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Intermittent Versus Continuous PEG-Asparaginase to Reduce Asparaginase-Associated Toxicities: A NOPHO ALL2008 Randomized Study

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abstract

PURPOSE Asparaginase is an essential drug in childhood acute lymphoblastic leukemia (ALL) therapy and is frequently given for months to obtain continuous asparagine depletion. We randomly assigned patients to continuous versus intermittent pegylated-asparaginase (PEG-asp) treatment, hypothesizing there would be decreased toxicity with unchanged efficacy.

METHODS Children (median age, 4.2 years) treated for non–high-risk ALL according to the Nordic Society for Pediatric Hematology and Oncology ALL2008 protocol received five intramuscular PEG-asp injections (1,000 IU/m^2) every two weeks and were then randomly assigned to additional three doses (6-week intervals [experimental arm], n = 309) versus 10 doses (2-week intervals [standard arm], n = 316). The primary end point was noninferior (6% margin) disease-free survival. Toxicity reduction was a secondary end point. Occurrence of asparaginase-associated hypersensitivity, pancreatitis, osteonecrosis, and thromboembolism were prospectively registered.

RESULTS After a median follow-up of 4.1 years, the 5-year disease-free survival was 92.2% (95% CI, 88.6 to 95.8) and 90.8% (95% CI, 87.0 to 94.6) in the experimental and standard arms, respectively. The 3-year cumulative incidence of any first asparaginase-associated toxicity (hypersensitivity [n = 13]; osteonecrosis [n = 29]; pancreatitis [n = 24]; thromboembolism [n = 17]) was 9.3% in the experimental arm and 18.1% in the standard arm (P = .001). Asparaginase-associated toxicity reduction was confirmed in sex- and risk-group–adjusted Cox regression analysis stratified by age (≥ 10 and < 10 years; hazard ratio, 0.48; P = .001). The experimental arm had the lowest incidences of all four toxicities, reaching significance for pancreatitis (6-month risk, 5.8% *v* 1.3%; P = .002).

CONCLUSION The excellent cure rates and reduced toxicity risk support the use of intermittent PEG-asp therapy after the first 10 weeks in future childhood ALL trials that apply prolonged PEG-asp therapy.

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ASSOCIATED CONTENT

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Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

For decades, intensification of chemotherapy to improve cure rates of childhood acute lymphoblastic leukemia (ALL) has been a dominating strategy, but it also increases the toxicity burden and treatment costs. The overall survival rate of ALL now exceeds 90% in the best contemporary programs,[1-7] and the balance between survival and toxicities has become critical.[8]

Asparagine is an essential amino acid for lymphoblasts. Since the 1970s, the enzyme asparaginase has played a key role in the treatment of ALL.[9,10] Furthermore, to fully exploit its potential, extended asparaginase treatment up to 30 weeks has been incorporated in many ALL protocols.[11-14] However, asparaginase also interferes with protein synthesis in normal cells, and toxicities may necessitate discontinuation of treatment and thus potentially increase risk of relapse. We hypothesized that intermittent pegylated-asparaginase (PEG-asp) treatment, similar to the intermittent use of other antileukemic agents, would not lead to an inferior disease-free survival (DFS) compared with continuous administration, but would significantly reduce the number of asparaginase-associated toxicities.

PATIENTS AND METHODS

The ALL2008 protocol opened on July 1, 2008, for patients with Philadelphia chromosome negative

B-cell precursor or T-cell ALL. Included in the current study were children (ages 1.0 to 17.9 years) with non–high-risk ALL treated according to the Nordic Society for Pediatric Hematology and Oncology (NOPHO) ALL2008 protocol in Denmark, Finland, Iceland, Norway, or Sweden. Patients were included from January 1, 2009, in Sweden and Denmark; February 11, 2009, in Norway; June 1, 2009, in Finland; and January 7, 2010, in Iceland. The randomization was closed on March 1, 2016, when all study patients who were still in the intensive PEG-asp arm shifted to the intermittent arm, due to results obtained in interim analysis (Data Supplement).

The randomization excluded patients with ALL predisposition syndromes, previous cancer, chemotherapy intolerance (eg, Charcot-Marie-Tooth disease, vincristine intolerance), patients receiving more than 1 week of treatment with antileukemic agents before diagnosis of ALL, or incomplete registration of risk group–stratifying cytogenetic aberrations. The protocol was amended in November 2009 to exclude from random assignment patients with t(12;21)[*ETV6/RUNX1*] and WBC count at diagnosis greater than 100×10^9/L.

The protocol was approved by the National Medicines Agencies (Eudract no. 2008-003235-20), relevant ethical committees, and registered at www.clinicaltrials.gov (NCT00819351).

Treatment and Risk-Group Stratification

Risk grouping and therapy has been described in detail[2,15-17] (Data Supplement). All patients received 4 weeks of induction with vincristine, doxorubicin, and glucocorticoids (ie, dexamethasone if T-cell ALL and/or WBC count $\geq 100 \times 10^9$/L; otherwise prednisolone).

Non–high-risk patients were offered back-to-back participation in a randomization of fixed versus increasing doses of 6-mercaptopurine during consolidation therapy (www.clinicaltrials.gov: NCT00816049).[18] The present randomization balanced this previous randomization but was otherwise independent.

Asparaginase Treatment of Non–High-Risk Patients and Randomization

PEG-asp 1,000 IU/m^2/dose intramuscularly was given from treatment day 30 until 33 weeks from diagnosis. All patients received five doses at 2-week intervals during consolidation therapy. For patients with hypersensitivity reactions to PEG-asp, treatment was truncated, and subsequently they received *Erwinia* asparaginase 20,000 IU/m^2/dose three times per week for 2 weeks during delayed intensification and were not eligible for randomization, if this occurred before randomization.

After consolidation therapy, patients were randomly assigned to either 10 additional doses at 2-week intervals (standard arm) or three additional doses at 6-week intervals (experimental arm). In contrast to the standard arm, patients in the experimental arm were not exposed to PEG-asp during delayed intensification, when dexamethasone was given for 2 weeks.

Enzyme Activity Measurements

Blood samples were supposed to be collected before each PEG-asp dose for activity measurements. Results were not reported to the clinicians. Patients randomly assigned to the standard arm were to have samples taken 14 times, and patients randomly assigned to the experimental arm, seven times.

On the basis of enzyme activity measurements, patients were considered to be asparagine depleted if they had trough enzyme activity greater than 100 IU/L in samples obtained 14 days $\pm$ 2 days after administration.[19,20] Patients with fewer than four available samples during treatment were categorized as asparagine depleted during therapy if they had at least one activity measurement greater than 100 IU/L provided before the fourth or fifth dose.

Randomization Procedure

Block randomization was computer assigned (three patients to each arm for every six patients randomly assigned), stratification was by country, risk group, and 6-mercaptopurine randomization arm. The study was closed March 1, 2016, when interim analyses showed significantly reduced risk of asparaginase-associated toxicity in the experimental arm and that inclusion of the projected remaining 233 patients was unlikely to provide significant difference in DFS (Data Supplement).

Capture of Asparaginase-Associated Toxicities and Asparaginase Treatment Duration

Toxicities were captured or recaptured by several strategies, including (1) quarterly prospective toxicity registration of PEG-asp–associated hypersensitivity, osteonecrosis, pancreatitis, and thromboembolism; (2) individual case-report forms after discontinuation of PEG-asp treatment; (3) detailed online registration of premature PEG-asp treatment discontinuation (including date, reason, and number of doses given); and (4) deep phenotyping studies of individual PEG-asp–associated toxicities (AspTox).[15,21-28] If toxicity information was inconsistent, the toxicities (including dates of onset) were clarified by contacting the treating centers.

Toxicities were defined as AspTox if they occurred during PEG-asp or *Erwinia* asparaginase treatment, except for osteonecrosis. Toxicities were categorized as being asparaginase associated when they were identified up to 18 days after PEG-asp administration, when most patients have been shown to have enzyme activity levels greater than 100 IU/L after intramuscular administration.[19] The total number of PEG-asp doses was calculated as the number of PEG-asp doses plus the number of *Erwinia* asparaginase doses divided by six. Severity of pancreatitis

and osteonecrosis was graded according to the Ponte di Legno Toxicity definitions.[29]

Outcome Measures

The primary outcome was DFS with a noninferiority margin of six percentage points between experimental and standard treatment arms. Accordingly, the study was designed to enroll 429 patients in each arm and had an 83% power to determine if the experimental arm was noninferior with respect to relapse rate. Secondary outcome was any first AspTox (ie, hypersensitivity, osteonecrosis, pancreatitis, or thromboembolism). Sensitivity analyses included analysis of toxicity-specific hazard ratios (HRs) instead of risks, exclusion of patients with no enzyme activity, and adjustment for risk group (only for any first toxicity), and sex and stratification (because of nonproportional hazards) by age group (1.0 to 9.9 years and 10.0 to 17.9 years). The adjustment variables were selected a priori. Interim analyses were performed as part of the annual reporting to the Data and Safety Monitoring Committee (DSMC) to comply with Good Clinical Practice guidelines and assure safety. The toxicity and relapse data in these DSMC reports were not revealed to the treating clinicians.

Statistical Analysis

Study patients were followed from start of randomization until the date of the first event (ie, relapse, death in first remission, or second cancer), loss to follow-up or December 31, 2016, whichever came first. Comparison of groups within each randomization arm was done by χ^2 test. The follow-up time was estimated using the reverse Kaplan-Meier method. DFS was estimated by the Kaplan-Meier method, and noninferiority was evaluated on the basis of the corresponding 95% CIs. Cumulative incidences of first toxicity were estimated by the Aalen-Johansen estimator considering relapse, death in first remission, and second cancer as competing events, and the estimates per age-, sex, and risk group were compared with Gray's test. Cox proportional-hazards model was used to estimate unadjusted, adjusted, and stratified toxicity-specific HRs with significance evaluated with Wald tests. For the analyses of time to specific toxicity, the patients were followed until the date of the first specific toxicity, any competing event, or 18 days after the last PEG-asp dose. Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Of the 828 children (between 1.0 and 17.9 years old) who were eligible for random assignment (Fig 1), 631 (76%) were randomly assigned. The main reason for nonrandomization was parental refusal (80%).[30] Subsequently, six patients were excluded due to withdrawal of consent or misinterpretation of randomization arm, leaving 309 and 316 patients randomly assigned to the experimental and standard arms, respectively (Table 1). The 2015 annual report to the DSMC showed almost identical DFS in the two arms but significantly less AspTox in the experimental am. The DSMC recommended closure of the randomization. When the randomization closed on March 1, 2016, 15 patients treated according to the standard arm shifted to the experimental arm, which is treated as a censoring event in the analyses. None of these patients experienced an event and only one had a toxicity (thromboembolism) after randomization closure.

Disease-Free-Survival

After a median follow-up of 4.1 years (interquartile range [IQR], 2.6–5.9) since date of randomization, four patients had died during first remission (median, 0.4 years; IQR, 0.4–0.5), seven patients developed a second cancer (median, 2.5 years; IQR, 2.0–3.6), and 30 developed a relapse (median, 2.7 years; IQR, 1.5–3.7); 14 relapses involved the CNS. The 5-year cumulative incidence of relapse in the experimental and the standard arm was 6.6% (95% CI, 3.3% to 10.0%) and 6.0% (95% CI, 2.9% to 9.1%), respectively ($P = .81$).

The 5-year DFS was 92.2% (95% CI, 88.6% to 95.8%) for the experimental arm and 90.8% (95% CI, 87.0% to 94.6%) for the standard arm (Fig 2), thus not exceeding the noninferiority limit of 6%. Adding the six randomly assigned but noneligible patients did not make a noteworthy change the outcome data.

Enzyme Activity Measurements

Most of the randomly assigned patients (n = 614 of 625; 98%) had sampling for activity measurements, allowing 580 patients to be classified as asparagine depleted during treatment and with no significant difference of the distribution of such patients between the two randomization arms ($P = .70$; Data Supplement). Thirty-five of the 580 patients were categorized as asparagine depleted on the basis of only one enzyme activity measurement taken late in therapy (a median of8 weeks from initiation of PEG-asp; experimental arm, n = 1; standard arm, n = 34); however, we assumed they have been sufficiently exposed. Their 5-year DFS was 93.9% (95% CI, 85.8% to 100.0%). Among the 34 patients with no enzyme activity at any measured time point, the 5-year cumulative incidence of relapse was 15.8% (95% CI, 3.0% to 28.7%), compared with 5.9% (95% CI, 3.5% to 8.2%) for the 580 asparagine-depleted patients ($P = .013$), but the 5-year DFS did not significantly differ between the two groups (84.2%; 95% CI, 71.3% to 97.0% *v* 91.8%; 95% CI, 89.0% to 94.5%, respectively; $P = .084$). All relapses among the 34 patients involved the bone marrow, including one in combination with CNS relapse.

Asparaginase-Associated Toxicities

Fifteen patients were registered with a toxicity before the start of the randomized treatment (two had pancreatitis and 13 had thromboembolism, equally divided between the two arms), and these were not included in the toxicity summary.

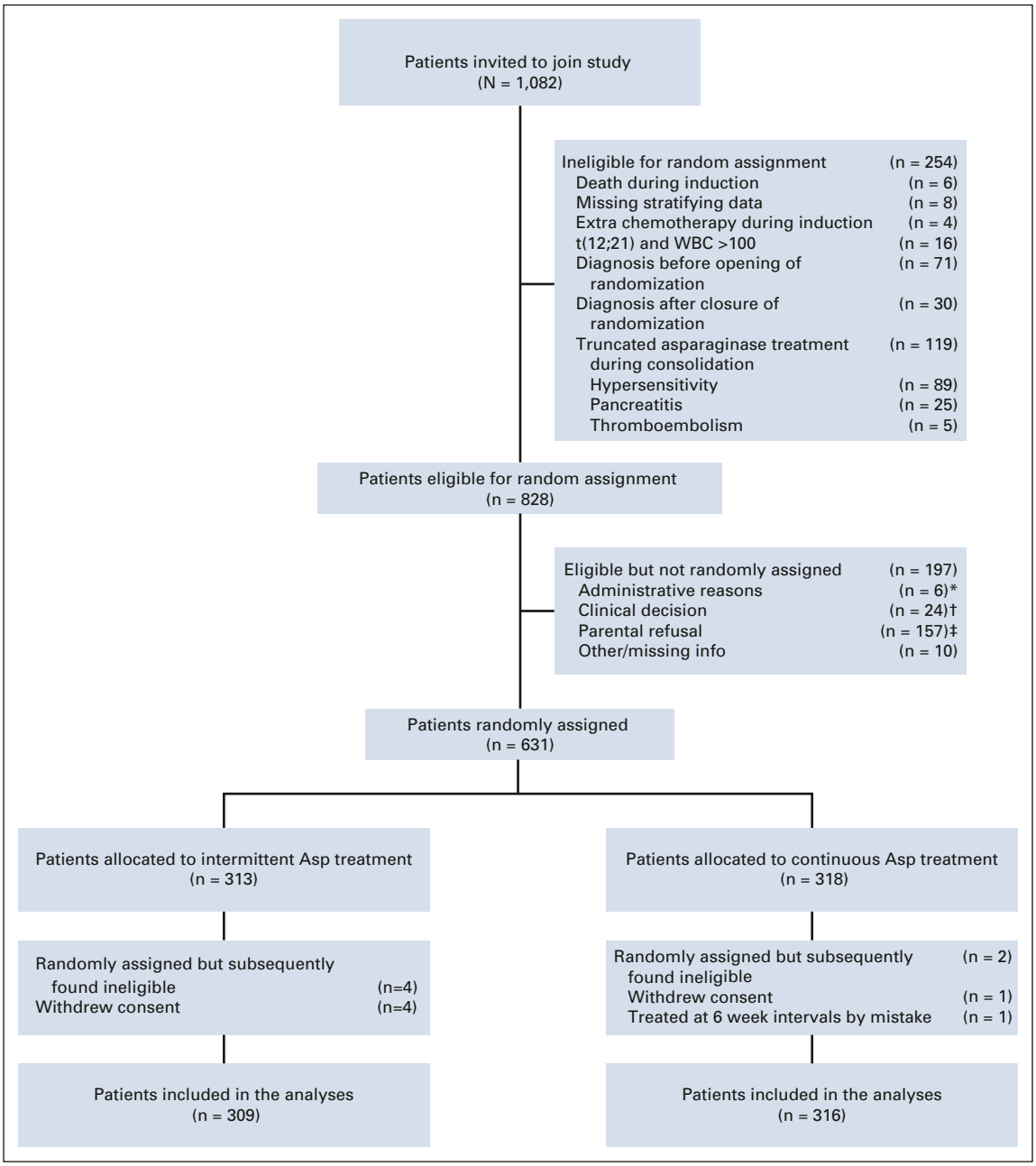

FIG 1. Study profile. One thousand eighty-two Nordic children (age 1.0-17.9 years) with non-high risk (non-HR) acute lymphoblastic leukemia (ALL), either pre-B or T-cell, diagnosed from January 7, 2008, to February 29, 2016. WBC, white blood cell count at diagnosis ($\times 10^9$); Asp, asparaginase. (*) Not randomly assigned, due to forgetfulness of the physician; (†) language or communication problems; (‡) parents afraid of decrease of treatment or not wanting to participate in randomized studies in general.

Disregarding AspTox before randomization start, 60 patients experienced their first toxicity during PEG-asp treatment and 23 after the last dose (13 had hypersensitivity, 29 had osteonecrosis, 24 had pancreatitis, and 17 had thromboembolisms), with a median of 2.4 months (IQR, 0.76−4.80) until any first toxicity after start of the randomized treatment (Data Supplement).

The 3-year cumulative incidence of any first AspTox after randomization was significantly higher for children age 10 years or older (32.8%; 95% CI, 22.8% to 41.5%) compared with children younger than 10 years (9.8%; 95% CI, 7.2% to 12.3%; $P < .001$), but did not differ between boys (13.0%; 95% CI, 9.2% to 16.7%) and girls (14.5%; 95% CI, 10.3% to 18.4%; $P = .55$) or between patients at intermediate risk (15.3%; 95% CI, 10.6% to 19.8%) and standard risk (12.7%; 95% CI, 9.2% to 16.0%; $P = .42$). The 3-year cumulative incidence of any first AspTox after start of randomized therapy was significantly lower for the

TABLE 1. Baseline Characteristics of Randomly Assigned Patients (n = 625)

Characteristic	Intermittent Asparaginase (n = 309)	Continuous Asparaginase (n = 316)
Sex		
Male	159 (51)	169 (53)
Female	150 (49)	147 (47)
Age at diagnosis, median (range), years	4.0 (1.0-17.9)	4.5 (1.0-17.9)
Immunophenotype		
BCP	290 (94)	290 (92)
T cell	19 (6)	26 (8)
Risk group		
SR	189 (61)	193 (61)
IR	120 (39)	123 (39)
WBC count at diagnosis, median (range), 100×10^9/L	9.20 (0.40-394)	9.50 (0.7-825)
6-MP randomization during consolidation		
Increments	134 (43)	136 (43)
Fixed	141 (46)	146 (46)
Eligible, not randomized	34 (11)	33 (11)
Not eligible	—	1

NOTE. Data are given as No. (%) unless otherwise indicated.
Abbreviations: 6-MP, 6-mercaptopurine; BCP, B-cell precursor acute lymphoblastic leukemia; IR, intermediate risk; SR, standard risk.

experimental arm (9.3%; 95% CI 6.0% to 12.6%) than for the patients in the standard arm (18.1%; 95% CI, 13.74% to 22.4%; $P = .001$; Fig 3).

The sex- and risk-group–adjusted, as well as age-group–stratified toxicity-specific HR was significantly associated with the treatment (experimental arm, 0.48; 95% CI, 0.30 to 0.75; $P = .001$), but not with sex (female, 1.16; 95% CI, 0.76 to 1.79; $P = .49$), or risk group (intermediate risk, 0.95; 95% CI, 0.61 to 1.49; $P = .83$). The unadjusted toxicity-specific HR remained significantly associated with the treatment when including only the 328 boys in the analyses (0.31; 95% CI, 0.15 to 0.62; 41 toxicities; $P = .001$) or only the 518 children younger than 10 years (0.44; 95% CI, 0.24 to 0.79; 50 toxicities; $P = .006$), but not for the 297 girls (0.71; 95% CI, 0.38 to 1.31; 42 toxicities; $P = .27$) or for the 107 children age 10 years or older (0.55; 95% CI, 0.27 to 1.12; 33 toxicities; $P = .098$; Fig 4). In the sensitivity analysis including only the 580 patients with measurable enzyme activity, the adjusted and stratified toxicity-specific HRs showed the same pattern: experimental arm (0.54; 95% CI, 0.33 to 0.86; $P = .009$), female sex (1.11; 95% CI, 0.71 to 1.75; $P = .64$) and intermediate risk group (0.92; 95% CI, 0.57 to 1.47; $P = .72$).

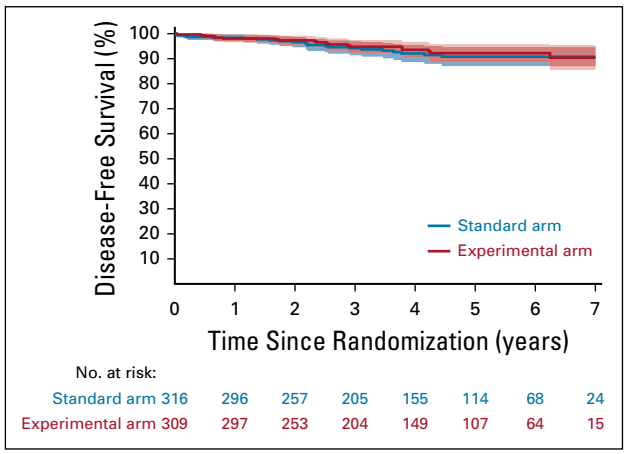

FIG 2. The 5-year disease-free survival for the experimental arm was 92.2% (95% CI, 88.6 to 95.8) and for the standard arm was 90.8% (95% CI, 87.0 to 94.6).

Considering first individual AspTox, hypersensitivity (n = 13 patients), osteonecrosis (n = 35 patients, of whom 20 had low-grade and 15 had high-grade osteonecrosis), pancreatitis (n = 22 patients, severe in 19), and thromboembolism (n = 14 patients), the hazard rate and the cumulative incidence of pancreatitis was significantly lower in the experimental arm than in the standard arm (HR, 0.22 [95% CI, 0.073 to 0.64], $P = .006$; cumulative risk, 1.3% *v* 5.8%, $P = .002$), whereas it was nonsignificantly lower for the other toxicities (Fig 4; Data Supplement). The sex-adjusted and age-group stratified HRs showed similar results, as did the HRs from the sensitivity analyses including only patients with enzyme activity (Data Supplement).

Asparaginase Treatment

The proportion of patients who received the full treatment of 15 or eight planned PEG-asp doses was significantly lower for the standard arm (82%) than the experimental arm (94%; $P < .001$; Data Supplement). The median number of

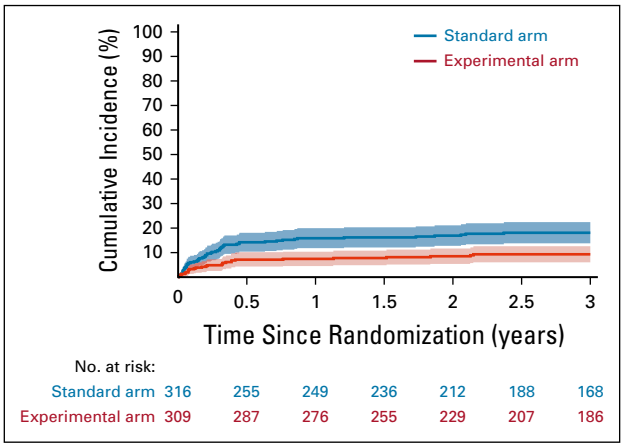

FIG 3. The 3-year cumulative incidence of any first asparaginase-related toxicity was 9.3% (95% CI, 6.0 to 12.6) and 18.1% (95% CI, 13.74 to 22.4) in the experimental and standard arm, respectively ($P = .001$).

the total doses for patients with truncated treatment was 10 (range, 5 to 14) in the standard arm and six doses (range, 5 to 7) in the experimental arm. The 68 patients with truncated therapy due to AspTox did not have a 5-year DFS that differed significantly from the remaining 557 patients who received full asparaginase therapy according to protocol (88.7%; 95% CI, 79.3 to 98.1 *v* 91.8%; 95 CI, 89.1 to 94.5; $P = .43$).

DISCUSSION

Intensification of chemotherapy has been the main strategy to improve event-free survival for childhood ALL, but at significant costs.[1,5-7] For asparaginase, several studies have supported that prolonged asparaginase treatment of 30 weeks increases DFS, not least by reducing the incidence of relapse involving the CNS.[31-33] This study convincingly demonstrates that intermittent therapy as given in ALL2008 provides significant reduction in AspTox risk with no inferior DFS. In the present randomized study, the cumulative incidence of relapse did not differ between the two arms and beyond 5 years of follow-up, only one relapse was diagnosed.

The recruitment to the current study was less than anticipated, mostly because parents declined treatment reduction, fearing inferior treatment of the disease itself[30].

The reduction of AspTox was most pronounced for pancreatitis, which is among the most burdensome complications of ALL therapy, and may be associated with potentially lifelong severe morbidity. To facilitate the comparison of various therapy-associated acute toxicities

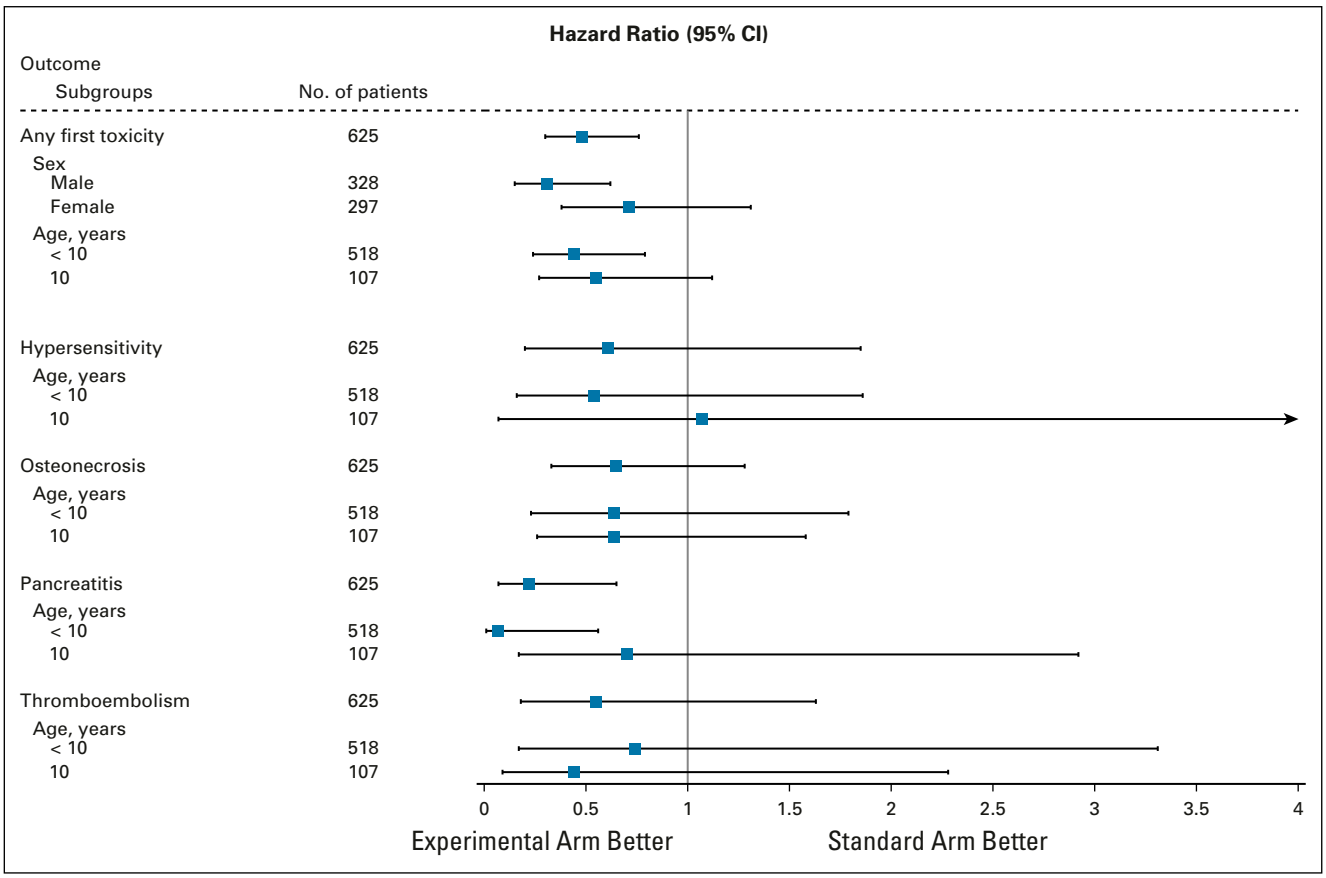

FIG 4. Forest plot showing the unadjusted hazard ratios (experimental *v* standard arm) for any first asparaginase-related toxicity after randomization start and for each toxicity separately.

between protocols, a worldwide initiative within the frame of the Ponte di Legno Toxicity recently established consensus definitions of toxicities associated with ALL therapy.[29] The phenotype of pancreatitis in ALL2008 has been described in detail.[22,23,34] This toxicity may potentially be life threatening and may be followed by persistent pain as a result of pseudocysts, and by chronic pancreatitis, insulin-dependent diabetes mellitus, and impairment of the exocrine function.[8,34,35]

In NOPHO ALL2008, the cumulative risk of PEG-asp hypersensitivity was 13.2% and occurred after a median of two doses (75% occurred between second and fourth doses), which is comparable to reports from other groups.[11-13,21] Thus, the very few hypersensitivity reactions observed in the current study primarily reflect that most of the patients who were prone to develop this complication[36] had already done so and thus become ineligible for randomization.

The association between asparaginase therapy and osteonecrosis remains uncertain, although hyperlipidemia caused by the combination of asparaginase and glucocorticoids, not least dexamethasone (eg, during delayed intensification), has been proposed as a risk factor.[27] In this study, patients in the experimental arm did not receive PEG-asp during dexamethasone-containing delayed intensification. However, the reduced frequency of osteonecrosis in the experimental arm did not reach statistical significance. The occurrence of osteonecrosis in ALL2008 has been investigated in depth, and has a 5-year cumulative incidence of 6.3%.[26]

Thromboembolism is a well-known complication during cancer therapy.[24,25,28,37-39] In ALL2008, the cumulative incidence of thromboembolism is 6.1% (95% CI, 4.8% to 7.7%), including 2% risk of cerebral sinus venous thrombosis, and occurring most frequently during PEG-asp treatment.[24,25,28] The lack of a significant association between randomization arm and the risk of thromboembolism could reflect that predisposing host genome variants[40] are relatively more important for risk of thromboembolism and, furthermore, that the low study power for this infrequent toxicity so late in therapy.

Finally, hepatic sinusoidal obstruction syndrome has recently been associated with PEG-asp treatment during maintenance therapy.[41] However, data on sinusoidal obstruction syndrome was not systematically captured for the entire ALL2008 study cohort.

The duration of asparaginase treatment differs among trials. Traditionally, Berlin-Frankfurt-Münster trials have used much less asparaginase than what was given in the present experimental arm,[42] whereas Dana-Faber Cancer Institute trials have used a duration similar to the ALL2008 standard arm.[12] Furthermore, Children's Cancer Group showed that the outcome in lower-risk patients was not correlated with the number of doses of asparaginase received.[43] In spite of these differences in asparaginase therapy, the survival does not vary between present protocols.[1-7]

PEG-asp treatment of patients with ALL is a considerable health care cost. By reducing the number of doses from 15 to eight, the drug cost per patient is almost halved from approximately $27.000 to 15.000 (prize provided by the Danish Medicines Agency), to which is added the costs associated with hospital admissions.

Historically, intensification of therapy by adding a delayed intensification phase to low-risk patients resulted in better event-free survival in the CCG-1881 trial,[44] whereas other randomized trials in line with the current study have shown that intensification of chemotherapy may not result in higher event-free survival rates,[45,46] stressing that there is a limit for achieving better survival results by increasing the intensity of chemotherapy.

Our findings may reflect that maximum antileukemic effect of PEG-asp has been provided during the first 10 weeks of therapy. Although the observational studies that support longer therapy do not support such a conclusion,[11-14] the results of an ongoing randomized trial comparing short and extended PEG-asp therapy (www.clinicaltrials.gov: NCT01117441) may clarify that issue.

In conclusion, the current study demonstrates that after the first five doses of PEG-asp, additional PEG-asp at just 6-week intervals reduces toxicity and costs with equal efficacy compared with treatment every 2 weeks.

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PRIOR PRESENTATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.18.01877.

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Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Intermittent Versus Continuous PEG-Asparaginase to Reduce Asparaginase-Associated Toxicities: A NOPHO ALL2008 Randomized Study

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