PAPERS AND ORIGINALS

Management of Adult Acute Myelogenous Leukaemia

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Summary

Consecutive adult patients admitted to St. Bartholomew's Hospital with acute myelogenous leukaemia have been treated with a remission induction drug schedule consisting of daunorubicin and cytosine arabinoside. Intermittent five-day courses were used in 72 patients, and a complete remission was obtained in 39 patients (54%). An alternative drug schedule in 22 patients resulted in fewer remissions but this may have been due to age differences in the two groups. Age and initial platelet count were found to be important factors in determining the success of remission induction therapy; the older patients and those with low platelet counts responded less well.

A series of 23 patients who achieved remissions was divided into two groups; one received intermittent combination chemotherapy as the only form of maintenance, and the other was given weekly immunotherapy in addition to the chemotherapy. The immunotherapy consisted of irradiated allogeneic leukaemic cells and B.C.G. Eight of the 10 patients on chemotherapy alone have already relapsed compared with five out of 13 patients in the immunotherapy group. It is hoped that these promising initial results with this form of maintenance will be confirmed as more patients enter the maintenance trials.

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Introduction

Much has been written in recent years about the treatment of acute lymphoblastic leukaemia, in which the aim is now to eradicate the disease with the hope of permanent cure. The situation in acute myelogenous leukaemia is different. Until recently, it was rare to obtain complete remissions in this disease and difficult to maintain them for any length of time. There are now several regimens in existence which produce complete remissions in about half of the patients. We have used a combination of daunorubicin and cytosine arabinoside which, when used as single agents, give a higher percentage of remissions than any other single agent, and our preliminary results in 37 patients were reported by Crowther *et al.* (1970).

The purpose of this paper is to record our experience at St. Bartholomew's Hospital of treating 94 patients since 1969 with these two drugs, because they highlight many of the difficulties. Firstly, the difficulty of obtaining a remission and the complications which arise during this time; secondly, the problems arising during the maintenance of remission; thirdly, the problem of those who do not remit; and, finally, the treatment of the relapsed patients.

Materials and Methods

Patients.—Altogether, 94 unselected patients with acute myelogenous leukaemia have been admitted to three trials since May 1969, with 40 patients in trial 1, 22 in trial 2, and 32 in trial 3. The type of acute leukaemia present in these patients is given in table I. There were 56 with acute myeloblastic leukaemia, 23 with acute myelomonoblastic leukaemia, six with acute promyelocytic leukaemia, eight with erythroleukaemia, and one with acute monoblastic leukaemia. No patients were excluded from the first two trials, but three patients were excluded from trial 3 because one had received previous therapy with daunorubicin and cytosine arabinoside, another refused treatment and discharged himself on the day of admission to hospital, and, in the third patient, there was an error in diagnosing the type of leukaemia. In nearly all patients a diagnosis of acute myelogenous leukaemia was confirmed within a few hours of admission. Chemotherapy usually started on the evening of admission, but in a few patients treatment was postponed for 24 to 48 hours because of serious infection.

TABLE 1—Relation Between Type of Leukaemia and Remission Rate in Adult Patients with Acute Myelogenous Leukaemia. Figures in Parentheses are Patients Achieving Complete Remission.

	No. of Patients				Complete Remission (%)
	Trial 1	Trial 2	Trial 3	Total	
A.M.L. ..	25 (17)	11 (5)	20 (9)	56 (31)	55
A.M.M.L. ..	7 (4)	8 (1)	8 (6)	23 (11)	48
A.P.M.L. ..	3 (1)	1 (0)	2 (1)	6 (2)	33
E.L. ..	4 (1)	2 (1)	2 (0)	8 (2)	25
A. Mono. L. ..	1 (0)	0 (0)	0 (0)	1 (0)	0
Total	40 (23)	22 (7)	32 (16)	94 (46)	49

A.M.L. = Acute myeloblastic leukaemia. A.M.M.L. = Acute myelomonoblastic leukaemia. A.P.M.L. = Acute promyelocytic leukaemia. E.L. = Erythroleukaemia. A. Mono. L. = Acute monoblastic leukaemia.

Definition of Remission.—Complete remission was judged to have occurred when the patient became asymptomatic, clinically free from disease, the bone marrow cellularity was normal, there were no abnormal blast cells in the marrow and less than 5% of apparently normal blast cells, the peripheral blood count showed a haemoglobin level greater than 12 g/100 ml not maintained by transfusion, a white blood count greater than 3,000/mm³ with a normal differential count and neutrophils numbering more than 1,500/mm³ and a platelet count above 100,000/mm³. These are the criteria for complete remission used by the Midwest Co-operative Chemotherapy Study Group (Hewlett *et al.* 1964). The remission lengths were estimated from the date of complete remission (M1) bone marrow to the date of haematological relapse. There were no remissions terminated by central nervous system leukaemia in this series.

INITIAL CHEMOTHERAPY

In each of the three trials, daunorubicin and cytosine arabinoside were the two drugs used for inducing a remission but were given in a different way in trial 2 from trials 1 and 3.

Trials 1 and 3

The chemotherapy is set out in fig. 1. It consisted of five-day courses of daunorubicin 1.5 mg/kg body weight (55 mg/m²) given by fast intravenous infusion on day 1, and cytosine arabinoside 2 mg/kg body weight (70 mg/m²) given on days 1 to 5 by intravenous injection every 24 hours. Courses were repeated at intervals of about 10 days until remission was achieved. A course of treatment was given if there was evidence of persisting leukemic blast cells in the blood or bone marrow. Courses were with-

FIG. 1—Treatment schedule for acute myelogenous leukaemia in adults, trial 1. The same remission induction therapy was used in trial 3. ARA-C = Cytosine arabinoside. MTX = Methotrexate. MP = Mercaptopurine.

held when bone marrow examination showed severe hypocellularity with less than 20% blast cells remaining. A further course was given when peripheral blood examination indicated marrow recovery from the hypoplastic episode. Bone marrow examination was usually carried out at intervals of 10 days.

Trial 2

This trial included 22 unselected patients and was designed to test remission induction therapy when using the same drug combination but a different timing of drug administration (fig. 2).

FIG. 2—Induction programme for acute myelogenous leukaemia, trial 2. The same maintenance regimens were used as in trial 3.

Six intravenous injections of cytosine arabinoside were given at eight-hourly intervals. Cytosine arabinoside (4 mg/kg body weight) was given in divided dosage during this initial 48-hour period. There was a treatment-free interval of 24 to 72 hours before daunorubicin was given at a dose of 1.5 mg/kg body weight (55 mg/m²) by fast intravenous infusion, and cytosine arabinoside 2 mg/kg body weight (70 mg/m²) by intravenous injection. Further intravenous injections of cytosine arabinoside were given 24 and 48 hours later to complete the course. The courses were repeated after a five-day treatment-free interval. The time interval between the cytosine arabinoside pretreatment and the injection of daunorubicin varied between 24 and 48 hours in the second and subsequent courses according to the results of tritiated thymidine labelling studies in some of the patients. Tritiated thymidine in-vitro labelling of the bone marrow was carried out at 24 hours, 48 hours, and 72 hours after the cytosine arabinoside in order to determine the time of the peak labelling index. Labelling studies were performed in eight patients early in the trial. These patients had a 72-hour gap between the cytosine arabinoside pretreatment and the injection of daunorubicin in the first course. Seven patients had a 24-hour gap in the first course when it was realized that the peak labelling index occurred at this time in most patients. Further labelling studies are in progress and will be reported later.

REMISSION MAINTENANCE

Trial 1

After remission induction, a further course of daunorubicin and cytosine arabinoside was given, and this was followed by a four to six-week period of cytoreduction using mercaptopurine 70 mg/m² daily by mouth and methotrexate 12 mg/m² twice-weekly by mouth. After this, the patients were placed into two groups at random. One group continued to receive the above doses of chemotherapy as maintenance therapy, the other group received only immunotherapy (fig. 1). Drug doses were adjusted to maintain the white blood count between 3,000 and 3,500/mm³, and the platelet count above 100,000/mm³.

Nine patients received immunotherapy given in three ways: intradermal B.C.G. (bacille Calmette Guérin) alone (4), autologous leukaemic cells alone (3), or a combination of allogeneic leukaemic cells with B.C.G. (2). The first four patients receiving immunotherapy were given B.C.G. only, using two methods on separate limbs (the scarification technique and the 60 needle puncture technique). In the two patients receiving allogeneic leukaemic cells, the B.C.G. was given by the 40 needle puncture technique.

Trials 2 and 3

Maintenance therapy in these trials was designed to study the effect of combined chemotherapy with immunotherapy. After an additional five-day consolidation course of daunorubicin and cytosine arabinoside, all patients received alternating five-day courses of cytosine arabinoside with daunorubicin and cytosine arabinoside with thioguanine at monthly intervals. The patients were placed into two groups at random, one receiving chemotherapy alone and the other receiving immunotherapy in addition to chemotherapy, as shown in fig. 3. For these trials all the patients had the same form of immunotherapy (weekly B.C.G. and irradiated allogeneic leukaemic cells) as described below. All chemotherapy was stopped after one year of remission, but immunotherapy was continued in the appropriate group. In trial 2, four patients received chemotherapy alone and three had immunotherapy as well. In trial 3, six patients were treated during remission with chemotherapy only and 10 with immunotherapy and chemotherapy.

FIG. 3—Treatment schedule for trial 3.

Immunotherapy

Reagents used were B.C.G. and irradiated leukaemic cells.

The B.C.G. used in all trials was the Glaxo freeze-dried percutaneous vaccine (moist weight 10 mg/ml; $150-750 \times 10^6$ viable organisms/ml). The total bacterial count was about five times the viable count. The Pasteur liquid vaccine has a lower concentration of live organisms (about 50×10^6 viable organisms/ml), but the moist weight is much higher (75 mg/ml). It has been estimated that when using the multipuncture technique with 40 needle punctures set to a depth of 2 mm, the number of viable organisms introduced is in the same order of magnitude as Mathé *et al.* (1969) obtained using the Pasteur liquid vaccine and the scarification technique, but the latter is accompanied by a more severe local inflammatory reaction than the multipuncture technique. The 40 puncture technique was used in the M.R.C. trial of immunotherapy in acute lymphoblastic leukaemia (1971).

Leukaemia cells for immunotherapy were obtained from the peripheral blood of untreated patients with acute myelogenous leukaemia by using an I.B.M. cell separator (Buckner *et al.*, 1959; Powles *et al.*, 1971). These cells were stored at -179°C in a viable state and before injection were rapidly thawed, washed, and irradiated to 10,000 rads.

Method of Giving Immunotherapy

In trial 1, three types of immunotherapy were used—intradermal B.C.G., autologous irradiated leukaemic cells, and a combination of B.C.G. and allogeneic irradiated leukaemic cells. The immunotherapy was given at weekly intervals. B.C.G. was given by one of three methods. The first method used a Heaf gun which was applied 10 times (60 needle punctures) at 2 mm penetration, and the second involved 20 scarifications, each 10 cm long, in a similar way to that described by Mathé *et al.* (1969). In the four patients receiving B.C.G. alone, both these methods were used on different arms in the same patient. The third method was used in all patients receiving allogeneic leukaemic cells and involved a 20-needle multiple puncture gun set to a depth of 2 mm and fired twice. It was calculated that the latter method would deliver about one million viable organisms intradermally, but this estimate is subject to considerable error.

Irradiated leukaemic cells were given by weekly subcutaneous and intradermal injections, 10^9 cells being distributed between three limbs, and if B.C.G. was used in addition this was given in the fourth limb. The sites of injection into the four limbs were rotated each week.

In trials 2 and 3 only one combination of immunotherapy was used—B.C.G. by the 20-needle multiple puncture gun and allogeneic irradiated leukaemic cells each week.

Supportive Care

Bacteriological investigations were carried out on the urine, blood, swabs of the nose, throat, and any obviously infected region in patients with fever. During the course of treatment the aim was to start antibiotic therapy within one hour of a fever being noticed. Ampicillin and cloxacillin were usually used initially if there was no obvious site of infection. Gentamycin with carbenicillin or cephaloridine were used if a Gram-negative infection was suspected. The appropriate antibiotic was used when the results of bacteriological studies were known. Oral antibiotics were used where possible in patients who, in spite of the fever, remained clinically well. Prophylactic antibiotic therapy was not used, but prophylactic antifungal agents were regarded as necessary to limit the growth of candida in the mouth, which frequently occurred in these susceptible patients. All patients were nursed in open general medical wards; no "isolation units" were used. Anaemia was treated where necessary by transfusion of packed red cells from stored blood, and fresh whole donor blood was given for severe haemorrhage. Thrombocytopenia accompanied by haemorrhage was treated with fresh ABO compatible platelet transfusions from random donors at a dose of 4 units per m^2 at each transfusion. Platelet transfusions were not used prophylactically in the absence of haemorrhage from mucosal surfaces, but extensive retinal or skin haemorrhage was considered to be an indication for their use. Allopurinol was given routinely to prevent hyperuricaemia during remission induction in a dose of 300 mg daily by mouth.

Results

REMISSION INDUCTION

The number of patients who achieved a complete remission in the three trials is shown in table 1. In trials 1 and 3 where the patients received the same induction programme (fig. 1), 39 of 72 patients had complete remissions (54%) and a further six had useful partial remissions. Ten patients in trial 1 received L-asparaginase in addition to daunorubicin and cytosine arabinoside. The L-asparaginase was given at a dose of 30,000 units/ m^2 daily for a period of up to 28 days. We have described previously how this drug increased the side effects of treatment without altering the remission rate (Crowther *et al.*, 1970).

When using the different drug schedule in trial 2, only seven

out of 22 patients (32%) achieved a complete remission, but this group of patients was not entirely comparable due to age distribution (see below).

FACTORS INFLUENCING REMISSION RATES

Early Deaths

An important point is shown in table II. It took an average of three courses of chemotherapy to produce a remission, and this means that patients dying during the first month of treatment did not receive an adequate trial of chemotherapy. If one therefore excludes them the remission rate in all three groups is greatly increased, from 58% to 82% in trial 1, 32% to 58% in trial 2, and 50% to 70% in trial 3. The significance of this lies in the causes of death at this stage, which are haemorrhage and infection. Two major factors contributing to haemorrhage and infection are thrombocytopenia and neutropenia, but there may be others as well.

TABLE II—Treatment of Adult Acute Myelogenous Leukaemia Using Drug Regimens with Different Timing But the Same Total Dose of Drugs

Drug Regimen	Complete Remission	Complete Remission (Excluding Patients Dying during 1st Month)
Trial 1: DR + ARA-C without ARA-C pretreatment	23/40 (58%)	23/28 (82%)
Trial 2: DR + ARA-C given after 48 hr pretreatment with ARA-C	7/22 (32%)	7/12 (58%)
Trial 3: DR + ARA-C as in trial 1	16/32 (50%)	16/23 (70%)
Total	46/94 (49%)	46/63 (73%)

DR = Daunorubicin. ARA-C = Cytosine arabinoside.

There is no doubt that in acute myelogenous leukaemia, unlike lymphoblastic leukaemia, a period of severe marrow hypoplasia must occur before a complete remission is obtained. We have no patients in whom a complete remission was obtained who did not have pancytopenia due to marrow hypoplasia. The early deaths represent a failure to prevent the fatal effects of pancytopenia in a significant number of patients.

The treatment chart in fig. 4 is that of a typical patient which shows two important features. First, there is the inevitable pancytopenic phase lasting about four weeks, and then there is the recovery phase when the counts steadily return to normal levels despite continuing chemotherapy. It is quite clear that the effect of these drugs on a marrow infiltrated with leukaemia is

FIG. 4—Progress of a typical patient during treatment.

quite different from that on a normal marrow. The first course caused a fall in the platelet and neutrophil counts but subsequent courses once remission had occurred had no significant effect on the counts.

Altogether, 21 out of the 72 patients (29%) in trials 1 and 3 died during the first month of treatment, compared with 10 out of the 22 patients (46%) in trial 2. The complete remission rate of patients in trials 1 and 3 who survived the first month of treatment was 39 out of 51 (77%). Only seven out of 12 patients (58%) in trial 2 analysed in the same way achieved a complete remission. Although the number of patients is small, the altered drug schedule used in trial 2 did not appear to offer any advantage over the schedule used in trial 1, and this was the reason why, in trial 3, we reverted to the remission induction regimen of trial 1. With both regimens, on average, three courses were required to produce a remission.

Age

The age of a patient was an important factor influencing response to treatment. The age distribution of all 94 patients in the series is shown in fig. 5. The median age was 50 years. Sixty-eight patients were below 60 years of age at presentation, and 40 of these obtained complete remissions (59%). None of the nine patients over 70 years old and only six out of the 26 patients aged 60 years or more achieved complete remissions (23%).

FIG. 5—Relation between age and incidence of complete remission in all 94 patients included trials 1, 2, and 3.

Age was also an important factor in the lower incidence of remission seen in trial 2. In this trial the median age was 53 years and there were nine patients over 60 years old, only one of whom achieved a complete remission. In trials 1 and 3, five out of 15 patients over the age of 60 achieved remissions. Therefore, in spite of the age difference in the trials, the altered drug schedule did not seem as effective in trial 2.

Previous Chemotherapy

Altogether, 28 patients received chemotherapy before admission to St. Bartholomew's Hospital, but only a few had received more than two weeks' treatment elsewhere. Eight patients had received mercaptopurine and prednisolone; nine prednisolone alone; two mercaptopurine alone, and the remaining patients were previously treated with prednisolone combined with busulphan, vincristine, or cyclophosphamide. Patients who had received earlier treatment with daunorubicin or cytosine arabinoside were excluded. Of the 28 patients who had received previous chemotherapy, 50% achieved complete remissions compared with 48% of patients who had not. The fact that patients

received cytotoxic drugs other than those used in the induction programme before admission to St. Bartholomew's Hospital did not appear to affect their response to the treatment adversely.

Initial Platelet Count

The platelet count estimated at the time of admission to St. Bartholomew's Hospital was related to the incidence of complete remission in the 94 patients, as shown in table III. There was a significant difference in remission rates between patients presenting with a platelet count of less than 20,000/mm³ and those with an initial platelet count greater than this (P 0.05). A total of 55% of patients with platelet counts of more than 20,000/mm³ achieved remissions, whereas only 29% of patients with platelet counts below this figure obtained remissions. Of those who had not received earlier chemotherapy, four out of 11 achieved complete remissions in the low platelet group and 26 out of 55 with platelet counts in the higher group.

TABLE III—Relation Between Remission Rate in Acute Myelogenous Leukaemia and Initial Platelet Count in Trials 1, 2, and 3

Initial Platelet Count:	<20,000/mm ³	>20,000/mm ³
Complete remission	6 (29%)	40 (55%)
Partial remission	3	3
Failure	12	30
Total	21	73

Peripheral Blood Blast Count

Out of 26 patients with blast counts of less than 100/mm³, 16 achieved a complete remission, compared with only 30 out of 68 patients with blast counts greater than this. This difference was too small to be of significance, and although the initial blast count may be a factor influencing remission induction the effect is not a major one.

Of those patients who had not received earlier chemotherapy, six out of nine with low initial blast counts achieved complete remissions, and 27 out of 57 with blast counts greater than 100/mm³ entered remission. There was no significant difference between these groups.

Type of Leukaemia

Details of the different types of acute myelogenous leukaemia in the three trials are given in table I. Nearly all patients were suffering from acute myeloblastic or myelomonoblastic leukaemia. Over half of those with these types of acute leukaemia achieved complete remission (53%), whereas patients with the other types of acute myelogenous leukaemia had fewer remissions. Only four out of 15 patients with acute promyelocytic, acute monoblastic, or erythroleukaemia obtained remissions. The number of patients in this group was too small to make a definitive statement regarding the incidence of complete remission. The difficulty in obtaining remissions in these patients gave no indication of their subsequent prognosis. One patient with acute promyelocytic leukaemia and another with erythroleukaemia who obtained remissions in trial 1 had the longest remissions, and were still continuing in remission at 115 + and 120 + weeks respectively.

MAINTENANCE OF REMISSION

Survival figures can be given only for patients in trial 1, and are shown in fig. 6. The median survival for this whole group was only 30 weeks. The median survival for the 23 patients achieving

FIG. 6—Survival curve of adult patients with acute myelogenous leukaemia, trial 1.

FIG. 7—Lengths of remission. First two columns show remission lengths in trial 1, and the second two columns show remission lengths in trials 2 and 3. Open circles = Patients continuing in remission. Closed circles = Relapsed patients. MP = Mercaptopurine. MTX = Methotrexate. DR = Daunorubicin. Ara-C = Cytosine arabinoside. TG = Thioguanine.

remission was 50 weeks. The median survival for the 48 patients who failed to achieve a remission in trials 1, 2, and 3 was less than one month. This emphasizes the known importance of remission induction on survival in this disease.

Complete follow-up data on all patients in trials 1, 2, and 3 up to 1 October 1972 is given in fig. 7. The patients receiving all forms of immunotherapy as a collective group in trial 1 had similar remissions lengths to those receiving mercaptopurine and methotrexate maintenance (fig. 8). Nevertheless, it was of great interest that the two longest remissions in the immunotherapy group were two patients receiving irradiated allogeneic leukaemic cells and B.C.G. Their remission lengths were 60 and 115 + weeks. This prompted the use of this type of immunotherapy in combination with intermittent chemotherapy in trials 2 and 3. The remission lengths comparing the value of chemotherapy alone with chemotherapy and immunotherapy are shown in fig. 7. Eight of the 10 patients on chemotherapy alone have already relapsed compared with only five out of 13 patients in the immunotherapy group. The median remission lengths for the group receiving only chemotherapy maintenance in trials 2 and 3 was about 30 weeks. The median remission lengths for the group receiving chemotherapy and immunotherapy had not been reached at the time of writing but was in excess of 40 weeks, and three patients were continuing in re-

FIG. 8—Lengths of complete remission of patients in trial 1.

mission for more than one year. A preliminary analysis of these data has been reported by Powles *et al.* (1972).

REINDUCTION THERAPY FOR RELAPSED PATIENTS

Altogether, 21 patients in trial 1 relapsed and, of these, 19 received reinduction therapy. One patient died of serum hepatitis in complete remission and another died in relapse before receiving further treatment. Six of the treated patients (32%) obtained a further remission. In four of these cases reinduction was similar to the initial induction programme using daunorubicin and cytosine arabinoside. One patient received courses in thioguanine and cytosine arabinoside in addition, and a further patient was successfully reinduced with thioguanine, cyclophosphamide, and prednisolone.

TREATMENT OF PATIENTS WHO FAILED TO REMIT

There was a total of 17 patients who failed to remit with cytosine arabinoside and daunorubicin but who survived the first month (five in trial 1, five in trial 2, and seven in trial 3). No patient achieved a complete remission with the other drugs we then used—that is, adriamycin, cyclophosphamide, thioguanine, mercaptopurine, and prednisolone. One patient survived 13 months but the remaining 16 died within the first six months.

DRUG TOXICITY

There were no clinical problems associated with cardiotoxicity from daunorubicin in this series of patients. Although minor electrocardiographic changes were observed occasionally during courses of treatment, there were no arrhythmias. Bone marrow suppression was invariable and seemed necessary before remission occurred. Some nausea and vomiting occurred during a course of treatment, but this was not usually severe. Some alopecia was common, but hair growth returned during the maintenance phase. Some oral ulceration occurred, but it is uncertain whether this was attributable to the drugs or to complicating infections in a neutropenic patient. Other complications were uncommon. Daunorubicin is a vesicant if injected outside a vein, and although the utmost care was taken to prevent this areas of cellulitis were produced in a few patients. Transient fever after daunorubicin was observed occasionally, and one patient developed a severe urticarial reaction immediately after an injection. This patient had a similar hypersensitivity reaction to a subsequent dose of adriamycin.

Discussion

INDUCTION OF COMPLETE REMISSION

It is difficult to compare complete remission rates for acute myelogenous leukaemia reported by different centres. Patient selection, variety of acute myelogenous leukaemia, age, clinical condition, previous treatment, quality of supportive care, and the assessment of responses are all important factors influencing the remission rate. For example, many groups exclude patients dying before or shortly after cytotoxic drug therapy is started and this markedly influences the success rate. Several patients in the present series died within 24 to 48 hours of admission, and some of these died before cytotoxic chemotherapy could be instituted. Most groups exclude the promyelocytic or erythroleukaemic variants of acute myelogenous leukaemia. In this study only three patients were excluded for reasons already given. All the other patients admitted to the hospital with a diagnosis of acute myelogenous leukaemia were included in the trials. Our overall remission rate was 49% of 94 patients. If we exclude trial 2, which had more elderly patients and a different schedule for administering the drugs, the complete remission rate was 54% of 72 patients. Our results compare favourably with the results obtained by other centres. Gee *et al.* (1969) reported 15 complete remissions in a series of 38 patients treated with thioguanine 2.5 mg/kg orally in the morning and cytosine arabinoside 3 mg/kg as a single intravenous injection six to eight hours later. This daily treatment continued for eight to 32 days until bone marrow hypoplasia occurred. Most patients obtaining remissions required two or three courses. A further four patients in their series achieved good partial remissions which were complete in every respect except for low haemoglobin levels. In all instances this was due to suppression of erythropoiesis by continuing therapy and not to disease. This gave a remission rate of 50% in the 38 patients. The same group at the Memorial Hospital, New York, has since changed the timing and dose of drug administration to repeated courses of cytosine arabinoside 3 mg/kg by intravenous injection and thioguanine 2.5 mg/kg orally, both every 12 hours (L6 protocol) (Clarkson, 1972). A total of 28 (65%) of 43 patients with acute myeloblastic or acute myelomonoblastic leukaemia have achieved complete remissions using this drug schedule. There were fewer elderly patients in this series than in the present series, and no cases of erythroleukaemia or acute promyelocytic leukaemia were included.

Other series have been reported with remission rates in the region of 50%, but fewer patients were studied. For example, Rosenthal and Moloney (1972) obtained complete remissions in 11 of 23 previously untreated patients with acute myelogenous leukaemia using a combination of vincristine, cytosine arabinoside, and daunorubicin.

Larger series published by co-operative groups have suffered from the criticism that many centres are involved with varying management techniques and response rates. The remission induction rate in acute myelogenous leukaemia has been low in several series reported by the Acute Leukaemia Group B, but remissions were obtained in about 36% of 66 patients treated with cytosine arabinoside and thioguanine. In this series, further groups were treated with cytosine arabinoside alone or in combination with mercaptopurine or daunorubicin, but the remission rate was no greater than 27% (J. F. Holland, 1972, personal communication).

Whitecar *et al.* (1972) have also reported useful remission rates in patients treated with intensive combination chemotherapy. In this series complete remissions were obtained in 44% of 39 patients with acute myelogenous leukaemia using a combination of cyclophosphamide, vincristine, cytosine arabinoside, and prednisone (COAP). The patients achieving a complete remission were maintained with the same drugs. The age distribution in this series was similar to our own, but only three out of 20 patients over 50 years old achieved remissions. The remission rate in our series was 38% of 50 patients over 50 years old. Although this is the best remission rate so far published in

the elderly with acute myelogenous leukaemia, the response rate is much lower than in younger patients.

We feel that the combination of daunorubicin and cytosine arabinoside remains as good, if not better, than any other drug combination used for remission induction in adult acute myelogenous leukaemia. The schedule is simple, and both drugs are given by intravenous administration, which means that timing and drug dosage are accurate. The timing of drug administration may well be critical if optimum results are to be obtained, and comparisons between different series suffer from the difficulty that the drug schedules are not usually comparable, even when the same drugs are given. The South-West Co-operative Chemotherapy Group has found that the remission rate was significantly higher ($P 0.05$) when cytosine arabinoside was administered by continuous infusion over a period of 120 hours than when the drug was given continuously over 48 hours (Freireich *et al.*, 1971). Although our remission rate appeared lower in the 22 patients treated in trial 2 with the altered drug schedule, this may have been because of the age difference in the two groups.

The importance of supportive care during remission induction has already been emphasized. All patients who achieved remissions in this series underwent a variable period of severe pancytopenia and bone marrow hypoplasia. During this time many patients became very ill, and without correct supportive care would have died. Graw *et al.* (1972) have now provided evidence in a controlled study that granulocyte transfusions are helpful in treating Gram-negative septicaemia in patients with acute myelogenous leukaemia. Ideal supportive care should now include these, but they were not used in the present series of patients because to do so requires an I.B.M. continuous blood cell separator which was not available during this study. Haemorrhage can be effectively treated with whole blood and platelet transfusions, but it is still not known whether platelet transfusions are helpful in preventing haemorrhage in a patient with severe thrombocytopenia. Similarly, the role of prophylactic antibiotics is not clear, and the value of "isolation units" in increasing remission rates and reducing mortality is not yet proved in controlled trials (Levine *et al.*, 1972). There are serious disadvantages in the use of prophylactic platelet transfusions, and isolation units and their place has not yet been clearly established.

TREATMENT OF PATIENTS FAILING TO REMIT WITH DAUNORUBICIN AND CYTOSINE ARABINOSIDE

Altogether, 31 of our 92 patients died within the first month and a further 17 failed to achieve a complete remission, and must be regarded as initial treatment failures. The 17 who survived the first month but failed to remit were treated with thioguanine, cyclophosphamide, mercaptopurine, adriamycin, or prednisolone, either singly or in combination, but none achieved a complete remission and they are all now dead. Failure to support the patients during the initial weeks of treatment and the inability to achieve remissions with other drugs when the initial treatment with daunorubicin and cytosine arabinoside has failed remain the two major problems to be solved before the remission rate in acute myelogenous leukaemia can be significantly improved.

REMISSION MAINTENANCE

Until very recently the results of maintaining remissions in acute myelogenous leukaemia have been poor. Whitecar *et al.* (1972), however, reported a median remission length of 42 weeks in a series of 17 patients maintained on intermittent combination chemotherapy using cyclophosphamide, vincristine, cytosine arabinoside, and prednisone (COAP). A preliminary report by Clarkson (1972) has indicated that their

remission lengths after the L6 protocol, which involves the sequential use of many drugs, are also promising; of 28 patients achieving remissions on the L6 protocol, 18 were continuing in remission for 2+ to 24+ months, five of them for over 12 months. The results appear comparable to our patients maintained with intermittent chemotherapy and immunotherapy in trials 2 and 3, and better than our chemotherapy-only group.

To our knowledge, there have been no other published studies involving the use of active specific and non-specific immunotherapy in patients with acute myelogenous leukaemia. These preliminary follow-up data on a small number of patients show promising results in favour of combined intermittent chemotherapy and immunotherapy in these forms of acute leukaemia. A previous study by Mathé and his colleagues (1969) using B.C.G. (Pasteur liquid vaccine) alone, B.C.G. with irradiated allogeneic leukaemic cells, or irradiated leukaemic cells alone as immunotherapy in patients with acute lymphoblastic leukaemia, showed some improvement in remission lengths, but the numbers were small, and eventually all patients received both. As in this series, the control group contained only 10 patients, and further studies are required before any benefits of immunotherapy can be clearly assessed. Until there is clear confirmation that immunotherapy has a definite part in prolonging survival in a large carefully controlled group of patients it must be regarded as an experimental procedure. This study is continuing in the hope that our preliminary results may be confirmed with a large number of patients.

A study such as this would have been impossible without the full co-operation from departments concerned with general medical care. The personnel of departments of radiology and pathology have provided helpful advice throughout the trials.

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