Today's Treatment

Blood and Neoplastic Diseases

Acute Myeloblastic Leukaemia

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Myeloblastic leukaemia (A.M.L.) and its closely related cytological variants are less responsive to chemotherapy than acute lymphoblastic leukaemia (A.L.L.). A considerable problem still exists with remission induction; a high proportion of patients fail to achieve complete remission, especially among older adults with the disease. The contribution of maintenance chemotherapy after remission is less certain, and the place of prophylactic irradiation of the central nervous system is debatable in the light of the poor duration of control of the systemic disease by current methods. No clear-cut pattern of overall management can therefore be defined as for A.L.L. The present achievement in control of A.M.L. is similar to that of A.L.L. seven to eight years ago. One hopeful development, however, is the possible contribution of immunotherapy to the management of this disease.

Remission Induction

Reduction in the mass of leukaemic myeloblasts necessary for remission is usually achieved only by "ablative" chemotherapy, equally toxic to normal marrow cells, rather than by "selective" cytotoxicity, as with A.L.L. Vincristine (VCR) and corticosteroids alone will seldom produce a complete remission in A.M.L. Instead the relatively myelotoxic drugs cytosine arabinoside (ARA-C), thioguanine (TG), and daunorubicin (DAUNO) have to be used. Combinations of these drugs are more effective than the single drugs,¹ but at the cost of increased marrow depression, since all three drugs have this side effect in common. Supportive therapy to tide the patient over the inevitable period of pancytopenia preceding remission must be a planned component of management.

A remission rate of over 50% in adult A.M.L. has been obtained by several drug combinations, all of which incorporate ARA-C (see table). ARA-C and TG, which together seem to possess a degree of synergism, are the cornerstones of chemotherapy in A.M.L.²

These five-day "pulses" of chemotherapy, given at two or three-week intervals, allow recovery of immunosuppression and myelosuppression between courses, thereby permitting repeated exposure of the tumour to the multidrug therapy. These drug schedules would be too toxic for continuous administration. It is not entirely proved, however, that such

Remission Induction Rates in Adult A.M.L. obtained with newer Drug Schedules

Drug Combination	Complete Remissions	Authors
ARA-C + VCR + Pred + CYCLO (COAP)	17/39 (44%)	Whitecar <i>et al.</i> ⁵
ARA-C + VCR + DAUNO	11/23 (48%)	Rosenthal and Maloney ¹¹
ARA-C + TG (Daily)	19/38 (50%)	Gee <i>et al.</i> ¹²
ARA-C + DAUNO	39/72 (54%)	Crowther <i>et al.</i> ¹³
ARA-C + TG (12-hourly) ("L-6" Protocol).	28/42 (65%)	Clarkson ⁴

ARA-C = Cytosine Arabinoside (intravenous)

VCR = Vincristine (intravenous)

Pred = Prednisone or Prednisolone (oral)

CYCLO = Cyclophosphamide (oral)

DAUNO = Daunorubicin (intravenous)

TG = Thioguanine (oral)

pulse therapy is more effective than equally toxic continuous chemotherapy in either A.L.L. or A.M.L.

Consolidation

Because of the high incidence of early relapse undoubtedly many leukaemic cells persist in the body at the time when complete remission is first obtained. If about 10¹² leukaemic cells are present at diagnosis a 99.9% tumour cell kill will still leave 10⁹ cells. A reasonable practice is, therefore, to give a similar and equal number of courses of chemotherapy immediately after blood and bone-marrow remission (C.R.) in the hope that this will further reduce the number of remaining leukaemic blast cells. This concept is used in the L-6 schedule.² A variant of this is to give a series of different combination chemotherapy courses such as COAP, POMP, and TRAP (see below) at this stage so that the possible advantage from exposure to different drugs and combinations is obtained. This concept is used in the current Medical Research Council trial for adult A.M.L. and the "Hammersmith Protocol".^{3,4}

Patients may be allowed home for this phase of therapy with visits to the haematology clinic for assessment and intravenous injections at the beginning of each new course. Intramuscular or subcutaneous injections during the later days of some of these courses can be given by their own doctor, a district nurse, or in some patients by self administration.

Maintenance Therapy

The "Hammersmith" regimen and also one arm of the current M.R.C. trial for adult A.M.L. employs continuing five-day courses of TRAP, (TG, rubidomycin, ARA-C, and Pred),

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COAP (Cyclo, oncovin, ARA-C, Pred) and POMP (purinethol, oncovin, MTX, Pred) at two-three week intervals, according to tolerance, for at least two years.³ The median duration of complete remission in patients having repeated courses of COAP every 14 days was 10½ months.⁵

The L-6 protocol from the Memorial Hospital, New York, incorporates a complex sequence of drugs consisting of four-day courses of "cycle-active" drugs (that is, drugs active against dividing cells) followed on the fifth day of the course by a "non-cycle active" drug (active also against resting cells).

Thus:

Oral MTX 10 mg × 4, BCNU 1-2 mg/kg/intravenous × 1, nine-day rest period, then
Oral TG 10 mg/kg × 4, Cyclo 10-20 mg/kg/intravenous × 1, nine-day rest period, then
Oral hydroxyurea 60-80 mg/kg × 4, DAUNO 1 mg/kg/intravenous × 1.

This L-6 protocol has given the best long-term survival results so far published for adult A.M.L. In the 43 previously untreated patients entered on the trial a life-table plot suggests that 50% will be surviving at two years. In the 28 out of 43 who achieved complete remission the curve predicts that 70% of these will survive two years.

Immunotherapy

Not only is the chance of obtaining an initial complete remission greater in patients with A.M.L. who retain intact immunological reactivity during this phase of treatment,⁶ but the addition of immunotherapy in the maintenance phase, given between monthly courses of chemotherapy, prolongs remission and survival.⁷

A combined trial at St. Bartholomew's and the Royal Marsden hospitals used ARA-C and daunorubicin for remission induction in 107 patients with A.M.L. aged 14 to 59 years. The 45 patients achieving complete remission had been randomized to receive monthly five-day courses of chemotherapy with or without intervening weekly injections of B.C.G. plus irradiated allogeneic myeloblasts. Of the 19 on chemotherapy alone, seven are surviving with a median survival in this group of seven months, while of the 23 on chemotherapy plus immunotherapy 16 are surviving, the median duration of survival in the immunotherapy group being 18 months. Part of the improved survival may be due to the greater chance of obtaining a second complete remission with chemotherapy in the patients who have been having immunotherapy, a finding also suggested by a recent report from Manchester. It is still, however, an open question whether better results cannot be obtained by optimum chemotherapy without immunotherapy as in the L-6 protocol mentioned above.

Supportive Therapy

At the time of presentation patients with acute leukaemia may be dehydrated, infected, bleeding, anaemic, and with impaired renal and hepatic function. Appropriate biochemical assessment and fluid and electrolyte replacement may be as necessary as the more obvious need for packed cell and platelet concentrate transfusion. Particular attention should be paid to the possibility of hyperuricaemic acidosis or nephropathy developing during the early stages of tumour destruction. It is now standard practice to determine the serum uric acid level at diagnosis and to institute allopurinol therapy, 10 mg/kg/day in divided doses, before starting antileukaemic drugs. If there are large tumour masses (for example, spleen or thymus) or if there are over 50,000 blasts/m³ in the peripheral blood one must also ensure a high fluid intake (2-3 l./m²/day) and give oral bicarbonate so as to keep the urine neutral or alkaline (3 g/m²/day in divided doses). Other metabolic disturbances

such as lactic acidosis, hypocalcaemia, and hyperkalaemia may also occur during remission induction.

Platelet transfusions (4 units/m²) are indicated when there is bleeding in the presence of a platelet count of below 20,000/mm³. They are usually available in the form of platelet concentrates and must be given with a special "platelet-giving set" and siliconized size 19 or 21 butterfly scalp vein sets or through plastic cannular sets (for example, Argyll catheters). Bleeding rapidly responds unless there is concomitant sepsis or disseminated intravascular coagulation. Red cell requirements are calculated on the basis that 6 ml of whole ACD blood per kg/body weight raises the circulating haemoglobin level by about 1 g/100 ml. From this number of "pints" of whole blood one arrives at the same number of "units" of packed cells required.

Every venepuncture must be performed with the greatest possible sterility because of the ever-present hazard of infection during the remission induction phase. By elaborate methods using protected patient environments and special nursing techniques as well as topical antiseptic regimens it is possible greatly to reduce the patient's endogenous bacterial and fungal flora and to protect them from cross infection. These measures, which are likely to be available only in centres with a special interest in the treatment of leukaemia, are more clearly justified in A.M.L. than in A.L.L. because the drugs used cause a greater degree of marrow depression and longer neutropenia. A randomized trial showed a striking reduction in the incidence of life-threatening infections, and elimination of fatal infections, by sterilizing the gut with unabsorbable oral antibiotics (gentamicin, vancomycin, and nystatin) used in conjunction with a protected environment (laminar flow or plastic isolator) plus a topical antiseptic regimen to skin and mucous membranes.⁸

The problem remains of the patient who at diagnosis has serious bacterial infection plus neutropenia or agranulocytosis. To add immunosuppression and possible further marrow depression by starting antileukaemic drugs in the presence of active infection must increase the chance of a fatal outcome. Yet there is not usually time to identify the causative organism and test its sensitivity. After collecting blood and other samples for culture it is probably justifiable to institute "blind" multiple antibiotic therapy in serious infections. A combination of parenteral gentamicin, cephalothin, and carbenicillin plus oral clindamycin covers virtually all likely bacterial pathogens and has been advocated for use in this situation.⁹ With this treatment hypokalaemia usually develops, requiring additional potassium supplements, but I have not met other hazards such as renal damage when the drugs are used for only five to seven days. By the latter time the specific organism may have been isolated or the infection may have resolved. An additional approach that may be available in special centres is to give granulocyte transfusions to severely neutropenic patients with infection. These cells may be harvested by conventional plasmapheresis techniques from donors with active chronic myeloid leukaemia if available, or more conveniently, from a healthy donor (usually a relative) by means of a continuous-flow IBM or AMINCO cell separator.

The granulocytes should be irradiated with 1,500 r before transfusion so as to reduce the risk of graft-versus-host reaction. The donor must be ABO-compatible with the recipient. The closer the HL-A concordance the more effective the rise in granulocyte count in the recipient. With multiple granulocyte transfusion all of 12 leukaemic patients with proved Gram-negative septicaemia survived.¹⁰

These apparently heroic supportive measures in the first few weeks of treatment are justified in new cases of leukaemia because of the greatly improved long-term prognosis. The occurrence of severe, life-threatening infection or haemorrhage during the remission induction phase bears no relation to the long-term prognosis. A child who might otherwise be

cured of its leukaemia could perish from septicaemia in the first week of treatment.

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Any Questions?

We publish below a selection of questions and answers of general interest

Removal of Dead Nits

After treating cases of scalp hair nits with application dicophane or with gamma benzene hexachloride B.P.C. the dead nits are difficult to remove. Could you please advise how this might be done?

The question is a good one, and, as any outpatient sister will tell you, there is no magic answer. Nowadays, the treatment of scalp lice infection—if carried out correctly—is so effective that the residual hair nits are truly dead. Nymphs will not emerge and the old obsession about removing them (because treatment did not guarantee death of their contents) is no longer with us. Thus removal is necessary only on cosmetic grounds. There is still nothing better than a metal fine-toothed comb (difficult to get, but a pet shop rather than a chemist may be best) used carefully on wet hair. Removal may be easier if the hairs are rubbed previously between a swab moistened with vinegar. When the number of nits is small individual ones may be picked off with a finger nail. If these tips do not help, then patience may be the answer. As hair grows the nits are carried to the free edge and a hair cut (or a new "style") may be the most convenient and acceptable answer.

Long-term Administration of Belladonna

What are the hazards of long-term administration of small doses of belladonna such as are contained in some laxatives?

There are few ethical pharmaceutical preparations marketed as laxatives which now contain belladonna but no doubt there are several "over the counter" remedies of this nature available. The amount of belladonna in the ethical preparations is of the order of 1-5 mg of dried extract of belladonna. It is unlikely that such small doses of belladonna even if taken over a long period would have any serious effects. The experience gained in the days when relatively large doses of belladonna or similar drugs were used in the treatment of Parkinsonism was that patients readily became tolerant to the effects of the drug and that any side-effect did not persist. It is much more likely that the long-term effects of the laxative itself upon the colon might give rise to undesirable effects. The syndrome of colitis due to abuse of laxatives is now a well recognized clinical entity.

Low-serum Iron with Normal Haemoglobin

A patient with a normal haemoglobin level has low serum iron. Is this unusual?

The combination of normal haemoglobin level with low serum iron (that is less than 50 µg/100 ml) is probably not unusual since in most cases it represents the early stage of a sideropenia that will eventually develop into iron-deficiency anaemia. Serum iron estimation is rarely asked for until anaemia has appeared. Iron deficiency causes anaemia only when iron stores in the tissues are exhausted and when inadequate iron for haemoglobin synthesis is reaching the marrow. Fairbanks and Beutler¹ give a good account of the progressive stages of iron deficiency. Several workers have associated this sideropenia syndrome of low serum iron without anaemia with a definite clinical picture of persistent fatigue occurring in women of all ages and in both sexes over 60. Rarely, dysphagia and even koilonychia can also occur.² Before undertaking a possibly prolonged search for the cause of the iron deficiency, it is best to confirm the sideropenia by having two serum iron estimations taken at an interval of a few days.

¹ Fairbanks, V. F., and Beutler, E., in *Hematology*, ed. W. J. Williams, et al., p. 305. New York, McGraw-Hill, 1972.

² *Lancet*, 1968, 1, 462.

Notes and Comments

Postoperative Care after Intestinal Surgery.—Dr. C. D. HOLDSWORTH of Sheffield writes: with reference to the answer to this question ("Any Questions?" 21 September, p. 737) I think your expert has not indicated the importance of knowing the stool volume and fat content before making any decision on the mechanism for the postoperative diarrhoea. He also does not indicate the vital importance of knowing how much ileum was removed, as only then can any decision be made on aetiology and management with, for example, restriction of fat intake or cholestyramine.

OUR EXPERT replies: It was difficult to reply in a few lines to a question which well merits a review article. I agree with and am grateful for the amplifications in this short statement.