (Figure 2 and Table 4). For the 18 patients who had Ph+ ALL, 14 (78%) achieved CR, 2 relapsed and 8 remain in CR1. For the 74 patients who had Ph− ALL, 64 (86%) achieved CR, 12 relapsed and 47 remain in CR1. The 4-year DFS and OS for Ph− patients with B-cell ALL was 66% (CI 50–78%) and 68% (CI 53–79%), respectively. The 4-year DFS and OS for patients with T-cell ALL was 87% (CI 56–97%) and 76% (CI 49–90%), respectively (Figures 2c and d and Table 4). EFS, DFS and OS rates were similar for patients between 18–30 and 31–50 years (Table 4). Outcomes by Philadelphia chromosome status, immunophenotype, age and white blood count are shown in Table 4 and Figure 2. All Ph+ patients had B-lineage ALL. Additional analyses of DFS and OS for Ph− patients with B-lineage disease was performed, with patients transplanted in CR1 censored at the time of transplant. Results were unchanged (data not shown).

### Asparaginase tolerance

The primary focus of this study was to determine the feasibility of administering weekly IM *E. coli* asparagnase during the 30-week intensification phase. Among the 92 eligible patients, 57 patients were evaluable for the asparaginase end point. The 35 patients not evaluable for asparaginase tolerance had induction failure ($n=10$) or death ($n=1$), initiated imatinib (3 patients), underwent allogeneic stem cell transplantation (16 patients) and 5 were unevaluable as described above. Of the 57 evaluable patients,

**Table 3.** Patient demographics and disease characteristics

| | *N (%)* |
|---|---|
| *N* eligible patients | 92 |
| *Age years, median (range)* | 28 (18, 50) |
| 18–29 years | 48 (52) |
| 30–50 years | 44 (48) |
| Sex, male | 56 (61) |
| *WBC at Dx* $\times 10^{-3}$*, median (range)* | 15.5 (1.0, 360.0) |
| $<20$ | 56 (61) |
| $\geqslant 20$ | 35 (38) |
| Unknown | 1 (1) |
| *Immunophenotype*[a] | |
| B cell | 74 (80) |
| T cell | 18 (20) |
| *CNS status* | |
| CNS-1 (−) CSF WBC $<5$ without blasts | 79 (86) |
| CNS-2 (+) CSF WBC $<5$ with blasts | 4 (4) |
| CNS-3 (+) CSF WBC $\geqslant 5$ with blasts | 1 (1) |
| Unknown | 8 (9) |
| Philadelphia chromosome positive[b] | 18 (20) |
| MLL rearrangement | 8 (9) |
| Other Translocation | 11 (12) |
| *Ploidy* | |
| Hypodiploidy ($<45$) | 3 (3) |
| ($=45$) | 4 (4) |
| Diploidy ($=46$) | 60 (65) |
| ($=47$, 48, 49, 50) | 9 (10) |
| Hyperdiploidy (>50) | 4 (4) |
| Unknown | 12 (13) |
| *Performance status* | |
| 0 | 27 (29) |
| 1 | 39 (42) |
| 2 | 20 (22) |
| Unknown | 6 (7) |
| *ECOG risk classification*[c] | |
| SR | 41 (45) |
| HR | 51 (55) |
| *Race* | |
| White | 81 (88) |
| Black or African American | 4 (4) |
| Asian | 2 (2) |
| American Indian or Alaska native | 1 (1) |
| Other | 4 (4) |
| *Ethnicity* | |
| Hispanic | 5 (5) |
| Non-Hispanic | 86 (94) |
| Other | 1 (1) |

Abbreviations: CSF, cerebrospinal fluid; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HR, high risk; SR, standard risk; WBC, white blood cell. [a]Eight B-cell patients and 1 T-cell patient had myeloid coexpression. [b]Detected by cytogenetics ($n=17$), both reverse transcriptase-PCR and fluorescence *in situ* hybridization ($n=1$). [c]ECOG risk is defined as follows: HR includes any patients with an MLL rearrangement or Ph+ and B-cell patients with WBC $\geqslant$ 35 K or age $\geqslant$ 35 years and T-cell patients with WBC $\geqslant$ 100 K.

36 (63%) completed all 30 doses with a one-sided lower exact 90% binomial confidence bound of 54%, and 41 patients (72%) completed 26 or more doses of asparaginase with a one-sided lower exact 90% binomial confidence bound of 63%. Of the 21 patients who did not complete the 30 doses of asparaginase, 7 developed pancreatitis, 2 had allergic reactions to all asparaginase preparations, 6 had either a deep vein thrombosis or hepatic toxicity, 2 relapsed during the intensification phase, 1 withdrew due to non-compliance and 3 had other toxicities.

### Asparaginase toxicity

Asparaginase-related toxicities included allergic reactions in 5 patients (5%), thrombosis in 16 patients (17%) and pancreatitis in 10 patients (11%). There was 1 death related to pancreatitis, which occurred 10 days after completion of the 30th dose of asparaginase. There were 8 bone fractures reported in 7 patients and 5 patients developed osteonecrosis. Hepatic toxicity during the intensive asparaginase course was seen in 33 patients (53%), including 10 patients who developed grade 3 or 4 hyperbilirubinemia, 3 patients who had liver dysfunction or failure (1 death); the remaining patients had transient elevations in the aspartate transaminase or alanine transaminase enzyme levels. Both asparaginase-related and toxicities based on the CTCAE v. 2.0 are summarized in Table 5 by treatment phase. No second malignancies or clinical congestive heart failure were reported.

### Individualized asparaginase dosing

Asparaginase activity was measured in 365 serum samples obtained from 54 patients 7 days after the prior dose of IM *E. coli* asparaginase during the intensification phase. The median number of evaluable NSAA samples obtained from each patient was 7 (range: 1–11). The median asparaginase dose (including starting dose and all adjusted doses administered to patients during the intensification phase) was 15 000 IU/m$^2$ (range: 6000 –25 000 IU/ml) (Figure 3). Enzyme activity was $<0.025$ IU/ml in 20% ($n=74$) of the samples, 0.025–0.099 IU/ml in 45% ($n=165$), 0.100–0.14 IU/ml in 14% ($n=51$) and $>0.140$ IU/ml in 21% ($n=75$). The weekly median NSAA increased progressively until a plateau was achieved following the sixth dose. The steady-state median NSAA was 0.083 IU/ml (range: $<0.025$–0.66 IU/ml) for the 263 samples collected from 48 patients after 6 weeks of dosing during which the median dose was 18 144 IU/m$^2$.

In the presence of suspected silent allergy indicated by very low serial NSAA samples, 12 patients switched asparaginase preparation. Three patients received *Erwinia* asparaginase from which a total of 17 samples were collected: 6 were $<0.025$ IU/ml, 6 were 0.025–0.099 IU/ml and 5 were $>0.14$ IU/ml with an overall median of 0.057 (range: $<0.025$–0.595 IU/ml). In addition, 9 patients received PEG asparaginase owing to unavailability of *Erwinia* asparaginase from which a total of 37 samples were collected: 3 were $<0.025$ IU/ml, 3 were 0.025–0.099 IU/ml and 31 were $>0.14$ IU/ml, with an overall median of 0.44 IU/ml (range: $<0.025$–2.45 IU/ml).

### CNS status

Five patients had CNS-2 or CNS-3 disease at the time of initial diagnosis. Subsequently, three of these patients experienced a relapse (one bone marrow, one CNS and one bone), one patient was a remission death and one died after having completed protocol therapy. There were no CNS relapses among the patients with CNS-1 disease at diagnosis.

## DISCUSSION

Several retrospective analyses have compared treatment outcomes for young adult patients treated with either pediatric or adult regimens, all of which have demonstrated superior outcomes for patients treated with pediatric ALL protocols.[9–13] These striking differences in outcome cannot be explained simply on the basis of different biology or median age, because the pediatric and young adult cohorts in these studies had similar rates of Ph+ and *MLL* gene-rearranged ALL, and other high-risk and immunophenotypic features.

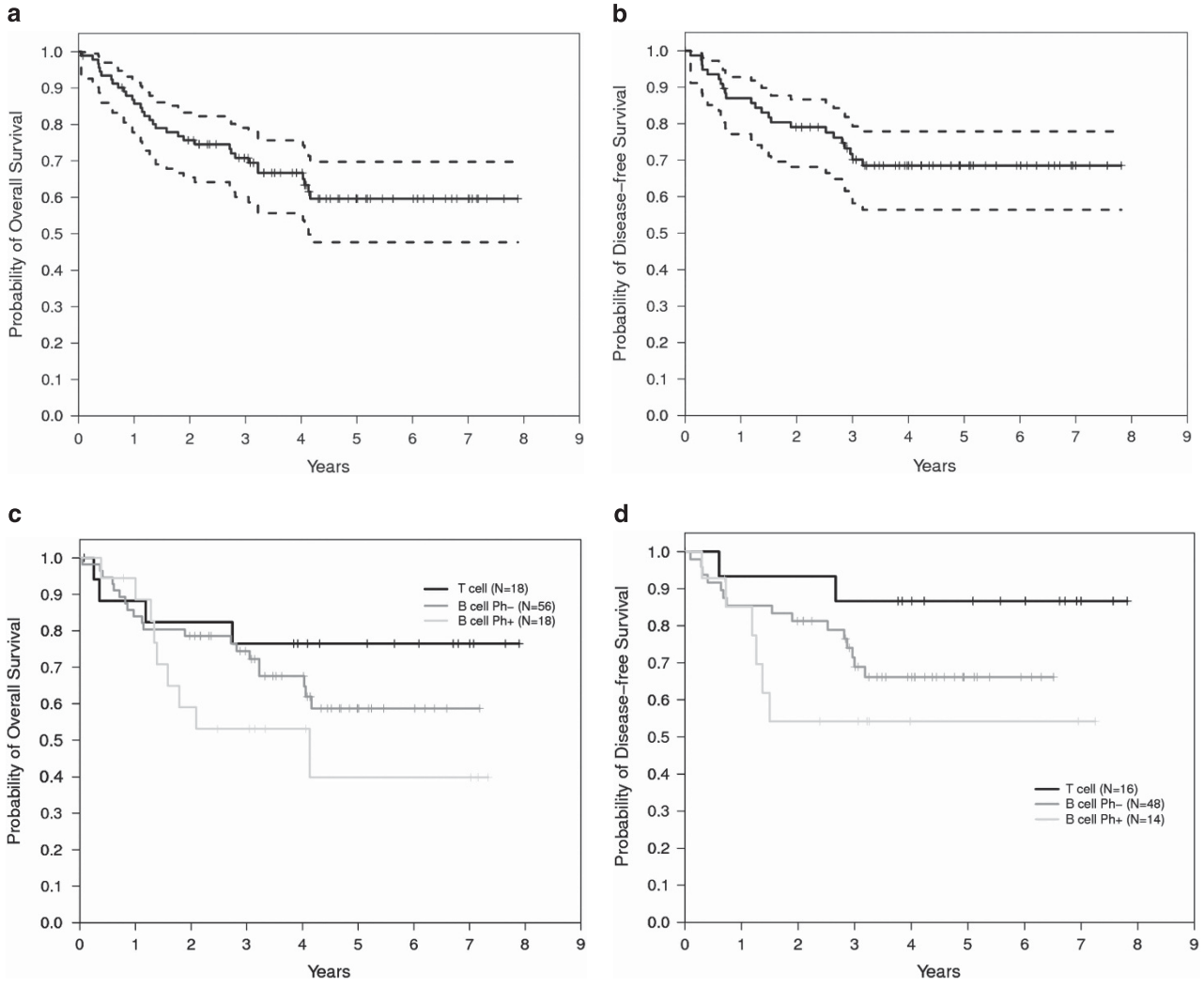


**Figure 2.** (**a** and **b**) represent the OS for 92 eligible patients and DFS for 78 patients who achieved a CR, respectively. With a median follow-up of 4.5 years, the 4-year OS for all 92 patients on protocol was 67% (95% CI; 56–76%) and the 4-year DFS was 69% (95% CI; 56–78%) for the 78 patients who achieved a CR. The solid lines represent the Kaplan–Meier estimates, and the dashed lines represent the 95% confidence bands about those estimates. (**c** and **d**) Represent OS and DFS by immunophenotype and Philadelphia chromosome status, respectively.

Some of the reported differences between pediatric and adult outcomes have been attributed to attention to detail of therapy, such as attaining maximal dose intensification and timely scheduling of drug delivery.[10] The latter has been reported to result in systematic delays in administering drugs. Most children with ALL are referred to academic centers and treated on clinical trials, whereas most adults with ALL are not. In addition, pediatric regimens administer early and more intensive CNS therapy as compared with adult regimens.

In addition, it is possible that many young adults and adolescents are currently being 'under dosed' when treated on standard adult ALL regimens due to lower total doses of corticosteroids, vinca alkaloids and asparaginase. Our experience suggests that adults 50 years old and younger tolerate a pediatric regimen, and that such therapy resulted in improved outcomes compared with historical controls. These findings were consistent with recent reports from French, Canadian and Spanish investigators.[22–24] In both the French and the Canadian studies, patients received significantly more prednisone, vincristine and asparaginase than in prior adult regimens. Those experiences differed from ours in that the same pediatric regimen was not offered to adult patients; instead, the investigators employed a regimen of intermediate intensity between typical pediatric regimens and adult regimens. Nevertheless, the 2-year EFS was 56% in the French study with a 2-year OS of 66%, both improvements from historical controls.[8] The French GRAALL study made use of an intensified induction therapy for poor steroid responders, allocation of higher risk (based on disease features) patients to allogeneic transplant and enrollment of patients up to an age of 60 years. However, the improved outcomes noted in the French study were limited to patients under the age of 45 years. The Spanish study administered the pediatric PETHEMA ALL-96 regimen to patients up to the age of 30 years and showed a similar outcome as compared with adolescent patients of age 15–18 years.[24] Furthermore, a recent meta-analysis further supports the administration of pediatric-inspired regimens for young adult patients.[25]

A critical biologic difference between the pediatric and young adult populations pertains to the relative incidence of Ph+ disease. In our concurrently conducted pediatric (1–18 year olds) and young adult (>18–50 year olds) protocols, the incidence of Ph+ leukemia was 3 and 18%, respectively. As shown in Table 4 and Figure 3, the outcome for Ph− patients treated on the current study was relatively favorable. This finding is of particular importance because outcomes from a recent Eastern Cooperative Oncology Group/ Medical Research Council trial reported that allogeneic stem cell

**Table 4.** Outcome by patient characteristics

| | *4-year DFS (%) 95% CI* | P-*value* | *4-year EFS (%) 95% CI* | P-*value* | *4-year OS (%) 95% CI* | P-*value* |
|---|---|---|---|---|---|---|
| *N* | 78 | | 92 | | 92 | |
| All patients | 69 (56–78) | | 58 (47–68) | | 67 (56–76) | |
| *Age (years)* | | | | | | |
| 18–29 | 70 (52–83) | 0.54 | 55 (39–69) | 0.61 | 68 (52–80) | 0.93 |
| 30–50 | 67 (50–79) | | 61 (44–74) | | 65 (49–77) | |
| *Sex* | | | | | | |
| Male | 64 (47–77) | 0.47 | 51 (37–64) | 0.15 | 64 (50–76) | 0.28 |
| Female | 75 (56–87) | | 69 (51–81) | | 71 (52–83) | |
| *% Blasts at Dx* | | | | | | |
| 0–30 | 70 (53–82) | 0.77 | 58 (43–71) | 0.92 | 65 (50–77) | 0.79 |
| >30 | 67 (47–81) | | 58 (40–72) | | 69 (52–82) | |
| *WBC at Dx* $\times 10^{-3}$ | | | | | | |
| <20 | 74 (59–84) | 0.073 | 70 (56–80) | <0.001 | 80 (66–88) | 0.001 |
| ⩾20 | 55 (32–73) | | 37 (21–53) | | 45 (28–61) | |
| *Immunophenotype* | | | | | | |
| B cell | 64 (50–75) | 0.11 | 53 (41–64) | 0.11 | 64 (52–74) | 0.20 |
| T cell | 87 (56–97) | | 77 (49–91) | | 76 (49–90) | |
| *CNS status* | | | | | | |
| CNS-1 (−) | 75 (62–84) | <0.001 | 62 (50–72) | 0.005 | 71 (59–80) | <0.001 |
| CNS-2/3 (+) | 0 (NA) | | 0 (NA) | | 0 (NA) | |
| *Ph+* | | | | | | |
| Yes | 54 (25–76) | 0.13 | 42 (19–63) | 0.091 | 53 (28–73) | 0.12 |
| No | 71 (58–81) | | 62 (49–72) | | 70 (58–79) | |
| *MLL rearrangement* | | | | | | |
| Yes | 63 (23–86) | 0.48 | 63 (23–86) | 0.86 | 60 (20–85) | 0.83 |
| No | 69 (56–79) | | 58 (46–68) | | 67 (56–77) | |
| *Ploidy* | | | | | | |
| High hyperdiploid (>50) | 75 (13–96) | 0.95 | 75 (13–96) | 0.57 | 75 (13–96) | 0.74 |
| Other | 66 (52–77) | | 54 (42–65) | | 64 (52–74) | |
| *Performance status* | | | | | | |
| 0–1 | 69 (55–80) | 0.52 | 59 (45–70) | 0.81 | 70 (57–80) | 0.42 |
| 2 | 63 (36–82) | | 57 (32–76) | | 55 (30–75) | |
| *ECOG risk* | | | | | | |
| SR | 81 (63–91) | 0.016 | 70 (53–82) | 0.051 | 80 (64–90) | 0.038 |
| HR | 57 (41–71) | | 48 (33–61) | | 55 (40–68) | |
| *Immuno/Ph+ status* | | | | | | |
| T cell | 87 (56–97) | 0.14 | 77 (49–91) | 0.11 | 76 (49–90) | 0.12 |
| B-cell Ph− | 66 (50–78) | | 57 (42–69) | | 68 (53–79) | |
| B-cell Ph+ | 54 (25–76) | | 42 (19–63) | | 53 (28–66) | |

Abbreviations: CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; EFS, event-free survival; HR, high risk; Ph, Philadelphia chromosome; OS, overall survival; SR, standard risk; WBC, white blood cell.

transplantation offered superior OS compared with either chemotherapy or autologous stem cell transplantation for adults with standard-risk ALL.[26] However, the OS for the Philadelphia-negative patients in the Eastern Cooperative Oncology Group/Medical Research Council study was only 53%, compared with an OS of 68% for Ph− patients treated on the current protocol. The 4-year OS for T-ALL patients on the current trial (76%) also compares favorably to published outcomes for adults with this subtype.[27]

We sought to determine the feasibility of treating a young adult population with an intensive pediatric-inspired ALL regimen. Our primary end point was the proportion of patients who completed 30 weeks of high-dose asparaginase therapy. This end point was chosen because we had previously shown that, in children, tolerance to asparaginase was associated with an exceptionally favorable outcome.[28] There was uncertainty whether adults could tolerate such intensive therapy. Our *a priori* protocol definition of feasibility was based on completion of the full 30 weeks of asparaginase, but our pediatric data suggest that completion of 26 or more of the planned 30 weeks of asparaginase was similarly efficacious.[28] We found that 72% of the patients who initiated the 30-week asparaginase course were able to receive 26 or more doses (87% of targeted therapy), similar to, although slightly lower than the proportion of pediatric patients. The incidence of major asparaginase-related toxicities, such as pancreatitis, and thrombosis was also similar to that reported in older children.[29]

**Table 5.** Toxicity summary in eligible patients–overall and by treatment phase

| | *Overall N (%)* | *Induction N (%)* | *CNS N (%)* | *Intensification N (%)* | *Continuation N (%)* |
|---|---|---|---|---|---|
| No. patients reporting | 92 | 92 | 67 | 62 | 48 |
| *CTC grade 3–5 toxicity* | | | | | |
| Neutrophils | 86 (93) | 82 (89) | 10 (15) | 52 (84) | 22 (46) |
| Platelets | 75 (82) | 72 (78) | 1 (1) | 17 (27) | 5 (10) |
| Febrile neutropenia | 30 (33) | 20 (22) | 0 (0) | 10 (16) | 3 (6) |
| Infection with grade 3/4 neutropenia[a] | 49 (53) | 41 (45) | 1 (1) | 11 (18) | 6 (13) |
| Infection—other | 7 (8) | 2 (2) | 1 (1) | 3 (5) | 2 (4) |
| Hepatic[a] | 57 (62) | 24 (26) | 5 (7) | 33 (53) | 21 (44) |
| Hyperglycemia | 41 (45) | 36 (39) | 1 (1) | 12 (19) | 5 (10) |
| Stomatitis | 10 (11) | 4 (4) | 1 (1) | 5 (8) | 0 (0) |
| CNS hemorrhage[a] | 1 (1) | 1 (1) | 0 (0) | 1 (2) | 0 (0) |
| Seizure | 4 (4) | 1 (1) | 0 (0) | 3 (5) | 1 (2) |
| Asparaginase-related toxicity | | | | | |
| Pancreatitis[a] | 10 (11) | 1 (1) | 0 (0) | 8 (13) | 2 (4) |
| Allergy/rash | 5 (5) | 1 (1) | 0 (0) | 4 (6) | 0 (0) |
| Thrombosis/embolism | 16 (17) | 1 (1) | 0 (0) | 14 (23) | 2 (4) |
| Bone fracture | 7 (8) | 0 (0) | 0 (0) | 3 (5) | 5 (10) |
| Avascular necrosis | 5 (5) | 0 (0) | 0 (0) | 2 (3) | 4 (8) |

Abbreviation: CNS, central nervous system. [a]There were five grade 5 events—one in each category shown and one leukoencephalopathy.

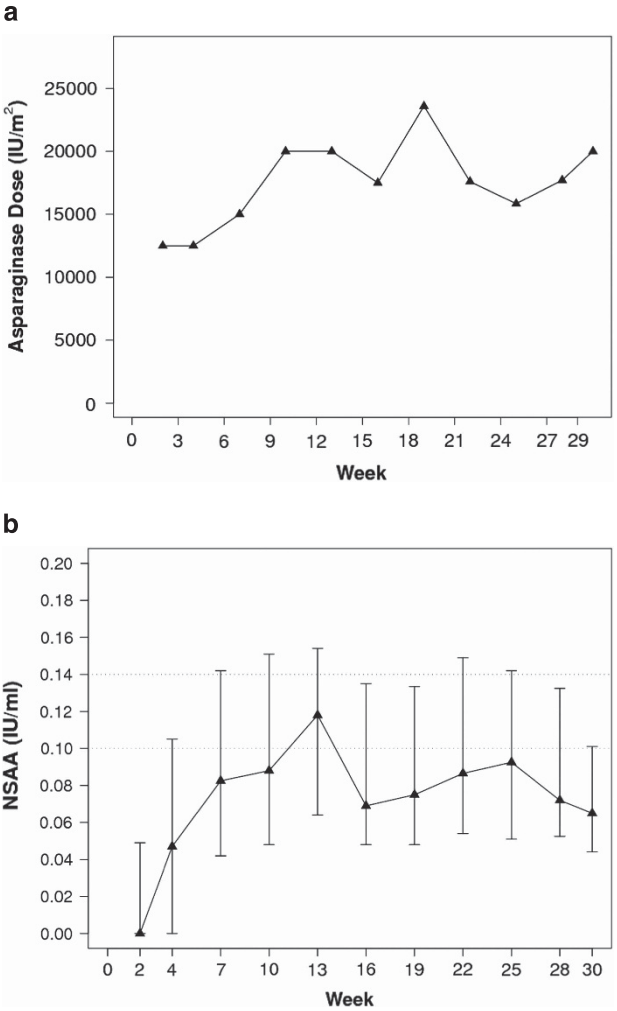


**Figure 3.** (**a** and **b**) Median asparaginase dose and nadir serim asparaginase activity during the 30-week Consolidation Course. Error bars extend to the 25th and 75th percentiles.

Routine sampling of CSF at time of diagnosis (and concomitant administration of intrathecal chemotherapy) is a pediatric standard of care, but not necessarily so in adult ALL. Our study prospectively determined the incidence and outcome of CNS status at the time of diagnosis. We found asymptomatic CSF involvement in five (5%) patients at the time of diagnosis. Such patients received more intensive CNS therapy (a higher dose of cranial radiation and additional doses of intrathecal therapy). Of these five patients, only one relapse involved the CNS and supports the routine use of both CNS-directed diagnosis and risk-stratified treatment of adults with ALL.

Most, but not all, adult ALL trials report the incidence of CR after 2 months of therapy.[6,30,31] In the current trial, we employed a strategy of removing patients from protocol therapy if they did not achieve a CR after 4 weeks of therapy, as several pediatric trials reported that absence of CR after 1 month, despite presence of CR after 2 months, was associated with poor long-term outcomes.[32–34] Although this strategy may have increased our rate of induction failure compared with studies, which allowed for two induction attempts, the CR rate on our protocol was still 85%. In our current second-generation pediatric-inspired therapy for adults with ALL, we allow two cycles of chemotherapy prior to deciding induction results (NCT00476190). We believe such an approach will lead to a higher CR rate and provide an opportunity for more young adults with ALL to potentially benefit from pediatric-type consolidation strategies.

In conclusion, the results of this study support that the use of a pediatric-inspired chemotherapy regimen is associated with excellent long-term results in children, and can be safely and efficaciously applied to adults aged 18–50 years.[5] The 69% 4-year DFS rate reported in the current study suggests that the administration of a pediatric-inspired regimen to adult patients is meritorious, resulting in a high rate of durable CRs. Further studies, such as the US intergroup trial CALGB 10403, will hopefully confirm these results with the goal that the natural history of ALL in adults under age 50 years will be favorably impacted.

## CONFLICT OF INTEREST

DJDA has received honoraria for speaking engagements from Sigma Tau. LBS has received honoraria for serving on advisory boards for Sigma Tau and EUSA. JGS has received research support from Sigma Tau Research Inc. and EUSA Pharma (US) Inc.

LAS has received honoraria for speaking engagements from Sigma Tau and Celgene. SES has received research support honoraria for speaking engagements from Sigma Tau, and consulted for Jazz Pharmaceuticals. The remaining authors declare no conflict of interest.

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## AUTHOR CONTRIBUTIONS

DJDA was the overall principal investigator, performed research, analyzed data and wrote the manuscript. KES was the principal statistician, analyzed data and edited the manuscript. SED was the principal statistician, analyzed data and edited the manuscript. LBS, SES and RMS assisted in the writing of the protocol, performed research and edited the manuscript. SC, JGS, PCA, KKB, MDS, ART, BL, KH-J, KK, SC, JHM, LS, MW, LAS and IG performed research and edited the manuscript.

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