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ACTIVE IMMUNOTHERAPY IN ACUTE MYELOGENOUS LEUKAEMIA AND THE INDUCTION OF SECOND AND SUBSEQUENT REMISSIONS

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Summary.—One hundred and ninety-one adults with acute myelogenous leukaemia were treated with combination chemotherapy consisting of daunorubicin and cytosine arabinoside (Barts III). Sixty-three patients achieved remission and were admitted to one of 3 trials of active immunotherapy: immunotherapy alone, immunotherapy and maintenance chemotherapy or neither of these. All patients had weekly clinical and blood examination and monthly marrow examination. Reinduction chemotherapy was given as soon as relapse was diagnosed in the marrow. The most striking observation was that immunotherapy was associated with easy and repeated reinduction of remission and marked prolongation of survival after first relapse when compared with immunotherapy plus chemotherapy. The possible reasons for this and the value of immunotherapy are discussed in relation to the third trial still in progress which includes 2 maintenance arms, immunotherapy alone and surveillance only.

IN 1971 we began a trial of active immunotherapy for acute myelogenous leukaemia (AML) using a regime of remission induction and maintenance which was based upon that of Crowther *et al.* (1973) but included routine monthly diagnostic marrow examination for the early detection of relapse. We found that second remissions were the rule (6/7 patients), while third and subsequent remissions commonly occurred (Freeman *et al.*, 1973), in contrast to the general experience that relatively few patients achieved second remission in adult AML (Wiernik and Serpick, 1970; Bailey *et al.*, 1971; Crowther *et al.*, 1973; Powles, 1973; Powles *et al.*, 1973, 1977). There are few reports of third remissions (Whittaker and Slater, 1977), although we have achieved at least 75% third remissions in some groups of patients. Following the encouraging results from our first trial, we subsequently participated in randomized MRC trials of immunotherapy which necessitated several changes of therapeutic protocol; nevertheless the use of monthly marrow examination remained constant.

The present communication describes our experience over a 6-year period of 3 trials of active immunotherapy in AML in which immunotherapy has been associated with relatively short first remissions but easy second and subsequent remission with long post-relapse survival and an excellent quality of life.

PATIENTS AND METHODS

Patients entered into 3 Manchester AML trials since 1971 and followed up to 15 March 1977, have received one of the therapeutic protocols summarized in Table I. Patients were not selected, and all who were referred to Manchester Royal Infirmary were treated. The diagnosis of AML was confirmed by blood examination and by marrow examination carried out by sternal or iliac-crest puncture. The aspirated material was fixed,

stained and examined usually on the same day. Complete remission was judged to have occurred when the aspirate showed <5% blasts with no abnormal forms, recovery of other normal elements, a rising peripheral platelet and neutrophil count, a steady or rising haemoglobin level not maintained by transfusion, and the absence of abnormal clinical signs. All patients who went into remission were seen weekly for clinical assessment and for blood counts. Marrow examination was at monthly intervals, and relapse was diagnosed on the basis of an increased level of abnormal blasts (>5%). If the blast count showed a slight rise, say 5–8%, marrow examination was repeated within 2 weeks. A blast count >8% was taken as definite indication of relapse, even in the absence of clinical and peripheral blood changes. Immunotherapy with irradiated allogeneic AML blast cells and BCG (Glaxo) was administered at weekly intervals as described previously (Freeman *et al.*, 1973).

RESULTS

One hundred and ninety-one patients have been entered into the Manchester AML trials since October 1971, and 63 have achieved remission, an overall induction rate of 33%. Fig. 1 is a life table of survival from presentation for patients who remitted, using the 5 protocols summarized in Table I. Table II summarizes the data relevant to length of first remission, frequency of second and subsequent remissions and duration of survival after first relapse. Seven patients are still in their first remission and 10 patients have survived more than 2 years from first relapse. Of the 9 surviving longest, 2 have survived for 5 years, 2 over 4 years and the rest have survived over 3 years. The survival curves in Fig. 1 do not show any statistical difference between the different arms of treatment.

Amongst the 39 patients who achieved first remission but who have since died, the average duration of survival following first relapse was >8 months. Although there was no significant difference in overall survival after relapse, including living patients in the second trial, the average times between first relapse and death was 290·7 days for patients receiving immunotherapy only and 145·6 for those receiving immunotherapy with maintenance chemotherapy (Fig. 2). This difference is highly significant ($P<0·01$) although this method of analysis may be open to criticism (R. Peto, personal communication).

DISCUSSION

Our first remission-induction figures are lower than the best reported (*e.g.* Gale

TABLE I.—*Manchester Immunotherapy Trial Protocols*

Phase	Trial I (Pilot)	Trial II (MRC VI)	Trial III (MRC VI modified)
Induction	A	A	A
*N + 1	+	+	+
Consolidation	B	Nil	B
Maintenance chemotherapy	Nil	Randomize Nil or C	Nil
Immunotherapy	I	I	Randomize I or Nil

* N + 1 = one extra course of daunorubicin and cytosine arabinoside once marrow indicated remission.

A = Daunorubicin 1·5 mg/kg on Day 1.
Cytosine arabinoside (Ara C) 2·0 mg/kg daily by i.v. pulse Days 1–5
} Barts III induction

B = Cyclophosphamide 200 mg/m² weekly for 6 weeks.
Thioguanine 2·5 mg/kg daily for 6 weeks.

C = 5-day course of Arc C + Thioguanine and A alternating monthly, except that dosage of thioguanine was 2·0 mg/kg daily orally (Barts chemotherapy maintenance).

I = 10^9 irradiated allogeneic leukaemic cells plus 10^6 Glaxo BCG (Freeman *et al.*, 1973).

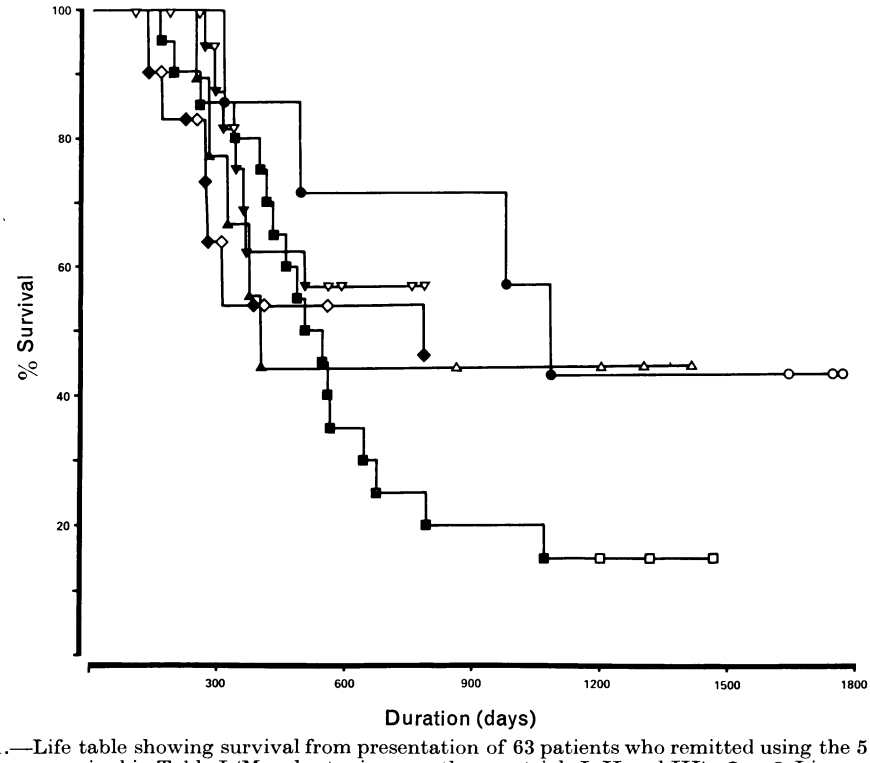

FIG. 1.—Life table showing survival from presentation of 63 patients who remitted using the 5 protocols summarised in Table I (Manchester immunotherapy trials I, II and III). ●—○ I imm. $n = 7$; ▲—△ II imm. + chem. $n = 9$; ■—□ II imm. $n = 20$; ▼—▽ III imm. $n = 16$; ♦—◇ III nil $n = 11$.

and Kline, 1977) but are not unusually low for the Barts III regime (Powles *et al.*, 1973, 1977) and could be improved if better facilities for supportive care were available. However, it is important to take the induction rate into consideration when analysing reinduction frequency, since a low first-remission induction rate may conceivably eliminate relatively drug-resistant patients before randomization. Adequate induction chemotherapy probably plays a large part in determining length of first remission and duration of survival. For example, patients in the first Manchester immunotherapy trial had significantly better first-remission lengths and duration of survival than the immunotherapy-only arm of the second trial. The difference in survival is significant only at 2 years ($P<0{\cdot}05$, Table I) and is attributed to the omission of cyto-reduction (consolidation) chemotherapy from the MRC 6th AML trial protocol. Maintenance chemotherapy may in this case have partly compensated for inadequate induction treatment. Those patients who achieved remission have generally experienced remarkably good overall survival times, even following relapse. First-remission length is not correlated with duration of survival in our series, mainly because second and subsequent remissions have been achieved in a high proportion of patients, and second and subsequent remissions were often longer than the first. It is likely that routine monthly marrow examination while in remission is partly responsible for both short remissions and easy re-induction. This practice allows early diagnosis of relapse and prompt re-introduction of chemotherapy whilst the leukaemia cell mass is still small. If marrow examination is not carried out

TABLE II.—*Lengths of First Remission, Frequency of Second and Subsequent Remissions and Duration of Survival after First Relapse*

Trial		M/C I	M/C II		M/C III	
Dates patients admitted		Oct/71–Oct/72	Jan/73–Sept/74		Jan/75—Patients still being admitted (maximum survival possible only 26 months)	
No.		32	77		82	
Patients entering remission (%)		25	37·6		33	
Trial arm		Immunotherapy	Imm.	Imm. + Chem.	Imm.	No maintenance
No. randomized		7 (not randomized)	20	9	16	11
Still in first remission		Nil	Nil	Nil	5	2
Proportion of relapsed patients achieving 2nd and subsequent remissions	2nd	6/7	15/20	6/9	5/11	2/8
	3rd	3/4	9/15	1/4	1/4	1/2
	4th	2/3	5/8			
	5th	2/2	1/3			
	6th	1/2				
Median length of first remission (days)		161	80.5	126	206.5	154
Remitters median survival from presentation (days)		1089	514	404	328	262
Median survival after relapse (days)		757	310	260	150	95·0
Median relapse to death (days)		549	286	155	150	112·5

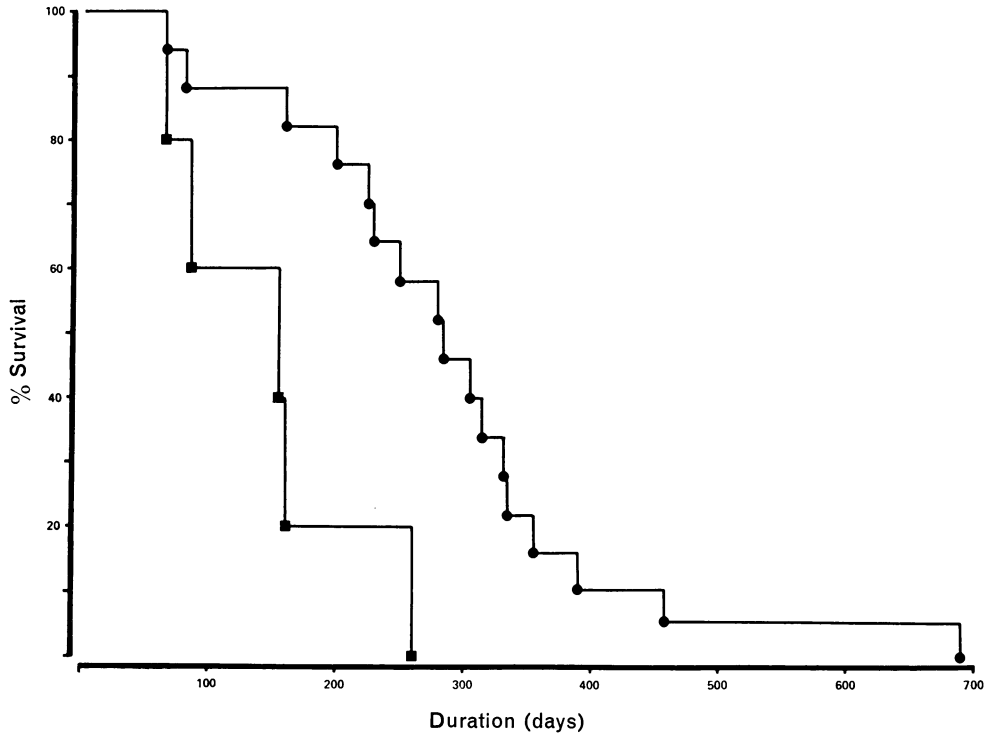

FIG. 2.—Life table showing survival after relapse for patients who died (excluding long survivors) in Manchester II Trial. ● immunotherapy $n = 17$; ■ immunotherapy + chemotherapy $n = 5$. $P < 0{\cdot}01$.

routinely or carried out only when the peripheral-blood examination or clinical signs suggest that relapse is imminent, first remission length may appear to be relatively long, but reinduction in the presence of more advanced relapse may be more difficult and consequently post-relapse survival short.

Immunotherapy appears to prolong first remission (Crowther *et al.*, 1973; Powles *et al.*, 1977), facilitate reinduction (Freeman *et al.*, 1973) and lengthen post-relapse survival (Powles *et al.*, 1977). These observations have received some support in the results of the MRC VI trial (1978). It is still not clear whether immunotherapy is actively beneficial or whether the apparent advantages are due to avoidance of drug resistance and to monthly marrow examination.

Our current direct trial is designed to overcome these uncertainties by comparing immunotherapy with no treatment during remission (Table I). This trial allows for the first time an assessment of immunotherapy uncomplicated by maintenance chemotherapy. The patients in both arms of the trial are subject to identical weekly clinical and haematological assessment and routine monthly marrow examination. Although it is still too early to analyse this third Manchester trial in terms of length of survival, it is interesting to note that the median duration of first remission is 30 weeks for the 16 immunotherapy patients and only 22 weeks for 11 patients in the surveillance-only group.

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APPENDIX

Data for 63 Patients Randomized into Manchester First, Second and Third Trials (to April 1977).

Trial No.	Diagnosis	Manchester trial	Treatment	First remission length (days)	Survival after relapse (days)	Survival from presentation (days)
M/C1	AML	I	Imm.	161	757	984
M/C6	AMML	I	Imm.	196	56	311
M/C14	AML	I	Imm.	126	341	499
M/C19	AML	I	Imm.	602	1137	1771 Alive
M/C21	AMML	I	Imm.	98	1608	1757 Alive
M/C26	EL	I	Imm.	126	952	1089
M/C29	AML	I	Imm.	1438	180	1644 Alive
M3	AML	II	Imm.	140	333	560
M7	AML	II	Imm.	77	1346	1460 Alive
M18	AMML	II	Imm.	21	198	262
M23	AMML	II	Imm.	126	332	536
M30	AML	II	Imm.	628	1259	1314 Alive
M33	AMML	II	Imm.	84	249	404
M34	AML	II	Imm.	49	78	201
M37	EL and AML	II	Imm.	168	226	457
M40	AML	II	Imm.	245	353	668
M45	AML	II	Imm.	535	388	492
M48	AML	II	Imm.	35	936	1096 Alive
M52	AML	II	Imm.	42	66	163
M56	AML	II	Imm.	70	226	396
M60	EL and AML	II	Imm.	84	286	536
M65	AML	II	Imm.	77	306	786
M66	AMML	II	Imm.	273	690	1060
M75	AML	II	Imm.	91	158	330
M77	AMML	II	Imm.	77	281	442
M79	AMML	II	Imm.	119	315	473
M87	AML	II	Imm.	112	457	642

Trial No.	Diagnosis	Manchester trial	Treatment	First remission length (days)	Survival after relapse (days)	Survival from presentation (days)
M9	AML	II	I. and C.	147	161	378
M14	AML	II	I. and C.	252	1160	1412 Alive
M15	AML	II	I. and C.	126	155	317
M32	AMML	II	I. and C.	56	1182	1305 Alive
M44	AML	II	I. and C.	63	86	248
M47	AMML	II	I. and C.	259	859	1201 Alive
M51	AMML	II	I. and C.	63	260	404
M71	AML	II	I. and C.	70	66	280
M91	AML	II	I. and C.	441	281	860 Alive
M83	AML	III	Imm.	107	39	268
M84	EL	III	Imm.	81	201	368
M101	AMOL	III	Imm.	645	In remission	795 Alive
M106	APL	III	Imm.	457	243	748 Alive[
M107	AMML	III	Imm.	109	162	330
M118	AML	III	Imm.	246	198	499
M125	AML	III	Imm.	130	35	278
M131	AML	III	Imm.	359	186	545 Alive
M127	AMML	III	Imm.	441	In remission	572 Alive
M136	AML	III	Imm.	203	84	362
M150	APL	III	Imm.	238	14	326 Alive
M152	AML	III	Imm.	99	150	313
M156	EL	III	Imm.	210	In remission	229 Alive
M153	AML	III	Imm.	219	40	283 Alive
M158	AML	III	Imm.	140	In remission	147 Alive
M160	AML	III	Imm.	68	In remission	105 Alive
M88	AMML	III	No maintenance	87	84	260
M90	AML	III	No maintenance	165	441	784
M108	AML	III	No maintenance	89	95	224
M128	EL	III	No maintenance	522	In remission	563 Alive
M129	AML	III	No maintenance	98	36	148
M141	AMML	III	No maintenance	173	147	383
M145	AMML	III	No maintenance	328	In remission	390 Alive
M147	AML	III	No maintenance	78	130	262
M151	EL	III	No maintenance	154	122	318 Alive
M157	AML	III	No maintenance	126	35	203 Alive
M155	AML	III	No maintenance	175	5	244 Alive