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Long-term Results of the HEAVD Protocol for Adult Acute Lymphoblastic Leukaemia

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Between 1979 and 1987, 82 adults (age 14–71 years) with acute lymphoblastic leukaemia (ALL) were treated with a 6-course protocol called HEAVD, the main feature of which was the early postremission administration of escalating doses of doxorubicin (total 405 mg/m^2) and cyclophosphamide (total 2.5 g/m^2). A complete remission (CR) was attained in 66 patients (80%, 95% confidence intervals, [CI] 71%–89%). Factors affecting favourable CR achievement were age < 60 years and absence of lymphadenopathy–hepatosplenomegaly at presentation ($P < 0.05$). Median duration of CR was 27 months. 26 patients remain in first continuous and unmaintained CR, 18 of whom between 5.9 and 11.1 years, for an estimated 39% prolonged disease-free survival (95% CI 27%–51%). CR duration correlated significantly with absolute blast cell count (15 × 10^9/l or less compared to more) and age (30 years or under compared to over). Overall, 29 patients are alive with a median follow-up of 6.7 years, the projected long term survival being 35% at 11 years (95% CI 24%–46%). Treatment-related toxicity included 1 lethal case of L-asparaginase-related thromboembolism and 3 toxic deaths among 66 CR patients. Late-onset toxicity was not observed in long-term survivors. The relatively late occurrence of endpoint events (relapse and death) in adult ALL confirms that long-term updating is necessary to determine the curative potential of modern chemotherapy programs for the disease.
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INTRODUCTION

ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL) in adults is a rare and most often fatal neoplastic disease. Although as many as 80% of patients may initially achieve a complete remission (CR), most subsequently relapse and eventually die [1]. Since with modern treatment strategies a CR duration of 18–24 months is not unusual and systemic relapses occur as late as the fourth or fifth year of observation [1], clinical studies with a median follow-up period extended beyond 5 years are needed if the impact of a potentially curative therapeutic approach is to be properly assessed.

Starting in 1979, we have conducted an open uncontrolled study in adult ALL employing a regimen akin to HEAVD from St Bartholomew's Hospital (SBH, London, UK) [2],

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characterised by intensive induction and consolidation, comprising escalating doses of doxorubicin and cyclophosphamide in addition to vincristine, L-asparaginase, and prednisolone, followed by central nervous system (CNS) prophylaxis and prolonged maintenance therapy. Median follow-up of patients is now 6.7 years, range 2.3–11.1. In the light of the opening remarks, here we present the long term results obtained with this protocol in 82 adults with ALL.

MATERIALS AND METHODS

Acute leukaemia diagnosis

ALL diagnosis relied on French-American-British (FAB) criteria [3]. Periodic acid-Schiff, myeloperoxidase or Sudan black, and non-specific esterase cytochemical stains of bone marrow smears were performed in all cases. Immune marker analysis with polyclonal anti-human immunoglobulin antisera, murine monoclonal antibodies to B (CD10, CD19, CD20) and T (CD2, CD3, CD5, CD7) cell lineage surface antigens, and nuclear deoxynucleotidyl terminal-transferase antiserum was performed in 40 patients [4]. Chromosome analysis was not routinely done.

HEAVD regimen

The SBH's HEAVD protocol for adult ALL [2, 5] combines a four-drug induction phase (courses nos 1 and 2) to four 3-day consolidation courses (nos 3–6) with escalating doses of doxorubicin and cyclophosphamide, total cumulative doxorubicin dose being 405 mg/m^2 and cyclophosphamide 2.5 g/m^2, respectively. Details of the regimen are given in Table 1. Course 2 was generally given on day 14 to 21 from start of therapy. The timing between each of subsequent consolidation courses depended on patient clinical status and peripheral blood count (white blood cells [WBC] $> 3 \times 10^9$/l, platelets $> 100 \times 10^9$/l). A 3-week interval was adopted as a general rule. During remission induction, patients were nursed in open wards, and received oral allopurinol and prophylactic paromomycin and nystatin. Packed red cells were given to maintain the haemoglobin concentration above 8 g/dl. Platelet transfusions were not routinely employed. Courses 3–6 were generally given as outpatients.

Once blast cells had cleared from peripheral blood, methotrexate 12.5 mg was instilled intrathecally. In patients achieving CR, methotrexate was subsequently administered on day 1 of course 2–6, and 3 times during cranial irradiation (24 Gy), which was normally given after course 4.

Upon completion of induction–consolidation and CNS phases, maintenance chemotherapy with methotrexate 30 mg intramuscularly weekly and 6-mercaptopurine 75–100 mg orally daily was prescribed for 3 years to CR patients. Dosages were adjusted to maintain the leukocyte count at 3×10^9/l. In patients haematologically able to tolerate it, cyclophosphamide 300 mg orally, weekly, was added.

Response evaluation and data analysis

Achievement of CR required the patient to have no clinical evidence of leukaemia, with a self-sustaining haemoglobin concentration > 10 g/dl, a granulocyte count $> 1.5 \times 10^9$/l, platelets $> 100 \times 10^9$/l, and no obvious leukaemic blast cell in a normocellular bone marrow [5]. Remission marrow was checked after course 1 or 2, depending on patient status and blood count. Patients not in CR after course 2 generally were not given alternative treatment and went on to receive the next HEAVD cycle.

Table 1. HEAVD protocol for ALL: induction and consolidation phases

Course no.	Drugs	Dosage	Day(s)
1.	Doxorubicin	30 mg/m^2	1.
	Vincristine	1.4 mg/m^2 (max 2 mg)	1.
	L-asparaginase	10.000 U/m^2	1–14.
	Dexamethasone	8 mg/bd	until CR
	(or prednisolone)	40 mg/m^2	
2.	Doxorubicin	25 mg/m^2	21
	Vincristine	(as above)	21
3.4.*	Doxorubicin	25 mg/m^2	1–3.
	Vincristine	(as above)	2.
	Cyclophosphamide	500 mg/m^2	2.
5.6.*	Doxorubicin	40 mg/m^2	1.
		30 mg/m^2	2, 3.
	Vincristine	(as above)	2.
	Cyclophosphamide	750 mg/m^2	2.

* Interval between courses nos 3–6 approximately 21 days.
All drugs by intravenous route.
H = hydroxydaunomycin/doxorubicin, E = cyclophosphamide, A = L-asparaginase, V = vincristine, D = dexamethasone.
Remission induction: courses no. 1, 2; consolidation: courses no. 3–6.
bd = twice a day.

Proportions of patients achieving CR in different prognostic groups were compared using the Fisher's exact test; 95% confidence intervals (CI) were also determined [6]. Duration of remission and survival curves (including 95% CI) were plotted by the Kaplan–Meier method, and compared using the log-rank method [7]. Survival was taken from date of diagnosis to death, and CR duration from the date of CR to relapse. Deaths occurring in CR were considered negative events in CR curves.

The significance of prognostic factors in determining the achievement of CR was evaluated by logistic regression analysis, whereas duration of CR and overall survival differences were determined using the Cox's proportional hazards model procedure [8]. The factors tested for correlation with achievement of CR, duration of CR and survival were age, sex, FAB class, blast cell count and immunophenotype, lymphadenopathy, hepatomegaly, splenomegaly, time to CR (days), and administration of cyclophosphamide during maintenance. Results were analysed as of end of May, 1990.

RESULTS

Patients

82 previously untreated, consecutive and unselected adults with newly diagnosed ALL were entered into this two-institution study between February 1979 and June 1984 (63 patients), throughout 1987 (18 patients), and early in 1988 (1 patient). 1 patient had Down's syndrome. Main clinical and laboratory characteristics of patients at diagnosis are summarised in Table 2. A rather high incidence (9%) of FAB L3 leukaemia was observed; however only 2 of 7 L3 cases were immunophenotyped to confirm B-ALL diagnosis. Between July 1984 and December 1986, 24 other patients were treated with a modified regimen utilising postremission consolidation with high-dose cytarabine (2 g/m^2/bd for six days), reduced doxorubicin (total dose 120 mg/m^2), and no cyclophosphamide. These cases are

Table 2. Clinical characteristics of 82 adult patients with ALL

Age (years)	
Range	14–71
Mean	32
Median	26
Sex M:F	42:40
Lymphadenopathy†	17
Hepatomegaly	35
Splenomegaly	36
None	32
Blast cell count (x 10^9/l)	
Range	0–315
Mean	35.8
Median	6.8
FAB subtype*	
L1	11 (13)
L2	64 (78)
L3	7 (9)
Immunophenotype (n = 40)*	
Common	14
Null	17
T	7
B	2

* No. of cases (%)
† Including mediastinal mass on chest X-ray film.

Table 3. Complete remission rate in relation to presenting characteristics

Patient groups	Presenting feature	No.	Complete remission No.	% (95% CI)	P
Age (years)	14–30	43	37	86 (72–100)	
	31–45	18	15	83 (67–99)	
	46–59	16	12	75 (59–91)	0.01
	≥ 60	5	2	40 (28–52)	
FAB class	L1	11	10	91 (73–100)	
	L2	64	51	80 (68–92)	NS
	L3	7	5	71 (55–87)	
Blast cells	0–10	44	36	81 (67–95)	
(x 10^9/l)	> 10–50	20	16	80 (74–96)	NS
	> 50	18	14	78 (62–94)	
Phenotype	"Common"	14	13	93 (78–100)	
(n = 40)	Null	17	15	88 (71–100)	NS
	T	7	7	100 (81–100)	
	B	2	1	50 (36–64)	
L/H/S*	All three	10	5	50 (37–63)	
	Any one/two	40	33	82 (68–96)	0.01
	None	32	28	87 (72–100)	

* L = lymphadenopathy, H = hepatomegaly, S = splenomegaly.
NS = not significant.

excluded from the present study and have been reported elsewhere [9].

Achievement of CR

CR was attained in 66/82 patients overall (80%, 95% CI 71%–89%). The median time to CR resulted 26 days, and range 14–49. In the majority of cases (46/66, 67%), a CR marrow was obtained within 30 days from start of therapy. The factors found to correlate unfavourably with CR rate in both univariate and multivariate analyses were age 60 years or more and the combination of lymphadenopathy, hepatomegaly and splenomegaly. Table 3 displays the CR rates according to all the factors analysed.

16 patients died without achieving CR, generally because of infection and/or haemorrhage. Leukaemia was present in 11 of them at the time of death. 1 patient however died of pulmonary thromboembolism possibly in relation to L-asparaginase treatment before response could be evaluated.

Duration of CR and relapse

The median duration of the first CR for the 66 patients was 27 months. 2 patients were lost to follow-up after 8 months. 26 patients remain in their first continuous CR and are regularly followed up, 18 of whom between 5.9 and 11.1 years, giving an estimated 39% (95% CI 27%–51%) prolonged disease-free survival (Fig. 1) On log-rank and multivariate analyses, blast cell count at diagnosis (15 × 10^9/l or less compared to more) and patient age (30 years and under compared to older) were the two independent factors found to correlate with CR duration, this being significantly shorter in patients with higher blast count and more advanced age (Table 4). The combined evaluation of either clinical characteristic led to characterisation of standard risk patients (aged 30 or less and/or blast count ≤ 15 × 10^9/l), in whom median CR length was more than 2 years and projected long-term survival in remission between 39–51%, and high risk patients (aged more than 30 and > 15 × 10^9/l blast cells), in whom CR lasted less than 6 months and less than 20% were projected to be alive in remission after 5 years (Table 4 and Fig. 2). Time to CR (28 days or less compared to more than 28 days), FAB subtype, presence of adenopathy or hepatosplenomegaly, and adminstration of cyclophosphamide during maintenance (20 patients) were not found to affect in any way CR duration. Median CR duration for 15 cases with null cell phenotype resulted 18 months (10 failures), 27 months for 13 patients with "common" ALL (8 failures), and 20 months in the 7 cases with T-cell disease (4 failures) (P value NS). Of note, 2 patients with L3 leukaemia became long-term disease-free survivors at 7 and 10 years, respectively.

34 patients have so far relapsed: 30 in the bone marrow, 2 in both marrow and CNS, 1 in CNS and 1 with a testicular relapse heralding marrow relapse. The relapse rate appears initially

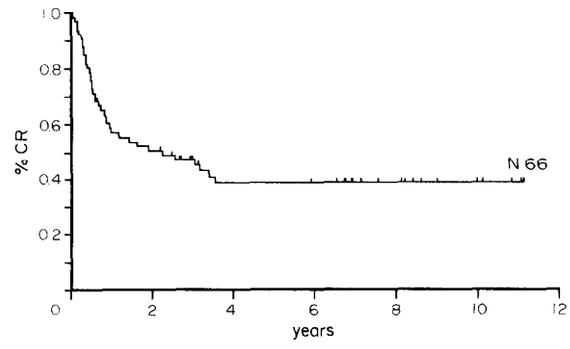

Fig. 1. Duration of first complete remission (66 patients). Vertical bars indicate cases at risk.

Table 4. Duration of complete remission: identification of standard and high risk groups according to age and absolute blast cell count

Patient groups	No.	Complete remission: Median duration (mos)	Complete remission: % at 5–10 years (95% CI)	P‡
Age (years)				
≤ 30	38	38	48 (33–63)	
> 30	28	11	27 (12–42)	0.01
Blast count (x 10⁹/l)				
≤ 15	38	41	45 (30–60)	
> 15	28	11	30 (15–45)	0.02
Age and blast count*				
≤ 30 and ≤ 15	23	>37§	51 (30–72)	
> 30 and > 15†	30	27	39 (22–56)	
> 30 and > 15	13	5	15 (0–34)	< 0.01

* The difference between groups 1 and 2 is not significant.
† Other parameter in lower class.
§ Not reached.
‡ From Cox's proportional hazards model.

Table 5. Factors affecting long term survival in 82 adult ALL patients treated with HEAVD protocol

Patient groups	No.	Survival: Median (mos)	Survival: % at 5–10 years (95% CI)	P: U/V	P: M/V
Complete remission					
yes	66	46	43 (32–54)		
no	16	0.6	0	< 0.001	0.0001
Age (years)					
≤ 30	43	> 48	50 (35–65)		
> 30–59	34	11	22 (9–35)	< 0.02	NS
≥ 60	5	0.6	0		
Blast count (× 10⁹/l)					
≤ 15	46	46	44 (31–57)		
> 15	36	9	22 (9–35)	< 0.05	NS
L/H/S*					
All three	10	7	15 (0–38)		
Any one/two	40	13	33 (20–46)	NS	NS
None	32	22	45 (30–60)		

* L = lymphadenopathy, H = hepatomegaly, S = splenomegaly.
U/V = univariate and M/V = multivariate analyses.
NS = not significant.

steep (Fig. 1), until approximately 12 months (66 at risk: 25 failures, 38%), at which point it decreases progressively to shift into the plateau phase towards the end of the fourth year of follow-up (38 at risk: 9 failures, 24%, i.e. 8% per year). The last relapse occurred after 3.6 years of follow-up.

The different CR duration in standard risk and high risk cases could be explained by the higher proportion of early relapses, i.e. within 12 months from achievement of CR, observed in the high risk group (8/13, 61% vs. 17/53, 32%; $P < 0.1$, χ^2 test). Relapsing patients were intensively retreated with either HEAVD or high-dose cytarabine-containing regimens. Although second and subsequent CR of worthwhile duration were achieved in some, nobody has become a long-term survivor as yet (i.e. disease-free survival more than 3 years), including a patient submitted to allogeneic bone marrow transplantation.

Survival

Overall, 29 patients are still alive and regularly followed-up. 4 patients (3 from the high risk group) died in CR. Median survival for all patients is 18 months, and projected long term survival 35% (95% CI: 24%–46%) (Fig. 3). Achievement of CR, lower blast cell count, and age were the only factors correlating with survival; absence of lymphadenopathy–hepatosplenomegaly was also advantageous though not in a statistically significant manner (Table 5).

Toxicity and treatment modifications

HEAVD-related toxicity was mainly haematological and globally manageable, with the exception of 1 case of lethal coagulopathy developing during induction in relation to L-asparaginase administration, 2 toxic deaths occurring early in CR after a consolidation course (one fungal infection, one haemorrhage), and two further CR deaths after 7 months (intracranial bleeding unrelated to acute leukaemia diagnosis and management) and 29 months (pneumonia), respectively.

During induction chemotherapy, L-asparaginase was withdrawn in 16 cases after 3–11 doses (median 7, i.e. 50% dose

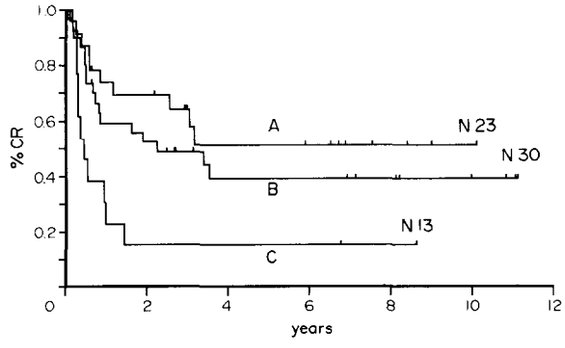

Fig. 2. Duration of first complete remission in relation to age (years) and absolute blast cell count (× 10⁹/l) at presentation: aged 30 or younger and blast count ≤ 15, $n = 23$ (A); aged more than 30 or blast count > 15, with other parameter in lower class, $n = 30$ (B); aged more than 30 and blast count > 15, $n = 13$ (C); $P < 0.01$ (A and B vs. C).

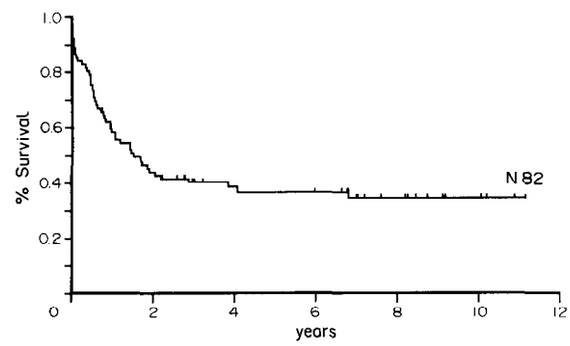

Fig. 3. Overall survival of 82 adult ALL patients treated with HEAVD.

reduction) because of severe liver dysfunction and/or glucose intolerance and/or fibrinogen reduction < 50 mg, and was not used in 2 further patients due to pre-existing contraindications. Notwithstanding, a CR was achieved in the majority of these cases (16/18, 89%). 17 patients among those entering CR (7 of whom had had reduced L-asparaginase) received less than the 4 intended consolidation cycles (range 1–3 courses, median 2), the reason being unsatisfactory haematological tolerance and repeat infectious episodes. Less intensive chemotherapy substituted for the missing HEAVD courses in 6 of these patients. Overall, postremission treatment modifications did not appear to worsen outcome, a subsequent relapse having occurred in 9 out of these 17 (53%). Clinically, no chronic CNS and heart toxicity was noted in the group of long-term disease-free survivors.

DISCUSSION

The overall results show that with intensive HEAVD chemotherapy 35% of adult patients with ALL are expected to survive in first continuous CR at 10 years, hence at great "risk for cure".

The initial four-drug induction chemotherapy, comprising a limited amount of the most myelotoxic drug doxorubicin, was well tolerated and brought about a 80% CR rate. This was usually within 4 weeks from start of treatment, with a quick rise in granulocyte and platelet count permitting early discharge in many cases and reducing the risk of infectious and haemorrhagic complications. The observation that achievement of CR within 28 days improves its duration [10, 11] was not confirmed. It is possible that the subsequent administration of intensive doxorubicin-based chemotherapy might have counterbalanced the adverse effect of entering CR in more than 28 days in some patients. Induction therapy was however associated with significant L-asparaginase-related toxicity in one-fifth of all patients, including one lethal case of thromboembolic disease [5]. Currently we monitor closely fibrinogen and other coagulation factors level (including antithrombin-III) and withdraw the drug in those cases in whom a fibrinogen concentration < 50 mg/dl is reached within 1 week. The second doxorubicin and vincristine injection is then anticipated. Because of L-asparaginase's potential toxicity and since CR can be induced in up to 90% of cases if an anthracyclin is added to a basic vincristine and prednisone regimen [10, 12–17], it is not clear whether L-asparaginase should be retained in protocols for remission induction of adult ALL.

A non-conventional characteristic of the HEAVD protocol was the postremission administration of a high cumulative doxorubicin dose within a relatively short period of time. This treatment was clearly unable to eradicate the leukaemic clone in patients who relapsed in the marrow within the first year of follow-up, i.e. during or shortly after consolidation cycles and early on during maintenance, representing 38% (25/66) of all CR cases. Simultaneity of age over 30 and blast cell count $> 15 \times 10^9$/l at presentation conferred the highest risk for early recurrence (61% vs. 32%), suggesting an association with adverse biological features. A greater incidence of the Philadelphia (Ph) translocation, which increases with age in *de novo* ALL, might be anticipated in this group, as recently suggested [18]. HEAVD was indeed less effective in the lymphoblastic phase of Ph+ chronic myelogenous leukaemia in a previous study [19]. Unfortunately the frequency of early failures was only marginally reduced by high-dose cytarabine consolidation in a subsequent trial, although the prognosis of patients with higher blast count and adverse immunophenotype (B, T, null) seemed initially improved [9]. However a sharp decrease in the recurrence rate was noted after the first year of follow-up in the current HEAVD study, only 9 relapses having occurred during the next 3-year period among 38 patients at risk (relapse rate 8% per year), and none subsequently. These data suggest that cure of adult ALL—or alternatively, failure—might be achieved relatively early with HEAVD, while prolonged low-dose maintenance therapy could only delay the timing of relapse in patients with residual yet still drug-sensitive leukaemia. The strategy of short-term intensive chemotherapy excluding maintenance as already proved effective against rapidly proliferating lymphoid tumours, such as advanced stage large-cell and lymphoblastic lymphomas [20–22], and is the rationale behind the ultimate form of intensive treatment for haematological malignancies, i.e. supralethal chemoradiotherapy followed by bone marrow transplantation. On the whole, the role of standard maintenance therapy could be reassessed in the context of modern intensive chemotherapy for adult ALL.

Our long-term results compare very favourably with other series. As detailed in Table 6, the most recent clinical trials on large patient number (more than 50) with long enough follow-up to determine the percent of cure (median more than 3–5 years) have shown that it is now possible to achieve a 80% CR rate with a median duration of about 2 years, that approximately 30% of all CR cases relapse within one year independent of treatment intensity, that late relapses may be seen until 4–5 years from start of therapy, and that more than 20% of patients are disease-free survivors at 5 years and beyond [2, 9–14, 16, 23–27]. Basically it appears that two distinct approaches have made possible to achieve the best figures overall: a prolonged multidrug plan of treatment exemplified by L-protocols from Memorial Hospital and the German multicentric study, yielding a 28–39% long-term survival rate [10, 11, 27], and a relatively short-termed and possibly anthracyclin-based schedule such as HEAVD (present study) and HOP-L [16], resulting in a superimposable 35%.

However, original treatment results have not always been duplicated by others [10, 27]. With the HEAVD protocol we had better results than the SBH study. The unusually high number of patients more than 60 years old (10/48, 20% vs. 5/82, 6%) may partly account for the lower CR rate (60% vs. 80%) and duration in the SBH series [2]. Age over 60 years is a known poor prognostic factor in ALL [2, 10]. Such patients are not included in some studies [12, 15] and, whenever specified, their average incidence is around 5% (refs 10 and 24 and current study). In addition, total number of cases, length of follow-up period, genetic diversity (country and race), selection criteria, incidence of risk factors—essentially time to CR, blast count, age, immunological subtype, chromosomal abnormalities [18] and degree of adherence to the plan of intensive treatment [10] may all interfere at some extent with treatment outcome. The final impact these variables may exert should be addressed by formal studies if intercentre variability is to be explained and consistent treatment strategies are to be developed in the future.

Improving treatment results appears difficult, particularly in the poor risk patient population. Limited variations of well-established protocols seem to offer no advantage, and follow-up is generally too short to allow definite interpretation [15, 28, 29]. It is still uncertain whether heavy intensification of treatment with high-dose cytarabine [9, 14, 17] or marrow-ablating therapy followed by autologous blood stem cell rescue [17, 30, 31] might enhance the proportion of long-term survivors, whereas patient selection and treatment-induced toxicity may

Table 6. Long-term results in adult ALL series comprising > 50 patients with median follow-up > 3 years

Ref.	Patients no.	Age (yrs) Median (range)	Blast cells/ (total WBC)*	Complete remission No. (%)	Median	% at 5 yr	Overall survival Median	% at 5 yr
[12]					10	23		18
[13]	62	23 (12–59)	(79% < 35)	45 (72)	18	25	17	18
[23, 24]	124†	32 (> 19)	(65% < 30)	97 (78)	17	30	18	30
[2]	99	23 (15–70)	(61% < 35)	80 (79)	18	26	24	24
[25]	111	26 (15–69)	4.6	73 (66)	23	32	18	21
[14]	69	30 (16–66)	(45% < 10)	54 (78)	24	42	23	NR
[11]	124	27 (16–65)	NR	92 (74)	24	37	22	39
[26]	368	25 (15–65)	(64% < 30)	272 (74)	28	38	27	37
[16]	199	26 (> 14)	(61% < 15)	163 (82)	50	53	31	35
[27]	59	37 (15–74)	2.9	44 (75)	23	30	28	28
Current	168	28 (15–85)	(53% < 15)	115 (68)	27	39	18	37
study	82	26 (14–71)	6.8	66 (80)			18	

* Median blast cell count × 10^9/l (or % of cases with total white blood cell (WBC) count below given value).
† Daunorubicin-treated cases.
NR = not reported.
Median remission and survival duration in months.

be increased. In patients selected for allogeneic bone marrow transplantation (BMT) on the basis of an HLA-matched sibling and being aged below 50, the probability of leukaemia-free survival in first CR at 5 years ranges from 28% [32] to 63% [33]. When data from several centres are pooled, as in the European and International BMT Registries, the probability is 42–50% [34, 35], a marginal gain over some of the chemotherapy programs listed in Table 6. Certainly of great interest is the improved survival obtained with BMT in high risk patients [36], although age over 25 years once again worsens the prognosis [37].

The data thus far collected demonstrate that as many as one-third of all adults with ALL, and about one-half or more of those with low risk features can be given a chance for cure by adopting intensive yet heterogeneous polychemotherapy programs, none of which can be deemed superior. Although second malignancies and late toxicity to gonads, heart, immune system and CNS have been rarely reported [1, 38], more detailed prospective investigations are needed as the proportion of long survivors increases with time. It is encouraging that doxorubicin-related heart toxicity was virtually absent during induction–consolidation nor developed in our long-term survivors, in agreement with the SBH and HOP-L doxorubicin-based studies [2, 16]. HEAVD and other time-honoured protocols may serve as control arms in new innovative studies, but it is unclear how to improve further the long-term prognosis of adults with ALL.

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Iridium Implant Treatment without External Radiotherapy for Operable Breast Cancer: a Pilot Study

I. S. Fentiman, C. Poole, D. Tong, P. J. Winter, H. M. O. Mayles, P. Turner, M. A. Chaudary and R. D. Rubens

A pilot study has been conducted to examine a new approach to the treatment of operable breast carcinoma. 27 patients with tumours measuring up to 4 cm in diameter have been treated by tumourectomy, axillary clearance and high dose iridium-192 implant (55 Gy) without any external beam radiotherapy. This enabled the entire local primary treatment of the breast carcinoma to be given in five days. The technique was compatible with adjuvant chemotherapy for those with involved axillary nodes. Local complications have been few and locoregional control has to date been satisfactory. With a relatively short median follow-up of 27 months, cosmesis was objectively rated as good or excellent in over 80% of cases and subjectively rated good/excellent in 96%. High dose brachytherapy now requires testing in a prospective clinical trial to determine whether it is as effective as standard breast conservation techniques for management of early breast cancer.
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INTRODUCTION

THERE IS little doubt that for selected patients breast conserving therapy is a safe alternative to mastectomy. Apart from several uncontrolled historical studies there are now data from prospective randomised trials which have shown similar relapse free survival and overall survival rates in patients with tumours up to 4 cm in diameter treated by either mastectomy or breast conservation [1–3]. However, both the Guy's Hospital wide excision trial and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 have shown that either suboptimal or no radiotherapy will lead to an unacceptably high rate of local relapse [2, 4]. In the Guy's wide excision trial this local failure rate was followed by the earlier appearance of distant metastases and reduced survival in patients treated by conservative means.