Post-remission therapy in acute myeloid leukemia: what should I do now?

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Today, we are unable to select an indisputable winner as the single best post-remission therapy for an individual patient with acute myeloid leukemia (AML) who achieves first remission (CR1) after induction chemotherapy. Choices for subsequent treatment are made based on the probability of future relapse: low risk patients traditionally receive only cytotoxic chemotherapy; conversely, high risk patients undergo allogeneic transplantation in CR1, if possible. However, many low risk patients still eventually die of disease relapse, and some high risk patients have durable remissions without receiving a transplant. Based on available risk stratification tools such as clinical status, cytogenetics, and molecular markers of disease as well as considering practical matters including an available source of allogeneic stem cells, current recommendations for post-remission therapy depend on whether the relapse risk is high enough to merit the potential toxicities of allogeneic transplantation, or sufficiently low to forgot the procedure. Fortunately, advances in risk stratification and improved understanding of the molecular basis of AML are together steadily improving our ability to select the optimal post-remission therapy for each patient.

In this issue of the journal, two articles describe challenges in the selection of the best post-remission therapy for patients with AML. Messerer *et al.* highlight problems of decreased quality of life faced by AML survivors who received allogeneic transplantation in CR1, compared to survivors who received other post-remission treatments.[1] Foulliard *et al.* remind us of the complexities involved in donor selection and timing of allogeneic transplantation in their retrospective study of syngeneic transplantation in acute leukemia.[2] This review summarizes current evidence guiding the selection of post-remission therapy for AML in CR1.

How do we assess risk?

Clinical factors, cytogenetics, and molecular techniques

Clinical factors including performance status, age, presenting white blood cell count, presence of an antecedent hematologic disorder, and response to the first cycle of induction chemotherapy remain critically important in assessment of risk and the appropriate selection of post-remission therapy. Beyond medical assessment of eligibility for various modalities of therapy, cytogenetics performed from bone marrow collected at the time of diagnosis are currently the most important prognostic factor in predicting outcome of AML in CR1. Though differences in the classification of karyotypes exist between various co-operative groups, AML patients are generally classified into good, intermediate, or poor risk groups based on cytogenetics. At least in younger AML patients (age < 55-60 years), cytogenetics are a powerful tool, with 5-year survival in good risk patients being 55-65% compared to less than 20% in poor risk patients.[3–5] Cytogenetics have predictive value in older patients as well, but dismal overall survival outcomes for the vast majority of AML patients over the age of 60 render the information somewhat less helpful in choosing subsequent therapies than it is in younger patients.[6]

While powerful, cytogenetic information as a predictor for risk of relapse is imprecise, and emerging research is now taking risk stratification to the molecular level, refining the stratification process. A number of genes are under investigation as prognostic markers; these genes may be mutated, aberrantly overexpressed, or aberrantly silenced. The search for molecular markers is applicable to all patients but has been particularly successful in further delineation of risk for AML patients with a normal karyotype (Table 1). Internal tandem duplication (ITD) of the fms-like tyrosine kinase 3 gene (*FLT3*) may be the most clinically useful molecular marker studied to date; it is particularly relevant in this subset. Several studies have shown that the presence of a *FLT3*-ITD adversely affects outcome,[7] a fact even more striking for patients who lack a copy of the wild type allele.[8] More recently, *FLT3*-ITD status and mutation of the nucleophosmin (*NPM1*) gene were reported together to have important prognostic value regarding the benefit of allogeneic transplantation for patients in CR1.[9] *NPM1* mutations are among the most common mutations in AML yet known, and they are associated with a more favorable outcome.[10] Among patients receiving an allogeneic transplant from a matched sibling, no benefit of transplantion in CR1 was seen in those whose leukemia was *NPM1*-mutated/*FLT3*-ITD negative. Conversely, a significant survival

Table 1. Prognostically significant genetic aberrations in cytogenetically normal acute myeloid leukemia.

Molecular alteration	*Location*	*Prognostic Impact*
FLT3-ITD	13q12	OS: significantly shorter DFS: significantly shorter CRD: significantly shorter
ERG overexpression	21q22.3	OS: significantly shorter CIR: significantly shorter
BAALC overexpression	8q22.3	OS: significantly shorter DFS: significantly shorter EFS: significantly shorter
NPM1 mutations	5q35	OS: significantly longer CR rate: significantly higher
CEBPA mutations	19q13.1	OS: significantly longer DFS: significantly longer CRD: significantly longer
MLL-PTD	11q23	OS: significantly shorter EFS: significantly shorter CRD: significantly shorter

CR: complete remission, CIR: cumulative incidence of relapse, CRD: complete remission duration, DFS: disease free survival, EFS: event-free survival, OS: overall survival. Modified from Baldus CD et al. Clinical outcome of de novo acute myeloid leukaemia patients with normal cytogenetics is affected by molecular genetic alterations: a concise review. Br J Haematol 2007;137:387-400.

benefit from transplantation was seen in patients who were either *FLT3*-ITD-positive or *NPM1* wild type/*FLT3*-ITD-negative.[9] A number of other mutated or aberrantly overexpressed genes have been reported to have a negative prognostic value, including partial tandem duplications of *MLL* (*MLL*-PTD), and overexpression of *WT1*, *BAALC*, *ERG,* or *EVI1*. Other abnormalities, such as *CEPBA* mutations, are associated with a more favorable outcome (Table 1 and Figure 1).[10] Complex interrelationships between these and other genes remain under study.[10] Recently, unique microRNA signatures were also reported to have prognostic value.[11] Finally, microarray profiling has shown promise in providing insights into the complex network of dysregulated cellular pathways in leukemic cells,[12–14] although this methodology has not yet matured to a level that is clinically useful in optimizing selection of post-remission therapy in AML.

Assessment of minimal residual disease

The development of novel methods for the detection (and eradication) of minimal residual disease during morphologic remission is a critical area of ongoing research. The presence of residual disease detected by conventional flow cytometry (detection of a persistent aberrant immunophenotype) after induction therapy is a sufficient criterion for defining treatment failure;[15] detection of a persistent cytogenetic abnormality by metaphase cytogenetics for patients in morphologic remission after induction therapy predicts future relapse.[16] Both of these are common sense examples of productive research in this area. New methods of detecting minimal residual disease by advanced, multicolor flow cytometry are under study. At the American Society of Hematology meetings in 2007, Meshinchi *et al.* reported impressive results with use of multicolor flow cytometry in pediatric AML patients in remission.[17] Using a multicolor flow cytometry technique that examined deviation from a normal pattern (and thus one that did not require diagnostic material for testing), the authors found that patients with evidence of minimal residual disease were at a markedly higher risk of relapse, with a relapse-free survival rate of 36% in those with evidence of minimal residual disease after induction therapy, compared with 70% for other patients ($p<0.001$). The overall survival rate at 2 years was 63% *vs.* 86%, respectively ($p=0.003$). In addition to multicolor flow cytometry, polymerase chain reaction (PCR) techniques are used to detect minimal residual disease. The results of PCR performed during remission have enormous value in patients with acute promyelocytic leukemia. The detection of the abnormal *PML/RARA* fusion during CR1 is associated with an increased risk of relapse[18] and, today, is a sufficient criterion to initiate salvage treatment (arsenic trioxide) when confirmed on repeat testing. While persistent detection of the fusion gene by PCR has less certain prognostic value in t(8;21) or inv(16) AML, the technique remains of research interest in these cases as well as in AML with other fusion/mutated genes.

The detection of under-expressed genes during remission may also have prognostic value. Aberrant promoter hypermethylation in a gene is associated with transcriptional silencing; in the case of tumor suppressor genes,

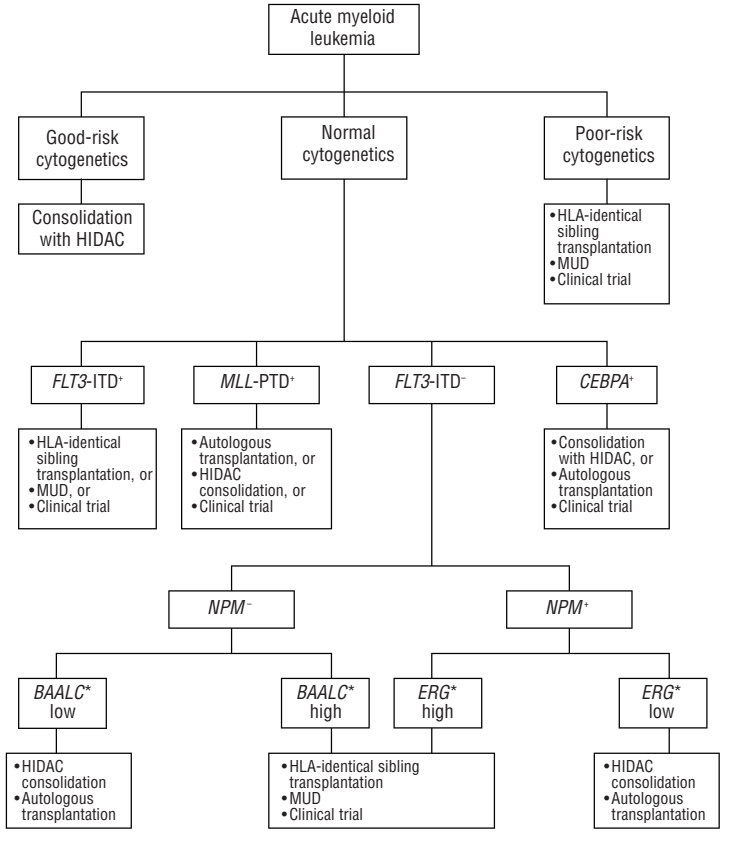

Figure 1. Recommendations for optimal consolidation therapy for younger AML patients in CR1, based on cytogenetic and genetic abnormalities.

*HIDAC: high dose cytarabine, HLA: human leukocyte antigen, MUD: matched unrelated donor transplantation. *Note, testing for BAALC and ERG expression is currently not individualized but rather is based on generalized "cut-off" levels for populations of patients. Whether further development of these markers will facilitate individualized decision-making remains an ongoing area of research. Adapted from Mrozek et al.*[10]

this silencing appears to have a role in leukemogenesis. Recently, aberrant methylation of p15 and estrogen receptor, detected during remission, was shown to be a risk factor for relapse of AML.[19] Residual aberrant methylation as a marker of minimal residual disease is being targeted in several ongoing studies utilizing hypomethylating agents such as decitabine as prolonged investigational maintenance therapy for AML in CR1.

How should we treat the AML patient in CR1?

Post-remission chemotherapy

For AML patients who achieve CR1 and then, by choice or necessity, receive no further intensive consolidation chemotherapy, durable remissions are rare.[20] In younger patients, there is a clear benefit from intensive post-remission therapy, but many questions remain about the best type, dose, and duration of treatment. From a vast selection of different regimens utilized by various co-operative groups, except in a few select subsets of disease, it is difficult to profess one approach superior to another. Notably, many physicians believe that repeated cycles of high dose cytarabine (HIDAC) should be administered to patients with core binding factor (CBF) AML, a subset of AML consisting of the good risk karyotypes t(8;21) and inv(16). The CALGB helped to establish this approach with evidence derived initially from a large study of 596 younger AML patients.[21] Patients achieving complete remission with standard 7+3 induction were randomized to HIDAC (3 mg/m^2 every 12 hours on days 1, 3 and 5), low dose cytarabine (100 mg/m^2/day for 5 days as a continuous intravenous infusion) or intermediate dose cytarabine (400 mg/m^2/day for 5 days as a continuous intravenous infusion). The 4-year disease-free survival was superior in patients who received HIDAC. This benefit was particularly evident for patients with CBF AML.[22] Compared to lower cytarabine doses (100 mg/m^2 or 400 mg/m^2), repeated cycles of HIDAC consolidation therapy produced prolonged disease-free survival in patients with CBF AML and normal karyotype AML, respectively, but not in those with other cytogenetic abnormalities.[22] Further retrospective analyses established that repeated cycles of HIDAC (three to four cycles) given to CBF AML patients in CR1 yielded superior disease-free and overall survival rates compared to a strategy that included only a single cycle of HIDAC.[23,24] This repeated dosing approach has become the standard consolidation therapy for patients with CBF AML in the United States. Of interest, mutations in *KIT* appear to adversely affect clinical outcomes in patients with CBF AML, suggesting that alternative consolidation strategies should be considered when *KIT* mutations are detected.[25]

The benefit of additional intensive cytotoxic therapy as consolidation for older patients (>60 years) in CR1 is less clear; as yet, no standard post-remission approach has been proven to improve survival substantially in this age group. Outside of clinical trials, most physicians administer one cycle of intensive post-remission therapy, at least for patients not in the poor risk cytogenetic subset in whom the benefit of any such therapy is far from certain. At the very least, available data suggest that intensification of post-remission treatment in older patients by either increasing the number of cycles[26] or intensifying the regimen itself[27] adds little beyond added toxicity. Clinical trials are the best therapy for older AML patients.

Transplantation as consolidation for AML in CR1

The role of allogeneic transplantation for AML in CR1 is best summarized by results from a recent landmark meta-analysis, performed by the HOVON-SAKK investigators.[28] This meta-analysis, which included data from multiple European cooperative group studies, demostrated an overall survival benefit from allogeneic transplantation in CR1 from a matched sibling donor, with myeloablative conditioning, of 12% for patients in intermediate or poor risk cytogenetic groups. This benefit was lost in older patients (>35 years), likely due to increased transplant-related mortality with increasing age. Thus, the data show relatively clearly that younger patients with an HLA- matched sibling donor who are fit and not in the good risk cytogenetic group should undergo allogeneic transplantation in CR1.

Unfortunately, many patients lack an HLA matched sibling donor. Extension of transplantation in CR1 to include the use of alternative donors is an ongoing area of research. Although emerging data suggest that patients transplanted from 10/10 HLA allele-matched volunteer unrelated donors may have outcomes similar to those transplanted from matched sibling donors, there is no clear consensus about the use of unrelated donors for AML in CR1. Many physicians currently utilize matched unrelated donor transplantation for AML patients in CR1 with poor risk cytogenetics but remain reluctant to do so for those with intermediate risk. Umbilical cord blood is a readily available source of stem cells, but there are as yet no definitive prospective data to support its use in AML CR1.

Clinical trials investigating the tolerability and efficacy of less toxic, non-myeloablative conditioning regimens for older AML patients in CR1 are incredibly important. Given the uncertain benefit of post-remission cytotoxic chemotherapy in older patients who already have a high risk of relapse and little hope of long-term survival, immunotherapy via the allogeneic graft-versus-leukemia effect is a promising alternative to watchful waiting. There is no debate that older patients tolerate the transplant process much better with non-myeloablative conditioning than with intensive conditioning approaches; whether the approach can effectively improve survival remains to be seen. Physician support for large cooperative group studies in this area is critical. If the approach proves successful in reducing the risk of relapse in older patients, extension of non-myeloablative conditioning approaches to younger patients would be the logical next step.

Although favorable results with autologous transplantation in patients with AML in CR1 have been reported, there are no definitive data indicating that this approach is superior to chemotherapy alone, at least not for all patients. In an EORTC/GIMEMA trial, patients who were randomized to autologous transplantation had superior leukemia-free survival compared to those receiving chemotherapy, but no overall survival benefit

was seen.[29] Conversely, in a GOELAM trial in which the chemotherapy group received higher doses of cytarabine than in the EORTC trial, there was no leukemia-free or overall survival benefit from autologous transplantation compared to chemotherapy.[30] The role of autologous transplantation in CR1 remains undefined, and the use of this approach outside of clinical studies should probably be reserved for special circumstances. Perhaps, molecular subsets of patients will be identified who have benefit from an autologous transplant in CR1; for example, the CALGB recently published data showing that patients with *MLL*-PTD may benefit from an autologous transplant in CR1.[31]

Conclusion

Advances in our understanding of the molecular basis of AML are beginning to allow individualization of post-remission therapy based on relapse risk, but we have a long way to go. The augmentation of cytogenetic risk stratification by molecular testing in patients with normal karyotype AML provides a provocative glimpse of the potential for new methods to improve outcomes for patients. Today, there are two certainties with regards to innovation in post-remission therapy for AML. First, new methods (such as testing for *FLT3* and *NPM1* mutations) must actually be implemented to be effective; roadblocks to implementation of new tests must be overcome in both academia and community practice. Second, further improvements in clinical outcomes and understanding of AML will come only through development and dedication to novel clinical trials and tumor registries. The current data on post-remission therapy for AML patients in CR1 suggest that dose modification/intensification of presently available cytotoxic drugs is unlikely to improve outcomes further. Resources should be focused on novel approaches including immunotherapies (expanding allogeneic transplantation, vaccines, others) or "targeted" drugs (inhibitors of FLT3, azanucleosides, others) during the post-remission period.

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Neonatal alloimmune thrombocytopenia

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Neonatal alloimmune thrombocytopenia is the commonest cause of early onset isolated thrombocytopenia in an otherwise healthy neonate.[1]

This syndrome is comparable to hemolytic disease of the newborn, although it frequently affects the first infant. The thrombocytopenia results from maternal immunization against specific platelet alloantigens paternally inherited by the fetus. During pregnancy, the maternal alloantibodies can cross the placental barrier as soon as 14 weeks of gestation. The fetal opsonized platelets are then cleared in the reticulo-endothelial system. The resulting thrombocytopenia is not only due to increased platelet destruction but also to impaired platelet production.

The incidence of neonatal alloimmune thrombocytopenia in the unselected Caucasian population has been estimated by prospective studies to be 1/800 to 1/1000 live births.[2,3] The most feared complication is intracranial hemorrhage (ICH) in the case of severe thrombocytopenia. The morbidity has been estimated to be 20% of the reported cases and mortality up to 15%.[4,5] Alloimmune thrombocytopenia can be diagnosed during pregnancy or at birth.

Clinical presentation

The neonate

Since the first description by Harrington in 1953[6] to the breakthrough of fetal medicine in the 1980s the diagnosis has essentially been made in a full-term neonate who exhibits bleeding at birth or a few hours afterwards. Otherwise the infant is well with no signs of infection, malformation or chromosomal abnormalities. The isolated thrombocytopenia is severe, with the platelet count being below 20×10^9/L. In this situation, appropriate therapy must be instituted immediately in order to reduce the risk of significant hemorrhage.

Conversely the infant may be symptomless and thrombocytopenia (a platelet count below 150×10^9/L) is discovered incidentally on a complete blood count performed for a different indication.[7]

Identifying the cause of unexpected or unexplained neonatal thrombocytopenia or severe early onset thrombocytopenia in both preterm and term babies is a matter of concern. The diagnosis of the thrombocytopenia is of importance for both the infant and future pregnancies. The possibility of alloimmune thrombocytopenia in those conditions may be raised and investigations must be conducted accordingly.

The fetus

With the development of fetal medicine, fetal alloimmune thrombocytopenia has been recognized as the most severe form of fetal thrombocytopenia.[8] By the end of the first trimester of pregnancy, the mean fetal platelet count is above 150×10^9/L.[9] A platelet count below this threshold, therefore, defines thrombocytopenia regardless of the gestational age. Severe thrombocytopenia has been observed from 21 weeks of gestation[10] without spontaneous correction as gestation progresses.

Fetal alloimmune thrombocytopenia may be suspected in the case of ICH. Retrospective studies have shown that in feto-maternal alloimmunization 80% of the