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Bringing Transplant to More Patients With AML

— Conditioning with radiolabeled antibody leads to successful transplantation in 84% of older patients

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ORLANDO -- A radiolabeled anti-CD45 antibody led to a high rate of allogeneic hematopoietic stem cell transplant (HSCT) in older patients with relapsed/refractory acute myeloid leukemia (AML), interim results from a randomized trial showed.

Conditioning with ^{131}I apamistamab (Iomab-B) allowed 31 of 37 patients to undergo HSCT. That compared with seven of 38 patients randomized to standard-of-care conditioning therapy. Subsequently, 20 patients who did not achieve CR with conventional therapy crossed over to Iomab-B, and all of them received therapeutic doses of Iomab-B and underwent HSCT.

Iomab-B conditioning and allo-HSCT led to neutrophil and platelet engraftment in 100% of patients with no graft failures, as reported here at the Transplantation and Cellular Therapy Meetings.

"After 50% of enrollment in the SIERRA trial, we observed high rates of allogeneic transplant with curative potential in patients with relapsed and refractory AML," said Boglarka Gyurkocza, MD, of Memorial Sloan Kettering Cancer Center in New York City. "This is a population who are not generally considered candidates for transplant."

"There was a low rate of nonrelapse mortality associated with Iomab-B-based conditioning, and the Iomab-B-based conditioning regimen had a favorable nonhematologic toxicity profile."

Enrollment in the multicenter trial is continuing, she added.

Background and Design

CD45 is expressed by many hematopoietic cells, including most malignant myeloid and lymphoid cells. At high doses Iomab-B depleted hematopoietic cells, including early progenitors, said Gyurkocza. The radiolabeled antibody targets radiation directly to leukemic cells and elicits a direct anti-tumor effect.

In nine phase I and II trials, Iomab-B demonstrated robust safety and long-term efficacy in a total of 271 patients. A subsequent phase II trial yielded promising data for Iomab-B in patients with relapsed/refractory AML, setting the stage for the phase III SIERRA trial.

Eligible patients were a minimum age of 55 and had marrow blast counts ≥5% or presence of peripheral blasts; medically cleared matched related/unrelated donors; and active relapsed or refractory AML (primary or secondary/treatment-related).

Investigators defined active relapsed/refractory AML as primary induction failure after two or more cycles of therapy (chemotherapy or at least two cycles of venetoclax [Venclexta] with azacitidine or decitabine); relapse within 6 months of first complete remission (CR); relapse/refractory to salvage combination chemotherapy; or second or subsequent relapse.

Gyurkocza reported findings from a planned analysis when half of the final target of 150 patients were accrued. Thus far, 75 patients have been randomized to Iomab-B or conventional pretransplant conditioning therapy. The trial's primary endpoint was the rate of durable CR, defined as persisting for at least 6 months.

Patients allocated to the radiolabeled antibody received Iomab-B, followed by nonmyeloablative therapy and then allo-HSCT (matched related/unrelated donors) plus total body irradiation. Patients randomized to conventional care received physician's choice of standard conditioning regimens. Patients who achieved CR underwent allo-HSCT plus additional standard therapy. Patients who did not achieve CR with conventional care had the option to cross over to Iomab-B.

Key Results

Median patient age was 65, and two-thirds had adverse cytogenetic/molecular risk. Median marrow blast concentration was 25%-30%, about half the patients had primary induction failure, and they had received a median of three prior regimens. Gyurkocza said 85% of the patients had failure of at least two prior regimens, and one-third failed targeted therapies.

The interim data showed that 84% of patients in the Iomab-B arm received therapeutic doses of the antibody and underwent HSCT. In contrast, 18% of patients allocated to conventional therapy achieved a CR and underwent HSCT. All control patients who crossed over to Iomab-B subsequently underwent HSCT.

In the Iomab-B arm, the median time to neutrophil engraftment was 15 days with no graft failure versus 18 days with one graft failure in the control group. Median time to platelet engraftment was 20 days with Iomab-B and 22 with conventional care, and the time to HSCT was 30 days with Iomab-B and 67 with conventional care. The patients who crossed over to Iomab-B had similar times to neutrophil and platelet engraftment and no graft failures. Median time to HSCT was 64 days.

Nonrelapse mortality at 100 days was 6% in the Iomab-B arm (2/31), 29% with conventional care (2/7), and 10% in the crossover group (2/20).

The most common grade 3/4 nonhematologic adverse events in the Iomab-B arm were febrile neutropenia (22.9%), pneumonia (17.1%), hypertension (17.1%), and mucositis (11.4%). In the conventional care group febrile neutropenia was most common (45.9%), followed by sepsis/septic shock (21.6%), pneumonia (18.9%), catheter-related infection (13.5%), and mucositis (10.8%).

During the discussion that followed the presentation, an audience member questioned whether the trial design was appropriate for a phase III clinical study. "You're giving one group of patients therapy and taking them directly to transplant. You're giving the other patients a therapy and then evaluating whether they got a remission, and if not, they're considered treatment failure.... You're showing that you can transplant these patients reasonably safely, but whether this is better than another treatment cannot really be evaluated in this study," he said.

Another audience member, however, pointed out that the endpoint of durable remission addresses those issues to some extent. "Keep in mind that all of these patients had failed primary therapy.... The idea, one, is that many patients across the country are not getting transplanted and showing that there are other ways of getting effectively transplanted. Two, the crossover helps make this possible."

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Disclosures

The SIERRA trial is sponsored by Actinium Pharmaceuticals.

Gyurkocza disclosed an institutional relationship with Actinium Pharmaceuticals.

Primary Source

Transplantation and Cellular Therapy Meetings

Source Reference: Gyurkocza B, et al "Targeted conditioning with anti-CD45 iodine (^{131}I) apamistamab leads to high rates of allogeneic transplantation and successful engraftment in older patients with active, relapsed or refractory AML after failure of chemotherapy and targeted agents: Preliminary midpoint results from the prospective, randomized phase III SIERRA trial" *TCTM 2020*; Abstract 39.