Simply put, the treatment of acute myelogenous leukemia (AML) has 2 steps: the first step involves therapy to get it into remission, and the second step involves therapy to prevent it from coming back. Over several decades our approach to the first step has largely remained the same, but our approach to the second step has evolved significantly. The fundamental clinical decision for the second step has become: is the prospect for durable control better with posttransplantation chemotherapy or with hematopoietic cell transplantation? Insights gathered incrementally from research have allowed us to tailor our therapies and avoid a “one size fits all” approach. Perhaps the most important insights for step 2 decision-making are the identification of biologic markers present at diagnosis before treatment and the characterization of minimal residual treatment after step 1 therapy.

Recognition of the prognostic significance of clonal cytogenetic abnormalities has revolutionized the management of these patients; however, considerable variation in clinical response and survival remains, indicating molecular heterogeneity within each cytogenetic risk group. Molecular markers are now beginning to revolutionize the management of AML. Today, we have the ability to identify subgroups within the cytogenetic risk groups to further refine our treatment options. Identification of FLT3 and CEBPA mutations in patients who are otherwise cytogenetically normal have emerged as very strong negative and positive prognostic indicators. We now recognize that combinations of certain mutations add even more prognostic information. The World Health Organization classification for AML has recognized NPM1 and CEBPA as provisional entities and recommends that all patients be tested for FLT3. Both the NCCN and the European Leukemia Net guidelines recommend use of FLT3, NPM1, and CEBPA to categorize cytogenetically normal patients. Additionally, the increased sensitivity of these molecular tests or the use of flow cytometry allows us to detect small numbers of residual leukemic cells after treatment, even when the patient appears to be in a histological and cytogenetic remission, again providing prognostic significance.

The challenge for molecular markers in the coming decade will be how best to use them in our patients to personalize our approach for each patient. Molecular markers are not mutually exclusive, and the prognostic impact of a particular molecular marker can vary in the presence or absence of another marker. New markers are constantly being identified, which further complicates the prognostic evaluation. Additionally, the impact of assessing molecular markers on the outcomes after stem cell transplantation remains an important unanswered question. This issue contains a review of a symposium that took place at the 2010 BMT Tandem Meeting in Orlando, FL. The topics review the current knowledge of molecular markers and their impact on treatment and outcome, minimal residual disease (MRD) monitoring, and the status of transplantation in the era of molecular testing.
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Barrett Installed As President; Shpall Elected Vice President

A. John Barrett, MD, has been installed as president of the American Society for Blood and Marrow Transplantation. He is section chief for stem cell allotransplantation in the Hematology Branch of the NIH National Heart Lung and Blood Institute, Bethesda, MD.

Elizabeth J. Shpall, MD, the Ashbel Smith Professor of Medicine at the University of Texas MD Anderson Cancer Center, is the newly elected and installed vice president, to become president in 2012. She is also the cancer center’s Cell Therapy Laboratory medical director and the Cord Blood Bank director.

The installation of new officers and directors occurred at the society’s annual meeting, the BMT Tandem Meetings, on February 26 in Orlando. The election was by ballot among members of the society in December and January.

Newly elected and installed directors are:

Linda J. Burns, MD, of the University of Minnesota Medical School in Minneapolis, MN
Peter A. McSweeney, MD, of the Rocky Mountain Blood and Marrow Transplant Program in Denver, CO
Warren D. Shlomchik, MD, of the Yale University School of Medicine in New Haven, CT

All took office at the close of the BMT Tandem Meetings.

Daniel J. Weisdorf, MD, was elevated to president-elect and will assume the presidency in 2011. He is professor of medicine at the University of Minnesota in Minneapolis, the director of the University of Minnesota’s Adult Blood and Marrow Transplant Program, and scientific director for the National Marrow Donor Program and senior research advisor for the CIBMTR.

The new ASBMT president, Dr. Barrett, trained at St. Bartholomew’s Hospital London in 1968, and specialized in hematology and stem cell transplantation, studying in London and Paris. In 1982 he was appointed Professor of Hematology at Charing Cross and Westminster Medical School, and from 1988 at the Hammersmith Hospital, London. Since 1993 he has served at the NIH in Bethesda, MD, as Chief of the National Heart, Lung, and Blood Institute’s Bone Marrow Stem Cell Allotransplantation Section in the Hematology Branch.

Dr. Barrett has been a member of the ASBMT since its foundation. He has a long association with the CIBMTR, as a Member of the Advisory Committee, Councilor, Member of the Executive Committee, Co-Chairman of the GVHD-GVL Working Committee, and Scientific Program chair 2007. He is a member of the International Society for Cellular Therapy and senior editor of their journal Cytoterapy. He is also a member of the European Bone Marrow Transplantation Group and was EBMT president between 1983-1985.

Two New Investigators Win BBMT Editorial Awards

Two medical scientists are the recipients of editorial awards for new investigators for their articles published this past year in Biology of Blood and Marrow Transplantation.

Both are recipients of a $5000 prize, supported by grants from StemCell Technologies, Inc., and StemSoft Software, Inc. Selection of the winning articles was by the BBMT Editorial Board and the ASBMT Publications Committee.

Veronica Bachanova, MD, of the University of Minnesota, in Minneapolis is the winner of the Ernest Mcculloch & James Till Award for best basic science article by a new investigator. The award is supported by an education grant from StemCell Technologies, Inc.

Her article, published in the in February 2009, was “Activated Notch Supports Development of Cytokine Producing NK Cells Which Are Hyporesponsive and Fail to Acquire NK Cell Effector Functions.”

Cristina Fondi, MD, of the University of Florence, in Florence, Italy, is recipient of the George Santos Award for best clinical science article by a new investigator. The award is supported by an education grant from StemSoft Software, Inc.

Her article, published in the August 2009 issue, was “Increase in FOXP3+ Regulatory T Cells in GVHD Skin Biopsies is Associated with Lower Disease Severity and Treatment Response.”

The awards were presented by BBMT Editor-in-Chief Robert Korngold, PhD, and representatives of StemSoft Software and StemCell Technologies.

The awards were presented at the 2010 BMT Tandem Meetings in Orlando.

Lifetime Achievement Award Given to Jon Van Rood

The 2010 recipient of the ASBMT Lifetime Achievement Award is Jon van Rood. Dr. van Rood was recognized for his pioneering work in the field of human leukocyte antigens (HLA).

The ASBMT Lifetime Achievement Award is supported by Pfizer Inc.

Six abstracts chosen as best of 2010 bmt tandem meetings

A total 498 abstracts from 35 countries were accepted for the 2010 BMT Tandem Meetings.

Six of the abstracts were selected for awards by the abstract review committees.

Recipients of the ASBMT Best Abstract Awards for Basic Science Research were:

- Denise Kellar, MD, M.D. Anderson Cancer Center – CD56+ T Cells Co-Expressing a CD56-Specific Chimeric Antigen Receptor Can Target CD56+ Malignancies without Autolysis
- Daniel Kraft, Stanford University – Identification of a Clonogenic Osteochondral Skeletal Progenitor which Forms the Functional Hematopoietic Stem Cell Niche
- Yanling Liao, PhD, Columbia University Morgan Stanley Children’s Hospital – Derivation and Expansion of Neural Stem Cell (NSC) Like Cells from Human Umbilical Cord Blood (HUCB)
- Patrick Stiff, MD, Loyola University Medical Center – Diagnostic Value as a Biomarker for Acute Graft-Versus-Host Disease
- Sophie Pacesny, MD, PhD, University of Michigan – Frequency of CD4+CD25highFoxP3+ Regulatory T Cells has Diagnostic and Prognostic Value as a Biomarker for Acute Graft-Versus-Host Disease
- Sophie Pacesny, MD, PhD, University of Michigan – Frequency of CD4+CD25highFoxP3+ Regulatory T Cells has Diagnostic and Prognostic Value as a Biomarker for Acute Graft-Versus-Host Disease

Each received a $1000 prize. The Basic Science Research awards are supported by a grant from Histogenetics, Inc.

Recipients of the CIBMTR Best Abstract Awards for Clinical Research were:

- Yoshiko Atsuka, MD, Nagoya University Graduate School of Medicine – Comparison of Unrelated Cord Blood Transplantation and Human Leukocytic Antigen Mismatched Unrelated Bone Marrow Transplantation for Adult Patients with Hematological Malignancy
- Sophie Pacesny, MD, PhD, University of Michigan – Frequency of CD4+CD25highFoxP3+ Regulatory T Cells has Diagnostic and Prognostic Value as a Biomarker for Acute Graft-Versus-Host Disease
- Patrick Stiff, MD, Loyola University Medical Center – A Prospective, Randomized Double-Blind Phase III Trial of Aprepitant vs. Placebo Plus Oral Ondansetron and Dexamethasone for the Prevention of Nausea and Vomiting (N/V) Associated with Highly Emetogenic Preparative Regimens Prior to Hematopoietic Stem Cell Transplantation (HSCT)

Each also received a $1000 prize. The clinical research awards are supported by a grant from WellPoint, Inc.
Symposium Report

Therapy for Acute Myelogenous Leukemia: What Therapy and When?
Adapted from a continuing medical education symposium presented at the 2010 BMT Tandem Meetings on February 24, 2010, in Orlando, Florida.
This program is supported by an educational grant from Otsuka America Pharmaceutical, Inc.

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Statement of Need
Acute myeloid leukemia (AML) affects various white blood cells including granulocytes, monocytes, and platelets. Leukemic cells accumulate in the bone marrow, replace normal blood cells, and can spread to the liver, spleen, skin, or central nervous system. There is a greater incidence of leukemia among people exposed to large amounts of radiation and certain chemicals (eg, benzene). Although approximately 80 to 90 percent of children with acute myeloid leukemia attain remissions (absence of leukemic cells), some of those patients have later recurrences. About 70 percent of children with AML achieve long-term remissions with chemotherapy or stem cell transplantation.

Among treatment strategies, chemotherapy is the most common form of therapy for children with AML. Allogeneic stem cell transplantation (SCT), using stem cells harvested from bone marrow, cord blood, or peripheral blood, is the preferred treatment for those patients with AML who are at a high risk of relapse or who have disease that is resistant to other treatments. Allogeneic transplantations use stem cells from a donor. An evidence-based review by the ASBMT found that there is no significant advantage of autologous SCT versus chemotherapy. Most of the data reflect outdated treatment strategies, and studies using modern technologies may affect outcomes; however, the same review found there was a survival advantage for allogeneic SCT versus chemotherapy for patients younger than 55 years with high-risk cytogenetics. Based on the review in adults (and a companion review in children), a closer look at treatment options and therapy regimens warrants further analysis.

Target Audience
This continuing education activity is targeted to clinicians caring for patients undergoing bone marrow and stem cell transplantation.

Learning Objectives
- Interpret molecular prognostic data and the role of HSCT in subsequent therapy
- Describe current approaches to the measurement of minimal residual disease in patients with AML
- Evaluate the role of allogeneic and autologous HSCT in the management of AML

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Introduction

Jeffrey Szer, MD

Treatment for acute myeloid leukemia (AML) has progressed historically from primary chemotherapy to current modes including stem cell transplantation. Strategy has continually improved, as many cooperative group trials published over the years have translated into better outcomes. Transplantations in patients with AML have exceeded those in patients with other hematologic malignancies, eg, chronic myeloid leukemia, over the last decade. Additionally, transplantation grafts from unrelated donor sources have increased, based on better human leukocyte antigen (HLA) typing and matching of alleles. This has been reported in individual registries around the world and is a very common phenomenon, at least in the West.

In 1988, the first biologically randomized study of therapy for AML was published, which demonstrated the increasing effectiveness of allogeneic stem cell transplantsations from matched sibling donors for patients in first remission compared to chemotherapy [1]. This study formed the basis of expert opinion that these patients should at least be given an option for transplantation when in complete remission. The definition of complete remission may have changed since that time, but so have diagnosis, classification, and therapy.

For the future, molecular markers will weigh heavily in prognostic decisions. Analyses of genetic mutations are being refined with new technology. The impact of these mutations on treatment outcome is being analyzed, and patients will be selected accordingly for chemotherapy or stem cell transplantation. Individuals without matched siblings or a relative are being matched with unrelated donors, and cord blood is being used more often, especially in the pediatric population. Cord blood has the advantage of lower incidence and severity of graft-versus-host disease [2]. The next sections will review new findings in molecular markers and their impact on treatment and outcome, minimal residual disease (MRD) as a criterion for relapse following therapy, and the current status of bone marrow transplantation.

Molecular Prognostic Factors

Guido Marcucci, MD

AML is a clinically and genetically heterogeneous disease, and cytogenetic and molecular markers are very useful to guide treatment. Based on the presence or absence of non-random cytogenetic abnormalities, AML patients are divided into favorable, intermediate, and adverse risk groups. Patients with core binding factor (CBF) [ie, t(8;21) or inv(16) or t(16;16)] or acute promyeloctic leukemia (APL) [ie, t(15;17)] fall into the favorable risk category, and patients with complex karyotypes, 11q23, t(6;9), abnormality 5 or 7, and inv(3)/i(3,3) fall into the adverse risk group [3,4]. The remaining patients, including those with normal karyotype, t(9;11), and trisomy 8 are classified into the intermediate risk group; however, cytogenetic risk classification is not accurate in predicting outcome. For example, only 60% of the patients who fall into the favorable risk category have a good outcome. Therefore, the predictive value of cytogenetic aberrations needs to be improved.

Following development of molecular biological assays for testing mutational status or measure expression gene levels, each cytogenetic group is being categorized molecularly and this information is being used to add to that provided by cytogenetic analysis and to guide therapy.

Molecular Markers and Cytogenetic Risk

This section will focus on the molecular heterogeneity of 2 specific cytogenetic groups—core binding factor (CBF) and cytogenetically normal AML (CN-AML)—in which molecular markers have improved the ability to stratify patients to risk-adapted treatment.

CBF-AML

Of AML patients diagnosed with de novo AML, ~13% have CBF AML defined by the presence of t(8;21)(q22.23) or inversion in chromosome 16, inv(16)(p13q22), or the molecular equivalent of these (ie, RUNX1/RUNX1T1 and CBFB/MYH11 respectively) [5-8]. These patients are usually treated differently from other adult AML patients by administration of high-dose cytarabine (HiDAC). Cancer and Leukemia Group B (CALGB) studies have shown that the cure rate of 10% to 25% has improved to 50% or 60% in these patients [9,10]; however, 40% to 50% of adults <60 years old, based on these studies, are not cured, so it begs the question as to whether molecular markers aid in the choice of therapy to improve the cure rate.

There are molecular markers that are associated with outcome in CBF AML and allow us to recognize molecular high-risk patients in this otherwise favorable group. Studies are underway to test whether these molecular markers can be used in CBF AML for choosing the appropriate therapy. KIT (CD117) is a tyrosine kinase receptor that promotes cell proliferation and survival and has been the first mutation recognized to have a prognostic impact in CBF. Activating mutations of KIT usually associated with KIT overexpression predict a worse outcome in patients with CBF mutations. Patients with t(8;21) and/or inv(16) treated on the CALGB protocol and assigned to optimal post-remission therapy with HiDAC experience a long-term survival of only ~20% if they also harbor KIT mutation [11]. This finding was validated by multivariate analysis showing that a patient with KIT mutations has 5 to 6 times the risk of de novo AML than a CBF mutation.

Two abstracts recently presented at the 2009 American Society of Hematology meeting suggested that the type and number of KIT and other mutations may improve the prediction of outcome in CBF AML. These abstracts, the German-Austrian AML Study Group reported treating patients on an anthracycline/cytarabine-based induction therapy and HiDAC as consolidation therapy. In addition to KIT, these authors reported RAS mutations, FLT3-TKD (tyrosine kinase domain), and FLT3-ITD (internal tandem duplication) mutations [12,13]. Patients with more than 1 mutation have worse outcome. Interestingly, these studies showed that FLT3-ITD appears to be associated with worse outcome in CBF AML, but these results need to be confirmed.

CN AML

CN-AML patients harbor molecular heterogeneity that has been exploited to guide treatment. About 45% to 50% of de novo adult AML patients have CN-AML [14,15].
These groups have been categorized previously as having an intermittent cytogenetic risk. The cure rate for these patients when treated with autologous stem cell transplantation or 3 to 4 cycles of HiDAC is about 40% within the CALGB protocols [16]. Several molecular markers have emerged as strong prognostic indicators for this group of patients. At least 3 markers appear to be clinically relevant and should be tested for at diagnosis: FLT3-ITD, NPM1 mutations, and CEBPA mutations. FLT3-ITD has an adverse prognostic impact but NPM1 and CEBPA mutations are associated with better outcome.

The most recent World Health Organization (WHO) classification for AML includes AML with mutated NPM1 and CEBPA as new provisional entities for AML and also recommends that each patient be tested for FLT3 [17]. The National Comprehensive Cancer Network (NCCN) guidelines and the new European Leukemia Net guidelines both include the molecular risk based on the presence or absence of FLT3, CEBPA, and NPM1 mutations to categorize patients with CN-AML or normal AML as favorable or intermediate risk. These classifications, however, do not take into account other markers and newer emergent markers. For example, recent findings with patients expressing the Wilms tumor-1 (WT1) mutations show worse outcomes than patients with WT1 wild type. Furthermore, aberrant expression levels of genes may predict for a worse outcome. Three such genes have been validated by several groups: if patients have a high expression of the genes BAALC, ERG, or MN1, they have a significantly worse outcome than patients with lower expression [18-21]. The prognostic significance of other mutations such as FLT3-TKD is still being evaluated.

**Prognostic Significance of Markers in Patients Younger than 60 Years**

Why are molecular markers complicated for guiding treatment in AML? First, the markers are not mutually exclusive, and new ones are being identified continuously. Second, there are different types of mutations and polymorphisms with each gene that may have distinct prognostic impact. Using CEBPA in CN-AML as an example, 1 mutation is not enough to define the molecular risk. If 2 mutations, 1 on each allele, are concurrently present, it is possible to stratify these patients into a low molecular risk category. Figure 1 shows the associations of different mutations in patients. The dilemma is how to treat patients who have a combination of unfavorable factors like FLT3-ITD and favorable factors like NPM1 or CEBPA. The solution may be to combine these molecular markers and try to evaluate the prognostic impact of molecular combinations.

The prognostic impact of the combination of 2 markers, FLT3-ITD, and NPM1 mutations, were assessed in patients with cytogenetically normal AML. The event-free survival (EFS) at 5 years is approximately 50% in patients with FLT3-ITDmut/NPM1mut, and only approximately 25% in patients with FLT3-ITDmut/NPM1wt [22]. The former have been considered to be a molecular low-risk group and the latter, a molecular high-risk group. This classification has been refined by assessing the molecular risk in patients with the CEBPA mutation versus wild type. CEBPA mutations are not concurrently present with NPM1 mutations. Patients with CEBPA mutations, especially those carrying 2 concurrent mutations, have a relatively good prognosis, similar to patients with FLT-ITDmut/NPM1mut and fall into a molecular low-risk group [23]. By combining the 3 markers with other emerging markers, such as other mutations (WT1) or aberrant expression levels of genes (ERG, BAALC, MN1), the molecular risk classification can be further refined [23].

Other recurrent mutations are being identified in AML using a next generation sequencing approach. For some of them, their predictive or prognostic value remains to be fully validated. IDH1 and IDH2 gene mutations, for example, were found initially in glioma cells of brain tumors and more recently have been discovered in AML. In a study measuring IDH1 and IDH2 gene mutations from 358 patients with CN-AML from the CALGB patient data bank, approximately 30% of patients were found to

![Figure 1. Frequencies of combinations of common mutations. More than 1 mutation has been found in each patient with cytogenetically normal acute myelogenous leukemia (CN-AML). ITD indicates internal tandem duplication; TKD, tyrosine kinase domain; PTD, partial tandem duplication; WT1, Wilms’s tumor-1.](image-url)
have mutations [24]. These markers appear to impact the long-term outcome in younger NPM1 mutated patients, whereas the chemosensitivity in older patients needs to be validated as a prognostic indicator. There is evidence that IDH1 may refine the prognostic value of the NPM1 mutation and the FLT3-ITD mutation assessment, as they separate out patients with worse outcome among those patients with molecular low risk based on the NPM1 mutated FLT3-ITD™ status. IDH2 seemingly has an adverse impact on the older patients.

Prognostic Significance of Markers in Patients Older than 60 Years

Most molecular marker studies have been done in patients <60 years old with de novo AML, but two-thirds of patients diagnosed with AML are older than 60 years. Prognosis remains poor for older patients, and the prognostic impact of molecular markers has yet to be evaluated for these patients. A recent CALGB study analyzed 148 de novo CN-AML patients older than >60 years treated intensively with chemotherapy for NPM1 mutations. Patients with NPM1 mutation show higher complete response (CR) rate and a significant increase in OS compared with NPM1 wild type patients (84% versus 48%) [25]. This is an important finding because it may allow risk stratification of cytogenetically normal older patients into treatment regimens incorporating intensive chemotherapy rather than into low-intensity treatments or best supportive care.

In conclusion, a few molecular markers are usable in the clinic today—KIT, FLT3, NPM1, and CEBPA for the CBF and CN-AML. Others need to be validated. Several molecular markers are being identified and several more will be found when sophisticated sequencing techniques are used to define the mutations in AML. Other molecular markers that are being heavily investigated are micro RNAs. These are non-coding RNAs that appear to be independent prognostic factors when they are considered in parallel with other molecular markers, including the mutation or change in expression of coding genes [26]. For example, miR-181a expression has been independently associated with outcome in molecular high-risk CN-AML [27]. An important consideration is that what is being discussed today may not be relevant tomorrow. As we change therapies for AML, some markers may change their predictive and prognostic significance.

Impact of Minimal Residual Disease Measurement in Pediatric AML

Dario Campana, MD, PhD

Minimal Residual Disease

Periodic examination of bone marrow samples for residual leukemic cells is an inherent part of the clinical management of patients with leukemia, but morphology has very limited sensitivity, and even an experienced hemopathologist has difficulties in distinguishing leukemic cells that represent less than 5% of the bone marrow population. The rationale for studies of MRD (disease undetectable by conventional morphologic techniques) is that a more accurate assessment of the residual leukemic burden would lead to more tailored clinical management practices and consequently improve cure rates.

Methods to Identify MRD

A number of methods have been developed to study MRD in patients with acute leukemia. These include flow cytometry, polymerase chain reaction (PCR) amplification of immunoglobulin (Ig)/T-cell receptor (TCR) genes, fusion transcripts, and NPM1 mutations. Flow cytometric detection of aberrant immune-phenotypes, which are found in approximately 90% to 95% of patients with AML, has a sensitivity of 1 leukemic cell in 1000, although in some patients it may be as high as 1 in 10,000. PCR amplification of Ig/TCR genes is a method widely used in acute lymphoblastic leukemia (ALL) to detect MRD, but this technique is not applicable to AML because less than 10% of patients have rearrangement of these genes. The third technique is the PCR amplification of fusion transcripts, which can currently be used in approximately one-third of patients with AML. The sensitivity of this method varies from 1 in 1000 to 1 in 100,000. Among other methods available to study MRD in patients with AML is PCR amplification of NPM1 mutations, which is applicable to about 30% of patients, but less

Figure 2. Clinical significance of minimal residual disease (MRD) in childhood acute myelogenous leukemia (AML). Overall survival (OS) was based on MRD post induction-1. The patients were in morphologic remission [41].
than 10% of children with AML. The clinical value of this approach has not yet been established. Another method is PCR amplification of the WT1 gene. How many cases of AML actually overexpress WT1 in comparison to normal hematopoietic progenitors is not entirely clear, but recently published work indicates that when the bone marrow of AML patients is compared to normal bone marrow samples, about 13% of cases will have a greater than 2 log difference in overexpression [28]. If the comparisons are made using peripheral blood, about 46% of patients with AML will have WT1 overexpression. A prognostic difference was found in patients from the European Leukemia Net treated with induction therapy, where the WT1 expression had a signal decrease by greater than 2 logs compared to patients in whom the signal decreased by less than 2 logs. Those with a less than 2 log reduction had a 79% relapse rate, and patients with a >2 log reduction had a 48% risk of relapse.

**MRD as Prognostic Factor**

That MRD is a strong prognostic indicator in AML was first shown by reverse transcriptase (RT)-PCR studies of genetically defined subsets of AML targeting fusion transcripts of the promyelocytic leukemia retinoic acid receptor alpha gene (PML-RARA) [29,30]. Other studies indicated that RT-PCR amplification of fusion transcripts in AML1-ETO or inversion 16 AML can also provide useful prognostic information [31-33]. In adult AML, flow cytometry has been extensively used to monitor MRD. San Miguel and colleagues reported that detection of MRD after induction strongly correlated with subsequent relapse, and there was a direction correlation between level of MRD and risk of relapse. If MRD was >1%, >0.1% to <1%, or >0.01% to <0.1%, the incidence of relapse was 85%, 45%, and 14%, respectively [34]. Maurillo and colleagues reported that MRD post-induction and post-consolidation was a strong prognostic indicator. Their paper included an analysis of patients undergoing transplantation and specifically addressed the clinical importance of MRD pre-transplantation; they demonstrated that in patients undergoing allogeneic or autologous transplantation, detection of MRD pre-transplantation was a strong predictor of outcome [35].

The experience in children with AML is more limited. An early trial (AML97) in a small group of patients showed that MRD detection at the end of induction was the strongest independent prognostic indicator. No other factor, including cytogenetics, age, or leukocyte count, contributed to prognosis in this subset of patients (Figure 2). This analysis included morphologically negative patients, i.e., all patients who had blasts by morphology were excluded. Patients were divided into 2 groups according to the presence or absence of MRD: for children who were MRD-negative, the probability of 3-year survival was 63% ± 10%, whereas in those who were positive, survival was 36% ± 14% [36]. For children with AML undergoing transplantation, a recent report indicated the importance of MRD measurements pre-transplantation. Investigators used WT1 with a threshold of 0.5 units, which was the level they found expressed in normal bone marrow samples, and noticed that patients who had levels of WT1 higher than the threshold had a significantly higher risk of relapse post-transplantation [37].

Evidence put forth by different groups looking at different subsets of patients using different methodologies suggests that MRD is a very strong prognostic indicator in AML. In 2002, we initiated a multicenter trial (AML02) in which MRD was used for risk stratification and guiding the intensity of therapy. Several institutions participated in this trial, and all samples were tested for MRD monitoring by flow cytometry.

According to the schema of the AML02 trial, MRD was measured at many different time points. The most critical points were after induction 1 and after induction 2. In this trial, 210 samples were measured at diagnosis, and aberrant phenotypes were found in 95% of the patients (Figure 3). MRD could be measured in 99% of the 1313 follow-up samples that were received. Initially, because the samples were shipped with a 24- or 48-hour delay, there was a concern that the samples would not be suitable for MRD analysis, but in fact the majority of samples were adequate.

The prevalence of MRD ≥ 0.1% after first induction was 39%, similar to that previously reported [38]. The overall survival was 71%. MRD remained a significant predictor of outcome. Patients who were MRD positive at the end of induction 1 still did worse than those who were MRD negative. Mean cumulative incidence of relapse was 38.6% for those who had MRD ≥0.1% and 16.9% for those with MRD <0.1%. The outcome of patients with low levels of MRD (0.1% to <1%), however, was not significantly different than that of MRD-negative patients. This suggests that intensification of therapy may be beneficial for patients who have low levels of MRD, but
for patients who have very high levels, current treatment strategies still are not adequate. New agents are needed for this patient population. At the end of the induction 1 none of the 21 patients with inv(16) had MRD; by contrast, 25 of 29 patients with FLT3-ITD were MRD positive. This trial, measurements of MRD in bone marrow were compared to MRD in peripheral blood, and the prevalence of MRD was higher in bone marrow than in peripheral blood. A new trial (AML08) uses MRD to guide therapy as it was used in AML02. Patients who have high levels of MRD after first induction are reclassified as having high-risk AML. If they have low levels of MRD, but it persists after second induction, they are also reclassified as high risk. All high-risk patients are candidates for transplantation.

Advances in MRD Detection
All of the studies reviewed so far were done with second-generation flow cytometry instruments that are capable of 4-color analysis. The instruments available now are capable of analyzing more parameters. With these instruments it may be possible to achieve a sensitivity of 1 in 10,000 in every patient with AML. In efforts to identify additional markers for MRD studies, we compared the gene expression profiles of 200 cases of AML to those of normal CD34+ and CD33-positive cells. This allowed us to identify a new set of markers for MRD studies. Another interesting advantage of multiparameter flow cytometry is the possibility of looking not only at MRD but also at some biologic features of the MRD cell population such as leukemia stem cells and drug resistance molecules.

Flow cytometry can be used to analyze signaling pathways that are targeted by tyrosine kinase inhibitors. For example, in some of our current trials we are measuring the effect of sorafenib on the signaling pathways that it targets directly in leukemic cells. This presents a new possibility for MRD techniques that goes beyond defining prognosis. It should provide interesting information about how drugs work and about drug resistance.

Current Status of Allogeneic and Autologous Hematopoietic Stem Cell Transplantation in AML Management

Frederick R. Appelbaum, MD

This section will provide a review of the current status of hematopoietic stem cell transplantation (HSCT) in the management of adult AML. It will focus predominantly on randomized prospective trials or meta-analyses, and when those are lacking, on the expert panel conferences that have been held and published recently.

In adults younger than 60 years, 3 categories of patients need to be considered: (1) patients with primary induction failure; (2) those with recurrent disease; and (3) those in first remission. Primary induction failure is defined as the condition in individuals who have persistent disease after 2 cycles of induction containing conventional dose cytarabine or a single cycle of HiDAC. Persistent disease in this instance is defined as more than 5% blasts in the bone marrow. If disease persists after 2 cycles of induction, there is no potential for cure with chemotherapy. Some patients who undergo an allogeneic transplantation at that time can be salvaged. A paper from the City of Hope shows that about 20% of patients given an allogeneic transplantation for primary induction failure can turn out to be long-term survivors more than a decade after the transplantation [39]. A study by Craddock and colleagues found that the results from unrelated donor transplantation (URD) for primary induction failure are similar to those for related donor transplantsations. This trial involved 186 patients identified through the registry who had received 2 to 3 courses of induction therapy, failed induction, and then received URD transplantsations. The day 100 mortality rate was 16%, and the 2-year survival rate was 31%. In a multivariate analysis, shorter duration from diagnosis to transplantation, having better intermediate risk cytogenetics, and receiving a reduced intensity regimen were all associated with improved outcome [40]. The studies of Fung and Craddock emphasize the importance of incorporating HLA typing into the initial evaluation of new patients with AML so that they can expeditiously move on to transplantation if initial induction chemotherapy fails.

In individuals who have recurrent disease, a clinically useful prognostic index can improve choice of therapy. To evaluate the management of patients under age 60 who have failed first-line chemotherapy, a multivariate analysis was done in 667 AML patients in first relapse who were selected from 1540 newly diagnosed non-M3 AML patients from several consecutive Cooperative Group trials. Patients could be divided into 3 risk groups with favorable, intermediate, or poor outcomes, based on age, cytogenetics, and the interval from first remission to subsequent relapse. Within each of these groups were patients who received either chemotherapy or a transplantation. Within each group, the outcome, based on whether they received chemotherapy or transplantation after their first relapse, showed a remarkable improvement in patients who received a transplantation versus chemotherapy (Table 1) [41]. There has not been and may never be a prospective randomized study of transplantation versus chemotherapy for patients who have failed first-line chemotherapy. Given this type of data, one could suggest that allogeneic transplantation is appropriate for any younger patient who has failed first-line chemotherapy.

To address the role of allogeneic hematopoietic cell transplantation during first remission, a recent meta-analysis was conducted involving 23 clinical trials and more than 5800 patients. Patients were given induction chemotherapy, and if they achieved complete remission, they were then assigned to an allogeneic transplantation if they had a matched sibling donor. If they did not, they were given chemotherapy or autologous transplantation. In order to be included in the meta-analysis, the studies had to have survival as their outcome, and all had to have been analyzed on an intent-to-treat basis so

Table 1. Management of Recurrent Acute Myelogenous Leukemia in Younger Patients [41]

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Treatment</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>Chemotherapy</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>Hematopoietic stem cell transplantation</td>
<td>88%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Chemotherapy</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Hematopoietic stem cell transplantation</td>
<td>48%</td>
</tr>
<tr>
<td>Poor</td>
<td>Chemotherapy</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Hematopoietic stem cell transplantation</td>
<td>26%</td>
</tr>
</tbody>
</table>
that patients who had matched siblings but did not receive a transplantation were included within the transplantation group. The results of this meta-analysis showed that there was a significant OS benefit for individuals who received an allogeneic transplantation in first remission. When the results were analyzed according to cytogenetic risk group, transplantation provided a survival benefit for those with intermediate- or high-risk cytogenetics, but not for those with favorable risk disease. Based on this analysis, one could recommend an allogeneic transplantation from a matched sibling for all patients with AML in first remission, except those who were a good risk [42]. Within this good risk group are some individuals, particularly those with AML with a mutation in c-KIT, who have a very poor outcome. Though it has not been proven that allogeneic transplantation would benefit these individuals, it is a reasonable hypothesis. Also among those with otherwise favorable risk cytogenetic AML are a portion with secondary leukemia, i.e., leukemia developing after exposure to chemotherapy, often an anthracycline. These individuals have a poor outcome with conventional chemotherapy and thus also might be considered for allogeneic transplantation in first remission.

The intermediate risk group, made up of mostly cytogenetically normal individuals, can be further subdivided into those who have mutant CEBPA and those that have mutant NPM1 but wild-type FLT3-ITD. Those individuals tend to have a favorable outcome, whereas all other genotypes tend to do unfavorably. A landmark paper published in the *New England Journal of Medicine* in 2008 by Schlenk showed that if the patient had mutant NPM1 without FLT3-ITD, there was no apparent advantage for transplantation in first remission because, in an intent-to-treat analysis, for patients with NPM1mut/FLT3wt, RFS was the same regardless of whether or not a donor was available. If the patient had any genotype other than NPM1mut/FLT3wt, there was definite benefit to receiving the allogeneic transplantation or at least having the donor and the potential for transplantation while in first remission [43].

**Poor Risk AML**

Finally, there are the individuals who have poor-risk AML. A study from the Southwest Oncology Group (SWOG), where patients with high-risk AML were assigned to allogeneic transplantation if a matched sibling donor was available, showed a benefit for receiving an allogeneic transplantation in first remission with a 44% 5-year survival rate compared with 14% in those who did not receive the transplantation [44]. This unfavorable risk group can be further subdivided into those with a poor and those with a very poor prognosis. Recently, a distinct group of patients have been identified as having a monosomal karyotype defined as having AML with 2 or more distinct autosomal chromosome monosomies or 1 single autosomal monosomy and an additional structural abnormality [45]. In a study of 134+ AML patients treated on SWOG protocols, we identified 176 patients with a monosomal karyotype. Their overall survival at 4 years was only 3%, and the only survivors have been treated with hematopoietic cell transplantation.

**Unrelated Donor Transplantation**

More than two-thirds of patients do not have matched sibling donors. With modern HLA typing that relies on molecular rather than serologic methods, transplantation from 8 of 8 (HLA-A, B, C, and DRb1) matched unrelated donors for AML in first remission yields essentially the same results that are seen using matched siblings. There may be more graft-versus-host disease, but the 2 are similar in OS [46].

A recent study from the FHCRC and University of Minnesota compared the outcomes of matched unrelated donor transplantation to that seen using double cord blood as the source of stem cells. In this study, the preparative regimens used for unrelated and cord blood transplantation were essentially the same: cyclophosphamide and total body irradiation (CY/TBI) or cyclophosphamide, fludarabine, and total body irradiation (CY/FLU/TBI). The form of graft-versus-host prophylaxis was likewise similar to calcineurin inhibitor (CNI) and methotrexate in unrelated donors or a CNI and mycophenolate mofetil (MMF) in cord blood patients. There were no differences in DFS between the matched unrelated donors and the double cord blood group. OS likewise was similar in both groups [47]. These individuals were aged 47 years or less. There was more transplantation-related mortality with double cord blood transplantation, but there was markedly less relapse with double cords than with matched unrelated donors. In this situation, because matched siblings have the same result as matched unrelated donors and matched unrelated donors have the same result as double cord blood transplantations, by that logic, one could substitute any of these 3 sources of stem cells for individuals in need of a transplantation.

**Autologous Transplantation**

What is the role of autologous transplantation in AML? A meta-analysis that combined all the
randomized trials of autologous transplantation for AML analyzed on an intent-to-treat basis showed that there was no clear advantage for autologous transplantation for AML in first remission based on randomized trials [48]. A single autologous transplantation appears to be no better or worse than going through 3 or 4 cycles of intensive consolidation therapy (Figure 4).

Reduced Intensity Transplantation in Patients Older than 60 Years

A randomized study of intensive chemotherapy that compared initial induction chemotherapy using either 45 mg/m² or 90 mg/m² per day for 3 days was recently reported [53]. This study was restricted to patients who had a performance status of 2 or better. The trial showed an advantage for the higher anthracycline dose in patients’ ages 60 to 65 years, but even with this improvement, the estimated survival at 2 to 3 years post-induction was approximately 25%. Above age 65 years, there was no advantage to escalating the dose of the anthracyclines, and OS was 15%. Even with the NPM1-positive group, the results were not much better than a 20% survival rate going out 2 or 3 years [49].

Reduced intensity transplantation may be considered for this population of patients. A number of phase 2 trials of reduced intensity allogeneic transplantation for older patients with AML in first CR have recently been reported, with survival at 4 years averaging around 40% to 45%. For example, a recent report by Gyurkiczka, et al described 160 patients, older than 55 years, treated with reduced intensity conditioning with fludarabine and low-dose total body irradiation. The 5-year overall survival was 40% and was not different between patients with matched related donors versus those with unrelated donors [53]. There is, of course, significant selection bias as to who receives transplantsations and who does not, and the selection bias is not necessarily predictable. Some doctors may prefer to perform transplantations on someone with high-risk cytogenetics and may avoid it in those with favorable cytogenetics. Alternatively, healthier individuals with fewer comorbidities are likely to be referred for transplantation [50].

There are at least 2 other studies, both retrospective, that suggest an advantage for transplantation compared with chemotherapy. One is from a Japanese group showing the outcomes comparing allogeneic transplantation to chemotherapy for a large group of patients aged 50 to 70 years. The transplantation group had a more favorable outcome than those assigned to chemotherapy [51]. Finally, there are data from the Medical Research Council (MRC). In the favorable- and intermediate-risk groups, allogeneic transplantation seems to benefit those who are older than 45 years, but in cytogenetically poor disease, the outcomes are unfavorable whether reduced intensity transplantation occurs in first remission or not.

Conclusion

For patients with matched related donors who are younger than 60 years, what are the indications for transplantation? For patients who fail to achieve first remission (primary induction failure), allogeneic hematopoietic cell transplantation offers the best, and likely the only, chance for cure. Recurrent disease in any category, even in those who have CBF leukemia, is generally an indication for transplantation. For patients in first remission in the cytogenetic good risk group, transplantation should be considered only for those who are c-KIT positive and those who have secondary AML. For intermediate risk candidates, transplantation should be considered for all patients, except for the subgroup who are CEBPA positive, or those who are NPM1 positive and FLT3 negative. Transplantation should be strongly considered for all individuals with poor risk cytogenetics who have matched related donors.

For patients with AML in first remission older than 60 years, and probably up to age 70 and in selected cases even older, reduced intensity transplantation is a reasonable approach if the goal of the patient is long-term survival. There is little question but that allogeneic transplantation can reduce the quality of life in the short term, but for those who understand the risks and benefits of the procedure, available data would support considering this option.

For younger and older patients, outcomes using matched related and matched unrelated donors are similar. Transplantation outcomes using double cords as the source of stem cells look very similar to those with matched unrelated donors, at least in our hands, for patients under age 45 years. There are more complications with double cord transplantations than there are with matched unrelated or related donors, but relapse rates appear to be significantly lower, leading to similar overall survivals.

References

12. Paschka P, Du J, Schlenk RF, et al. Type and number of secondary molecular lesions improve outcome prediction in acute myeloid leukemia (AML) with inv(16) or t(16;16): a study of the German-Austrian AML Study Group (AMLSG)


Therapy for Acute Myelogenous Leukemia: What Therapy and When?

CME Assessment Test

1. Several large studies have helped categorize chromosomal abnormalities into good, intermediate, and poor risk. Choose one the correct answer(s).
   A. Patients with inv (16)/t(16;16)/del(16q) fall in the good risk category.
   B. SWOG/ECOG indicate that Normal, +8, +6, -Y fall into the good risk category.
   C. Complex karyotypes fall into the poor risk categories.

2. Two abstracts presented at the last American Society of Hematology meeting suggested that the type and number of secondary mutations may improve prediction of outcome in acute myelogenous leukemia (AML). Choose the correct answer(s).
   A. Expression levels of genes, ie, high expression of genes such as BAALC or ERG predict for worse outcome.
   B. FLT3 mutations showed a trend for shorter overall survival.
   C. JAK2 kinase mutations were often seen in patients with AML.

3. Molecular marker analyses have been done mostly in patients younger than 60 years with de novo AML. Which statements are true?
   A. Most patients diagnosed with AML are older than 60 years.
   B. Age is not a prognostic marker.
   C. A CALGB study found that NPM1 mutation in older patients does not really predict a good outcome.

4. A number of methods are used to determine minimal residual disease (MRD). These include flow cytometry and polymerase chain reaction (PCR) amplification of fusion transcripts or immunoglobulin T-cell receptor (TCR) genes. Which statements are true?
   A. Flow cytometry is not very sensitive.
   B. PCR can pick up false positives.
   C. PCR amplification of TCR genes can only be used in children with acute lymphoblastic leukemia (ALL).

5. MRD post-induction and post-consolidation is a strong prognostic indicator. Which statement is not true?
   A. If MRD was ≥ 1% the incidence of relapse was 85%.
   B. If patients were MRD positive after induction, subsequent therapy was more intensive.
   C. MRD could be determined by the presence of blasts either circulating or in the bone marrow.
   D. Identification of MRD is not useful for predicting outcome after therapy.

6. In the AML 08 trial the presence of MRD was used to recommend further therapy. What would you do?
   A. The presence of high levels of MRD after induction requires readministration of induction.
   B. The presence of high levels of MRD after induction requires intensification of therapy for second induction.
   C. The presence of MRD in a patient after second induction is recommended for transplant.

7. There are 3 categories of patients younger than 60 years who will benefit from transplantation. Which category is NOT included?
   A. Patients with intermediate risk cytogenetics
   B. Patients with primary induction failure
   C. Patients with recurrent disease
   D. Patients in first remission

8. In individuals with recurrent disease, a clinically useful prognostic index can improve the choice of therapy. Is this a reasonably true hypothesis?
   A. Yes
   B. No

9. Which of the following will benefit the recipient of a transplantation the most?
   A. The availability of a related donor
   B. Using one’s own cells, ie, an autologous transplantation
   C. In the absence of a related donor, the use of a matched unrelated donor
   D. Being of poor risk
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