Treatment of adult lymphoblastic leukaemia using cyclical chemotherapy with three combinations of four drugs (COAP, POMP, TRAP schedule)

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Summary

Seventeen adult patients with previously untreated acute lymphoblastic leukaemia (ALL) were entered into a schedule of chemotherapy in which 3 combinations, each of 4 drugs, were administered in a predetermined cyclical rotation in combination with cranial irradiation and intrathecal injections of methotrexate. Of the 17 patients, 16 completed induction therapy and 15 (94%) entered remission. The only patient with T-ALL died before receiving any therapy. The median survival for all patients (17) was 22 months. Meningeal leukaemia did not occur during the haematological remission phase although 3 patients developed this complication following relapse. The authors conclude that the addition of cyclophosphamide and cytosine arabinoside to vincristine/prednisone provides excellent remission induction but the aggressive maintenance schedule employed has not led to significant long-term survival.

Introduction

Of the various prognostic indicators in acute lymphoblastic leukaemia (ALL), age is one of the most reliable. It is well known that patients over the age of 15 years have a much worse prognosis than children with morphologically similar disease (Henderson, 1969; Willemze *et al.*, 1975). Various authors (Spiers, 1972; Capizzi and Castro, 1975; Clarkson *et al.*, 1975; Lister *et al.*, 1978) have consequently adopted a more aggressive approach to induction and maintenance therapy. This has led to the use of drugs normally associated with the treatment of acute myeloblastic leukaemia in addition to the vincristine and prednisone universally employed in all cases of acute lymphoblastic leukaemia. The present report in an assessment of the use of a modified COAP/POMP/TRAP schedule devised by

Spiers *et al.* (1975) and applied prospectively to 17 consecutive adults with ALL.

Patients and methods

Seventeen patients with the diagnosis of acute lymphoblastic leukaemia (ALL) were entered into this prospective study. Eleven were male and 6 were female and their ages ranged from 15 to 51 years with a mean age of 22 years (Table 1). ALL was diagnosed by examination of Romanowsky-stained films of peripheral blood and bone marrow. Cytochemical stains (Sudan black, PAS, non-specific esterase and acid phosphatase) were performed on all patients. The Sudan black and esterase stains were negative in all patients, the acid phosphatase showed dot positivity in the single case of T cell leukaemia and the PAS was positive in 8 patients. T and B lymphocyte markers were looked for in 12 of the 17 patients, 10 at diagnosis and a further 2 at the time of relapse. T cells were identified by the ability to form sheep red blood cell rosettes (E rosettes) and B cells by the presence of cell surface immunoglobulin which was assessed by direct immunofluorescence. Surface marker studies indicated that 11 patients were non-B/non-T, one patient had T-ALL and the remaining 5 remained unclassified. Assessment of terminal deoxynucleotidyl transferase and common ALL antigen were not available in these patients.

Treatment schedule

The scheme of treatment is illustrated in Fig. 1 and the details of the drug treatment are summarized in Table 2. Initial treatment was with vincristine and prednisolone alone for 2 weeks. Following this, 3 courses of COAP were given and the second bone marrow performed. All patients entering remission were in remission at this stage and 4 injections of

intrathecal methotrexate were given on alternate weeks along with 3 additional courses of COAP. The criteria for complete remission were a Hb > 11 g/dl, WBC $> 2 \times 10^9/l$ with a normal differential, platelet count $> 150 \times 10^9/l$ and bone marrow with $< 2\%$ blast cells. Cranial irradiation was given to all patients entering remission at this stage using a dose of 2400 rad given in 10 to 15 fractions. The one patient who achieved remission on second line chemotherapy was given cranial irradiation when

haematological remission had been achieved. Consolidation and maintenance treatment was by intermittent courses of treatment using COAP, POMP and TRAP in the doses indicated in Table II. Treatment was conducted by patients attending as an out-patient once every 14 days in the majority of cases. In patients who became recurrently pancytopenic, the treatment-free interval was lengthened from 9 to 16 days but full doses of drugs were given. Following remission induction, the bone marrow was examined

TABLE 1. High WBC count at presentation indicated a poor response to therapy. Where remissions occurred they were of short duration (patients 6, 14). Hb and platelet counts were not of prognostic value

Patient	Sex Age (years)	Lymphocyte surface markers	Hb. gm/dl	WBC $\times 10^9/l$	Platelets $\times 10^9/l$	CNS disease during remission	CNS disease after relapse	Duration of remission (months)	Survival (months)
1	F 18	NB, NT	4.9	14.5	30	—	+	34	43
2	M 21	NB, NT	5.8	5.6	50	—	—	27	40+
3	M 20	NB, NT	7.7	2.2	132	—	—	50+	52+
4	F 15	NB, NT	5.6	7.9	70	—	—	29+	31+
5	M 21	NB, NT	5.7	29.0	80	—	—	24+	26+
6	M 15	NB, NT	7.3	100.0	40	—	+	7	15
7	M 15	NB, NT	7.0	2.4	90	—	+	7	13
8	F 18	NB, NT	6.3	11.0	110	—	—	16	22
9	M 20	Not done	12.3	8.5	70	—	—	25	28
10	F 42	NB, NT	8.2	16.4	48	—	—	3	12
11	M 17	Not done	8.4	33.0	40	—	—	6	19
12	M 15	Not done	6.8	2.8	35	—	—	15	23
13	F 15	Not done	7.6	3.6	80	—	—	6	16
14	F 51	Not done	4.4	170.0	34	—	—	2	7
15	M 23	NB, NT	5.9	7.2	90	—	—	10+	13+
16	M 28	NB, NT	9.5	6.0	400	—	—	12 (no remission on COAP, remitted on 2nd line therapy)	18+
17	M 21	E rosette+ T-ALL	7.4	640.0	10	CNS involved at presentation	—	—	1 day

NB=non-B; NT=non-T.

FIG. 1. Vc, vincristine. Give at a constant dose of 2 mg i.v. Each COAP, POMP and TRAP lasted 5 days. The treatment-free interval was 9 days during the induction phase. Following POMP treatment in the maintenance phase, the treatment-free interval was often lengthened to 16 days because of neutropenia. Following completion of a 16-week maintenance phase, the cycle was repeated for a minimum of 2 years or until relapse. I/T=intrathecal.

at 6- to 8-week intervals for the first 6 months and at 4-month intervals thereafter or wherever peripheral blood suggested an abnormality. Lumbar punctures were performed at 4-month intervals and methotrexate (10 mg) was given intrathecally on each occasion. Cyclical maintenance treatment was continued until relapse occurred or for 2 years from the time that bone marrow remission had occurred.

TABLE 2. Details of combination chemotherapy used

	Duration	Route
COAP		
cyclophosphamide, 100 mg/m ²	Days 1-5	oral
Oncovin (vincristine), 2 mg	Day 1	i.v.
Ara C (cytosine arabinoside), 100 mg/m ²	Days 1-4	i.v.
prednisolone, 60 mg daily	Days 1-5	oral
POMP		
prednisolone, 60 mg daily	Days 1-5	oral
Oncovin (vincristine), 2 mg	Day 1	i.v.
methotrexate, 7.5 mg/m ²	Days 1-3	oral
Puri-Nethol (6-mercaptopurine), 300 mg/m ²	Days 1-3	oral
TRAP		
thioguanine, 100 mg/m ²	Days 1-5	oral
rubidomycin (daunorubicin), 30 mg/m ²	Day 1	i.v.
Ara C (cytosine arabinoside), 100 mg/m ²	Days 1-4	i.v.
prednisolone, 60 mg daily	Days 1-5	oral

Results

The only patient with T-ALL died rapidly before receiving any treatment and was found to have multiple diffuse cerebral haemorrhages and marked leukaemic infiltration of the brain and meninges. Fifteen of the remaining 16 patients entered remission (94%). The patient who failed to enter remission subsequently obtained remission by use of additional drugs (TRAMPOL – thioguanine, rubidomycin*, Ara C†, methotrexate (high dose infusions), prednisolone, vincristine and asparaginase). This patient subsequently was maintained on a modified maintenance regime using alternate courses of POMP and TRAP.

Central nervous system leukaemia

During remission none of the patients developed symptoms or clinical signs of CNS leukaemia. Following haematological relapse, 3 patients developed signs of meningeal irritation and were shown to have meningeal leukaemia. Further intrathecal methotrexate prevented progression of CNS involvement but did not eradicate leukaemia from this site.

* daunorubicin; † cytosine arabinoside.

Duration of remission and survival

The median survival of all patients (17) was 22 months. The median survival of patients entering remission (15) was 23 months. When patients relapsed during or following completion of the schedule, COAP was of little use in inducing second remissions. Only one patient of the group achieved a second remission and this was of short duration. On relapse, the policy was to adopt a palliative approach, which in the majority of cases involved the use of oral 6-mercaptopurine and methotrexate. After 2 years in continuous remission, the initial policy was to stop all cytotoxic drug treatment. Patient 3 stopped therapy at 24 months and remains in remission at 52+ months. Patients 2 and 9 relapsed soon after discontinuing therapy. As a result of these relapses therapy is continued after the 2-year period, using oral 6-mercaptopurine daily (100 mg/m²) and oral methotrexate once per week (15 mg/m²).

General adverse effects of treatment

Cranial irradiation always caused total alopecia. The hair regrew despite the aggressive maintenance chemotherapy. Following cranial irradiation, the authors recognized a syndrome of depression in the adults, occurring in the same time sequence as the somnolence encountered in children who have had cranial irradiation. Prophylactically, 10 patients received a tricyclic anti-depressant started during the cranial irradiation which prevented depressive episodes. There were no episodes of major infection during the induction or maintenance periods. Only one patient demonstrated adverse reaction to intrathecal methotrexate which involved severe headaches lasting several days.

Discussion

ALL in adult patients responds to the same drugs which are used successfully in childhood disease although complete remission rates are less and of shorter duration than in children (Pinkel, 1976). In attempts to improve remission rates and survival times in adult ALL, increasingly aggressive chemotherapeutic schedules have been devised. Rodriguez *et al.* (1973) demonstrated that POMP produced a 61% complete remission rate in 38 patients with ALL, and Whitecar, Bodey and McCredie (1972) showed a 43% remission rate with the COAP regimen. As a logical extension of these findings, Spiers *et al.* (1975) combined the COAP/POMP schedule with an additional 4-drug combination – CART – consisting of cytosine arabinoside, asparaginase, rubidomycin and thioguanine. This combination contained all known drugs active in ALL and it was hoped the effects would be additive. This schedule was applied to a mixed group of 42 adults and children with

previously untreated ALL. The conclusion was that the more aggressive regime had little to recommend it over the more conventional regimes for childhood ALL. The authors noted an improved response in the 9 patients who were over 16 years of age but details of survival were not specified. The present authors' initial intention had been to use the schedule devised by Spiers *et al.* (1975) prospectively in a group of adult patients with ALL. However, in a preliminary pilot study, severe allergic reactions were occurring in patients treated with asparaginase (Bayer), and TRAP was substituted for CART in order that the patients might be exposed to daunorubicin in the maintenance phase. They have subsequently used asparaginase (Porton Down) as a second line drug. In addition, the drug combinations were modified by utilizing prednisolone at a constant dose of 60 mg daily. In their patients, the addition of cytosine arabinoside and cyclophosphamide to vincristine and prednisone (COAP) gave a remission rate of 94% (15/16). This compares favourably with remission rates published in other recent series (Lister *et al.*, 1978; Arlin, Fried and Clarkson, 1978; Gee *et al.*, 1976). The duration of remission and survival was similar to the group of 51 patients treated by Lister *et al.* (1978) using the OPAL scheme (vincristine, prednisolone, adriamycin and asparaginase for induction, and 6-mercaptopurine, cyclophosphamide and methotrexate for maintenance). Gee *et al.* (1976) indicated the advantages of the L2 protocol (vincristine, prednisolone, daunorubicin for induction, thioguanine, vincristine, hydroxyurea, daunorubicin, methotrexate, BCNU and cyclophosphamide for consolidation and maintenance) which provided a median duration of remission of 23 months and a median duration of survival of 33 months. Recently, preliminary results from the L10 protocol (Arlin *et al.*, 1978) shows similarly promising results but it is too early to say whether survival will be radically improved.

Central nervous system leukaemia did not occur during the period of induction or during haematological remission, contrary to experience of Lister *et al.* (1977) who saw 4 out of 28 patients with ALL developing meningeal involvement shortly after complete remission had occurred. Undoubtedly, the use of intrathecal methotrexate and cranial irradiation was responsible for this effect but the regular use of cytosine arabinoside which was always given i.v. in this schedule during the remission phase may also have been of value in this respect. Clinical testicular relapse in the male patients during haematological remission did not occur although testicular biopsies were not performed in these patients. The use of this protocol has led to only one long-term survivor who is disease-free at 54+ months and has been off all treatment for 24+ months.

The authors have found that the COAP induction schedule gives highly satisfactory remission induction rates but, as in all other protocols published to date, the aggressive maintenance therapy has not led to ultimate cure. The authors agree with the view of Pinkel (1979) that further progress in adult ALL will only be made when more is known of the chemotherapeutic sensitivities of the emerging biological sub-groups (Chessels *et al.*, 1977).

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