

Intensified Treatment and Stem Cell Transplantation for Acute Myeloid Leukemia, Based on Risk Factor Assessment

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Since the early 1980s the standard induction therapy for adult patients with acute myeloid leukemia has relied on a combination of an anthracycline with cytosine arabinoside. Using this regimen the majority of patients (55–60%) could be put into complete remission, but an even larger majority (65–70%) would eventually relapse and only a small minority of patients (15–25%) would enjoy long-term disease-free survival⁽¹⁾.

Since then, the addition of newer anthracyclines, such as mitoxantrone and idarubicin, the use of Ara-C dosage increases and the advent of improved supportive care measures have led to a progressive improvement of CR rates. A modern state-of-the-art protocol should be able to induce CR in at least 70–80% of adult patients.

In some, but not all, studies these newer anthracyclines have also led to a better survival rate, but some controversy exists around the equivalence of the dosages of the various anthracyclines used^(2,3).

Higher doses of Ara-C (up to 24g/m²) in remission induction have not led to improved CR rates but might be associated with prolonged remission and improved disease free, but not overall, survival⁽⁴⁾.

While further improvement of the complete remission induction rates thus seem hard to realise, many international cooperative groups have concentrated their efforts on the optimisation of post-remission or consolidation therapies, aiming at disease-free survival rates of 50% and more. In many instances this has included dose-intensification of existing schemes or various forms of stem cell transplantation, much less the exploration of long term maintenance therapy.

Intermediate (1g/m² for 12 doses) or high dose Ara-C (3g/m² for at least six doses), used in the consolidation phase, with or without other agents such as m-Amsa or Etoposide, have enabled five-year disease-free survival rates in younger adults (less than 60 years) of about 40%⁽⁴⁻⁶⁾.

However, only allogeneic transplant protocols have been able to substantially improve long-term disease-free survival, albeit in the small minority of patients for whom a suitably matched allogeneic donor could be found⁽⁷⁻⁹⁾. The transplant-related mortality often remains unacceptably high, especially when non-sibling donors are used. Whether the use of growth factor primed peripheral blood stem cells rather than bone marrow stem cells or the application of so-called mini-transplant protocols will improve long-term outcomes remains to be proven.

One of the major disappointments of recent comparative trials has been that neither autologous bone marrow

nor peripheral blood stem cell transplantation have been able to substantially improve long-term outcome. In only one of the four published studies—the MRC-AML10 trial⁽¹⁰⁾—autologous transplantation reduced the risk of relapse and had a statistically significant effect on disease-free survival and a benefit in overall survival. A recent meta-analysis of all available data, however, could not confirm this survival advantage. The MRC data suggest that, if auto BMT is to have an effect, it is best performed after intensive and prolonged (three courses) consolidation therapy.

In interpreting the data from these randomized studies one should also realize that many patients in all published studies, randomized to receive transplants, failed to complete the assigned treatment, which may introduce considerable bias.

Moreover, not all patient categories seem to benefit from intensification and transplantation. Often an high toxicity price is paid for a marginal clinical benefit. Treatment related mortality for auto BMT ranges from 9 to 15%⁽⁷⁻¹⁰⁾, versus 3 to 7% for chemotherapy and 20–25% for allo BMT. Risk factor adapted treatment has therefore become standard of care.

The major prognostic factors for adult AML are :

- age
- cytogenetics
- the drug resistance phenotype (MDR)
- a preexisting myelodysplastic phase of more than six months duration.

A high number of circulating blasts has been considered an independent negative prognostic factor in some, but not all, studies. Especially in some subtypes (e.g. M3) this may be relevant.

The worse prognosis in older age groups (more than 65) is often caused by a poorer performance status and the presence of concomitant chronic diseases, but in the elderly also more MDR phenotypes and underlying myelodysplasia are found.

Novel therapeutic approaches for these age groups will therefore more rely on MDR modulation (e.g. PSC833), monoclonal antibodies (e.g. anti-CD33) and improved supportive care (e.g. growth factors as G-CSF) than on intensified transplant protocols⁽¹¹⁾.

In the meantime the “younger” 60 to 65 years old AML patient with good performance status and with favorable or standard cytogenetics should be treated with standard dose Ara-C and an anthracycline. In those with a rapid response, moderately intensive consolidation is warranted. In the near future minitransplant protocols may allow the application

of allogeneic transplants with accompanying graft versus leukemia effect in these categories as well.

The karyotype and correlating molecular findings remain the most reliable prognostic indicators. Patients with the t8;21, the inv16 and the t15;17 karyotypes will respond most favorably to standard induction, show higher CR rates, lower relapse rates, better DFS and improved response to reinduction chemotherapy. For these subcategories the value of auto- and allo-BMT in first complete remission is debatable. The unavoidable transplant-related mortality has to be weighed against the 50% or more long-term survivors with standard therapy and against the fact that about 30% of relapse patients can be reinduced successfully. However, in some studies (e.g. MRC-AML10) higher doses of Ara-C seem to be able to further improve outcome, even in this favorable subgroup.

For patients with unfavorable karyotypes (especially with abnormalities of chromosomes 5, 7 and also 3) little doubt exists on the value of an intensified approach, inclusive auto- and/or allo-BMT. However, even then, the results in this subgroup remain poor and significantly worse than for patients with standard or favorable karyotype. Alternative approaches (e.g. exploiting the graft-versus-leukemia effect of the minitransplants and donor lymphocyte infusions) are urgently needed.

The large majority of adult AML patients (70%) present with a standard risk karyotype. In these patients remission induction with high dose Ara-C in combination with idarubicin, followed by high-dose consolidation for at least two, preferably three, consolidation courses, remains the golden standard. Allogeneic transplant in CR1 is warranted for those presenting with a molecularly compatible donor. The role of autotransplant in CR1 is uncertain.

The success of risk-adapted treatment strategies depends largely on the refinement in the definition of prognostic factors. It is to be hoped that the rapid evolution in the molecular diagnosis of AML will allow even better delineation of prognostic subgroups.

Finally, it looks as though the outer limits of chemotherapy will soon be reached and that novel approaches, relying on manipulation of grafts, immunotherapy with monoclonals, minitransplants, together with improved supportive care (growth factors, cytokines) and better ways of combatting viral and especially fungal disease will be needed.

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