

Improving Outcomes in Hematopoietic Stem Cell Transplant: Recent Advances

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Presenter's disclosure of conflicts of interest is found at the end of this article.

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Abstract

During JADPRO Live Virtual 2020, Maritza Alencar, DNP, MBA, APRN-BC, BMTCN, described advances in the management and prevention of infectious disease complications and graft-vs.-host disease following transplant. Dr. Alencar also emphasized the role of advanced practitioners in post-transplant care.

As the number of recipients continues to rise, recent advances in hematopoietic stem cell transplant have led to improved outcomes. During JADPRO Live Virtual 2020, Maritza Alencar, DNP, MBA, APRN-BC, BMTCN, of the University of Miami Sylvester Comprehensive Cancer Center, described advances in the management and prevention of both infectious disease complications and graft-vs.-host disease following transplant. Dr. Alencar also discussed advances in post-transplant therapy and the contribution of advanced practitioners to overall outcomes in stem cell transplant.

CAUSES OF DEATH AFTER TRANSPLANT

As Dr. Alencar reported, among unrelated donor allogeneic hematopoietic stem cell transplants (HSCT), within 100 days, mortality related to infection, organ failure, and graft-vs.-host disease accounts for 66% of deaths.

After 100 days, however, 51% of deaths are related to primary disease.

Conversely, among human leukocyte antigen (HLA)-matched sibling transplant recipients, primary disease accounts for 34% of deaths within the first 100 days, while infection and organ failure represent 42% of deaths. After 100 days, 59% of deaths are attributed to primary disease.

"Recently we have seen reductions in mortality after allogeneic transplant attributed to a decrease in organ damage due to better treatment methods and monitoring," said Dr. Alencar. "We have better prophylaxis, we have improved techniques in treatment strategies for infectious complications, and we have improved techniques for the prevention and management of graft-vs.-host disease."

INFECTION CONTROL

With respect to infection control, Dr. Alencar underscored the importance of becoming familiar with the differ-

ent phases of transplantation, “when the opportunities to acquire infections are the most prevalent.” In phase 1, the pre-engraftment period, there is more bacterial involvement, including a higher risk for Gram-negative bacilli, Gram-positive organisms, and gastrointestinal *streptococci* species. Providers should also monitor for Herpes simplex virus along with respiratory and enteric viruses and look for fungal infections such as *Aspergillus* and *Candida* speciosus throughout the entire transplant period.

In phase 2, the post-engraftment period, there is still a risk of bacterial infections, said Dr. Alencar, but providers are increasingly focused on preventing cytomegalovirus (CMV). *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis is also started during this period.

In phase 3, providers watch for encapsulated bacteria and varicella zoster virus while continuing with PJP and aspergillus prophylaxis.

According to Dr. Alencar, CMV is the most opportunistic infection in the allogeneic transplant population, and the mortality rate can be as high as 60% for patients who develop CMV pneumonitis (Camargo et al., 2018).

“We must be vigilant in how we monitor for CMV and approach CMV treatments,” she said.

Molecular diagnostic testing for CMV viremia and acceptance of preemptive antiviral therapy for prevention of symptomatic CMV disease has been shown to be highly effective in decreasing CMV end-organ disease, said Dr. Alencar, who noted that CMV monitoring occurs once to twice weekly. Although CMV level thresholds vary widely across centers, initiation of preemptive therapy at low CMV levels is associated with shorter episodes of viremia and shorter courses of therapy.

INVASIVE FUNGAL INFECTIONS

If not treated early, invasive fungal infections are associated with a high mortality. This has led to recent changes in treatment options, including the widespread adoption of fluconazole prophylaxis (Cornely et al., 2007). Although fluconazole prophylaxis does not have mold coverage, other antifungal medications such as voriconazole and itraconazole do.

The introduction of novel agents posaconazole (Noxafil) and isavuconazole (Cresemba)—both for

prophylaxis and therapy—have also led to less toxicity when compared with amphotericin.

“This is a great way for us to treat patients,” said Dr. Alencar. “These novel agents are often used with patients who are undergoing graft-vs.-host disease therapy and are severely immunocompromised. Some centers have even started using posaconazole as a prophylaxis method compared with fluconazole.”

Dr. Alencar also noted that improved testing techniques have led to earlier diagnosis and treatment. These include sensitive radiologic studies, such as CT scans and MRIs, microbiologic and histopathologic techniques, and biomarker assays, such as galactomannan, fungal polymerase chain reaction, and beta-d-glucan.

“In the long run, having all of these tools available will lead to better outcomes,” she said.

GRAFT-VS.-HOST DISEASE

The cumulative incidence of acute graft-vs.-host disease is approximately 40% to 60% among patients undergoing allogeneic HCT, but advances in early intervention have been tremendous, said Dr. Alencar, who noted that the use of tacrolimus prophylaxis rather than cyclosporine has helped decrease the incidence of acute graft-vs.-host disease (both grades II-IV and III-IV). Despite the toxicities associated with tacrolimus, drug level monitoring has also led to improved outcomes, and most transplant centers have adopted tacrolimus-based prophylaxis (Norkin & Wingard, 2017).

In addition, better high-resolution human leukocyte antigen-matching techniques have led to better unrelated donor selection, which in turn has led to an increased use of reduced-intensity conditioning regimens, which is also associated with the reduction of the incidence of graft-vs.-host disease.

“It’s like a domino effect,” said Dr. Alencar. “New treatments and new approaches also affect our ability to formulate better plans that will likely help improve our patients’ outcomes.”

ACUTE GVHD TREATMENT

For a long time, steroids have remained the mainstay of treatment, despite being effective in only 50% of cases and being associated with significant

toxicities. In May 2019, however, the FDA approved ruxolitinib (Jakafi) for adults and pediatric patients older than 12 years with steroid-refractory acute graft-vs.-host disease.

FDA approval was based on findings from the phase III REACH1 trial, which showed that the combination of ruxolitinib with corticosteroids elicited a 62% overall response rate at day 28 in patients who had steroid-refractory acute graft-vs.-host disease (Zeiser et al., 2020).

“Ruxolitinib has given us a promising option for patients who are refractory to steroids,” said Dr. Alencar, who noted that adverse events include thrombocytopenia, anemia, and CMV.

CHRONIC GVHD TREATMENT

Ibrutinib (Imbruvica) was approved by the FDA in August 2017 for adults with chronic graft-vs.-host disease following the failure of one or more lines of systemic therapy. Approval was based on data from a single-arm, phase Ib2 study in which ibrutinib induced an overall response rate of 67% (complete response of 21% and partial response of 45%) and showed clinically meaningful durable responses in patients who failed at least one prior treatment (Miklos et al., 2017).

“We’ve seen great improvement with ibrutinib,” said Dr. Alencar. “We now have another option for patients suffering from chronic graft-vs.-host disease.”

POST-TRANSPLANT MAINTENANCE THERAPY

Lenalidomide (Revlimid) was approved by the FDA for multiple myeloma in the post-transplant setting in 2017 and is typically started approximately 90 to 100 days post transplant. The big question is how long to continue lenalidomide, said Dr. Alencar, who noted that lenalidomide has been administered for 2 years post transplant or until disease progression.

A meta-analysis of studies conducted by three groups and 1,208 patients showed a median progression-free survival of 52.8 months for patients in the lenalidomide group and 23.5 months for the placebo group (McCarthy et al., 2017). Median overall survival for patients who received lenalidomide was not reached compared with 86% in the control group. Treatment-related adverse events

include thrombocytopenia (1% to 2.7%), neutropenia (2% to 2.2%), and secondary malignancies (2.3% to 7.1%).

Brentuximab vedotin (Adcetris) was approved in August 2015 for classical Hodgkin lymphoma based on data from the phase III AETHERA trial, which compared up to 16 cycles (approximately 1 year) of brentuximab to placebo following autologous HSCT in patients at high risk of relapse or progression. The median progression-free survival in the brentuximab group was 42.9 months compared with 24.1 months in the placebo group (Moskowitz et al., 2015).

“There has been some controversy about the complete effects of using brentuximab, but overall, we’ve seen that it has been effective in delaying recurrence of disease in patients with unfavorable risk factors,” said Dr. Alencar.

ROLE OF THE ADVANCED PRACTITIONER IN POST-TRANSPLANT CARE

Dr. Alencar also underscored the pivotal role played by transplant advanced practitioners in managing patients and improving their outcomes. By the year 2030, it’s estimated that there will be approximately 500,000 transplant survivors (Majhail et al., 2013). It’s also estimated that the number of oncology and hematology providers will decrease.

“These statistics highlight the growing importance of advanced practitioners,” said Dr. Alencar. “We’re there to help support our patients as we develop new therapies that will allow them to have more longevity.”

According to Dr. Alencar, advanced practitioners play a key role in symptom management, long-term care follow-up, vaccine management, and advanced practice–driven clinics.

“Advanced practitioner–driven clinics are a model that we can foresee being the future for our practice,” said Dr. Alencar, who noted that these clinics provide post-transplant follow-up care, perform procedures, conduct urgent care visits, and offer supportive care management. “The result is decreased hospital admissions and emergency department utilization. I can also attest that we’ve seen enhanced patient satisfaction overall.” ●

Disclosure

Dr. Alencar has served on the speakers bureau for Kite Pharma.

References

Camargo, J. F., Kimble, E., Rosa, R., Shimose, L. A., Bueno, M. X., Jeyakumar, N.,...Komanduri, K. V. (2018). Impact of cytomegalovirus viral load on probability of spontaneous clearance and response to preemptive therapy in allogeneic stem cell transplantation recipients. *Biology of Blood and Marrow Transplantation*, 24(4), 806–814. <https://doi.org/10.1016/j.bbmt.2017.11.038>

Cornely, O. A., Maertens, J., Winston, D. J., Perfect, J., Ullmann, A. J., Walsh, T. J.,...Angulo-Gonzalez, D. (2007). Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *New England Journal of Medicine*, 356(4), 348–359. <https://doi.org/10.1056/nejmoa061094>

Majhail, N. S., Tao, L., Bredeson, C., Davies, S., Dehn, J., Gajewski, J. L.,...Kuntz, K. M. (2013). Prevalence of hematopoietic cell transplant survivors in the United States. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, 19(10), 1498–1501. <http://doi.org/10.1016/j.bbmt.2013.07.020>

McCarthy, P. L., Holstein, S. A., Petrucci, M. T., Richardson, P. G., Hulin, C., Tosi, P.,...Attal, M. (2017). Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: A meta-analysis. *Journal of Clinical Oncology*, 35(29), 3279–3289. <https://doi.org/10.1200/jco.2017.72.6679>

Miklos, D., Cutler, C. S., Arora, M., Waller, E. K., Jagasia, M., Pusic, I.,...Jaglowski, S. (2017). Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. *Blood*, 130(21), 2243–2250. <https://doi.org/10.1182/blood-2017-07-793786>

Moskowitz, C. H., Nademanee, A., Masszi, T., Agura, E., Hollowiecki, J., Abidi, M. H.,...Walewski, J. (2015). Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*, 385(9980), 1853–1862. [https://doi.org/10.1016/s0140-6736\(15\)60165-9](https://doi.org/10.1016/s0140-6736(15)60165-9)

Norkin, M., & Wingard, J. R. (2017). Recent advances in hematopoietic stem cell transplantation. *F1000Research*, 6, 870. <https://doi.org/10.12688/f1000research.11233.1>

Zeiser, R., von Bubnoff, N., Butler, J., Mohty, M., Niederwieser, D., Or, R.,...Socié, G. (2020). Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. *New England Journal of Medicine*, 382(19), 1800–1810. <https://doi.org/10.1056/nejmoa1917635>