
Michel Duval, Stefan Suciu, Alina Ferster, Xavier Rialland, Brigitte Neiken, Patrick Lutz, Yves Benoit, Alain Robert, Anne-Marie Manel, Etienne Vilmer, Jacques Otten, and Noël Philippe, for the European Organisation for Research and Treatment of Cancer—Children’s Leukemia Group

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) S8881 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. 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.

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. 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 S8881 of the European Organisation for Research and Treatment of Cancer—Children’s Leukemia Group (EORTC-CLG). 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 cytomorphology 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 cytocentrifugation 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, Ipsen, 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 splenomegaly. A very-high-risk group was defined by the presence of at least one of the following criteria regardless of risk factor: more than 1000 blasts/μL in the blood after 7 days of prednisolone and intrathecal blasts/L in the blood.

Randomization was done centrally (EORTC Data Center, Brussels) and was stratified according to center, disease (leukemia versus lymphoma), risk factor, and asparaginase (V ANDA block). V ANDA was followed by interval therapy with only 3 administrations of high-dose methotrexate, combined with high-dose cytarabine during interval therapy.

Induction: protocol IA
- Prednisolone (PO) 60 mg/m², Days 1-21
- Vincristine (IV) 1.5 mg/m² (max. 2.5 mg), Days 1-21
- Doxorubicin (IV) 30 mg/m², Days 1-21
- Methotrexate (intrathecal) 12 mg†, Days 1-21

According to randomization
- E coli-asparaginase (IV) or Erwinia-asparaginase (IV) 10 000 IU/m², Days 1, 15, 18, 22, 25, 29, 32, 35
- E coli-asparaginase (IV) 10 000 IU/m², Days 1, 15, 18, 22, 25, 29, 32, 35

Consolidation: protocol IB
- Cyclophosphamide (IV) 1 000 mg/m², Days 36, 59-62
- Cytarabine (IV) 75 mg/m², Days 38-41, 45-48, 52-55, 59-62
- Methotrexate (intrathecal) 60 mg/m², Days 36-63

Interval therapy
- Methotrexate (intrathecal) 12 mg†, Days 9, 23, 37, 51
- Cytarabine (IV) 1 000 mg/m², Days 9, 10, 23, 24, 37, 38, 51, 52

Reinduction: protocol II
- Dexamethasone (PO) 10 mg/m², Days 1-21
- Vincristine (IV) 1.5 mg/m² (max. 2.5 mg), Days 1-21
- Doxorubicin (IV) 30 mg/m², Days 1-21
- Methotrexate (intrathecal) 12 mg†, Days 1-21
- Cyclophosphamide (IV) 1 000 mg/m², Days 36
- Cytarabine (IV) 75 mg/m², Days 38-41, 45-48
- Methotrexate (intrathecal) 12 mg†, Days 38-41, 45-48

According to randomization
- E coli-asparaginase (IV) or Erwinia-asparaginase (IV) 10 000 IU/m², Days 8, 11, 15, 18
- Erwinia-asparaginase (IV) 10 000 IU/m², Days 8, 11, 15, 18

Definitions

Complete remission was defined as cellular bone marrow with fewer than 5% leukemic cells and no evidence of leukemia or lymphoma at any other site. Remission failure was defined as failure to reach CR at the completion of protocol I. Relapse was defined as the reappearance of more than 25% leukemic cells in the bone marrow or of any leukemic cell at another site. Coagulation abnormalities were defined as any clinical or biologic abnormality requiring a modification of chemotherapy or supportive care. Investigations were advised to consider such a modification for hypofibrinogenemia below 0.5 g/L. Allergy, neurotoxicity, liver toxicity, and infection were graded according to World Health Organization (WHO) criteria. To ensure comparability with other studies, National Cancer Institute (NCI) risk groups for leukemia patients were used according to consensus conference recommendations: NCI standard-risk group consisted of patients aged 1 to 9 years at diagnosis with an initial white blood cell (WBC) count less than 50 × 10⁹/L. Other patients were considered as having NCI high-risk leukemia.

Statistical methods

Randomization was done centrally (EORTC Data Center, Brussels) and was stratified according to center, disease (leukemia versus lymphoma), risk factors. Maintenance therapy was a combination of daily oral mercaptopurine adjusted to maintain leukocytes 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.
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 Erwinia-asparaginase arm versus the one in E coli–asparaginase arm and its 95% CI was estimated using the Cox proportional hazards model. This model was also used to adjust the treatment difference for several prognostic factors. A total of 750 patients were initially planned to detect a significant (α = 5%) difference of 10% in event-free survival rate at 5 years (from 65% to 75%) with a statistical power of 85%. The Peto stopping rule was adopted: a comparison yielding a log-rank \( P < .001 \) was considered sufficient to stop enrolment. All analyses were performed according to the intention-to-treat principle.

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.

## 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 lymphoblastic lymphoma were randomized and the 2 arms were also comparable at presentation.

### Protocol compliance and toxicity

During protocol IA, 81% of the patients in the E coli–asparaginase and 88% of the patients in the Erwinia-asparaginase arm received 8 doses of the asparaginase they had been randomized to receive (Table 3). Coagulation abnormalities were more often observed in the E coli–asparaginase arm: 30.2% versus 11.8%; odds ratio, 3.20; \( P < .0001 \) (Table 4). The incidence of other grade 3 or 4 toxic effects observed during protocol IA was low and comparable in the 2 arms. Three patients died before reaching CR. Grade 3 or 4 allergy had a low incidence in the 2 groups: 2.5% versus 2.6%.

During protocol IIA a similar proportion of patients in the 2 arms received the planned asparaginase treatment: 66% versus 69% (Table 3). Twenty-nine percent of patients in each arm received at least one dose of the asparaginase they had not been randomized to. Such a proportion did not allow comparison of toxicity in protocol IIA.

### 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, \( P = .038 \) (Table 5).

Median follow-up was 6.9 years (range, 4.8-9.0 years). Relapse rate was approximately 1.5 times higher in the Erwinia-asparaginase arm, regardless of the site, in leukemia (Table 6) and in lymphoma patients (2 versus 5 relapses). The rate of death in CR was similar: 11 patients (3.2%) versus 8 (2.4%). Event-free survival was shorter in the Erwinia-asparaginase arm (\( P = .0004 \); Figure 1A). 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 patients randomized for additional monthly intravenous mercaptopurine during maintenance had a shorter disease-free outcome than patients randomized to receive the other asparaginase. Second, the addition of high-dose cytarabine during interval therapy 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, but 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, 1.22-2.09) 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.

The effects of the other 2 randomizations on the difference between outcome for the 2 types of asparaginase were as follows. 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, but 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 versus 75.1% (2.3%) in the Erwinia-asparaginase arm (P = .002; Figure 1B). Estimated hazard ratio for death was 1.66 (95% CI, 1.20-2.23). The overall toxicity of asparaginase was low. The most frequent side effects were coagulation abnormalities, which were more frequent in the E coli–asparaginase arm, as previously reported. However, their frequency (2.5% grade 3 or 4 neurotoxicity, 1.7% convulsions) remained moderate compared to the rate of relapse and death.

In accordance with previous reports, we found no difference between the 2 types of asparaginases in the rates of allergy, liver toxicity, or insulin-requiring diabetes. Frequency of pancreatitis and severe infections was similar, whereas other reports concerning these side effects are conflicting. Three controlled studies have randomized patients to receive additional asparaginase during postremission therapy in childhood lymphoid malignancies. In 2 of them, additional E coli–asparaginase improved outcome for patients with ALL and advanced stage lymphoblastic lymphoma. The largest study, which randomized 1085 patients, administered either E coli– or Erwinia-asparaginase at equal dosage. It failed to show any impact on outcome of additional asparaginase during postremission therapy. Although our study closed in 1993, it is still, to our knowledge, the only comparative study of the 2 types of asparaginases during the remission-induction phase in such a large number of children, and certainly the only large study in which reliable 6-year survival figures are available. Its results suggest that asparaginase in the remission-induction phase may still have an impact on final outcome in this era of multiagent therapies.

This difference in efficacy between asparaginases was not expected when the trial was begun, but is in keeping with recent comparison yielded a similar result when adjusted for NCI risk group and sex, and, for leukemia patients, for very-high-risk features or for t(9;22) in those with a successful cytogenetic examination.

**Discussion**

Seven hundred children with ALL or lymphoblastic lymphoma were randomized to receive either E coli– or Erwinia-asparaginase. Median follow-up was 6.9 years. Two main conclusions can be drawn from the results of this randomized trial. First, E coli–asparaginase is more toxic because it induces more coagulation abnormalities. Second, clinical efficacy of E coli–asparaginase is superior to that of Erwinia-asparaginase at the dosage of 10 000 IU/m² twice weekly. The type of asparaginase not only affects early response to treatment but also the risk of relapse, event-free survival, and overall survival.

Overall toxicity of asparaginase was low. The most frequent side effects were coagulation abnormalities, which were more frequent in the E coli– asparaginase arm, as previously reported. Our results confirm a trend toward more neurotoxicity and convulsions with E coli– asparaginase. However, their frequency (2.5% grade 3 or 4 neurotoxicity, 1.7% convulsions) remained moderate compared to the rate of relapse and death.

In accordance with previous reports, we found no difference between the 2 types of asparaginases in the rates of allergy, liver toxicity, or insulin-requiring diabetes. Frequency of pancreatitis and severe infections was similar, whereas other reports concerning these side effects are conflicting. Three controlled studies have randomized patients to receive additional asparaginase during postremission therapy in childhood lymphoid malignancies. In 2 of them, additional E coli–asparaginase improved outcome for patients with ALL and advanced stage lymphoblastic lymphoma. The largest study, which randomized 1085 patients, administered either E coli– or Erwinia-asparaginase at equal dosage. It failed to show any impact on outcome of additional asparaginase during postremission therapy. Although our study closed in 1993, it is still, to our knowledge, the only comparative study of the 2 types of asparaginases during the remission-induction phase in such a large number of children, and certainly the only large study in which reliable 6-year survival figures are available. Its results suggest that asparaginase in the remission-induction phase may still have an impact on final outcome in this era of multiagent therapies.

This difference in efficacy between asparaginases was not expected when the trial was begun, but is in keeping with recent

---

### Table 3. Evaluation of compliance with allocated asparaginase

<table>
<thead>
<tr>
<th></th>
<th>E coli-asparaginase no. (%) of patients</th>
<th>Erwinia-asparaginase no. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>During IA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients received all planned doses</td>
<td>354 (100)</td>
<td>346 (100)</td>
</tr>
<tr>
<td>Patients switched to other asparaginase*</td>
<td>287 (81)</td>
<td>303 (88)</td>
</tr>
<tr>
<td>During IIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients received all planned doses</td>
<td>39 (11)</td>
<td>24 (7)</td>
</tr>
<tr>
<td>Patients switched to other asparaginase*</td>
<td>300 (100)</td>
<td>277 (100)</td>
</tr>
</tbody>
</table>

* Switch denotes a patient who received at least one injection of asparaginase he was not randomized to receive. Some patients did not receive all planned doses but were not switched to the other asparaginase.

### Table 4. Toxicity during induction (protocol IA)

<table>
<thead>
<tr>
<th></th>
<th>E coli-asparaginase no. (%) of patients</th>
<th>Erwinia-asparaginase no. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy (WHO 3-4)</td>
<td>9 (2.5)</td>
<td>9 (2.6)</td>
</tr>
<tr>
<td>Coagulation abnormalities</td>
<td>107 (30.2)</td>
<td>41 (11.8)</td>
</tr>
<tr>
<td>Neurotoxicity (WHO 3-4)</td>
<td>9 (2.5)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Convulsions</td>
<td>6 (1.7)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (0.3)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Diabetes requiring insulin</td>
<td>5 (1.4)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Liver toxicity (WHO 3-4)</td>
<td>16 (4.5)</td>
<td>13 (3.8)</td>
</tr>
<tr>
<td>Infection (WHO 3-4)</td>
<td>18 (5.1)</td>
<td>16 (4.6)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
</tr>
</tbody>
</table>

### Table 5. ALL and lymphoblastic lymphoma patients: short-term outcome by arm

<table>
<thead>
<tr>
<th></th>
<th>E coli-asparaginase N = 354 (100%)</th>
<th>Erwinia-asparaginase N = 346 (100%)</th>
<th>Odds ratio (95% CI) (P)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR not reached</td>
<td>19 (5.4)</td>
<td>31 (9.0)</td>
<td>1.74 (0.93, 3.32) (.078)</td>
</tr>
<tr>
<td>Remission failure</td>
<td>7 (2.0)</td>
<td>17 (4.9)</td>
<td>2.56 (0.99, 7.39) (.038)</td>
</tr>
</tbody>
</table>

Remission failure means patient never achieved CR at the end of induction-consolidation.

* Fisher exact test.
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,20,12 (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/m² 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.

Acknowledgment

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


Appendix

Participating institutions and investigators of EORTC-CLG: EORTC Data Center, Gabriel Solbu, Stefan Suciu, Christine Waterkeyn; HU des Enfants, Bruxelles, Dr Azzi, Dr Ferster, Dr Sariban; CHR Grenoble, Dr Bachelot, Dr Plantaz; AZK VUB Brussels, Dr Maurus, Dr Otten; Hôpital Americanic Reims, Dr Behar, Dr Munzer; UZ Gent, Dr Benoit, Dr Dhoooge, Dr Laureys; Hospital Debrousse Lyon, Dr Bertrand, Dr Manel, Dr Philippe, Dr Souillet; CHU Angers, Dr Blanchet, Dr Daulet, Dr Gamelin, Dr Le Moine, Dr Pein, Dr Pellier, Dr Kialland; CHU Strasbourg, Dr Babin-Boiletot, Dr Falkendott, Dr Lutz; CHU Caen, Dr Bourdat, Dr Mirkles; UZ Gasthuisberg Louvain, Dr Brock, Dr Uyttebroeck; CHR Citadelle Liège, Dr Chantaine, Dr Dresse, Dr Hoyoux; Hôpial Edouard-Herriot Lyon, Dr Charrin, Dr Magaud; CHU Toulouse, Dr Dastugue, Dr Robert, Dr Rubie; Hôpial Saint Antoine Lille, Dr Demory; Fondation Lenvial Nence, Dr Deville, Dr Soler; Institut Curie, Paris, Dr Fagnou, Dr Michon, Dr Paquemien; CHU Lille, Dr Fournier, Dr Mazine, Dr Nelken; CH St-Joseph-l’Ésparre, Montigne, Dr Francette, Dr Hainaut, Dr Philippet; Hôpital Robert-Debré, Paris, Dr Duval, Dr Fenneteau, Dr Grandchamp, Dr Lescoe, Dr Rohrlich, Dr Vilmer; AK Antwerpen, Dr Gyselinck; CHU Nantes, Dr Harousseau, Dr Bitar, Dr Paulus; Clinique de l’Esparre, Montigne, Dr Philippet; CHU Reims, Dr Pignon; CHU Besançon, Dr Plouvier; Centre Lacassagne, Nice, Dr Thys.

From www.bloodjournal.org by guest on April 13, 2017. For personal use only.
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

Updated information and services can be found at: [http://www.bloodjournal.org/content/99/8/2734.full.html](http://www.bloodjournal.org/content/99/8/2734.full.html)

Articles on similar topics can be found in the following Blood collections

- Clinical Trials and Observations (4511 articles)
- Neoplasia (4182 articles)

Information about reproducing this article in parts or in its entirety may be found online at: [http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests](http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests)

Information about ordering reprints may be found online at: [http://www.bloodjournal.org/site/misc/rights.xhtml#reprints](http://www.bloodjournal.org/site/misc/rights.xhtml#reprints)

Information about subscriptions and ASH membership may be found online at: [http://www.bloodjournal.org/site/subscriptions/index.xhtml](http://www.bloodjournal.org/site/subscriptions/index.xhtml)