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Editorial

Infectious disease in hematopoietic stem cell transplantation

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Hematopoietic stem cell transplantation (HSCT) is one of the aggressive treatments for a variety of hematologic malignancies, bone marrow failure syndromes, and rare genetic disorders. Unfortunately, despite all the newer developments, HSCT is not the end of the trouble for many patients and often they have to suffer a spectrum of complications during the post-transplant phase. The risk is specifically high for patients receiving allogeneic HSCT. A few of these complications are graft-*versus*-host disease, sinusoidal obstruction syndrome, post-HSCT infections, and there are many more. Infections in HSCT are amongst the major causes of morbidity and mortality in the post-transplant period.[1]

Timeline of infections

Infections following HSCT to which recipients are vulnerable can be broadly divided based on the time elapsed since HSCT: (A) pre-engraftment period, which is the time from HSCT till neutrophil count recovery (ranges till day 20–30 approximately), (B) immediate post-engraftment period, which is from the engraftment day till day 100, and (C) late post-engraftment period is beyond day 100.[2,3] Knowledge of most likely infections during these specific time periods helps in expediting the infection disease workup.

Susceptibility to infection following HSCT

The risk of acquiring an infection during the post HSCT period depends on the complex interaction of at least three factors: (A) patient-related factors, (B) disease-related factors, (C) transplant-related factors.

Patient-related factors are old age, obesity, diabetes mellitus, arrhythmias, pulmonary hypertension, chronic kidney disease, peptic ulcer disease, and so on. Hematopoietic cell transplantation-specific comorbidity index (HCT-CI) is one of the tools which is commonly used for the risk assessment before allogeneic transplant. Based on the HCT-CI index, transplant physicians can classify their patients into three risk groups: low risk (non-relapse mortality 14% at 2 years), *versus* intermediate risk (non-relapse mortality 21% at 2 years) *versus* high risk (non-relapse mortality 41% at 2 years).

One of the disease-related factors is the type of malignancy. For instance, multiple myeloma is associated with immune system perturbances, which primarily impacts the normal immune globulin (antibody) production. Similarly, another disease-related factor is the prior therapy used before the transplantation. For instance, patients with multiple myeloma and acute lymphoblastic leukemia usually receive significant doses of steroids as a part of the treatment regimen. Other factors, such as the presence of pretransplant-specific immunity to various viral infections (cytomegalovirus, herpes simplex virus etc.), the status of iron homeostasis, and functional hyposplenism, can also significantly add to the morbidity and mortality associated with acquired infections.[4]

Transplant related factors that can contribute to infections are: (A) type of transplant, (B) type of stem cell graft, (C) type of conditioning regimen used, (D) immunosuppression regimen used, and (E) donor type, with the degree of mismatch of human leukocyte antigen mismatch between donor and recipient.

Type of infections

Infections during the post HSCT period could result from bacteria, fungus, virus, or parasite.[5–9] As also discussed above, intense conditioning regimens, central venous lines, ports, and lengthy immune suppression periods are major risk factors to make recipients susceptible to these infections. For instance, a prior fungal infection can flare up during conditioning therapy or post HSCT during prolonged immunosuppression.[10,11]

Uncommon but fatal infections such as mycobacterial and parasitic infections have also been a matter

of concern, especially in endemic countries.[12–15] Most of the reports on tuberculosis in post HSCT are from developing counties where mycobacterial infection tends to be an endemic disease. In such places, tuberculosis is predominantly because of the reactivation of latent infection.[16] In the United States, studies have shown the incidence of mycobacterial infections in HSCT recipients to be anywhere from 0.0014% to 3%.[17]

Newer therapies and associated infections

Advancements in the HSCT have provided more options to treating transplant physicians. T-cell depletion, donor leukocyte infusion, and immunotherapy using chimeric antigen receptor (CAR) T-cells have been increasingly in use.[18–21] Tisangenlecleucel (Kymriah) is the first approved CAR T-cell therapy. However, little is known in terms of infectious complications following this relatively new therapy.[22,23] Recent studies have shown a higher incidence of infections in the first 30 days following CD 19-targeted CAR T-cell therapy.[24] Cellular therapy is the new addition to the transplant world, and we are still in an initial phase with regard to understanding its utility, effectiveness, and associated complications. As we gather more data on cellular therapeutics, we will be able to consolidate the findings in a better way.

Key infection control principles

Following the infection control precautions and guidelines is the best and time-tested modality to minimize infection in post-transplant settings.[25] Centers for Disease Control and Prevention, the Infectious Disease Society of America, and the American Society of Transplant and Cellular Therapy have also cosponsored guidelines to prevent opportunistic infections amongst the transplant recipients.[26] Similarly, the European Conference on Infections in Leukaemia and Infectious Diseases Working Party from EBMT are also involved in promoting and organizing various scholastic activities and clinical investigations pertinent to prevention, diagnosis, and the treatment of infections following HSCT.[27,28]

Apart from following the published recommendations, cellular therapy and transplant centers should also work closely with the institutional infection control team to understand the local antibiotic stewardship guidelines.

Conclusion

To conclude, the field of bone marrow transplantation continues to evolve. While scientists and scholars are working tirelessly in developing newer anti-cancer drugs, immunotherapies, and condition regimens, it is equally important to address the concerning aspect of high-morbidity-and-mortality related deaths in post HSCT patients. This special edition aims to sensitize the transplant physicians and infectious disease specialists by discussing various aspects of infectious complications in HSCT settings.

Conflict of interest statement

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