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Asparaginase is an enzyme used in the treatment of acute lymphoblastic leukemia and lymphoblastic lymphoma in children. It has minimal bone marrow toxicity. Its major side effects are anaphylaxis, pancreatitis, diabetes, coagulation abnormalities, and thrombosis, especially intracranial. It is derived from 2 different sources: Escherichia coli and Erwinia chrysanthemi. Nonrandomized clinical studies have suggested a similar efficacy of these 2 types of asparaginases and a lower toxicity for Erwinia-asparaginase. The European Organisation for Research and Treatment of Cancer—Children’s Leukemia Group (EORTC-CLG) 58881 trial randomized 700 children with acute lymphoblastic leukemia or lymphoblastic lymphoma to either E coli– or Erwinia-asparaginase at the same dosage of 10 000 IU/m² twice weekly to compare toxicity and efficacy. Coagulation abnormalities were more frequent in the E coli–asparaginase than in the Erwinia-asparaginase arm of the study (30.2% versus 11.9%, P < .0001). The incidence of other toxicity was not significantly different. In the Erwinia-asparaginase arm, more patients failed to achieve complete remission (4.9% versus 2.0%, P = .038) and the relapse rate was higher, leading to shorter event-free survival (hazard ratio,1.59; 95% CI, 1.23-2.06; P = .0004). The estimate of event-free survival rate (SE) at 6 years was 59.8% (2.6%) versus 73.4% (2.4%). Overall survival rate at 6 years was also lower in the Erwinia-asparaginase arm at 75.1% (2.3%) versus 83.9% (2.0%), P = .002. With the dose scheduling used in this protocol, E coli–asparaginase induced more coagulation abnormalities but was superior to Erwinia-asparaginase for the treatment of childhood lymphoid malignancies. (Blood. 2002;99:2734-2739) © 2002 by The American Society of Hematology

Introduction

The enzyme L-asparaginase has been used in the treatment of lymphoblastic malignancies in children since 1970.1-6 Its antileukemic effect is believed to result from the depletion of circulating asparagine, which is not essential for normal cells but essential for most malignant lymphoblastic cells. Asparaginase has minimal bone marrow toxicity. Its main side effects are anaphylaxis, pancreatitis, diabetes, and coagulation abnormalities that may lead to intracranial thrombosis or hemorrhage.7-12 Clinically available asparaginase is derived from 2 sources: Escherichia coli and Erwinia chrysanthemi. In many countries, asparaginase from only one of these sources is available for front-line therapy of lymphoblastic malignancies. In 1990, when the study reported here was started, the 2 types of asparaginase were used as if they were one and the same drug. Doses and schedule, although variable from one protocol to another, were defined without consideration for the source of the enzyme. One clinical study using a historical comparison had in fact suggested that Erwinia-asparaginase was as effective as E coli–asparaginase but was less toxic.11 To get a clearer view on the relative efficacy and toxicities of the 2 drugs, we conducted the first randomized trial to compare them in front-line chemotherapy in children with newly diagnosed acute lymphoblastic leukemia (ALL) and lymphoblastic non-Hodgkin lymphoma.

Patients and methods

Patients

Patients were enrolled in 28 pediatric centers in Belgium, France, and Portugal in trial 58881 of the European Organisation for Research and Treatment of Cancer—Children’s Leukemia Group (EORTC-CLG).13,14 To be eligible for the trial, patients less than 18 years of age had to be...
diagnosed with ALL according to French-American-British L1 or L2 cytology, morphology, or lymphoblastic non-Hodgkin lymphoma. Patients previously treated with corticosteroids for more than 7 days were excluded.

Patients were considered to have central nervous system (CNS) involvement if they had cranial nerve palsy or at least 5 leukocytes/μL cerebrospinal fluid with leukemic cells seen on cytocentrifuged preparations. Immunophenotype was determined using standard techniques, and positivity for each marker was defined as more than 20% of leukemic cells expressing that marker. Chromosome analysis used standard techniques. Bone marrow smears, immunophenotypes, and cytogenetics were reviewed centrally.

### Treatment

Patients were randomized to Erwinia-asparaginase (Erwinia, Iepsen, Maidenhead, United Kingdom) or E coli–asparaginase (Paronal, Medac, Hamburg, Germany for the Belgian centers, or Kidrolase, Bellon, Montrouge, France for the French and Portuguese centers, both produced by Kyowa Hakko, Tokyo, Japan). Physicians had to switch to the other asparaginase in case of allergy grade 1 or higher. In case of pancreatitis or thrombosis, asparaginase was eliminated from the treatment. Informed consent was required before entry, in accordance with the Helsinki protocol. The trial also randomized patients to receive additional monthly intravenous mercaptopurine during maintenance therapy, and high-risk patients (see below) to receive high-dose cytarabine during interval therapy.

Protocol design was similar to that of the BFM-90 protocol. Patients were stratified into low- and high-risk categories according to their risk factor calculated as a function of blood blast count, hepatomegaly, and positivity for each marker was defined as more than 20% of leukemic cells expressing that marker. Chromosome analysis used standard techniques. Bone marrow smears, immunophenotypes, and cytogenetics were reviewed centrally.

#### Induction: protocol IA

- **Prednisolone (PO)**: 60 mg/m², 1-28
- **Vincristine (IV)**: 1.5 mg/m² (max. 2.5 mg), 8, 15, 22, 29
- **Daunorubicin (IV)**: 30 mg/m², 8, 15, 22, 29
- **Methotrexate (intrathecal)**: 12 mg†, 1, 8, 22, 38, 52
- **According to randomization**
  - **E coli-asparaginase (IV)** or **Erwinia-asparaginase (IV)**: 10 000 IU/m², 12, 15, 18, 22, 25, 29, 32, 35

#### Consolidation: protocol IB

- **Cyclophosphamide (IV)**: 1 000 mg/m², 36, 63
- **Cytarabine (IV)**: 75 mg/m², 38-41, 45-48, 52-55, 59-62
- **6-Mercaptopurine (PO)**: 60 mg/m², 36-63

#### Interval therapy

- **6-Mercaptopurine (PO)**: 25 mg/m², 1-56
- **Methotrexate (24 h IV infusion with leucovorin rescue)**: 5 000 mg/m², 8, 22, 36, 50
- **Methotrexate (intrathecal)**: 12 mg†, 9, 23, 37, 51

#### Maintenance therapy was a combination of daily oral mercaptopurine adjusted to maintain leukucytosis between 2000 and 3000/μL and methotrexate 20 mg/m² once a week. According to randomization, some patients received intravenous mercaptopurine 1000 mg/m² every 4 weeks.

*Adjustments were made for clinical condition and marrow recovery.
†Doses were adjusted for children under age 3 years.

#### Statistical methods

Randomization was done centrally (EORTC Data Center, Brussels) and was stratified according to center, disease (leukemia versus lymphoma), risk
factor (< 0.8, 0.8-1.19, ≥ 1.2), and immunophenotype (B versus T lineage) for leukemia patients, and by Murphy stage (stage I-II versus III-IV) for lymphoma patients. Randomization was not stratified by the presence of t(9;22). Subsequent randomizations were stratified according to treatment arm and initial risk factor or Murphy stage.

The primary end point was event-free survival calculated from the date of CR to the date of first relapse or death. For patients who failed to reach CR by the end of protocol I, the failure was considered as an event at time 0. The secondary end points were the rate of CR after induction and consolidation, disease-free survival (time from CR until relapse or death), and survival (time from randomization until death, whatever the cause). Actuarial curves were computed using the Kaplan-Meier technique, and the SEs of the estimates were obtained using the Greenwood formula. To summarize the overall treatment difference, the hazard ratio for the daily risk of event in the Cox proportional hazards model. This model was also used to adjust one in E coli–69% (Table 3). Twenty-nine percent of patients in each arm received the planned asparaginase treatment: 66% versus 29% (Table 3). 29% of patients died before reaching CR. Grade 3 or 4 allergy had a low proportion IA was low and comparable in the 2 arms. Three incidence of other grade 3 or 4 toxic effects observed during incidence of other grade 3 or 4 toxic effects observed during induction period.

The Fisher exact 2-tailed test was used (StatExact) to compare the rates of complete remission after induction and consolidation. The odds ratio estimates and their exact 95% CIs were used to express the results. The same methods were used for treatment comparisons of the incidence of grade 3 to 4 toxicity during the induction period.

Table 2. Patient characteristics by arm

<table>
<thead>
<tr>
<th></th>
<th>E coli-asparaginase</th>
<th>Erwinia-asparaginase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%) of patients</td>
<td>no. (%) of patients</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>206 (58)</td>
<td>202 (58)</td>
</tr>
<tr>
<td>Female</td>
<td>148 (42)</td>
<td>144 (42)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger than 10</td>
<td>10 (3)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>10 through 17</td>
<td>282 (80)</td>
<td>275 (80)</td>
</tr>
<tr>
<td>18 through 17</td>
<td>62 (17)</td>
<td>60 (17)</td>
</tr>
<tr>
<td>ALL</td>
<td>334 (94)</td>
<td>319 (92)</td>
</tr>
<tr>
<td>WBC count (10^9/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 25</td>
<td>215 (64)</td>
<td>201 (63)</td>
</tr>
<tr>
<td>25 to 100</td>
<td>66 (20)</td>
<td>69 (22)</td>
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<tr>
<td>At least 100</td>
<td>53 (16)</td>
<td>49 (15)</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>17 (5)</td>
<td>15 (5)</td>
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<tr>
<td>Immuneophenotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Β lineage</td>
<td>289 (87)</td>
<td>267 (84)</td>
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<tr>
<td>T lineage</td>
<td>45 (13)</td>
<td>52 (16)</td>
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<tr>
<td>Karyotype</td>
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<td>Successful examinations</td>
<td>261 (78)</td>
<td>235 (74)</td>
</tr>
<tr>
<td>Hyperdiploidy</td>
<td>70 (27)</td>
<td>52 (22)</td>
</tr>
<tr>
<td>t(9;22)</td>
<td>3 [1]*</td>
<td>11 [5]*</td>
</tr>
<tr>
<td>t(4;11)</td>
<td>5 [2]*</td>
<td>6 [3]*</td>
</tr>
<tr>
<td>Near-haploidy</td>
<td>1 [&lt; 1]*</td>
<td>1 [&lt; 1]*</td>
</tr>
<tr>
<td>Normal and others</td>
<td>182 [70]*</td>
<td>165 [70]*</td>
</tr>
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<td>Response to prephase: blasts (/μL) on D8</td>
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<td></td>
</tr>
<tr>
<td>Less than 1000</td>
<td>292 (87)</td>
<td>278 (87)</td>
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<tr>
<td>1000</td>
<td>42 (13)</td>
<td>41 (13)</td>
</tr>
<tr>
<td>Initial very-high risk features</td>
<td>47 (14)</td>
<td>54 (17)</td>
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<td>NCI risk groups</td>
<td></td>
<td></td>
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<tr>
<td>NCI standard risk</td>
<td>212 (63)</td>
<td>203 (64)</td>
</tr>
<tr>
<td>NCI high risk</td>
<td>122 (36)</td>
<td>116 (36)</td>
</tr>
<tr>
<td>Lymphoblastic lymphoma</td>
<td>20 (6)</td>
<td>27 (8)</td>
</tr>
<tr>
<td>Murphy stage III or IV</td>
<td>20 (100)</td>
<td>23 (85)</td>
</tr>
<tr>
<td>T lineage</td>
<td>19 (95)</td>
<td>22 (81)</td>
</tr>
</tbody>
</table>

*Percentages were computed on successful cytogenetic examinations. NCI risk groups were as defined by the consensus conference.

Results

Patient characteristics

Between November 1990 and October 1993, 702 patients were enrolled. Seven hundred were considered eligible for entry into the study, 354 in the E coli–asparaginase arm and 346 in the Erwinia-asparaginase arm. Two patients with Burkitt lymphoma, one in each arm, initially erroneously diagnosed and subsequently treated with another protocol were excluded from the analysis. Enrollment was stopped early because the treatment difference in terms of event-free survival yielded a P < .001.

Patient characteristics according to treatment arms are shown in Table 2. A total of 653 patients (93%) had ALL. The 2 arms were comparable for usual prognostic factors, except for a slight imbalance in the incidence of t(9;22). Forty-seven patients with t(9;22) were more often observed in the Erwinia-asparaginase arm: odds ratio, 3.23; P = .0004 (Table 4). For the whole group, the estimated odds ratio for remission failure was 2.56, P = .038 (Table 5).

Efficacy

After induction (protocol IA), 335 leukemia or lymphoma patients (94.5%) reached CR in the E coli–asparaginase arm and 315 (91.0%) in the Erwinia-asparaginase arm (Table 5). Four leukemia patients (1.2%) never achieved CR at the completion of protocol I in the E coli–asparaginase arm and 12 (3.8%) in the Erwinia-asparaginase arm: odds ratio, 3.23; P = .042 (Table 6). Three patients with lymphoblastic lymphoma in the E coli–asparaginase arm and 5 in the Erwinia-asparaginase arm did not achieve CR. For the whole group, the estimated odds ratio for remission failure was 2.56, P = .0004; Figure IA). Its rate at 6 years (SE) was 59.8% (2.6%) versus 73.4%
The hazard ratio for death was 1.66 (95% CI, 1.20-2.23). The survival. Among the patients randomized for asparaginase, 638 had no effect on disease-free survival, and it did not interact with sex, which appeared to be independent strong prognostic factors. When restricted to leukemia patients with a successful cytogenetic examination, the comparison adjusted for the presence of t(9;22) yielded similar results.

The effects of the other 2 randomizations on the difference between outcome for the 2 types of asparaginase were as follows. First, the addition of high-dose cytarabine during interval therapy yielded similar results. When restricted to leukemia patients with a successful cytogenetic examination, the comparison adjusted for the presence of t(9;22) yielded similar results.

The effects of the other 2 randomizations on the difference between outcome for the 2 types of asparaginase were as follows. First, the addition of high-dose cytarabine during interval therapy had no effect on disease-free survival, and it did not interact with the difference in outcome between the asparaginase arms. Second, patients randomized to receive additional monthly intravenous mercaptopurine during maintenance had a shorter disease-free survival. Among the patients randomized for asparaginase, 638 remained in CR at the beginning of maintenance therapy. A total of 224 patients were randomized to receive additional monthly intravenous mercaptopurine, 229 were randomized not to receive it, and 185 were not randomized. In the 3 subgroups the hazard ratio for death or relapse according to the type of asparaginase was calculated. The three 95% CIs for these hazard ratios were, respectively, 1.32 to 3.37, 0.65 to 1.92, and 1.02 to 2.98. They all contained the overall estimate of 1.63 calculated in the 638 patients, so there is no proof so far that addition of monthly mercaptopurine interacts with the difference in outcome between the asparaginase arms.

Estimated overall survival rate at 6 years was 83.9% (2.0%) in the E coli–asparaginase arm, and the estimated hazard ratio for remission failure, relapse, or death was 1.59 (95% CI, 1.20-2.23). For leukemic patients the estimated hazard ratio for remission failure, relapse, or death was 1.60 (95% CI, 1.22-2.09) after adjustment for NCI risk group, very-high-risk features, and sex, which appeared to be independent strong prognostic factors. When restricted to leukemia patients with a successful cytogenetic examination, the comparison adjusted for the presence of t(9;22) yielded similar results.

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data. The serum half-life of *Erwinia*-asparaginase activity is significantly shorter, 0.65 day versus 1.24 days for *E coli*-asparaginase.\(^{26}\) Asparagine depletion during reinduction in the BFM-90 trial was achieved in 26% of patients receiving *Erwinia*-asparaginase and in 60% to 90% of the patients receiving *E coli*-asparaginase.\(^{27}\) Time to recovery of serum asparagine level after administration was 4 days for *Erwinia*-asparaginase versus 11 days for *E coli*-asparaginase.\(^{27}\)

In all treatment protocols so far, the dosing schedule of asparaginase has been defined regardless of the type of asparaginase used,\(^{15}\) although the regimens have varied considerably from one protocol to another, from 6000 IU daily to 25 000 IU once a week. IU is defined by a chemical in vitro activity and not by a biologic in vivo effect. A recent study suggests that increasing the dose and decreasing the time interval between *Erwinia*-asparaginase administrations results in pharmacodynamics similar to that of lower and less frequent doses of *E coli*-asparaginase.\(^{28}\) However, it has not been demonstrated that this strategy leads to the same clinical outcome, and it may be more toxic. Whether other as yet unknown qualitative differences between the 2 sources of asparaginases could be responsible for their unequal efficacy cannot be demonstrated by these studies and remains undecided.

Thus, *E coli*-asparaginase can be recommended for first-line therapy, reserving *Erwinia*-asparaginase for allergic patients, because (1) most patients allergic to the former are not immediately allergic to the latter,\(^{10,12}\) (2) our results were analyzed according to the intention-to-treat principle and 29% of patients in the *E coli*-asparaginase arm were actually switched to *Erwinia*-asparaginase because of allergy, and (3) it has been demonstrated that this switch does not modify clinical outcome.\(^{29,30}\) The effect of *Erwinia*-asparaginase should be monitored by measuring asparaginase activity or perhaps more simply asparagine depletion.\(^{28,31}\) Asparaginase linked to polyethylene glycol (PEG-asparaginase) is now available. Its immunogenicity is lower and its serum half-life longer. Pharmacokinetic studies suggest that it may be substituted for *E coli*-asparaginase, but clinical trials are needed to study the impact of substitution on clinical outcome.\(^{5,32,33}\)

In conclusion, our trial demonstrates the superiority of *E coli*-asparaginase compared to *Erwinia*-asparaginase in lymphoid malignancies of childhood, when used at the dose of 10 000 IU/m\(^2\) twice a week. Our findings underscore the importance of asparaginase in induction therapy of childhood lymphoid malignancies. In modern multiagent therapies, minor differences in treatment regimens may lead to substantial differences in outcome, suggesting the need for caution when modifying current therapeutic protocols.

**Table 6. ALL patients: outcome by arm**

<table>
<thead>
<tr>
<th></th>
<th><em>E coli</em>-asparaginase (N = 334 (100%))</th>
<th><em>Erwinia</em>-asparaginase (N = 319 (100%))</th>
<th>Odds ratio (95% CI) (P*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR not reached after induction</td>
<td>12 (3.6)</td>
<td>21 (6.6)</td>
<td>1.89 (0.87, 4.29)</td>
</tr>
<tr>
<td>Remission failure</td>
<td>4 (1.2)</td>
<td>12 (3.8)</td>
<td>3.23 (0.96, 13.84)</td>
</tr>
<tr>
<td>CR reached</td>
<td>330 (98.8)</td>
<td>307 (96.2)</td>
<td>0.87 (0.87, 4.29)</td>
</tr>
<tr>
<td>Continuous CR</td>
<td>242 (73)</td>
<td>190 (62)</td>
<td>1.16 (0.77, 1.74)</td>
</tr>
<tr>
<td>Death in CR</td>
<td>11 [3]</td>
<td>7 [2]</td>
<td>0.87 (0.50, 1.53)</td>
</tr>
<tr>
<td>Relapses</td>
<td>77 [23]</td>
<td>110 [36]</td>
<td>1.43 (0.87, 2.37)</td>
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<tr>
<td>Bone marrow</td>
<td>45 [14]</td>
<td>64 [21]</td>
<td>1.46 (0.75, 2.86)</td>
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<tr>
<td>CNS (isolated)</td>
<td>12 [4]</td>
<td>18 [6]</td>
<td>1.50 (0.75, 2.96)</td>
</tr>
<tr>
<td>CNS (combined)</td>
<td>13 [4]</td>
<td>15 [5]</td>
<td>1.00 (0.57, 1.74)</td>
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<tr>
<td>Other isolated</td>
<td>3 [1]</td>
<td>5 [2]</td>
<td>1.00 (0.57, 1.74)</td>
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<tr>
<td>Other combinations</td>
<td>4 [1]</td>
<td>8 [3]</td>
<td>1.00 (0.57, 1.74)</td>
</tr>
</tbody>
</table>

Remission failure means patient never achieved CR at the end of induction-consolidation. Parentheses for columns 2 and 3: percentages were computed on all patients included. Brackets for columns 2 and 3: percentages were computed on patients having reached CR.

*Fisher exact test.

**Acknowledgment**

A complete list of the participating institutions and investigators appears in the Appendix at the end of this article.
References


Appendix

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Comparison of *Escherichia coli*–asparaginase with *Erwinia*-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organisation for Research and Treatment of Cancer—Children's Leukemia Group phase 3 trial

Michel Duval, Stefan Suciu, Alina Ferster, Xavier Rialland, Brigitte Nelken, Patrick Lutz, Yves Benoit, Alain Robert, Anne-Marie Manel, Etienne Vilmer, Jacques Otten and Noël Philippe

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