Strategies in the treatment of acute myeloid leukemia

The term acute myeloid leukemia (AML) collectively refers to a mixture of distinct diseases that differ with regard to their pathogenetic evolution, genetic abnormalities, clinical features, response to therapy and prognosis. Cytogenetic and molecular analyses have been instrumental in identifying disease entities among the mixed bag of AML subtypes, which are currently catalogued as suboptimally defined categories with widely different prognoses. These classifications are mainly based upon cytogenetic knowledge. They provide leads in clinical decision-making, e.g. with regard to treatment choice. The disclosure of genetic abnormalities may also offer potential targets for treatment intervention. Today such specific interventions into the molecular intracellular derangements of leukemic cells are only available for exceptional genetically defined entities of AML, such as acute promyelocytic leukemia with the translocation t(15;17). The microarray technology for analyzing differences in gene expression among clinical specimens of leukemia, advances in protein technology, the use of clinically relevant animal models, the development of drug design technology and the use of appropriate relevant animal models, the development of drug design design technology and the use of appropriate cellular in vitro systems, promise to accelerate our understanding of AML, pathogenesis as well our ability to recognize specific AML disease entities in the near future. With this perspective in mind, what are current and emerging strategies in AML therapy?

Remission induction strategies

Since the introduction of the anthracyclines (daunorubicin and doxorubicin) and cytarabine, these therapeutic agents have been the cornerstones of remission induction therapy for adult AML. With some variations, most centers apply treatment schedules based on these drugs, sometimes supplemented with etoposide. Instead of daunorubicin, some remission induction therapies have incorporated idarubicin, mitoxantrone or amscarine. These combinations induce complete remissions in an average of 70% to 80% of adults aged less than 60 years and in approximately 50% of patients of older age. The overexpression of a membrane protein designated P-glycoprotein (P-gp) is a typical phenotypic marker of pleiotropic drug resistance. P-gp belongs to a group of phosphorylated glycoproteins. In patients, primary or acquired resistance to chemotherapy has been associated with specific immunophenotypes and particular molecular and functional markers eg, with the expression of P-gp (P glycoprotein or MDR1). Efforts to overcome chemotherapy resistance by including multidrug resistance modifiers (eg cyclosporin or its analogue PSC 833) in the induction schedule have as yet not met with reproducible success in prospective comparative studies.1-3 These MDR modulators have been associated with enhanced toxicity. Due to the impact of the modulator on chemotherapy pharmacokinetics and the risk of increased toxicity, the dosages of chemotherapeutic drugs in the experimental groups had to be reduced. The dose reductions and the enhanced early toxicity may have jeopardized any potential benefit. Remission induction with growth factor priming is currently receiving renewed interest. AML is a prototype malignancy expressing functional hematopoietic growth factor receptors on their cellular surface.4 Growth factor receptors offer targets for therapeutic intervention. Co-incubation of AML cells with granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (G-CSF) and the cell cycle dependent chemotherapeutic agent cytarabine increases intracellular levels of the active metabolite cytosine arabinoside-triphosphate, elevates incorporation of cytarabine into cellular DNA and enhances cytarabine cytotoxicity against leukemic blasts and leukemic progenitor cells.5 The therapeutic concept of sensitizing AML to chemotherapy with G-CSF or GM-CSF, a phenomenon frequently referred to as growth factor priming, has been examined until recently in uncontrolled and small size randomized studies mainly. In two larger randomized studies in which GM-CSF was applied after the days of chemotherapy to accelerate hematopoietic recovery, it was also administered concomitantly with the chemotherapy.6 The latter two studies were performed in patients of older age, i.e., mainly patients with AML of unfavorable prognosis. In one of these studies in 240 patients of 55+ yr age, GM-CSF conferred a better disease-free survival1 but it was not possible to distinguish the effect of AML priming from an effect of enhanced hematopoietic recovery following marrow suppression. A recent large randomized study (enrolling 640 patients) focussed on the G-CSF priming question.1 The study was conducted in young and middle aged adults with previously untreated AML, thus representing a broader prognostic diversity. G-CSF was selectively applied from day -1 of chemotherapy through the last day of chemotherapy of both induction cycles I and II. G-CSF was not continued after chemotherapy during the hypoplastic phase. In this study the anthracyclin was scheduled at the end of the cycle to avoid interference with cytarabine cell cycle dependent cytotoxicity. Among patients in the study attaining CR, the
probability of relapse was considerably reduced when they had been assigned to treatment with G-CSF along with induction chemotherapy. This difference translated into a significant DFS benefit at 4 years for G-CSF primed patients. The benefit of G-CSF sensitization was particularly evident among the intermediate-subset of patients (72% of cases) as evidenced by improvements of overall survival, disease-free as well as event-free survival.5 Consistent with laboratory data, the latter benefit may have been achieved through G-CSF mediated activation of subpopulations of leukemic cells initially insensitive to the chemotherapy. Further exploration of the approach of G-CSF sensitization of chemotherapy seems warranted.

Post-remission strategies
During the last 20 years there has been a shift from low-dose maintenance chemotherapy administered for prolonged times (1-2 years) toward intensified cycles of chemotherapy delivered within a concentrated time.4-6 These dose-escalated and time-condensed cycles are given once a complete remission has been induced and serve the objective of eradicating minimal residual leukemia. Most commonly, these regimens are based on high-dose cytarabine with or without autologous or allogeneic hematopoietic stem cell transplantation. Survival rates in large Phase III studies of high-dose chemotherapy for AML patients 60 years of age or younger have been estimated at 40% to 55% at 4 years. These results would indicate a dose-response relationship for chemotherapy in patients with AML. High-dose cytotoxic therapy followed by autologous stem cell transplantation (auto-SCT) has been compared with either no further postremission treatment or conventional-type postremission chemotherapy. In certain studies9 but not others,12 disease-free survival was improved after auto-SCT due to a reduction in the probability of relapse. In none of these studies a significant advantage in overall survival auto-SCT (ranging from 40% to 55% at 4 years) was noted. The lack of survival benefits is explained by the fact that a proportion of patients relapsing after chemotherapy can be rescued by an autograft in second remission. The procedure-related mortality following auto-SCT has also been somewhat greater than after chemotherapy, partially offsetting the advantage of the reduced relapse frequency with autologous transplantation. Further, only a limited fraction of complete responders proceed to transplantation. Premature withdrawal from autografting is the consequence of the harvest of an insufficient number of hematopoietic cells for grafting, intercurrent infections, or early relapse of leukemia. A question that remains to be resolved is whether certain subgroups of patients with AML benefit from auto-SCT selectively. There is evidence suggesting that patients with intermediate-risk AML (according to cytogenetics) derive more benefit from auto-SCT than from intensive chemotherapy alone but this has not been confirmed in other studies.10,12 Definite conclusions regarding the potential benefit of autologous stem cell transplantation in distinct prognostic subsets of AML, will require additional studies enrolling larger numbers of patients. Allogeneic stem cell transplantation (allo-SCT) following myeloablative cytotoxic therapy currently offers the most powerful antileukemic treatment modality for AML in remission. When an HLA-matched allogeneic sibling donor is available, the option of all-SCT is usually the first choice in patients with AML in complete remission; following allo-SCT the probability of relapse is significantly reduced. The risk of relapse in patients with AML in first complete remission follow-

Table 1. Molecular markers additional to cytogenetics with independent prognostic significance for remission duration or survival in AML of adults.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Frequency (%)</th>
<th>Predictive for relapse</th>
<th>Survival</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>P53 mutation</td>
<td>9/200 (4.5)</td>
<td>–</td>
<td>Unfavorable</td>
<td>Nakano et al.44</td>
</tr>
<tr>
<td>High BCL2 and WT1 mRNA expression</td>
<td>35/98 (36)</td>
<td>Unfavorable</td>
<td>Unfavorable</td>
<td>Karakas et al.38</td>
</tr>
<tr>
<td>MLL partial tandem duplica-</td>
<td>18/221* (8)</td>
<td>Unfavorable</td>
<td>NS</td>
<td>Döhner et al.42</td>
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<td>tion</td>
<td></td>
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<tr>
<td>High EVI1 mRNA expression</td>
<td>32/319 (10)</td>
<td>Unfavorable</td>
<td>Unfavorable</td>
<td>Van Waalwijk et al.10</td>
</tr>
<tr>
<td>C/EBP α mutation</td>
<td>15/135 (11)</td>
<td>Favorable</td>
<td>Favorable</td>
<td>Preudhomme et al.40</td>
</tr>
<tr>
<td></td>
<td>12/277 (4.3)</td>
<td>Favorable</td>
<td>Favorable</td>
<td>Van Waalwijk et al.21</td>
</tr>
<tr>
<td>c-KIT mutation</td>
<td>34/110° (31)</td>
<td>Unfavorable</td>
<td>NS</td>
<td>Care et al.44</td>
</tr>
</tbody>
</table>

*Normal cytogenetics only. °AML with t(8;21) and inv(16) only.
ing transplantation of an HLA-matched sibling allograft may vary from 10% to 25%. Accumulating evidence suggests that disease-free survival is better following allo-SCT, although this observation has not always been consistent.10 The advantage of a reduced probability of relapse of AML after allo-SCT is partially sacrificed due to enhanced procedure-related mortality of 10–25% (caused by acute and chronic graft-versus-host disease and post-transplant immunodeficiency complicated by interstitial pneumonia and serious opportunistic infections). As the application of an allograft is practically dependent on the availability of a fully matched family donor and specific age eligibility limitations, comparisons of outcome following allografting and autografting or chemotherapy have not been based upon true randomizations. More recently, investigators have compared outcome between patients with an HLA-matched donor (regardless of whether or not the transplant was done) and those without an available donor in an effort to mimic an intention-to-treat evaluation.13–17 The results indicate reduced relapse rates for patients with AML in first complete remission with a donor but clear evidence of an overall benefit is still lacking. Considering the clinical heterogeneity of AML, an important issue has been whether certain subsets of patients would benefit more from an allograft than do others. For instance, in patients with good-risk AML (based on cytogenetics) with an a priori risk of relapse of 25% or less, it makes no sense to apply an allograft in first complete remission considering the associated enhanced procedure-related death rate. Also, patients with good-risk AML have a greater chance of being rescued in case of relapse. This argues for reserving allotransplantation strategies in good-risk AML for those with relapse only. HLA-matched unrelated donor (MUD) transplants are increasingly employed when a genotypically HLA-matched donor is not available. Although such transplants are mainly applied to restricted categories of high-risk cases (poor-risk AML in CR1, or AML in CR2 or CR3 in early relapse) their value remains to be critically assessed in large series of patients.

**Treatment strategies in older patients**

The majority of patients with AML are 60 years of age or older. While results of treatment have improved steadily in younger adults over the last 20 years, there have been limited improvements in outcome among individuals of 60+ years of age. When treated with chemotherapy alone, the older patients have an estimated survival of approximately 20% at 2-years and 10% at 4 to 5 years. The reasons for the unsatisfactory outcome in the elderly likely relate to the increased frequency of unfavorable cytogenetics among older patients with AML, a greater frequency of antecedent myelodysplasia, as well as the limited abilities of the patients to tolerate intensive chemotherapy. High-dose chemotherapy is not beneficial to the elderly with AML.18,19

There has been an intense interest in the introduction of new modalities. Examples of these strategies are the use of antibody directed treatment (e.g. the use of the antiCD33-calicheamycin toxin conjugate, Mylotarg,20 and the development of molecular targeting (egfarnesyl transferase inhibitors). Also interesting is the development of allotransplantation following conditioning with non-myeloablative preparative regimens. The goal of these approaches is to establish chimerism following immunosuppressive therapy and then exploit the graft-versus-leukemia of the allografts, so that donor chimerism can be used as a platform for subsequent infusions of donor lymphocytes. Early clinical trials afford proof of principle of this approach, but for the time being they are based on small patient numbers and they have limited follow-up.21–23 In older patients with various hematologic disorders (mixed) donor chimerism can be established, but more mature data will be needed for an assessment of the clinical value of this strategy.

**What have genetics to offer?**

Cytogenetic classifications employed with some variation by different groups in AML roughly distinguish three risk groups, one with favorable outcome (probability of relapse of 30% or less and 4-years survival of 70% or more), a second intermediate prognostic group with a risk probability of relapse of 50% and an overall survival at 4 4 years of 40–50%, and thirdly an adverse prognostic category characterized by a high relapse rate (more than 70%) and an overall survival rate at 4 years of 20% or less. These values of outcome refer to averages for adults between 15 and 60 years of age. More recently, various new molecular markers have been identified that allow for dissecting these composite risk categories. For instance, FLT3 internal tandem repeat mutations have been recognized as the single most common abnormality in AML. FLT3 internal tandem duplications (FLT3-ITD) represent activating mutations of the FMS-like tyrosine kinase 3 (FLT3), a hematopoietic receptor. AML with FLT3-ITD are seen in 15–30% of pediatric and adult patients. FLT3-ITD are associated with significantly greater risk of relapse and reduced survival.24–27 Other studies with large numbers of patients could not (yet) unquestionably reproduce the prognostic value of FLT3-ITD for survival.28–30 It has been suggested that a high mutant/wild type FLT3 ratio enhances that predictive power of FLT3 mutations for survival as well.31 Interestingly FLT3 mutations are mainly seen in the largest category of
intermediate cytogenetic risk of AML. Hence, detection of FLT3-ITD’s offers an important addition to recognizing a new subset of aggressive AML. Another recurrent Asp835 point mutation of the FLT3 receptor, seen in approximately 5–10% of de novo AML, has not (or not yet) been correlated with prognosis. Mutations of the tumor suppressor gene p53 predict for negative outcome.\(^4\) Immunodiagnosis of bcl2 positivity was shown to have negative predictive value in AML.\(^5\)\(^6\) By RT-PCR analysis high BCL2 and WT1 expression have been suggested in combination to define AML with poor risk.\(^7\) ETV1 (ectropic virus integration site 1) is an oncogene overexpressed in AML with translocations of 3q26 and characterizes AML with poor risk outcome. Recently it was shown that ETV1 mRNA overexpression in AML in the absence of 3q26 cytogenetic abnormalities also predicts for notably bad prognosis.\(^8\) C/EBP-\(\alpha\) (CCAAT enhancer-binding protein alpha) is a transcription factor that has a key role in myelopoiesis. C/EBP-\(\alpha\) mutations have been found in patients with AML in a few percent of acases. The latter mutations define AML with relatively good risk leukemia.\(^9\)\(^10\) These cases are hidden among the intermediate cytogenetic risk subset of patients with AML and can now be separated. Similaty, partial duplicions mediate cytogenetic tisk subset of patients with AML also been suggested in combination to define AML with poor risk.\(^11\)\(^12\) EVI1 (ectropic virus integration site 1) is an oncogene overexpressed in AML with translocations of 3q26 cytogenetic abnormalities also predicts for notably bad prognosis.\(^13\) Also high expression of a gene designated BAALC (Brain and Acute Leukemia, Cytoplasmic) which is normally expressed on neuro-ectoderm-derived tissues and hematopoietic progenitors has been suggested in a study of limited size (86 cases) to predict for poor survival among patients with AML with normal cytogenetics.\(^14\) Each of these molecularly defined groups is of relatively small proportion, consistent with the considerable genetic heterogeneity of AML. The presence of point mutations of the hematopoietic receptor c-kit in patients with abn(16) AML and t(8;21) AML, generally considered to be of favorable prognosis, defines a subset with an enhanced risk of recurrence.\(^15\) With the introduction of high throughput analysis for molecular abnormalities and gene expression profiling, it will in the near future probably be possible to define other classes of AML. The introduction of expression array chips may yield composite mRNA signatures of AML cells with prognostic value as well. These distinctions when validated in clinical studies, are foreseen to provide powerful tools for guiding treatment strategies in AML.\(^16\)\(^17\) A precise recognition of the diverse genetic abnormalities will be of value in distinguishing AML subsets with distinct pathogenetic origin; most likely some of these diagnostic targets may provide convenient markers for monitoring the effect of therapy and quantifying the disappearance of leukemia cells following therapy. One might anticipate that these analyses will provide insights into molecular pathways and disclose why certain leukemias are unresponsive to traditional chemotherapy. Thus they may provide keys towards new avenues for treating high risk AML, e.g. based on interventions directed at genetic abnormalities. Examples of these strategies currently in trial are interventions aimed at suppressing the oncogene BCL2 (eg with anti-sense oligonucleotide modalities)\(^18\) and the use of molecules that act as kinase inhibitors. The latter category for instance comprises a series of molecules (eg CEP 701)\(^19\) that inhibit the constitutive active FLT3 receptor mutants in AML. Various of these molecules are currently in therapeutc development.

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Position paper/statement by members of the Ponte di Legno group on the right of children to have full access to essential treatment for acute lymphoblastic leukemia

Improved outcome of childhood acute lymphoblastic leukemia (ALL), the most common cancer in children, is one of the great success stories in modern medicine. The approach taken to dramatically improve the cure rate involved the combination of clinical and basic research, mostly conducted with public funds, and intensive collaboration of cooperative groups. As a result, the cure rate has improved from 3% in the 1960s to 80% currently in resource rich countries. We believe that this improved possibility of survival should be considered among a fundamental right of affected children. Providing access to the necessary diagnostic and therapeutic resources for children afflicted with leukemia should be a priority for those who play a role in the relevant areas of medicine and health.

The physicians, clinical investigators, and basic scientists who have signed this statement have been responsible for transforming ALL into a model disease for which there is hope of cure when optimal treatment is accessible. These professionals are fully aware that their successes have also widened the gap of inequality between children living in the resource-rich countries and those living in low-income countries (LICs). Most children live in LICs; hence, most patients with ALL reside in these countries and therefore are subjected to an increased risk of possibly avoidable death.

As citizens, doctors, and researchers, we feel an urgent priority to correct this inequality in ALL treatment. The following is a summary of short- and medium-term plans in this regard:

(i) The first and most rapidly achievable goal is the recognition by international agencies and by concerned regulatory authorities that the treatment protocols and guidelines developed for children with ALL are essential. In this regard, antileukemic drugs used in these protocols should be qualified as essential drugs.

(ii) Centers or groups of excellence should be developed in LICs. Our experience in various LICs has shown that the efficacy and safety of chemotherapy can be ensured in centers and by groups who are trained and motivated to adopt policies of high–quality ALL care, which include the use of well-designed protocols.

(iii) On the basis of concepts and strategies developed for use in other disease areas (from tuberculosis to AIDS), we recommend broadening the scope of the essential drugs list and documenting not only the selection and use of drugs but also the implementation of the treatment strategy.

(iv) Within a framework in which the fundamental rights of children are the reference value, we commit our groups to strongly support all activities toward this goal; but we request the recognition by WHO and other concerned national and international agencies that the care of children with ALL (as well as with other curable cancers) is deemed essential.

(v) We advocate a price policy for drugs used in the protocols; the purpose of the policy will be to diminish the treatment barrier of high drug costs substantially; we recommend that the national authorities support the centers where staff are committed to essential protocols and that national authorities document compliance with these protocols.

We are only too aware that the resource allocation for ALL does not currently coincide with public health priorities in many countries. However, we are convinced – and supported by our experience – that ALL is a model for all curable cancers; expanding efforts in treatment of ALL in LIC will result in the mobilization of important new energies, stimulation of imaginative solutions, enrichment of motivations, and broadening of public awareness. We emphasize that a policy of drastic cost-cutting in ALL treatment is feasible for two main reasons (besides and beyond any ethical consideration): (i) the market implications are minimal, because the size of the patient population is relatively small; and (ii) there will be no risk of misdirection or mismanagement of drugs as they become available, because their use will be accounted for by centers of expertise who are committed to documenting compliance through registration of all patients enrolled on treatment protocols.

All subscribers to this memorandum, representing the majority of the Childhood Leukemia Treatment Consortia, herewith emphasize the right of all children in the world to full access to the essential treatment of ALL and other cancers, and call upon all authorities concerned to recognize and support all measures that