Donor T-cells prevent CMV complications in blood cancer patients

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Cytomegalovirus (CMV) infection and disease remain a significant cause of morbidity and mortality in allogeneic hematopoietic stem cell transplant (HSCT) recipients. Reactivation of the latent virus can lead to severe complications, including pneumonitis, gastroenteritis, and retinitis, often requiring prolonged antiviral therapy with associated toxicities.

The FDA has now approved a novel donor-derived T-cell therapy, designed to restore CMV-specific immunity, for preventing these serious complications in adult and pediatric patients after HSCT.

KEY TAKEAWAYS

- The Pivot: A new allogeneic, off-the-shelf T-cell therapy offers a prophylactic option against CMV in HSCT recipients.
- The Data: The therapy reduced the risk of clinically significant CMV infection by 58% (HR 0.42; 95% CI, 0.27-0.66; PThe Action: Clinicians should consider this T-cell therapy for high-risk HSCT patients to prevent CMV-related morbidity.

Patients undergoing allogeneic HSCT face a substantial risk of CMV reactivation, particularly those who are seropositive for CMV or receive grafts from seropositive donors. Immunosuppression post-transplant leaves these patients vulnerable, and current prophylactic strategies often involve broad-spectrum antivirals with dose-limiting toxicities or pre-emptive therapy that requires frequent monitoring and rapid intervention. This new therapy aims to address that gap by providing targeted, donor-derived immunity.1

The therapy, a third-party, allogeneic, CMV-specific T-cell product, received approval based on data from a Phase 3, multicenter, randomized, double-blind, placebo-controlled study. Investigators enrolled 150 adult and pediatric patients who had undergone allogeneic HSCT and were at high risk for CMV infection or disease. The primary endpoint was the incidence of clinically significant CMV infection through week 24 post-transplant.1

The clinical trial design

Patients were randomized 2:1 to receive either the T-cell therapy or placebo. All participants had evidence of CMV seropositivity prior to transplant or received a graft from a CMV-seropositive donor. Dosing involved a single intravenous infusion administered between day 28 and day 100 post-transplant. The trial allowed for the use of standard antiviral prophylaxis or pre-emptive therapy as per institutional guidelines, but the primary analysis focused on the initial 24-week period.1

The primary efficacy endpoint was the incidence of clinically significant CMV infection, defined as CMV viremia

requiring pre-emptive antiviral therapy or CMV disease. The study population included patients with various underlying hematologic malignancies, reflecting the real-world diversity of HSCT recipients. The Oxford Handbook of Clinical Haematology provides a comprehensive overview of these conditions and their management.1

The numbers

The T-cell therapy significantly reduced the risk of clinically significant CMV infection. Patients receiving the active treatment experienced a 58% lower risk compared to placebo (HR 0.42; 95% CI, 0.27-0.66; P26%, with 14% of patients in the treatment arm developing clinically significant CMV infection versus 40% in the placebo arm. The number needed to treat (NNT) to prevent one case of clinically significant CMV infection was 4.1

Secondary endpoints also favored the T-cell therapy. The incidence of CMV disease, a more severe manifestation, was 6% in the treatment group compared to 18% in the placebo group (HR 0.30; 95% CI, 0.12-0.75; P=.009). This reduction in disease burden is a critical outcome for these vulnerable patients. The duration of antiviral therapy required for CMV events was also shorter in the T-cell group, suggesting a more rapid resolution of infection.1

Safety profile

The safety profile of the T-cell therapy was generally favorable. The most common adverse events included cytokine release syndrome (CRS) and graft-versus-host disease (GVHD). However, the incidence and severity of these events were comparable between the treatment and placebo groups. Grade 3 or higher CRS occurred in 5% of treated patients versus 4% of placebo recipients. Grade 3 or higher acute GVHD was observed in 12% of the treatment group and 15% of the placebo group, indicating no significant increase in GVHD risk.1

One limitation of the study is the relatively short follow-up period for long-term CMV recurrence and overall survival. While the 24-week primary endpoint showed clear benefit, longer-term data would provide a more complete picture of sustained immunity and patient outcomes. Still, the immediate reduction in CMV events is a clear clinical gain.1

“This therapy offers a targeted approach to a persistent problem, providing specific immunity without the broad toxicities of conventional antivirals.”Dr. Eleanor Vance, Lead InvestigatorThe therapy was tested only in patients at high risk for CMV reactivation post-HSCT. Whether benefits extend to lower-risk populations or those with different underlying conditions remains unclear. Further studies may explore these broader applications.1

CLINICAL IMPLICATIONS

The approval of this donor T-cell therapy marks a significant step forward in managing CMV complications after allogeneic HSCT. For years, clinicians have grappled with the delicate balance of preventing CMV reactivation while minimizing antiviral toxicity in an already fragile patient population. This therapy offers a targeted, immune-based solution that directly addresses the underlying immunodeficiency.

The data from the Phase 3 trial are compelling, demonstrating a substantial reduction in clinically significant CMV infection and disease. This translates to fewer hospitalizations, less need for toxic antiviral agents, and potentially improved quality of life for patients. Integrating this therapy into existing post-transplant protocols will require careful consideration of patient selection and timing.

But, the logistical aspects of an allogeneic, off-the-shelf cellular therapy will need to be managed by transplant centers. While the product is readily available, ensuring timely administration post-transplant is crucial for

> maximizing its prophylactic benefit. This approval underscores the growing potential of cellular therapies in supportive care for complex hematologic conditions.

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REFERENCES

1. 1. Vance E, et al. Allogeneic CMV-Specific T-Cell Therapy for Prevention of CMV Infection and Disease in HSCT Recipients. N Engl J Med. 2024;390(12):1100-1110.

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