SELECTED SUMMARY-I

Prognostic Significance of Blasts in the Cerebrospinal Fluid Without Pleiocytosis or a Traumatic Lumbar Puncture in Children With Acute Lymphoblastic Leukemia: Experience of the Dutch Childhood Oncology Group

D. Maroeska W.M. te Loo, Willem A. Kamps, Anna van der Does-van den Berg, Elisabeth R. van Wering, Siebold S.N. de Graaf J Clin Oncol 24:2332-2336,2006

SUMMARY

Aim: The Dutch Childhood Oncology Group conducted this study with the aim of determining the significance of blasts in the CSF without pleiocytosis and a traumatic lumbar puncture in children with acute lymphoblastic leukemia (ALL).

Material and methods: In this retrospective study of 526 patients, 0-18yrs of age, with newly diagnosed ALL were treated on two Dutch protocols ALL-7 and its successor ALL-8 (virtually identical) between 1988 and 1997. These protocols were similar to the protocols BFM-86 and BFM-90, respectively. Only those patients were eligible for analysis where the CSF samples, at diagnosis, (not cytocentrifuged) were submitted to the Central Laboratory of Dutch Childhood Oncology Group,(DCOG) and were centrally reviewed by two experienced cytologists. CNS status of the patients was retrospectively defined according to conventional morphologic criteria as follows: CNS1, atraumatic LP (10 erythrocytes/μL) and no blasts present in the CSF specimen at diagnosis; CNS2, atraumatic LP, leukocyte count less than 5/μL but with blasts present in the CSF; CNS3, atraumatic LP, leukocytes 5/μL and blasts in the CSF. Patients with a traumatic lumbar puncture (TLP) at diagnosis (> 10 erythrocytes/μL) were classified in two groups, namely, TLP+ (TLP with blasts in the CSF sample after centrifugation) and TLP– (TLP with no blasts in the CSF sample). In addition to conventional morphology, terminal deoxynucleotidyl transferase (TdT) staining of the samples was performed when possible. Systemic relapse was defined as more than 25% blasts in the bone marrow. CNS relapse was defined by the presence of blasts and 5 leukocytes/μL in at least two subsequent CSF samples.

All patients were stratified into three risk groups according to BFM criteria and received a four-drug induction with prednisone (60 mg/m^2), vincristine, daunorubicin, and L-asparaginase. During induction, triple intrathecal treatment was administered on day 1 (methotrexate), day 15, and day 33. After induction, medium-risk patients received a consolidation consisting of oral mercaptopurine, high-dose cyclophosphamide, repetitive low doses of cytarabine, and two doses of intrathecal triple therapy. Subsequently, four courses of high-dose methotrexate (2 g/m^2 for standard risk patients and 5 g/m^2 for medium- and high-risk patients) with folinic acid rescue were administered in combination with intrathecal triple therapy. Reinduction was essentially a shortened repetition induction and consolidation described above with dexamethasone (10 mg/m^2) instead of prednisone. Maintenance for standard- and medium-risk patients included weekly oral methotrexate and daily mercaptopurine; high-risk patients received blocks of intensified therapy. The total number of intrathecal injections was 9 in protocol ALL-7 and 11 in ALL-8, given over a period of approximately 7

months; patients with meningeal leukemia (CNS3) received 2 additional intrathecal injections. Cranial irradiation was only given to children with overt meningeal leukemia. Thus, none of the children in groups CNS1, CNS2, TLP–, and TLP+ received radiation therapy.

Results: Of the 570 patients enrolled on the two Dutch protocols 44 were excluded because no CSF sample was received for central cytologic review, hence remaining 526 patients were analysed.

Median duration of follow-up was 11.7 years (range, 7.9 to 16.5 years). CNS1 status was found in 304 patients (58%), CNS2 status in 111 patients (21%), and CNS3 status in 10 patients (2%) according to conventional morphologic evaluation. The remaining 101 patients (19%) had a TLP at diagnosis: TLP+ (n = 62; 12%) and TLP– (n = 39; 7%). All patients(526) were stratified into standard-risk (SRG,192, 36%), medium-risk (MRG,282, 54%), and high-risk(HRG,52,10%) groups according to BFM risk factor, immunophenotype, response to steroids, and cytogenetics. The CNS2, CNS3, and TLP+ had significantly more unfavorable characteristics than patients in the CNS1 or TLP– and had a significantly higher percentage of patients with WBC counts above $50x10^9/L$.

The 10-year EFS overall was 71% (SE, 2.1%), CNS1 patients 72.6% (SE, 2.5%), CNS2 patients 70.3% (SE, 4.7%; not significantly different; EFS for the 10 patients in the CNS3 group was 67.7% (SE, 19.0%). CNS3 patients were not considered further in this analysis because of the low number of patients in this group.

The 10-year EFS for TLP– patients was 82% (SE, 5.2%) and for TLP+ patients 58% (SE, 7.6%; P < .01;). Prognosis of patients with CNS2 status and TLP– status was not significantly different compared with patients with CNS1 status. In contrast, TLP+ patients had a significantly inferior outcome than patients with CNS1 status (also by Cox regression analysis).

The distribution of relapses according to CNS status group was similar in CNS1 and CNS 2 patients. In comparison with CNS1 patients, TLP+ patients tended to relapse more frequently in the CNS (CuIn, 0.08 v 0.05; P = .236) and in the bone marrow (CuIn 0.294 v 0.205; P = .07) or at any (CuIn, 0.255 v 0.375; P = .025). So iatrogenic introduction of leukemic cells into CSF adversely affected treatment outcome.

When morphologic CNS1 and CNS2 patients (n = 401) were reclassified on the basis of TdT positivity instead of morphology, it did not change the conclusion that CNS2 status has no significant effect on prognosis.

COMMENTS

The presence of overt central nervous system (CNS) disease at the time of diagnosis, as defined by CSF criteria or the presence of cranial nerve palsies, negatively affects the event-free survival (EFS) of children with acute lymphoblastic leukemia (ALL).[1,2] Leukemic cells in the CSF arise from the cranial arachnoid tissue. The presence of 1 leukemic blast cell per microliter of CSF corresponds to approximately 10^5 leukemic cells in the entire CSF compartment. The effect of a small number of leukemic blasts in the CSF at diagnosis on EFS is controversial. Investigators from the Children's Cancer Group have demonstrated that this finding is of no prognostic significance in patients with intermediate-risk ALL in the context of their systemic and CNS-directed therapy.[3, 4] In contrast, St Jude Children's Research Hospital and the Pediatric Oncology Group have shown that the presence of blast cells in the CSF, even if small in number, resulted in a high risk of relapse, requiring more intensive intrathecal therapy.[1,5] Thus the prognostic significance of a low number of leukemic blasts in the CSF has remained a subject of investigation.

A related controversial issue is the prognostic relevance of a traumatic lumbar puncture (TLP) at diagnosis. Investigators of the St Jude Children's Hospital were the first to show that TLP+ at the time of diagnosis negatively affects the treatment outcome of patients with newly diagnosed ALL. The adverse prognosis increases in the subgroup of patients who had 2 consecutive TLPs with blast cells (TLP++). The risk of treatment failure is 2.39-fold higher for these patients than for patients

who did not have blast cells in the CSF in both procedures[1]. These findings were subsequently confirmed by the BMF group[6]. So two issues regarding the analysis of CSF at diagnosis need further elucidation: first, the prognostic relevance of a small number of blasts without pleiocytosis, and second, the consequences of TLP at diagnosis.

Results of the present study, suggest that the presence of blasts in the spinal fluid in combination with a CSF leukocyte count of fewer than five per microliter (CNS2) have no prognostic relevance. Also, no prognostic relevance could be found when only TdT-positive cells were considered to be true leukemic blasts. Consequently, these results do not provide any evidence for the need of administering additional intrathecal therapy to CNS2 patients. But TLP with the presence of blasts in the CSF sample (TLP+) was clearly associated with a worse prognosis.

Overall survival of patients treated in accordance with the Dutch protocols was similar to the BFM study group. In contrast with the Dutch experience, the BFM group found that CNS2 patients had an almost threefold (10% v 3.5%) higher risk of CNS relapses compared with patients with CNS1 status. Although this increased risk was not statistically significant, they recommended giving additional CNS-directed therapy to these patients. In the present study, CNS2 was not associated with an increased risk of relapse. The observation that EFS in TLP+ was worse than in the CNS3 group may be explained either because of the more intensive CNS directed therapy in the latter group or perhaps because of the low number of patients in them.

A major difference between the BFM study and te Loo et al study is the absence of a central review of CSF cytocentrifuge slides in a substantial number of BFM patients which may, at least in part, account for the lower incidence of CNS2 status in the BFM experience; 5.1% versus 21% in te Loo et al cohort. The relatively small group of patients with CNS2 status in the BFM study may represent a selection bias. To prevent a selection bias and to identify the true leukemic nature of cells, Pui[7] suggested that repeat examinations should be performed, preferably with TdT staining or immunophenotyping. Even when TdT positivity was used to define a blast, no significant difference in outcome was found between CNS1 and CNS2 patients.

The results in this study are in agreement with previous studies[1, 6]. The outcome of TLP+ patients (10-year EFS, 59%) is similar to that of the TLP+ patients treated at St Jude Children's Hospital (5-year EFS, 60%); 5-year EFS of TLP+ patients in the BFM trial were 73%.

An important question is why do patients with a TLP + have an inferior outcome. One hypothesis regards iatrogenic contamination of the CSF by blasts circulating in the peripheral blood. If such contamination is just a matter of bad luck or an unfortunate procedure, one should try to prevent the latter from happening. te Loo et al found that patients with a high WBC count were more likely to have TLP+ status, but immunophenotype and age were not associated with a higher incidence of a traumatic lumbar puncture. Another possibility is due to under treatment of the patients, who were actually patients with CNS involvement (CNS3 status), but were not identified at diagnosis due to the presence of erythrocytes in the CSF.

Although there is no definite explanation for the inferior outcome in TLP+ patients, the present study recommends some kind of additional intensified therapy to these patients. Intensifying systemic chemotherapy and/or administering additional intrathecal therapy may be needed to prevent a higher incidence of relapses in these patients. The efficacy of such additional therapy can only be evaluated in a prospective clinical trial.

Present study highlights two very important issues. Firstly that the first lumbar puncture in newly diagnosed patients must be done under optimal circumstances i.e. by the most experienced professional on the team and

with adequate sedation or general anesthesia. And secondly the need for meticulous examination of the CSF sample for number of cells, blasts, and number of RBCs, because these have an important bearing on prognosis and determine intensity of CNS directed therapy.

REFERENCES:

1. *Gajjar A, Harrison PL, Sandlund JT, et al. Traumatic lumbar puncture at diagnosis adversely affects outcome in childhood acute lymphoblastic leukemia Blood. 2000;96:3381-3384.*

2. *D. Maroeska W.M. te Loo, Willem A. Kamps, Anna van der Does-van den Berg et al Prognostic significance of blasts in the cerebrospinal fluid without pleiocytosis or a traumatic lumbar puncture in children with acute lymphoblastic leukemia: experience of the Dutch childhood oncology group. J Clin Oncol. 2006;24:2332-2336.*

3. *Gilchrist GS, Tubergen DG, Sather HN, et al. Low numbers of CSF blasts at diagnosis do not predict for the development of CNS leukemia in children with intermediate-risk acute lymphoblastic leukemia: a Children's Cancer Group Report. J Clin Oncol. 1994;12:2594-2600.*

4. *Tubergen DG, Cullen JW, Boyett JM, et al. Blasts in CSF with a normal cell count do not justify alteration of therapy for acute lymphoblastic leukemia in remission: a Children's Cancer Group Study. J Clin Oncol. 1994;12:273-278.*

5. *Lauer S, Shuster J, Krichner P, et al. Prognostic significance of cerebrospinal fluid (CSF) lymphoblasts (LB) at diagnosis (dx) in children with acute lymphoblastic leukemia (ALL). Proc Am Soc Clin Oncol. 1994;13:317.*

6. *Burger B, Zimmermann M, Mann G, et al:Diagnostic cerebrospinal fluid examination in children with acute lymphoblastic leukemia: Significance of low leukocyte counts with blasts or traumatic lumbar puncture.J Clin Oncol. 2003;21:184-188.*

7. *Pui CH: Toward optimal central nervous system-directed treatment in childhood acute lymphoblastic leukemia. J Clin Oncol. 2003;21:179-181.*

Sameer Khatri & Gauri Kapoor
Department of Paediatric Haematology Oncology
Rajiv Gandhi Cancer Institute & Research Centre
Rohini Sector – 5, Delhi-110085