Chemotherapy of Acute Myelocytic Leukemia in Children[a]

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Acute myelocytic leukemia (AML) in both children and adults is a more complex and resistant disease than acute lymphocytic leukemia. Progress has been slower and therapy more complicated, but with intensive myelosuppressive induction and further postremission therapy one-third of such patients may now achieve long-term survival and probably be cured.[1-5]

In the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) hospital services are, in principle, free to all citizens. Private hospitals are very few, and "lost to follow-up" patients a rarity. These countries offer, therefore, a unique possibility for performing population-based studies and to trace patients for follow-up. The Nordic Society of Paediatric Haematology and Oncology (NOPHO) was established in 1981, and we now have documented information on every case of any childhood acute leukemia in a population of 23 million inhabitants. Examples will be drawn from our experience during the last decade.[6]

The major focus of this chapter will be on therapy, but a brief review of epidemiology and biology will be given as a background.

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TABLE 1. Number and Incidence (Inc) of Acute Leukemias in the Nordic Countries from July 1984 through December 1992

	Total	% AML	Inc_{TOT}[a]	Inc_{AML}[a]
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

[a] Per 100,000 children < 16 years per year.

EPIDEMIOLOGY

TABLE 1 shows the incidence of all acute leukemias in the Nordic countries: 4.6 new cases are diagnosed every year per 10^5 children younger than 16 years of age. AML accounts for 16% of these, which means that slightly less than one child per 100,000 per year develop this disease. In black children the relative incidence of AML is significantly higher due to the lower incidence of ALL.[1]

The age distribution of our patients is seen in FIGURE 1. The distinct peak incidence in the lower age group is higher than has been reported in other material. Part of this can be explained by the high frequency of Down's syndrome in our series. Children with trisomy 21 actually account for 13% of all new cases.[7,8]

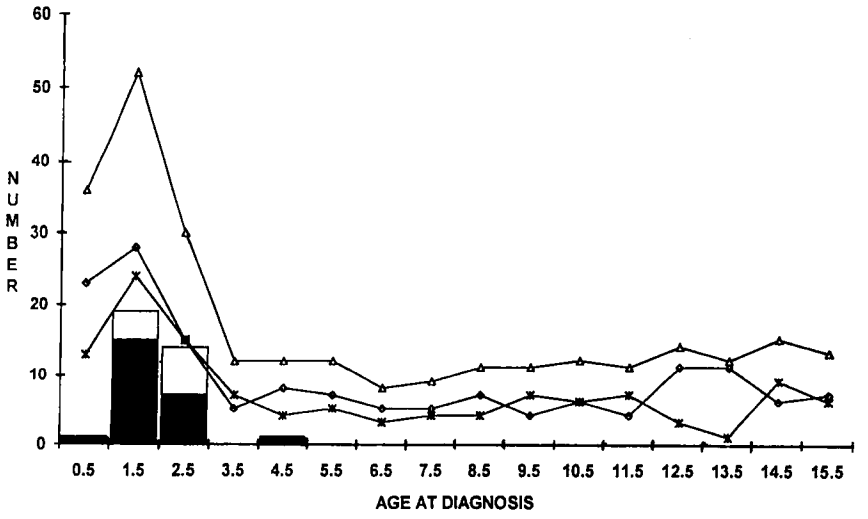

FIGURE 1. Age distribution of children with acute myelocytic leukemia. ■ Down's syndrome females; □ Down's syndrome males; —△— Total; —◇—females; and —*— males.

BIOLOGY

The French–American–British (FAB) classification from 1985 distinguished seven subgroups (M1-M7) on the basis of conventional morphology, cytochemical, and immunological methods.[9] M0 has been added by the same working group as a very undifferentiated leukemia.[10]

In children with AML, the types M1 and M2 account for 30–40% and M4 for about 25%. The megakaryoblastic leukemia (M7) is strongly associated with Down's syndrome.

Specific chromosomal abnormalities have been found in the various FAB subclasses. Translocation between chromosomes 8 and 21 is found almost exclusively in M1 and M2. All cases with M3 should carry the translocation t(15:17). Furthermore, M5 is associated with t(9;11). Abnormalities of chromosome 16 are seen predominantly in patients with M4. A recent review has been published by the Children's Cancer Group.[11] The chromosomal translocations often affect transcription factors that are involved in regulation of myeloid differentiation. In recent years great interest has been focused on the chromosomal changes involving 11q23 which is commonly seen in infants. The gene has recently been characterized and given various names (MLL, HRX, and ALL-1). It is related to a homebox gene in *Drosophila* which, when mutated, gives rise to bizarre malformations in chest and abdomen. Also, the chromosomal products of t(8;21) and t(15;17) have recently been defined. It is one of the most exciting developments in the biology of leukemias that the promyelocytic (M3) leukemia responds to all-*trans* retinoic acid (ATRA). Accordingly, it may be treated separately from all the other forms of AML.[12,13] The α-receptor for ATRA is located at the breakpoint on chromosome 17.

THERAPY

Before the 1970s, nearly every child with acute myelocytic leukemia died. After effective agents, including cytosine arabinoside (ara-C) and anthracyclines, became available in the 70s, a temporary remission could be induced in some patients, but most of them relapsed. It is the increased intensity of later protocols that has made it possible to cure at least some of the children. The first primary objective is to achieve a complete remission.

Remission Induction

TABLE 2 presents the remission induction results of some recent studies. Failure to enter remission may be due either to resistant disease or to death in aplasia. It is clear from the table that lack of intensity may cost death from resistant disease while increasing intensity beyond a certain level makes death from aplasia unacceptably high. In spite of several randomized studies, the most effective induction regimen that exists still consists of a 5- to 7-day course of ara-C (by continuous infusion or twice daily) with three days of anthracycline with or without other agents such as VP 16. With such regimens, remission rates of 70–85% in children with AML can be expected.

A topic of great debate is the effect of induction therapy, not only on remission rates but also on long-term survival. In their recently published paper, Woods and coworkers[14] have shown that very intensive timed sequential induction therapy

TABLE 2. Results of Chemotherapy in Childhood AML

	CCG-213[17]	POG-8498[18]	POG (1996)[19]	CCG-2891 intens[14]	CCG-2891 stand[14]	CCG-2861[20]	AIEOP[21]	BFM-83[16]	BFM-87[16]	MCR-10[22]	NOPHO-84[8]	NOPHO-88[8]
Years entered	1986–89	1984–88	1988–93	1989–93	1989–93	1986–89	1987–90	1982–86	1986–91	1988–93	1984–88	1988–92
Number evaluable	591	285	552	295	294	142	161	173	210	270	105	118
Death in aplasia (%)	6	7	11	14	26	13	7	7	5	9	8	12
Resistant disease (%)	15	8	4	11	4	11	14	13	17	9	14	3
Complete remission (%)	77	85	85	75%	70%	76	79	80	78	91	78	85
pDFS	0,39	0,45				0,4	0,31	0,61	0,52	0,56	0,43	0,56

improves the outcome in AML. When their protocol (DCTER, which is an intensive protocol of five drugs in four days) is given seven days apart regardless of blood counts, the results are much better than the standard time interval when the second DCTER is given after bone marrow recovery. The price to pay is that 11% die of toxicity during induction compared to 4% with the standard timing.

Post Remission Therapy

TABLE 1 also presents the disease-free survival of the studies mentioned above. It is always difficult to compare studies, but it is evident that many different protocols may lead to the same final result. Space does not allow a detailed discussion of the various protocols. However, most of the studies use many cytostatics in a cyclic fashion and in high-intensity dosages. The most simple post-remission therapy is in NOPHO-84, where the children are given four courses of high-dose ara-C only.[15] It is quite clear from the table that more is not necessarily better.

The ultimate intensity therapy is bone marrow transplantation (BMT). With increasingly intensive chemotherapy the role of BMT is more difficult to define. TABLE 3 presents some studies in which BMT has been compared in a randomized fashion with post-remission chemotherapy only. Those studies in which BMT has proven advantageous are early studies in which chemotherapy had a lower intensity than in most recent studies.

The subset promyelocytic leukemia is unfortunately rare in children, but should be treated separately. Probably the best therapy is to induce remission by ATRA, and then consolidate with chemotherapy. Several studies are currently addressing this question.

Because there still is a high hematopoetic relapse rate in children with AML, the true incidence of central nervous leukemia in AML remains unknown. However, most of the current protocols use high-dose therapy that would also have an effect on the central nervous system. One of the best results in AML has been presented by the German group. In a challenging paper from 1993, they propose that cranial irradiation may also reduce the risk of bone marrow relapse in AML.[10]

As survival has increased, the possibility of looking for risk factors have also been possible. Again, the German group has clearly identified two risk groups in their patients and are stratifying the therapy accordingly. With the exception of patients with M3 leukemia and children with Down's syndrome, no other group

TABLE 3. Bone Marrow Transplantation in Childhood AML

		alloBMT		Auto BMT	Chemotherapy Only
	No. in CR	No	DFS (%)	DFS (%)	DFS (%)
CCG 251[17]	381	85	50	—	36
CCG 213[20]	439	92	46	—	38
CCG 2861[23]	108	16	55	51	—
MRC AML-10[24]	766	174	58	54	52
AIEOP/LAM 87[21]	127	22	51	21	27
	1821	389 (21%)			

NOTE: CR, complete remission; CCG, Children's Cancer Group.

has so far stratified their patient in risk groups, although many have reported on high white cell burden as a risk factor. In the Nordic studies we could not identify white cells as a risk factor. However, gender did carry a prognostic significance with girls doing better than boys.[8]

FUTURE DIRECTIONS

There are two reasons for treatment failures: therapy-related mortality and relapse. Part of the improvement seen during the last decade is certainly related to better supportive care, but 20–25% of the children still fail induction therapy and 5–10% die during intensive post-remission therapy. Reducing intensity will certainly increase the problem of resistant disease. The use of growth factors is still controversial in AML.

New and more effective drugs are not on the horizon. Better variants of the presently used drugs are continuously being developed, such as the various analogues of anthracyclines. However, we do not even know what is the best combination of the presently available drugs. Correct doses and timing of ara-C is still a topic of debate. And what about the role of mitoxantrone, VP16, and amsacrin? It is hard to see that we will ever find a protocol so good that it will be universally accepted. To lose a child as a result of therapy-related complications is among the most difficult events to handle in pediatric oncology. Only centers with experience and all possible supportive care facilities can take on the responsibility of caring for these children.

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