COMMENT

Predicting risk of progression to lower respiratory tract infection in allogeneic hematopoietic cell transplant recipients with respiratory viral infections: where are we now?

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In this issue of *Bone Marrow Transplantation*, Ogimi and colleagues report on a large cohort of 1027 allogeneic hematopoietic cell transplant (HCT) recipients from a single center infected with respiratory viruses (excluding severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2) to identify risk factors for progression to lower respiratory tract infection (LRTI). The authors evaluated in their cohort the use of the Immunodeficiency Scoring Index (ISI) [1], a combination of different predictors of LRTI, in addition to risk factors such as hyperglycemia and hypoalbuminemia. Prior studies identified lymphopenia, neutropenia, age, time from transplantation, exposure to steroids, graft-versus-host disease, prior autologous HCT, smoking history, and type of transplant as risk factors for progression to an LRTI [2]. Our group developed the ISI for respiratory syncytial virus (RSV) that combines seven major risk factors to predict the rate of LRTI in allogeneic HCT recipients in a large cohort ($n = 237$) [1]. The ISI assigns a weighted score to each risk factor based on its adjusted hazard ratio. These factors include neutropenia (absolute neutrophil count <500/μl), lymphocytopenia (absolute lymphocyte count <200/μl), patient age of at least 40 years, use of a myeloablative conditioning regimen, acute or chronic graft-versus-host disease, use of corticosteroids within 30 days of RSV infection, and transplantation within 30 days of or in the pre-engraftment period during RSV infection [1]. This quantifiable ISI stratifies patients into low-risk (0–2), moderate-risk [3–6], and high-risk (≥7) categories regarding progression or death. Studies have validated the ISI for different respiratory viral infections in allogeneic and autologous HCT recipients at multiple centers with varying success [2–6].

In addition to a high ISI score (≥7), Ogimi and colleagues identified factors not reported before in multivariate models, such as hypoalbuminemia (<3 g/dL), more than one HCT prior to infection, and hyperglycemia (peak glucose level >200 mg/dl), with the highest risk for progression to LRTI in patients with RSV and metapneumovirus infections. Notably, some of these factors are potentially modifiable, such as hyperglycemia and hypoalbuminemia. Not surprisingly, influenza infection was not associated with significant progression to LRTI in their analysis, as therapy with a neuraminidase inhibitor such as oseltamivir may have altered the course of the infection. In a previous study, we showed that early therapy (within 48 h of symptom onset) with oseltamivir was associated with decreased rates of LRTI and death regardless of the ISI score [7]. Influenza vaccines in allogeneic HCT recipients may also impact outcomes, but this remains to be determined in future studies [7]. The variable definitions in this study were consistent with those in prior studies by their group and others [6, 8, 9], including LRTI and lymphopenia. The Use of consistent variable definitions across studies increases the reliability of quantitative models like the ISI score in predicting outcomes from respiratory viral infections, which will lead to better design and planning of future clinical trials in this patient population.

Ogimi and colleagues did not analyze mortality or risk factors for mortality in their study. We believe this information may be of great value to better delineate strategies to prevent this outcome. The ISI was intended to predict mortality in allogeneic HCT recipients with RSV, with 0%, 3%, and 29% rates of 90-day mortality due to RSV associated with low, moderate, and high ISI scores, respectively ($p < 0.0001$) [1]. Our group validated the association of a high ISI score with 30- and 90-day overall mortality in RSV-infected HCT recipients in another study [10]. Preventing progression to LRTI would reduce mortality rates, and strategies such as early therapy or "pre-emptive therapy" at the upper respiratory tract infection phase and vaccination prior to infection are strongly recommended in allogeneic HCT recipients. Vaccination to prevent these complications is limited to influenza and Coronavirus disease 2019 (COVID-19) vaccines at this time, however. In nontransplant patients, early treatment of influenza infection with oseltamivir [11, 12] and of COVID-19 with molnupiravir [13] was effective in preventing poor outcomes, such as hospitalization or even death. However, conducting large clinical trials in allogeneic HCT recipients with infection with a respiratory virus is challenging at best because of the seasonality of many of these infections and a limited number of transplant recipients affected.

High-risk allogeneic HCT recipients who would benefit the most from therapeutic intervention should be the targeted patient population for inclusion in clinical trials for respiratory viral infections. In a recent trial assessing the efficacy of molnupiravir in preventing hospitalization and death in patients with COVID-19, Bernal et al. [13] selected a population at high risk for

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complications at early stages of their infections. Their risk factors included unvaccinated status as well as age greater than 60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, serious cardiac conditions, and diabetes mellitus. The study demonstrated superiority of molnupiravir over a placebo based on a reduction in the rate of hospitalization after 29 days (treatment difference of −6.8% [95% CI, −11.3% to −2.4%]) and the rate of conjoint outcome of hospitalization or death after 29 days (treatment difference of −3.0% [95% CI, −5.9% to −0.1%]). In contrast, in a phase 2 trial of presatovir, a fusion inhibitor with activity against RSV, to prevent progression to LRTI in HCT recipients with RSV upper respiratory tract infections, investigators enrolled all types of HCT recipients, including autologous HCT recipients [14]. Although the study did not meet the coprimary endpoints of reducing the proportion of patients developing lower respiratory tract complications and the time-weighted average decline in the nasal RSV viral load between Days 1 and 9, a subset analysis of lymphopenic HCT recipients and patients transplanted within a year of diagnosis of RSV upper respiratory tract infection suggested treatment benefit with presatovir [14]. These two studies are vastly different in terms of targeted population, respiratory virus, number of participants, and study endpoints. However, these studies show that targeting high-risk patients at early stages of their respiratory viral infections may increase the likelihood of positive outcomes if an antiviral effect is present. Furthermore, Ljungman et al. [4] analyzed 382 autologous or allogeneic HCT recipients with COVID-19 to identify mortality risk factors. The overall reported mortality rate was 28.4%, and multivariate analysis identified age (hazard ratio, 1.21 [95% CI, 1.03–1.43]) and moderate to high ISI score (hazard ratio, 1.84 [95% CI, 1.02–3.33]) as independent predictors of 6-week overall mortality and good performance status (hazard ratio, 0.83 [95% CI, 0.74–0.93]) as a protective factor against 6-week overall mortality [4]. These findings are of the utmost significance, as prompt and aggressive management of these high-risk patients with either monoclonal antibody or targeted therapy and enrollment in future trials may reduce mortality.

Finally, the initial intent of developing the ISI was to stratify allogeneic HCT recipients infected with RSV URTI into risk categories to target patients with high ISI for treatment with ribavirin to improve outcomes, such as progression to LRTI and mortality [2]. Although we originally developed the ISI for RSV-infected allogeneic HCT recipients, Ogimi and colleagues demonstrated its utility in a large cohort of patients infected with multiple respiratory viruses. These host risk factors incorporated in the ISI and those newly identified by Ogimi and colleagues in their study are easily measured and can be readily available to clinical providers. Whether the use of the ISI enriches the enrollment of allogeneic HCT recipients with respiratory virus infection in future clinical trials remains to be determined.

REFERENCES

1. Shah DP, Ghantoji SS, Ariza-Heredia EJ, Shah JN, El Taoum KK, Shah PK, et al. Immunodeficiency scoring index to predict poor outcomes in hematopoietic cell transplant recipients with RSV infections. Blood. 2014;123:3263–8.
2. Khawaja F, Chemaly RF. Respiratory syncytial virus in hematopoietic cell transplant recipients and patients with hematologic malignancies. Haematologica. 2019;104:1322–31.
3. Kmeid J, Vanichanan J, Shah DP, El Chaer F, Azzi J, Ariza-Heredia EJ, et al. Outcomes of Influenza Infections in Hematopoietic Cell Transplant Recipients: Application of an Immunodeficiency Scoring Index. Biol Blood Marrow Transpl. 2016;22:542–8.
4. Ljungman P, de la Camara R, Mikulska M, Tridello G, Aguado B, Zahrani MA, et al. COVID-19 and stem cell transplantation; results from an EBMT and GETH multicenter prospective survey. Leukemia. 2021;35:2885–94.
5. Houist AL, Bondeelle L, Salmona M, LeGoff J, de Latour RP, Rivière F, et al. Evaluation of prognostic scores for respiratory syncytial virus infection in a French multicentre cohort of allogeneic haematopoietic stem cell transplantation recipients. Bone Marrow Transpl. 2021;56:3032–41.
6. Ogimi C, Xie H, Waghmare A, Ueda Oshima M, Mallhi KK, Jerome KR, et al. Risk factors for seasonal human coronavirus lower respiratory tract infection after hematopoietic cell transplantation. Blood Adv. 2021;5:1903–14.
7. Kumar D, Ferreira VH, Blumberg E, Silveira F, Cordero E, Perez-Romero P, et al. A 5-Year Prospective Multicenter Evaluation of Influenza Infection in Transplant Recipients. Clin Infect Dis. 2018;67:1322–9.
8. Seo S, Xie H, Leisenring WM, Kuypers JM, Sahoo FT, Goyal S, et al. Risk Factors for Parainfluenza Virus Lower Respiratory Tract Disease after Hematopoietic Cell Transplantation. Biol Blood Marrow Transpl. 2019;25:163–71.
9. Ogimi C, Waghmare AA, Kuypers JM, Xie H, Yeung CC, Leisenring WM, et al. Clinical Significance of Human Coronavirus in Bronchoalveolar Lavage Samples From Hematopoietic Cell Transplant Recipients and Patients With Hematologic Malignancies. Clin Infect Dis. 2017;64:1532–9.
10. Foolad F, Aitken SL, Shigle TL, Prayag A, Ghantoji S, Ariza-Heredia E, et al. Oral Versus Aerosolized Ribavirin for the Treatment of Respiratory Syncytial Virus Infections in Hematopoietic Cell Transplant Recipients. Clin Infect Dis. 2019;68:1641–9.
11. Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. JAMA. 2000;283:1016–24.
12. Oboho IK, Reed C, Gargiullo P, Leon M, Aragon D, Meek J, et al. Benefit of Early Initiation of Influenza Antiviral Treatment to Pregnant Women Hospitalized With Laboratory-Confirmed Influenza. J Infect Dis. 2016;214:507–15.
13. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med. 2022;386:509–20.
14. Chemaly RF, Dadwal SS, Bergeron A, Ljungman P, Kim Y-J, Cheng G-S, et al. A Phase 2, Randomized, Double-blind, Placebo-Controlled Trial of Presatovir for the Treatment of Respiratory Syncytial Virus Upper Respiratory Tract Infection in Hematopoietic-Cell Transplant Recipients. Clin Infect Dis. 2020;71:2777–86.

AUTHOR CONTRIBUTIONS

Both RFC and FK contributed equally to this manuscript.

COMPETING INTERESTS

RFC serves a scientific consultant/adviser for Merck, Ansun Biopharma, Takeda/Shire, Oxford Immunotec, ADMA Biologics, Pulmotec, Enanta, ReViral, and Genentech, and received research funding from Merck, Takeda/Shire, Oxford Immunotec, AiCuris, Ansun Biopharma, Viracor, Karius, Genentech, and Janssen. FK has none to report.

ADDITIONAL INFORMATION

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