

# Etoposide in Acute Nonlymphocytic Leukemia

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Previously untreated patients with acute nonlymphocytic leukemia (ANLL) aged 15 to 70 years were randomized to either cytosine arabinoside 100 mg/m<sup>2</sup>/d continuous intravenous (IV) infusion days 1 through 7, daunorubicin 50 mg/m<sup>2</sup>/d IV days 1 through 3 (7-3), or the same drugs intensified with etoposide 75 mg/m<sup>2</sup>/d IV days 1 through 7 (7-3-7) as induction therapy. Patients achieving complete remission (CR) received two courses of consolidation therapy (5-2 or 5-2-5) followed by maintenance therapy. Of 264 eligible patients, CR occurred in 56% of 7-3 and 59% of 7-3-7 patients; 7-3-7 significantly improved remission duration ( $P = .01$ ). The median remission duration was 12 months for 7-3 and 18 months for 7-3-7. Survival was similar when the two arms were compared overall. Subset analysis performed to identify patients with the most benefit showed that etoposide significantly prolonged remission duration in younger patients (less than 55 years)

with a median of 12 months for 7-3 and 27 months for 7-3-7 ( $P = .01$ ). Survival appeared to be prolonged with 7-3-7 in patients aged less than 55 years, with a median of 9 months for 7-3 as compared with 17 months for 7-3-7 ( $P = .03$ ). In older patients (aged  $\geq 55$  years), 7-3-7 was more toxic, with significantly more severe [World Health Organization (WHO) grade 3 or 4] stomatitis ( $P = .02$ ) and no additional clinical benefit. Hematologic toxicity for induction courses was similar, with granulocytopenia  $<0.5 \times 10^9/L$  for a median of 16 days per course for 7-3 and 15 days for 7-3-7. Hematologic toxicity was more severe for 5-2-5 consolidation courses ( $P = .003$ ). Induction and consolidation therapy intensified with etoposide resulted in significantly improved remission duration but not survival.

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**T**REATMENT OF ACUTE nonlymphocytic leukemia (ANLL) has improved considerably in the last two decades.<sup>1,2</sup> However, with standard induction regimens, 30% to 40% of previously untreated patients still fail to achieve complete remission (CR) and, for all patients, median survival is only about 12 months. There is clearly a need for more effective induction regimens. We attempted to improve remission induction therapy by adding a new drug to standard therapy in previously untreated patients.

Etoposide (VP16-213, NSC 141540) induces CR in 15% to 25% of previously treated patients with ANLL when used as a single agent.<sup>3-5</sup> Etoposide has been used in combination with cytosine arabinoside, doxorubicin, vinblastine, or *m*-AMSA for relapsed patients with leukemia.<sup>6-8</sup> The Australian Leukemia Study Group (ALSG) conducted a pilot study of the combination cytosine arabinoside, daunorubicin, and etoposide (7-3-7) in previously untreated patients with ANLL and showed it to be active and well tolerated.<sup>9</sup> This intensified induction and consolidation regimen has now been compared with the commonly used two-drug regimen of cytosine arabinoside and daunorubicin (7-3) to determine the relative efficacy and toxicities of these regimens.

## MATERIALS AND METHODS

The ALSG activated this study in 1984, and patients were accrued from 21 institutions in Australia and from one in Hong Kong. The protocol was written to conform with the ethical guidelines of the National Health and Medical Research Council of Australia and the Australian Federal Health Department. The Ethics Committees of each participating institution approved the final protocol.

**Patient eligibility.** Patients aged 15 to 70 years were eligible provided that they had a diagnosis of ANLL, had not previously received treatment, and had Eastern Cooperative Oncology Group (ECOG) performance status 0 to 3. All patients gave written informed consent before randomization. Patients with severe cardiac disease precluding use of daunorubicin or with previous myeloproliferative diseases, myelodysplastic syndromes, or neoplasms were excluded. Diagnostic bone marrow aspirations and biopsies were classified according to the French-American-British (FAB)

classification<sup>10</sup> and were reviewed by an independent, expert morphology panel.

**Treatment plan.** Patients were randomized to receive either cytosine arabinoside 100 mg/m<sup>2</sup>/d as a continuous intravenous (IV) infusion for 7 days plus daunorubicin 50 mg/m<sup>2</sup>/d for days 1 through 3 (7-3) or to receive the same two drugs at the same dose and schedule but intensified with etoposide 75 mg/m<sup>2</sup>/d IV in 1 hour on days 1 through 7 (7-3-7) (Fig 1). Patients with residual disease with more than 5% blasts at day 21 of the induction regimen could receive a second or third course of the same induction regimen. Patients with hypocellular or regenerating bone marrows (BMs) were rebiopsied weekly until their remission status was clear. If no CR occurred after three induction courses or if the percentage of blasts had not changed substantially after two courses, patients were taken off study. Dose reductions of all drugs to 66% of the initial dose for subsequent induction courses were permitted only for severe treatment-related toxicity such as gastrointestinal toxicity. Patients in CR received attenuated consolidation regimens with the induction doses of cytosine arabinoside and daunorubicin but for 5 and 2 days, respectively (5-2), or with etoposide added (5-2-5) depending on the randomization arm. The first and second consolidation courses were planned 28 days after the last treatment.

Maintenance therapy was identical in both arms and was similar to that used by the Cancer and Acute Leukemia Group B (CALGB).<sup>1</sup> Maintenance was started on day 28 of the second consolidation course and was administered every 8 weeks for 2 years (Fig 1). When a maximum cumulative dose of 550 mg/m<sup>2</sup> daunorubicin was reached, 6-thioguanine was substituted for the daunorubicin.

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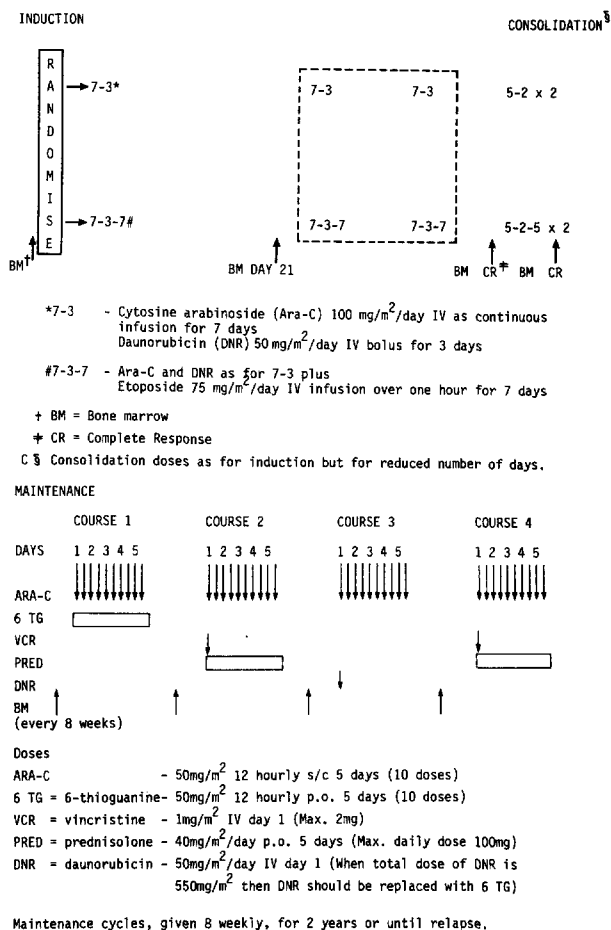


Fig 1. Treatment schema.

**Evaluation of response.** CR was defined as  $\leq 5\%$  blasts in a normocellular bone BM with  $> 1 \times 10^9/L$  neutrophils and  $> 100 \times 10^9/L$  platelets in the peripheral blood (PB) and disappearance of all signs attributable to leukemia. Relapse was defined as  $> 5\%$  blasts in BM. BM biopsies were performed at least on day 21 of each induction course, on day 28 of each consolidation course, and every 8 weeks while patients were receiving maintenance treatment. All toxicity was graded into five categories using standard World Health Organization (WHO) criteria.<sup>11</sup>

**Statistical methods.** Patients were stratified before randomization according to participating institutions. CR rates were compared with the chi-square test with Yates continuity correction. Remission duration, relapse-free survival (RFS), and survival were estimated using the Kaplan-Meier method and compared with the log-rank ( $P_1$ ) and Breslow ( $P_2$ ) tests.<sup>12</sup> Graded toxicity data were compared with a chi-square test for trend. Other discrete data were compared with the Pearson chi-square test for contingency tables. Dichotomous variables were compared with the chi-square test with Yates continuity correction or Fisher's exact test when small numbers were involved. The incidence of severe toxicities (grade 3 or 4) was similarly compared. Noncensored continuous data, such as duration of granulocytopenia, were compared using the Wilcoxon rank-sum test. All  $P$ -values are two-sided. Remission duration was measured from the date of complete remission and RFS from randomization. Patients who died in CR had their remission duration (and RFS) censored at the time of death. Survival was measured from randomization, with all deaths treated as failures. All eligible patients were

included in the survival curves. A closeout date of January 1, 1989 was used for all data.

The possibility of an interaction between the randomization arm and age was tested with a Cox's regression analysis with age dichotomized first at 50, then at 55, and then at 60 years. The significance of the age-arm interaction was measured by the change in log-likelihood when an interaction term was included in a model incorporating age and arm. There was a significant interaction with age cut at 55 ( $P = .02$ ) but not with age cut at 50 ( $P = .17$ ) or 60 years ( $P = .19$ ).

Similarly, the significance of treatment arm in prolonging remission adjusting for prognostic factors was measured by the change in the log-likelihood when arm was included in a model incorporating all other significant factors.

## RESULTS

**Accrual.** The ALSG entered 274 patients between January 1984 and February 1987. Ten patients (3.6%) were ineligible for study entry, including five with acute lymphoblastic leukemia, four with a previous myeloproliferative disease, and one with blastic transformation of chronic granulocytic leukemia. Of the remaining 264 patients, 132 were randomized to receive 7-3 and 132 were randomized to receive 7-3-7. The median follow-up for patients alive at the time of analysis was 40 months (range 18 to 60 months).

**Patient characteristics.** At study entry, there were more FAB M1 patients on 7-3 and more FAB M3 patients on 7-3-7 (Table 1). Patients on the 7-3 arm tended to have a higher PB blast count. This did not influence the comparison of treatment arms as described, however. Other factors were well-balanced between the arms.

**Dose delivery.** For induction chemotherapy,  $\geq 80\%$  of the planned protocol dose of daunorubicin was delivered to 92% of patients on 7-3 and 91% on 7-3-7. Similarly,  $\geq 80\%$  of the specified dose of cytosine arabinoside was delivered to 95% of 7-3 patients and 92% of 7-3-7 patients. Eighty percent or more of the specified dose of etoposide was delivered to 90% of patients on the 7-3-7 arm. Thus, the drugs were delivered at doses specified in the protocol in most patients. There was a median of a 27-day interval between the start of induction course 1 and course 2, 34 days between courses 2 and 3, and 33 days between consolidation courses. More than 80% of the planned protocol dose of each drug was administered to more than 96% of patients during consolidation.

**CR.** For all 264 patients, CR ( $\pm$ SE) was achieved in  $56\% \pm 4\%$  of 7-3 patients and  $59\% \pm 4\%$  of 7-3-7 patients ( $P = .7$ ). On 7-3, 22% achieved CR after one induction course, a further 27% achieved CR after course 2, and 7% achieved CR after course 3. For 7-3-7, 30% achieved CR after course 1, 24% achieved CR after course 2, and 5% achieved CR after course 3. The median time to CR was 49 days in both arms. The median time to CR after one induction course was 30 days, 29 days after the second induction course and 25 days after course 3. Thirteen patients were refractory to three induction courses: six on 7-3 and seven on 7-3-7. Thirty-nine patients (17 on 7-3 and 22 on 7-3-7) who died before response could be evaluated have been included as nonresponders. If these patients are excluded, 64% of patients achieved CR with 7-3 and 71%

**Table 1. Patient Characteristics (264 Patients, 132 on 7-3, 132 on 7-3-7)**

On Study Data	7-3(%)	7-3-7(%)	Total(%)	P Value*
ECOG PS†				
0	52	45	48	
1	27	32	29	
2	12	17	15	
3	9	6	8	.60
Sex				
M	53	55	54	
F	47	45	46	.80
FAB‡				
M1	30	20	25	
M2	20	30	25	
M3	12	18	15	
M4	17	21	19	
M5	17	11	14	
M6	4	1	2	.03
Febrile/infected				
No	53	60	56	
Yes	47	40	44	.26
DIC				
No	88	82	85	
Yes	12	18	15	.23
Age (yr)				
<30	16	20	18	
30-39	21	20	21	
40-49	14	8	11	
50-59	33	29	31	
60-70	15	23	19	.67
WBC count ( $\times 10^9/L$ )				
<10	48	53	50	
10-19	8	11	10	
20-29	13	11	12	
30-49	8	8	8	
50+	23	16	20	.22
Platelet count ( $\times 10^9/L$ )				
<20	18	16	17	
20-49	31	33	32	
50-99	24	24	24	
100+	27	27	27	.98
PB blasts ( $\times 10^9/L$ )				
<10	55	69	62	
10-19	12	11	11	
20-29	6	6	6	
30-49	5	4	4	
50+	21	11	16	.08
BM blasts (%)				
<20	8	5	6	
20-49	13	14	14	
50+	79	81	80	.47

Abbreviation: DIC, disseminated intravascular coagulation.

\*Described in Statistical Methods section.

†ECOG performance status.

‡FAB classification.<sup>10</sup>

achieved CR with 7-3-7 ( $P = .4$ ). There were no statistically significant age-related differences in CR between the two arms. Sixty-seven percent of patients aged less than 30 years achieved CR with 7-3 as compared with 81% with 7-3-7 ( $P = .3$ ). Fifty-seven percent of patients aged less than 55 years achieved CR in with 7-3 as compared with 68% with 7-3-7 ( $P = .18$ ). Conversely, of older patients, aged  $\geq 55$

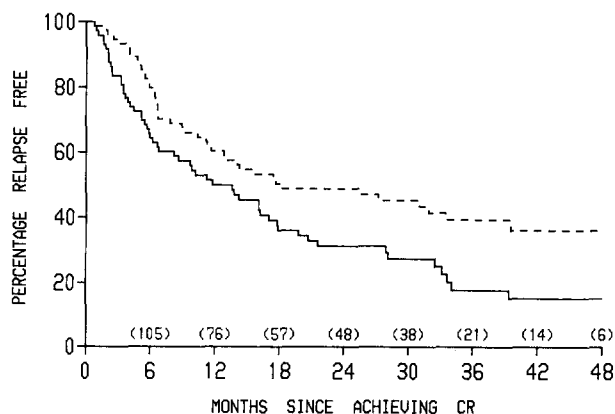
years, 54% achieved CR with 7-3 as compared with only 43% with 7-3-7 ( $P = .4$ ).

**Remission duration.** Remission duration was significantly prolonged with 7-3-7 ( $P_L = .01$ ,  $P_B = .02$ , Fig 2). The median overall remission duration was 12 months for 7-3 and 18 months for 7-3-7. Similarly, RFS was significantly prolonged with 7-3-7 (median 21 months) as compared with 7-3 (median 14 months,  $P_L = .01$ ,  $P_B = .02$ ). RFS was 15% at 4 years with 7-3 and 36% with 7-3-7. The improved remission duration could not be explained by an imbalance in prognostic factors. A multivariate analysis of prognostic factors identified onstudy ECOG performance status ( $P = .0001$ ) and PB blast count ( $P = .004$ ) as the only significant factors influencing remission duration. When adjustment was made for these factors, the 7-3-7 arm was still significantly superior ( $P = .016$ ). The median duration of follow-up for patients in CR is 32 months with only 24% alive, in CR and at risk of relapse at the time of this analysis.

In a subset analysis of patients aged less than 55 years, the median remission duration was 12 months for 7-3 as compared with 27 months for 7-3-7 ( $P_L = .01$ ,  $P_B = .02$ , Fig 3). Older patients, aged  $\geq 55$  years, however, did not appear to benefit from 7-3-7, with a median remission duration of 14 months for 7-3 but only 9 months for 7-3-7 ( $P_L = .9$ ,  $P_B = .7$ ).

**Survival.** Two hundred nine patients (79%) had died. The median overall survival was 9 months for 7-3 and 13 months for 7-3-7 ( $P_L = .4$ ,  $P_B = .4$ , Fig 4). Twenty-five percent of patients died during induction; 1% during consolidation and 1% during maintenance, with the remainder of patients off protocol therapy at the time of death. For all patients entered on study, infection in 69% and hemorrhage in 33% was a contributing cause of death. For patients dying within 40 days of an induction course, infection in 82%, hemorrhage in 45%, and progressive leukemia in 27% was a contributing cause of death.

As detailed in the statistical section, there was a statistically significant interaction between age and arm ( $P = .02$ ) for duration of survival. In an attempt to identify patients who may benefit most from etoposide, a subset analysis



**Fig 2. CR duration ( $P_L = .01$ ,  $P_B = .02$ ), by randomization arm based on ALSG 7-3 versus 7-3-7 database March 1989. Numbers in brackets refer to patients at risk at the beginning of the period. (---), ARM 737, 78 cases; (—), ARM 73, 74 cases.**

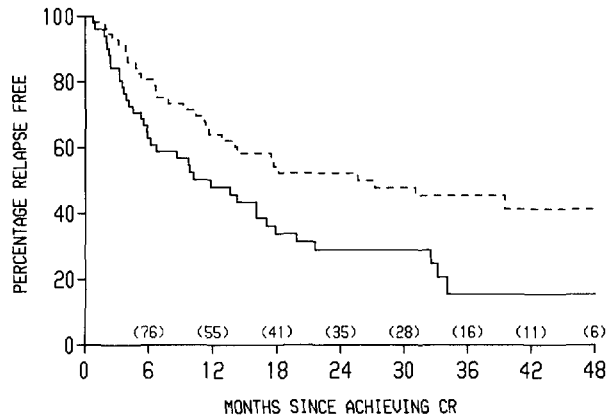


Fig 3. CR duration for patients aged less than 55 years ( $P_L = .01$ ,  $P_B = .02$ ), based on ALSG 7-3 versus 7-3-7 database March 1989. Numbers in brackets refer to patients at risk at the beginning of the period. (---), ARM 737, 58 cases; (—), ARM 73, 51 cases.

revealed that patients aged less than 55 years survived longer with 7-3-7 ( $P_L = .03$ ,  $P_B = .03$ , Fig 5). For these younger patients, the median survival was 9 months for 7-3 and 17 months for 7-3-7 with  $42\% \pm 5\%$  of 7-3 patients and  $61\% \pm 5\%$  of 7-3-7 patients alive at 1 year. Conversely, for older patients, aged  $\geq 55$  years, the median survival was 8 months for 7-3 and 5 months for 7-3-7 ( $P_L = .16$ ,  $P_B = .15$ ). No other age subset appeared to benefit from addition of etoposide.

**Toxicity.** Overall, the nonhematologic toxicity experienced during induction was equivalent when the two study arms were compared, with the exception of significantly more diarrhea with 7-3-7 ( $P = .05$ , Table 2). In patients aged  $\geq 55$  years, however 26% had severe stomatitis (WHO grade 3 or 4) on the 7-3-7 arm as compared with 7% on the 7-3 arm ( $P = .02$ ). This increased toxicity was not observed in younger patients ( $<55$  years), with severe stomatitis in 11% for 7-3 and in 13% for 7-3-7.

Overall, the hematologic toxicity of induction was equivalent when the two study arms were compared. The median number of days with granulocytes  $<0.5 \times 10^9/L$  was 16 per course for 7-3 and 15 for 7-3-7. The median number of days with platelet count  $<50 \times 10^9/L$  was 15 days on both arms.

However, for consolidation courses the etoposide arm was significantly more toxic since consolidation with 5-2-5 produced longer granulocytopenia  $<0.5 \times 10^9/L$  (median 8 v 5 days,  $P = .003$ ), longer thrombocytopenia  $<50 \times 10^9/L$  (median 7 v 3 days,  $P < .001$ ) and more alopecia ( $P < .001$ ) as compared with consolidation with 5-2.

Toxicity from maintenance therapy was similar in both study arms; however, 33% of patients on maintenance experienced granulocytopenia  $<0.5 \times 10^9/L$  and 26% experienced thrombocytopenia  $<50 \times 10^9/L$ .

For the above data, we performed an "intent-to-treat" analysis with all patients analyzed as randomized regardless of outcome after randomization. Nineteen patients were removed for allogeneic BM transplantation after they had obtained a CR (7 on 7-3 and 12 on 7-3-7). When these patients were censored at the time of transplantation, the median remission duration for 7-3 was 10 months as com-

pared with 14 months for 7-3-7 ( $P_L = .03$ ,  $P_B = .03$ ). Subset analyses for patients aged less than 55 years showed that significant improvement in remission duration ( $P_L = .02$ ,  $P_B = .03$ ) and survival ( $P_L = .04$ ,  $P_B = .03$ ) with 7-3-7 persisted.

Eighty-five patients with FAB M4 or M5 were treated on this trial. Complete response was achieved in 59% of patients treated with 7-3 and in 63% treated with 7-3-7 ( $P = .9$ ). The median remission duration was 11.3 months in FAB M4 or M5 patients treated with 7-3 and 12.8 months in those treated with 7-3-7 ( $P_L = .43$ ,  $P_B = .18$ ). The median survival was 8.6 months on 7-3 and 8.2 months on 7-3-7 ( $P_L = .77$ ,  $P_B = .68$ ). There were no significant differences when FAB M4 or M5 categories were considered separately, although the numbers in each subset are very small.

## DISCUSSION

The two-drug combination cytosine arabinoside and daunorubicin (7-3) has been successfully used for induction in ANLL for several years. Efforts to improve 7-3 induction therapy by adding 6-thioguanine,<sup>2,13</sup> lengthening the duration of cytosine arabinoside,<sup>2</sup> or substituting daunorubicin with doxorubicin<sup>1</sup> or *m*-AMSA<sup>14</sup> have not been successful strategies in randomized trials. Therefore, evaluation of new antileukemic drugs in induction is important.

Etoposide is a semisynthetic podophyllotoxin and a potent inhibitor of the microtubular assembly in dividing cells.<sup>15</sup> Etoposide has single-agent activity in ANLL, a different mechanism of action to that of cytosine arabinoside and daunorubicin, and is well-tolerated in combination with these two agents. In vitro, etoposide is synergistic, with cytosine arabinoside.<sup>16</sup> Therefore, etoposide is an ideal drug to add to the commonly used two-drug induction regimen 7-3.

In this study, etoposide significantly prolonged remission duration and RFS in previously untreated adults with ANLL. The 50% improvement in median remission duration was sufficiently large to be of major benefit to our patients; however, this improvement was not translated into an overall significant difference in survival between the two arms.

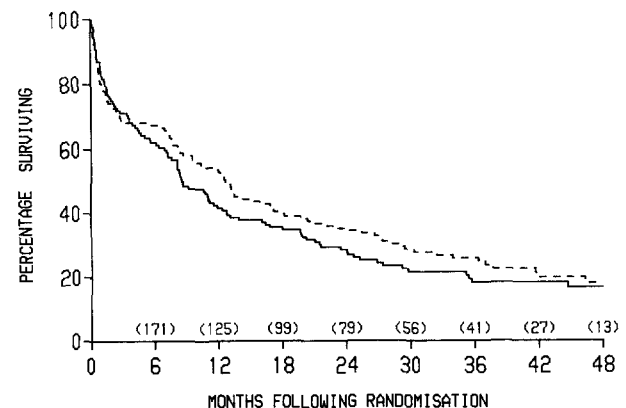


Fig 4. Survival by randomization arm for all eligible patients ( $P_L = .4$ ,  $P_B = .4$ ), based on ALSG 7-3 versus 7-3-7 database March 1989. Numbers in brackets refer to patients at risk at the beginning of the period. (---), ARM 737, 132 cases; (—), ARM 73, 132 cases.

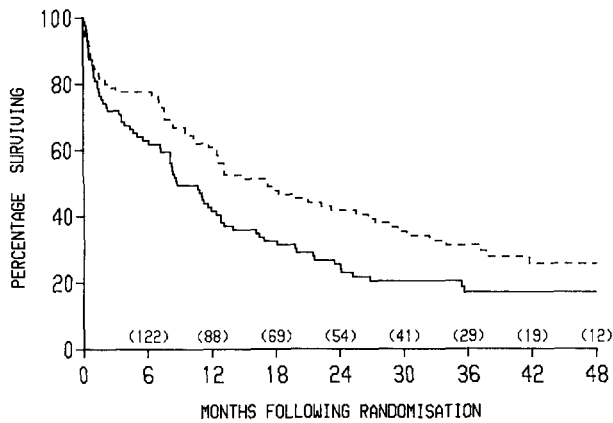


Fig 5. Survival of patients aged less than 55 years ( $P_t = .03$ ,  $P_b = .03$ ), based on ALSG 7-3 versus 7-3-7 database March 1989. Numbers in brackets refer to patients at risk at the beginning of the period. (—), ARM 737, 85 cases; (---), ARM 73, 89 cases.

Age appears to have important effects on treatment outcome. Subset analysis suggested that the benefits of 7-3-7 may be limited to younger patients.

The median remission duration was increased by 14 months in patients aged less than 55 years, and survival was increased by 8 months. Another 19% of etoposide-treated patients aged less than 55 years were alive at 12 months as compared with patients on the 7-3 arm. Because the apparent benefit of etoposide in patients less than 55 years has been identified by subset analysis, however, its value in these patients remains a hypothesis that will require confirmation in other trials. The estimated survival at 4 years was not significantly different in younger patients, with  $17\% \pm 4\%$  alive with 7-3 and  $22\% \pm 6\%$  alive with 7-3-7, suggesting that prolongation of remission may be translated into improved short-term survival in younger patients but does not ensure a significant improvement in long-term survival.

Older patients (aged  $\geq 55$  years) treated with etoposide tended to have an inferior clinical outcome, although there were few patients in this subset. Older patients tolerated 7-3-7 poorly, with significantly more severe stomatitis. These findings are consistent with reports that more intense regimens were poorly tolerated by older patients with more

stomatitis, a lower CR rate, and more induction infections and deaths.<sup>1</sup>

The CR rate obtained with 7-3 in this trial is similar to the CR rate of 53% to 66% reported by other cooperative groups with the same regimen.<sup>1,2,17-20</sup> Because there were no significant differences in response rates between the arms, the intensified and more toxic consolidation therapy may have contributed to the improved remission duration with 7-3-7. The clinical implication is that more intense and prolonged initial therapy in induction and or consolidation may be appropriate, at least for younger patients.

For all patients, the hematologic toxicity experienced during induction courses was similar on both arms, with no important differences in the number of days of granulocytopenia or thrombocytopenia. Consolidation intensified with etoposide was significantly more toxic as compared with the standard consolidation, with significantly longer duration of granulocytopenia and thrombocytopenia. To place these results in context, however, the toxicity of standard 5-2 consolidation was mild and the etoposide-intensified consolidation was also very well-tolerated. Approximately one quarter of patients experienced severe myelosuppression on maintenance therapy.

Etoposide has been suggested to be most effective in myelomonocytic leukemia<sup>3-5</sup>. In this study, the benefits of etoposide were not specifically confined to patients with FAB M4 or M5, and the significant prolongation of remission duration appeared to hold for all patients, regardless of FAB subgroup.

#### APPENDIX

The Australian Leukaemia Study Group (ALSG) includes Executive: J. Bishop (Chairman), G. Young (Vice-Chairman), M. Wolf (Secretary); Statisticians: J. Matthews, L. Tan; Data Managers: L. Morton, A. Tester, F. Page, A. McMullen, J. Willis, W. Morgan, T. Worotniuk; Morphology Panel: H. Kronenberg, B. Rush, B. Farragher, D. Parkin; Participating Investigators: M. Pidcock, Woden Valley Hospital, A.C.T.; D. Rosenfeld, Liverpool General Hospital, NSW; M. Rosenberg, Prince Henry's Hospital, NSW; Y.L. Kwan, R. Lam Po Tang, and C. Grace, Prince of Wales Hospital, NSW; A. Enno and M. Seldon, Royal Newcastle Hospital, NSW; P. Isbister, R. Ravich, and D. Ma, Royal North Shore Hospital, NSW; H. Kronenberg, D. Joshua, and J. Gibson, Royal Prince Alfred Hospital, NSW; P. Vincent, W. Benson, and G. Young, Kanematsu Institute, Royal Prince Alfred Hospital, NSW; A. Manoharan and C.N. Chesterman, St George's Hospital, NSW; J. Biggs, A. Concannon, A. Dodds, I. Thompson, and K. Atkinson, St Vincent's Hospital, NSW; R. Cobcroft, Princess Alexandra Hospital, QLD; I. Bunce and G. Hill, Royal Brisbane Hospital, QLD; M. Harris, Mater Hospital, QLD; R. Lowenthal, M. Bakie, and D. Jupe, Royal Hobart Hospital, Tasmania; K. Rooney and M. Beamish, Launceston General Hospital, Tasmania; M.G. Whiteside, J. Bishop, J. Szer, P. Elliott, M. Van der Weyden, and B. Firkin, Alfred Hospital, Victoria; J. Wiley, P. Thurlow, and R. Woodruff, Austin Hospital, Victoria; G. Brodie, J. Griffiths, and P. Ellims, Prince Henry's Hospital, Victoria; I. Cooper, J. Ding, M. Wolf, and J. Bishop, Peter MacCallum Cancer Institute, Victoria; D. Parkin and J. Duggan, Repatriation General Hospital, Victoria; R. Fox, M. Green, and W. Sheridan, Royal Melbourne Hospital, Victoria; B. Rush and O.M. Garson, St Vincent's Hospital, Victoria; R. Herrmann, M. Jackson, and A. Barr, Royal Perth Hospital, W.A.; D. Todd, T.K. Chan, R. Ling, and S.C. Tso, Queen Mary Hospital, Hong Kong.

Table 2. Nonhematologic Toxicity for 264 Patients Receiving Induction Therapy

Toxicity	Regimen	WHO Toxicity Grade <sup>11</sup> (%)					P Value
		0	1	2	3	4	
Stomatitis	7-3	29	24	37	8	2	.34
	7-3-7	30	20	33	12	5	
Nausea and vomiting	7-3	10	30	36	22	2	.33
	7-3-7	16	32	26	26	1	
Alopecia	7-3	11	14	42	33	—	.08
	7-3-7	12	5	35	48	—	
Clinical bleeding	7-3	22	30	27	16	5	.23
	7-3-7	17	25	38	14	7	
Neuropathy	7-3	98	1	0	1	0	.56
	7-3-7	98	2	0	0	0	
Diarrhea	7-3	40	26	20	13	1	.05
	7-3-7	34	18	27	19	2	

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