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New Trends in the Treatment of Adult Acute Myeloid Leukaemia

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During the past 20 years, the EORTC Leukaemia Cooperative Group has performed four large randomised clinical trials in patients with acute myeloblastic leukaemia (AML) who were under the age of 60 years. Results of these studies support the use of intensive remission induction schedules. Although consolidation therapy with high-dose or standard-dose chemotherapy did not improve long-term survival substantially, marked improvements were noted in patients receiving autologous or allogeneic bone marrow transplantation (BMT), especially in those aged 45 years or younger. Preliminary results of study AML-10, in which patients are receiving stem cell transplantation after a very intensive induction course and a single high-dose consolidation regimen, are especially encouraging. Improvements in the results of remission induction can be achieved by optimising the use of existing antileukaemic agents, decreasing the number of fatal complications, administering new chemotherapeutic or immunostimulatory agents, and making use of early allogeneic stem cell transplantation. Improved consolidation may be achieved by repeated administration of high-dose chemotherapy or by autologous BMT or transplantation with autologous peripheral blood stem cells. Prevention of relapse following BMT may be enhanced by the administration of immunomodulatory agents, such as interleukin-2 or linomide. Better definition of prognostic groups in AML may make possible the recruitment of more homogeneous patient populations for clinical trials and facilitate the development of individualised treatment regimens that will be associated with increased long-term survival. To encourage advanced research in leukaemia, the EORTC and the Italian Leukaemia Group (GIMEMA) are now establishing a network of molecular and cytogenetic laboratories throughout Western Europe. © **1997 Published by Elsevier Science Ltd.**

Key words: acute myeloblastic leukaemia, allogeneic bone marrow transplantation, autologous bone marrow transplantation, bone marrow transplantation, consolidation therapy, cytogenetics, immunomodulation, induction therapy, leukaemia, stem cell therapy
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INTRODUCTION

ACUTE LEUKAEMIAS are a heterogeneous group of malignant diseases of haematopoietic precursor cells that originate in the bone marrow. Acute leukaemia has been subclassified on the basis of morphological, immunological, and cytogenetic differences. The distinction between acute lymphoblastic (ALL) and acute myeloblastic (AML) leukaemia has led to the development of different treatment strategies utilising different antileukaemic agents.

Using the French–American–British (FAB) classification, AML and ALL are divided into a number of subtypes, each with certain cytological characteristics. Other subtypes of acute leukaemia are based on specific cell membrane marker profiles and/or chromosomal and molecular abnormalities that have distinct clinical presentations and prognoses. These prognostic characteristics may be treatment dependent.

During the last 20 years, the poor prognosis for patients with some of the most aggressive leukaemias, such as T-cell ALL and mature B-cell ALL, has improved due to the application of certain drug combinations and adjusted treatment strategies. At the same time, the relatively favourable prospects of patients with other subtypes of acute leukaemia, such as common ALL, has not changed impressively. As a result, there has been a reversal of prognoses between the two groups [1].

Also during this period, severe, often fatal haemorrhagic complications of acute promyelocytic leukaemia have virtually disappeared due to the addition of all-*trans*-retinoic acid, a vitamin A derivative, to the induction regimen. Use of this compound has transformed the prognosis of patients with this subtype of AML from a dismal one to one that is among the most favourable in terms of long-term survival [2].

Table 1. Summary of four randomised EORTC–LCG/GIMEMA studies in AML [3–5]

Study number	Duration	Age range (years)	Total no. of patients
AML-5	1978–1982	15–60	285
AML-6	1982–1986	15–60	452
AML-8A	1987–1993	15–45	941
AML-8B	1987–1993	46–60	282
AML-10	1993–present	15–60	1136*

*As of October 1996.

Fortunately, due to increasing intensification of treatment regimens, including the use of bone marrow transplantation (BMT), and to improvements in supportive care, the outlook for patients with other types of acute leukaemia has also become considerably better during the last two decades.

This paper will review the most recent treatment strategies for adult AML patients under the age of 60 years that have been developed by the European Organization for Research and Treatment of Cancer (EORTC) Leukaemia Cooperative Group (LCG) in cooperation with the Italian Leukaemia Group (GIMEMA). It will also highlight some of the new preclinical and clinical approaches that may help in designing new studies that may lead to further improvement of the prognosis of AML patients.

RECENT EORTC-LCG EXPERIENCE

The management of a patient with acute leukaemia consists of a remission induction phase and a post-remission phase. The post-remission phase consists of a consolidation regimen that may or may not be followed by some form of maintenance treatment. During the last 20 years, the EORTC–LCG has performed four large, consecutive, prospective, randomised studies in patients with AML who are under the age of 60 years (Table 1) [3–5].

AML-5 Trial

From 1978 until 1982, 285 patients between the ages of 15 and 60 years entered the AML-5 trial (Figure 1) [3]. The protocol consisted of a remission induction schedule of moderate intensity. Twenty-seven percent of the patients achieved a complete remission in one course; 60% of patients had achieved complete remission after one to three courses. After an identical course of consolidation therapy, patients with complete remission were randomised to four arms consisting either of one or two types of low-dose maintenance chemotherapy for a maximum of 2 years, or to one of these schedules combined with androgen therapy or with immunotherapy using irradiated blasts treated with neuraminidase. For each of these schedules, promising results had been suggested in non-randomised, single-institution studies. In AML-5, however, we could not detect a difference with respect to disease-free survival or survival among the four groups of patients (Table 2).

AML-6 Trial

Between 1982 and 1986, 452 patients between 15 and 60 years of age entered the AML-6 trial (Figure 2) [4]. Patients were given one or two intensive induction courses followed by an almost identical consolidation course. Randomisation of patients who achieved a complete remission was intended to determine whether intensification of the consolidation phase by repeated administration of alternating courses of short-term, high-dose chemotherapy would increase disease-free survival and survival compared with repeated administration of conventional-dose consolidation courses. This approach was prompted by a report by Weinstein and colleagues, in which it was claimed that this particular intensive consolidation schedule improved the prognosis not only of children, but also of adults with AML [6].

The results of AML-6 were disappointing. We were unable to show that this type of short-term, high-dose chemotherapy was associated with superior disease-free survival and survival. Since a more recent randomised study from the

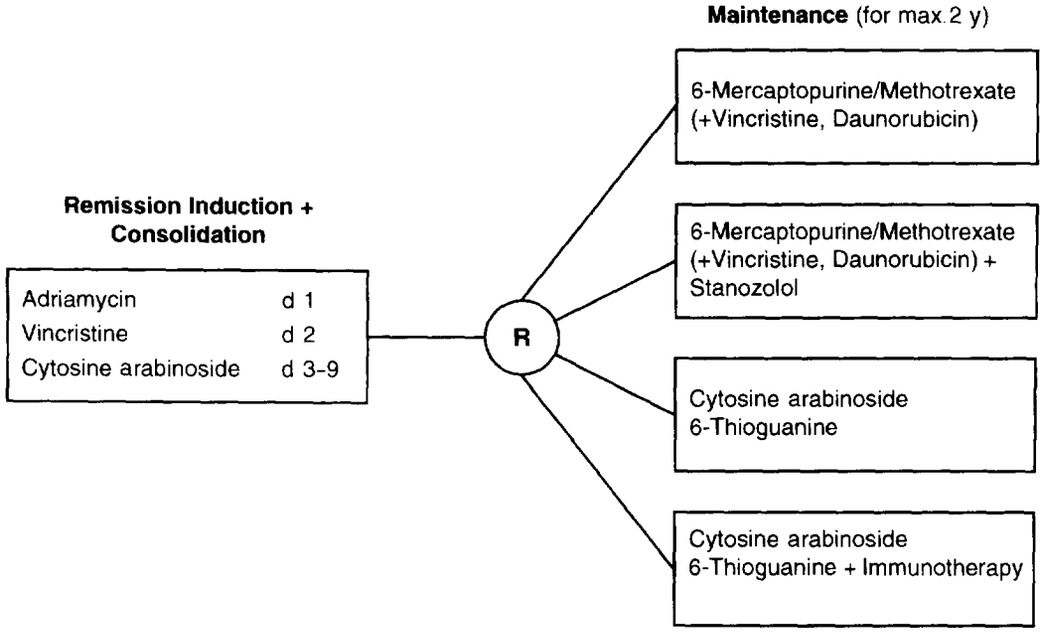

Figure 1. EORTC–LCG AML-5 clinical trial, 1978–1982 [3]. R = randomisation.

Table 2. Results of treatment in four successive EORTC–LCG/GIMEMA studies including patients with AML between the ages of 15 and 60 years [3–5]

Variable	AML-5 ($n = 285$)	AML-6 ($n = 452$)	AML-8 ($n = 1516$)	AML-10 ($n = 591$)
CR (%)	60	69	64	72
CR (%) after first course	27	51	52	66
DFS (%) at 5 years	22	22	32	NA
Median survival from CR (weeks)	95	96	129	NA
5-year survival (%) from CR	29	29	42	NA
Median survival from diagnosis (weeks)	53	66	66	NA
5-year survival (%) from diagnosis	18	21	30	NA

CR, complete remission; DFS, disease-free survival; NA, not available.

CALGB (Cancer and Leukaemia Group B) demonstrated a beneficial effect of high-dose cytosine arabinoside (Ara-C) consolidation courses in patients under the age of 60 years [7], it is possible that our failure was caused by the use of high-dose courses with a shorter duration and lower frequency than were used in the more recent study.

AML-8 Trials

By the mid-1980s, the question of the value of BMT compared with consolidation courses of intensive chemotherapy had become more relevant. In 1986, therefore, the EORTC–LCG, in cooperation with GIMEMA, began the AML-8A trial (Figure 3) for patients under the age of 46 years and the AML-8B trial (Figure 4) for patients between the ages of 46 and 60 years [5].

All patients received an intensive remission induction schedule that was repeated if a partial remission was obtained on day 28. In the AML-8A trial, this was followed by a high-dose consolidation course. Patients under the age of 46 years who happened to have an HLA-compatible (human lymphocyte antigen) family-donor underwent allogeneic BMT (allo-BMT) after total body irradiation or a chemotherapy-based conditioning regimen. All other patients were randomised to receive either a second intensive consolidation course or to undergo autologous BMT (auto-BMT) after a similar conditioning regimen. In AML-8B, patients between 46 and 60 years of age were randomised to one of two intensive consolidation courses as in AML-8A; patients then received a standard-dose consolidation course followed by a maintenance regimen.

From 1986 to 1993, 941 eligible and evaluable patients entered AML-8A; 916 of these patients were between the target ages of 15 and 45 years. The complete remission rate was 66% after one or two induction courses. For 168 patients in complete remission who had an appropriate family donor, allo-BMT was planned, but transplantation was actually performed in only 145 patients. Two hundred and fifty-four patients were randomised to receive either auto-BMT or a second intensive consolidation course. Only about 50% of all patients who achieved complete remission actually received treatment according to the full protocol. Reasons for this low rate included early relapse, previous severe toxicity, and patients' refusal to continue treatment or to undergo randomisation.

Results were calculated on the basis of the intent-to-treat principle. Five per cent of the patients given the second consolidation course died in first remission, compared with 10%

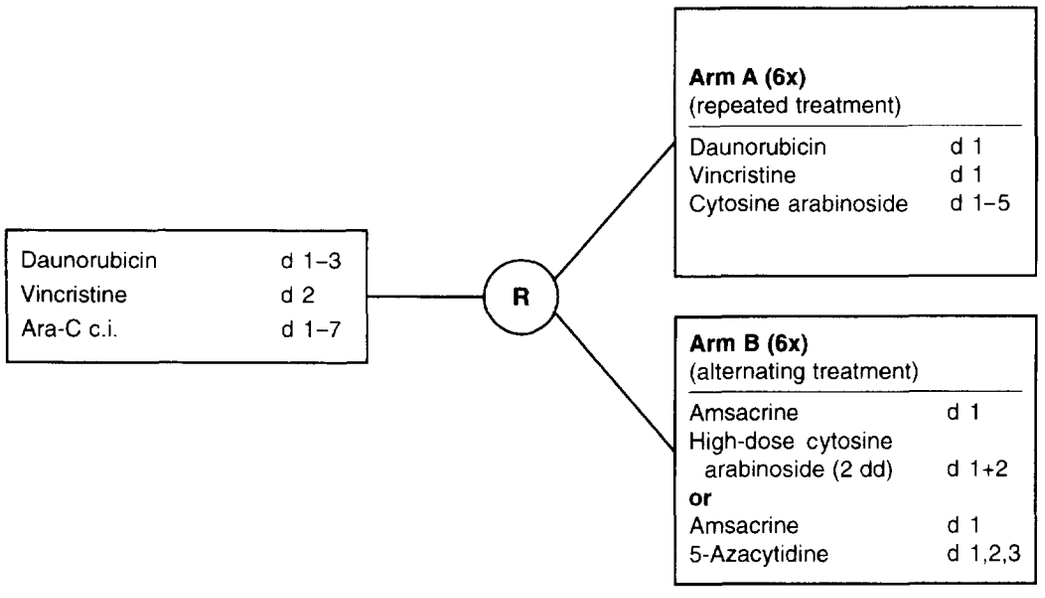

Figure 2. EORTC–LCG AML-6 clinical trial, 1982–1986 [4]. R = randomisation.

of patients randomised to receive an auto-BMT and 20% of those with an identical family donor. Relapse rates for the same groups, however, were 67, 46, and 29%, respectively. Disease-free survival at 4 years was significantly higher for patients in the transplantation groups (30, 48, and 55%, respectively). Overall survival from the moment of complete remission was 48% at 5 years. There were no significant differences between the three treatment arms because a substantial number of patients who received a second consolidation course and then relapsed underwent BMT during second remission. Prognostic variables for disease-free survival were initial white blood cell count, FAB subtypes, cytogenetic abnormalities, and time needed to reach a complete remission.

During the same period, 531 patients between the ages of 46 and 60 years were enrolled in the AML-8B study. A total of 282 patients were randomised; the complete remission (CR) rate after one to two courses was 61%. In the intensive consolidation arm, a lower relapse rate compensated for the higher treatment-related mortality that occurred. At the time this paper was written, no significant difference between the two randomised arms had been demonstrated for disease-free survival and overall survival.

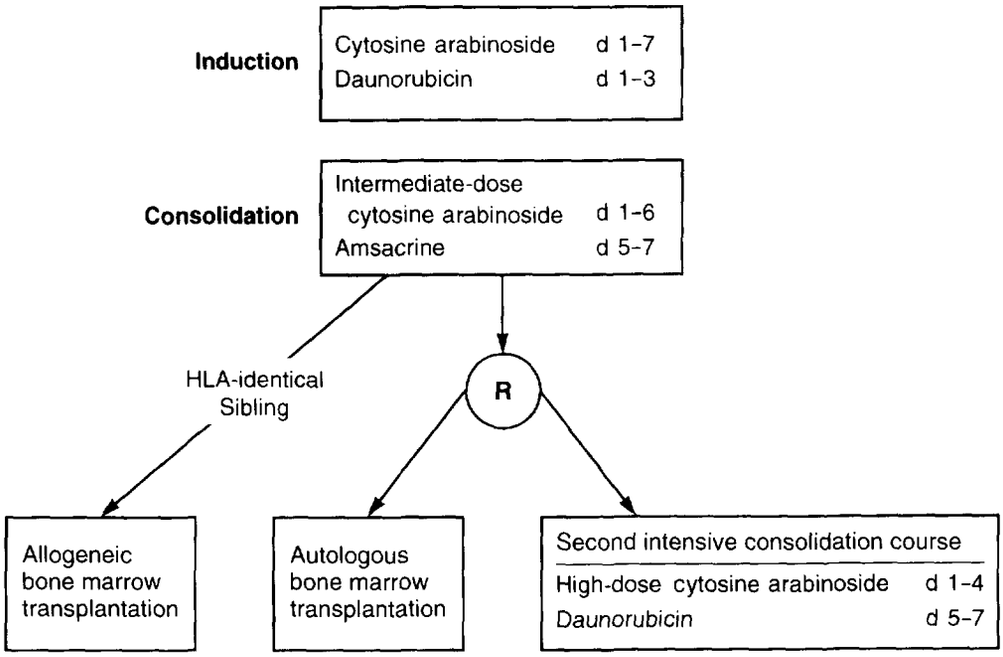

Figure 3. EORTC-LCG/GIMEMA AML-8A clinical trial, 1986–1993 [5]. R = randomisation.

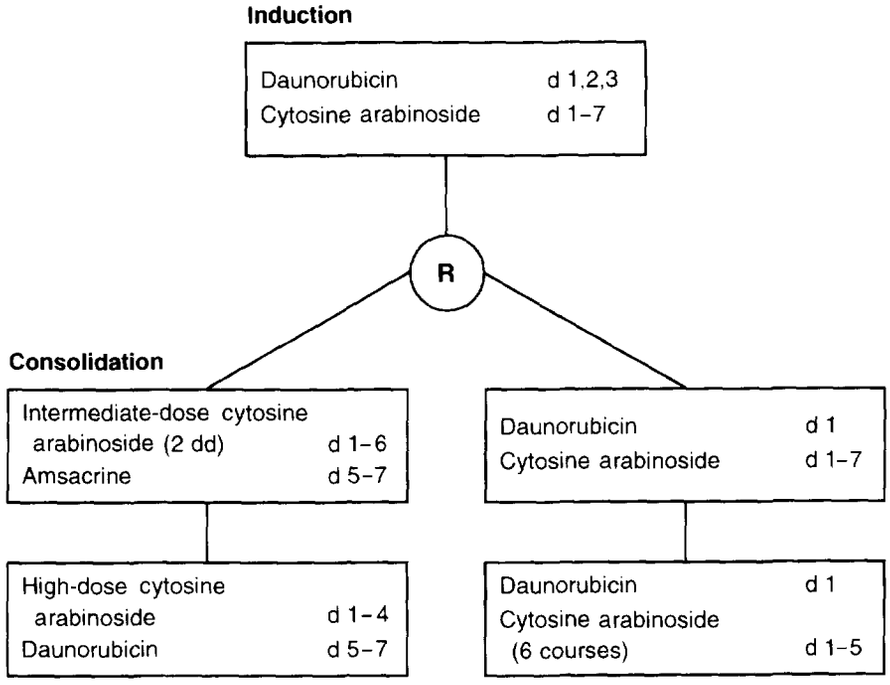

Figure 4. EORTC-LCG/GIMEMA AML-8B clinical trial, 1986–1993 [5]. R = randomisation.

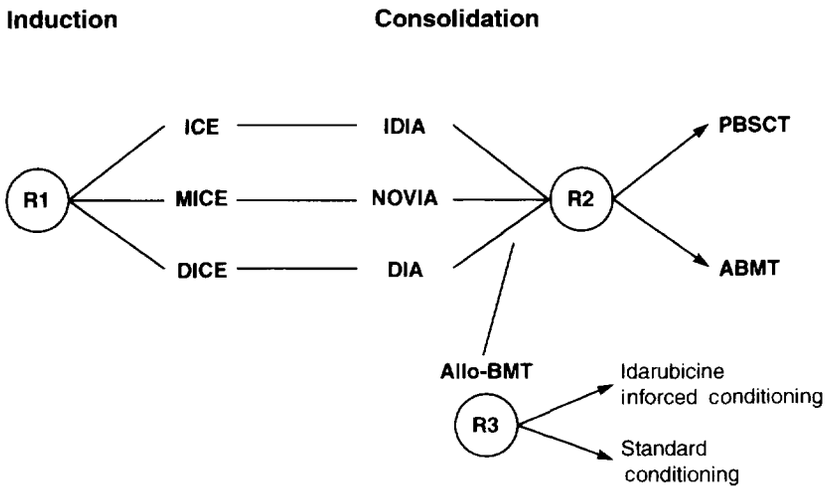

Figure 5. EORTC–LCG/GIMEMA AML-10 clinical trial, 1993-present. ICE, idarubicin, cytosine arabinoside, etoposide; MICE, mitoxantrone, cytosine arabinoside, etoposide; DICE, daunorubicin, cytosine arabinoside, etoposide; IDIA, idarubicin + intermediate-dose cytosine arabinoside; NOVIA, mitoxantrone + intermediate-dose cytosine arainoside; DIA, daunorubicin + intermediate-dose cytosine arabinoside; PBSCT, peripheral blood stem cell transplantation; ABMT, autologous bone marrow transplantation; Allo-BMT, allogeneic bone marrow transplantation; R, randomisation.

A pilot randomised study was conducted to assess the use of granulocyte-macrophage-colony stimulating factor during and/or after the remission induction course of patients included in the last period of the AML-8A and -8B [8]. No benefit in terms of remission rate or disease-free survival was found in patients receiving the growth factor.

AML-10 Trial

AML-10 was designed by EORTC–LCG in cooperation with GIMEMA, partly in response to the conclusions of AML-8A and -8B (Figure 5). Its aims were: (1) to increase the complete remission rate after one or two intensive remission induction courses containing different anthracycline analogues; (2) to randomise all patients under the age of 61 years who were without a family-donor to either auto-BMT or autoperipheral blood stem cell transplantation; and (3) to decrease the relapse rate after allo-BMT by randomising standard conditioning and idarubicin-intensified conditioning, thus increasing disease-free survival and overall survival. This trial began in November 1993 and is now in progress. During its first two and a half years, approximately 1000 patients had enrolled in the study.

The complete remission rate after a single course of the induction schedule is currently 66%, compared with 52% in the AML-8A and -8B trials. The overall complete remission rate after one or two courses is 72% for AML-10 patients and 64% for AML-8A and -8B patients. Results of the first randomisation to different anthracyclines will be available within 1 year. Since the second randomisation to peripheral blood stem cell transplantation versus BMT started only recently, those results will not be available for several years.

Conclusions from the cooperative trials

A number of conclusions can be drawn on the basis of the results of these four clinical trials (Table 3, Figure 6). From the AML-5, we can conclude that treatment with a moderately intensive remission induction schedule finally resulted in an acceptable complete remission rate, although a considerable proportion of patients required two or three courses to reach complete remission [3]. Furthermore, the four different maintenance schedules used after the consolidation course led to similar results.

Using a more intensified induction schedule, the remission rate after a single induction course increased, as observed in

Table 3. Results of four successive EORTC–LCG/GIMEMA randomised clinical trials in patients with AML by age group

	AML-5 ($n=285$)		AML-6 ($n=452$)		AML-8 ($n=1516$)		AML-10 ($n=591$)	
Variable	15–45 years ($n=165$)	46–60 years ($n=120$)	15–45 years ($n=238$)	46–60 years ($n=214$)	15–45 years ($n=914$)	46–60 years ($n=602$)	15–45 years ($n=335$)	46–60 years ($n=256$)
CR (%)	64	55	74	64	66	60	75	68
CR (%) after first course	30	23	53	50	53	51	67	65
DFS (%) at 5 years	19	27	25	17	38	22	NA	NA
Median survival from CR (weeks)	100	92	102	86	172	91	NA	NA
5-year survival (%) from CR	29	30	33	22	48	34	NA	NA
Median survival from diagnosis (weeks)	55	48	77	53	73	56	NA	NA
5-year survival (%) from diagnosis	19	16	26	15	35	22	NA	NA

CR, complete remission; DFS, disease-free survival; NA, not available (too early).

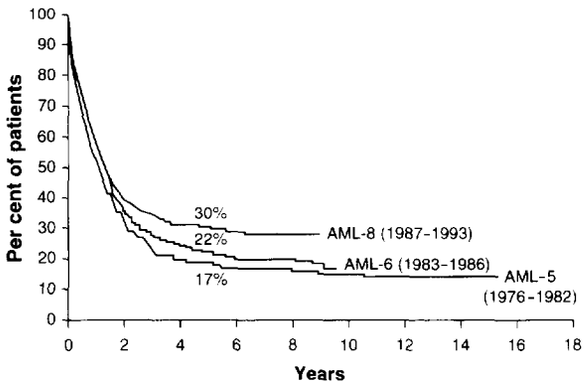

Figure 6. Survival in EORTC–LCG/GIMEMA trials.

the AML-6, -8, and -10 trials [4, 5]. It is disappointing that high-dose or standard-dose consolidation chemotherapy, with or without maintenance, did not improve long-term survival substantially. Given the more positive results reported from some other clinical trials, our results may be due to inadequate dosage, suboptimal schedules of high dose Ara-C, or flawed patient selection.

The real improvements observed in AML-6, -8, and -10 are related to auto-BMT and allo-BMT, especially in patients up to the age of 45 years. In AML-10, all patients between 15 and 60 years of age are proposed to receive stem cell transplantation after a very intensified induction course and a single high-dose consolidation regimen. Preliminary results for the induction phase are encouraging.

In conclusion, during these four consecutive trials, the percentage of patients with complete remission after a single induction course, the overall survival from diagnosis, disease-free survival, and survival for patients in first remission improved slowly (Tables 2 and 3, Figure 6). Plans are now being made to design a successor trial (AML-12) to begin in approximately December 1997. The following suggestions for further improving treatment results may serve as a basis for that study design.

NEW AND FUTURE TRENDS IN THE TREATMENT OF ACUTE LEUKAEMIA

Improvement in the overall prognosis of patients with AML may be achieved by increasing the percentage of complete remission, improving the duration of the first remission, and designing strategies to improve survival after a relapse has occurred.

Improving the results of remission induction

It may be possible to improve the results of remission induction by optimising the use of existing antileukaemic agents, decreasing the number of fatal complications, administering new chemotherapeutic or immunostimulatory agents, and making use of early allogeneic stem cell transplantation.

Optimising the use of existing agents. Standard antileukaemic agents include Ara-C and the anthracyclines. In several randomised trials, administration of increased dosages of Ara-C has not been accompanied by an increase in the rate of patients who attained a complete remission [9]. Some studies performed by the Australian Group, however, have shown a trend toward the prolongation of the duration of the remission with higher doses [10].

Studies to optimise the effects of anthracyclines on potentially resistant leukaemic cells by the usage of multidrug resistance reversal agents are underway. AML-10 will help to resolve current questions about the value of mitoxantrone and the relatively new anthracycline, idarubicin.

Decreasing the number of fatal complications. Decreasing the fatal complications caused by antileukaemic treatment may be the easiest way to improve remission induction results, since approximately 10% of patients continue to die during the remission induction phase; most mortality is due to infection. Formerly, the majority of these infections had a bacterial aetiology, but recently, fungal infections have become a more common cause of death. Decreasing the severity of mucositis, which acts as a *porte d'entree* for these microorganisms, shortening the duration of the aplastic period by the use of haematopoietic growth factors, and developing new antibiotics and fungicidal agents may result in a reduction of fatal complications.

Use of new antileukaemic agents. New antileukaemic agents such as deoxycytidine and anthracycline analogues have been investigated. They are currently being evaluated for their ability to induce remission and increase disease-free survival in some randomised trials [11], although there is little hope that they will be a major therapeutic breakthrough. New unrelated compounds, such as the minor-groove-binding agents, exhibit a preferential haematopoietic toxicity. For this reason, it may be worthwhile to assess their value in the treatment of patients with leukaemia.

Another experimental approach is the use of allogeneic stem cell transplantation following a chemo-radiotherapy-based conditioning regimen as part of a remission induction strategy. The use of cytotoxic cells, monoclonal antibodies, or immunostimulatory agents, such as interleukin-2 (IL-2), in conjunction with chemotherapy is also under investigation.

Improved consolidation

Improved consolidation aims to prolong the first remission. In one study, repeated administration of courses of high-dose chemotherapy resulted in a 4-year disease-free survival of almost 50% in patients under the age of 60 years [7]. Furthermore, auto-BMT after an intensive conditioning schedule also has resulted in long-term survival of approximately 50% in patients under the age of 46 years [5].

Transplantation of autologous peripheral blood stem cells will probably have a similar effect, perhaps with less toxicity due to a shorter period of pancytopenia. However, the effect of this type of stem cell on the incidence of relapse is still unknown. Whether peripheral blood stem cell transplantation following a conditioning regimen can be repeated or administered after successful BMT remains to be proven.

Purging of leukaemic cells following auto-BMT has not yet proven to have an impact on the overall incidence of relapse. However, this approach may be beneficial when used in conjunction with other new treatment approaches.

The use of allogeneic peripheral blood stem cells or cord blood stem cells may increase the percentage of patients who can undergo allogeneic stem cell transplantation. Nevertheless, only about 50% of these relatively young patients will survive. Patients transplanted with an allogeneic graft have been shown to have a poorer quality of life than patients transplanted with autologous stem cells or those treated by intensive chemotherapy alone [12].

Another unresolved issue is the impact on overall survival of BMT that is delayed until the second remission. The incidence of relapse in patients receiving allo-BMT is approximately 25%, compared with approximately 50% in patients receiving autologous stem cell transplantation [5]. One of the major challenges for the future will be improving these results by reducing the incidence of relapse, especially after auto-BMT.

Prevention of relapses after BMT

Measures to prevent relapses after BMT have been inspired by the finding that donor buffy coat cells have an impressive antileukaemic effect on the relapse of chronic myeloid leukaemia (CML) after allo-BMT [13]. More than two-thirds of patients achieved long-lasting complete remissions. This was not only true in patients with a minimal tumour cell load, but also in those who were calculated to possess more than 1 kg of leukaemic cells when donor-cell infusions were initiated.

Since the failure of immunotherapy in the treatment of leukaemia in the 1970s, this model is the first demonstration that immunological manipulation may result in a major antitumour response in human leukaemia. In contrast to patients with CML, however, the infusion of donor buffy coat cells in patients with a relapse of AML following allo-BMT leads to remission in only a minority of patients [14, 15]. Less efficient antigen presentation by AML cells or other antigen-presenting cells may result in a failure to generate anti-leukaemia or anti-host-specific cytotoxic T lymphocytes. The future will show whether we can increase antigenicity in patients with AML or generate *in vitro* leukaemia-specific allogeneic or autologous cytotoxic T lymphocytes that are also active *in vivo*.

Genetic manipulation of cells to make them more cytotoxic is being studied in several laboratories, but clinical application is still years away. Today, the most thoroughly investigated approach to the *in vivo* manipulation of immunity against leukaemia is the use of IL-2 [16–19] IL-12, and the agent linomide. Interest in IL-2 was intensified by the study of Meloni and colleagues, which showed that remissions can be induced by short-term escalating doses of IL-2 in patients with gradually relapsing AML [16]. In a pilot study, we have shown that low to intermediate doses of IL-2, administered as daily subcutaneous injections for several months after auto-BMT, are well tolerated [17]. An immunological reaction and eosinophilia, with little effect on the remaining blood cells, was demonstrated in all patients. EORTC–LCG and GIMEMA will soon begin to assess the value of IL-2 in patients relapsing after auto-BMT. Another potentially valuable immunomodulator is linomide. Several ongoing randomised trials organised by the pharmaceutical industry are investigating its effect following auto-BMT.

Definition of prognostic groups in AML

Among patients with AML, several prognostic groups can be defined on the basis of clinical features or cytogenetic abnormalities. It has been shown, for example, that increased age is associated with a poorer prognosis. Cytological FAB subtypes M2 and M3 have a better prognosis than the other subtypes. Initial leucocyte counts of >50 or 100×10^9/l are associated with a low remission rate and a short survival. Patients who do not reach a complete remission or who achieve remission only after several courses of induction treatment usually have a poor prospect for long-term survival. Secondary leukaemia following a phase of myelodysplasia or another malignant disease has a lower remission rate and a shorter disease-free survival than *de novo* acute leukaemia.

Cytogenetic factors. Some cytogenetic abnormalities, including t8;21, inv 16, and tl5;17, are associated with a relatively good prognosis, whereas other cytogenetic abnormalities have a poor prognosis [20]. Normal karyotypes have an intermediate prognosis. Intensive repetitive consolidation courses or BMT seem to improve the prognosis of patients with good-prognosis cytogenetic abnormalities and normal karyotypes, but have limited effects on patients with poor-prognosis cytogenetic abnormalities. In view of this heterogeneity of prognoses, it may be worth designing studies that include patients with more homogeneous prognostic factors. However, it is important to remember that the long-term survival of even the patients in the groups with the best prognoses is seldom greater than 60%. Furthermore, we do not know whether patients are cured or whether their relapses are merely delayed.

Molecular research. A new development in leukaemia research is the use of molecular techniques to follow the behaviour of leukaemic cells and to be able to detect small quantities of leukaemic cells during the remission phase, making it possible to intervene in the face of imminent relapse. To validate these techniques, large numbers of patients in different stages of their disease must be studied. Accordingly, the EORTC–LCG and GIMEMA are now creating a network of molecular and cytogenetic laboratories in Europe, through the Clonal Remission after Intensive Antileukaemic Therapy (CRIANT) project supported by the European Commission (Biomed Program-DGXII) and the Prognostic Impact of Molecular Screening (PIMS) project (submitted to the European Commission for funding). This network will play an important role in future studies of minimal residual disease in patients with acute leukaemias and myelodysplasia as a prelude to using this information in a preventive or therapeutic setting.

CONCLUSION

Successive randomised trials on the treatment of AML have succeeded in doubling the survival chances of AML patients under the age of 60 years. Such large-scale trials can only be performed as joint efforts between several cooperative leukaemia study groups. Further improvements in survival will require more facilities that can provide optimal haematological intensive care. Networks of cytological, immunological, cytogenetic, and molecular laboratories are mandatory if substantial additional progress is to be made in the treatment of leukaemia. Support of the European Commission has been very helpful in the formation of these networks, and will be even more necessary in the future to meet the demanding criteria for clinical research in Europe. New immunotherapy approaches with cultured cytotoxic cells may require a network of laboratories working according to the rules of Good Laboratory Practice in Europe. The establishment of such laboratories is the main challenge for the first part of the 21st century.

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