PAPERS AND ORIGINALS

Combination chemotherapy for acute lymphoblastic leukaemia in adults

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Summary and conclusions

Fifty-one adults with acute lymphoblastic leukaemia were entered into a trial of intense initial chemotherapy and early "prophylaxis" of the central nervous system (CNS). Initial treatment with OPAL (Oncovin (vincristine), prednisolone, adriamycin (doxorubicin), and L-asparaginase (colaspase)) followed by craniospinal or cranial irradiation and intrathecal methotrexate produced remission in 36 patients (71%). Seventeen of these patients relapsed three to 18 months after the start of remission; the remainder had been in remission for 12 to 52 months by the end of the study. The predicted median duration of complete remission was 18·5 months. None of the four patients who initially had clinical evidence of CNS disease, three of whom also had leukaemic cells identical to those found in Burkitt's lymphoma, achieved remission. Those patients who initially had hepatomegaly or splenomegaly had a shorter remission than those without. The predicted median survival was 27 months in those who achieved complete remission, one month in those who did not, and 21 months overall.

The addition of colaspase and doxorubicin to vincristine and prednisolone and the use of early CNS treatment clearly improved the remission rate among adults with acute lymphoblastic leukaemia, though the presence and length of remission was affected by the extent of disease at presentation. Burkitt-like leukaemia, which had a poor prognosis, is probably a separate disease and may benefit from a different therapeutic approach.

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Introduction

It has been shown repeatedly that among patients with acute lymphoblastic leukaemia adults have a worse prognosis than children.[1] This finding has been confirmed at St Bartholomew's Hospital, where in 1970-2 complete remission was achieved in only 15 out of 32 adults (47%) on vincristine and prednisolone alone (unpublished data). This combination induces remission in most children, although it became evident in the late 1960s that high-risk groups existed in which the remission rate was lower and overall survival shorter. The identification of those high-risk groups was followed by the study of more intensive chemotherapy programmes. Bernard *et al*[2] and Mathe *et al*[3] added an anthracycline to vincristine and prednisolone and achieved 100% complete remission in small series of such high-risk patients. Aur *et al*[4] added colaspase (L-asparaginase) to the above combination and obtained identical results without excess toxicity. This four-drug combination was also effective in patients who had relapsed on other treatment.[5]

These results prompted us to try to improve the results of treatment for adults by intensifying the initial chemotherapy and introducing early "prophylaxis" of the central nervous system (CNS). We report here the results in the first 51 patients entered into the study.

Patients and methods

The 51 consecutive untreated patients who entered the study from December 1972 to May 1976 were all aged over 15 and had acute lymphoblastic leukaemia (see table II). All patients were evaluable and none had to be excluded.

All patients satisfied the minimum diagnostic criteria of bone marrow infiltration with at least 30% blast cells with a high nuclear: cytoplasmic ratio and one or two nucleoli. Five patients whose leukaemic cells were morphologically identical to those found in Burkitt's lymphoma,[6] as described by Flandrin *et al*,[7] were included in the series. The blast cells were negative to the Sudan black stain, and cytogenetic analysis showed that all 51 patients were negative for the Philadelphia chromosome.

DEFINITIONS

Complete remission was considered to have occurred when there were no clinical manifestations of leukaemia; the peripheral blood count was normal; the bone marrow contained less than 5% blasts, none of which were obviously leukaemic; and a cytocentrifuge preparation of the cerebrospinal fluid (CSF) contained no blast cells. Patients with blast cells in the CSF at clinical and haematological remission were deemed to be in complete remission when there had been two consecutive blast-free specimens of CSF during CNS treatment.

Relapse—When blast cells reappeared in the peripheral blood, bone marrow, or CSF the patient was considered to have relapsed. After January 1975 the bone marrow and CSF were studied routinely every two months. Before then they were examined only when there were clinical or haematological indications.

Remission duration was taken as the length of time from the date of complete remission to relapse.

Survival was the length of time from the date of diagnosis to death.

TREATMENT PROGRAMME

The treatment programme included three main elements: the induction and consolidation of remission (table I), treatment of the CNS or CNS prophylaxis, and maintenance treatment.

TABLE I—*Treatment given for inducing and consolidating remission* (OPAL*)

Drug	Administration	Dose	Intervals of treatment
Doxorubicin	Intravenous	30 mg m^2	Days 0, 14, 28, 42†
Vincristine	Intravenous	1·4 mg m^2 (max 2 mg)	Days 0, 14, 28, 42†
Prednisolone	By mouth	40 mg	Daily
Colaspase	Intravenous	10 000 IU m^2	Days 0–14
Allopurinol	By mouth	200 mg three times a day	Daily until blasts cleared from blood

*Oncovin (vincristine), prednisolone, adriamycin (doxorubicin), and L-asparaginase (colaspase).

†Bone marrow was assessed on day 49: if leukaemic infiltration persisted two further injections of doxorubicin and vincristine were given about 14 days apart.

Induction and consolidation of remission—The OPAL regimen is shown in table I. At the start of the study we planned to give doxorubicin (adriamycin) and vincristine every week for a minimum of four courses regardless of the peripheral blood count. But the incidence of pancytopenia after the second injection was so high that the schedule was modified and the second course of doxorubicin and vincristine was given at least 14 days after the first. The interval between the later courses of doxorubicin and vincristine depended on the bone marrow findings.

CNS prophylaxis and treatment—In the early part of the study lumbar puncture for CSF cytology was not performed until clinical and haematological remission had been achieved. Patients with no evidence of infiltration then proceeded to CNS prophylaxis. This consisted of cranial irradiation (2400 rads) given in 15 fractions over three weeks with concomitant intrathecal methotrexate 12·5 mg twice weekly for five doses during the same period. Analysis of the CSF findings in the first 28 patients who achieved complete remission indicated a high incidence of asymptomatic leukaemia disease.[5] The first injection of intrathecal methotrexate was therefore introduced during the induction of remission, when the platelet count reached 50×10^9/l in the absence of circulating blast cells. The total number of doses of methotrexate was also increased to seven. Patients with proved CNS disease who were in clinical and haematological remission received more intensive radiotherapy and intrathecal chemotherapy. Craniospinal irradiation (2400 rads) was given in 20 fractions together with five doses of intrathecal methotrexate 12·5 mg followed by five doses of intrathecal cytarabine 50 mg, all given over four weeks.

Maintenance treatment—This consisted of oral mercaptopurine 75 mg daily, starting when complete remission had been achieved and always after allopurinol had been stopped. Once CNS therapy had finished oral cyclophosphamide 300 mg week and oral methotrexate 30 mg week were started together. The doses of all the drugs were adjusted to maintain the total white cell count at 3×10^9/l, and treatment was continued for three years and then stopped.

STATISTICAL ANALYSIS

Survival curves and graphic presentations were developed by standard life-table formulae,[9] and statistical significance was determined by the Wilcoxon tests modified to deal with life-table data by Gehan.[10] χ^2 tests with Yates's correction or Fisher's exact test were used to test significance in 2×2 table.

Results

REMISSION

Thirty-six patients (71%) achieved complete remission on doxorubicin, vincristine, prednisolone, and colaspase (table II). This remission rate was significantly better ($P < 0.05$) than that in our previous study using only vincristine and prednisolone, in which only 15 (47%) out of 32 patients achieved complete remission.

Twenty-four patients achieved haematological remission after four courses of doxorubicin and vincristine and the remaining 12 after a further two courses (and in four cases a small amount of oral chemotherapy). At the time of haematological remission four of the 36 patients had clinical evidence of disease. Two of these patients had splenomegaly, which was treated by splenectomy, and one had lymphadenopathy and underwent lymph node biopsy; neither the spleens nor the lymph nodes were found to contain leukaemic cells. The fourth patient had radiological evidence of residual tumour in the chest, which disappeared after local radiotherapy. All four patients achieved complete remission after this further treatment.

Examination of the cytocentrifuge specimen of the CSF at this stage showed unequivocal blasts in six of the 36 asymptomatic patients (table II). Details of these patients have been reported elsewhere.[5] They included both patients with Burkitt-like leukaemia who achieved clinical and haematological remission. In all cases blasts were cleared from the CSF by CNS treatment—that is, treatment with five doses of intrathecal methotrexate 12·5 mg followed by five doses of intrathecal cytarabine 50 mg given over four weeks in combination with craniospinal irradiation (2400 rads) in five cases and with cranial irradiation (2400 rads) in one case. Complete clinical, haematological, and CNS remission was therefore finally achieved in 36 patients.

Twenty-eight of the 30 patients whose CSF was clear at clinical and haematological remission received prophylactic cranial irradiation (2400 rads) with intrathecal methotrexate as outlined in the treatment programme. The remaining two patients received prophylaxis over about two months, with five doses of intrathecal methotrexate 12·5 mg followed by five doses of intrathecal cytarabine 50 mg but no irradiation.

PATIENTS WHO DID NOT ACHIEVE REMISSION

Of the 15 patients who did not achieve complete remission seven died after receiving only one course of doxorubicin and vincristine. Five died after two courses of doxorubicin and vincristine; all of these five deaths occurred early in the study, before the interval between the first and second courses of doxorubicin and vincristine was prolonged to at least two weeks. None of these patients had any circulating blasts at the time of death. One of the three patients who received four courses of doxorubicin and vincristine died with unresponsive disease. The other two patients achieved haematological remission but they continued to have clinical evidence of disease and rapidly developed CNS complications and died.

TABLE II—*Details of patients at presentation and details on remission and survival*

Case No	Age and sex	Data at presentation: Presence of clinical CNS disease	Liver felt (+) or not felt (−)	Spleen felt (+) or not felt (−)	Circulating blast cells (× 10^9 l)	Platelets (× 100^9 l)	Periodic acid Schiff stain*	Morphology†	Blast cells in CSF at remission	Vincristine and adriamycin: Weeks between 1st and 2nd courses	Vincristine and adriamycin: No of courses	Duration of complete remission (months)	Survival (months)
Patients who achieved complete remission													
1	16 M	−	+	+	12·9	22	+	C	−	<2	4	11	23
2	21 F	−	+	+	0·4	55	+	C	−	<2	4	>52‡	>53‡
3	15 F	−	+	+	1·5	18	−	B	+	<2	4	5	13
4	19 M	−	+	+	215·0	<10	−	C	+	<2	6	4§	25
5	32 F	−	+	+	52·3	167	−	C	−	<2	4	11	26
6	31 F	−	+	+	1·2	12	+	C	+	<2	4	18	34
7	47 F	−	−	−	245·0	83	+	C	−	<2	4	4	6
8	17 F	−	−	−	0	247	−	B	+	<2	5	16§	40
9	16 M	−	+	+	137·0	37	+	C	−	<2	4	3§	21
10	19 M	−	−	−	2·8	14	+	C	−	<2	4	11	17
11	38 M	−	−	−	0	35	−	C	−	<2	4	12	20
12	27 M	−	+	+	28·8	60	−	C	−	<	4	13	20
13	17 M	−	+	+	66·0	21	−	C	−	<2	4	10	17
14	17 M	−	+	−	4·6	146	+	C	−	<2	6	>40	>42
15	35 M	−	+	+	7·2	61	+	C	−	<2	6	>34	>35
16	27 M	−	−	+	22·0	<10	+	C	−	<2	4	>29	>31
17	18 F	−	−	−	2·5	13	+	C	−	>2	4	>26	>29
18	22 F	−	−	+	42·4	200	−	C	+	>2	6	>23	>25
19	52 M	−	−	−	0·1	177	ND	C	−	>2	4	>21	>24
20	15 F	−	−	−	1·9	287	ND	C	−	<2	6	>20	>23
21	31 F	−	+	+	16·8	<10	−	C	−	>2	4	>23	>24
22	42 M	−	+	+	2·0	40	−	C	−	>2	4	>4	6
23	46 F	−	−	−	0·1	<10	+	C	−	>2	4	>20	>22
24	40 M	−	−	−	9·4	20	−	C	+	>2	6	>17	>22
25	16 M	−	−	+	0·4	12	+	C	−	>2	6	>18	>20
26	25 M	−	−	−	1·4	27	+	C	−	>2	4	>19	>21
27	21 M	−	+	+	9·3	15	−	C	−	>2	6	1	5
28	18 M	−	+	+	occ	<10	ND	C	−	>2	4	4§	>25
29	19 M	−	+	+	2·4	30	+	C	−	>2	4	9	>18
30	18 M	−	−	+	61·2	61	−	C	−	>2	4	>8	>9
31	28 M	−	+	+	21·0	10	−	C	−	>2	4	5§	>12
32	25 F	−	−	−	1·1	120	ND	C	−	>2	6	>12	>17
33	20 F	−	+	+	270·0	30	−	C	−	>2	4	5	>13
34	21 M	−	+	−	0·4	284	−	C	−	<2	6	>33	>34
35	29 M	−	+	+	4·0	24	−	C	−	<2	6	NA	NA
36	51 M	−	−	+	6·6	23	+	C	−	<2	4	>34	>35
Patients who did not achieve remission													
37	68 M	−	+	+	63·3	66	+	C	NR	<2	2	NR	<1
38	19 M	−	+	+	145·0	36	+	C	,,	NR	1	,,	<1
39	17 M	−	−	−	0·2	<10	ND	C	,,	NR	1	,,	<1
40	18 F	−	−	+	2·6	26	−	C	,,	<2	2	,,	<1
41	43 M	−	+	−	2·3	9	+	C	,,	<2	2	,,	<1
42	27 F	+	+	+	0	75	+	C	,,	NR	1	,,	<1
43	20 M	−	+	+	255·0	20	+	C	,,	NR	1	,,	<1
44	43 M	+	+	+	1·0	11	−	B	,,	<2	4	,,	5
45	50 F	−	−	−	1·8	55	+	C	,,	<2	2	,,	<1
46	48 F	−	−	−	0	35	+	C	,,	NR	1	,,	<1
47	32 M	+	+	−	0	10	−	B	,,	<2	4	,,	3
48	26 M	−	+	+	1·8	300	−	C	,,	<2	2	,,	1
49	32 F	−	?	?	0	0	−	C	,,	NR	1	,,	<1
50	43 F	−	−	+	0	105	ND	C	,,	<2	2	,,	<1
51	21 M	+	−	−	>100·0	45	−	B	,,	NR	1	,,	<1

*Fine granularity was considered negative. †C = Classic acute lymphoblastic leukaemia; B = Burkitt-like variant. ‡ > indicates that remission or survival continues. §CNS was 1st site of relapse.
NA = Not available. ND = Not done. NR = Not relevant.

LENGTH OF REMISSION

Thirty-five of the patients with complete remission received continuous maintenance treatment. The other patient (case 35) returned home to India and subsequently relapsed and died while not taking maintenance treatment. He was not included in the analysis of the length of remission or survival. One patient (case 22) died in complete remission at four months during an influenza epidemic. Another (case 30) elected to stop maintenance treatment and relapsed one month afterwards and died. He was included in the analysis until his attendance at the clinic ended at eight months, when he announced his intention to stop maintenance treatment (he was in remission at that time). Seventeen patients relapsed three to 18 months after the start of remission; the rest had been in continuous remission for 12 to 52 months at the time of writing. The predicted median duration of complete remission was 18·5 months (fig 1).

Thirteen of the 30 patients who received CNS prophylaxis relapsed. The first site of relapse was the CNS in three patients, who relapsed at three, four, and five months. One of these patients subsequently relapsed in the bone marrow. In one patient CNS prophylaxis had been delayed because of an episode of bacterial meningitis. The first evidence of relapse in the other 10 patients was haematological.

Four of the six patients who had blast cells in the CSF at the time of the first lumbar puncture relapsed. In two the first site of relapse was the CNS (at 4 and 16 months) and both later relapsed in the bone marrow. In the other two, the first evidence of relapse was haematological (at 5 and 18 months).

Fifteen patients relapsed in the bone marrow. Complete remission was reinduced in nine, but the second remissions were all short.

FACTORS AFFECTING INDUCTION OF REMISSION

Favourable factors—Prolonging the interval between courses of doxorubicin and vincristine from one week to at least two weeks produced a significant improvement in the complete remission rate in patients surviving to receive at least two courses ($P < 0·02$; table III).

Unfavourable factors—None of the four patients with clinical evidence of CNS disease at presentation or shortly after treatment began achieved complete remission (three of these had Burkitt-like morphology of their blast cells). There was a significant difference ($P < 0·005$ by Fisher's exact test) in the complete remission rate

TABLE III—*Influence of the interval between first and second courses of vincristine and doxorubicin on complete remission rate. (All patients received at least two courses)*

Interval:	≤14 days	>14 days	Total
No of patients	28	16	44
No (%) who achieved complete remission	20 (71)	16 (100)	36 (82)

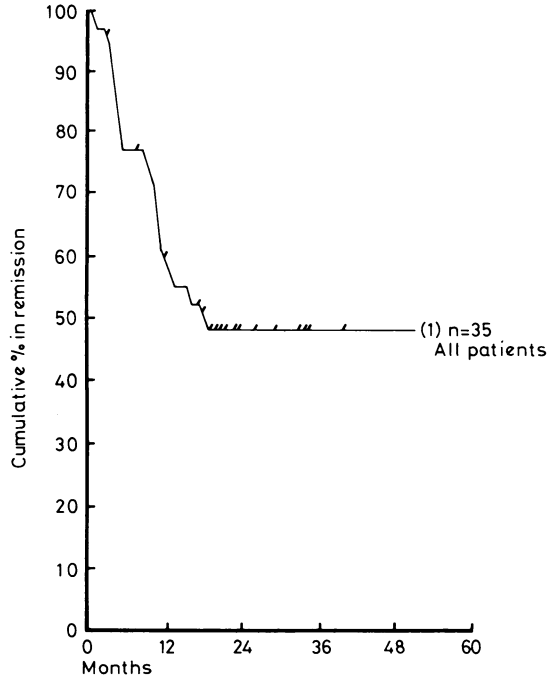

FIG 1—Duration of complete remission. Each patient in remission is represented by dash; patient shown in parentheses was in remission when curve stopped.

between these patients (0 out of 4) and those with no clinical CNS disease (36 out of 47).

None of the other factors investigated (age, sex, presence of hepatomegaly or splenomegaly, morphology of the blast cells, the periodic acid Schiff reactivity of the blast cells, the height of the blast cell count, or the platelet count at presentation) had a significant effect on the complete remission rate, although both increasing age and Burkitt-like morphology tended to influence the complete remission rate adversely.

FACTORS AFFECTING LENGTH OF REMISSION

The extent of disease at presentation influenced the duration of complete remission. Clinical hepatomegaly and clinical splenomegaly both reduced the duration of complete remission significantly ($P=0.01$ and $P=0.05$ respectively; table IV), and a combination of

TABLE IV—*Prognostic factors and length of remission in adult acute lymphoblastic leukaemia*

Clinical features on presentation	No of patients	% in complete remission* at:			Significance (P value)
		12 months	24 months	36 months	
Splenomegaly	22	50	39	39	0·05
No splenomegaly	13	90	75	75	
Hepatomegaly	19	39	28	28	0·01
No hepatomegaly	16	93	73	73	
Hepatosplenomegaly	17	32	19	19	0·001
No hepatosplenomegaly	18	94	76	76	
Blast cells $\geq 10 \times 10^9/l$	13	35	26	26	0·03
Blast cells $< 10 \times 10^9/l$	22	75	61	61	

*Life-table analysis.

the two reduced it very significantly ($P<0.001$) (fig 2). Patients with an initial peripheral blood blast cell count greater than $10 \times 10^9/l$ had a shorter remission than those with a blast cell count of less than $10 \times 10^9/l$ ($P<0.03$) (table IV). This difference was emphasised by the fact that all four patients whose blast cell count at presentation was greater than $100 \times 10^9/l$ relapsed within six months. There was no correlation between the duration of remission and the age or sex of the patient. Both patients with Burkitt-like leukaemia cells who achieved complete remission relapsed before the median duration of remission (5 and 16 months).

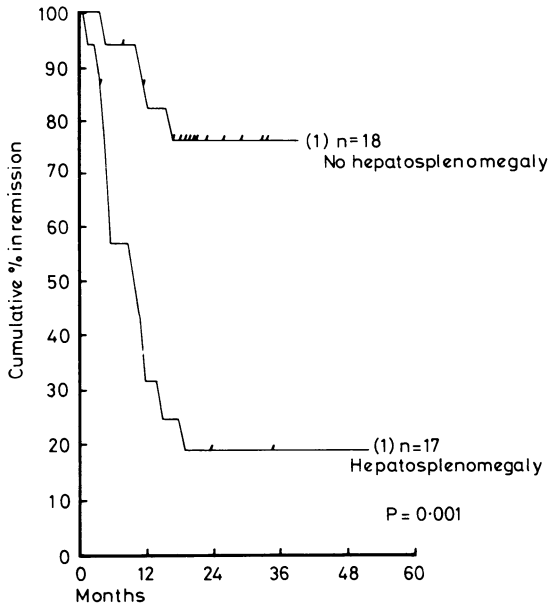

FIG 2—Influence of hepatosplenomegaly on duration of complete remission.

SURVIVAL

The predicted median survival of all patients was 21 months, with patients who achieved remission having a predicted median survival of 27 months and those who did not achieve remission a median survival of less than 1 month ($P<0.01$) (fig 3).

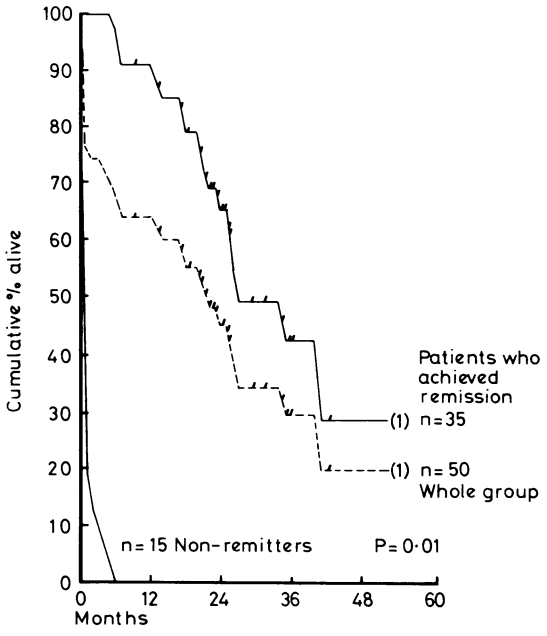

FIG 3—Survival curve. Each patient surviving is represented by dash; patient shown in parentheses was surviving when curve stopped.

TOXICITY

All patients suffered alopecia and myelosuppression. Only one had severe neurotoxicity. Nausea and vomiting were rarely problems provided appropriate antiemetics were given before chemotherapy, but four patients had to stop taking colaspase because of nausea and vomiting. About half the patients developed glycosuria while receiving prednisolone and colaspase, and about 10% needed either insulin or an oral antidiabetic agent. Antidiabetic treatment was no longer required after colaspase was stopped. The colaspase was stopped in one patient because of a raised blood urea concentration. Hypersensitivity and pancreatitis were not observed.

Discussion

The complete remission rate in adults with acute lymphoblastic leukaemia treated at St Bartholomew's Hospital has been improved significantly by the addition of doxorubicin and colaspase to vincristine and prednisolone. The modification of the treatment programme by increasing the intervals between courses of doxorubicin and vincristine to a minimum of two weeks has improved the results further, with complete remission being achieved in all 16 of the patients who received at least two courses.

These results were found in the largest series of adults with acute lymphoblastic leukaemia treated at one centre and are supported by the results of other studies. With two exceptions,[11 12] both reporting small numbers of cases, all groups of workers have found it necessary to supplement vincristine and prednisolone with additional drugs to obtain high complete remission rates in adults with acute lymphoblastic leukaemia. In most cases[13-18] an anthracycline antibiotic has been used, although other combinations have also been shown to be effective.[19-21] From our data we cannot comment on the value of colaspase, although the results of a randomised study of patients with both acute lymphoblastic and acute myeloblastic leukaemia have suggested that it does not improve the complete remission rate.[22]

The length of complete remission is probably related to the intensity of initial treatment. The longest remissions have been reported by Gee *et al*,[15] who used very intensive early treatment. Others, using less intensive early therapy, have reported considerably shorter remissions, which did not seem to be influenced by reinduction treatment.[11 13 14]

The predicted median duration of complete remission in our series was 18·5 months, which, although slightly shorter than that of Gee *et al*, is better than any other. It was clearly influenced by the extent of disease at presentation, both hepatosplenomegaly and a high circulating blast count being adverse prognostic factors. Patients with these presenting features might benefit from a further intensification of treatment.

CNS prophylaxis with cranial irradiation and intrathecal methotrexate clearly improves the prognosis in childhood lymphoblastic leukaemia.[23-25] We cannot yet evaluate fully the role of early CNS treatment in our patients, since only 17 patients have relapsed so far. The incidence of CNS relapse before bone marrow relapse was disturbingly high in our series (three of the 13 patients receiving CNS prophylaxis and two of the four receiving CNS treatment). This may not be representative of the whole group, however, since 18 patients remain in remission. In children there is some suggestion that methotrexate alone, given either intrathecally or intrathecally and intravenously, may be as effective as when combined with CNS prophylaxis. A high incidence of CNS relapse in adults treated with intrathecal methotrexate alone as CNS prophylaxis has been reported,[15] but treatment was continued for only a short period. Willemze *et al*,[13] using intrathecal methotrexate during remission and at increasing intervals during maintenance, reported it to be as effective as the combination of intrathecal methotrexate and cranial irradiation and showed a very low incidence of relapses occurring in the CNS first. Clearly, more information is required on the comparative effectiveness of prophylactic methotrexate with or without the addition of CNS irradiation.

From our data and those of others we have therefore reached the following conclusions. Firstly, intensification of the early treatment of acute lymphoblastic leukaemia improves the complete remission rate and probably the length of remission, but the courses of treatment do not have to be given at very close intervals. Secondly, early CNS treatment is essential. Thirdly, the extent of disease at presentation influences the prognosis, and the amount of early treatment in patients with extensive disease should probably be increased. Finally, Burkitt-like leukaemia can be recognised as a separate entity associated with CNS disease and a poor prognosis and may benefit from a different therapeutic approach.

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