Haematology and Blood Transfusion Vol. 33
Acute Leukemias II
Edited by Büchner, Schellong, Hiddemann, Ritter

High-Dose Ara-C as a Single-Agent Consolidation Therapy in Childhood Acute Myelogenous Leukemia

S. O. Lie [1], G. Berglund [2], G. Gustafsson [2], G. Jonmundsson [3], M. Siimes [4], and M. Yssing [5]

Acute myelogenous leukemia (AML) represents a difficult and heterogeneous group of leukemias from cells of myeloid origin [6, 8]. In the Nordic countries, all cases of acute childhood leukemias have been registered since 1 July 1981 [17]. By 31 December 1987, 1297 cases of leukemias had been registered, among which 184 (14%) were classified as AML. Traditionally the results of therapy in this group of leukemias are markedly inferior to those with acute lymphocytic leukemias, where progress is well known and well documented [8]. In recent years, however, the treatment of AML has slowly improved due to more aggressive and intensive chemotherapy. Many protocols now report a 70%–80% induction response rate with about 25%–50% long-term survivors after intensive consolidation therapy [1, 9, 11, 12, 16, 25, 28, 31, 34]. This paper is a preliminary report of the first Nordic trial on AML in children. Its main contribution is that it is a population-based study, and that it investigates the role of cytosine arabinoside (Ara-C) given at a high dose as the only drug in consolidation therapy.

[1] Dept. of Pediatrics, Rikshospitalet, Oslo, Norway
Nordic Society of Paediatric Hematology and Oncology (NOPHO), [1] Norway, [2] Sweden, [3] Iceland, [4] Finland, and [5] Denmark

Materials and Methods

One hundred and thirteen children with AML less than 15 years of age were entered into the trial from 1 July 1984 through 31 December 1987. To the best of our knowledge this represents every child with AML in our countries during this period. The diagnosis of AML was based on morphological examinations of bone marrow and histochemical stains. In most cases an extensive investigation with monoclonal antibodies was included. The study had no central review panel. Chromosome analysis of the malignant clones was performed in some centers but is not included in the present report.

Therapy

An outline of the protocol is shown in Fig. 1. Induction therapy consisted of three series including bolus Ara-C (100 mg/m^2 i.v. q12 h days 1, 2, 3, 4), 6-thioguanine (100 mg/m^2 p.o. q12 h days 1, 2, 3, 4), and doxorubicin (75 mg/m^2, given either as the DNA complex [21] on day 5 or as free drug divided in equal doses on days 5, 6). Consolidation therapy consisted of high-dose Ara-C (2 g/m^2 q12 h days 1, 2, 3) repeated four times with a 3- to 4-week interval (total length of therapy, 7–9 months). Some children received high-dose retinol as maintenance [22, 23], but its role will not be analyzed further in this report.

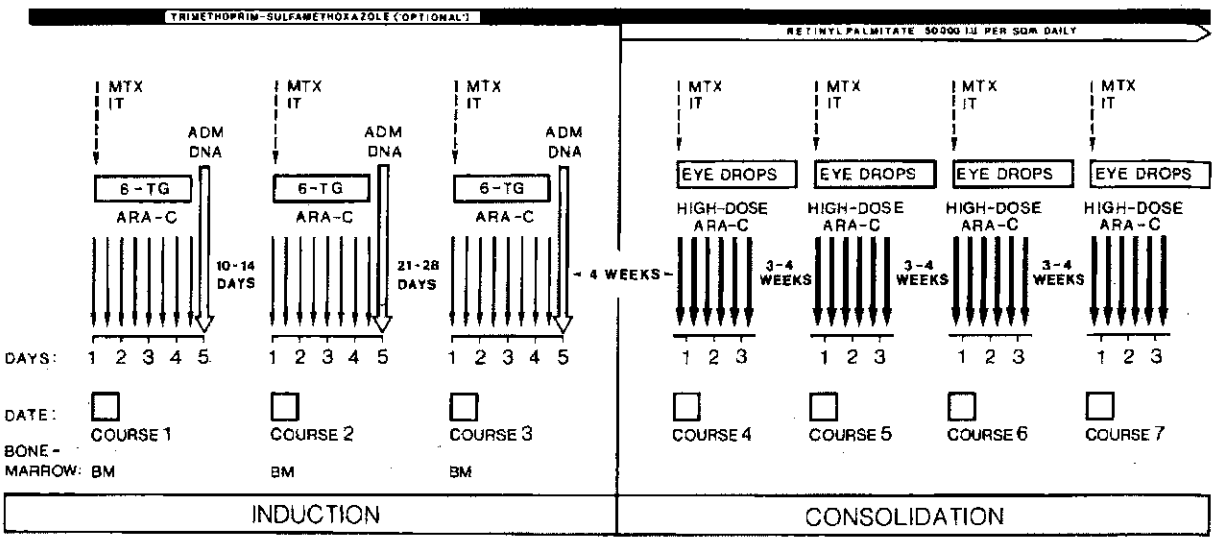

Fig. 1. Induction and consolidation regimen in AML study NOPHO-84

Prognostic Factors

Age, sex, presenting white blood cell count, platelet count, morphological subtypes, and the number and interval between induction courses needed to achieve a remission were evaluated for influence on remission induction rate and disease-free survival. The statistical methods used were life table analysis according to Kaplan Meyer and significance tests according to the chi square distribution test [18].

Results

Epidemiological Data

Table 1 presents the total number of cases reported to the study from the participating countries each year. Table 2 compares the French-American-British (FAB) subtypes in the 102 patients where this information was available, with the distribution presented by the BFM-78 study [11]. The relative frequencies are rather similar, but with a somewhat higher incidence of monocytic leukemia in the German series.

We were surprised to find a high frequency of Down's syndrome in our study. Eighteen out of 109 de novo AML cases had trisomy 21 (17%). Table 3 shows the distribution according to country and sex. It is surprising that in each country there is a preponderance of trisomy 21 girls developing AML. Table 4 shows that the age distribution in children with Down's syndrome is different from that in the total material.

Table 1. No. of AML cases/year

	1984*	1985	1986	1987	Total
Denmark	6	5	7	8	26
Finland	2	11	2	4	19
Iceland	1	0	0	1	2
Norway	4	7	8	8	27
Sweden	3	6	15	14	39
Total	16	29	32	34	113

* (6 months)

Table 2. FAB subtypes in NOPHO 84 and BFM 78

FAB	NOPHO *n* (%)	BFM 78 *n* (%)
1	22 (21)	36 (24)
2	33 (31)	34 (23)
3	7 (7)	6 (4)
4	18 (17)	40 (26)
5	12 (12)	32 (21)
6	8 (8)	3 (2)
7	2 (2)	–
	102 (100)	151 (100)

Table 3. NOPHO 1984: Down's syndrome and AML

	Male	Female
Denmark	1	3
Finland	0	1
Iceland	0	0
Norway	1	4
Sweden	1	7
Total	3	15

Eighteen out of 109 de novo AMLs = 17%

Table 4. Age distribution

Years	*n*	Down's + AML
< 1	14	0
1 – 2	20	10
2 – 5	28	8
5 – 10	20	0
> 10	27	0
Total	109	

Most cases of Down's syndrome were close to 24 months of age at diagnosis, and only one was more than 3 years old.

There was also an unsuspected high frequency of preleukemic syndrome in our patients. Twenty-two out of the 109 children had been evaluated for a hematological disorder for more than 2 months because of a cytopenia in at least two of the three cell lines. Ten of these were Down's syndromes.

Induction of Remission

The patient material is summarized in Table 5. Seventeen cases were excluded from further analysis, four because of a secondary malignancy, seven children were electively not treated (six with Down's syndrome, one with a probably transient leukemoid reaction), five were treated on a different protocol, while one died of a massive disease before therapy could be initiated. Remission was obtained in 70 of the 96 remaining evaluable cases (73%). Seven children died in aplasia, while 19 had resistant disease. Three of the seven that died in aplasia had

Table 5. Acute myelogenous leukemia: NOPHO 1984 (January 1988)

Total No. entered		113
Exclusions: secondary malignancy	4	
No therapy	7	
Other protocol	5	
Death before therapy	1	
	17	
On study		96
Death in aplasia	7	
Resistant disease	19	
	26	
Complete remission		70 (73%)
Bone marrow transplant	14	
Chemotherapy group		56

M5 and one had Down's syndrome. There was no identifiable prognostic variable that indicated resistant disease. However, of the 19 resistant cases, 14 received a variety of other protocols after the failure of the initial therapy. Twelve of these patients were resistant also to these other very intensive therapies. Only two achieved a remission; both of these were bone marrow transplanted and remain in remission at 4+ and 22+ months.

Therapy of Down's syndrome cases is usually considered to be difficult. Only 9 of the 18 children received the NOPHO (Nordic Society for Pediatric Hematology and Oncology) protocol. Eight of the nine achieved a remission. Two received other protocols and both died. One received a therapy unknown to us and six received no therapy. All six untreated children died from progressive disease.

Preleukemia may be a prognostic factor in children with AML. Twenty-two were diagnosed as having a definite preleukemic phase in their disease. Twelve of the children with preleukemia received the NOPHO protocol and only seven of these achieved a complete remission.

Consolidation Therapy

Fourteen children were bone marrow transplanted in first remission at various time points after remission was obtained. They

will not be analyzed further here – but are censored at 5 months from diagnosis.

Fifty-six children received a total of 224 courses of high-dose Ara-C. One girl, 13 years of age, with an M2 leukemia, died unexpectedly and from unexplained reasons after the first course of high-dose Ara-C. It remains unclear whether or not the fatal outcome was related to the high-dose therapy. No other death in complete remission has been reported.

Duration of Remission

Figure 2 shows the probability of remaining in complete remission for the 70 patients achieving a complete response on the NOPHO induction protocol. The 5-year actuarial disease-free survival is about 40%. Of the prognostic factors analyzed, only white blood cells at diagnosis turned out to be a statistically significant prognostic factor (Fig. 3). The promising aspect of the survival curve is that there seems to be a definite plateau, with most of the relapses taking place during the first 2 years and with only one relapse observed after 24 months from diagnosis. Seven of the eight patients with Down's syndrome responding to induction therapy remain in remission.

Discussion

This study on acute myelogenous leukemia in the Nordic countries is a population-based study. Two interesting epidemiological findings deserve emphasis. Seventeen percent of the cases had Down's syndrome. The increased incidence of leukemia in Down's syndrome is well known [24, 29] and affects both the myeloid and lymphoid lineages. However, in most of the multicenter studies on AML reported so far they contribute less than 5% of the cases [29], which probably must mean that patients with Down's syndrome are not included in these studies.

The high frequency of preleukemia (20%) is also a new finding. In adults this is certainly well known and carries a grave prognosis [3]. In children it is reported to be less frequent [4, 10, 19, 20, 30, 32, 33]. In our series half the patients with preleukemia also had Down's syndrome, 12 children not having this diagnosis with a preleukemic phase. It seems that this factor carries a significant poor prognosis also in children since only three of these children are alive.

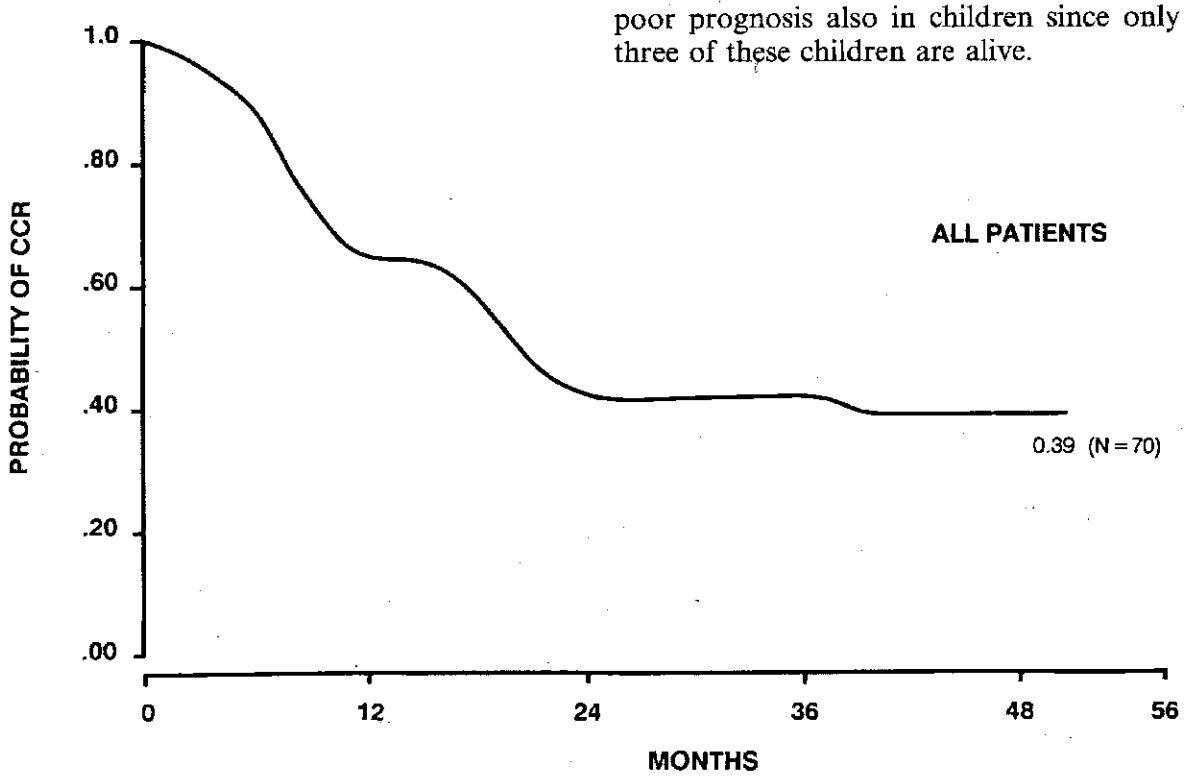

Fig. 2. Probability of disease-free survival in the complete responders

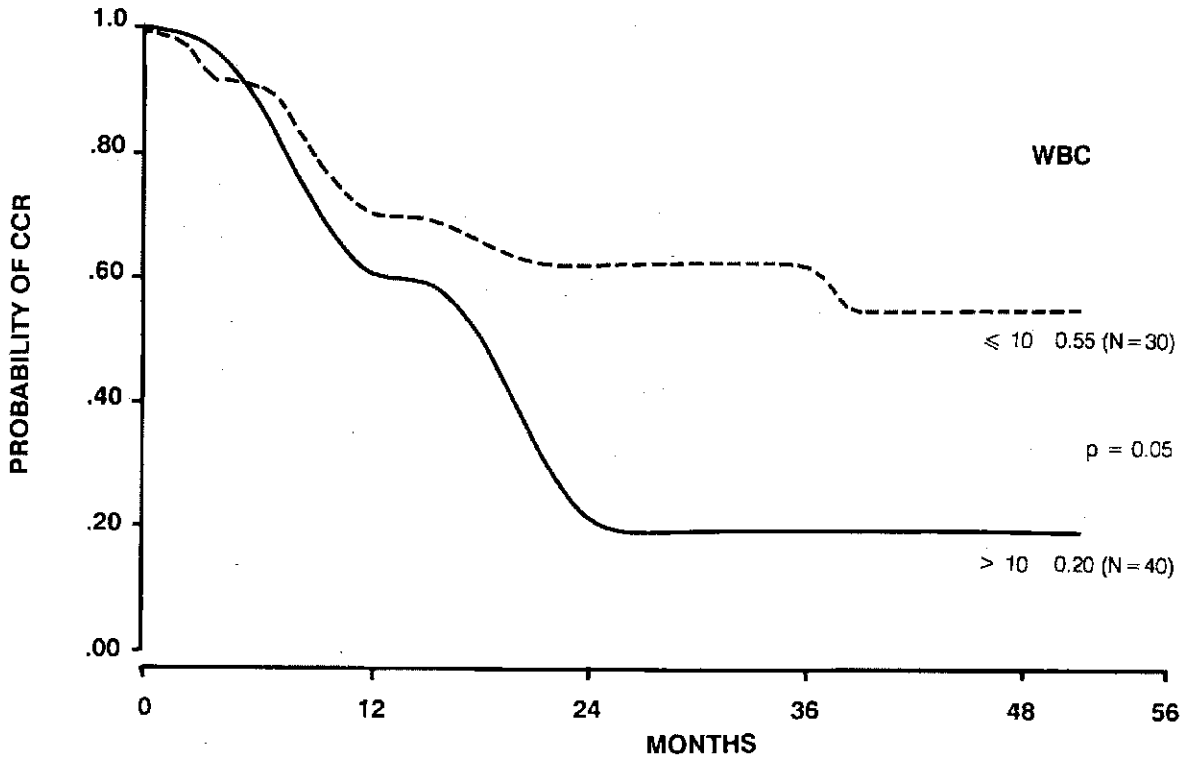

Fig. 3. Probability of disease-free survival in the complete responders according to WBC at diagnosis

The results of the induction part of the protocol are comparable to most intensive studies reported so far. Perhaps the frequency of resistant disease is a little higher while death in aplasia is lower. However, even though 14 of the 19 resistant cases were tested on other very high intensity protocols, only 2 of these children achieved a new remission, indicating that resistance to first-line therapy as used in this study carries a very grave prognosis.

The consolidation phase of the protocol is very simple, consisting of only four courses of high-dose Ara-C (2 g q12 h for six doses). This drug is certainly the mainstay of antileukemic therapy [13, 15] and its use in high doses is part of many protocols today [2, 5, 7, 14, 26, 27, 34]. In our multicenter study it was shown to be a safe therapy with acceptable side effects.

The shape of the survival curve certainly indicates that 40% of the responders may be cured of their disease since there is a definite plateau in the survival curve. This compares favorably with many other reported studies but leaves much room for improvement.

References

1. Amadori S, Ceci A, Comelli A, Madon E, Masera G, Nespoli L, Paolucci G, Zanesco L, Covelli A, Mandelli F (1987) Treatment of acute myelogenous leukemia in children: results of the Italian Cooperative Study AIEOP/LAM 8204. J Clin Oncol 5:1356–1363
2. Barrios NJ, Tebbi CK, Freeman AI, Brecher ML (1987) Toxicity of high dose Ara-C in children and adolescents. Cancer 60:165–169
3. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Gralnick HR, Sultan C (1982) Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 51:189–199
4. Blank J, Lange B (1981) Preleukemia in children. J Pediatr 98:565–568
5. Bloomfield CD (1985) Postremission therapy in acute myeloid leukemia. J Clin Oncol 3:1570–1572
6. Champlin R, Gale P (1987) Acute myelogenous leukemia: recent advances in therapy. Blood 69:1551–1562
7. Champlin R, Ho W, Winston D, Decker R, Greenberg P, Burnison M, Holly EE, Gale PG (1987) Treatment of adults with acute myelogenous leukemia: prospective evalua-

tion of high-dose cytarabine in consolidation chemotherapy and with bone marrow transplantation. Semin Oncol 14 (Suppl 1) 2:1–6
8. Chessels J (1986) Acute leukaemia in children. In: Gale RP, Hoffbrand AV (eds) Clinics in haematology. Saunders, Philadelphia 15:727–753
9. Chessells JM, O'Callaghan U, Hardisty RM (1986) Acute myeloid leukaemia in childhood: clinical features and prognosis. Br J Haematol 63:555–564
10. Creutzig U, Cantú-Rajnoldi A, Ritter J, Romitti L, Odenwald E, Conter V, Riehm H, Masera G (1987) Myelodysplastic syndromes in childhood. Report of 21 patients from Italy and West Germany. Am J Pediatr Hematol Oncol 9:324–330
11. Creutzig U, Ritter J, Riehm H, Budde H, Schellong G (1987) The childhood AML studies BFM-78 and BFM-83. Treatment results and risk factor analysis. In: Büchner T, Schellong G, Hiddemann W, Urbanitz D, Ritter J (eds) Acute leukemias. Prognostic factors and treatment strategies. Springer, Berlin Heidelberg New York, pp 71–75
12. Dahl GV, Kalwinsky DK, Mirro J, Look AT (1987) A comparison of cytokinetically based versus intensive chemotherapy for childhood acute myelogenous leukemia. In: Büchner T, Schellong G, Hiddemann W, Urbanitz D, Ritter J (eds) Acute leukemias. Prognostic factors and treatment strategies. Springer, Berlin Heidelberg New York, pp 83–87
13. Desforges JF (1983) Cytarabine: low-dose, high-dose, no dose? N Engl J Med 309:1637–1639
14. Early AP, Preisler HD, Slocum H, Rustum YM (1982) A pilot study of high-dose 1-β-D-arabinosufranosylcytosine for acute leukemia and refractory lymphoma: clinical response and pharmacology. Cancer Res 42:1587–1594
15. Freireich EJ (1987) Arabinosyl cytosine: a 20-year update. J Clin Oncol 5:523–524
16. Grier HE, Gelber RD, Camitta BM, Delorey MJ, Link MP, Price KN, Leavitt PR, Weinstein HJ (1987) Prognostic factors in childhood acute myelogenous leukemia. J Clin Oncol 5:1026–1032
17. Gustafsson G, Garwicz S, Hertz H, Johanesson G, Jonmundsson G, Moe PJ, Salmi T, Seip M, Siimes MA, Yssing M, Åhström L (1987) A population-based study of childhood acute lymphoblastic leukemia diagnosed from July 1981 through June 1985 in the five Nordic countries. Acta Pædiatr Scand 76:781–788
18. Harrell F (1980) The PHGLM procedure. In: SAS supplement users guide. SAS Inst Inc, Cary, NC pp 119–131
19. Kleihauer E (1980) The preleukemic syndromes (hematopoietic dysplasia) in childhood. Eur J Pediatr 133:5–10
20. Kobrinsky NL, Nesbit ME Jr, Ramsay NKC, Arthur DC, Krivit W, Brunning RD (1982) Hematopoietic dysplasia and marrow hypocellularity in children: a preleukemic condition. J Pediatr 100:907–913
21. Lie SO, Lie KK, Glomstein A (1979) Clinical and pharmacologic studies with Adriamycin-DNA complex in children with malignant disease. Cancer Chemother Pharmacol 2:61–66
22. Lie S, Slørdahl S (1984) Vitamin A and/or high-dose Ara-C in the maintenance of remission in acute myelogenous leukaemia in children? Scand J Haematol 33:256–259
23. Lie SO, Wathne K-O, Petersen L, Slørdahl SH, Norum KR (1988) High-dose retinol in children with acute myelogenous leukemia in remission. Eur J Haematol 40:460–465
24. Miller RW (1967) Persons with exceptionally high risk of leukemia. Cancer Res 27:2420–2423
25. Nesbit M, Buckley J, Lampkin B, Bernstein I, Kim T, Piomelli S, Kersey J, Feig S, Coccia P, O'Reilly R, August C, Thomas ED, Hammond D (1987) Comparison of allogeneic bone marrow transplantation (BMT) with maintenance chemotherapy in previously untreated childhood acute non-lymphocytic leukemia (ANLL). Proc Am Soc Clin Oncol 6:163
26. Peters WG, Colly LP, Willemze R (1988) High-dose cytosine arabinoside: pharmacological and clinical aspects. Blut 56:1–11
27. Plunkett W, Liliemark JO, Estey E, Kreating MJ (1987) Saturation of ara-CTP accumulation during high-dose ara-C therapy: pharmacologic rationale for intermediate-dose ara-C. Semin Oncol 14 (Suppl 1) 2:159–166
28. Rees J, Gray R, Swirsky D, Hayhoe F (1986) Principal results of the Medical Research Councils 8th acute myeloid leukaemia trial. Lancet 2:1236–1241
29. Robison LL, Nesbit ME, Sather HN, Level C, Shahidi N, Kennedy M, Hammond D (1984) Down's syndrome and acute leukemia in children: a 10-year retrospective survey from Childrens Cancer Study Group. J Pediatr 105:235–242
30. Wegelius R (1986) Preleukaemic states in children. Scand J Haematol 36 (45):133–139
31. Weinstein HJ, Mayer RJ, Rosenthal DS, Coral FS, Camitta BM, Gelber RD (1983) Chemotherapy of acute myelogenous leukemia in children and adults: VAPA update. Blood 62:315–319
32. Weiss K, Stass S, Williams D, Kalwinsky D, Dahl GV, Wang W, Johnson FL, Murphy SB, Dow LW (1987) Childhood monosomy 7

syndrome: clinical and in vitro studies. Leukemia 1:97–104
33. Wering ER van, Kamps WA, Vossen JM, List-Nuver CJA van der, Theunissen PMV (1985) Myelodysplastic syndromes in childhood: three case reports. Br J Haematol 60:137–142
34. Wolff SN, Marion J, Stein RS, Flexner JM, Lazarus HM, Spitzer TR, Philips GL, Herzig RH, Herzig GP (1985) High-dose cytosine arabinoside and daunorubicin as consolidation therapy for acute nonlymphocytic leukemia in first remission: a pilot study. Blood 65:1407–1411