Some Implications of Current Therapy in Leukaemia

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SUMMARY

Improved survival in acute leukaemia follows aggressive combination chemotherapy based on a proper understanding of tumour cell kinetics and principles of modern pharmacology. Such cytoreduction regimens reduce tumour mass to a level at which eradication by immune mechanisms becomes feasible, a fact presently being exploited by immunotherapy programmes. Further improvement is possible by the judicious use of sophisticated support facilities such as laminar flow isolation areas and blood fraction separators, but the cost and expertise of operating such facilities limits availability to a few specialised centres. Logically, patients with acute leukaemia should have the benefit of management in these units.

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Leukaemia may be divided into an acute form, where rapid deterioration leads to death from haemorrhage or infection in days or weeks, and a chronic type, in which the relentless advance of this process may be very much slower. These broad clinical patterns can be correlated with the type of white cell present in the blood and the bone marrow; in the former, primitive or blast cells predominate, while greater degrees of leucocyte maturity and differentiation are found in the latter. This classification may be extended to further subdivide the leukaemias into either granulocytic or lymphocytic varieties, but such a distinction cannot always be made with certainty. Nevertheless, the precise morphological diagnosis is worthy of special attention since it will influence the choice of antileukaemic agents employed and so become an important contribution to the long survival being reported with increasing frequency in treated patients.

The fact that significant prolongation of life is now being achieved has necessitated a critical revision of the general philosophy attending the treatment of patients with leukaemia. In the past, when the outlook for survival was practically hopeless and when only a few rather poor therapeutic agents were available, some justification could perhaps be found for the use of palliative therapy. Today, however, the employment of more effective regimens has so improved the results of treatment that a more aggressive approach, with curative intent, is justified as the aim of therapy. Unfortunately, the complexity of the modern chemotherapeutic and radiotherapeutic schedules, especially when superimposed upon an already ill patient, require intensive care, meticulous isolation and sophisticated haematological support. Understandably, therefore, aggressive therapy is restricted to those few hospitals willing to create and staff specially equipped units.

The clear-cut improvement obtained in response to treatment reflects, to a large extent, an increased awareness of pharmacology and cell kinetics; both of these interact to provide a logical basis for much of our present-day drug scheduling. In addition to a better understanding of these basic concepts, progress has also been made in developing the necessary support programmes designed to keep patients alive during intensive and myelosuppressive chemotherapy. Since each of these advances has substantial implications for current therapy in patients with leukaemia, further comment is warranted.

Concept of Cell Division

The most important aspect of pharmacology has perhaps been the recognition of an interrelationship that exists between drug action and cell division. During this latter process a definite pattern of behaviour occurs, in which mitosis is followed by a variable time in which very little metabolic activity is evident—a period designated G_0 or G_1. The next period is occupied by DNA synthesis —the S phase; a second rest period, or G_2, precedes further cell division. This cell cycle plays a central role in chemotherapy since certain drugs are maximally cytotoxic during specific phases of division, and are designated phase- or cycle-specific. By way of contrast, others interfere with cell division non-specifically throughout the cycle—the phase or cycle non-specific drugs. Manipulation of drugs on the basis of this phenomenon can confer some selectivity on the percentage kill achieved in any given tumour depending upon its growth characteristics; for example, phase-specific drugs are most effective during times of rapid cell turnover, while phase non-specific drugs have greater application in the treatment of large tumour volumes with a low growth fraction.

Cellular Site of Activity of Drugs

In addition to these broad principles of action, the cytotoxic drugs may also be grouped on the basis of their specific sites of activity within the cell. Alkylating agents produce damage during all phases of the cell cycle by interstrand binding between N^7 in the guanine of one

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DNA strand to the identical portion on the opposite strand; antimetabolites are small molecules which resemble the normal substrate in chemical structure, but differ sufficiently to interfere with some vital chemical reaction involving the metabolite—examples include methotrexate and 6-mercaptopurine; the vinca alkaloids cause metaphase arrest by binding to the microtubular protein necessary for mitotic formation; certain antibiotics, such as daunorubicin, bind to DNA and thus damage RNA polymerase so that RNA synthesis is selectively blocked. Clearly, familiarity with each aspect of drug action is mandatory for doctors using these potentially dangerous and sometimes lethal substances in the treatment of patients.

Cell Kinetics

Turning now to cell kinetics, it is pertinent to emphasise two aspects which have particular implication in the treatment of leukaemia. Firstly, it is established that normal and abnormal cells vary in their growth rate as a function of tumour mass. Under physiological circumstances, as in the fetus, initial cell turnover is rapid, but as development progresses and the mass increases, a plateau is reached. A similar pattern is recognised in many tumours. The phenomenon was characterised mathematically by Gompertz in the 18th century and is known as Gompertzian growth. This particular relationship between cell mass and growth rate has important application in chemotherapy, since, in the periods when division is rapid, tumours are vulnerable to cycle-specific drugs and a high percentage kill can be achieved with these agents. In contrast, cycle non-specific chemicals are more effective in tumours having a large volume and a relatively slow turnover.

A second aspect of cell kinetics that bears significantly on treatment is the log cell-kill hypothesis which states that a fixed percentage of cells are destroyed by a given dose of drug. It is noteworthy that this cell-kill follows a negative exponential function, making possible certain predictions about therapy. Thus, it is estimated from studies in humans and in experimental animals that symptomatic acute leukaemia relates to a body burden of 1 kg or about 10^{12} malignant cells. A 2 log cell-kill will convert a marrow which is grossly leukaemic to one which is morphologically normal, although the patient still harbours 10^{10} cells, and relapse is inevitable unless further treatment is given. This observation can be integrated with those referred to above, so that drug scheduling can be arranged to achieve maximum tumour cell-kill while allowing regeneration of the faster-growing normal tissue to occur.

Immunotherapy

Clearly, chemotherapy alone would take a long time to destroy all malignant cells and would also severely damage normal tissue. The fact that very long survival has been achieved when less than optimal chemotherapy is given, implies the presence of some other defence mechanism within the body. To accommodate this observation it has been suggested that once a tumour mass has been reduced from 10^{12} to about 10^{5}, the immune surveillance mechanism may well be able to contain residual tumour and perhaps even destroy these cells. Such a function for the reticulo-endothelial system is exciting, and is now being intensively examined with the object of developing methods of enhancing any natural capacity that exists for the eradication of foreign cells—an approach known as immunotherapy.

Danger of Infections

In addition to harnessing pharmacology and cell kinetic data in planning the treatment of patients with leukaemia, a new dimension in management has been added by the recent development of support programmes suitable for maintaining life during periods of severely compromised marrow function. Two aspects are especially noteworthy. Firstly, individuals receiving intensive chemotherapy are frequently severely immunosuppressed and at a risk from a variety of infections. It has been shown that careful isolation, combined with the judicious use of antibiotics, may tide patients over this hazardous period. Technical advances in the form of life-islands and laminar-flow rooms, are further contributing to the successful outcome of treatment by reducing the bacterial and viral content of the air actually reaching the patients. Unfortunately, the cost and expertise involved in providing these facilities has, of necessity, restricted their availability to medical schools and hospitals willing to accept the responsibility and make a special commitment for their provision.

Secondly, it is well known that severe depression of white cell and platelet levels occurs during the early intensive phase of treatment, and it is logical that these deficiencies should be corrected by the administration of granulocyte-rich suspensions and platelet packs. The routine use of these components, although tedious to prepare, is often lifesaving. The introduction of blood-fraction separators has greatly simplified the problem of meeting these important requirements so that thrombocytopenic bleeding and granulocyte-responsive bacterial infections now pose a lesser problem. An additional benefit accruing from the availability of these machines is the ease with which an individual donor may be re-used, just the particular fraction required being removed and the remainder of the blood returned to the donor. This technique has important therapeutic application when repeated infusions with the possible production of iso-antibodies is considered. Understandably, careful white cell and tissue typing has assumed new importance in patients where repeated but selected components form an integral part of aggressive cytotoxic chemotherapy.

IMPLICATIONS OF THESE ADVANCES

Treatment Centres

There is considerable literature to support the fact that successful induction of complete remission in leukaemic

patients, when followed by maintenance of a disease-free state, is associated with a significantly prolonged survival. Furthermore, the successful achievement of these objectives is directly related to the proper selection and effective administration of initial chemotherapy, two decisions that largely depend upon thorough familiarity with the drugs used and the availability of intensive support facilities for the patient. In view of the obvious benefit and the unavoidable complexity of this modern approach, the place of the 'occasional therapist' in treating haematological malignancy must be seriously questioned. There is increasing support for the suggestion that all patients with leukaemia, Hodgkin's disease, and other haematological malignancies be referred, immediately upon diagnosis and before receiving any therapy, to special units having appropriate facilities and expertise for their detailed evaluation and over-all management. Implicit in such a referral is the clear understanding that close liaison will be maintained between primary physician and staff of the special unit.

Acute Lymphoblastic Leukaemia

In focusing more specifically upon some of the benefits that recent therapeutic changes have effected in the course of leukaemia, special mention should first be made of acute lymphoblastic leukaemia, since it occurs predominantly in childhood. Relatively little difficulty is usually experienced in achieving complete remission with a combination of vincristine and prednisolone, although the antitumour antibiotic, rubidomycin, may be added to the regimen in those cases refractory to these two standard induction drugs.

Two problems continue to plague the therapist dealing with this form of leukaemia. Firstly, a number of these children die from strange and exotic infections, frequently caused by organisms which are normally commensals. The question is not yet resolved, and urgent study is necessary to improve performance in this area, including perhaps a critical analysis of the length of maintenance treatment during the time when the patient is immunosuppressed.

Secondly, it is known that children enjoying good health and having no evidence of leukaemia in the peripheral blood or in the bone marrow, may relapse with overt disease in the central nervous system. It was shown that leukaemic cell rests or sanctuaries developed in this anatomical site and were protected from the effects of systematically administered agents. The problem has been largely overcome by combining 2 400 rads of cranial irradiation with intrathecal methotrexate. The addition of craniospinal treatment has substantially improved the outlook for these children so that longer disease-free periods may be anticipated.

At the present time new avenues are being explored to further prolong survival, and perhaps the most topical of these is the question of immunotherapy. It is known that neoplastic cells can be recognised by lymphocytes of the immune surveillance mechanism and, under normal circumstances, are destroyed. The basis for this recognition is the fact that malignant cells carry on their membranes new tumour-associated antigens, and it was predicted that an immunological approach might therefore exist for the treatment of leukaemia, especially when the number of cells was not too great.

Initially, passive immunotherapy was employed in which serum containing cytotoxic antibodies directed against tumour-specific antigens was administered, but contamination with blocking antibodies has prevented clinical evaluation. Adoptive immunotherapy was next tried: here the thymus-dependent lymphocytes responsible for cell-mediated immunity were used; difficulty has been experienced in control of both engraftment and graft-versus-host reaction. On the other hand, active immunotherapy, in which the patient's own immune reactions are stimulated, have been extensively examined by Mathe and his co-workers in Paris,[1] and these investigators present some evidence for prolonged survival with this therapeutic approach.

Acute Granulocytic Leukaemia

Turning to the question of acute granulocytic leukaemia, the difficulties are most formidable. Induction of remission and maintenance are both less easily achieved and are each associated with a significant degree of bone marrow depression. For this reason a greater finesse and experience is needed in delivery of adequate amounts of the essential therapy. At the present time a combination of daunorubicin and cytosine arabinoside are used for induction of remission. Continuous cytosine arabinoside appears to have advantages over the intermittent administration of this drug, and early results suggest that induction may be more easily achieved in the responsive patient with this regimen.

The question of craniospinal treatment is less clearly defined in acute granulocytic leukaemia, probably because patient survival has been so short. However, a number of individuals have clearly experienced meningeal relapse at a time when blood and marrow are morphologically disease-free; a situation analogous to that encountered in acute lymphoblastic leukaemia. It is therefore logical that as survival periods increase further, patients should be protected from this complication by prophylactic radiotherapy and intrathecal drugs. Our own practice has been to deliver 3 500 rads to the cranium and instil cytosine arabinoside into the cerebrospinal fluid.

The question of immunotherapy has received attention in acute granulocytic leukaemia, largely from the group at St Bartholomew's Hospital in London. Studies reported by Dr Crowther and his colleagues[2] indicate that active non-specific immunotherapy with irradiated lymphocytes and BCG will prolong disease-free survival, and this approach deserves further critical study.

The subvariety of acute granulocytic leukaemia, occurring late in the course of chronic granulocytic leukaemia, is particularly difficult to treat, and it is generally considered that such blastic transformation is refractory to therapy. We have recently had 3 consecutive patients enter remission after continuous intra-

venous cytosine arabinoside and daunorubicin. The numbers are small and statistically meaningless, but they have stimulated us to examine our patients with chronic granulocytic leukaemia more closely in an attempt to identify this complication early and then use the more aggressive chemotherapy.

Chronic Leukaemia

The whole question of chronic leukaemia is a confused one and poses many therapeutic problems. It is likely that part of the confusion results from the less rapid clinical course and the unwillingness of doctors, therefore, to administer potentially harmful therapy, at least in the early stage of these diseases. However, it is important to appreciate that nothing has prolonged median survival in chronic granulocytic or chronic lymphocytic leukaemia, a fact that is vitally important, since it should surely stimulate us to review this policy and perhaps initiate more aggressive but carefully selected treatment. This latter qualification is important since some of these patients are likely to enjoy a variable period of good quality life before treatment becomes necessary, hence the choice of therapy and its timing become matters of fine judgement, in which a familiarity with the natural history of these diseases is essential.

In chronic lymphocytic leukaemia, an asymptomatic or benign form and an aggressive form are recognised on clinical grounds. It is generally held that the former does not require any therapy, but this philosophy should not prevent careful study of the tumour so that information can be obtained about its behaviour and the specific cell type involved. Only in this way will some prediction be possible as to which of these tumours are likely to alter their course and become aggressive; presumably such subtypes would justify earlier treatment.

The approach to the aggressive form of chronic lymphocytic leukaemia is more clear-cut. The development of anaemia, thrombocytopenia, loss of weight and fever constitute indications for treatment. In most of these patients the choice of agents can be made after due consideration of the bone marrow status. Chlorambucil and prednisolone have long been the cornerstones of therapy, although it should be recognised that this regimen may aggravate thrombocytopenia at a time when the marrow is densely infiltrated and residual haematopoietic cells are scanty. In this situation we have been most impressed with the combination of vincristine and bleomycin, given parenterally once a week for a month. Both of these two agents are relatively non-myelotoxic and vincristine may actually promote some degree of thrombocytosis via unknown mechanisms. Once substantial depopulation of the marrow has been achieved, administration of chlorambucil poses less of a problem.

Chronic granulocytic leukaemia is an equally distressing problem in which median survival has also not changed in the last decade, irrespective of the therapy used. The British Medical Research Council trial indicated that busulphan was preferable to radiotherapy, although details of splenic irradiation were not given. Busulphan is a potent drug with substantial toxicity, and for this reason we have undertaken a re-evaluation of this modality of therapy in controlling the white cell count and spleen size in patients with chronic granulocytic leukaemia. In 15 consecutive patients who received local radiotherapy to the spleen, a gratifying response has been documented in every patient. It is, however, too early to know whether retreatment with radiotherapy will be necessary and, if so, how frequently. Even less certain at this stage is the question of whether this approach will challenge the place of busulphan as the first modality of treatment in these patients. Indeed, it is not yet clear whether radiotherapy may not actually shorten the median survival, as was suggested in the report from the British Medical Research Council.

CONCLUSION

From these brief remarks it will be evident that, while the salvage rate in leukaemia is still low, some progress is being made in the treatment of acute leukaemia, mostly in the area of acute lymphoblastic leukaemia in childhood. By way of contrast a certain complacency has prevailed with regard to the chronic leukaemias, possibly related to their slower progression. Since no form of therapy has significantly changed the median survival of patients with either chronic granulocytic or chronic lymphocytic leukaemia, a plea is made that these diseases should receive additional study as a basis for developing new therapeutic regimens and applying these at the appropriate time.

It may be concluded that chemotherapy for leukaemia has advanced, but is yet in its infancy, employing methods which are essentially non-selective. Nevertheless, the rational use of cytotoxic agents has been given some basis by studies of pharmacology and cell kinetics as a means of determining the most appropriate forms of drug scheduling. Significantly, further improvement in patient survival can be attributed to the development of support facilities such as laminar-flow isolation rooms and blood-fraction separators. On the other hand, the modest progress made thus far should not in any way detract from further studies aimed at elucidating aetiology, because only in this way will specificity eventually be conferred upon our therapeutic attempts.

Finally, the rapid changes that have occurred in the treatment of haematological malignancy in the last decade have necessitated the creation of special centres for the total care of these patients. It is emphasised that the therapy of these diseases is complex, and its optimal delivery depends upon special knowledge of the chemotherapeutic regimens coupled with availability of well-developed intensive nursing and support programmes. Under these circumstances, there exists sound reason for referring all such patients to centres offering special care and expertise in their management.

REFERENCES

1. Mathe, G. (1972): Clin. Haemat., **1**, 165.
2. Crowther, D., Powles, R. L., Bateman, C. J. T., Beard, M. E. J., Gauci, C. L., Wrigley, P. F. M., Malpas, J. S., Hamilton Fairley, G. and Scott, R. B. (1973): Brit. Med. J., **1**, 131.