Today's Treatment

Blood and Neoplastic Diseases

Chronic Granulocytic Leukaemia and Chronic Lymphocytic Leukaemia

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Both chronic granulocytic leukaemia (C.G.L.) and chronic lymphocytic leukaemia (C.L.L.) are typified by an appreciable leucocytosis, prominent organ infiltration, and a chronic course —that is, one which extends over years rather than months. Almost the only other respect in which these two diseases resemble one another is in the lack of any proved major advances in therapy in recent years. Their management is very different and is considered separately.

Chronic Granulocytic Leukaemia

C.G.L. is not as chronic as is sometimes thought: the median survival of untreated patients is only about 19 months from diagnosis.[1] With few exceptions, patients require treatment from diagnosis, and in about 98% of cases clinical and haematological improvement are secured by simple therapy,[2] often without admission to hospital or the necessity of blood transfusion. In the short term, improvement can be maintained with simple therapy, but unfortunately in over 70% of cases the disease eventually enters a refractory phase,[3] in which even heroic treatments are generally ineffective. When this phase is characterized by the progressive accumulation of primitive cells in the bone marrow and peripheral blood, so that an acute leukaemia is mimicked, the term "acute transformation" is applied and death within six months is usual. Occasionally the onset is sudden and deterioration is rapid, leading to death within a few weeks: these very florid cases are sometimes called "blastic crisis." Nevertheless, the alteration of the C.G.L. may be more subtle: refractory anaemia, myelosclerosis, or thrombocythaemia may dominate the picture, and clinical deterioration may be only gradual. Refractoriness to previously effective therapy is a common denominator of all these changes, and the term "metamorphosis" has been proposed to encompass the many variants which are encountered.[4] Since no form of therapy has any major effect on the duration of life once metamorphosis has occurred, the success of any form of treatment in improving survival in C.G.L. is a measure of its effectiveness in postponing the onset of this change.

Treatment

For over 50 years radiotherapy was the mainstay of treatment in C.G.L. This was generally applied externally to the spleen, or occasionally as an abdominal "bath." Radiophosphorus administered systemically was also effective but was less widely used. In 1968 a Medical Research Council trial compared the effects of intermittent external irradiation with those of orally administered busulphan.[3] The median survival of 54 patients treated with radiotherapy was 28 months and 32 of them eventually received busulphan—whereas the median survival of 48 patients treated initially with busulphan was 39·5 months and in only four cases was it considered necessary to administer any irradiation. These results, together with the ease of administration and ready availability of busulphan, have led to a steady decline in the use of radiotherapy in C.G.L. Busulphan is of special value in geographical areas where expensive radiotherapy apparatus is not available.

USE OF BUSULPHAN

It is safest to begin busulphan treatment cautiously, at a dose of 4 mg daily, or 0·0625 mg/kg/day, whichever is the less, and to increase the dose only if response is inadequate after three weeks' trial. Very occasionally it is desirable to reduce the leucocyte count rapidly—for example, when leucocytosis is so great that there is hyperviscosity of the blood with retinal haemorrhages or priapism. In such cases 1-2 mg/kg of busulphan may be administered as a single dose and no further busulphan given for about four weeks. With either form of treatment, but particularly the latter, prophylactic allopurinol is advisable since a great mass (1-5 kg) of granulocytic tissue has to be lysed and hyperuricaemia is not uncommon: frequently it is present before treatment is begun.

With conventional doses of busulphan, little effect may be seen in the first 10 days, but this is not an indication to increase the dose. When the leucocyte count begins to fall, the more immature granulocytic forms begin to disappear from the peripheral blood, characteristically in the order of their immaturity until only mature neutrophils remain. The haemoglobin level begins rising as the leucocyte count falls and continues rising after the leucocyte count has reached normal values. Regression of the enlarged spleen may take many weeks. Over—enthusiastic busulphan treatment can cause marrow aplasia with a mortality of about 50%, and it is wise to interrupt treatment when the leucocyte count reaches 20,000/μl, since the count generally falls for about two weeks after busulphan is discontinued. It is advisable never to prescribe at any one time more busulphan than will span the gap until the patient's next appointment since disasters have occurred when patients have missed their appointments but continued to take the drug.

Most doctors use some form of maintenance treatment—for example, to maintain the leucocyte count between 7,000 and 12,000/μl. Doses as low as 2 mg of busulphan once a week are often sufficient, and the patient's wellbeing and normal

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life may be maintained with monthly visits and no hospital admissions.

DRAWBACKS OF BUSULPHAN

Busulphan has numerous side effects,[2] of which the commonest are pigmentation and amenorrhoea, while the most serious is pulmonary fibrosis, which is sometimes fatal. Its most serious disadvantage, however, is that while it improves the quality of life it adds only about 20 months to its duration, so that many patients with acute lymphoblastic leukaemia now outlive patients with "chronic" granulocytic leukaemia. In addition, an unwarranted satisfaction with the excellent results of busulphan therapy in the short term has probably retarded research into other therapies for C.G.L.

OTHER DRUGS IN C.G.L.

Many other drugs (including mercaptopurine, melphalan, cyclophosphamide, mitobronitol, and hydroxyurea), are effective in the chronic phase of C.G.L.[2 5] Nevertheless, none has been shown to be significantly superior to busulphan and several are less convenient to use, so that experience with them has been comparatively limited.

TREATMENT OF C.G.L. AFTER METAMORPHOSIS

Various drugs and drug combinations which are effective in the acute myeloid leukaemias have been used in C.G.L. when metamorphosis takes the form of an acute leukaemia, but results have been strikingly poor.[2] About one patient in six may respond to the combination of vincristine and prednisolone[6] and about half the patients respond temporarily to the drastic combination (thioguanine + daunorubicin + cytarabine + methotrexate + prednisolone + cyclophosphamide + vincristine).[7]

POSSIBLE THERAPEUTIC ADVANCES

Attempts to postpone the onset of metamorphosis in C.G.L. by immunotherapy,[8] by aggressive chemotherapy during the chronic phase, and by splenectomy[9] have shown some promise in pilot studies. The M.R.C. is conducting a controlled clinical trial of elective splenectomy carried out shortly after clinical remission of the C.G.L. has been obtained by initial therapy with busulphan.

Chronic Lymphocytic Leukaemia (C.L.L.)

There has also been a tendency to overstress the long and often very benign course of C.L.L. Nevertheless, in large series of patients the median survival is found to be only about four years.[2] Though a few patients survive for one or two decades, suffer little disability from the disease, and never require any treatment, most do much less well. An attempt has been made to subdivide C.L.L. on haematological findings and trends into benign and malignant groups, but primarily the disease is a spectrum rather than two discrete groups, and not every case is readily classifiable into a prognostic category. Current treatment for C.L.L. probably does not greatly alter survival: the most important factors affecting the duration of life are the stage of the disease at diagnosis and its rate of evolution. Earlier diagnosis, even in the absence of any treatment, would consistently produce a dramatic but factitious improvement in survival.

INDICATIONS FOR TREATMENT

There is general agreement that many patients with C.L.L. require no treatment at the time of diagnosis: this view is reinforced because many of the patients are old and frail and the treatment is not altogether harmless. Though practice varies among different centres, the generally accepted indications for treatment are: evidence of bone marrow failure (anaemia, neutropenia, or thrombocytopenia); the development of autoimmune acquired haemolytic anaemia; splenomegaly which is symptomatic or accompanied by hypersplenism; and troublesome involvement of lymph nodes, skin, or other tissues.

Lymphocytosis alone, even if extreme, is not considered to be an indication for treatment, and patients with C.L.L. who have no indications for treatment are merely observed and the rate of progression of their disease recorded, preferably in graphic form.[10]

In the typical elderly patient with C.L.L. it is wise to exclude other causes of illness such as gastrointestinal bleeding, vitamin or iron deficiencies, and tuberculosis before undertaking specific treatment for their leukaemia.

RADIOTHERAPY

In modern practice irradiation is usually reserved for prominent lymph node masses when systemic chemotherapy is not indicated or has failed to reduce the nodes adequately. Radiotherapy is sometimes administered to an enlarged spleen which has not regressed with chemotherapy, but considerable caution is needed since serious pancytopenia is readily produced. The response of the systemic disease to splenic irradiation is usually much less satisfactory in C.L.L. than it is in C.G.L.

CHEMOTHERAPY

When chemotherapy is begun in the presence of appreciable bone marrow failure, it is usual to treat at first with an adrenocortical steroid hormone—for example, prednisolone in a dose of 1 mg/kg/day by mouth, and for the first four weeks it is wise to prescribe in addition allopurinol, 5-7 mg/kg/day. Evidence of diabetes mellitus should be sought before and during prednisolone treatment. The peripheral blood lymphocytosis often increases initially but after two to three weeks decreases, while platelet and neutrophil counts improve. At this stage chlorambucil (0·1-0·2 mg/kg/day) is added; in the presence of thrombocytopenia, cyclophosphamide (2 mg/kg/day) may be preferred. Chlorambucil is continued until the blood picture has been restored as near to normal as attainable and splenomegaly and lymphadenopathy have regressed. Steroid therapy is gradually discontinued between the fourth and sixth weeks of therapy but low-dose chlorambucil may be continued for several months. Decreased lymphocytic infiltration of the bone marrow, if it occurs, usually requires over three months' therapy to achieve. In most patients it is reasonable to discontinue treatment once the desired result has been achieved, and observe the patient, since the need to resume therapy may not arise for months or years. Protracted treatment has no proved advantages and carries a risk of chronic bone marrow depression.

Steroid therapy may be avoided altogether if marrow failure is not severe at the onset of treatment. If used, steroids should be discontinued as soon as possible, since the hazards of long-term therapy are enhanced in elderly patients who may have diabetes, hypertension, congestive cardiac failure, or osteoporosis even before steroids are begun. Patients with C.L.L. are prone to infection because of neutropenia and frequently hypogammaglobulinaemia. The latter defect rarely improves with treatment, and continued steroid therapy increases the risk of serious infection. Reactivation of old tuberculous lesions occasionally results in fatal miliary tuberculosis and chest radiography is important in any patient with C.L.L. who becomes unwell, even if they have no fever. Resistance of the C.L.L. to chlorambucil, or autoimmune haemolysis which cannot be controlled by chlorambucil or low-dose (10-15 mg daily) prednisolone, poses special problems. The risks of pro-

tracted treatment with substantial doses of steroid must be weighed against those of imperfect control of the disease.

OTHER MEASURES

Primary or secondary failure of response to conventional chemotherapy is difficult to manage. Antimetabolite drugs and vincristine appear valueless—and often harmful—in C.L.L. The failing bone marrow may respond to treatment with androgenic steroids,[8] but frequently does not. Hypersplenism or uncontrollable autoimmune haemolysis commonly improve after splenectomy,[9] but many patients with C.L.L. are poor surgical risks. Recent studies suggest that total body irradiation may benefit patients with advanced C.L.L.,[11] but this mode of therapy has yet to be fully evaluated. The administration of human gammaglobulin as an adjunct to the treatment of infection in C.L.L., or as a prophylaxis against infection, is quite widely practised, though unequivocal evidence of its efficacy is lacking.

UNANSWERED PROBLEMS

A major problem is our present inability to detect in advance the minority of patients with C.L.L. who will not require treatment at any stage of their disease. Most patients do need treatment at some time, and, though the policy of treating only when specific indications are present is generally accepted, there is no good evidence that such a policy is correct. Would patients do better if they were treated—perhaps radically—at a time when no haematological complications had arisen? There is a real need for properly controlled trials in C.L.L., particularly in the younger patients, whose disease is likely to limit their lifespan.

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Any Questions?

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

Subconjunctival Haemorrhages in the Elderly

Is it necessary to treat subconjunctival haemorrhages in the elderly?

I have never considered that subconjunctival haemorrhages in elderly people require active treatment. If it is possible to identify a vessel responsible for repeated haemorrhages cauterization would seem logical, but I have had no personal experience of this procedure.

Side Effects of Lithium

What side effects may be expected from the use of lithium carbonate? For how long is it safe to maintain treatment?

The unwanted effects of lithium carbonate include relatively common acute symptoms and signs, and uncommon or insidious changes. The acute developments are toxic effects usually due to excessive dosage and can include nausea, vomiting, diarrhoea, abdominal cramps, slurred speech, blurred vision, vertigo, tremor, choreoathetotic movements, tinnitus, deafness, paraesthesiae, lethargy, confusion, cardiac arrhythmia, and rashes. In most cases of excessive dosage, however, one of these symptoms occurs in isolation, other symptoms developing only if the high dosage is continued. Such toxic effects can be avoided in most patients by using a small dose initially and increasing this according to the results of serum lithium estimations, the first being taken after six days. It has been suggested that the use of lithium for six days a week helps to avoid gradual cumulation in some patients. Sometimes gastrointestinal symptoms and mild tremor occur during the early stages of lithium therapy when the dose is steadily raised. If the dose is appropriate these are usually transient. Later recurrence of these symptoms is an indication for lowering the dose and in some cases discontinuing treatment. If neurological symptoms and signs, epilepsy, weight loss, or cardiac abnormalities develop lithium should be withdrawn. To avoid the development of marked toxic effects during the early stages of treatment the patient can be warned to stop using lithium carbonate and to use additional fluids and common salt for 48 hours, or until the effects have disappeared, and to seek medical advice before returning to the use of lithium.

The uncommon chronic effects are myxoedema and renal impairment, and though these conditions can occur within a few weeks of the introduction of lithium their development is insidious. Myxoedema can be particularly difficult to detect if the initial symptoms are psychiatric and superimposed on the existing picture of illness. The later appearance of lethargy, or any sustained change in personality, should alert the doctor to this possibility and the need for investigation of thyroid function. Renal changes result in an inability to concentrate the urine, and the development of polyuria after the initial stages of treatment is suggestive of this development. As renal impairment occurs, the serum level of lithium is likely to rise despite maintenance of a previously satisfactory dose, and the appearance of the toxic effects mentioned earlier may be the first indication of adverse effects.

Despite the seriousness of unheeded toxic effects of lithium, their occurrence during well managed treatment is very uncommon. Provided they are detected early, they are all fully reversible. If the patient is physically fit and the dose of lithium is appropriate there is no limit to the period over which the salt can be given. Apart from the few cases in which the drug cannot be used, the advantages of the treatment in a majority of cases far outweigh the small risks of adverse effects.

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