Today's Treatment

Blood and Neoplastic Diseases

Acute Lymphoblastic Leukaemia

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The treatment of acute leukaemia is still evolving largely by multicentre clinical trials, and today's therapeutic programmes will almost certainly be improved in the future. The most fruitful way of treating acute leukaemia is to join a co-operative group, such as the M.R.C., if this is at all possible.¹

Success in treating acute leukaemia depends not only on the use of antileukaemic drugs but also on supportive therapy to combat both the consequences of the disease and the side effects of the drugs. Long-term control of the disease is also related to certain innate characters of the individual leukaemic cell line. In lymphoblastic leukaemia a high blast cell count in the peripheral blood or gross enlargement of spleen and hilar lymph nodes at diagnosis usually carries a bad long-term prognosis. Both features probably reflect a high rate of proliferation of the leukaemic cell line. In myeloblastic leukaemia this relationship is less prominent, but here the age of the patient has a more appreciable effect on survival, patients under the age 40 faring better than older ones.²

Acute lymphoblastic leukaemia (A.L.L.) is the typical form of acute leukaemia in childhood, but it also occurs less commonly in adults. It is in A.L.L. of childhood that great strides in the long-term control of the disease have taken place, so that even a "cure" may be attainable in 25% or so of such patients. In due course some of the principles that have emerged from clinical trials in childhood A.L.L. may become applicable to other types of acute leukaemia including those of adults. For these reasons A.L.L. is discussed first. The component parts of the treatment of A.L.L. have now been fairly well established (see figure).

Remission Induction

During the initial period of therapy there are hazards of infection, haemorrhage, and hyperuricaemia, but there is usually no major problem in killing sufficient leukaemic cells to produce a complete remission by relatively simple chemotherapy. This is a contrast to myeloblastic leukaemia, where highly marrow-depressive drug combinations have to be used to obtain remission. With vincristine (VCR) and prednisone or prednisolone (Pred) alone at least 85% of children with A.L.L. obtain a complete clinical, peripheral blood, and marrow remission (C.R.) in four to six weeks. In adults with A.L.L. the remission rate is somewhat lower, 50%.³ Additional drugs must be added to VCR + Pred in the minority of patients

VCR = Vincristine, (intravenous)
Pred = Prednisolone or Prednisone, (oral)
ASP = L-Asparaginase, (intravenous)
DAUNO = Daunorubicin, (intravenous)
MTX = Methotrexate, (oral or intrathecal)
6-MP = 6-Mercaptopurine, (oral)
CYCLO = Cyclophosphamide, (oral)

"Boxes" enclose the currently most favoured therapy in my opinion, but valid alternatives are also shown.

with A.L.L. failing to show some response within two to three weeks or to show a complete marrow remission in six weeks. Asparaginase (ASP) or daunorubicin (DAUNO) or even cytosine arabinoside (ARA-C) may be added in these circumstances but at the cost of added toxicity, making the supportive facilities of a special centre desirable. With the combination of DAUNO, VCR, and Pred close to 100% C.R. has been obtained in childhood A.L.L., but the addition of DAUNO is more toxic to the normal marrow elements than VCR + Pred alone.

It was in the field of remission induction that the clinical advantages of combination chemotherapy were first demonstrated. Ideally, the combination should have at least additive, and possibly synergistic, tumouricidal action but the individual drugs used should have largely different types of tissue toxicity in the patient. Fortunately the usual limiting toxicities of VCR (neuromuscular, alopecia), Pred (hypercorticism), ASP (allergic, metabolic) and DAUNO (marrow, cardiac) are essentially different. Nevertheless, all are to some extent immunosuppressant.

C.N.S. Prophylaxis

Early in the period of remission, commonly at about six to eight weeks from diagnosis, additional tumouricidal therapy is given to the central nervous system (C.N.S.). Without such specific therapy up to half of children with A.L.L. eventually

Dosage of Drugs for Acute Leukaemia

Drug	Amount	Dosage
VCR Pred	1.5 mg/m ² I.V.* 40 mg/m ² Oral	weekly (days 1, 8, 15, etc) daily in three to four divided doses
ASP DAUNO ARA-C	8,000 U/m ² I.V. (or I.M.)* 20 mg/m ² I.V. 80 mg/m ² I.V., S.C., (or I.M.)	three times per week days 1, 2, 8, 9, etc. usually in five-day courses

I.V. = Intravenous
I.M. = intramuscular
S.C. = subcutaneous

*All intravenous injections must be given with the greatest care and aseptic precautions. These patients' veins are their life lines. "Butterfly" scalp vein sets are strongly recommended. Intramuscular injections must not be given in the presence of thrombocytopenia (a platelet count of <50,000/mm³).

have their first remission terminated by recurrence in the nervous system, presenting as meningeal leukaemia with headache, vomiting, and papilloedema. Probably this arises from "seeding" of the arachnoid with blast cells at the time of initial florid systemic leukaemia, and these cells are not effectively reached by orally or parenterally administered anti-leukaemic drugs. In a randomized trial the first remission was terminated by this type of relapse in only two out of 45 children given "prophylactic" irradiation to the nervous system compared with 33 out of 49 children not given this treatment.⁴ The additional imposition of this prophylactic therapy is justified not only by the 15-fold reduction of primary nervous system relapse but also by the reasonable hope that one may thereby be removing a potential source of leukaemic "reseeding" to the bone marrow. Though difficult to prove this hypothesis, undoubtedly the best results in long-term total freedom from recurrence of A.L.L. have been from schedules using early, effective prophylactic irradiation of the nervous system.⁵

Two equally effective types of prophylaxis have been demonstrated in randomized clinical trials. These are either irradiation of the entire craniospinal axis with 2,400 r supravoltage (in 14-15 fractions over two and a half to three weeks), or similar irradiation of only the cranium combined with a course of five intrathecal injections of methotrexate (MTX) at a dose of 12 mg/m² given about twice weekly. The concept is that intrathecal MTX or spinal irradiation are equally capable of "sterilizing" the spinal arachnoid of blast cells, but that intrathecally administered MTX fails to penetrate the cortical ramifications of the arachnoid in adequate concentrations. Cranial irradiation, however, succeeds in this area. A reduction in incidence of subsequent meningeal leukaemia has been obtained with intrathecal MTX without radiotherapy, but this has been in schedules where intrathecal injections were given monthly afterwards,⁶ and these later doses could be merely masking recurrence in the nervous system without eradication. This did not apply in the two schedules using radiotherapy described above.

At present cranial irradiation plus intrathecal MTX is the preferred method of prophylaxis, rather than craniospinal irradiation, since there is a lower incidence of long-term marrow depression and liability to infections.² Practical difficulties may arise, however, when the radiotherapy department is far removed from the paediatric unit giving the intrathecal MTX. Temporary alopecia is usual with either therapy and wigs should be ordered beforehand, at least for all the girls. In children under 2 years the irradiation dosage should be limited to 2,000 r, and under 1 year to 1,500 r.

During the period of prophylaxis this aspect of treatment takes precedence over systemic chemotherapy. The patient will usually have been stabilized on a maintenance dose of 6-mercaptopurine (6-MP) (say, 50-70 mg/m²/day) in the two to three weeks since remission, and this can be continued throughout much of the prophylaxis, but should be reduced or stopped if a falling white cell count (say below 2,000/mm³) threatens to compromise the scheduled course of intrathecal MTX or spinal irradiation.

Maintenance Therapy

Early trials by Acute Leukaemia Group B unequivocally showed that maintenance chemotherapy prolonged remission

in A.L.L. The two drugs 6-MP and MTX, though seldom used for remission induction, are the cornerstones of maintenance chemotherapy for A.L.L. in remission and after completion of central nervous system prophylaxis. Whereas there is good evidence that MTX is more active in remission if given in high intermittent doses, rather than low daily doses, there is no evidence that this is so for 6-MP. These observations, as well as the probable advantage of combination chemotherapy, have been combined in the formulation of three basic maintenance schedules consisting of:

	A.L.G.B.*	Pinkel†	M.R.C.‡
6-MP	daily oral	90 mg/m ²	50 mg/m ²
	+		
MTX	once per week oral	15 mg/m ²	20 mg/m ²
			15 mg/m ²

*Acute Leukaemia Group B protocol 6801.¹

†Plus once per week oral cyclophosphamide 200 mg/m².⁷

‡Current Medical Research Council protocol—UKALL III.

Individual adjustment of the above doses are necessary and few patients in Britain seem to tolerate the Acute Leukaemia Group B dose of 6-MP. The total white cell count should be kept between 2,000 and 3000/mm³, with avoidance of prolonged lymphopenia or neutropenia. In the presence of infection or buccal ulceration MTX is temporarily omitted. If the white cell count falls below 1,000/mm³ all drugs are stopped until a rise occurs. A high fluid intake is encouraged after the administration of cyclophosphamide in the Pinkel schedule. During this phase of therapy the patient is at home and leading a full and normal life appropriate to his age. The drug schedule is monitored and adjusted at weekly or fortnightly clinic visits.

There is conflicting evidence regarding the value of "pseudoreinduction" or "reinforcement" chemotherapy with monthly or three-monthly pulses of VCR + Pred superimposed upon the above-mentioned maintenance schemes. The outstandingly good long-term results, with 18 out of 31 patients still in their first complete remission for over five years, have been obtained by Pinkel's group using VCR + Pred pulses at 12-week intervals superimposed on the 6-MP, MTX, cyclophosphamide combination described above and after cranial irradiation plus intrathecal MTX.⁴ A very similar, and highly satisfactory, remission duration curve is being found in the A.L.B. 6801 protocol, with monthly VCR plus seven days Pred superimposed on daily 6-MP plus weekly MTX, and following a prolonged course of intrathecal MTX as prophylaxis.⁸ Twenty-one out of 27 patients are still in complete remission at between two and a half to three and a half years. These results seem to justify the continued use of VCR + Pred reinduction at present. Some discretion is needed, however, and the planned course should be delayed in the presence of viral or bacterial infection or fever.

Many alternative ways of using the above drugs for maintenance therapy have been investigated by the Acute Leukaemia Group B and the Medical Research Council. These include: repeated five-day courses of oral MTX (15 mg/m²/day) with periodic VCR + Pred reinduction with or without intervening periods on 6-MP.⁹ Good results have been obtained when effective nervous-system prophylaxis has preceded the maintenance therapy. The value of intermittent high-dose cyclophosphamide in maintenance therapy is not entirely proved and is one of the variables being investigated in a current M.R.C. trial, UKALL II.

When to Stop Chemotherapy

There are undoubted hazards from long-term chemotherapy and the most effective of the above maintenance schedules have unfortunately also been the most immunosuppressive and myelodepressive. A distinct hazard of fatal infection from

"opportunistic" viral, protozoal, and fungal agents exists,¹⁰ as well as from the more obvious pathogens.* Pneumonitis and hepatic toxicity can also result from chronic methotrexate toxicity. Deaths from these causes in a patient in remission are especially tragic now that there is the possibility of cure in childhood A.L.L. There is also a possible hazard of carcinogenesis from prolonged exposure to cytotoxic drugs.

The optimum duration of multidrug chemotherapy is probably between two and three years. The best recorded five-year results with over 50% of patients still in the first complete remission were obtained by Pinkel's group, who stopped chemotherapy at three years. The subsequent relapse rate while off therapy was 10%, and most of these relapses occurred in the first 10 months off drugs.⁴ Medical Research Council trials in Britain and others in the United States are specifically investigating this important question of optimum duration of multidrug maintenance at the present time. Beyond a certain point all the leukaemic cells may have been killed and thereafter chemotherapy would be doing more harm than good.

It is an open question whether or not immunotherapy would reduce the 10% relapse rate after stopping chemotherapy. The immunotherapy might be non-specific (for example, B.C.G.) or specific (that is, irradiated pooled lymphoblasts). A controlled trial by the M.R.C. showed no beneficial effect from B.C.G. in A.L.L. after highly effective but short-term cytoreductive chemotherapy.¹¹ Relevant to this question is the remarkable degree of "immunological rebound" that occurs in the weeks after cessation of multidrug chemotherapy,¹² even without the benefit of B.C.G. or other immunostimulation.

The Chances of Cure

Follow-up of long-term survivors by Burchenal, gleaned from a world-wide survey, showed that half of those surviving free of disease for five years remained so for 10 years. Whether this implies that half those still in remission at five years as

*Immune zoster gammaglobulin is available for susceptible varicella contacts, and normal gammaglobulin should be given to susceptible measles contacts.

a result of modern therapy will likewise survive for 10 years remains to be seen. If so the 10-year "cure rate" could be in the neighbourhood of 25%.

Relapses in A.L.L.

These greatly improved results have been bought at the cost of much greater refractoriness to treatment in those patients who suffer a systemic (marrow) or central nervous system (meningeal) relapse in spite of maximal therapy. Obtaining a second remission can be much more difficult than in the past when patients relapsed after exposure to only a few drugs. Likewise, a second course of radiotherapy is undesirable. In general, a more palliative approach must be pursued in such patients, and this is justified by the extreme improbability of cure once a recurrence of any kind has taken place. An exception to this rule may be the patient who relapses after a prolonged period off chemotherapy. Such patients may respond to VCR + Pred almost in the same way as "new" A.L.L. patients and should perhaps be treated as such. Recurrent leukaemia in the nervous system can be well controlled by monthly or eight-weekly intrathecal MTX (10-12 mg/m²).

References

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Any Questions?

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

Long-term Use of Aloin

What are the hazards of long-term use of a laxative containing aloin?

Aloin is the active principle of aloes, the most irritant member of the anthracene group of purgatives which also includes senna, cascara, rhubarb, and the free anthraquinone, danthron. These drugs act directly on the colon by stimulating the neurones of the myenteric plexus. Both aloes and aloin are said to cause renal irritation but I have never encountered this. Though aloes and aloin have been deleted from the *National Formulary* the hazards of their long term use relate to purgation in general rather than to any specific toxic effect. All purgatives taken regularly may become drugs of addiction. Constipated patients feel that they must pass loose stools, which they produce by excessive purgation. Each purge is followed by a period in which there is no bowel action, proof to the patient that he is constipated again and

must purge himself once more. In the more advanced stages of addictive purgation, formerly called cathartic colon, there is no constipation, only diarrhoea accompanied by abdominal discomfort, flatulence, distention, heart burn, and the inability to take certain foods. The diarrhoea causes loss of fluid and electrolytes, especially potassium. In severe cases with gross potassium depletion the patient experiences extreme apathy, weakness, and thirst and may look haggard and ill. Sigmoidoscopy may disclose melanin pigmentation of the colonic mucosa. Barium enema studies reveal dilatation of the large bowel with loss of normal haustrations and pseudostrictures, which slowly come and go. Serum potassium is low and the blood urea raised. Histologically there are gross changes in the colon, probably dependent on damage to the myenteric neurones. The whole problem of addictive purgation is well discussed in *Management of Constipation*.¹

¹ Jones, F. A. and Godding, E. W., *Management of Constipation*, Oxford, Blackwell 1972.