Medical Xpress

Age no longer a barrier to stem cell transplantation for older patients

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Age alone no longer should be considered a defining factor when determining whether an older patient with blood cancer is a candidate for stem cell transplantation. That's the conclusion of the first study summarizing long-term outcomes from a series of prospective clinical trials of patients age 60 and over who were treated with the mini-transplant, a "kinder, gentler" form of allogeneic (donor cell) stem cell transplantation developed at Fred Hutchinson Cancer Research Center. The findings are published Nov. 2 in *JAMA*, *The Journal of the American Medical Association*.

"Age is no longer a barrier to allogeneic transplant," said Mohamed Sorror, M.D., M.Sc., an assistant member of the Hutchinson Center's Clinical Research Division and corresponding author of the paper.

Sorror and colleagues found that the five-year rates of overall and disease-progression-free survival among mini-transplant patients were 35 percent and 32 percent, respectively. Patients in three age groups – 60 to 64, 65 to 69 and 70 to 75 – had comparable survival rates, which suggested that age played a limited role in how patients tolerate the mini-transplant. Increased medical problems unrelated to cancer (comorbidities) and a higher degree of cancer aggressiveness were the two factors that affected survival among those older patients. For example, patients who had less-aggressive cancer and fewer comorbidities had a five-year survival rate of 69 percent, while patients with more aggressive cancer and a significant number of comorbidities had a survival rate of 23 percent, regardless of age.

Although a long-term survival rate of one-third of patients may seem low, these patients all would have died of their diseases within a matter of months without a transplant. "The majority of patients were referred for a transplant after they had exhausted all forms of conventional therapy," said Sorror, who works in the research group led by Rainer Storb, M.D., who developed the mini-transplant.

"While there is much room for improvement, particularly with regard to relapse, these results are encouraging given the poor outcomes with non-transplantation treatments, especially for patients with high-risk AML (acute myeloid leukemia), fludarabine-refractory CLL (chronic lymphocytic leukemia) or progressive lymphoma," the authors wrote.

The mini-transplant, known in medical circles as nonmyeloablative transplantation, was developed by researchers at the Hutchinson Center for older and medically sicker patients who otherwise could not tolerate the standard, more-toxic, high-dose regimens used to prepare patients for transplantation.

Conventional transplants, which are generally not perfomed on people over age 60 or others who are medically unfit, use high doses of total-body irradiation and potent chemotherapy to eliminate leukemic cells. The intense treatment destroys the blood and immune system and is fatal unless the patient is rescued by infusion of donor bone marrow or stem cells isolated from peripheral blood.

The mini-transplant, in contrast, relies on the ability of donor immune cells to target and destroy the cancer – without the need for high-dose chemotherapy and radiation. Instead, low-dose radiation and chemotherapy is used to suppress the immune system rather than destroy it. This helps the body accept the donor stem cells, which then go to work to attack cancer cells – called the graft-vs.-leukemia effect – and rebuild the immune system.

The study involved 372 patients ages 60 to 75 who were enrolled in prospective clinical trials between 1998 and 2008 at 18 collaborating U.S. and European cancer centers known as the "Seattle Consortium." All patients at these centers were treated with the same regimen, which was developed in Seattle. The patients in the study were treated for acute and chronic leukemia, lymphoma, multiple myeloma, myelodysplastic syndromes (which can progress to acute myeloid leukemia if not treated) and myeloproliferative diseases such as chronic myelogenous leukemia.

In addition to survival and the impact of comorbid conditions, the study examined rates of relapse, hospitalization, acute and chronic graft-vs.-host disease (GVHD, the most common side effect of transplantation), and the toxicity of the treatment to internal organs.

For example, two-thirds of patients five years after their transplants who were affected by chronic GVHD had complete resolution of their symptoms and were able to discontinue immunosuppressive medications after a median time of 2.5 years from diagnosis. This was comparable to the duration reported by previous studies on younger patients who were treated with high-dose radiation and chemotherapy. Half of the patients never required hospitalization after transplant.

"These findings, together with the normal to near-normal performance status of surviving patients, should help allay reluctance in entering older patients with hematologic cancers on nonmyeloablative transplantation protocols," Sorror said. The lack of a matched sibling donor also should no longer be a limitation given that transplants with matched unrelated donor grafts had comparable outcomes, he said.

Disease relapse risks and comorbidities, but not increasing age, were associated with worse outcomes. The Seattle Consortium investigators continue to explore novel approaches to be combined with the mini-transplant to reduce the relapse rate, particularly among patients with

more aggressive blood cancers.

Sorror and colleagues previously developed and published the Hematopoietic Cell Transplant-specific Comorbidity Index (HCT-CI) by studying the associations between single comorbidities (such as diabetes, heart diseases, etc) and mortality after a stem cell transplant. Laboratory and organ-function values were used to refine the definition of comorbidities. Based on extensive statistical analyses, scores were given to each of 17 different comorbidities that constitute the HCT-CI based on their correlation with accurate forecast of patient outcomes.

"The use of the HCT-CI in this study facilitated capturing the important role of comorbidities in defining survival of older patients. Ongoing research is focused on understanding the biology behind the association between pre-transplant comorbidities and post-transplant morbidity and mortality," he said.

The authors noted that 20 percent of the U.S. population will be 65 or older by 2030, and that increases of up to 77 percent in the number of newly diagnosed blood cancers among this population are expected to occur in the next two decades. Such malignancies are mainly diseases of the elderly. Yet, only 12 percent of patients who were treated with a transplant between 2004 and 2008 in U.S. institutions were over age 60 and a previous study suggested that only 26 percent of patients with acute myeloid leukemia were treated with a transplant, according to results reported by the Center of International Blood and Marrow Transplantation Research.

"These statistics clearly highlight the reluctance of providers in offering allogeneic stem cell transplantation to the elderly," Sorror said. "Little is known about the reasons behind the low referral rate of older patients to transplant or how mini-transplant outcomes compare to those of conventional therapies. We are initiating a multicenter study designed to

follow patients from the time of diagnosis to answer both questions." Sorror said.

More information: *JAMA*. 2011;306[17]:1874-1883.

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