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Long-Term Survivors of Adult Acute Nonlymphocytic Leukemia: Fact or Fiction?*

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A. Introduction

From 1970 to 1982, 157 consecutive patients with de novo acute nonlymphocytic leukemia (ANLL) were treated and followed by the Hematology Unit at the Brigham and Women's Hospital, Boston, Massachusetts. It was in 1970, with the addition of cytosine arabinoside and daunorubicin, that remission induction (RI) rates significantly increased from 30% to greater than 50% [1]. During the past decade, major emphasis has been placed on an attempt to prolong disease-free survival with intensive chemotherapy programs and more recently with allogeneic and syngeneic bone marrow transplantation [2, 3]. Since 1970, we have attempted to treat our patients with more aggressive remission and maintenance consolidation (RC) programs.

B. Patients and Chemotherapy Protocols

During the 12-year period ending 1982, 157 consecutive patients were followed and treated for de novo ANLL. All patients with a previously known hematologic dis-

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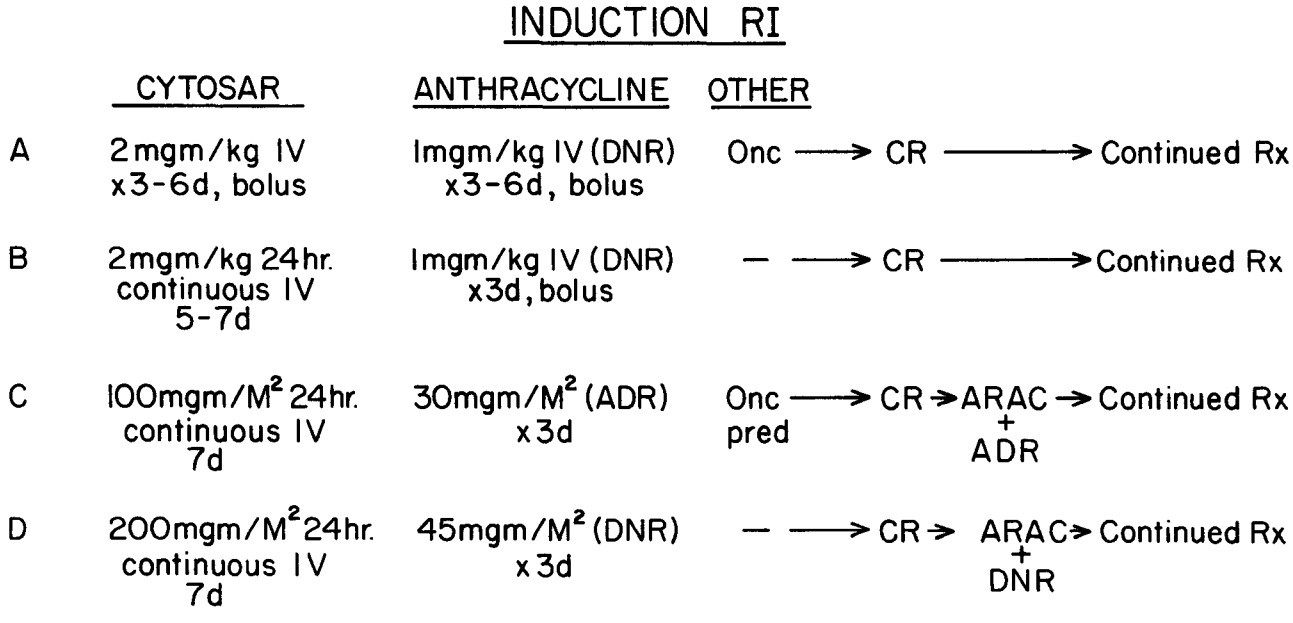
Fig. 1A–D. Chemotherapy of adult ANLL 1970–1982. Four major programs were in effect: COD (**A**), DAC 1 (**B**), VAPA (**C**), and DAC II (**D**)



order or who had previous chemotherapy were excluded from this study. In order to have at least a 2-year follow-up on all patients from date of RI therapy, only patients treated prior to June 1982 were analyzed. Four major protocols were in effect during this 12-year period (Table 1, Fig. 1). From 1970 to 1974 (program A), RI was the COD program, using intravenous bolus infusions of cytosar, oncovin, and daunorubicin [4]. RC utilized an ambulatory program of 5 days of cyclophosphamide, oncovin, cytosar, and prednisone (COAP) every 28 days, continuing indefinitely. Program B (DAC I), in effect from 1974 to 1977, had RI consisting of 24 h of continuous intravenous infusion of cytosar for 5–7 days with three bolus infusions of daunorubicin. The RC alternated COAP with cytosar and daunorubicin (to a maximum dose of 700 mg/m^2). RI of program C (1977–1980) was similar to program B, but RC (VAPA) was an attempt to give 14 months of very intensive chemotherapy utilizing higher doses of cytosar plus non-cross-resistant agents [2]. Program D (DAC II), evaluated from 1980 to 1982, involved more intensive RI with twice the dose of continuous intravenous cytosar used in previous RI. The RC period was shortened to 8–12 months, but the drug doses remained high.

C. Results

A total of 50 patients were treated with the COD program (A); 32 patients with DAC I

Table 1. ANLL treatment protocols

Year	Program	Median age	CR/total number	(%)	Alive	CCR[c]
1970–74	A	43	31/50	(62)	0	0
1974–77	B	54	15/32	(46)	1	1
1977–80[a]	C	46	22/41	(54)	4	4
1980–82[b]	D	49	25/34	(74)	13	0
			93/157	(59)	18	15

[a] In 1977–80, 3/22 BMT in first remission 1/3 in CCR (65+ months)
[b] In 1980–82, 1/25 BMT in first remission 1/1 in CCR (30+ months)
[c] CCR continuous CR

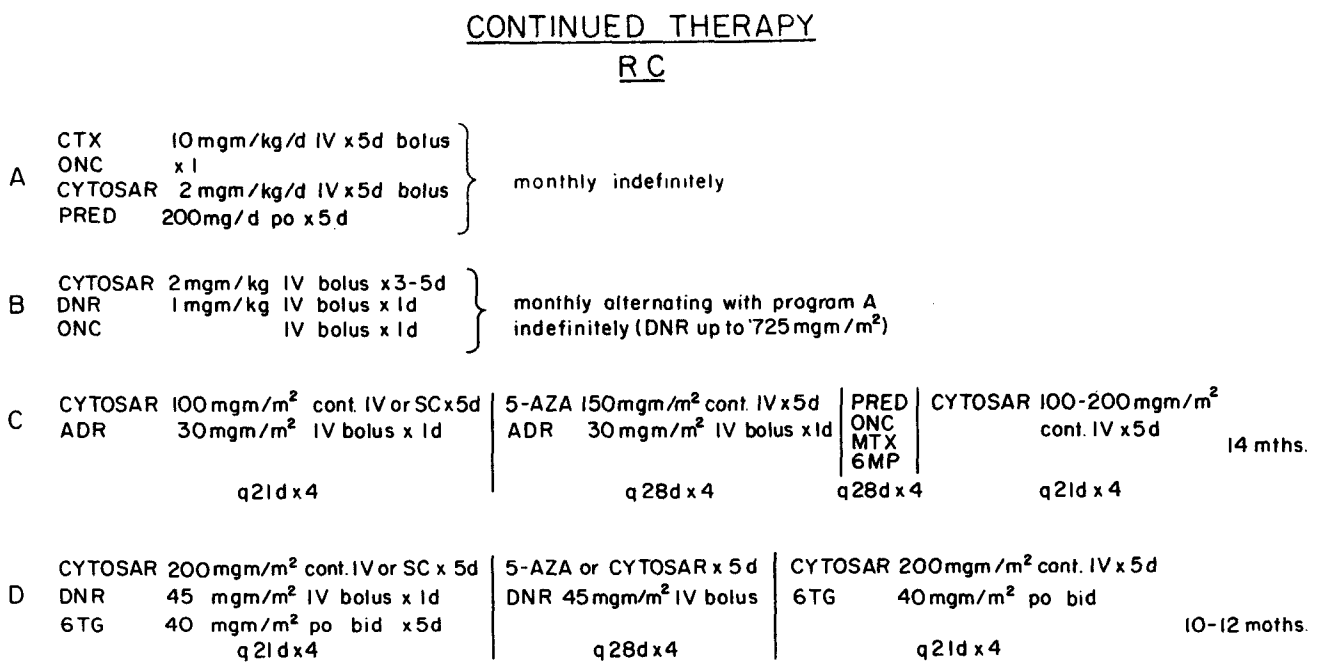


Table 2. Therapy of long-term survivors

CCR/total CR	RI	RC	CCR (months)
1/15	DAC I	2 years COAP, CAT	1 (96)
4/22	VAPA	16 months – full VAPA	2 (56, 54)
		BMT	1 (65)
		16 months – ½ dose VAPA	1 (61)
10/25	DAC II	12 months DNR, Arac-C 6-TG, 5-Aza	2 (37, 39)
		9 months DNR, Ara-C, 6-TG, 5-Aza	1 (47)
		12 months DNR, Ara-C 6-TG	4 (22, 30, 34, 34)
		8 months DNR, Ara-C, 6-TG	1 (26)
		BMT	1 (30)
		2 months DNR, Ara-C, 6-TG	1 (35)

(B); 41 patients with VAPA (age < 50 years) or with modified VAPA (age > 50 years) (C); and 34 patients with DAC II (D) (see Table 1). Of the 157 patients, 93 (59%) achieved complete remission (CR). CR rates have been 62% in program A, 46% in B, 54% in C, and 74% in D. Currently, 18 of the 93 CR patients are still alive (19%) and 15 of the 93 (16%) still in continuous complete remission. The longest survivor is 96 months and is the only survivor of program A and B. Four patients from program C are still in CR (54–65 months), one of whom received a marrow transplant (BMT) while in first remission. Ten patients are still in CR from program D, one for 22 months, six for 26–35 months, and three for 37–47 months. One of the ten patients received a BMT. Table 2 illustrates the actual therapy of the 15 long-term survivors. Although the RI programs were usually carried out per protocol, there were many CR patients who did not receive the full RC programs. In fact, two were removed from protocol for allogeneic BMT during the first 3 months after RI and four had significantly reduced length of treatment owing to toxicity.

Survival curves from programs A, B, and C demonstrated a long-term disease-free status of less than 20% (Fig. 2). Program D with the shortest follow-up demonstrates by life table analysis a disease-free survival of 38%. However, since relapses in the previous programs have occurred as late as 2–3 years after CR, the length of follow-up for program D is too short to predict an increased percentage of long-term survivors.

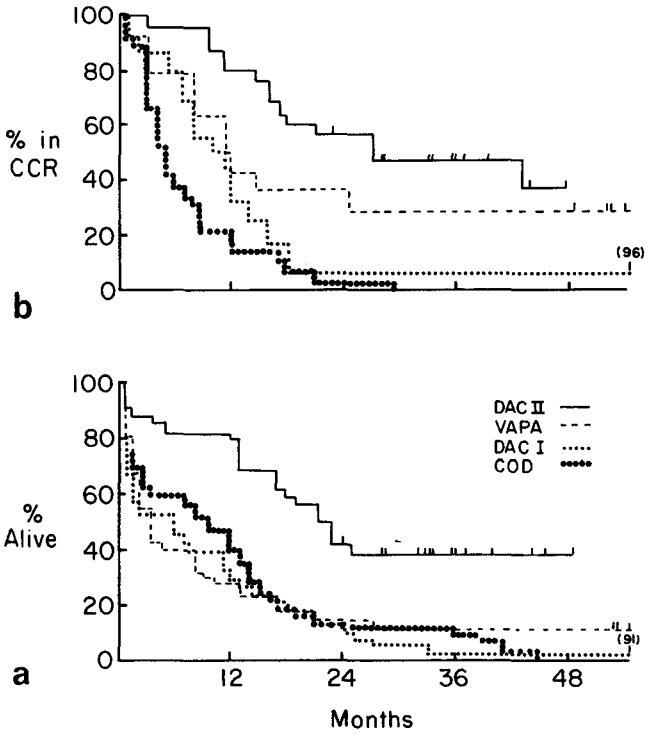


Fig. 2a, b. Actual survival curves for **a** total group and **b** disease-free survival for all complete remissions broken down according to treatment program

D. Summary and Conclusions

From 1970 to 1982, remission rates from large series of patients with a median age of approximately 50 years continue to exceed 50% and in series of younger patients may be as high as 75% [1]. These improved results have been due to the combination of cytosar and an anthracycline in RI programs. The current major question is whether or not "consolidation" therapy has improved long-term disease-free survival

[5–7]. Our current results, covering the decade 1970–1980 and using more and more intensive RC programs, do not demonstrate an increase in the percentage of long-term survivors. The results from 1980 to 1982 are encouraging, but must be tempered by the fact that late relapses of adult ANLL are becoming more frequent and 2-year follow-up is much too short an evaluation period. In addition, the prolonged survival in program D may be due to the more intensive RI program and not at all related to the RC. At the present time, our experience lends no support to the theory that more intensive RC programs meaningfully prolong long-term survival.

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