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Progress in Acute Myeologenous Leukemia

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A. Introduction

Experimental and potentially life threatening combination chemotherapy has been used for the induction of remission of acute myelogenous leukaemia (AML) for a little over 10 years. During that time the proportion of patients entering remission has risen from less than a quarter to approaching three-quarters. Furthermore, there is now evidence to suggest that about one-fifth of those now entering remission will remain disease free for more than 3 years and be "at risk for cure".

Between 1969 and 1980 588 consecutive adults with AML were treated at St. Bartholomew's Hospital, 443 of them in prospective trials. Selected data from these studies, which have been reported in part elsewhere (Crowther et al. 1973; Powles et al. 1977; Lister et al. 1980) are presented to illustrate what has been learnt during the last decade and to provide a new base line, instead of the natural history of the disease, with which to compare future studies.

B. Materials and Methods

I. Patients

Five hundred and eighty-eight consecutive adults were treated for AML at St. Bartholomew's Hospital between June 1969 and July 1980. Four hundred and forty-three were treated on prospective trials of combination chemotherapy. Exclusions from the trials were made because of advanced age and extensive prior chemotherapy. No patient under the age of 60 years who had not received therapy was excluded. Clinical details of the patients entered in to the different trials are shown in Tables 1–3.

II. Treatment Programmes

Three generations of combination chemotherapy experiments have been undertaken since 1969: in each of them cytosine arabinoside and an anthracycline antibiotic have been the central component of the treatment. At the outset, adults of all ages were treated the same (Trials I, II, III). For the duration of Trials IVA–VIII patients of more than 60 years of age were treated in a separate programme (Trial IVB). This policy was reversed in 1978 at the beginning of Trial IX, since which time adults of all ages have received the same initial therapy. Antibio-

Table 1. Patient details. n = 443; Sex M:F = 243:200

Age	Range	14–77 years
	Mean	49 years
	Median	53 years
Platelet count	Range	5–704
	Mean	69.89
	Median	45
Blast count	Range	0–495.0
	Mean	29.76
	Median	3.8

Table 2. Morphological variants

FAB classification	No. of patients
M1	108
M2	109
M3	27
M4	138
M5	39
M6	22
Total	443

Table 3. Patient entry and exclusions

Date	Trial	No.	Non-trial		Total
			Prior chemotherapy	Transfusion only	
June 1969–July 1970	Barts I	41	6	7	54
August 1970–February 1971	Barts II	20	0	2	22
February 1971–July 1972	Barts III	55	5	10	70
July 1972–April 1973	Barts IVA	37	0	0	37
May 1973–June 1974	Barts V	36	10	9	55
July 1974–November 1974	Barts VII	18	4	3	25
November 1974–February 1978	Barts VIII	86	0	0	86
August 1974–February 1978	Barts IVB	59	31	57	147
March 1978–July 1980	Barts IX, X	91	1	0	92
Total		443	57	88	588

tic and blood component therapy have changed gradually during the decade and are outlined in Table 4.

C. Results

I. Response to Initial Therapy

Complete remission was achieved in 187 out of 443 (42%). The two most important factors correlating with the response to therapy were the age of the patient at presentation and the initial treatment received (Table 5). The complete remission rate was significantly higher for patients under the age of 60 than those of 60 years and older ($P=0.003$). It was also significantly highest for patients receiving intensive chemotherapy comprising adriamycin, cytosine arabinoside and 6-thioguanine (ACT II), especially in the under 60 age group.

Thrombocytopenia at presentation was

Table 4. Initial therapy

Trial	Remission induction	Programme name	Continuation therapy	Antibiotics		Platelet support
				Prophylactic	Therapeutic	
I, II, IVA, V	Daunorubicin[a] cytosine arabinoside[b]	DR+Ara-C	CT[d]±IT	–	Ampicillin+ Flucloxicillin	Fresh blood
II, III	Kinetic modification of DR+Ara-C	DR+ Ara-C(KM)	CT±IT	–	Ampicillin+ Flucloxicillin	Pooled platelets
IVB	Intensification of DR+Ara-C	DR+Ara-C(I)	CT±IT	–	Ampicillin+ Flucloxicillin	
VIII	Adriamycin, vincristine prednisolone, cytosine arabinoside[e]	AD-OAP	CT+IT	FRACON[e]	Aminoglycoside +Carbenicillin or Cephazolin	Single donor
X[f]	Adriamycin, cytosine arabinoside, thioguanine[a]	ACT I	None	None	Aminoglycoside +Cephazolin	Single donor
IX[f]	Adriamycin, cytosine arabinoside, thioguanine[a]	ACT II	None	FRACON[e]		Single donor

[a] Bell et al. (to be published)
[b] Crowther et al. (1973)
[c] Lister et al. (1980)
[d] CT=Chemotherapy; II=Immunotherapy
[e] Schimpff et al. (1975)
[f] ACT I more intensive than ACT II

Treatment		<60	≥60	Total
DR+Ara-C	I III IVA V	69/148 (47%)	5/21 (24%)	74/169 (44%)
DR+Ara-C modifications	II	5/13 (39%)	2/7 (29%)	7/20 (35%)
	VII	3/18 (17%)	–	3/18 (17%)
	IVB	–	19/59 (29%)	15/59 (29%)
AD-OAP	VIII	39/86 (45%)	–	39/86 (45%)
ACT I	X	11/27 (40%)	4/14 (29%)	15/41 (37%)
ACT II	IX	29/36 (80%)	5/14 (36%)	34/50 (68%)
Total		156/328 (48%)	31/115 (27%)	187/443 (42%)

Table 5. Response to initial treatment. ACT II vs DR+Ara-C: $P=<0.02$; ACT II vs ACT I: $P=<0.05$; and ACT II vs AD-OAP: $P=<0.05$

a poor prognostic factor overall, with complete remission only being achieved in 29 out of 96 patients in whom the platelet count was less than 20×10^9/l compared with 158 out of 347 ($P=0.05$) in whom it was more. However, since the introduction of the routine use of platelet concentrates in Trial VIII this prognostic difference has disappeared, with complete remission being achieved in 18 out of 42 patients in whom the platelet count was less than 20×10^9/l compared with 70 out of 135 in whom it was more ($P=$n.s) in Trials VIII, IX and X bombined.

II. Duration of First Complete Remission

Out of 187 patients in whom complete remission was achieved 50 are alive without relapse and three died in complete remission, one of coliform septicaemia during consolidation, one (aged 70) of myocardial infarction and one in a car accident (Fig. 1). No patient has relapsed so far after 5 years.

D. Possible Factors Influencing Duration of First Complete Remission

I. Intensity of the Initial Therapy

Comparison of the duration of first remission in patients receiving Daunorubicin and cytosine arabinoside (Trials I, III, IVA and V) with those receiving AD-OAP (Trial VIII), ACT I (Trial X) and ACT II (Trial IX) show a significant advantage over those receiving ACT I and all the rest and a significant advantage of AD-OAP over those receiving daunorubicin and cytosine arabinoside (Fig. 2). The intensity of treatment had increased with each change of chemotherapy (see Table 4).

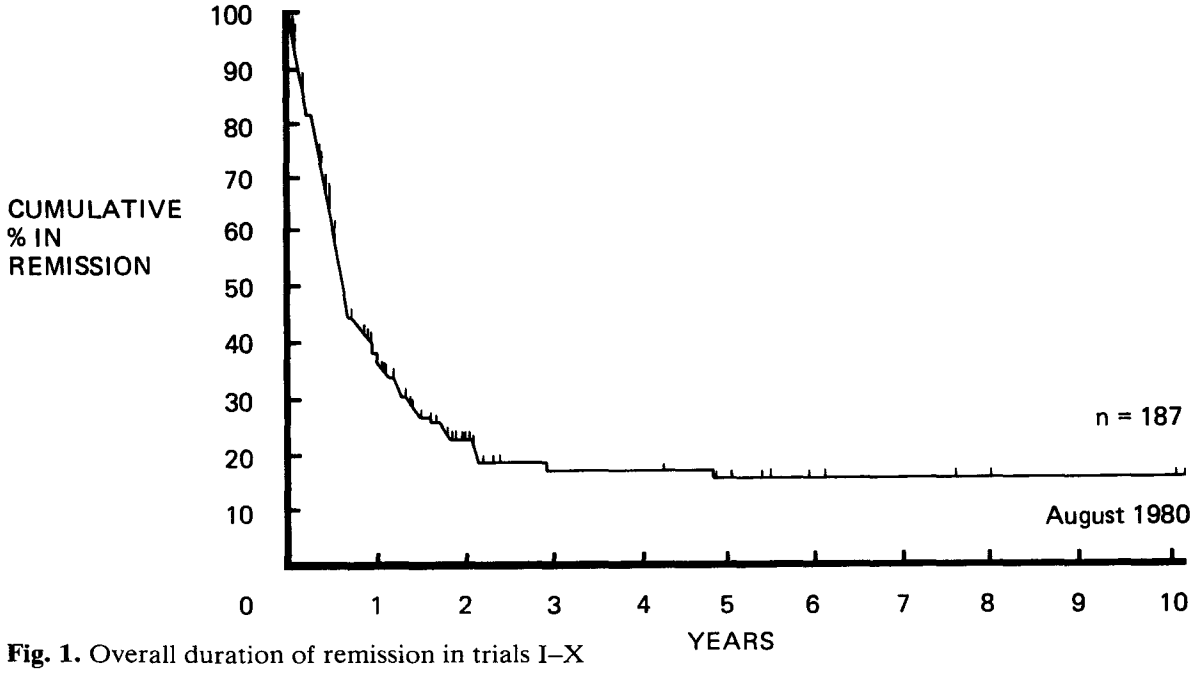


Fig. 1. Overall duration of remission in trials I–X

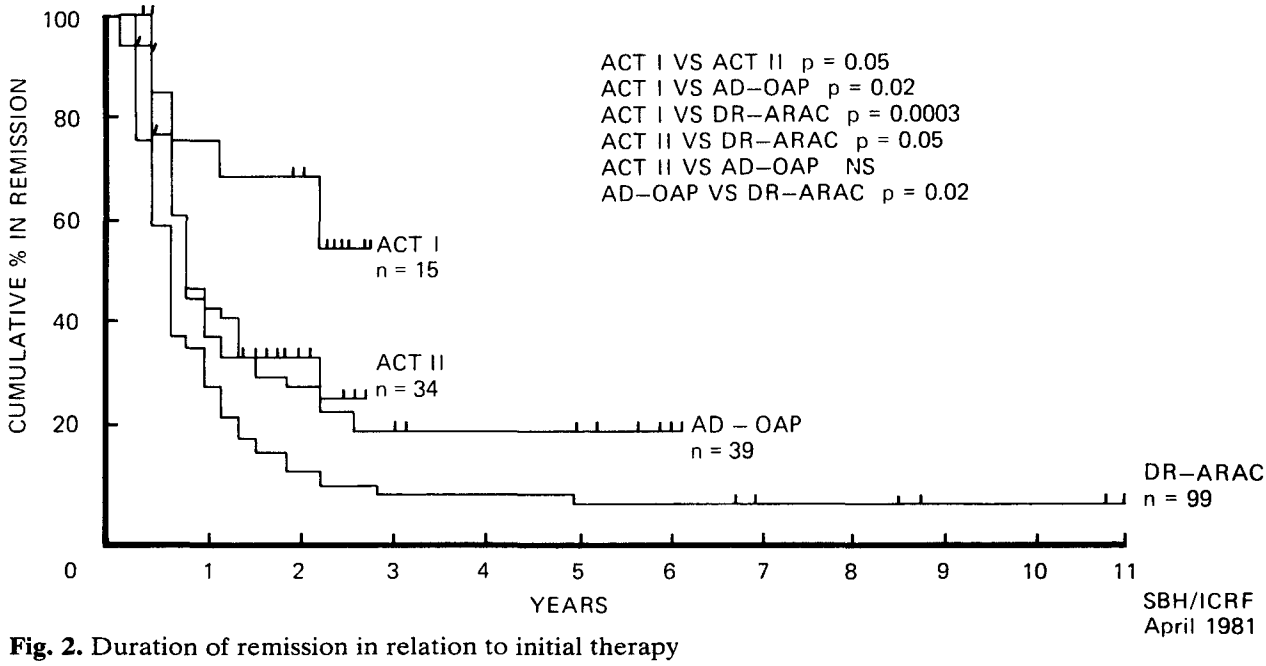


Fig. 2. Duration of remission in relation to initial therapy

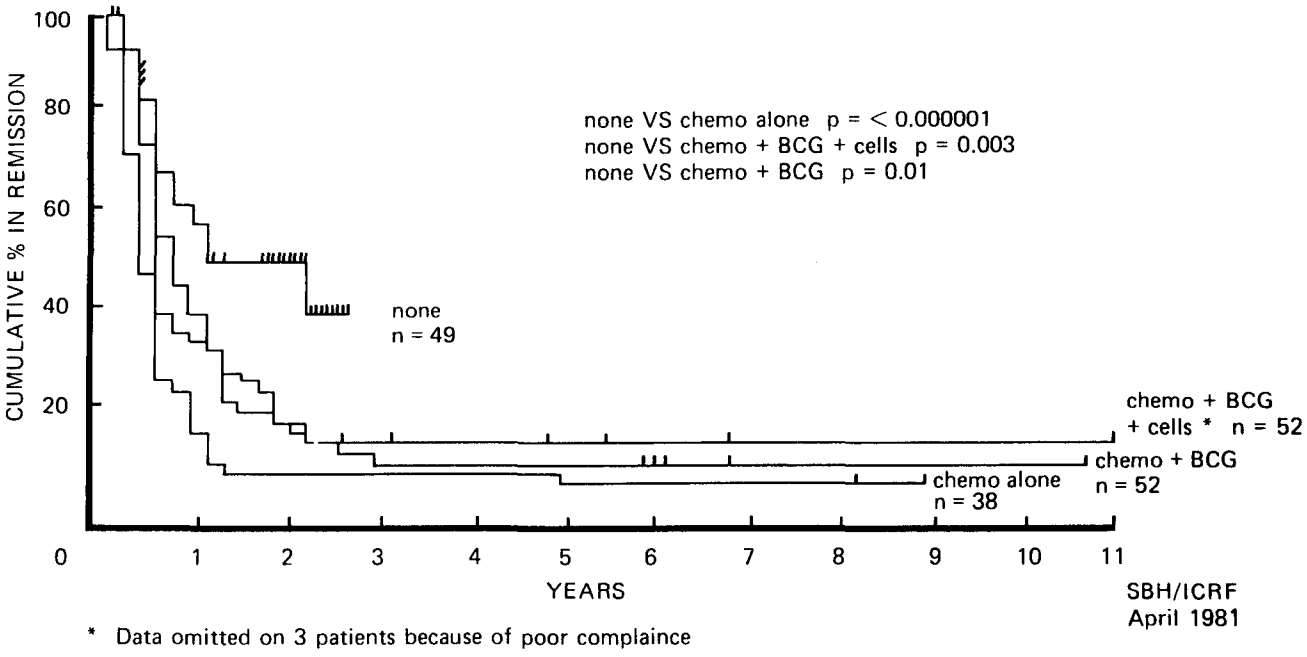
II. Continuation Therapy

Four different types of continuation therapy were used: –

1. None (Trials IX and X);
2. Chemotherapy alone [Trials II, III and IVA (randomised study)];
3. Chemotherapy and "immunotherapy" comprising BCG and allogeneic blast cells: Trials II, III, IVA (randomised study), Trial V (all patients), and Trial VIII (randomised study); and
4. Chemotherapy and immunotherapy with BCG [Trial VIII (randomised study)].

Comparison of the duration of remission of these four groups demonstrates no advantage for continuation of therapy after consolidation (Fig. 3). The group with the best duration of remission was in fact that receiving no continuation therapy but the most intensive initial (remission induction and consolidation) treatment. There are not, however, comparisons between concurrently randomised groups of patients and the follow up is shortest in the group with the most favourable result.

The different "immunizing" manœuvres, with the addition of either BCG alone or BCG and allogeneic blast cells, did not confer any



* Data omitted on 3 patients because of poor complaince

Fig. 3. Duration of remission influence of continuation therapy

advantage in terms of duration of first complete remission.

None of the other factors analysed, particularly age (or inital physical findings, blast count, platelet count, blast cell morphology) correlated with the duration of first complete remission.

E. Survival

The most important factor determining survival was the outcome of initial therapy (Fig. 4). Sixty-two patients remain alive between 3 months and 11 years.

F. Long Survival

Thirty-six patients have lived more than 3 years. Only 2 out of 13 cases who were in first complete remission at that time have subsequently relapsed, the latter at 4.5 years. An additional four patients recurred within 6 months of the first remission, entered second remission and have remained disease free subsequently for a minimum of 4 years. Detailed analysis of the presentation features of these patients reveals them to be a heterogenous group with no specific factors in common other than long survival.

G. Discussion

The results of combination chemotherapy for adults with AML at St. Bartholomew's Hospital have been presented. They confirm the trend reported by others (Keating et al., to be published; Priester et al. 1980; Gale and Cline 1977; Rees et al. 1977; Mayer et al. see this volume) that intensification of early therapy can result in complete remission being achieved in the majority of adults under the age of 60. It is important to qualify this with the rider that intensification of the cytotoxic chemotherapy without adequate supportive care is valueless. This is clear from the results of Trial VIII, in which the initial treatment was intensified. The routine use of platelet concentrates and powerful antibiotic combinations obliterated the prognostic disadvantage of thrombocytopenia and infectious complications at presentation. However, the management of infection during the neutrophil nadir was not adequate with a high incidence of fatal gram negative infection, especially in patients not receiving gastrointestinal tract decontamination. The apparent advantage of this was not appreciated until a similar high incidence of fatal gram negative infection was observed in Trials IX and X (Rohatiner et al. 1981). The high complete remission rate for patients under 60 in Trial IX (ACT II) was achieved against a background of more intensive sup-

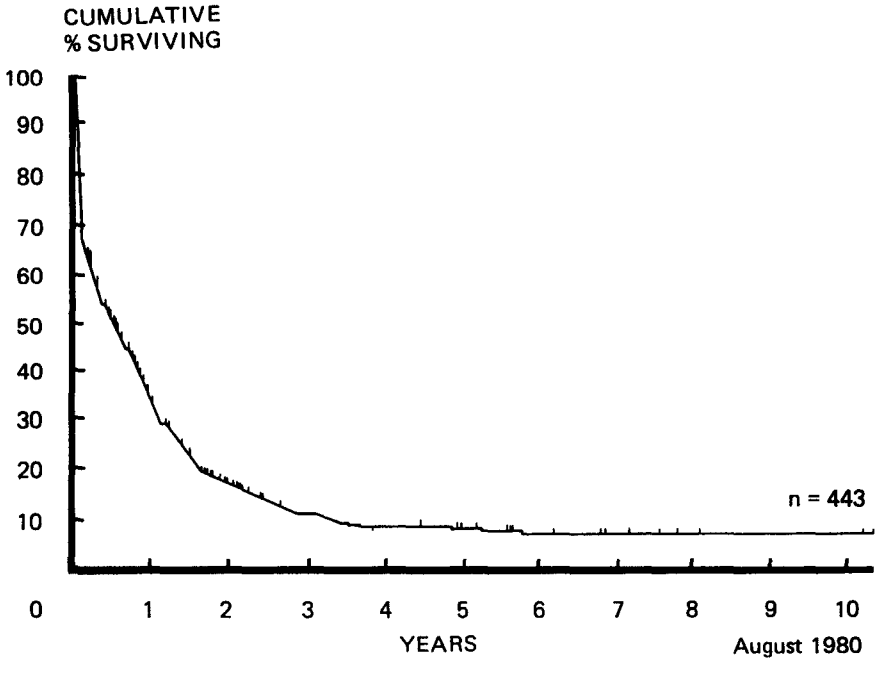


Fig. 4. Overall survival in trials in 1–10

portive care, including the use of gastro intestinal tract decontamination, aggressive antibiotic therapy for fever as before, and scrupulous attention to the increased incidence of pneumonia. The use of transtracheal aspiration has made it possible to obtain bacterial isolates and thus potentially influence antibiotic therapy in approximately 50% of the patients with suspected chest infection from whom sputum could not be obtained (Slevin et al.1981).

Early analysis of the most recent Trials (IX, X) suggest that the intensity of the very early therapy is critical to the duration of remission. It is not possible to comment yet on the relevance of "consolidation" therapy, although there is some evidence to support the contention that "early intensification" improves the duration of remission (Bell et al., to be published). The role of maintenance or continuation (philosophically more attractive) therapy has certainly not been established. However, the comparisons made have not all been concurrent nor has identical early therapy been used in all the studies analysed.

As in all other reported series, a very close correlation between the response to initial therapy and survival has been observed. The obvious corollary of this, namely that overall survival in all studies must now be better than previously since the complete remission rate is so much higher, has yet to be established. There is, however, no doubt that long survival has never been seen in patients in whom the bone marrow is not returned to normal. Extensive analysis of those patients surviving more than 3 years has revealed a wealth of negative correlations between presentation features and survival with only a suspicion that the intensity of the early therapy is important. This is based solely on the fact that a high proportion of the long survivors were treated in the Trial VIII study and must be tempered by the fact that this is the most recent study, by definition, in which long survivors have occurred. Further long follow up is obviously required.

In spite of all these reservations, we believe that these results should be viewed with optimism. Ten years ago the major publications on this subject were only able to record, with justifiable optimism, that it was possible to achieve remission in AML and that it should be treated with curative intent. The data presented here in complete concordance with that of others (Ellison and Glidewell 1979; Keating et al., to be published) show that a significant proportion will live at least 3 years. Exciting experiments with bone marrow transplantation, both in terms of eradication of leukaemia and mismatched grafting, further manipulation of chemotherapy and the design of good clinical experiments may lead to the speculation of the seventies becoming the reality of the eighties.

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References

Bell R, Rohatiner AZS, Ford J, Slevin ML, Amess J, Malpas JS, Lister TA (to be published) Short term therapy for acute myelogenous leukaemia – Crowther D, Powles RL, Bateman CJT, Beard MEJ, Gauci CL, Wrigley PFM, Malpas JS, Hamilton Fairley G, Bodley Scott R (1973) Management of adult acute myelogenous leukaemia. Br Med J 1:131–137 – Ellison RR, Glidewell 0 (1979) Improved survival in adults with acute myelocytic leukaemia. Proc Am Assoc Cancer Res 20:651 – Gale RP, Cline MJ (1977) High remission-induction rate in acute myeloid leukaemia. Lancet 1:497–499 – Keating MJ, Smith TC, McCredie KB (to be published) A four year experience with Anthracycline, Cytosine Arabinoside, Vincristine and Prednisone combination chemotherapy in 325 adults with acute leukaemia. Cancer – Lister TA, Whitehouse JMA, Oliver RTD, Bell R, Johnson SAN, Wrigley PFM, Ford JM, Cullen MH, Gregory W, Paxton AM, Malpas JS (1980) Chemotherapy and immunotherapy for acute myelogenous leukaemia. Cancer 46:2142–2148 – Powles RL, Russell J, Lister TA, Oliver RTD, Whitehouse JMA, Malpas JS, Chapuis B, Crowther D, Alexander P (1977) Immunotherapy for acute myelogenous leukaemia. A controlled clinical study 2½ years after entry of last patient. Br J Cancer 35:265–275 – Priesler H, Browman G, Henderson E, Hryniuk W, Freeman A (1980) Treatment of acute myelocytic leukaemia. Effects of early intensive consolidation. Proc. ASCO 21:C-493 – Rees JKH, Sandler RM, Challender J, Hayhoe FGJ (1977) Treatment of acute myeloid leukaemia with a triple cytotoxic regime: DAT. Br J Cancer 36:770–776 – Rohatiner AZS, Lowes LA, Lister TA (1981) Infection in acute myelogenous

leukaemia. An analysis of 168 patients. Journal of Hospital Infection, in press – Slevin ML, Lowes A, Bell R, Catto-Smith A, Ford JM, Malpas JS, Lister TA (1981) The role of transtracheal aspiration in the diagnosis of respiratory infection in neutropenic patients with acute leukaemia. Leukemia Research 5:165–168 – Schimpff SC, Green WH, Young VM, Fratner CC, Jepson J, Cusack N (1975) Infection prevention in acute non-lymphocytic leukaemia. Laminar air flow room reverse isolation with oral non-absorbable antibiotic prophylaxis. Ann Intern Med 82:351–358