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Defibrotide improves response rate in patients with severe veno-occlusive disease of the liver

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Defibrotide, a novel drug which modulates the response of blood vessels to injury, was markedly more effective than standard treatment in post-stem cell transplant patients with hepatic veno-occlusive disease, a life threatening toxicity of transplant caused by blockages in tiny blood vessels of the liver, according to a study led by Dana-Farber Cancer Institute scientists.

A phase III trial being reported at the American Society of Hematology's (ASH) annual meeting on Monday, Dec. 7, showed that 24 percent of patients had complete responses to defibrotide, compared to 9 percent of historical controls, referring to a rigorously analyzed group of patients with this syndrome, previously treated with best supportive care, which is the current standard approach to this often fatal syndrome.

"There was a highly significant improvement in the complete response rate using defibrotide, and this translates into an encouraging trend for improved survival," said Dana-Farber's Paul Richardson, MD, first author of the study that involved patients at 35 medical centers across the United States, Canada and Israel. The mortality rate 100 days after transplant was reduced to 62 percent for patients receiving defibrotide, compared with 75 percent in the control patients who did not get the drug.

Veno-occlusive disease (VOD) is an important complication of stem-cell

transplants in cancer patients. Obstructions from clots and debris in the very small vessels of the liver cause the organ to swell, leading to an excessive accumulation of bilirubin (a breakdown product of red blood cells), progressive jaundice, fluid retention, kidney failure and respiratory failure (so called multiple organ failure, or MOF), and death.

Defibrotide, derived from porcine tissue, is a polydeoxyribonucleotide that modulates damage to the lining of blood vessels when given orally or by injection. Previous studies showed that defibrotide could reverse VOD and MOF and was effective in preventing these complications in both adults and children undergoing transplant, with minimal toxicity.

The 102 patients treated with defibrotide in the current study had a mean age of 21 years, and the mean duration of treatment with the drug was 21 days. They were already very seriously ill when treatment was started. For comparison, the researchers identified 32 similar historical control patients from a survey of almost 7000 previous transplant patients at participating centers. The study used a novel method for evaluating historical controls compared to prospectively treated patients, in part because the death rate from this complication is so high, making a randomized prospective approach neither feasible or ethical in this setting.

Richardson said that children treated with defibrotide had an especially high complete response rate - 36 percent compared with just 7 percent in the historical controls, and patients undergoing autologous (versus allogeneic) stem cell transplant also did well.

Based on these and previous results, he said, it is justifiable to consider giving defibrotide earlier, and before the complications of the syndrome have become so severe, to further improve patient outcome.

Adverse effects from defibrotide treatment included bleeding problems,

but these were generally mild and proved manageable, with up to 18 percent of patients who received defibrotide taken off the drug because of possible toxicities, although the drug was otherwise well tolerated.

Source: Dana-Farber Cancer Institute