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Study explores use of checkpoint inhibitors after relapse from donor stem cell transplant

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Immunotherapy agents known as checkpoint inhibitors have shown considerable promise in patients with hematologic cancers who relapse after a transplant with donor stem cells. Preliminary results from the first clinical trial in these patients of one such agent - nivolumab - indicate that along with signs of effectiveness, it also produced significant side effects at the dose initially studied. The findings indicate a need for further clinical trials in this group before being considered for off-label use with these patients, Dana-Farber Cancer Institute investigators report.

Results from the investigator-initiated, multicenter study, which were presented at an oral abstract session at the 59th American Society of Hematology (ASH) Annual Meeting and Exposition in Atlanta also include encouraging follow-up data from a trial in which the checkpoint inhibitor ipilimumab produced responses in nearly one-third of patients with relapsed hematologic malignancies after an allogeneic (donor) stem cell transplant.

The trial of nivolumab - which blocks a protein called PD-1 that can blunt the immune system's attack on cancer - was spurred by retrospective studies that showed that the drug could be effective but often produced harsh side effects, including graft-versus-host disease, a disorder in which immune system cells in transplanted tissue attack a patient's healthy cells. The first six patients in the trial received a dose of 1 mg/kg of body weight. While a patient with lymphoma responded well to the treatment, several others experienced adverse side effects,

including two who died of complications that were possibly treatment-related. The next eight participants received a 0.5 mg/kg dose, and the occurrence of significant side effects appears to be less so far, researchers report.

"We're now exploring whether this lower dose is safe and efficacious," says the study's lead author, Matthew Davids, MD, MMSc, Associate Director, Center for Chronic Lymphocytic Leukemia, Dana-Farber Cancer Institute. "Because of toxicity concerns, we emphasize that treating patients with nivolumab post-transplant should be done in the context of a clinical trial, not off-label."

In the ipilimumab trial - results of which were published last year in the *New England Journal of Medicine* - many of the participants continue to fare well, Davids remarks. The *NEJM* paper reported that 32 percent of patients treated with a 10 mg/kg dose responded to the drug after relapsing from an allogeneic stem cell transplant, while none of those receiving a 3 kg/mg dose did. At the ASH meeting, researchers will report that of the 22 patients treated at the 10 mg/kg level, nine remain alive and three are free of disease progression a median of 15 months after the trial ended. One of the patients with leukemia cutis remains in complete remission more than three years from initial dosing.

Because of the divergence of results at the 10 and 3 mg/kg levels, investigators have also been testing a mid-range dose of 5 mg/kg to determine if it strikes the right balance of efficacy and safety. In the 15 patients treated at 5 mg/kg, efficacy appeared to be slightly less than at the 10 mg/kg dose, while the toxicities were "fairly equivalent," Davids remarks. These results indicate that 10 mg/kg is probably the optimal dose for this group of patients, he adds.

Provided by Dana-Farber Cancer Institute