Progress in the Treatment of Childhood Leukaemias

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The Nordic Society for Pediatric Hematology and Oncology (NOPHO) has run a population-based registry on all cases of acute leukaemias in the Nordic countries since 1981. Data on close to 2000 children with these diagnoses are presented and used as a background for a general discussion of progress in the therapy of these challenging conditions. Our material is unique in that it is population based. The results obtained are comparable to those obtained by all other major cooperative groups. Since January 1992, the treatment protocols for all types of acute leukaemias in childhood have been harmonized in the Nordic countries.

Key words: acute leukaemia; children; Nordic countries.

Introduction

About one-third of the malignant disorders of childhood are acute leukaemias. Progress in the treatment of these disorders is well known and well documented (1–4). During the past decade, advances have mainly been seen in the poor prognosis subgroups and in the diagnostic categorization and stratification of the disease. We will briefly focus on the epidemiology, diagnosis, staging and treatment and will use as a background the experience gained by the Nordic Society for Pediatric Hematology and Oncology (NOPHO). Since 1981 this Society has run a population-based registry of all acute leukaemias in the Nordic countries (total population = 23 million) and have shared the improvements experienced by all other major cooperative groups.

Epidemiology

The frequency of acute childhood leukaemias in Norway has not changed during the last three decades (5). Table 1 shows the incidence appearing in the NOPHO material. It is impressive how similar the frequencies are in the Nordic countries. We have observed the well-known peak incidence between 2 and 3 years in acute lymphocytic leukaemias (ALL) and have also been able to distinguish a distinct peak incidence at the age of 1–2

years in the acute myelogenous leukaemias (AML) (Fig. 1a, b).

Leukaemia-prone Syndromes

Children with immune deficiencies, chromosome breakage syndromes, Fanconis anaemia, ataxia telangiectasia and Blooms syndrome have a definite increased incidence of leukaemias, but only contribute to a minor proportion of the acute leukaemias. However, in AML we have shown that a very significant part (18%) of the patients have Down's syndrome (6). Age of onset in this group is clearly distinct from that of normal children in that almost all are around 2 years of age at diagnosis.

Risk factors connected to the epidemiology of leukaemias are ill-defined and unconfirmed in many studies. However, there is continuous concern about background irradiation, nuclear reactor accidents and electromagnetic waves (7); these are currently being studied in several large population-based studies in the

Table 1. Acute childhood leukaemia in the Nordic countries July 1981–July 1991.

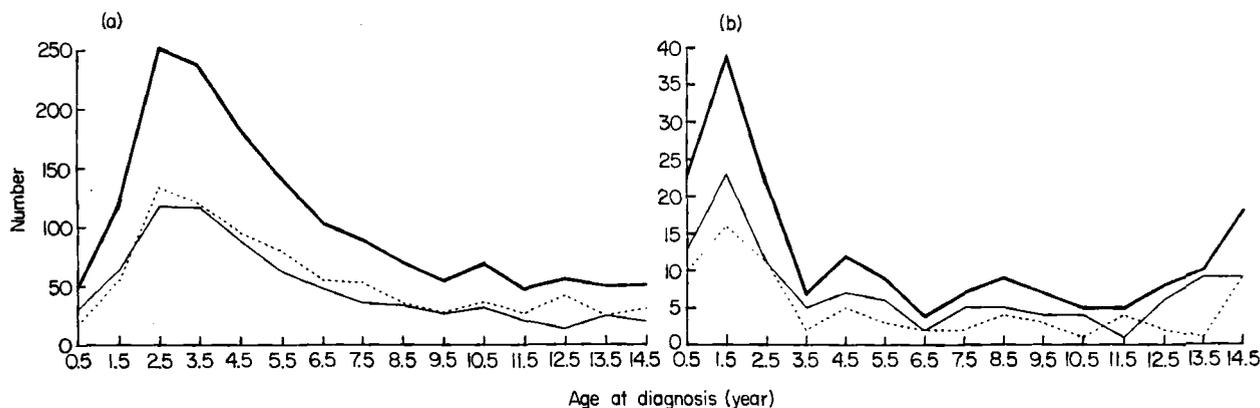|	Number	Incidence (100,000/year)
Denmark	412	4.4
Finland	446	4.6
Iceland	29	4.6
Norway	361	4.4
Sweden	692	4.5
Total	1940	4.5
	ALL	3.8/100,000/year
	AML	0.7/100,000/year

Fig. 1. Age at diagnosis in childhood acute lymphocytic leukaemias (a) and acute myelogenous leukaemias (b): males (– – – –),
females (————) and total (————).

Nordic countries. However, the constant incidence of leukaemias throughout the last 30 years certainly supports the notion that environmental factors do not significantly contribute to the development of childhood leukaemias.

Diagnosis

The clinical symptoms of acute leukaemias reflect deficiencies in the normal peripheral blood cells. The malignant cells proliferate autonomously and displace the normal elements of bone marrow more or less completely. The anaemic child with fever and bleeding problems is one in which acute leukaemia certainly should be excluded. A pre-leukaemic state is sometimes observed, especially in AML and we have seen a pre-leukaemic state in half of the children with Down's syndrome prior to the development of leukaemia. In some cases symptoms may develop after a prolonged period of bone pain and in an occasional patient with AML the onset may be very dramatic. In most instances, however, the diagnosis is not difficult and more sophisticated investigations can be performed.

One of the greatest advantages in recent years is the precise characterization of the leukaemic cell. Ten years ago the diagnosis relied primarily on morphology and cytochemistry alone. Today immunocytochemistry, immunophenotyping, cytogenetics and a variety of molecular genetic methods have improved the specificity of diagnosis. The entity of acute undifferentiated leukaemia is now rare in childhood and most ALL patients are found to have pre-B or B-cell precursor leukaemia with 10-15% of the ALL patients having the T-cell phenotype. There is a subset of patients with a definite hybrid phenotype in which markers from both lymphoid and myeloid lineages can be found. The prognostic significance of such hybrid leukaemias is not completely known, but most authors would consider this variant to carry a poor prognosis (8, 9).

Advances in the specificity of the diagnostic tests have not been paralleled by increased sensitivity in detection of leukaemic cells. A variety of methods has been used to find evidence of minimal residual disease

in patients in remission in order to detect children with an increased risk of relapse. Recent progress in molecular genetics, in particular the PCR method, may now detect a leukaemic clone in a very small fraction of a bone marrow specimen (10). These techniques are likely to develop very quickly and may in the future be very accurate in identifying children with a definite minimal residual disease having a high risk of relapse.

Staging

Twenty years ago there was just one leukaemia prognostic group. The vast majority of the patients died and it was very difficult to define subgroups of patients with a better or worse prognosis. In the 70s, however, as a consequence of the improvements in therapy, prognostic variables could be defined. Since the mid 70s, continuous efforts have been made to stratify patients in large-scale multicentre clinical trials in order to define differences in prognosis related to therapy rather than to inherent biological differences in the disease.

The variable most likely to affect outcome is of course therapy. However, various risk groups have been defined through stratified clinical studies and some of the risk factors are listed in Table 2. Not all of these are equally significant and some are not independent of other factors. Some factors such as leukocyte count and age are the most definite predictors of outcome. Lymphocyte leukaemia diagnosed in infancy or in children above 10 years of age is more difficult to treat, and a high leukaemic burden at diagnosis (e.g. WBC count) is also correlated with poor outcome. Once these are taken into account, T-cell leukaemia and organ enlargements add little of prognostic value.

Cytogenetics of the malignant clone seem to identify certain separate prognostic groups (11-13), but perhaps not to the extent that it was felt in the beginning. Only translocations t(4,22) and t(9,22) carry a very grave prognosis in ALL when therapy is intensive enough. Hyperdiploid leukaemias are now documented in several studies to have superior survival. In a recent study, DNA index of the leukaemic cell had a particular value as a predictor of late failure, and may be an alternative way to

Table 2. Staging of childhood ALL

Morphology	FAB L1, L2, L3
Cytochemistry	
Immunophenotyping	
Cytogenetics	
Response to therapy	
Clinical	
Age	
Race	
Sex	
Tumour burden	
CNS at diagnosis	
Laboratory	
White blood cell count	
Count platelet	
Count serum immunoglobulin	
Plasma drug clearance	

Fig. 2. Probability of event free survival (P-EFS) in ALL during July 81-June 84 (■), July 84-June 86 (□) and July 86-June 91 (◆).

identify the hyperdiploid cell (14). Sex seems to be an independent prognostic factor, in that boys have a worse prognosis than girls in several clinical situations. Initial response to chemotherapy can also be used as a measure of staging. The German group has convincingly shown that initial (=1 week) sensitivity to corticosteroids is an independent prognostic factor (1). Most other studies also show that early response to therapy (e.g. bone marrow on day 7 or 14) carry a good prognosis while slow responders carry a very grave prognosis (3).

Therapy

ALL

The reader will appreciate that it will be impossible to cover all the enormous effort and studies that have been made in defining optimal therapy for children with acute leukaemias. Rather, the experience from the Nordic countries will be used as an example of a cooperative group. In this population of 23 million people all the cases of acute leukaemias have been registered in a population-based manner since 1981. The weakness of our experience is that therapy in the five countries was not completely harmonized, but the strength is that no child has been lost to follow-up.

Figure 2 shows the event free survival (EFS) of patients in the Nordic material treated during three time periods. A progressive improvement in therapy is evident and is related to increased intensity of therapy.

In the following we will concentrate on the experiences gained in the period 1981-86 (the lower two curves in Fig. 2), since minimum time to follow-up is 5 years. The probability of event free survival (P-EFS) is 0.57.

In this group of 808 children, the prognostic factors defined by multivariate analysis according to Cox method were WBC at diagnosis (P<0.001), sex (P<0.001), age (P=0.002), platelet count (P=0.002) and year of diagnosis (P=0.004).

Figure 3 shows the risk distribution of different relapse localizations with regard to time in remission. It is illustrated that the bone marrow relapses often occur early
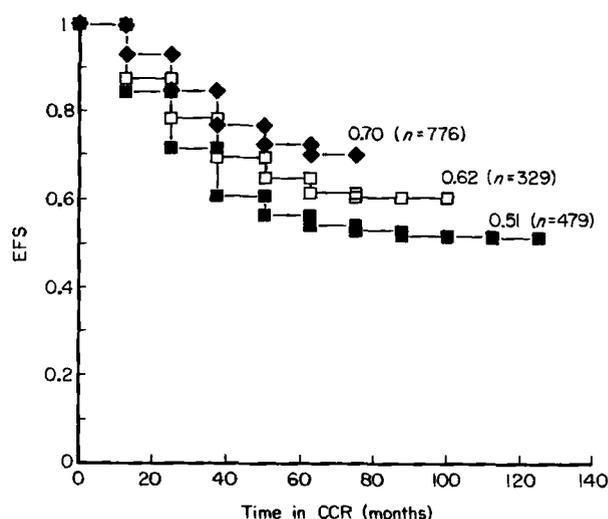
with the highest risk of relapse 10-20 months after remission. CNS- and testis relapses occur later and with lower frequencies. When calculating the probability for survival for the 808 patients treated between 1981 and 1986 it is close to 0.67, while P-EFS was 0.54. In other words, a significant number of relapses can be rescued. In the following we will focus on the prognosis of patients with relapses and on variables that might affect subsequent outcome.

Figure 4 shows the prognosis for patients after relapse according to the duration of first remission. It is evident that patients relapsing early have a grave prognosis compared to patients relapsing late.

Testis relapse did not carry a grave prognosis in our series, with a P-survival after relapse of 0.62. Isolated CNS-relapse gave a P-survival of 0.38, but a bone marrow relapse ± other localizations of relapse had a P-survival of only 0.21.

A special word about the CNS treatment. Three methods of CNS therapy are at present used in various combinations: cranial irradiation with intrathecal methotrexate, high-dose chemotherapy with effect within the central nervous system (high-dose methotrexate and high-dose cytosine arabinoside) and prolonged intrathecal therapy alone. In Norway, craniospinal irradiation has not been performed since 1975 when Moe introduced high-dose methotrexate as the only CNS prophylaxis together with intrathecal installations (15). In the Nordic study, there is no difference between patients in the high-risk group treated with high-dose methotrexate + intrathecal methotrexate compared to those with cranial irradiation + intrathecal methotrexate (P-EFS = 0.51 non-irradiated and P-EFS = 0.5 in the irradiate group) (16).

The tendency during recent years has certainly been to reduce the amount of irradiation due to the well-described side-effects. Several randomized studies are designed to answer the question of what is the optimal CNS therapy in this disease.
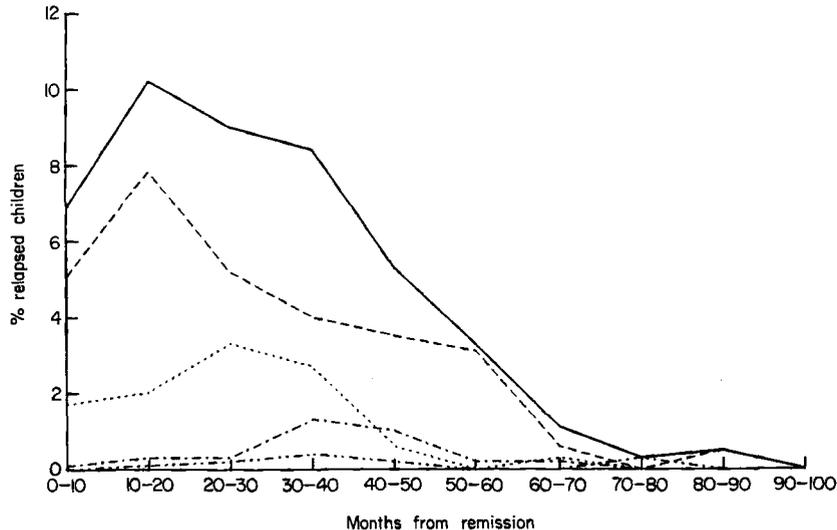
Fig. 3. Time to different types of relapse in childhood ALL: BM ± (— — — —), CNS (- - - -), testis (— · —), other (— ·· —) and total (————).

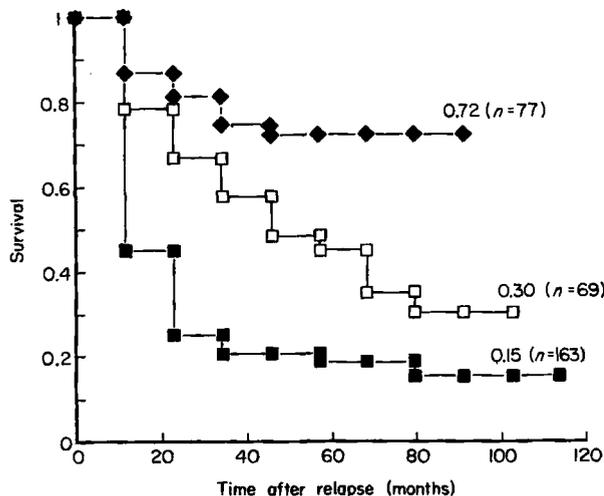**Fig. 4.** Survival after relapse as a function of duration of first remission in childhood ALL: ≤24 months (■), 24–36 months (□) and ≥37 months (◆).

AML

A recent review has extensively discussed this difficult and heterogenous disorder (17). This aggressive disease needs much more intensive therapy, and improvement in therapy has certainly lagged far behind the improvement seen in ALL. Symptoms at diagnosis are the same, but the disorders as such are much more complex. In the Nordic studies, we have had common protocols for this type of leukaemia since 1984 (6). Table 3 depicts preliminary results of the two Nordic studies (NOPHO-84 and NOPHO-88).

The staging of AML has not been defined well so far, but the BFM group (Berlin, Frankfurt, Münster), who in many ways has been reporting the best results in this disorder, has identified two risk groups where they claim that the presence of Auer rods, WBC, number of eosinophils and FAB (French, American, British) group be used to distinguish two risk groups in AML (18).

Table 3. Outcome of two NOPHO studies in AML (as of October 1991).

	NOPHO-84 (%)	NOPHO-88 (%)
Total number	123	99
Not evaluable	15	14
Evaluable	108	85
Death in aplasia	8 (7.3)	11 (13)
Resistant disease	17 (15.7)	5 (6)
Complete remission (%)	83 (77)	69 (81)
Death in CR	0 (0)	8 (11.5)
Relapse	48 (58)	20 (29)
Continuous complete remission	35 (42)	41 (60)
Second or subsequent remission	8	3
Total number in remission	43 (52) (40% of 108)	44 (63) (52% of 85)

NOPHO-84 contained cytosine arabinoside 6-thioguanine and doxorubicin during induction and four courses of high dose cytosine arabinoside as consolidation (6).

NOPHO-88 is intensified and contains in addition mitoxanthrone and VP-16 during induction and four alternate courses of high dose cytosine arabinoside with mitoxantrone or VP-16 during consolidation.

Prospectus

Up to now the therapy of acute leukaemias has been towards more intensive therapy ('more is better') (2)! The German group and later the American and English groups have clearly shown that late intensification is of value at least in the majority of patients in ALL. In AML in particular, intensification of therapy has been the standard during the last decade, with bone marrow transplant as the most dramatic therapy (19, 20).

However, it is equally clear that we now seem to have reached an upper limit for how much chemotherapy we can give to a child. The aim now is to define patients which do not need such an aggressive therapy and to define a minimal effective therapy. However, since the

Table 4. Relapse rate in three ALL risk groups (NOPHO material 1981–86).

	Relapse rate	% of relapse
SR*	137/359 (38%)	44
IR†	87/214 (41%)	28
HR‡	85/197 (43%)	28
Total	309/770 (40%)	100

*Standard risk (SR):	no HR-criteria Age 2– <10 years and WBC $<20 \times 10^9/l$.
†Intermediate risk (IR):	no HR-criteria Age 2– <10 years and WBC $21–50 \times 10^9/l$. Age <2 years or >10 years and WBC $<50 \times 10^9/l$.
‡High risk (HR):	WBC> $50 \times 10^9/l$ and/or CNS-involvement and/or Mediastinal mass and/or T-cell ALL

majority of the relapses in actual numbers still takes place in the standard risk groups (Table 4), we have not reached the stage where these groups can safely be defined.

There are signs on the horizon that other therapies may be approaching. The efficacy of retinoic acid in promyelocytic leukaemia is now well documented and seems to be clearly related to inducing differentiation in the malignant cell rather than killing it (21–23). This has been related to an abnormal retinoic acid receptor on chromosome 17 which has been rearranged by translocation with chromosome 15 (24). Since 1988 we have been running a randomized trial to investigate whether high-dose retinol may prolong the remission in AML (25). It remains to be seen whether this therapy can also benefit subgroups other than M3. The use of interferon and other cytokines are around the corner. The International Society for Pediatric Haematology and Oncology (SIOP) is starting a pilot study to investigate the effect of alpha-interferon on lymphoid malignancies. It will be one of the great challenges for the coming years to identify those children with acute leukaemias who cannot be cured by aggressive chemotherapy and to search for alternative approaches for this unfortunate group.

References

1. Riehm H, Gadner H, Henze G, et al. Results and significance of six randomized trials in four consecutive ALL-BFM studies. Haematol Blood Transf 1990; 33: 439–450.
2. Salian SE, Gelber RD, Kimball V, et al. More is better! Update of Dana-Farber Cancer Institute/Children's Hospital Childhood Acute Lymphoblastic Leukaemia Trials. Haematol Blood Transf 1990; 33: 459–466.
3. Bleyer W. Archie. Acute lymphoblastic leukaemia in children. Advances and prospectus. Cancer 1990; 65: 689–695.
4. Pieters R, Huismans DR, Loonen AH, et al. Relation of cellular drug resistance to long-term clinical outcome in childhood acute lymphoblastic leukaemia. Lancet 1991; 338: 399–403.
5. Lund E, Lie SO. Incidence of acute leukemia in Norway 1957–1981. Scand J Hematol 1983; 31: 448–95.
6. Lie SO, Berglund G, Gustafsson G, et al. High-dose Ara-C as a single-agent consolidation therapy in childhood acute myelogenous leukaemia. Haematol Blood Transf 1990; 33: 215–221.
7. London SJ, Thomas DC, Bowman JD. Exposure to residual electric and magnetic fields and risk of childhood leukemia. Am J Epidemiol 1991; 134: 923–937.
8. Wiersma SR, Ortega J, Sobel E, et al. Clinical importance of myeloid-antigen expression in acute lymphoblastic leukemia of childhood. N Engl J Med 1991; 324: 800–808.
9. Drexler HG, Thiel E, Ludwig W-D. Review of the incidence and clinical relevance of myeloid antigen-positive acute lymphoblastic leukemia. Leukemia 1991; 5: 637–645.
10. Negrin RS, Blume KG. The use of the polymerase chain reaction for the detection of minimal residual malignant disease. Blood 1991; 78: 255–258.
11. Arthur DC, Berger R, Golomb HM, et al. The clinical significance of karyotype in acute myelogenous leukemia. Cancer Genet Cytogenet 1989; 40: 203–216.
12. Kalwinsky DK, Raimondi SC, Schell M, et al. Prognostic importance of cytogenetic subgroups in de novo pediatric acute nonlymphocytic leukemia. J Clin Oncol 1990; 8: 75–83.
13. Rubin CM, Le Beau MM. Cytogenetic abnormalities in childhood acute lymphoblastic leukemia. Am J Ped Hematol Oncol 1991; 13: 202–216.
14. Pui C-H, Dodge RK, Look AT, et al. Risk of adverse events in children completing treatment for acute lymphoblastic leukemia: St Jude total therapy studies VII, IX and X. J Clin Oncol 1991; 9(8): 1341–1347.
15. Moe PJ, Seip M, Finne PH. Intermediate dose methotrexate (IDM) in childhood acute lymphocytic leukaemia in Norway. Haematologia 1981; 14: 257–263.
16. Kreuger A, Garwicz S, Hertz H, et al. Central nervous system disease in childhood acute lymphoblastic leukemia: Prognostic factors and results of treatment. Ped Hematol Oncol 1991; 8: 291–299.
17. Lie SO. Acute myelogenous leukemia in children. Eur J Pediatr 1989; 148: 382–388.
18. Creutzig U, Ritter J, Shellong G. Identification of two risk groups in childhood acute myelogenous leukemia after therapy intensification in study AML-BMF-83 as compared with study AML-BFM-78. Blood 1990; 75: 1932–1940.
19. Klingebiel Th, Ritter J, Schellong G, et al. Role and perspectives of BMT in AML: The BFM experience. Bone Marrow Transplant 1991; 7: 66–70.
20. Aurer I, Gale RP. Are new conditioning regimens for transplants in acute myelogenous leukemia better? Bone Marrow Transpl 1991; 7: 255–261.
21. Huang M, Ye H-C, Chen S-R, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Blood 1988; 72(21): 567.
22. Castaigne S, Chomienne C, Daniel MT, et al. All-trans retinoic acid as a differentiation therapy for acute promyelocytic leukemia. I. Clinical results. Blood 1990; 76: 1704–1709.
23. Warell RP, Frankel SR, Miller WH. Differentiation therapy of acute promyelocytic leukemia with tretinoin (ALL-trans-retinoic acid). N Engl J Med 1991; 324: 1385–1393.
24. de Thé H, Chomiennet C, Lanotte M, et al. The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. Nature 1990; 347: 558–562.
25. Lie SO, Wathne K-O, Petersen LB, et al. High-dose retinol in children with acute myelogenous leukemia in remission. Eur J Haematol 1988; 40: 460–465.