Inhibition of IL-6 offers protection from acute GVHD

Grade II/IV and grade III/IV acute graft-versus-host disease (GVHD) is significantly reduced in transplant recipients receiving a monoclonal antibody inhibiting interleukin-6 (IL-6), according to research results of a Phase I/II study.[1]

Lead author Dr. Glen Kennedy of the Royal Brisbane and Women’s Hospital, Brisbane, Australia, noted that previous investigations of IL-6 levels had shown levels of this cytokine peaked at day seven post transplant, and positively correlating with conditioning regimen intensity.

The incidence of grade III/IV acute GVHD was 5.6% in recipients of IL-6R inhibition vs. 20.8% in the control group (p=0.045).

One year incidence of relapse and disease-free survival in patients receiving IL-6R inhibition vs. the control group is 21.2% inhibition versus the control group. Donor chimerism and immune reconstitution of T and B cells was equivalent at day 30 in recipients of IL-6R inhibition versus 30.0% (p=0.28) and 73.1% vs. 62.4% (p=0.14). Donor chimerism and immune reconstitution of T and B cells was equivalent at day 30 in recipients of IL-6R inhibition versus 20.8% in the control group (p=0.045).

The reduction in grade II-IV acute GVHD occurred in patients conditioned with Cy/TBI (7.7% vs. 40.7%, p=0.045) and those conditioned with Flu/Mel (13.0% vs. 38.5%, p=0.044).

No patients experienced toxicity attributable to IL-6R antibody administration. Thirty-six patients were evaluable beyond day 100, and at a median follow-up of 297 days, the incidence of grade II IV GVHD was 11.1% in recipients of IL-6R inhibition versus 39.6% in a matched (n=53) control group (p=0.004).

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Key research in HCT from ASH Annual Meeting

Welcome to this edition of Transplant Connection, The University of Kansas Cancer Center (KUCC) newsletter focusing on issues in hematopoietic cell transplantation (HCT) that we think will be of interest to our referral community. This issue focuses on a selection of HCT research presented at the 55th American Society of Hematology (ASH) Annual Meeting held in New Orleans, LA.

View additional summaries of HCT research presented at ASH as well as the latest in the field. Visit BeTheMatchClinical.org/Advances.

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
• Medicare-approved since 1977
• More than 2,100 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

Dear Colleague,

Thank you for considering The University of Kansas Cancer Center as a partner in caring for your patients who need a stem cell transplant. We performed more than 300 transplants in 2013.

Recently, our team was honored by the National Marrow Donor Program Innovation Award for the development of new processes to drive best practices and by the Academy of Medical-Surgical Nurses Prism Award, recognizing exceptional nursing practice, leadership and outcomes. We strive to provide you with the highest quality care.

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

Unrelated donor, cord blood grafts extend survival in older AML CR1 patients

Allogeneic transplantation using either unrelated donor (URD) or umbilical cord blood (UCB) grafts “can produce extended and even curative long-term survival” in patients over age 50 with AML in first complete remission, according to results of a large multicenter study. [2]

Researchers analyzed the outcomes of 740 transplants between 2005 and 2010 that were reported to the CBMTR (Center for International Blood and Marrow Transplant Research) and Eurocord. Transplants were 8/8 HLA allelic matched UCB (n=44), 7/8 matched UCB (n=94), and UCB (n=205). Median follow-up times were 50, 61 and 37 months, respectively.

In his oral presentation, Dr. Daniel Weisdorf of the University of Minnesota noted that while 8/8 UDR transplants yielded the best outcomes, both 7/8 UDR transplants and UCB transplants can also yield acceptable survival rates. Three-year EFS for these groups were 36% (8/8 UDR transplants), 29% (7/8 UDR transplants), and 23% (UCB transplants).

Adjusted three-year survival of 8/8 UDR transplants, 7/8 UDR transplants, and UCB transplants were 43%, 37%, and 30%, respectively (p=0.003). This and other outcomes are shown in Table 1. Multivariate analyses revealed a significantly higher rate of transplant-related mortality (TRM) in UCB transplantation compared to 8/8 UDR transplants (HR: 2.83; p=0.0001), but only in the first three months post transplant.

After three months, both graft sources had comparable TRM (Hazard ratio (HR): 1.00; p=0.99). Compared to 8/8 UDR transplants, TRM was higher after 7/8 UDR transplants (HR: 1.73; p=0.005).

Table 1. Transplant outcomes in AML patients in CR1 older than 50 years.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>UCB</th>
<th>7/8 Matched</th>
<th>8/8 Matched</th>
<th>p-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year OS</td>
<td>68%</td>
<td>70%</td>
<td>76%</td>
<td>0.001</td>
</tr>
<tr>
<td>3-year TRM</td>
<td>91%</td>
<td>92%</td>
<td>92%</td>
<td>0.999</td>
</tr>
<tr>
<td>3-year GVHD</td>
<td>19%</td>
<td>14%</td>
<td>17%</td>
<td>0.001</td>
</tr>
<tr>
<td>3-year relapse</td>
<td>27%</td>
<td>34%</td>
<td>34%</td>
<td>0.004</td>
</tr>
<tr>
<td>3-year survival</td>
<td>56%</td>
<td>59%</td>
<td>60%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

There were no significant differences in relapse risks among the three groups. Compared to 8/8 UDR transplants, relapse risk after UCB transplantation was HR: 1.14 (p=0.36) and after 7/8 UDR transplantation was HR: 0.86 (p=0.47).

Dr. Weisdorf noted that these research results suggest that “allogeneic transplantation need not be withheld from older patients and for clinically suitable AML patients, which can produce extended and even curative long-term survival.”

Prior therapy does not affect transplant outcomes in high-risk MDS

Hypomethylating agents or chemotherapy prior to hematopoietic cell transplantation (HCT) have been reported to negatively affect subsequent transplantation outcomes. In the absence of an 8/8 HLA-matched UCB or when HCT is needed urgently, UCB can provide extended survival.

In a large study of adults with MDS ages 50-75 treated with allogeneic HCT or with matched unrelated donor (MUD) HCT, it is currently unknown whether the best outcomes in MDS are achieved with UCB or with a matched donor. Researchers led by Dr. Betul Oran of the MD Anderson Cancer Center, Houston, studied outcomes of unrelated donor, cord blood HCT in lymphoma.

A multicenter study of 1,593 adults with non-Hodgkin and Hodgkin lymphoma has found that HLA-matched and one-antigen mismatched unrelated donor transplants and cord blood transplants have comparable three-year progression-free survival (PFS) and overall survival (OS). [4]

Transplant graft sources were umbilical cord blood (UCB) (n=142), 8/8 HLA-matched adult unrelated donor (URD) (n=1,176), and 7/8 HLA matched UCB (n=275). Median duration of follow-up was 25, 57 and 65 months, respectively. All recipients were transplanted between 2000 and 2010, with outcomes reported to the CBMTR (Center for International Blood and Marrow Transplant Research).

UCB recipients experienced significantly less acute and chronic graft-versus-host disease (GVHD) compared to 8/8 URD and 7/8 UCB, and the cumulative incidence of treatment-related mortality (TRM) at three years was higher in 7/8 UCB. Other outcomes are shown in Table 2.

Table 2. Transplant outcomes in 1,593 adults with non-Hodgkin and Hodgkin lymphoma.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>UCB</th>
<th>7/8 Matched</th>
<th>8/8 Matched</th>
<th>p-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-day acute GVHD (IUV)</td>
<td>26%</td>
<td>37%</td>
<td>49%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic GVHD at 3 years</td>
<td>22%</td>
<td>51%</td>
<td>48%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3-year TRM</td>
<td>38%</td>
<td>35%</td>
<td>46%</td>
<td>0.002</td>
</tr>
<tr>
<td>3-year PFS</td>
<td>33%</td>
<td>33%</td>
<td>29%</td>
<td>0.186</td>
</tr>
<tr>
<td>3-year OS</td>
<td>44%</td>
<td>43%</td>
<td>34%</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

MDS CLINICAL TRIALS SPOTLIGHT

Although hematopoietic cell transplantation (HCT) remains the only curative option for patients with myelodysplastic syndromes (MDS), it is currently unknown whether the best outcomes in MDS are achieved with UCB or with a matched donor. The Blood and Marrow Transplant Clinical Trials Network (BMT CTN), KUC is participating in a clinical trial to answer this important question.

The BMT CTN 1102 trial will measure three-year outcomes in MDS patients ages 50-75 treated with allogeneic HCT or with non-transplant strategies (best supportive care, including hypomethylating agents).

Patients with MDS ages 50-75 with intermediate-2 or high-risk IPSS scores are eligible to participate. All enrollees will be HLA typed and a search initiated for a matched related or unrelated donor. Patients without a donor will receive best supportive care. Patients with a donor will undergo reduced-intensity HCT. This study is posted on clinicaltrials.gov as NCT0216781.

To enroll a patient contact the referral specialist at The University of Kansas Blood and Marrow Transplant Program: 913-945-7713.

Visit kumc.edu/bmtclinicaltrials to learn about this and additional BMT and hematologic malignancy clinical trials.

CME OPPORTUNITY – REGISTER NOW

We invite you to attend the second-annual Advances in the Blood and Marrow Transplantation: 2014 Symposium. This CME and CE-certified program explores the current state-of-the-art treatment strategies, clinical trials research and outcomes of hematopoietic cell transplantation.

Invited national speakers include: David Porter, MD - University of Pennsylvania; Sergio Grillot, MD - Memorial Sloan-Kettering Cancer Center; Mary Flowers, MD - Fred Hutchinson Cancer Research Center, and Asad Bashry - Northside Hospital Cancer Institute.

- Date: April 12, 2014
- Time: 8:45 am – 4:15 p.m.
- Location: Overland Park Convention Center 6000 College Blvd, Overland Park, KS

View program details and register. Visit kumc.edu/bmtsymposium and type “BMT” in the search field to review program details and register. There is no charge for the symposium.
Unrelated donor, cord blood grafts extend survival in older AML CR1 patients

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Adjusted three-year survival of 8/8 URD transplants, 7/8 URB transplants, and UCB transplants were 43%, 37%, and 30%, respectively (p=0.003). This and other outcomes are shown in Table 1. Multivariate analyses revealed a significantly higher rate of transplant-related mortality (TRM) in UCB transplantation compared to 8/8 URB transplants (HR: 2.83; p=0.0001), but only in the first three months post transplant.

After three months, both graft sources had comparable TRM (Hazard ratio (HR): 1.00; p=0.97). Compared to 8/8 URB transplants, TRM was higher after 7/8 URB transplants (HR: 1.73; p=0.005).

Prior therapy does not affect transplant outcomes in high-risk MDS

Hypomethylating agents or chemotherapy prior to hematopoietic cell transplantation (HCT) have conflicting effects on outcomes for high-risk myelodysplastic syndromes (MDS). Researchers led by Dr. Betul Ozdemir of the MD Anderson Cancer Center, Houston, studied outcomes of 293 MDS patients with a median age of 55 years (range, 18-71). (3)

Pre-HCT therapies were chemotherapy only (n=81), hypomethylating agents only (n=100), both (n=36) and no prior therapy (n=76). Donors were matched related (n=131), matched unrelated (n=114) and mismatched unrelated (n=46).

The median follow-up of 109 survivors was 45 months. There was no difference in event-free survival (EFS) among the different pre-HCT therapy groups, including untreated patients. Three-year EFS for chemo, hypomethylating agents, both chemo and hypomethylating agents and no prior therapy groups were 31.2%, 31.1%, 31.5% and 43.4% respectively (p=0.05).

In a multivariate analysis, use of a mismatched donor and monosomal karyotype were markers of poor prognosis, with significantly lower three-year EFS in patients with monosomal karyotype compared to patients with normal cytogenetics: HR 4.5; (CI: 2.9-7.0), p=0.001. Disease status (complete remission vs. more advanced disease at transplant) was not associated with EFS.

Dr. Ozdemir concluded that high-risk MDS patients should proceed to transplant without any delay, because additional therapy to achieve better disease control does not appear to lead to more favorable transplant outcomes.

Table 1. Transplant outcomes in AML patients older than 50 years. TRM=transplant-related mortality. GvHD=graft-versus-host disease.

In the absence of an 8/8 HLA-matched URD or when HCT is needed urgently, UCB can provide extended survival.

There were no significant differences in relapse risks among the three groups. Compared to 8/8 URD transplants, relapse risk after UCB transplantation was HR: 1.15 (p=0.36) and after 7/8 URB transplantation was HR: 0.86 (p=0.47).

Dr. Weisdorf noted that these research results suggest that “allogeneic transplantation need not be withheld from older patients and/or for clinically suitable AML patients, which can produce extended and even curative long-term survival.”

1. Ozdemir B, Ercan B, known members of the respective transplant teams and/or the transplant center itself.

Table 2. Transplant outcomes in 1,593 adults with non-Hodgkin and Hodgkin lymphoma.

The study also found a lower risk of treatment failure in transplants performed after 2007 as compared to transplants performed between 2000 and 2003 (HR: 0.79; 95% CI 0.66-0.96; p<0.01).

“Lack of a matched unrelated donor should not be a barrier to transplant for patients with high-risk lymphoma.”

Compared outcomes for unrelated donor, cord blood HCT in lymphoma

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Transplant Referral Timing Guidelines

View referral timing guidelines published jointly by the National Marrow Donor Program/Be The Match® and the American Society for Blood and Marrow Transplantation. Visit BeTheMatchClinical.org/guidelines.

KUCC-specific guidelines: kucancercenter.org/bmtreresources.

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To enroll a patient

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Visit kucancercenter.org/celltrialstos learn about this and additional BMT and hematological malignancy clinical trials.

Visit the Physicians Resource Center at: BeTheMatchClinical.org