British Journal of Haematology, 1996, **94**, 82–88

A population-based study of 272 children with acute myeloid leukaemia treated on two consecutive protocols with different intensity: best outcome in girls, infants, and children with Down's syndrome

SVERRE O. LIE,[1] GUDMUNDUR JONMUNDSSON,[2] LOTTA MELLANDER,[3] MARTTI A. SIIMES,[4] MINNA YSSING[5] AND GÖRAN GUSTAFSSON[6] on behalf of the Nordic Society of Paediatric Haematology and Oncology (NOPHO)
Departments of Paediatrics, [1]National Hospital of Norway, Oslo, Norway, [2]Landspitalinn, Reykjavik, Iceland, [3]Östra Sjukhuset, Gothenborg, Sweden, [4]University of Helsinki, Helsinki, Finland, [5]National Hospital of Denmark, Copenhagen, Denmark, and [6]Karolinska Hospital, Stockholm, Sweden

Received 14 November 1995; accepted for publication 27 March 1996

Summary. From July 1984 the five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) have registered all children with acute myeloid leukaemia (AML) and treated them on two consecutive protocols of different intensity (NOPHO-84 and NOPHO-88). We probably have information on every child with this diagnosis in our region. We found an annual incidence of AML of 0·7 new cases per 100 000 children <16 years of age. We observed a distinct peak of incidence in the first 2 years of life. Children with Down's syndrome accounted for 13% of all cases.

Eighty of 105 cases treated on NOPHO-84 achieved remission (78%). In NOPHO-88, 100/118 patients entered remission (85%). The overall event-free survival (p-EFS) for the two studies was 0·32 for NOPHO-84 and 0·42 for NOPHO-88. The majority of relapses occurred within 2 years of diagnosis. When looking for prognostic factors the strongest significant adverse factor found was male sex. Children with Down's syndrome ($n = 35$) had a very favourable outcome if they received therapy according to protocol, and infants ($n = 26$) had a superior outcome compared to children 1–2 years or >10 years of age at diagnosis.

Keywords: children, leukaemia, myeloid, Nordic, therapy.

Acute myeloid leukaemia (AML) is a much more complex and resistant disease than the lymphoblastic variant, although progress in recent years has resulted in a third of such patients being long-term survivors (Lie, 1989; Boulad & Kernan, 1993; Ravindranath & Schultz, 1994). In an article on U.S.A. Childhood Cancer Survival in 1973–87, AML was said to be the childhood tumour with the worst prognosis (Novakovic, 1994). The majority of studies published are based on institutional patients and the real impact of the disease at population level is largely unknown.

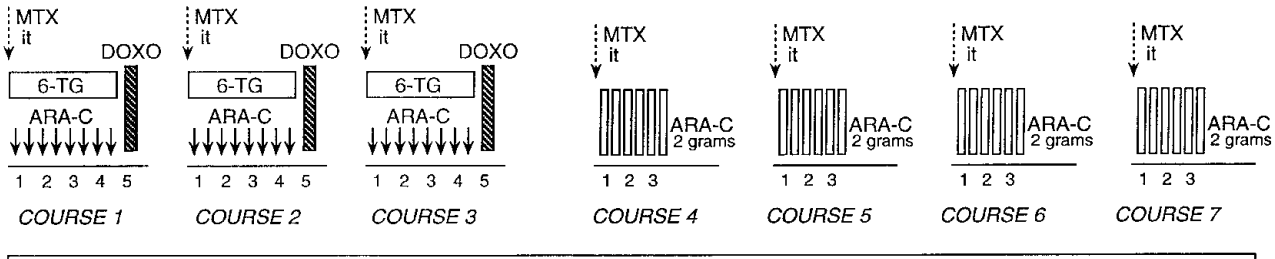
In the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) there is a unique possibility to perform population-based studies and to trace patients for follow-up. A common registry for children with acute lymphoblastic leukaemia (ALL) was established in 1981 and for children with acute myelogenous leukaemias in 1984 by the Nordic Society of Paediatric Hematology and Oncology (NOPHO). We have now documented information on every case of any childhood leukaemia in our population of 23 million inhabitants (Lie & Gustafsson, 1992).

In this study we present data on all the children diagnosed with AML in the Nordic countries over a period of 8·5 years. Both epidemiologic features and treatment results are described. In this period we have run two consecutive trials, with the second protocol (NOPHO-88) being more intense because resistant disease was the major problem in the first protocol (NOPHO-84).

Correspondence: Dr Sverre O. Lie, Department of Paediatrics, Rikshospitalet, National Hospital of Norway, N-0027 Oslo, Norway.

PATIENTS AND METHODS

Between July 1984 and December 1992, 272 children <16 years of age with AML were registered. The last protocol was



Cytarabine (Ara-C):	100 mg/m² twice daily
6-thioguanine (6-TG):	100 mg/m² twice daily
Methotrexate i.t.:	< 1 year 6 mg, 1-2 years 8 mg
	2-3 years 10 mg, > 3 years 12 mg
Doxorubicin (Doxo):	75 mg/m²

Fig 1. Outline of protocol NOPHO-84.

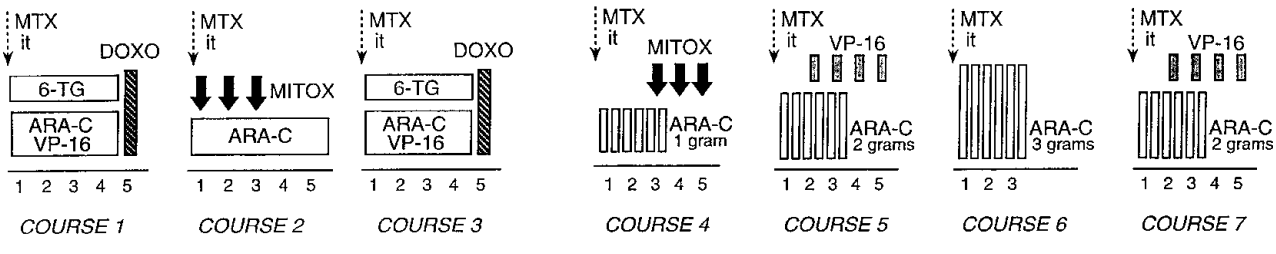
closed on 31 December 1992 and analysis performed on data collected during January 1995.

The diagnosis of AML was based on the presence of >25% abnormal blasts or promyelocytes as defined by regular staining, histochemistry, immunophenotyping or chromosome analysis when possible. With five countries involved, it was impossible to have a central review, but the diagnostic criteria were the same in all countries. Therapy was centralized to the University Hospitals and included 21 centres.

Therapy. An outline of the first protocol (NOPHO-84) is shown in Fig 1. Induction therapy consisted of three courses including bolus cytarabine (Ara-C), 6-thioguanine and doxorubicin given as an infusion on day 5. CNS prophylaxis with intrathecal methotrexate was given on the first day of each course in age-based dosages. Consolidation therapy consisted of high-dose Ara-C only (2 g/m^2 q12 h days 1, 2 and 3) repeated four times with a 3–4-week interval and with methotrexate intrathecally as during induction.

The therapy given in NOPHO-88 is shown in Fig 2. Therapy was intensified through the addition of etoposide and mitoxantrone both during induction and consolidation. Drug details are given in the figure. If the condition of the child allowed, course 2 was given not more than 2 weeks after course 1. During consolidation, VP-16 was given as an infusion over 1 h. In both induction and consolidation, mitoxantrone was given as an infusion lasting 30 min. Doxorubicin was given over 8 h.

Transplantation with allogeneic bone marrow was offered to all patients where an HLA-identical family donor was available. During the course of the study some centres started autologous bone marrow transplantation, but never before the second consolidation course. A conditioning regime consisting of busulfan and cyclophosphamide was used in the majority of patients with the remaining patients receiving total body irradiation (TBI) and cyclophosphamide according to the protocol of the bone marrow transplant centre involved. Patients with Down's syndrome were offered the same chemotherapy as other children. However, especially at the beginning of the period, many parents declined chemotherapy for their child with trisomy 21.



Cytarabine (Ara-C):	200 mg/m²/d continuous infusion
Etoposide (VP-16):	100 mg/m²/d continuous infusion
6-thioguanine (6-TG):	100 mg/m² twice daily
Mitoxantrone (Mitox)	10 mg/m²/d i.v.
Doxorubicin (Doxo):	75 mg/m²/d
Methotrexate i.t.:	Age-based doses as in NOPHO-84

Fig 2. Outline of protocol NOPHO-88.

Table I. Number and incidence (Inc.) of acute leukaemias in the Nordic countries from July 1984 through to December 1992.

	Total	AML (%)	Inc.$^{*}_{Tot}$	Inc.$^{*}_{AML}$
Denmark	358	18	4·6	0·8
Finland	390	12	4·8	0·6
Iceland	22	23	4·1	0·9
Norway	289	18	4·2	0·8
Sweden	606	16	4·7	0·8
Nordic countries	1665	16	4·6	0·7

* Per 100 000 children <16 years per year.
Inc.$_{Tot}$: Total incidence rate; Inc.$_{AML}$: incidence rate of AML.

Statistical methods. Statistical analyses were performed with SPSS statistical software (Norusis, 1992). Survival curves were performed using the Kaplan-Meier method (Kaplan & Meier, 1958) and remission durations for subgroups were compared with the log-rank test (Mantel, 1966). Cox multivariate proportional hazard regression analyses were performed for evaluating prognostic factors (Cox, 1972).

RESULTS

Epidemiology

Of the 1665 children diagnosed with acute leukaemia in the Nordic countries, 272 patients were classified as acute myelogenous leukaemias (Table I). The proportion of ALL to AML was similar in all countries. Therefore the annual incidence of AML was 0·7 new cases per 100 000 children aged <16 years.

In contrast to many other studies (Neglia & Robison, 1988; Boulad & Kernan, 1993), there were more girls than boys in our series (M:F ratio 0·8). A peak incidence was seen in the first 2 years of life. Of the 272 patients, 35 had Down's syndrome (13%). The age-specific incidence in patients with Down's syndrome was strikingly different from the others. Of the 35 patients, 33 were diagnosed between 1 and 3 years of age.

Treatment outcome

Table II presents the overall results of our study. Of the 272 patients registered, 33 were excluded from further analysis for reasons indicated in the table.

Sixteen patients were treated with a variety of other protocols, especially in the first years of NOPHO-84; of these, only four are long-term survivors. There was no selection by sex, age or other risk features in this group.

This leaves 223 patients treated according to NOPHO-84 and NOPHO-88. Patients' characteristics are listed in Table III, including age, FAB subtype and WBC count as reported at diagnosis.

Of the 105 patients treated on NOPHO-84, 82 achieved a

Table II. Outcome in children with AML.

Total patients registered		272
Not evaluable		
No therapy	20	
Second malignancy	8	
Other reasons	5	33
Evaluable patients		239
Other protocols	16	
On study		223

	N-84	N-88
n	105	118
Death in aplasia	8	14
Resistant disease	15	4
CCR (*n*)	82	100
CCR (%)	78	84

	N-84			N-88			
Treatment	Allo.	AMBT 1	Cyto.	Allo.	ABMT 1	Cyto.	MUD
n	12	8	62	15	25	58	2
Death in CCR	2		1	0	0	10	
Relapse	5	5	35	5	14	19	1
CCR 01/95	5	3	26	10	11	29	1

Allo., allogeneic transplant; ABMT 1; autologous bone marrow transplant; Cyto.; chemotherapy alone; MUD, matched urelated donor; N-84, protocol NOPHO-84; N-88, protocol NOPHO-88; CCR, continuous complete remission.

Table III. Characteristics of patients enrolled on NOPHO-84 and NOPHO-88.

	NOPHO-84	NOPHO-88
Gender		
F	61	60
M	44	58
Age		
<1 year	12	15
1–2 years	16	27
2–10 years	45	42
⩾10 years	32	34
FAB		
M1	19	23
M2	30	30
M3	8	6
M4	19	17
M5	11	19
M6	6	4
M7	3	6
Unknown	9	11
WBC ($\times 10^9$/l)		
<20	57	72
20–50	18	22
⩾50	29	24
Unknown	1	0
Platelet count ($\times 10^9$/l)		
<20	27	23
20–50	26	35
50–100	33	38
⩾100	17	18
Unknown	3	0
Hb (g/dl)		
<7·5	33	34
7·5–10	49	59
⩾100	21	22
Unknown	2	0
CNS disease	5	4
Down's syndrome	9	14
Total	105	118

remission (78%). Eight patients died in aplasia, and 15 patients had resistant disease. Of the 118 patients on NOPHO-88, 100 (85%) achieved a remission, the failures being 14 children dying in aplasia, whereas only four had resistant disease. Thus, the pattern of failure was reversed and we observed no significant difference between the overall induction results.

None of our patient characteristics appeared to predict for a better or a worse induction outcome, including WBC count, FAB type or age. Girls had a slightly inferior induction outcome, but not significantly so.

The results according to post-remission therapy are listed in Table II. Of the 27 patients who received allogeneic transplant, 15 (55%) are at present in their first remission.

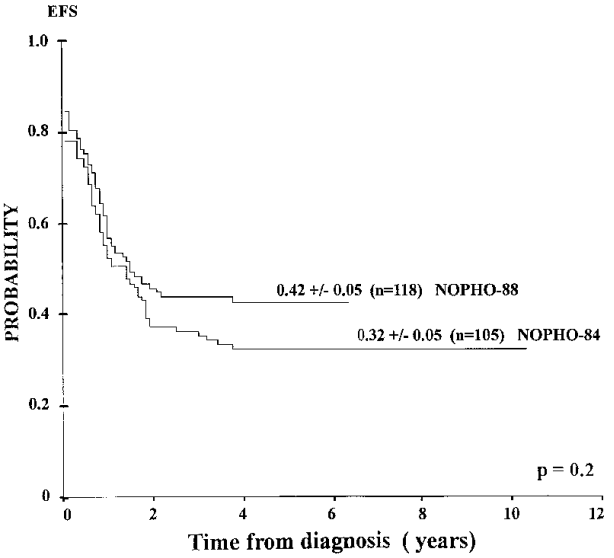


Fig 3. Probability of event-free survival (EFS) of all children on NOPHO-84 and NOPHO-88.

Of the 33 patients treated with an autologous bone marrow transplant, 14 (42%) are in their first remission. There was no selection of patients for transplant based on risk features. One child with Down's syndrome received an autologous transplant. Of the 120 children who received chemotherapy alone, 55 (50%) are disease-free. The probabilities of remaining in remission are presented in Figs 3–6.

Prognostic factors

Since there are no significant differences between the patient

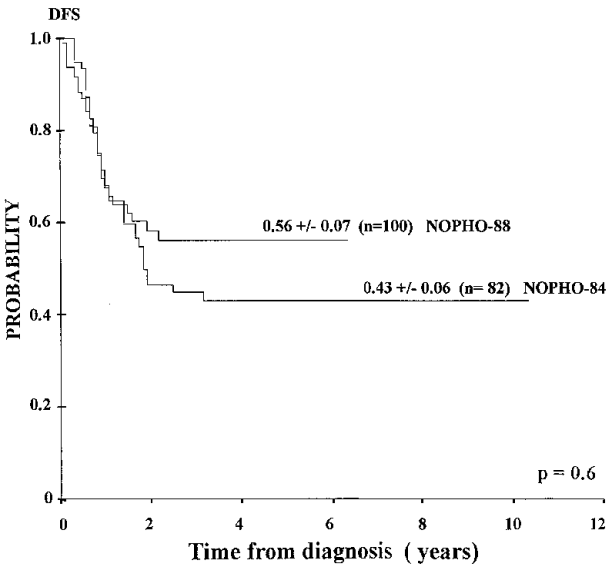


Fig 4. Probability of disease-free survival (DFS) in children receiving post-remission chemotherapy only. Children receiving a bone marrow transplant (being allogeneic or autologous) were censored at the time of transplantation.

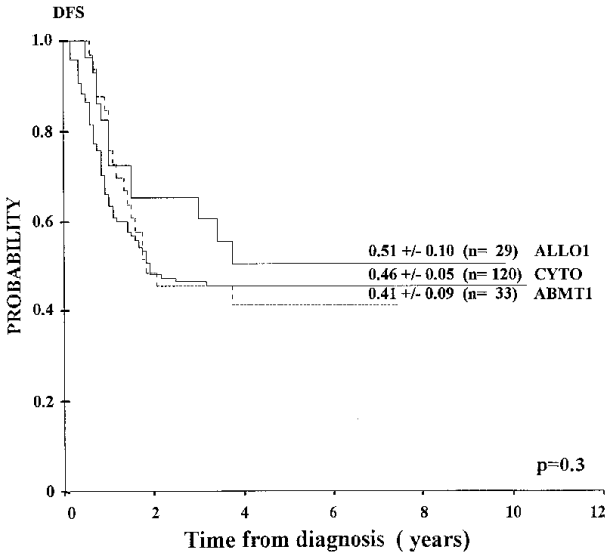


Fig 5. Probability of DFS in children according to whether they received allogeneic (including two unrelated) or autologous bone marrow transplantation or chemotherapy only. Data from NOPHO-84 and NOPHO-88 are pooled.

population in the two studies (Table III) and treatment outcome, it was possible to pool patient data before looking for prognostic factors.

Several clinical and laboratory characteristics were examined as potential markers of outcome in this population-based study.

Cox analyses were performed on all 223 children with regard to age, Hb, WBC, FAB, gender, year of diagnosis and Down's syndrome. These factors were also analysed for children who achieved remission. Gender was found to be the only significant prognostic factor ($P = 0{\cdot}01$). If only children with achieved remission were analysed, the factors with prognostic significance were Down's syndrome ($P < 0{\cdot}01$) and gender ($P = 0{\cdot}01$).

Of 23 children with Down's syndrome receiving appropriate chemotherapy, 17 went into remission and 13 are long-term survivors (p-DFS 0·79). This leukaemia is more responsive to treatment than the disease attacking non Down's syndrome children.

Gender was the only significant prognostic factor we observed (Fig 6). In both protocols females had a better prognosis. After the two studies were combined and the Down's children were excluded, p-EFS for girls was 0·43 *v* 0·26 for boys ($P < 0{\cdot}01$; Fig 6) and p-DFS 0·52 for girls and 0·31 for boys ($P < 0{\cdot}01$). If death in CCR is ignored, the significance is even greater (0·55 for girls versus 0·35 for boys).

Age at diagnosis did not strongly associate with outcome, the time to obtain remission or duration of the first remission. The prognosis was worst in patients aged between 1 and 2 years; only 35% of these patients remain in CCR. Of the infants <12 months of age, 58% remain in CCR. However, this difference is not statistically significant.

Other prognostic factors were not found. In contrast to many other studies, high white blood cell count at diagnosis did not influence treatment outcome.

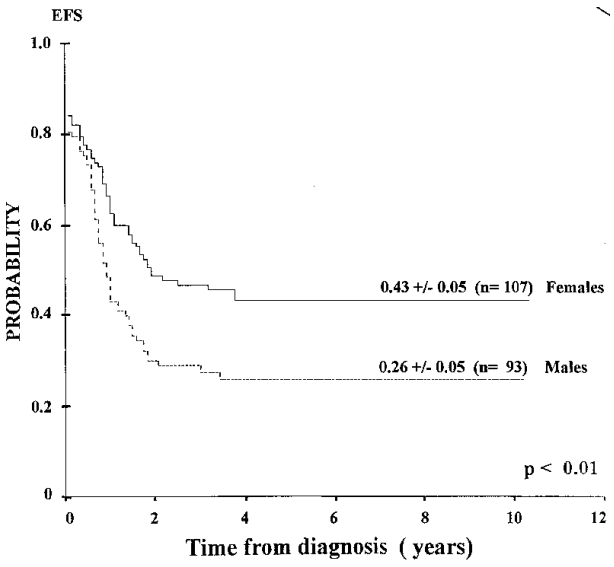


Fig 6. Probability of EFS according to gender. Data from NOPHO-84 and NOPHO-88 are pooled. Children with Down's syndrome are excluded.

DISCUSSION

We have presented data on all children with AML diagnosed in the five Nordic countries from July 1984 through to December 1992. The incidence was similar within the five countries with an annual incidence of 0·7 new cases per 100 000 children aged <16 years. When compared with other series (Neglia & Robison, 1988; Boulad & Kernan, 1993), it is surprising that we have a definite age peak in the first 2 years of life. This is explained partly by the high frequency of children with Down's syndrome in this age group. 35 of the patients (13%) had Down's syndrome and only one was <12 months of age. This is a much higher incidence than reported elsewhere. In the large German and Italian studies (Creutzig *et al*, 1990, 1993; Amadori *et al*, 1993), children with Down's syndrome are probably not included. In the U.K., 5·1% of children with AML are reported to have Down's syndrome (Stiller & Eatock, 1994), and a large survey conducted by the Childrens Cancer Group (CCG) in the U.S.A. reported 2% of AML cases to be Down's syndrome (Robison *et al*, 1984). In a Pediatric Oncology Group material, 12/285 children (4%) had Down's syndrome (Ravindranath *et al*, 1992). This discrepancy between our finding and other studies might reflect the fact that our study is population-based where every case is recorded.

The incidence over the years was similar, with about 30 new cases annually. The distribution of important disease characteristics, except for age and Down's syndrome, was not different from other series (Table III).

The two protocols used varied in intensity with NOPHO-88 being on the borderline of acceptable toxicity. Long-lasting aplasia followed the induction regimen in all treated children.

Table IV. Results of chemotherapy in childhood AML.

	CCG-251 (Nesbit *et al*, 1994)	CCG-213 (Wells *et al*, 1994)	POG-8498 (Ravindrath *et al*, 1991)	CCG-2861 (Woods *et al*, 1993)	AIEOP (Amadori *et al*, 1993)	BFM-83 (Creutzig *et al*, 1990)	BFM-87 (Creutzig *et al*, 1993)	MRC-10 (Stevens *et al*, 1994)	NOPHO-84	NOPHO-88
Years entered	1979–83	1986–89	1984–88	1986–89	1987–90	1982–86	1986–91	1988–93	1984–88	1988–92
No. evaluable	490	591	285	142	161	173	210	270	105	118
Death in aplasia (%)	10	6	7	13	7	7	5	9	8	12
Resistant disease (%)	12	15	8	11	14	13	17		14	3
Complete remission (%)	78	77	85	76	79	80	78	91	78	85
p-DFS	0·4	0·39	0·45	0·4	0·31	0·61	0·52	0·56	0·43	0·56

Death in aplasia was seen in 12% in NOPHO-88 and 8% in NOPHO-84. Of even greater concern was that 10 children died in CCR after consolidation therapy in NOPHO-88, whereas only one child died after consolidation in NOPHO-84. Therefore the addition of etoposide and mitoxantrone did not improve the overall results due to these complications.

Autologous bone marrow transplantation was added to the protocol in some centres. The overall results in this group were not better than in the group receiving conventional chemotherapy. Patients treated with allogeneic transplantation may turn out to have a better prognosis than patients treated with chemotherapy alone, but so far the difference is not statistically significant (Fig 5). Since bone marrow transplantation was not done in a randomized fashion, the effect of these therapies must be left open.

The strongest significant prognostic factor found in our study was the effect of gender (Fig 6). After obtaining remission, girls did significantly better than boys in both protocols. This effect of gender has not been detected in other studies of childhood AML, but we have previously reported on a remarkable effect of gender on high-risk ALL, with girls doing much better than boys (Lanning *et al*, 1992).

It is now a well-established fact that children with Down's syndrome developing AML have a disease which is more responsive to aggressive chemotherapy (Ravindranath *et al*, 1992; Slørdahl *et al*, 1992, 1993; Zipursky *et al*, 1992). A large number of cases appear to be of a distinct subtype related to M7 and with markers from several lineages on their malignant cell surface (Slørdahl *et al*, 1992, 1993).

NOPHO-84 had a simple consolidation therapy consisting exclusively of four courses of high-dose Ara-C with no other drugs added (Lie *et al*, 1990). The fact that the addition of etoposide and mitoxantrone (NOPHO-88) did not improve the treatment results suggest that more is not necessarily better. We observe that toxicity problems outweigh the possible benefit of the intensified therapy. Our current protocol takes this into consideration, since every child will receive the first induction course of NOPHO-88 and then remain without therapy until the child either achieves a remission or persistent disease is documented. Non-responders will then proceed to the intensified therapy with mitoxantrone and etoposide as in NOPHO-88, whereas in responders induction course 1 will be repeated. In this way we hope to reduce the toxicity by limiting the most aggressive therapy to the most resistant disease.

Our results compare favourably with other reported studies. The largest studies are presented in Table IV (Creutzig *et al*, 1990, 1993; Ravindranath *et al*, 1991; Amadori *et al*, 1993; Woods *et al*, 1993; Nesbit *et al*, 1994; Stevens *et al*, 1994; Wells *et al*, 1994). One of the most challenging preliminary reports is that of the timed intensive induction therapy reported by Woods *et al* (1994). Their very intensive induction did not improve the percentage of children entering remission, but certainly improved postremission outcome, regardless of post-remission therapy. Their results are in conflict with ours, where NOPHO-88 is an example of a very intensive 'up-front' therapy, but where problems of toxicity outweigh the benefit of increased therapy. Otherwise it is remarkable (Table IV) that most of the studies are comparable in terms of the proportion of long-term survivors. Extensive

use of bone marrow transplantation has certainly not led to a significant improvement. New strategies such as the use of growth factors, inducers of differentiation (such as retinoic acid in M3) and improved supportive care may improve outcome, but AML continues to be a major challenge in paediatric oncology.

REFERENCES

Amadori, S., Testi, A.M., Arico, M., Gomelli, A., Giuilano, M., Madon, E., Masera, G., Randelli, R., Zanesco, L. & Mandelli, F. (1993) Prospective comparative study of bone marrow transplantation and postremission chemotherapy for childhood acute myelogenous leukaemia. *Journal of Clinical Oncology*, **11**, 1046–1054.

Boulad, F. & Kernan, N.A. (1993) Treatment of childhood acute nonlymphoblastic leukemia: a review. *Cancer Investigation*, **11**, 534–553.

Cox, D. (1972) Regression models and life-tables. *Journal of the Royal Statistical Society*, **B4**, 187–202.

Creutzig, U., Ritter, J. & Schellong, G. (1990) Identification of two risk groups in childhood acute myelogenous leukemia after therapy intensification in study AML-BFM-83 as compared with study AML-BFM-78. *Blood*, **75**, 1932–1940.

Creutzig, U., Ritter, J., Zimmermann, M. & Schellong, G. (1993) Does cranial irradiation reduce the risk for bone marrow relapse in acute myelogenous leukaemia? Unexpected results of the childhood acute myelogenous leukaemia study BFM-87. *Journal of Clinical Oncology*, **11**, 279–286.

Kaplan, E.L. & Meier, P. (1958) Non-parametric estimation from incomplete observations. *Journal of the American Statistical Association*, **53**, 457–481.

Lanning, M., Garwicz, S., Hertz, H., Jonmundsson, G., Kreuger, A., Lie, S.O., Moe, P.J., Salmi, T.T., Schrøder, H., Siimes, M.A., Wesenberg, F., Yssing, M., Åhstrøm, L. & Gustafsson, G. (1992) Superior treatment results in females with high-risk acute lymphoblastic leukemia in childhood. *Acta Paediatrica*, **81**, 66–68.

Lie, S.O. (1989) Acute myelogenous leukaemia in children. *European Journal of Pediatrics*, **148**, 382–388.

Lie, S.O., Berglund, G., Gustafsson, G., Jonmundsson, G., Siimes, M. & Yssing, M. (1990) High-dose Ara-C as a single-agent consolidation therapy in childhood acute myelogenous leukaemia. *Haematology and Blood Transfusion*, **33**, 215–221.

Lie, S.O. & Gustafsson, G. (1992) Progress in the treatment of childhood leukaemias. *Annals of Medicine*, **24**, 319–323.

Mantel, N. (1966) Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy*, **50**, 163–170.

Neglia, J.P. & Robison, L.L. (1988) Epidemiology of the childhood acute leukemias. *Pediatric Clinics of North America*, **35**, 674–692.

Nesbit, M.E., Buckley, J.D., Feig, S.A., Anderson, J.R., Lampkin, B., Bernstein, I.D., Kim, T.H., Piomelli, S., Kersey, J.H., Coccia, P.F., O'Reilly, R.C., August, C., Thomas, E.D. & Hammond, G.D. (1994) Chemotherapy for induction of remission of childhood acute myeloid leukaemia followed by marrow transplantation or multiagent chemotherapy: a report from the Childrens Cancer Group. *Journal of Clinical Oncology*, **12**, 127–135.

Norusis, M.J. (1992) *SPSS Statistical Software 5.0 for Windows*. SPSS Inc., Chicago, Ill.

Novakovic, B. (1994) U.S. childhood cancer survival, 1973–1987. *Medical and Pediatric Oncology*, **23**, 480–486.

Ravindranath, Y., Abella, E., Krischer, J.P., Wiley, J., Inoue, S., Harris, M., Chauvenet, A., Alvarado, C.S., Dubowy, R., Ritchey, A.K., Land, V., Steuber, C.P. & Weinstein, H. (1992) Acute myeloid leukemia (AML) in Down's syndrome is highly responsive to chemotherapy: experience on Pediatric Oncology Group AML Study 8498. *Blood*, **80**, 2210–2214.

Ravindranath, Y. & Schultz, K.R. (1994) Acute myeloid leukaemias. *Neoplastic Diseases of Childhood* (ed. by C. Pochedly), Vol. 1, pp. 519–540. Harwood Academic Publishers, London.

Ravindranath, Y., Steuber, C.P., Krischer, J., Civin, C.I., Ducore, J., Vega, R., Pitel, P., Inoue, S., Bleher, E., Sexauer, C., Hutter, J. & Vietti, T. (1991) High-dose cytarabine for intensification of early therapy of childhood acute myeloid leukaemia: a Pediatric Oncology Group Study. *Journal of Clinical Oncology*, **9**, 572–580.

Robison, L.L., Nesbit, M.E., Sather, H.N., Level, C., Shahidi, N., Kennedy, A. & Hammond, D. (1984) Down syndrome and acute leukemia in children: a 10-year retrospective survey from Childrens Cancer Study Group. *Journal of Pediatrics*, **105**, 235–242.

Slørdahl, S.H., Gustafsson, G., Jonmundsson, G., Mellander, L., Siimes, M.A., Yssing, M. & Lie, S.O. (1992) Down's syndrome (DS) and acute myelogenous leukemia (AML): a population-based study in the five Nordic countries. (Abstract). *Medical and Pediatric Oncology*, **20**, 373.

Slørdahl, S.H., Smeland, E.B., Holte, H., Grønn, M., Lie, S.O. & Seip, M. (1993) Leukemic blasts with markers of four cell lineages in Down's syndrome ('megakaryoblastic leukemia'). *Medical and Pediatric Oncology*, **21**, 254–258.

Stevens, R.F., Hann, I.M., Burnett, A.K., Goldstone, A.H., Wheatley, K. & Gray, R.G. (1994) Improved outcome in pediatric acute myeloid leukemia: results of the MRC AML 10 Trial. (Abstract). *Medical and Pediatric Oncology*, **23**, 172.

Stiller, C.A. & Eatock, E.M. (1994) Survival from acute non–lymphocytic leukaemia, 1971–88: a population-based study. *Archives of Disease in Childhood*, **70**, 219–223.

Wells, R.J., Woods, W.G., Buckley, J.D., Odom, L.F., Benjamin, D., Bernstein, J., Betcher, D., Feig, S., Kim, T., Ruymann, F., Smithson, W., Srivastava, A., Tannous, R., Buckley, C.M., Whitt, J.K., Wolff, L. & Lampkin, B.C. (1994) Treatment of newly diagnosed children and adolescents with acute myeloid leukaemia: a Childrens Cancer Group Study. *Journal of Clinical Oncology*, **12**, 2367–2377.

Woods, W.G., Kobrinsky, N., Buckley, J., Neudorf, S., Sanders, J., Miller, L., Barnard, D., Benjamin, D., DeSwarte, J., Kalousek, D. & Lange, B.J. (1994) Timing intensive induction therapy improves post-remission outcome in acute myeloid leukemia (AML) irrespective of the use of bone marrow transplantation (BMT). *Blood*, **84**, (Suppl. 1), 232a.

Woods, W.G., Kobrinsky, N., Buckley, J., Neudorf, S., Sanders, J., Miller, L., Barnard, D., Benjamin, D., de Swarte, J., Kalousek, D., Shina, D., Hammond, G.D. & Lange, B.J. (1993) Intensively timed induction therapy followed by autologous or allogeneic bone marrow transplantation for children with acute myeloid leukaemia or myelodysplastic syndrome: a Childrens Cancer Group pilot study. *Journal of Clinical Oncology*, **11**, 1448–1457.

Zipursky, A., Poon, A. & Doyle, J. (1992) Leukemia in Down syndrome: a review. *Pediatric Hematology and Oncology*, **9**, 139–149.