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To the editor:

Treatment outcome in infant acute lymphoblastic leukemia

We read with interest the paper of Dördelmann et al[1] on prednisone (PDN) response as the strongest predictor value of outcome in infant acute lymphoblastic leukemia (ALL).

Between June 1989 and November 1998, 60 (3.1%) infants, among 1963 children less than 18 years of age, were registered and treated according to the Children Leukemia Cooperative Group-European Organization for Research and Treatment of Cancer (CLCG-EORTC) protocol 58881. Patients were stratified according to the same risk factor (RF) as defined in Dördelmann et als paper:[1] RF $<$ 0.8 assigned them to the low risk (LR) group, and RF $\geq$ 0.8 to the standard risk (SR) group. Patients with prednisolone poor response (PPR), with t(9;22) or t(4;11) and/or not in remission (marrow blasts $<$ 5%) on day 35 were assigned to the very high risk group (VHR).

Protocol CLCG-EORTC 58881 was very similar to the protocol ALL-BFM86 except for the following points: (1) prednisolone instead of prednisone and additional It MTX were used during induction, (2) protocol II was given to all LR and SR patients, (3) VHR patients, after induction, received 9 blocks of multi-agents chemotherapy, followed by conventional maintenance for 1 year. In addition, a proportion of the patients were randomized to receive the following: (1) either *Erwinia* or *E coli asparaginase* (all ALL patients in induction and consolidation) (2) HD MTX versus Ara-C plus HD MTX during interval therapy (standard risk patients) (3) pulses of 6 MP IV during maintenance therapy (all patients). In contrast with Berlin-Frankfurt-Münster (BFM) protocol, no patient received prophylactic or therapeutic cranial irradiation.

Outcome according to presenting features in infant ALL treated with EORTC protocol #58881

	n	EFS (%)*	HR†	*P* value
Age				
Less than 6 mo	34	30	1.7	.13
At least 6 mo	26	56	1	
WBC ($\times 10^3/\mu L$)				
Lower than 25	9	80	1	
Lower than 100	16	57	4.1	$<$.001
At least 100	35	26	11.6	
Prednisolone response				
Good ($<$1000/μL)	38	48	1	.02
Poor ($\geq$1000/μL)	21	29	2.1	
VHR feature				
No	19	64	1	.01
Yes	41	27	2.8	
Immunophenotype				
CD10−	39	29	3.7	.02
CD10+	11	79	1	
CD34+	18	15	2.3	.03
CD34−	21	56	1	
Cytogenetics				
T(4;11) Yes	26	23	2.5	.01
No	23	63	1	

*Event free survival rate at 4 years.
†Hazard ratio completed via the logrank O/E ratio method.

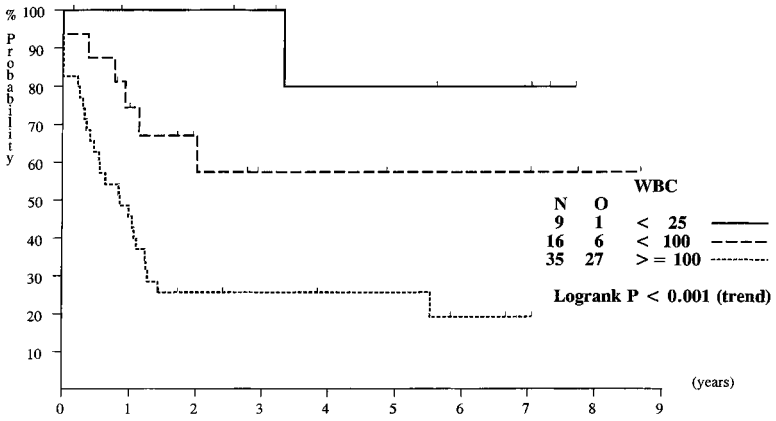

Figure 1. Probability of EFS for infants with ALL, according to white blood cell (WBC) counts at diagnosis.

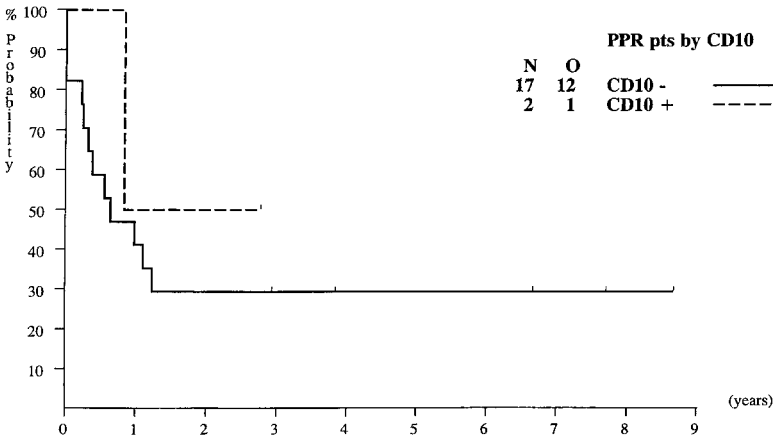

Figure 2. Probability of EFS for infants with ALL presenting poor prednisolone response (PPR), according to their CD10 expression.

The overall event free survival (EFS) rate at 4 years in the 60 ALL infants treated with the same protocol was 41%. Univariate analysis of prognostic factors is given in the Table. Age below 6 months had no significant influence on EFS, but white blood cell (WBC) counts of at least $100 \times 10^3/\mu L$, PPR, presence of very high risk features, immunophenotype (CD10− or CD34+) had a significative negative influence on EFS. The leucocyte count had the most important impact. The EFS of infants with initial leucocyte count lower than $100 \times 10^3/\mu L$ was 65%, which is comparable to that of older children with initial leucocyte count between 10 and $100 \times 10^3 \mu L$ (Figure 1).

In contrast with the ALL-BFM results, the EFS of the 17 PPR infants with CD10− ALL was 29% (Figure 2), whereas in the Germany study, none of these infants survived. The difference between the 2 studies might be treatment-related.

Nevertheless, the overall results are similar with a global EFS of 41%. Of note is that the proportion of infants with CD10+ and steroid good response (PGR) respectively was higher in the BFM study than in the EORTC 58881 trial: 40% versus 22% for CD10+ and 74% versus 64% for PGR. Probably, the percentage of VHR patients is higher in the EORTC series, as the proportion of PPR was higher, due to the late administration of the It MTX.[2]

The number of patients was small in both studies (although twice as high in the BFM study), and conclusions with regard to the relation weight of different prognostic features should not be accepted without qualification. Results of the ongoing international protocol Interfant 99 will be essential to a refined ranking of the most important prognostic factors and to further progress in the treatment of this high-risk group.[3-6]

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Response:

Early response in infant ALL determines prognosis

We are pleased that our study on prognostic factors in infant acute lymphoblastic leukemia (ALL) during BFM trials[1] provoked some discussion as indicated by Ferster et al's letter. We think their data may give some important additional information regarding the prognostic value of certain clinical and biologic features in infant ALL. But in our opinion, their results are neither new nor inconsistent with our results. They also do not substantially question the findings and conclusions of our study.

In contrast to Ferster et al's statement, we think that the EORTC used both different treatment stratification and different treatment for a substantial proportion of infants. Because antileukemic treatment itself is a well-known prognostic factor, this may significantly influence the prognostic value of clinical or biologic features.[2] On the one hand, patients treated under the CLCG-EORTC protocol 58881 were stratified according to the same risk features, namely, tumor cell burden (BFM risk factor) and prednisone response. But in contrast to BFM, the translocation t(4;11) qualified for treatment in the highest-risk group (VHR in EORTC), and this may explain the much higher percentage of VHR patients in the EORTC series as compared to our study also (68% vs 26%).

2000 95: 2729

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