Chemotherapy of the Myeloid Leukaemias

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During the last 15 years, the number of children with acute lymphoblastic leukaemia remaining in long-term remission for more than five years from diagnosis has increased from less than 1 per cent to 30-40 per cent. This has been achieved by better methods of inducing remission, so that 95 per cent of children now achieve full clinical remission, and by significant improvements in maintaining remission so that chemotherapy can be stopped at 2-3 years from diagnosis. In contrast, the treatment of adult patients with acute or chronic myeloid leukaemia has stagnated for much of this period. There is, however, recent evidence that a number of new approaches will lead to significant advances in management and it is therefore an appropriate time to examine the background to these developments.

The myeloid leukaemias are characterised by neoplastic proliferation and abnormal differentiation of the non-lymphoid cell lines in the marrow (Fig. 1). The clinical type of myeloid leukaemia that results is determined by the exact cell line or lines involved, the imbalance between proliferation and differentiation, and the stage of differentiation at which maturation arrest occurs. When the non-lymphoid (myeloid) stem-cell, common to several haematopoietic cell lines, is involved, the myeloid, monocytic, erythroid and/or megakaryocytic series may be affected. In at least some patients, however, the leukaemic process is restricted to the myeloid cell line only[1], the neoplastic change presumably occurring at a stage later than the common stem-cell. The major types of myeloid leukaemia are listed in Table 1.

Chronic Myelocytic Leukaemia (CML)

This myeloproliferative disorder is characterised by neoplastic proliferation of a clone of myeloid cells identified in 92 per cent of patients by the Philadelphia (Ph1) chromosome. This marker chromosome can be found in the myelocytic, erythroid, and megakaryocytic cell lines, all of which are involved in the leukaemic process. For the first three years of clinically recognisable disease the leukaemic cell line shows relatively normal differentiation, despite its excessive proliferation, so that the more mature myeloid cells predominate in blood and marrow. In time there is haematological, chromosomal and cytokinetic evidence of a more severe degree of maturation defect with arrest occurring at the blast cell stage. This metamorphosis from the chronic phase to 'blastic crisis' is accompanied by additional chromosomal defects in about 80 per cent of patients and is characterised in almost all patients by a high degree of refractoriness to chemotherapy. Death usually occurs within six months to give a median survival of 3.0-5.5 years from diagnosis.

Chemotherapy of the Chronic Phase

The use of combination, rather than single-agent, chemotherapy has proved to be a significant advance in the treatment of several leukaemia-lymphomas. This approach, using the combination of busulphan and 6-thioguanine, is the basis of a current Medical Research Council (MRC) trial in CML (Table 2). A similar combination (busulphan plus 6-mercaptopurine and allopurinol) used in a pilot study[2] has shown potential advantages over busulphan alone in the ease with which remission can be achieved and subsequently maintained. The MRC trial will determine whether the combination of the two agents, compared with busulphan alone,
increases survival by extending the period of control until metamorphosis occurs. Since the drug combination incorporates a lower weekly dose of busulphan there may be a reduction in busulphan toxicity. This study may be the forerunner of several trials of combination therapy for palliative control of the chronic phase but more aggressive forms of therapy, aimed at eradication of the leukaemic clone, are also under investigation.

Intensive combination chemotherapy is relatively ineffective once blastic crisis has developed but when given during the chronic phase may significantly reduce the number of Ph1-positive metaphases in the marrow[3, 4]. The reduction achieved by chemotherapy is temporary on the one hand but more intensive chemoradiotherapy used for marrow ablation prior to marrow transplantation has resulted in a more complete and prolonged suppression of up to 31 months[5].

Even though the Ph1-positive clone may not be permanently eliminated by such techniques it is possible that the marrow of a patient in the chronic phase may be rendered Ph1-negative for sufficiently long to allow Ph1-negative stem-cells to be obtained for cryopreservation in liquid nitrogen. Aggressive chemoradiotherapy to eliminate all residual Ph1-positive cells could then be given followed by reconstitution of the patient’s marrow with the autologous, cryopreserved Ph1-negative stem-cells. The success of this approach, however, may require the development of a more simple immunological marker for Ph1-positive cells so that the cryopreserved material, and also the patient’s remaining marrow cells, can be more effectively screened for residual cells of the leukaemic clone.

At present, studies of cryopreservation include the storage of a patient’s own stem-cells obtained by leucopheresis from his blood at the time of diagnosis. These cells are of necessity Ph1-positive but reinfusion of these autologous cells when the patient is beginning to undergo transformation may restore the chronic, rather than the accelerated, phase of the disease once again and usefully extend life[6].

Chemotherapy during Metamorphosis

Transformation of the chronic phase of CML into the acute phase, or blastic crisis, occurs abruptly over a few weeks in about one-third of patients but more commonly a progressive leucocytosis, refractory to alkylating agents, develops over 3-6 months. Hydroxyurea may achieve short-term control in the early stages of metamorphosis when the patient is refractory to busulphan but developing thrombocytopenia often limits further chemotherapy.

It has recently been shown that 20-30 per cent of CML patients develop a lymphoid rather than the more usual myeloid type of blastic crisis. The Ph1-defect in the former cases may have arisen in a pluripotential stem-cell, with lymphoid potential, rather than a myeloid stem-cell (see Fig. 1). It is well worth identifying these patients with lymphoid crisis since 60 per cent of them respond to vincristine and prednisone. However, the lymphoid form of blastic crisis cannot be recognised reliably by conventional Romanowsky staining of the blast cells, but these cells have three identifying markers. They are positive for a DNA polymerase, terminal deoxynucleotidyl transferase (TdT), they show a unique isoenzyme pattern of the lysosomal enzyme hexosaminidase, and they react with a specific antisera to lymphoblasts[7]. These are characteristics of lymphoblasts of the common form of childhood acute lymphoblastic leukaemia. Responsiveness to vincristine and prednisone seems to correlate well with the presence of TdT-positive cells[8].

Acute Non-lymphoid (Myeloid) Leukaemias

Childhood acute lymphoblastic leukaemia is a heterogeneous disease, the T-cell variant, for example, carrying a poorer prognosis and requiring more intensive chemotherapy. Adult acute non-lymphoid leukaemia is now also recognised to be a heterogeneous disease and the following pre-treatment assessment is becoming increasingly important for classification and assessment of prognosis. Both clinical and laboratory factors are involved in this assessment.

Pre-treatment Assessment

Pre-leukaemia or smouldering leukaemia. Certain patients, often the elderly, present with a slowly evolving leukaemia described as 'pre-leukaemia', 'smouldering leukaemia', or 'subacute leukaemia' which does not require immediate treatment. These patients may present with a refractory anaemia or with thrombocytopenia or a monocytosis. There may be evidence of abnormal development of one or more cell lines including dyserythropoiesis and ring sideroblasts (evidence of abnormal mitochondria) in the marrow, or agranular neutrophils (abnormal development of lysosomes) and giant platelets in the blood. There may be a small increase in marrow blast cells (10 per cent) to suggest pre-leukaemia, or there may be a more substantial increase (up to 30 per cent) suggesting an evolving or smouldering leukaemia. These disorders can best be classified into one of two distinct myelodysplastic syndromes: refractory anaemia with an excess of blasts; chronic myelomonocytic leukaemia.

These myelodysplastic cases may continue to follow a
subacute or chronic course for weeks or months. Additional evidence for a leukaemic process can be obtained from chromosome-banding studies or by the demonstration of abnormal colony formation on semi-solid agar. Chemotherapy should be delayed until there is unequivocal evidence of progressive leukaemia (marrow blast cells increasing up to 50 per cent) with deteriorating blood counts. These patients almost invariably have a low marrow reserve and show a poor clinical response to cytotoxic drugs with severe, potentially fatal, marrow hypoplasia.

**Acute promyelocytic leukaemia.** In an established case of acute leukaemia the maturation arrest usually occurs at the blast cell stage of differentiation but occasionally the leukaemic cell line progresses as far as the promyelocyte (see Fig. 1). These promyelocytes contain numerous lysosomal granules that release their constituent hydrodases when the cells are killed during remission induction. The lysosomal enzymes can precipitate disseminated intravascular coagulation but if fatal haemorrhage can be prevented by heparin prophylaxis, and remission obtained, patients with this more differentiated form of acute leukaemia show a better than average survival[9].

**Chromosome studies.** An assessment of the prognosis in adult acute myeloid leukaemia can be made by chromosome-banding studies. When chromosomal abnormalities are found, in about 50 per cent of patients, remission rate and prognosis are poorer, and in a study where the abnormal karyotype was found in every metaphase studied none of the eight patients had a complete remission[10]. If all the remaining marrow stem-cells are leukaemic there may be no normal stem-cells available to repopulate the marrow following chemotherapy and give rise to clinical remission.

**Marrow colony formation.** The remission rate has also been found to correlate with the ability of the marrow to form colonies in vitro on semi-solid agar medium[11]. A remission rate of 76 per cent was obtained in 21 patients who did not form cell colonies on agar compared with only 21 per cent in 15 patients who formed aggregates of more than 20 cells. The study of leukaemic cell colony-forming ability may be of more value in assessing prognosis, by identifying leukaemic cells with proliferative potential, than the earlier cell kinetic studies of mitotic activity.

**Classification of cell type.** When a clear-cut diagnosis of adult acute leukaemia is made the sub-type should then be determined by a combination of Romanowsky staining and cytochemistry. An attempt has recently been made to introduce an internationally-accepted standard classification[12] based on morphology and cytochemistry, but the development of immunocytochemical techniques using antisera to myeloid cells will doubtless allow further sub-classification. Accurate diagnosis of this type is of critical importance to standardise patient entry into multicentric clinical trials and thereby establish which sub-groups are potentially curable and which require additional chemotherapy of above-average intensity or duration.

**Chemotherapy**

**Induction of remission.** The objective of treatment—the prolongation of life of an acceptable quality—usually depends on achieving complete haematological remission. This is defined as reduction of marrow blasts to less than 5 per cent, return of blood counts to normal, and resolution of organomegaly. A substantial increase in remission rate has been achieved in recent years by means of a drug combination comprising a pyrimidine analogue (cytosine arabinoside), a purine analogue (6-thioguanine), and an anthracycline (daunorubicin). This combination, given as a 7-day and 5-day course respectively, has achieved complete remission rates of 79 per cent and 85 per cent in two recent studies[13, 14].

The DAT schedule (daunorubicin, cytosine arabinoside and 6-thioguanine) which has now achieved an 85 per cent complete remission rate in 40 consecutively treated patients in one centre[15] has been incorporated into the current MRC trial of acute myeloid leukaemia (Table 3). It remains to be seen whether such a high remission rate can be achieved in a multicentre study involving district general hospitals with a variable standard of patient support facilities.

**Supportive therapy during remission induction.** A major limiting factor to achieving complete haematological remission is death from infection during the induction period. Unlike childhood lymphoblastic leukaemia, where the lymphoblasts are rapidly destroyed by vincristine and prednisone, thus allowing the normal myeloid cell line to restore an adequate neutrophil count within about two weeks, the cytotoxic therapy required to suppress the blasts of myeloid leukaemia also suppresses the few remaining normal myeloid cells. A prolonged period of neutropenia (4-9 weeks) is common and substantial support facilities are required to prevent death from infection during this high-risk period.

Three major forms of support have been developed: patient isolation in a protected environment with filtered air, oral non-absorbable antibiotics to reduce enteric flora, and granulocyte transfusions. Although the value of these respective techniques, used singly or in combination, is still debated, most centres now use some form of oral prophylaxis (e.g. framycetin, colistin and nystatin (Fracon)[16] or co-trimoxazole[17]) with the patient nursed in a single cubicle. Whenever infection is
suspected, a broad-spectrum antibiotic combination (e.g. gentamicin, cloxacillin and carbenicillin) should be given intravenously and this is likely to be successful in 70 per cent of cases. Neutropenic patients who fail to respond to antibiotics in 48-72 hours should be given daily neutrophil transfusions prepared from an ABO-compatible relative or other donor.

The experience of a specialist team devoted to the care of the neutropenic patient is of paramount importance for the early detection and treatment of life-threatening infection. The early diagnosis of infection is a major problem, since almost all patients become febrile during remission induction, and when infection is suspected in the neutropenic patient with pyrexia it can be confirmed microbiologically in only 43 per cent of cases[18]. In the absence of a rapid screening test for infection it is usually necessary to embark on a 10-day course of intravenous antibiotics whenever the patient becomes pyrexial.

It has recently been shown[19] that the acute-phase reactant C-reactive protein (C-RP) rises to serum levels in excess of 100 mg/litre in leukaemic patients with clinically significant bacterial infection. Patients without infection, but with pyrexia caused by either active disease or a transfusion-reaction or the infusion of a cytotoxic drug, show intermediate values between the upper level of normal (10 mg/litre) and 100 mg/litre. Since C-RP can be measured immunologically by laser nephelometry within one hour, this test satisfies many of the requirements of a rapid screening test for infection in these patients. Daily monitoring, and twice daily estimations when pyrexial, provides a valuable assessment of the significance of a pyrexial episode and may also be of value in assessing the response to antibiotic therapy (Fig. 2). A continuing rise in C-RP level in this patient occurred in parallel with clinical deterioration despite triple antibiotic therapy and granulocyte infusions. The Klebsiella chest and blood infection responded rapidly to amikacin. Readmission was required for an Escherichia coli septicaemia that responded rapidly to tobramycin. This technique requires evaluation in other centres but is of promise in the early detection of the bacterial infection that accounts for more than 90 per cent of infections in these patients. Its value as a screening test in patients with viral or fungal infection needs to be determined.

Consolidation and maintenance therapy. Consolidation of remission by means of additional courses of chemotherapy is based on the reasonable assumption that leukaemic sub-clones with inherent drug resistance remain in the marrow and other tissues. These cells, with the same cytogenetic and sometimes also immunological markers[20] of the original cell line, proliferate to cause haematological relapse. This will occur within 6-12 months if treatment is stopped after remission induction. Periodic courses of chemotherapy during complete remission appear to prolong the remission as compared with no maintenance therapy[21, 22]. Although randomised trials are required to confirm the value and the optimal duration of consolidation/maintenance therapy, it is current practice to administer several post-induction courses of intensive therapy at 1-2 week intervals, to consolidate the remission, followed by maintenance courses at four-week intervals.

There is a lack of clinical trial data to guide the management of the patient who remains in apparent haematological remission beyond the current median duration of 7-10 months. Should chemotherapy be reintensified in an attempt to kill residual leukaemic cells or should it be stopped in the hope of preventing, or subsequently treating, the emergence of drug-resistant clones? The evaluation of remission status based on the morphology of a marrow aspirate is not satisfactory and more sophisticated techniques, such as immunocytochemical markers, to detect residual leukaemic cells are awaited.

Once haematological relapse has occurred, less than 25 per cent of patients achieve a second remission and the median survival is less than six months; thus, the main aim of new forms of treatment must be to extend the duration of the first remission by improved schedules of maintenance chemotherapy.

Prevention of meningeal leukaemia. Central nervous system (CNS) prophylaxis has become standard treatment for childhood lymphoblastic leukaemia. The combination of cranial irradiation and intrathecal methotrexate effectively prevents the CNS from acting as a sanctuary for leukaemic cells that may eventually repopulate the marrow and cause haematological relapse. Meningeal leukaemia is a relatively rare occurrence in adult myeloblastic leukaemia and is usually associated with widespread systemic disease[23]. Routine CNS prophylaxis is probably not yet justified for the
individual patient, although this assumption requires to be confirmed by randomised trial.

Bone Marrow Transplantation

Allogeneic transplantation of bone marrow from an HLA-identical sibling has been performed following chemoradiotherapy in relapsed patients[24, 25]. The trials have been sufficiently encouraging (15-20 per cent of patients with a two year remission) to extend this approach to the patient in first remission when the substantial drug and irradiation toxicity may be better tolerated. However, improved methods of conditioning the recipient prior to transplantation and of management of the post-engraftment graft-versus-host disease are urgently required. Patients who develop graft-versus-host disease show a lower relapse rate than do recipients without this complication[26] and future modifications of post-engraftment chemotherapy must attempt to retain this anti-leukaemic effect while reducing toxicity to the recipient.

An alternative approach, to avoid problems of histocompatibility, has been the transplantation of autologous bone marrow obtained from the patient during haematological remission and cryopreserved until relapse[27]. This is analogous to the autologous transplantation of cryopreserved stem-cells in CML, and its long-term success is again dependent on the development of immunocytotoxic or other methods for recognising residual leukaemic cells in both donor marrow and in the recipient, together with the development of methods for their removal.

Poor-risk Patients

Patients aged more than 60 years with acute non-lymphoid leukaemia have a relatively poor marrow reserve and do not tolerate intensive cytotoxic therapy. There is a high mortality from infection and bleeding during the induction period. The dose of cytotoxics should be reduced by 50 per cent during the first course and support facilities mobilised. Age is clearly a major risk factor during remission induction but, once achieved, the duration of remission is as good as in younger patients.

When it is considered inappropriate, for geographical or other reasons, to transfer a patient for treatment to a specialist centre, conservative out-patient management using an oral cytotoxic schedule (Table 4) may sometimes achieve satisfactory control for a few months. This combination achieved a complete remission rate of 35 per cent in 20 patients of mean age 51 years at this hospital. All of the patients had progressive, acute non-lymphoblastic leukaemia (16 newly diagnosed and four relapsed) and the mean duration of remission was 5.5 months. If there is no initial response, the intensity of each five-day course can be increased by 12 hourly, rather than daily, administration or by adding doxorubicin 50 mg/m² i.v. on day 1. If conservative management is the aim, the patient should be kept out of hospital as much as possible to reduce the risk of infection by a hospital pathogen, but the substantially increased remission rate achieved by specialist centres with adequate support facilities indicates that these facilities should be used whenever possible.

Summary

These advances in chemotherapy and supportive care of the myeloid leukemias offer substantially improved prospects for the future. At present the intensive treatment of acute and chronic myeloid leukaemia requires the resources of a specialist unit and as many patients as possible should now be referred for diagnostic classification and remission induction. Thereafter, courses of maintenance chemotherapy can be supervised jointly by the referring local physician and the specialist centre. This collaborative approach is to the mutual advantage of the patient, his local clinician, and the specialist centre.

This article is based on a paper read at the College Regional Conference in Birmingham in September 1979.

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Book Review

Medicine, Mind and Man. An introduction to psychology for students of medicine and allied professions. John Cohen and John H. Clark. W. H. Freeman and Company, San Francisco, 1979. 432 pages. Price $19.95 cloth, $9.95 paper.

Most people who have designed and taught Behavioural Sciences courses might agree that it is impossible to write an ideal textbook of psychology for medical students. A basic decision has to be made between the curate’s egg of the multi-authored book versus the idiosyncrasies of the single author or pairs. ‘Relevance’ involves other impossible compromises. For example, the understanding of perception, learning and memorising is relevant to patient compliance in general practice or hospital clinic but any lecturer can virtually hear medical students switch themselves off when these topics are mentioned.

John Cohen, a highly respected psychologist, and John Clark, his medical collaborator, have uncompromisingly chosen to write a learned, civilised book to talk and think about, designed to direct interest in students already stimulated to learn. At the risk of appearing cynical this picture may apply to Manchester, with its high academic requirements for medical students, but not to medical students elsewhere. Consequently, for the majority of students, I see this book as a gallant failure.

The layout of the material is orthodox, beginning with basic issues such as motivation, perception, learning, remembering, biological rhythms and consciousness. The remainder of the book is organised under a psychological-aspects rubric: of paediatrics, community medicine, psychiatry, geriatrics, neurology and neuropsychology and medical decision-making.

The selection of sub-topics often seems surprising and arbitrary. For example, for community topics, why select road safety and road accidents, eating and suicide? Perception is discussed in detail in 29 pages, learning, a far more important (‘relevant’) topic for medical students, is dealt with scrappily in 9 pages. Under Developmental Psychology Freud is given 9 lines and a reference, Piaget one page and H. S. Sullivan, a social psychiatrist and psychoanalyst who has never appealed to more than a few aficionados, is given the remainder of the section and much other space in this book.

Care has been given to the selection and description of references at the end of each chapter but my experience is that pre-clinical students do not follow up references. Topics must either be dealt with or left out. The writing style tends to be verbose. If the book goes to a second edition it would benefit from the discipline of pruning 150 pages and including more material.

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