Local Experience in the Treatment of Acute Non-Lymphoblastic Leukaemia

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SUMMARY

Seventy-six patients suffering from various forms of acute non-lymphoblastic leukaemia were seen at the Johannesburg Hospital over an 8-year period. During this time various forms of therapy were used. Results with 6-mercaptopurine and prednisone were very poor, with less than 10% of patients achieving complete remission. Daunorubicin, when used alone, proved too toxic, but when given in a smaller dose with other agents, was more effective. The best results were obtained in 22 patients in whom a combination of daunorubicin and cytosine arabinoside was used. Complete remissions occurred in 9 patients and partial remissions in 2. The median survival of these 11 patients was 42 weeks. It is noteworthy that 3 of these patients were still alive one-and-a-half years from the time of diagnosis, and 1 of them is still in complete remission, two years after she was first treated.

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Real progress in the drug treatment of acute leukaemia has been made since Farber *et al.*[1] demonstrated that the course of the disease could be modified by aminopterin. Several points emerge from the many subsequent studies. Firstly it is apparent that although remissions can be achieved with single agents, this only occurs in a minority of patients. For example, when 6-mercaptopurine was used to treat acute myeloid leukaemia, remission rates varied between 10 and 14%.[2,3] Results have been significantly better when two or more agents are used together, and recent trials using combinations of daunorubicin and cytosine arabinoside or daunorubicin and thioguanine in patients with acute myeloid leukaemia, reported initial remission rates of about 50%, with significant prolongation of survival.[4,5] Even more striking results were obtained in the acute lymphatic leukaemia that occurs in childhood. With a combination of vincristine and prednisone, initial remission rates in excess of 80% are obtained.[6] In addition it is clear that prolonged remissions can be maintained in a significant proportion of such patients if various types of chemotherapy are continued after the induction of the initial remission.[9]

Most of the results reported in the literature were obtained in units with special expertise in the management of acute leukaemia. While there has been a growing interest in the subject at the Johannesburg Hospital over the past several years, adult patients suffering from acute leukaemia are treated in the general medical wards. The present article records the findings in a retrospective analysis of the results obtained during an 8-year period.

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MATERIAL AND METHODS

Clinical Material

The clinical course and duration of survival of 87 patients with acute leukaemia were analysed retrospectively. All the patients had been seen at the Haematology Clinic of the Johannesburg General Hospital between 1965 and 1972. There was a steady build-up in the number of patients seen; only 1 patient in 1965 compared with 27 in 1972.

Seventy-six patients were suffering from some form of acute non-lymphoblastic leukaemia, the cytological diagnoses being: acute myeloblastic 39, acute myelomonocytic 18, erythroleukaemia 5, unspecified 4, leukaemia aplasticus 4, acute promyelocytic 3, and acute blastic crisis of chronic myeloid 3.

A cytological diagnosis of acute lymphoblastic leukaemia was made in the remaining 11 patients. This group included not only White adults but Black children. It was felt that further analysis of these 11 patients would not be contributory since the group was small and heterogeneous, and follow-up in the Black children was difficult, since several of them had been treated previously in other centres. The data that follow, therefore, refer only to the 76 patients with acute non-lymphoblastic leukaemia.

Therapeutic Regimens

A total of 59 patients received therapy, which was considered to be adequate for evaluation of its effects. In a further 7 patients a decision was made not

to give specific chemotherapy. They were either suffering from leukaemia aplasticus or had another severe chronic illness in addition to the leukaemia. Finally, there were 10 patients who died too early during the course of treatment for a proper evaluation to be made.

A combination of 6-mercaptopurine and prednisone was used as the initial therapy in 15 patients treated between 1965 and 1968. The dosage of 6-mercaptopurine varied between 1,5 and 2,5 mg/kg/day, and that of prednisone was 50 mg/day.

Seven patients were treated intravenously with daunorubicin in a dosage of 1 mg/kg/day for 5 days.[7] Additional courses of this therapy were given at 2- to 3-week intervals.

Ten patients were treated with a 4-drug regimen. It consisted of a combination of intravenous daunorubicin 0,75 mg/kg on day 1, oral 6-mercaptopurine 2,5 mg/kg daily for 5 days, intravenous cytosine arabinoside 3 mg/kg for 3 days and 40 mg oral prednisone daily for 7 days.

Twenty-two patients received therapy with a combination of intravenous daunorubicin 1,5 mg/kg on day 1, together with cytosine arabinoside 2 mg/kg daily for 5 days. The cytosine arabinoside was given intravenously as a push-in every 12 hours. The treatment schedule was repeated after intervals usually varying between 5 and 10 days.

Five patients received therapy with a 3-drug combination consisting of vincristine 1,4 mg/m^2, daunorubicin 1 mg/kg on day 1 and cytosine arabinoside 2 mg/kg daily for 3 days.[8] If blast forms persisted in the marrow, the same cycle of chemotherapy was repeated after an interval of 1 - 3 days.

Three patients seen before 1968 received miscellaneous forms of therapy and in a further 4 subjects more than one therapeutic regimen was used in an attempt to induce a remission.

Supportive Care

Vigorous measures were taken to prevent the development of hyperuricaemia; these included allopurinol, hydration and urinary alkalinisation. Blood transfusions were administered as required. The general aim was to keep the haemoglobin level above 10 g/100 ml. Platelet transfusions were given to patients with severe thrombocytopenia only when active bleeding occurred.

Although the patients were not nursed in a sterile environment, attempts were made to separate them from the other patients in the ward. Prophylactic systemic antibiotic therapy was not used. All pyrexial episodes lasting for more than 12 - 24 hours were treated initially as bacterial infections by using a combination of bactericidal antibiotics; therapy was changed appropriately when the results of cultures came to hand.

From 1971 onwards oral non-absorbable antibiotics, such as neomycin and kanamycin, were administered to all patients and the diet was limited to cooked foods. This was done in an attempt to limit bacterial growth in the bowel. In addition, oral non-absorbable antifungal agents were used as a routine.

RESULTS

The criteria used for assessing whether a patient had achieved a complete or partial remission were those applied by the Acute Leukaemia Group B and others.[9]

Early Deaths

It was impossible to evaluate 10 patients who died before completion of the first course of therapy. The mean duration of survival from the time of admission was 11 days, and death was caused by bleeding or infection, or both.

No Specific Therapy

The clinical course followed by the 4 subjects with the aplastic form of acute leukaemia was more like that of aplastic anaemia than acute leukaemia. They required supportive therapy with blood and platelet transfusions, and antibiotics for recurrent episodes of infection. The median duration of survival from the time of diagnosis was 22 weeks.

Specific Therapeutic Regimens (Table I)

Results with single-agent treatment were poor. The complete remission rate was only 7% with 6-mercaptopurine and 14% with daunorubicin. While it was also poor with a 4-drug combination of daunorubicin, cytosine arabinoside, prednisone and 6-mercaptopurine, a further 30% achieved partial remission on this treatment. Comparable results were obtained by using a combination of vincristine, daunorubicin and cytosine arabinoside.

The largest treatment group of 22 patients received cycles of daunorubicin and cytosine arabinoside. The complete remission rate was 31,5% and the partial remission rate 9%. The median survival was 19 weeks, and similar to that in the patients on the 4-drug regimen; median survival rates were less than 10 weeks in the other two groups (Fig. 1).

Further analysis shows that the median survival rate was significantly better ($P<0,05$) in the subjects who responded to daunorubicin and cytosine arabinoside, than in the group as a whole (42 weeks compared with 19 weeks).

Maintenance therapy was given to most subjects who achieved a remission with the initial treatment. In general, the inducing drugs were administered at intervals in a cyclical fashion. In addition, daily 6-mercaptopurine or 6-thioguanine and weekly methotrexate were given orally to the majority of subjects. The individual patterns of maintenance therapy administered to the 22 patients who were initially treated with daunorubicin and cytosine arabinoside, give a good reflection of the approach that was generally followed (Fig. 2). When haematological

TABLE I. HAEMATOLOGICAL DATA AND RESULTS OF TREATMENT IN 59 PATIENTS WITH ACUTE NON-LYMPHOBLASTIC LEUKAEMIA

Treatment	No. of patients	Mean age (years)	Mean Hb (g/100 ml)	Mean leucocyte count (per mm³)	Mean platelet count (per mm³)	Results of therapy: Partial remission (%)	Results of therapy: Complete remission (%)
6-mercaptopurine + prednisone	15	46	8,2	21 300	73 000	7	7
Daunorubicin	7	43	9,6	32 900	58 000	14	14
Daunorubicin + cytosine arabinoside + prednisone + 6-mercaptopurine	10	56	9,6	24 300	100 000	30	10
Daunorubicin + cytosine arabinoside	22	43	9,1	24 500	67 000	9	31
Vincristine + daunorubicin + cytosine arabinoside	5	36	11,0	8 200	85 000	20	20

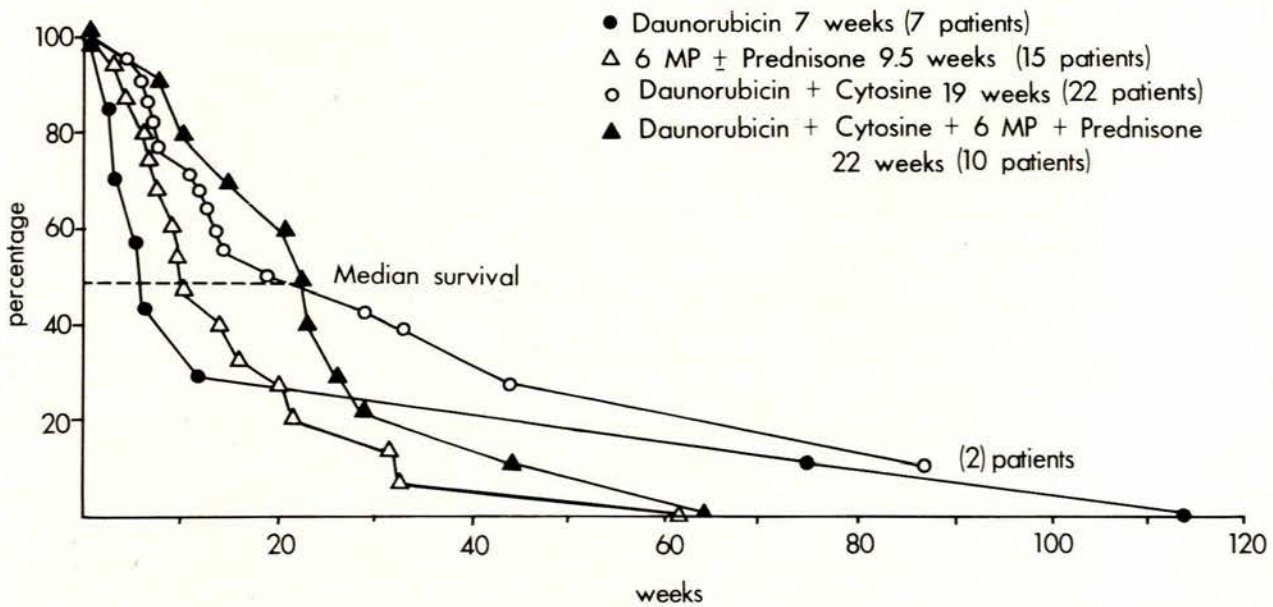

Fig. 1. Cumulative survival curves for patients receiving 4 different drug regimens as primary induction therapy.

relapse occurred, reinduction was usually attempted with the same agents that had been used for the initial remission induction.

Factors Affecting Prognosis

An unsuccessful attempt was made to find out whether it was possible to retrospectively predict the patients who went into remission on chemotherapy. It did not appear to depend on the patient's age, nor on the concentrations of haemoglobin, white cells or platelets. It was noted, however, that the mean age (62 years) of the group which received no therapy was older than that of the subjects who did receive treatment. The mean white cell count was lower in this group, but this was owing to the fact that several of these patients were suffering from the aplastic form of leukaemia.

Complications of Therapy

Minor complications of treatment, such as nausea and vomiting, were troublesome in the majority of patients. More serious was the haematological suppression induced by the cytostatic agents. The lowest mean post-treatment white cell count of 930/mm³ was found in the patients treated with daunorubicin alone. This figure was significantly lower ($P<0,05$) than the mean figure of 2 060/mm³ occurring with the 4-drug regimen and the mean figure of 1 580/mm³ in the patients treated with daunorubicin and cytosine arabinoside. Similarly, the mean platelet count (10 000/mm³) after treatment with daunorubicin alone was significantly lower ($P<0,05$) than that after other forms of treatment.

Cardiac complications which were ascribed to the use of daunorubicin, occurred in 3 patients. One patient died as a result of this complication. He had received a total

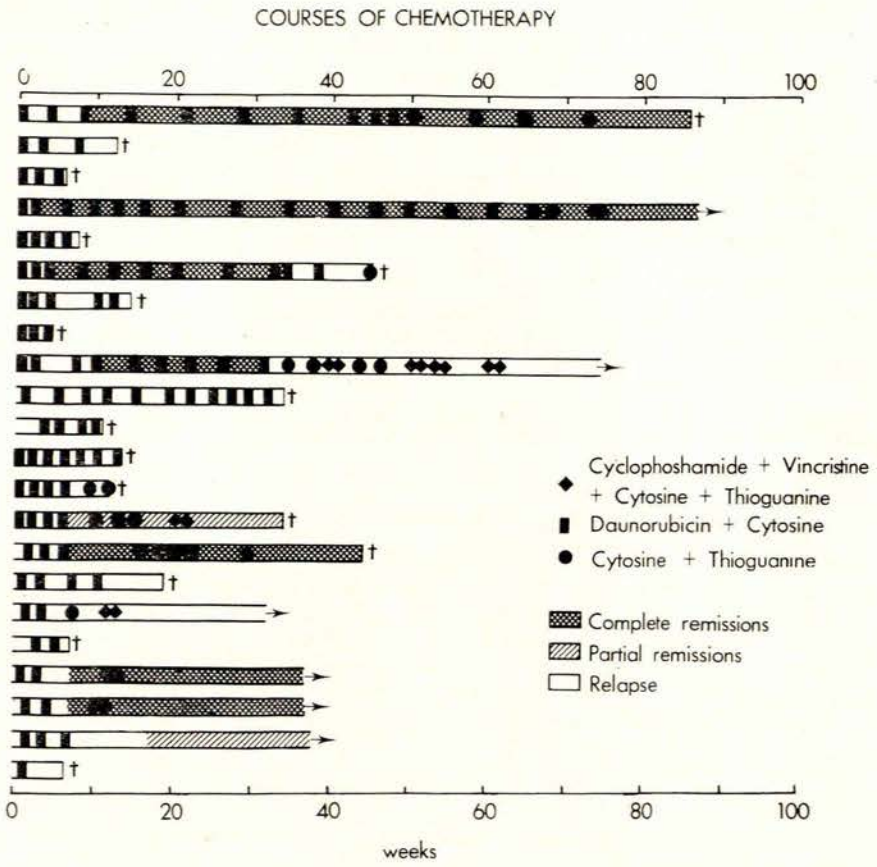

Fig. 2. The treatment schedules used as maintenance and reinduction therapy in 22 patients initially treated with daunorubicin and cytosine arabinoside. The periods which each patient spent in complete remission, partial remission and relapse are indicated. The majority of patients received most of their therapy on an outpatient basis.

dose of 37 mg/kg body mass over a period of more than 2 years. He complained of dyspnoea and tiredness and on examination was found to have a low systolic blood pressure, a small pulse volume, sinus tachycardia, prominent third and fourth heart sound gallops, and other evidence of biventricular cardiac failure. These findings were accompanied by a diminution of the QRS voltages in all 12 leads of the standard electrocardiogram and T-wave inversion over the left chest leads. No further daunorubicin was given but the cardiac status continued to deteriorate over several months. As a terminal event the patient developed complete atrioventricular dissociation, with a low cardiac output, which failed to respond to the administration of inotropic agents or to transvenous ventricular pacing.

A second patient, who was asymptomatic, developed electrocardiographic changes; these consisted of diminution of the QRS voltage and T-wave inversion. Daunorubicin was stopped and the ECG returned to normal over a period of 3 months. The third patient developed the clinical features of a congestive cardiomyopathy with biventricular failure, enlargement of the cardiac silhouette on X-ray examination, and diminished electrocardiographic voltages. She responded to a regimen of strict bedrest and conventional antifailure therapy. A year later the cardiac status was virtually normal.

Causes of Death

At the time of this analysis 68 of the patients had died. In 52 subjects this was the result of bleeding or infection, or both. Infection was the sole cause of death in 10 patients, and bleeding in a further 2. Death was ascribed to cardiac causes in 4 instances. As mentioned previously, daunorubicin was thought to be responsible in one instance. This patient died while in complete remission. The other 3 cardiac deaths occurred while the patients were in relapse.

In only 24 of the fatal infections was the responsible organism isolated. *Pseudomonas* septicaemia, which occurred in 7 patients, was the most commonly documented infection. *Escherichia coli* was isolated in 6 patients, while fungal septicaemia, usually *Candida albicans,* occurred in a further 6.

DISCUSSION

The therapeutic regimens used in the treatment of acute non-lymphoblastic leukaemia have improved significantly over the past few years.[6] This is to some degree reflected in the present experience. Initially a combination of 6-mercaptopurine and prednisone was given, and the results were almost uniformly poor. Daunorubicin, when used as a single agent, proved too toxic and was quickly abandoned. However, when administered in smaller doses in combination with cytosine arabinoside,[9] better results were obtained, with a complete remission rate of 31% and significantly prolonged survival.

The question arises as to how such results measure up to those obtained by others. The remission induction rate in acute non-lymphoblastic leukaemia has been low in several series reported by the Acute Leukaemia Group B. In addition, Wilkinson and co-workers[11] recently reported a median survival time of only 2 months in 115 patients treated with either single-agent or combination chemotherapy. In another series using POMP (nitrogen mustard, vincristine, methotrexate and prednisone) Rodriques and co-workers[12] obtained a complete remission rate of 28%, with a median survival of 28 weeks. Better results have been obtained with a combination of cytosine arabinoside and thioguanine, with complete remission rates varying between 39% and 65%.[6,13,15] Worthwhile results have also been obtained with cytosine arabinoside and daunorubicin. Crowther *et al.*[5] obtained a complete remission rate of 49% in 94 patients. Comparable results have been reported by Rosenthal and Moloney[8] using a combination of vincristine, cytosine arabinoside and daunorubicin, by Whitecar *et al.*[15] using COAP (cyclophosphamide, vincristine, cytosine arabinoside and prednisone), and by Paolino *et al.*[16] employing the latest MRC protocol, TRAP (thioguanine, daunorubicin, cytosine arabinoside and prednisone).

All this evidence taken together suggests that with currently available drugs it is possible to induce complete remission in between a third and a half of patients with acute non-lymphoblastic leukaemia. While this represents a significant therapeutic advance, the situation is still far from satisfactory.

There appear to be several reasons for the high failure rate. Firstly a number of patients succumb to overwhelming infection or to thrombocytopenic bleeding before the chemotherapeutic agents have had time to exert their effects. Attempts to induce remission are further complicated by the fact that none of the available drugs are sufficiently selective in killing the leukaemic cell population.[14] This means that severe marrow depression occurs as an inevitable sequela of effective chemotherapy. This lack of drug specificity not only bedevils the problems associated with remission induction but also hinders the consolidation of such remissions when they do occur. As a result, remissions tend to be of short duration, even when maintenance chemotherapy is given. Until better drugs become available other approaches will have to be tried. In this context, both specific and non-specific immunotherapy have been advocated as a means of attacking the small residual leukaemic population that remains during periods of remission.[5]

With a disease that is still almost uniformly fatal it is appropriate to ask whether the present aggressive therapeutic regimens are justifiable. Any team of doctors caring for such patients certainly has moments when the cumulative emotional drain impairs morale and judgement. But they do not last. The median survival rates do not adequately portray the quality of that survival. The majority of patients achieving complete or even partial remission enjoy good health for most of the survival period. In addition, it is possible in most to give later courses of therapy (Fig. 2) on an outpatient basis. This means that many continue working and enjoy a normal family life until very late in the course of the disease.

There is another reason for the present attitude—it is not yet possible to predict who will respond or how long that response will last. In each large group of sufferers there are thus individuals who will go into remission promptly on appropriate therapy, and who will continue in good health for months and even years. While the dividend is small, it is nevertheless very worth while.

One final point warrants stressing. The handling of patients with acute leukaemia requires considerable expertise, not only in terms of the medical management, but concerning the patients' emotional problems. The drugs used are extremely toxic and even when recognised regimens are followed, dosage and spacing of treatment often require modification. In addition, the handling of patients whose bone marrow has been seriously compromised by therapy, poses its own special problems. Difficulties are compounded by the many personal problems faced by the patient. The confidence required to manage these many facets comes only with experience, making it essential that patients are referred for treatment to recognised centres that have the necessary facilities.

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