produced by a simple horizontal infection. These viruses can be transmitted vertically (that is, inherited) after they have been incorporated into the host genome, and the infections they cause tend to have very long latent periods. Though leukaemia is rare in childhood, C-type viruses are probably widely distributed; so other infrequent host factors would have to come into play to allow the viruses to escape from being repressed. Such factors probably include heredity,8 exposure to physical or chemical agents (such as radiation1 or cytotoxic drugs2), and temporary alteration of immunity as might occur after infection with a non-oncogenic virus. In lymphoblastic leukaemia, such a factor might mediate its effect through the loss of a functional lymphocyte suppressor cell population, which theoretically might either fail to control aberrant malignant lympho-proliferation or alternatively, lead to increased autoimmune disease.10 Both are frequently observed in New Zealand mice, which lose such suppressor functions for both B and T cell activities spontaneously early in life. Interestingly, the first-degree relatives of children with lymphoblastic leukaemia have an increased incidence of autoimmune disease.11

The question posed in the title of this article cannot be answered. Information is slowly accumulating to indicate that C-type or similar viruses play at least some part in some cases of childhood leukaemia, but their role does not appear simple and may prove similar to an explosive charge which requires an unusual set of circumstances for detonation.


Regular Review

Advances in the management of adult acute myelogenous leukaemia

J A WHITTAKER

For many years now the results of treatment for adults with acute myelogenous leukaemia have made dismal reading, particularly when compared with the advances achieved in the past decade or so in the treatment of childhood acute lymphoblastic leukaemia. Nevertheless, some recent substantial improvements in chemotherapy and supportive care, coupled with impressive preliminary results of bone marrow transplantation, suggest a more encouraging future.

Acute myelogenous leukaemia represents a wide range of diseases lumped together under a heading of convenience, and current attempts to separate these diseases using new classification schemes, chromosomal changes, cell-growth patterns, cytochemical, and other differences may have prognostic significance and are aimed eventually at more individual treatment for the patient with acute myelogenous leukaemia.

The French-American-British classification of acute leukaemias1 has been widely accepted, though like any morphological classification system its reproducibility between independent observers is a major difficulty.2 Acute myelogenous leukaemia is divided into myeloblastic leukaemia without maturation (M1) or with features of maturation (M2), promyelocytic leukaemia characterised by hypergranular promyelocytes with abundant Auer rods (M3), and myelo-monocytic leukaemia (M4). The less frequently seen but more easily recognisable monocytic leukaemia is M5, and erythroleukaemia is M6. Immunological methods are particularly useful in characterising acute lymphoblastic leukaemia, but their application to acute myelogenous leukaemia has not yet proved of practical value, and cytochemical markers give only very approximate confirmation of the French-American-British classification.3

Induction chemotherapy — The first stage of treatment is to induce a complete remission—to reduce blood and bone marrow blast cells to morphologically undetectable levels, to re-establish normal bone marrow function, to return the granulocyte and platelet counts to normal, and, most important, to restore normal health without physical signs or symptoms.

When treatment was given with single-agent chemotherapy with drugs such as prednisone, vincristine, methotrexate, and 6-mercaptopurine (which had been used with some success in acute lymphoblastic leukaemia) the results in acute myelogenous leukaemia were disappointing (table 1). The excellent results of combination chemotherapy for acute lymphoblastic leukaemia in childhood soon led to the use of combinations of two or more agents for the treatment of acute myelogenous leukaemia. Remission rates of 20-30% were achieved, but it was not until the introduction of the pyrimidine analogue
cytosine arabinoside (ara-C) that the modern era of chemotherapy for acute myelogenous leukaemia began. This drug causes competitive inhibition of DNA polymerase, resulting in inhibition of synthesis of DNA. Used alone, ara-C has achieved remission rates of about 25%, but in combination with other drugs the remission rates have been as high as 56%.4 A further major advance was the introduction of the anthracycline antibiotics daunorubicin and doxorubicin. These drugs are chemically and pharmacologically closely similar and act by inhibiting replication of DNA. Complete remission rates of up to 50% have been seen when anthracyclines have been used as single agents5–10 (table I).

Modern treatment logically combines the purine antagonist 6-thioguanine and ara-C, in courses of five to seven days, with daily intravenous daunorubicin or doxorubicin for one to three days (table II). Ara-C is now often given as a continuous intravenous infusion, though its toxicity is probably less when given as a twice-daily injection is used without necessarily jeopardising the high remission rate. By using one or two such courses remission rates of 62-85% have been reported.11–15 These high remission rates can be expected only when an intensive approach is used, and they depend on the availability of excellent supportive care; they should not be attempted outside centres treating large numbers of patients with leukaemia.

**Maintenance chemotherapy**—Experimental evidence suggests that complete remission is achieved at a stage when the total number of tumour cells has been reduced to 108 or fewer. There are no reliable methods of measuring this residual leukaemia in man, and any estimate of the number of leukaemic cells remaining for an individual patient can only be a guess. Most patients subsequently relapse, presumably because their induction treatment did not completely abolish the leukaemia. On the other hand, a few patients have survived for up to 10 years without further treatment. Clearly, however, most patients have some residual leukaemic cells, which will probably begin to multiply as soon as induction chemotherapy stops. In theory, further treatment either with high doses of the drugs used in induction treatment (consolidation chemotherapy) or with lower doses of these or other drugs (maintenance chemotherapy) should improve results. Unfortunately, the place of both these types of treatment is based mainly on anecdotal, uncontrolled observations. The few controlled clinical trials of maintenance treatment reported have been on small numbers of patients and the results have been conflicting.16–18 Furthermore, the possible benefits of maintenance chemotherapy have to be weighed against the potential toxicity. This is seen most clearly with schedules which include the anthracycline antibiotics, because of the definite risk that their cardiotoxicity will rule them out for second or subsequent attempts to induce remission. On balance, some form of maintenance chemotherapy for one to two years seems reasonable, but many centres discontinue the anthracyclines once remission has been reached. Unfortunately, the median remission duration for most patients with acute myelogenous leukaemia has been short and the reported median survivals of between 10 and 21 months remain disappointing. Furthermore, the high remission rates being achieved seem to be associated with a high proportion of unexpectedly short remissions,14,15 which may reflect a more resilient disease process.

**Immunotherapy**—The discovery of tumour-specific antigens in experimental tumours and the regression induced in leukaemic mice treated with irradiated leukaemic blast cells or with BCG19 led to a number of clinical trials of immunotherapy. Data from experiments on animals have shown immunotherapy to be effective only at tumour loads of 105 cells or fewer, so that in human acute myelogenous leukaemia the place of immunotherapy has been in attempts to prolong remission. Several controlled clinical trials have shown a prolongation of survival20–28 using either specific active immunotherapy with leukaemic cells or non-specific immune stimulation with agents such as BCG or the methanol extraction residue of BCG. The improvement is due to a prolongation of survival after relapse, and appears to be associated with an increased occurrence of second and subsequent remissions. Immunotherapy may not, however, prolong remission; the evidence from trials is conflicting (table III). Furthermore, the improvements in survival reported in many clinical trials have been disappointingly short, so that the place of immunotherapy remains somewhat controversial. Nevertheless, as both specific and non-specific immunotherapy are relatively well tolerated and can be given on an outpatient basis their use might reasonably be extended.

**Central nervous system leukaemia**—The prophylactic treatment of meningeal leukaemia is usually with cranial irradiation and either methotrexate or ara-C intrathecally. Treatment of this kind has greatly improved survival in patients with acute lymphoblastic leukaemia; in children leukaemic infiltration has been reduced from 50% to less than 5%16 Nevertheless, the clinical incidence of meningeal infiltration in patients with acute myelogenous leukaemia is probably less than 10% (in Cardiff only two of 241 patients with acute myelogenous leukaemia presenting between 1972 and 1978 went on to develop central nervous system leukaemia), and, because of this low incidence and the relatively short survival of most

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**TABLE I—Induction chemotherapy using single drugs**

<table>
<thead>
<tr>
<th>Complete remission rate</th>
<th>Treatment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>Methotrexate 1-2.5 mg/kg daily</td>
<td>Vogler et al (1967)</td>
</tr>
<tr>
<td>13%</td>
<td>6-Mercaptopurine 2.5 mg/kg daily</td>
<td>Hayhoe (1959)</td>
</tr>
<tr>
<td>15%</td>
<td>Prednisone 40 mg daily</td>
<td>Medical Research Council (1966)</td>
</tr>
<tr>
<td>25%</td>
<td>Ara-C 50-100 mg/m² (1-hr or 12-hr infusion daily)</td>
<td>Ellinson et al (1968)</td>
</tr>
<tr>
<td>42%</td>
<td>Ara-C 4 mg/kg (8-hr infusion daily = 8-14 days)</td>
<td>Armentrout and Burns (1973)</td>
</tr>
<tr>
<td>50%</td>
<td>DNR 60 mg/m² or 1-3</td>
<td>Wernik and Serpick (1972)</td>
</tr>
</tbody>
</table>

Ara-C = Cytosine arabinoside. DNR = Daunorubicin.

**TABLE II—Induction chemotherapy schedules which include daunorubicin (or doxorubicin) and cytosine arabinoside**

<table>
<thead>
<tr>
<th>Complete remission rate</th>
<th>Treatment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>67%</td>
<td>DNR 45 mg/m²/day 1-3</td>
<td>Yates et al (1973)</td>
</tr>
<tr>
<td>70%</td>
<td>Ara-C 100 mg/m²/day 1-7 (iv infusion)</td>
<td>Glocszberg et al (1975)</td>
</tr>
<tr>
<td>72%</td>
<td>DNR 15 mg/kg/day 1-3</td>
<td>Gale and Clince (1977)</td>
</tr>
<tr>
<td>82%</td>
<td>Ara-C 2 mg/kg/day 1-5</td>
<td>Rees et al (1977)</td>
</tr>
<tr>
<td>85%</td>
<td>Ara-C 100 mg/m²/day 1-7</td>
<td>Gale and Clince (1977)</td>
</tr>
<tr>
<td>85%</td>
<td>Ara-C 150 mg/m²/day 1-7</td>
<td>Gale and Clince (1977)</td>
</tr>
<tr>
<td>90%</td>
<td>Ara-C 100 mg/m²/day 1-7</td>
<td>Gale and Clince (1977)</td>
</tr>
<tr>
<td>95%</td>
<td>DNR 50 mg/m²/day 1-3</td>
<td>Gale and Clince (1977)</td>
</tr>
</tbody>
</table>

Ara-C = Cytosine arabinoside. DNR = Daunorubicin. DXR = Doxorubicin. TG = 6-Thioguanine. VCR = Vinristine.
patients with acute myelogenous leukaemia, prophylactic treatment cannot be recommended as a routine. The observation that clinically inapparent central nervous system leukaemia occasionally occurs in patients with acute myelogenous leukaemia lends support, however, to periodic examination of the cerebrospinal fluid.

Bone marrow transplantation—Two relatively recent additions to the treatment of acute myelogenous leukaemia are allogeneic bone marrow transplantation from an HLA-identical sibling and the transplantation of autologous cryopreserved bone marrow collected during remission.

<table>
<thead>
<tr>
<th>Immunotherapy</th>
<th>Prolonged remission</th>
<th>Prolonged survival</th>
<th>Centre</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic cells + BCG</td>
<td>No</td>
<td>Yes</td>
<td>St Bartholomew's/Royal Marsden</td>
<td>Powles et al (1977)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hospitals</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Sweden</td>
<td>Reizenstein et al (1978)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Manchester</td>
<td>Zuhrlie et al (1980)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td>Medical Research Council</td>
<td>Medical Research Council (1978)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>South East Oncology Group (USA)</td>
<td>Vogler and Chan (1974)</td>
</tr>
<tr>
<td>BCG</td>
<td>Yes</td>
<td>Yes</td>
<td>Cardiff</td>
<td>Whitaker et al (1980)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Los Angeles</td>
<td>Gale and Zighelboim (1980)</td>
</tr>
<tr>
<td>C. parvum</td>
<td>No</td>
<td>No</td>
<td>Israel</td>
<td>Weiss and Stupp (1975)</td>
</tr>
<tr>
<td>MER</td>
<td>Yes</td>
<td>Yes</td>
<td>New York</td>
<td>Bekesi et al (1977)</td>
</tr>
<tr>
<td>Neuraminidase treated allogeneic cells</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Did not quite reach statistical significance.

MER = Methanol extraction residue of BCG.

Before treatment by allogeneic transplantation the patient's bone marrow is ablated using (typically) cyclophosphamide for two days followed about three days later by 900-1000 rads of total body irradiation. The infusion of bone marrow from an HLA-compatible donor is then given. Engraftment can be expected within four weeks, and the blood and bone marrow return to normal within three months.

Initially, one of the main problems encountered in patients with acute myelogenous leukaemia treated by bone marrow transplantation was recurrent leukaemia. The more recent reduction in the number of patients given transplants who subsequently relapse in this way may be related to the increased intensity of marrow ablation.28 In a recent series29 from Seattle only one of 19 patients developed recurrent leukaemia, compared with 15 of 54 recurrences in an earlier series reported from the same centre and treated with similar marrow ablation.30 Fifty-two of the 54 patients in the first Seattle series were in relapse at the time of transplantation, and the present low relapse rates31,32 may be related to a smaller leukaemic cell load; most centres now consider that transplantation offers the best hope of long survival in patients in remission at the time of transplantation. Fifteen to 20% disease-free survival has been reported for patients with acute myelogenous leukaemia resistant to cytotoxic drugs33,34 but when patients are given transplants during remission probability curves show survival plateaux at about 65%.31,32 30 32 Among the problems that remain, however, are acute graft-versus-host disease, which contributes to death in 15-20% of patients, and interstitial pneumonitis, sometimes associated with cytomegalovirus infection. Criteria for the diagnosis of interstitial pneumonitis vary and an incidence as high as 36% has been reported,35 but it causes relatively few deaths directly.36

Allogeneic marrow transplantation is likely to be available only to the 20% or so of patients with leukaemia who have an HLA-matched sibling willing to act as a donor, but the impression initial results suggest that in such cases transplantation should be given serious consideration soon after a first remission has been induced—a policy which can be justified on economic grounds.37

Autologous bone marrow transplantation has recently been tried in small numbers of patients.38,39 Bone marrow is collected from patients in their first remission and cryopreserved. At the time of relapse, patients receive marrow ablation similar to that used for allogeneic bone marrow transplantation followed by infusion of their own stored reconstituted bone marrow. The results are preliminary, but long disease-free survival has been reported for occasional patients, and the technique may be useful for those patients for whom an HLA-compatible donor is not available.

Supportive care—When they first present most patients with acute myelogenous leukaemia are prone to bleeding by virtue of platelet counts below 50 x 10^9/l and to infection from their granulocyte counts if fewer than 1 x 10^9/l. These counts are soon reduced further by chemotherapy, and most of the recent improvements in survival have been possible only because of advances in the management of bleeding and infection.

Skin petechiae and minor episodes of bleeding in the fundus, mouth, and gut become common when platelet counts fall below 20 x 10^9/l, but these symptoms can usually be controlled by intravenous infusion of platelets from random donors. These platelets are prepared from fresh blood as platelet-rich plasma, or a platelet concentrate. Platelet concentrate is better than platelet-rich plasma because of the danger of circulatory overload with large volumes of plasma. The platelets from four to six units of blood are usually given once daily until bleeding stops. With the use of platelets taken from random (HLA-mismatched) donors, up to half the patients treated develop platelet antibodies,40,41 so that the prophylactic use of platelet transfusion cannot be recommended. Immunisations can be overcome if HLA-matched platelets are used,42 but such a programme depends on the availability of tissue-typing facilities and, if it is to be practicable, requires facilities for collecting large numbers of platelets from a single donor before plateletpheresis and their cryopreservation. Where typing facilities are not freely available an alternative is to collect platelets for immediate use from the patient's siblings or other close relatives on the assumption that they will be partly HLA-matched.

Acute promyelocytic leukaemia is particularly associated with bleeding due to disseminated intravascular coagulation so much so that prophylactic low-dose heparin has been used successfully.43 The use of platelet transfusion has reduced deaths from haemorrhage, but this has been accompanied by an increase
in the number of deaths associated with infection, partly related to the severe neutropenia caused by increasingly intensive chemotherapy. The impaired immunity and the neutropenia associated with the leukaemia are other important predisposing factors. Infections of the mouth and the upper respiratory tract and pneumonia are particularly common, while infections of the skin and urinary tract and perianal abscesses are frequent. These and infection through un-identified portals of entry are associated with a high incidence of systemic sepsis, of which more than half is due to Gram-negative organisms, especially Escherichia coli, Klebsiella sp, and pseudomonas. Febrile neutropenic patients should be investigated with cultures from clinically suspect sites, which must include blood, urine, throat, and nose. All patients should then receive immediate broad-spectrum antibiotic cover, often nowadays a combination of an aminoglycoside and a semisynthetic penicillin. If the patient’s condition does not improve and fever does not respond, consideration should be given to early granulocyte transfusion. Results from controlled clinical trials of granulocyte transfusion show that they are effective in reducing morbidity and mortality; their use has been most impressive in Gram-negative septicaemia.

Granulocytes are usually collected by leucapheresis from the patient’s ABO-compatible relatives, and at least $1 \times 10^{10}$ are given fresh on four or more consecutive days. Granulocytes from donors with chronic myeloid leukaemia are undoubtedly effective and easy to collect from patients, most of whom have very high neutrophil counts at presentation. Nevertheless, there is a definite but small risk of engraftment of chronic myeloid leukaemia in the immunodepressed host, and their use is losing favour. Fungal infection is an increasing problem; it should be suspected in patients who do not respond to broad-spectrum antibiotics and granulocyte transfusion, and also in the large number of patients from whom a bacterial organism is not isolated.

Minor infections of the mouth, often with Candida albicans, are frequent during the induction period and may be very debilitating. Their incidence can be reduced by the use of a prophylactic antifungal agent, while general mouth hygiene may be improved by the regular use of an antiseptic mouthwash.

The sterilisation of the gut with oral non-absorbable antibiotics and the use of protected environments with isolation tents or laminar air flow are two further treatments that will remain controversial until convincing data are available from controlled trials.

Long survival and the possibility of cure—During the past 15 years the proportion of patients with acute myelogenous leukaemia reaching remission has steadily increased. Most of these patients relapse within 12 months and nearly all within two years. Nevertheless, occasional patients continue to survive in complete remission, and statistical predictions suggest a progressive decrease in the risk of relapse the longer a patient remains in remission.

A few patients survive in remission for more than three years, a point at which treatment is often stopped. We have recently studied 82 such patients and found that eight subsequently relapsed, including three patients who had been in remission for more than five years and off all treatment for more than three years. Though occasional patients may survive for very long periods, some seem to do so by suppression of their leukaemia, possibly with leukaemic stem cells entering a non-dividing phase. Whether other very long-term survivors are cured is a matter of speculation.

Further intensive chemotherapy after about 12 months’ remission has been advocated to kill leukaemia cells which continue to divide slowly or remain in a resting phase. Unfortunately, controlled comparisons of this late intensification chemotherapy have not been made, but the increase in survival is striking when compared with historical controls treated at the same centre and suggests that further study might be profitable.

**Prognostic factors**—Unlike acute lymphoblastic leukaemia, the factors which can give an accurate prognosis for acute myelogenous leukaemia patients at presentation have yet to be identified clearly. Acute myelogenous leukaemia which results from the transformation of other diseases, such as chronic myeloid leukaemia, polycythaemia vera, aplastic anaemia, or preleukaemia, appears to have a poor prognosis, but this represents only a fraction of all cases. The age of the patients was previously thought to be a major prognostic factor, but a recent trial of intensive induction treatment has not supported this belief.

Chromosomal abnormalities occur in about half the patients with acute myelogenous leukaemia, and these are most often trisomies of chromosomes 8, 9, or 21, and monosomy of chromosome 7, in addition to a translocation between chromosomes 8 and 21. An indistinct chromosome pattern is associated with a low rate of complete remission, and karyotypic abnormalities are associated both with a poor response to induction treatment and with poor survival, but these findings do not apply to patients with acute myelomonocytic leukaemia.

Recent observations suggest that it may be possible to predict a patient’s response to treatment by examining the growth pattern in vitro of leukaemic cells in agar. Growth of normal blood or bone marrow produces colonies or small aggregations of cells and clusters (large cell aggregations). Samples from patients with acute myelogenous leukaemia produce either poor growth or an increased number of colonies and clusters, and patients whose blood or bone marrow shows an excessive growth pattern with a predominance of clusters respond poorly to treatment.

In summary, therefore, the prospects for adults with acute myelogenous leukaemia have changed substantially in recent years. Remission induction rates of 70% or more are being reported, and the preliminary results of marrow transplantation suggest that a cure is possible for those patients who reach remission and have an HLA-matched sibling donor. Nevertheless, for the large number of patients who are not suitable for marrow transplantation the duration of survival remains disappointingly short. Other methods of treatment, including late intensification chemotherapy and autotransplantation of bone marrow collected during remission, are receiving close examination with these patients particularly in mind.

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20