Prospects for cure in leukaemia

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SUMMARY Patients with acute leukaemia have normal or near normal numbers of haemopoietic stem cells in their marrow at diagnosis. Remission is achieved when the administration of cytotoxic drugs eradicates the bulk of the leukaemic population while sparing normal haemopoiesis. The mechanism by which chemotherapy seems to act in this selective manner is essentially unknown. Nevertheless, remission rates of 80–95% can be achieved in children and in 50–80% of adults with acute leukaemia. Attempts to cure patients in remission may entail either "continuing curative chemotherapy" or "supralethal" doses of chemoradiotherapy followed by autologous or allogeneic bone marrow transplantation. The relative merits of these different methods remain highly controversial but chemotherapy is usually the preferred method of continuing treatment for children with acute lymphoblastic leukaemia in first remission; and allogeneic transplantation is recommended for younger adults with acute myeloid leukaemia who have suitable HLA-identical sibling donors. The role of autografting is still experimental. Patients with chronic myeloid leukaemia can achieve long term remission and probably cure following allogeneic bone marrow transplantation but the resultant risks of mortality are still appreciable. Chronic lymphocytic leukaemia currently remains incurable.

In the space of a mere 20 years the prospects for worthwhile treatment and cure for many patients with leukaemia have improved very considerably. The diagnosis of acute leukaemia in the 1950s and early 1960s was associated with justifiable pessimism; remissions were obtained with some regularity in children with acute lymphoblastic leukaemia (ALL) but rarely in adults with acute myeloid leukaemia (AML). Those remissions that were obtained lasted several months and second remissions were rare.

The results of treating leukaemia in 1987 prove that progress has been made. Perhaps 95% of children with "standard" risk ALL will achieve complete remission and 70–80% of these can expect long term disease free survival. For younger adults with AML the remission rate is nearly 80% and 25% of these patients who receive further chemotherapy in remission may be cured. Allogeneic bone marrow transplantation was introduced in the 1970s and has become standard treatment for selected patients with acute leukaemia. The "actuarial cure" rates are unquestionably high, but disease free survival curves invariably reflect the high risk of death in remission from complications associated with transplantation, notably graft versus host disease and pneumonitis. Other patients with acute leukaemia have been treated by autografting in first or second remission. It is still too early to evaluate the results of this approach but preliminary results are sufficiently encouraging to justify more widespread use of this technique.

Though the newcomer to the field may be familiar with the various advances outlined above, he or she may be less familiar with the details of the academic polemics in which some of the leading therapists have become involved. There have always been and continue to be caring clinicians who oppose the introduction of new schedules of cytotoxic drugs that seem to be very aggressive, or the application of new modalities, such as bone marrow transplantation, for diseases that at least in the short term seem to be innocuous. These conservative opinions are important, for they restrain the overenthusiastic chemotherapist by reminding him that ultimately many of his efforts must inexorably fail. This said, it is only by realising that today’s results, better though they are than those of yesteryear, are still inadequate, and it is only by constantly planning modifications in treatment schedules that we can hope to progress.

Principles of treatment

THE PHYSIOLOGICAL BASIS OF REMISSION
The typical patient with acute leukaemia has a bone...
marrow densely packed with blast cells and large numbers of blast cells in the circulation. If treatment is effective the same patient can have a bone marrow that appears entirely normal even to the experienced observer within three to four weeks. Even the most technologically advanced methods may be unable to detect the small numbers of residual leukaemic cells that are presumably present in the marrow. Though the term “complete remission in acute leukaemia” is formally defined as “less than 5% of blast cells in a marrow of normal cellularity in conjunction with a normal blood count,” for operational purposes the recognition of a smaller population of cells that are undoubtedly malignant casts doubt on the quality of the remission and may have therapeutic implications.

How, then, is it possible to destroy the bulk of leukaemic cells and restore apparently normal haemopoiesis in so short a time? It is conventional to suppose that the chemotherapeutic agents used in the treatment of acute leukaemia selectively damage or destroy leukaemic cells while sparing their normal counterparts. There is, in fact, no biochemical evidence to support this assumption, and the selective action of cytotoxic drugs could be based entirely on differences in cell cycle status and differences in repopulating potential between normal and leukaemic stem cells. In other words the beneficial effects of cytotoxic drugs in acute leukaemia could be due entirely to the fact that in standard doses they kill the bulk of proliferating leukaemic cells while sparing the normal stem cells that are apparently all or almost all inactive (Go). Leukaemic cells are probably also responsible for this suppression of normal haemopoiesis, and the abrupt removal of this leukaemic inhibitory influence probably facilitates rapid activation and differentiation of normal stem cells. If this is so, the ability to achieve complete remission depends not so much on the selective killing of leukaemic cells as on the capacity of normal stem cells, released from inhibition, to repopulate the marrow more rapidly than their leukaemic counterparts. If some leukaemic stem cells are also in Go at the time of treatment and are thereby also spared the destructive effects of cytotoxic drugs, a basis is provided for the relapse that is almost inevitable if no further treatment is given.

In some cases haemopoiesis in remission, as in relapse, still seems to be clonal.1 There are two possible explanations. It may be that the multistep leukaemic process entails a sequence of steps, each one of which represents clonal expansion from a single progenitor endowed with a proliferative advantage over the other cells in the cohort. According to this model, acute leukaemia develops when the progeny of a single leukaemic cell manifests a major block in differentiation; an earlier progenitor, abnormal but still with the capacity for differentiation, is suppressed. In remission, this earlier but abnormal progenitor is activated and re-establishes pseudo-normal haemopoiesis (Brito-Babapulle F, Catovsky D, Galton DAG, unpublished observations). The alternative explanation relies on the concept that haemopoiesis is maintained normally by successive recruitment of single or small numbers of stem cells. By this premise, if normal haemopoiesis is re-established within a few weeks of starting treatment, it would not be surprising if all haemopoietic cells originated from a single (clonal) normal stem cell.2,3 An extension of this theory means that the concept of an inhibitory effect exerted by leukaemic cells on normal haemopoiesis can be dispensed with, and accounts in part for the highly variable duration of complete remission. If normal haemopoiesis is maintained by proliferation of normal stem cells recruited in sequence overt leukaemia would develop when the next stem cell in line happened to be one that has been “immortalised” by a previously acquired genetic change. Relapse after remission occurs in a similar way.

MAINTENANCE TREATMENT FOR ERADICATION OF RESIDUAL LEUKAEMIC CELLS

Experimental studies performed by Skipper and Schabel in the 1960s showed that the injection of a single cell derived from a murine leukaemia cell line into a syngeneic experimental animal could induce leukaemia and subsequent death.4,5 Although the murine L1210 leukaemia cell line and the disease it produces in mice have little in common with acute leukaemias in man, this model system provided some support for the design of therapeutic regimens aimed at curing a patient whose leukaemia was already in remission. It was argued that merely to continue administration of further courses of the same cytotoxic drug (or drugs) that had secured the remission would eventually lead to the destruction of the last residual leukaemic cell and consequently to cure. Thus attempts to cure patients with AML in the 1970s relied mainly on this approach—continued administration of cytosine arabinoside with daunorubicin or 6-thioguanine at three or four week intervals for periods of up to one year.6 In general the proportion of patients cured by this type of “maintenance chemotherapy” was low, perhaps 5–10%.

The use of maintenance chemotherapy seems to have been more successful in curing patients with ALL. This may relate in part to the wider spectrum of drugs that are active against ALL cells. During the late 1960s and 1970s it became conventional to treat newly diagnosed patients with ALL with vincristine and steroids. Once remission was achieved treatment was continued with one or other schedule incorporating long term administration of 6-mercaptopurine,
Prospects for cure in leukaemia

methotrexate, and cyclophosphamide, together with periodic reinduction with vincristine and corticosteroids. If maintenance of this type was continued for two years or more, a cure rate approaching 50% could be anticipated.78 More recent experience has shown that a higher incidence of cure can be achieved mainly by changing the dose or scheduling of these drugs.9

There are, in fact, several lines of argument that cast doubt on, but by no means disprove, the suggestion that cure of leukaemia depends on physical eradication of all leukaemic cells. First, as mentioned above, it is likely that a minority—at least of the leukaemic stem cells—will be no more sensitive to cytotoxic drugs than normal stem cells. If so, their eradication by doses or schedules of cytotoxic drugs that spared the bulk of normal stem cells would be improbable. Secondly, there could be immunological effects: small numbers of leukaemic cells could, in some circumstances, be held in check and prevented from dividing for long periods of time; this hypothesis would fit well with the occasional relapses that occur many years after apparent cure. Thirdly, the apparent importance of the graft versus leukaemia (GVL) effect after allogeneic bone marrow transplantation also strongly supports the idea that the chemotherapy alone cannot eliminate leukaemia in most cases but rather that other factors, at present poorly defined, must play a part. Equally relevant may be the observation that some patients subjected to allogeneic bone marrow transplantation as treatment for CML may have occasional Philadelphia (Ph) positive (leukaemic) metaphases identified in their marrow months and even years after the transplant procedure without progressing to clinical relapse.1011 There are only two reasonable explanations for this observation: either the Ph positive cells are progeny of a cell line that no longer has full replicative capacity, or small numbers of residual Ph positive stem cells persist but their proliferation is restrained by some ill defined immunological or other factor.

OTHER APPROACHES TO TREATMENT AFTER REMISSION

The recognition that low dose maintenance chemotherapy for patients with AML was relatively unsuccessful12 led to the design and implementation of more intensive chemotherapy schedules. In some cases treatment was continued with one or more courses of the same schedule of cytotoxic drugs that induced remission, an approach sometimes called consolidation. An alternative method was to treat the patient with one or more combinations of non-crossreacting drugs either soon after remission induction—so called early intensification—or after one or more years of further chemotherapy—so called late intensification. All these techniques may be grouped under the general heading of continuing curative chemotherapy.13

The idea that increasing the dose of cytotoxic drugs administered in a single course might be the best method of curing acute leukaemia is inherent in the use of bone marrow transplantation, be it autologous or allogeneic stem cells, to rescue the patient from the prolonged and perhaps irreversible marrow failure that would otherwise follow. The use of transplant techniques also permits the administration of relatively high doses of radiotherapy to the whole body. The maximum possible dose, however, is limited by the susceptibility of the lung to damage by doses of radiation above 10 Gy, administered as a single dose or above 14 to 15 Gy administered in fractions over three to seven days.

Thus for the patient with acute leukaemia who achieves complete remission, there are three choices for continuing curative treatment: chemotherapy, autografting, or allografting. No one of these approaches is obviously optimal, and the best option for an individual patient will depend, inter alia, on the type of leukaemia and associated prognostic features, the availability of an HLA-matched donor, and, not least, the expertise and preferred practice at the centre of treatment.

Chemotherapy for remission induction

In the 1960s patients with AML used to be treated with corticosteroids, 6-mercaptopurine, or not at all. Remissions were obtained in 10–20% of patients but these were usually short lived, and for most patients the value of any but supportive treatment was not clear cut. The introduction of additional drugs with major antileukaemic activity, notably cytosine arabinoside and the anthracyclines, resulted in remission rates in the 1970s that ranged between 40 and 60% (table 1). In the past few years specialist centres in many countries have gained experience with the use of cytosine arabinoside administered by intravenous infusion for seven to 10 days in conjunction with three doses of an anthracycline (usually daunorubicin but sometimes doxorubicin). Some centres prefer to give

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**Table 1** Drugs that may be useful for treatment of AML

<table>
<thead>
<tr>
<th>Cytosine arabinoside</th>
<th>Mitoxantrone</th>
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<tr>
<td>5-azacytidine</td>
<td>Amscarine</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>Etoposide (VP 16–213)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Harringtonine</td>
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<tr>
<td>Epirubicin</td>
<td></td>
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<tr>
<td>Idarubicin</td>
<td></td>
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<tr>
<td>6-thioguanine</td>
<td></td>
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<tr>
<td>6-mercaptopurine</td>
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an additional third drug, usually 6-thioguanine. Results of such studies show that remission can be obtained in 70–80% of patients with AML under the age of 60; older patients tolerate such treatment much less well.

There is no evidence that adding additional antileukaemic agents, such as etoposide, increases the incidence of remission.

At this hospital the first course of chemotherapy for patients newly diagnosed with AML is currently cytosine arabinoside and 6-thioguanine administered daily for 10 days and daunorubicin given on days 1, 3, and 5.\textsuperscript{15} About 60% of patients under the age of 60 achieve complete remission after a single course of this combination. A further 20% of patients will enter remission after treatment with a second course of drugs. The failure rate is about 20% and includes patients in four main categories: (i) those who die of infection or haemorrhage before the effects of the cytotoxic drugs can be fully evaluated; (ii) those whose leukaemia seems to be partially (or totally) resistant to the full course of cytotoxic drugs; (iii) those in whom leukaemic cells are apparently eradicated but who fail to recover normal haemopoiesis and thus remain in a hypoplastic phase; and (iv) those in whom the eradication of leukaemic cells seems temporarily to be complete but who rapidly regenerate a blast cell population. It is important to distinguish these different pattern types of treatment failure because the causes and remedies are presumably different. For patients in category (i) the results might be better if supportive care could be improved. For patients in category (ii) the doses of cytotoxic drugs could have been inadequate; alternative or additional drugs might have yielded better results. For those in category (iii) there are two possible explanations: it could be that all normal stem cells were destroyed as a result of the evolution of the disease before diagnosis, thereby rendering restoration of haemopoiesis impossible; or that the chemotherapy was not sufficiently selective and indiscriminately killed leukaemic and normal cells. Patients in category (iv) have to some extent the combined problems of patients in categories (i) and (iii).

Patients with ALL may be treated initially with vincristine, corticosteroids, anthracyclines and possibly L-asparaginase (table 2).\textsuperscript{16} Remission is induced so regularly that one might believe that there was little room for improvement. In practice the remission rate is 90–95% in children with standard risk features, but rather lower, perhaps 80–90%, in children with poor prognosis features and in adults. This means that 10–20% of selected patients with ALL never achieve complete remission. In these cases failure is usually due to early death or relative resistance of the leukaemic population, and death in prolonged aplasia is rare. It is difficult, however, to see how a standardised remission induction could be intensified without jeopardising survival in the majority of patients for whom the more intensive treatment would be excessive. Future studies will probably attempt to define more precisely the small category of patients for whom more intensive remission induction is required.

In some senses the outstanding problems of remission induction are best exemplified by CML. At diagnosis the finding of the Ph chromosome in every or almost every marrow metaphase suggests that most haemopoiesis is leukaemic, but occasional patients can be restored to normal (Ph negative) haemopoiesis by appropriate chemotherapy. This suggests that all patients at diagnosis have substantial numbers of normal stem cells in their marrow which have been induced to a state of inactivity (prolonged Go) by the leukaemic proliferation, a situation analogous to that thought to exist in the acute leukaemias.

The experimental results of the Vancouver group, which showed the presence of appreciable numbers of normal progenitor cells when the marrow from newly diagnosed patients was cultured in vitro, substantiate this idea.\textsuperscript{17,18} The analogy with acute leukaemia breaks down, however, because none of the available cytotoxic drugs is sufficiently selective in its ability to damage leukaemic cells while sparing normal stem cells. It is likely, however, that methods will be developed for induction of complete remission in CML as is now the case in acute leukaemia.

### Continuing curative chemotherapy

#### CONSOLIDATION AND EARLY INTENSIFICATION IN AML

A considerable number of studies have now been reported in which patients who achieve complete remission after induction treatment have received further courses either with the same drugs as were used for induction or with other combinations. The present regimen used at this hospital incorporates both approaches.\textsuperscript{15} Thus patients in remission after one course receive a second course of cytosine arabinoside, 6-thioguanine (both for eight days), together with daunorubicin (on three alternate days). They subsequently receive up to four additional courses of cytotoxic drugs, together comprising in various schedules the use of amsacrine, 5-azacytidine, etoposide, cytosine arabinoside in high doses.

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**Table 2 Drugs that may be useful for treatment of ALL**

<table>
<thead>
<tr>
<th>Vincristine</th>
<th>Prednisolone</th>
<th>Methotrexate</th>
<th>Cyclophosphamide</th>
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<tbody>
<tr>
<td>L-asparaginase</td>
<td>Daunorubicin</td>
<td>Mitoxantrone</td>
<td></td>
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<tr>
<td>Doxorubicin</td>
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6-thioguanine, and daunorubicin (fig 1). Though logical, such treatment schedules do not produce long term disease free survival results that are demonstrably superior to what can be achieved with less intensive treatment.

**Late intensification**

A few studies have been designed in which patients in remission for periods between six months and more than one year have been treated with further courses of chemotherapy sufficiently intensive to produce short periods of profound neutropenia. In one study performed by the Medical Research Council more than 250 patients were randomised to receive two additional courses of consolidation chemotherapy or six cycles of intensification chemotherapy with drugs to which they had not previously been exposed.19 The median duration of remission and the proportion of patients surviving free of leukaemia at four years were better for the patients receiving late intensification. In other studies the results are less clear cut and statistical evaluation sometimes difficult.20 21

**Autografting in remission**

In the late 1970s several investigators attempted to treat patients with acute leukaemia in relapse by high dose chemotherapy or chemoradiotherapy followed by autografting with bone marrow cells collected soon after first remission had been achieved.22 In general the results of these studies were discouraging. In some cases it proved impossible to eradicate leukaemia in relapse; in some cases second remission was not achieved; and in most cases those remissions that were achieved were of short duration. Nevertheless, these studies proved the feasibility in principle of using autologous bone marrow cells to rescue patients subjected to supralethal chemoradiotherapy. They led to the idea that cure of acute leukaemia might be achieved by administration of high doses of chemoradiotherapy followed by autografting in first remission.

**The choice of chemoradiotherapy**

There is little consensus regarding the optimal anti-leukaemic regimen before the autograft procedure. One of the original studies on patients with acute leukaemia in relapse entailed the use of the experimental alkylating agent piperazinedione together with total body irradiation.22 Other studies used only combinations of cytotoxic drugs, such as TACC (6-thioguanine, cytosine arabinoside, cyclophosphamide, and CCNU).23 Most of the present protocols incorporate the use of total body irradiation,24 but there is undoubtedly room for improving the cytotoxic drug component of the combined modality schedules.

**The need for purging**

A major theoretical objection to the use of autologous bone marrow transplantation in the attempt to cure acute leukaemia relates to the possibility that leukaemic stem cells might be present in the bone marrow harvested in remission and that these cells might reinude leukaemia after its otherwise successful eradication. This, however, is far from certain; the number of leukaemic stem cells (as distinct from recognisable blast cells) capable of inducing acute leukaemia, which are present in the bone marrow in remission, could be very small, and high numbers might not necessarily be collected in a standard bone marrow harvest. Moreover, cure of leukaemia might not require total eradication of such stem cells (as mentioned above); a major reduction in their number, which could be achieved by an autograft procedure, might permit the reactivation of immune or other mechanisms that could indefinitely prevent their further proliferation. It is difficult to design studies to address this question at the clinical level. The alternative is to assume that viable leukaemia stem cells are inevitably present in the harvested marrow and to take measures designed to eliminate them.

All available methods designed to decontaminate or purge harvested marrow of residual leukaemic stem cells depend on the assumption that such cells can be differentiated from normal haemopoietic stem cells on the basis of some definable characteristic (table 3). Human haemopoietic stem cells, however, have not yet been characterised, and the degree to which committed progenitor cells (CFU-GEMM, CFU-GM, and BFU-E) resemble them is speculative. Furthermore, there are assays which permit the growth in culture of leukaemic blast cells, but the proximity of the in vitro leukaemic clone forming cell to the in vivo leukaemic stem cell is undefined. This much conceded, several approaches have been used to purge harvested marrow of leukaemic cells. These include incubating the marrow in vitro with cytotoxic drugs, such as 4-hydroperoxycyclophosphamide or mafosfamide,25 26 or complement fixing monoclonal antibodies (such as J5),27 28 or the use of differential centrifugation29 or sensitivity to heat.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Possible approaches for purging remission bone marrow before autologous bone marrow transplantation</th>
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<tbody>
<tr>
<td><strong>Physical:</strong></td>
<td>Density centrifugation</td>
</tr>
<tr>
<td>     </td>
<td>Sensitivity to heat</td>
</tr>
<tr>
<td><strong>Pharmacological:</strong></td>
<td>4-hydroperoxycyclophosphamide</td>
</tr>
<tr>
<td>   </td>
<td>Mafosfamide (Asta-Z-7557)</td>
</tr>
<tr>
<td>   </td>
<td>Deoxycoformycin</td>
</tr>
<tr>
<td><strong>Immunological:</strong></td>
<td>Monoclonal antibodies with</td>
</tr>
<tr>
<td>   </td>
<td>Complement cytotoxicity</td>
</tr>
<tr>
<td>   </td>
<td>Magnetic bead separation</td>
</tr>
<tr>
<td>   </td>
<td>Toxins</td>
</tr>
<tr>
<td><strong>Kinetic:</strong></td>
<td>Short term culture in vitro</td>
</tr>
<tr>
<td>   </td>
<td>(Repeat autografting)</td>
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</table>
The principal results of these clinical studies show that a chosen method for in vitro manipulation spares normal stem cells and permits reconstitution of autologous haemopoiesis. If relapse occurs it is difficult to discern whether it originated from leukaemic cells in the body or leukaemic cells in the harvested marrow. The distinction could perhaps be based on the finding of cytogenetic changes related to radiation in the cells at relapse after autografting. Eventually it will be essential to perform clinical studies in which the relapse rates in patients autografted with purged and unpurged marrow cells can be compared.

There are other possible approaches designed to cure patients that obviate the need for purging harvested marrow. Clinicians at the University College Hospital in London have reasoned that the chance of cure could be greatly increased if patients were subjected to a second autograft using bone marrow stem cells collected after the first procedure. This approach might act as a form of "in vivo purging" by which short term regeneration of marrow after the first procedure would favour the growth of normal haemopoietic cells and the number of leukaemic cells harvested on the second occasion would thus be minimal. Alternatively, blood stem cells present in the circulation could be used for the autograft procedure at appropriate times after remission was achieved. It seems reasonable to assume, though no proof exists, that leukaemic stem cells might circulate less than their normal counterparts. Several recent clinical studies document the ability of stem cells derived from blood to reconstitute haemopoiesis after suprathel chemoradiotherapy. It is too early to say whether their use will offer benefits comparable with the use of unpurged autologous marrow cells. A third method of purging entails the use of autologous marrow that has been maintained for some days in liquid culture. The Manchester group published preliminary data indicating that marrow cells obtained from patients with AML in remission can restore normal haemopoiesis, when transfused after administration of cyclophosphamide and total body irradiation. Presumably most of the leukaemic cells died during the in vitro incubation period.

RESULTS OF AUTOGRAFTING FOR ACUTE LEUKAEMIA

The results of treating patients with acute leukaemia in remission are still preliminary (table 4). In general no specialist centre has experience extending over a period greater than three years, and the survival plateaux are still therefore "unstable". Moreover, some of the results of the single centre series are open to the criticism that a proportion of patients autografted in remission had already been in remission for some months or even years before the autograft procedure was undertaken. Such selection will, of course, bias results in favour of autografting. There is undoubtedly a need for prospective multicentre studies in which the criteria for patient eligibility, the choice of antileukaemic treatment, and the assessment of results are all standardised. Such studies are now in progress.

**Allografting**

The techniques of bone marrow transplantation were developed in the 1960s and 1970s using animal models. The discovery of the HLA system in man—broadly analogous to the H2 histocompatibility system in mice, underpinned the first successful human transplants. It is now clear that transplantation using HLA-identical siblings of a patient are often successful, although graft versus host disease still occurs with an incidence of 40–70% and can be lethal in some cases. The other major cause of morbidity and mortality after transplantation is interstitial pneumonitis, sometimes associated with pulmonary infection with cytomegalovirus, but at other times without obvious cause. In the latter cases the pneumonitis is termed idiopathic, though the pulmonary reaction is probably a response to the combined toxic effects of alkylating agents and irradiation.

The first systematic efforts to treat acute leukaemia by allogeneic bone marrow transplantation were carried out in the 1970s. The patients were in relapse and their disease was, to varying extents, resistant to available antileukaemic drugs. Nevertheless, the administration of high doses of cyclophosphamide followed by total body irradiation and transfusion of allogeneic bone marrow cells resulted in long-term survival for about 12% of patients in the series reported from Seattle. These relatively encouraging results led to speculation that an allograft performed in remission might be expected to cure a higher proportion of patients. Since 1976 more than 5000
Prospects for cure in leukaemia

Table 5 Results of allogeneic bone marrow transplantation for leukaemia

<table>
<thead>
<tr>
<th>Disease and status</th>
<th>Actuarial probabilities at four years (%)</th>
<th>Leukaemia free survival</th>
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<tbody>
<tr>
<td></td>
<td>Survival</td>
<td>Relapse</td>
</tr>
<tr>
<td><strong>AML</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First complete remission</td>
<td>40-50</td>
<td>20-25</td>
</tr>
<tr>
<td>Later complete remission</td>
<td>22-35</td>
<td>40-60</td>
</tr>
<tr>
<td>Relapse</td>
<td>20</td>
<td>50-70</td>
</tr>
<tr>
<td><strong>ALL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First complete remission</td>
<td>40-50</td>
<td>25-35</td>
</tr>
<tr>
<td>Later complete remission</td>
<td>30-40</td>
<td>40-60</td>
</tr>
<tr>
<td>Relapse</td>
<td>20</td>
<td>60-70</td>
</tr>
<tr>
<td><strong>CML</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic phase</td>
<td>50-55</td>
<td>5-15</td>
</tr>
<tr>
<td>Accelerated phase</td>
<td>20-35</td>
<td>35-45</td>
</tr>
<tr>
<td>Blastic transformation</td>
<td>10-15</td>
<td>40-50</td>
</tr>
</tbody>
</table>

Patients with AML or ALL have been treated by allogeneic bone marrow transplantation, and some general conclusions can be drawn (table 5).

**ACUTE MYELOID LEUKAEMIA**

For patients with AML in first remission, the probability of disease free survival at four years is 40–50%.\(^{37}\) Though some relapses have occurred later than four years, these seem to be rare and most of the patients alive at four years can expect to be cured. For patients transplanted in second or subsequent remission, the chance of cure is about 30%.\(^{37,38}\) Some preliminary evidence suggests that patients transplanted in early relapse after a period of remission may fare almost as well as those transplanted in first remission.\(^{39}\) If this were confirmed it would provide a partial solution for the difficult question of whether to transplant the younger patient with AML in remission who has an HLA-identical sibling to act as donor. It would mean that the patient could be treated initially with the best available chemotherapy schedule as consolidation. He might have a 20–25% chance of being cured. If, however, he were to relapse, he could be transplanted with perhaps a 40% chance of cure. This would mean that the overall probability of cure for a patient newly in remission would be about 25% + \((40 \times 75%)\) = 55%. The main objections to this approach might be the difficulty in recognising the patient in early relapse and the inconvenience (and in some cases impossibility) of submitting a patient to what amounts in practice to an “emergency transplant”.

**ACUTE LYMPHOBLASTIC LEUKAEMIA**

For patients with ALL the questions of whether or when to offer treatment by bone marrow transplantation are equally complex. The results of intensive chemotherapy with neuroprophylaxis for the younger child with standard risk features are so good that it is difficult to see how bone marrow transplantation in first remission could surpass them. Transplantation would have the advantage that the total duration of treatment would be much curtailed.

![Graph](http://jcp.bmj.com/10.1136/jcp.40.9.985 on 1 September 1987. Downloaded from http://jcp.bmj.com/)
but this would be offset to some extent by the emotional impact of the procedure and the necessity of spending six or more weeks in the hospital, which a child receiving continuing consolidation chemotherapy could avoid. For the child with poor prognosis features, however, such as major organomegaly, high leucocyte count, T cell or B cell features, or the presence in leukaemic cells of a Ph chromosome, transplantation in first remission is a reasonable option. The same applies to all adult patients with ALL. The overall experience worldwide suggests that patients transplanted in first remission have an actuarial probability of relapse of about 30% and a probability of being alive and free of disease at four years of 40–50%.40–41 The corresponding figures for patients transplanted in second or later remissions are 55% and 30%, respectively.40–41

CHRONIC MYELOID LEUKAEMIA
There is no evidence that any form of conventional chemotherapy cures, or indeed, considerably prolongs life for patients with chronic myeloid leukaemia. In the 1970s the Seattle group reported the results of attempts to treat CML by allogeneic bone marrow transplant. These were largely unsuccessful. More recently the group in Seattle and others pioneered attempts to treat patients with CML by bone marrow transplantation in chronic phase.42–43 After about eight years of experience with this approach one can say with virtual certainty that though the mortality associated with transplantation is still substantial (fig 2), most patients who survive beyond three years can be regarded as cured. The probability of relapse is about 10% (table 5) and the probability of disease free survival at four years 45–55%.44 For patients transplanted in the accelerated or blastic phases of CML, the corresponding figures are about 40 and 20%, respectively.

On the basis of these figures, it can be confidently said that any patient with CML under the age of 45 or 50 who has an HLA-identical sibling should be offered the chance of treatment by bone marrow transplantation. The transplant should undoubtedly be performed while the patient remains in the chronic phase of CML, but the optimal timing of the procedure within the chronic phase can not yet be specified. Data from Seattle suggest that the duration of chronic phase is directly related to the probability of survival, a finding that would favour transplant as soon as is convenient after diagnosis.11 In the analysis performed by the International Bone Marrow Transplant Registry, however, no such correlation was identified (Goldman JM, Gale RP, Bortin MM, et al, unpublished observations). One approach is to use a patient’s prognostic factors at diagnosis to assess the probability of transformation within a given time period and to balance this against the estimated risk of mortality associated with the operation. For some patients, this approach leads to the conclusion that a delay of one or two years after diagnosis before transplantation might be a reasonable compromise.

MODE OF ACTION
An important question is how bone marrow transplantation actually results in cure of leukaemia.44 The simplest explanation is to assume that the chosen combination of cytotoxic drugs with and without irradiation of the whole body eradicates all leukaemic clone forming or stem cells and that the patient can be rescued by transfusion of donor stem cells. Data derived from many studies on animals, however, suggest that T lymphocytes in the graft may suppress the proliferation of host leukaemic cells. Moreover, evidence has accumulated to indicate that the probability of relapse in patients transplanted for acute leukaemia is lower if they subsequently sustain graft versus host disease.45–46 Conversely, the probability of relapse seems to be higher in patients with acute leukaemia transplanted with marrow from identical twins, a situation in which the donor T lymphocytes presumably have an immunological potential indistinguishable from that of the patient.44 Finally, it has
been recognised very recently that the probability of relapse in patients transplanted for CML, and probably also in patients with acute leukaemia, is significantly higher if they receive marrow cells depleted of T cells in vitro for prevention of graft versus host disease in man (Goldman JM, Gale RP, Bortin MM, et al, unpublished observations). These separate lines of evidence all suggest that the cure of leukaemia results both from the effects of the chemoradiotherapy and from a GVL effect mediated by T lymphocytes originating from the donor. An important challenge for the future will be to ascertain whether GVL in man is mediated by the same population of lymphocytes that are responsible for the generation of graft versus host disease.

**Prospects for the future**

There has been a steady increase in the incidence of complete remission for younger patients with acute leukaemia. Although several newer cytotoxic drugs have become available in the past few years, it seems unlikely that their use, instead of or in addition to existing schedules, will have any important impact on the incidence of complete remission. Furthermore, the problem for the older patient, who tolerates chemotherapy less well and who less predictably recovers normal haemopoiesis, will not be solved by escalating the intensity of chemotherapy. Of considerable interest, however, is the recent report from Manchester of the use of autologous bone marrow cells incubated in short term liquid culture to rescue patients after high dose chemoradiotherapy for AML in relapse. This culture system seems to permit selective survival of residual normal haemopoietic stem cells at the expense of leukaemic cells. If these fascinating results can be replicated in a larger number of patients the approach might be applied more widely to induce initial remission in patients whose disease is deemed unlikely to respond to cytotoxic drugs administered in standard doses.

For continuing curative chemotherapy the repeated use of cytotoxic drug combinations similar to those that induced complete remission does not seem to increase the probability of cure to any great extent. It seems more likely that schedules incorporating some of the newer drugs, such as amsacrine, mitoxantrone, or bisantrene, or existing drugs used in new ways, such as etoposide or high dose cytosine arabinoside, will contribute to cure. Conversely, it seems unlikely that minor chemical modifications of existing drugs, of which the various anthracycline analogues are examples, will make any worthwhile impact on the cure rate.

There is undoubtedly scope for designing new schedules of chemotherapy to precede autografting for acute leukaemia. Cyclophosphamide is not particularly active in AML and etoposide or cytosine arabinoside could prove more effective in eradicating leukaemic cells. The questions of whether or how to give total body irradiation before autografting are unresolved. Likewise the need for purging is not yet established; if it is, then many possible techniques are available. Indeed, the number of variables in the autograft procedure permit almost limitless combinations, but large multicentre clinical studies must nevertheless be designed to address and hopefully answer some of these questions.

The actuarial cure rates following allogeneic bone marrow transplantation for acute leukaemia and CML using unmanipulated donor marrow cells are undoubtedly higher than can be achieved by any other approach. Though graft versus host disease can largely be prevented by T cell depletion, preliminary evidence suggests that the relapse rate may be increased, especially in CML, and that survival for patients with CML and possibly for those with acute leukaemia is not correspondingly increased. Interstitial pneumonitis remains a major problem. Thus there is no immediate prospect of any worthwhile reduction in the incidence of mortality associated with transplantation nor consequently of any increase in the probability of disease free survival either in acute leukaemia or CML. It is more likely that progress in this area over the next five years will relate to more successful use of matched unrelated donors or one antigen mismatched family member donors. Furthermore, it may prove possible to transplant patients relatively safely in the fifth and even sixth decade of life. These developments will mean that transplantation may be more widely available but it will remain an extremely hazardous procedure for some time to come.

**References**


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