Spotlight on AML: Transplant outcomes improving

Worldwide, more than 7,000 allogeneic hematopoietic cell transplants (HCT) are performed annually for acute myeloid leukemia (AML), making it the most common and fastest-growing indication for allogeneic transplantation.

In AML, research has clarified the role of transplant, resulting in improved outcomes. In addition, non-myeloablative and reduced intensity conditioning regimens have expanded this therapy to more patients who would previously have been ineligible.

Table 1 shows National Marrow Donor Program (NMDP) data demonstrating steadily increasing one-year survival in adults undergoing allogeneic HCT for AML.

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<table>
<thead>
<tr>
<th>YEAR OF HCT</th>
<th>NUMBER OF CASES</th>
<th>ONE-YEAR SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008-2010</td>
<td>2,837</td>
<td>58%</td>
</tr>
<tr>
<td>2004-2007</td>
<td>2,362</td>
<td>52%</td>
</tr>
<tr>
<td>1999-2003</td>
<td>1,287</td>
<td>41%</td>
</tr>
<tr>
<td>1987-1998</td>
<td>919</td>
<td>26%</td>
</tr>
</tbody>
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Research defines optimal transplant timing and advances

The improvement in HCT outcomes in AML mirrors the trend for improved survival in nearly all diseases treated by allogeneic transplantation. [1,2] A key reason for improved survival is a better understanding of optimal timing for HCT. Research has shown, for example, that transplanting AML patients with high-risk cytogenetics while in first complete remission (CR1) improves outcomes compared with chemotherapy or delaying transplant. [3]

Other important reasons for improved survival include:

- Improved patient/donor human leukocyte antigen (HLA) matching using DNA-based tissue typing
- Better understanding of which HLA loci are most significant to outcomes
- Improved ability to manage post-transplant complications

Improved clinical outcomes from HCT for AML are driven by advances in the biology of AML which help identify patients at higher risk of relapse from chemotherapy alone. These biological markers provide clinicians with personalized information to guide the decision process for each patient.

Transplant consultation guidelines in AML

NMDP/Be The Match and the American Society for Blood and Marrow Transplantation (ASBMT) have jointly developed transplant consultation guidelines based on current clinical practice, medical literature and evidence-based reviews. According to the guidelines for AML, shown in Figure 1, patients with the following subtypes of AML should be HLA-typed and referred for transplantation consultation as soon as disease risk is known.

- High-risk AML including:
  - Antecedent hematological disease (e.g., myelodysplasia (MDS))
  - Treatment-related leukemia
  - Induction failure
  - CR1 with intermediate- or poor-risk cytogenetic or molecular markers
  - AML after relapse
  - CR2 and beyond

Acute Myelogenous Leukemia (AML)

This issue of Transplant Connection focuses on acute myeloid leukemia (AML) including recent transplant outcomes, advances in the understanding of AML genetic mutations and the impact of age on transplant outcomes.

In addition, I’d like to invite you to attend our Advances in Blood and Marrow Transplantation CME-certified symposium on April 27, 2013. I’m excited to discuss the latest in optimal pathways of care for patients with complex hematological malignancies. Details about this free event are on page 3.

Joseph P. McGuirk, DO
Director, Blood and Marrow Transplant (BMT) Program
University of Kansas Cancer Center

BMT program highlights

- Region’s largest BMT and acute leukemia program: The widest range of treatment options, including photopheresis and clinical trials
- Region’s first BMT program accredited by the Foundation for Accreditation of Cellular Therapy, or FACT
- More than 1,800 successful transplants
- Designated as a BMT-CTN core center
- Designated as a Center of Excellence for all payers that utilize this distinction
- Network member of the National Marrow Donor Program since 1995
- Medicare-approved since 1977
Unlike patients with AML who have low- and high-risk cytogenetic risk factors, AML patients in the intermediate-risk group have heterogeneous clinical outcomes and require a more individualized treatment plan. The majority of AML patients fall into the intermediate-risk group, and between 45% and 50% of these will have normal cytogenetics. In order to devise a personalized treatment plan for these patients, clinicians must understand and incorporate a growing number of molecular markers of prognosis. Although research on genetic mutations in AML has yielded dozens of genetic biomarkers with potential prognostic value, there are challenges to incorporating this fast-moving data in everyday patient care. For example, some genetic mutations only exert their influence when coexisting with other mutations or chromosomal translocations. Also, most of these recently identified markers have been isolated in small subsets of patients, making it difficult to know how generalizable the results may be.

Recent research, however, has identified three molecular markers in AML that have now also been integrated into clinical practice guidelines developed by the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) consortium. [1,2]

Prognostic utility of genetic markers in intermediate-risk AML

Three markers define genetic risk groups

The NCCN and ELN guidelines incorporate the FLT3-ITD, NPM1, and CEBPA molecular markers/genetic abnormalities, which were included in the World Health Organization (WHO) classification for AML in 2008. [3] Based on the mutational status of these markers, AML patients can be classified into four genetic risk groups: favorable, intermediate-I, intermediate-II, and adverse. In order to best stratify patients with normal cytogenetics, it is recommended that all patients with AML and normal cytogenetics have a complete remission according to ELN genetic risk groups. Patients in the favorable group also have significantly better CR, DFS, and OS rates compared to patients in the adverse classification (p<0.001). Results were similar in patients ≥60, with patients in the favorable group also having significantly better CR, DFS, and OS rates compared to patients in the adverse group.

Early consideration of transplant recommended

A recent review by two international experts in AML and stem cell transplantation, Drs. Stephen Forman and Jacob Rowe, highlights the need for consideration of transplantation for patients with AML, particularly given the difficulty of achieving a second remission for patients with relapsed AML. [5] Given the significantly worse outcomes for patients with AML in the intermediate-I, II, and adverse risk categories, allogeneic stem cell transplantation is recommended for all intermediate/adverse risk AML patients in first complete remission, depending upon donor availability.

Timely referral to a transplant center immediately following completion of induction chemotherapy is critically important to moving quickly to HCT while in remission.

Physicians at the University of Kansas Cancer Center Blood and Marrow Transplant (BMT) program are available to discuss treatment planning and stem cell transplantation evaluation for patients with hematologic malignancies, including AML, ALL, and MDS through our referral line at 800-332-6048. Physicians at the University of Kansas Cancer Center Blood and Marrow Transplant (BMT) program are available to discuss treatment planning and stem cell transplantation evaluation for patients with hematologic malignancies, including AML, ALL, and MDS through our referral line at 800-332-6048. The full conference brochure is available at continuinged.ku.edu/kumc/bmt. Registration is free of charge. Call 877-404-5823 or visit continuinged.ku.edu/kumc/bmt

Impact of age on outcomes

The 2008 revision of the World Health Organization (WHO) classification of myelodysplastic syndromes (MDS) has shown that age has no effect on outcomes. [1]

No significant impact of age on transplant outcomes in AML/MDS

A study of reduced intensity transplantation in 1,080 adults older than 40 years of age with AML in first complete remission or myelodysplastic syndromes (MDS) that has shown age has no effect on outcomes. [1]

Table 2: Three-year post-transplant treatment outcomes of younger (age <60 years) patients with primary AML according to ELN genetic risk groups. [4]

<table>
<thead>
<tr>
<th>Outcome at 3 years</th>
<th>ELN GROUP</th>
<th>FAVORABLE</th>
<th>INTERMEDIATE I</th>
<th>INTERMEDIATE II</th>
<th>ADVERSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR rate (%)</td>
<td>n=339</td>
<td>n=144</td>
<td>n=156</td>
<td>n=179</td>
<td></td>
</tr>
<tr>
<td>Complete remission</td>
<td>96%</td>
<td>76%</td>
<td>79%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>55%</td>
<td>23%</td>
<td>34%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>66%</td>
<td>28%</td>
<td>45%</td>
<td>12%</td>
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</tr>
</tbody>
</table>

Table 3: Two-year overall survival of patients >40 years transplanted for MDS or AML in first complete remission.

<table>
<thead>
<tr>
<th>AGE RAGE (yr)</th>
<th>MDS</th>
<th>AML</th>
</tr>
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<tr>
<td>55-59</td>
<td>54%</td>
<td>50%</td>
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<tr>
<td>60-64</td>
<td>43%</td>
<td>37%</td>
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A Phase II trial of PF-04449913, a Hedging inhibitor, in combination with low-dose Ara-C or decitabine in patients unfit for conventional induction chemotherapy. Hedging inhibitors have shown promise in targeting the leukemia stem cells in pre-clinical models, and this early phase study is designed to find the maximum tolerated dose and efficacy of the PF-04449913 in combination with traditional AML therapy.

References

Prognostic utility of genetic markers in intermediate-risk AML

Unlike patients with AML who have low- and high-risk cytogenetic risk factors, AML patients in the intermediate-risk group have heterogeneous clinical outcomes and require a more individualized treatment plan. The majority of AML patients fall into this intermediate-risk group, and between 40% and 50% of these will have normal cytogenetics. In order to devise a personalized treatment plan for these patients, clinicians must understand and incorporate a growing number of molecular markers of prognosis.

Although research on genetic mutations in AML has yielded dozens of genetic biomarkers with potential prognostic value, there are challenges to incorporating this fast-moving data in everyday patient care. For example, some genetic mutations only exert their influence when coexisting with other mutations or chromosomal translocations. Also, most of these recently identified markers have been isolated in small subsets of patients, making it difficult to know how generalizable the results may be.

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It is recommended that all patients with AML and normal cytogenetics have a diagnostic bone marrow sample sent for testing of mutations in FLT3-ITD, NPM1 and CEBPA.

Table 2. Three-year post-transplant treatment outcomes of younger (age <60 years) patients with AML according to ELN genetic risk groups.[4]

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Table 2 shows outcomes of the younger (age <60 years) patients according to ELN genetic risk groups. Patients in the favorable group had significantly better CR, DFS, and OS compared to patients in the adverse classification (p<0.001). Results were similar in patients ≥60, with patients in the favorable group also having significantly better CR, DFS, and OS rates compared to patients in the adverse group.

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A recent review by two international experts in AML and stem cell transplantation, Drs. Stephen Forman and Jacob Rowe, highlights the need for consideration of transplantation for patients with AML, particularly given the difficulty of achieving a second remission for patients with relapsed AML[5]. Given the significantly worse outcomes for patients with AML in the intermediate II and adverse risk categories, allogeneic stem cell transplantation is recommended for all intermediate/adverse risk AML patients in first complete remission, depending upon donor availability.

Timely referral to a transplant center immediately after completion of induction chemotherapy is critically important in moving quickly to HCT while in remission.

No significant impact of age on transplant outcomes in AML/MDS

A study of reduced-intensity transplantation in 1,080 adults older than 40 years of age with AML in first complete remission or myelodysplastic syndromes (MDS) has shown that age has no effect on outcomes.[1]

In this study of MDS (n=535) and AML (n=545) patients reported to CIBMTR (Center for International Blood and Marrow Transplant Research) between 1995-2005, patients were studied in four age groups: 40-54, 55-59, 60-64 and ≥65 years. Median follow-up time for the four age cohorts ranged from 25 to 37 months.

Most patients received peripheral blood stem cells (n=1,086) versus bone marrow (n=184), and most received unrelated donor grafts (n=611) versus identical sibling grafts (n=469). The following variables were well balanced in the different age groups: sex, interval from diagnosis to transplantation, performance status, donor recipiend/recipient cytomegalovirus match and degree of unrelated donor/recipient HLA match.

Two-year overall survival is shown in Table 3. Multivariate analysis found no significant impact of age on non-relapse mortality, disease-free survival or overall survival (all p>0.3). Day-100 incidence of grade II-IV acute graft-versus-host disease was similar across all groups for both diseases (AML: 33% - 35%, p=0.96; MDS: 31% - 36%, p=0.89).

Impact of age on outcomes

<table>
<thead>
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<th>AGE RANGE (yrs)</th>
<th>55-59</th>
<th>60-64</th>
<th>≥65</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>44%</td>
<td>50%</td>
<td>54%</td>
</tr>
<tr>
<td>MDS</td>
<td>42%</td>
<td>35%</td>
<td>45%</td>
</tr>
</tbody>
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Table 3. Two-year overall survival of patients ≥60 years transplanted for MDS or AML in first complete remission.

Older age was not associated with higher relapse rates, despite the higher percentages of patients with high-risk disease in the older patient groups. The researchers noted that HCT resulted in 2-year survival rates of >70% in all age groups, “whereas conventional chemotherapy offers almost no chance of extended survival for older patients with AML or MDS.” The researchers concluded that “older age alone should not be considered a contraindication to HCT.”

We invite you to attend our upcoming Advances in Blood and Marrow Transplantation Symposium. This CME–certified program will review the latest advances in the field of autologous and allogeneic transplantation and supportive care.

• Date: Saturday, April 27, 2013
• Time: 8:45 a.m.-5 p.m.
• Location: Robert E. Hemenway Life Sciences Innovation Center, Kansas City, Kan.

View program details

The full conference brochure is available at continueded.ku.edu/kumc/bmt

Register

Registration is free of charge.
Call 877-404-5823 or visit continueded.ku.edu/kumc/bmt

AML Clinical Trials Spotlight

Current University of Kansas Cancer Center clinical trials for patients with AML include:

• Phase III randomized trial of CPX-351 vsidarubicin plus cytarabine as induction for patients ages 60-75 with secondary AML or AML with high-risk cytogenetics. CPX-351 is a novel, liposomal formulation of daunorubicin and cytarabine with phase II data demonstrating improved CR rates and overall survival in patients with AML. Transplant candidates are eligible.

• Phase Ib/Ii trial of PF-04489113, a HedgHOG inhibitor, in combination with low-dose Ara-C or decitabine in patients unfit for conventional induction chemotherapy. HedgHOG inhibitors have shown promise in targeting the leukemia stem cells in pre-clinical models, and this early phase study is designed to find the maximum tolerated dose and efficacy of the PF-04489113 in combination with traditional AML therapy.

• Phase II study of a lenalidomide regimen or a sequential azacitidine plus lenalidomide regimen in older subjects with AML. Patients age 65 and older with newly diagnosed or secondary AML are eligible. Stem cell transplant candidates are excluded.

Visit kumcancercenter.org/criticaltrials to learn about these and additional BMT and hematologic malignancy clinical trials.

Refer a patient

Contact us at 913-588-1227 or toll free at 800-332-6048.