COVID-19 Vaccine Effectiveness in Patients with Hematologic Malignancy

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- COVID-19 vaccine response → HM<solid
- Breakthrough infections → HM>solid
- Vaccine effectiveness → Population studies urgently needed
- Early #COVID19CP could be lifesaving in immunocompromised HM pts

Patients with hematological malignancy (HM), specifically those with B-cell lymphoid malignancies and receipt of anticancer therapies within 12 months prior to COVID-19, are consistently reported to have worse COVID-19 severity, including higher rates of hospitalization, intensive care unit admission, mechanical ventilation, and death, compared to those with solid malignancy.[1,2] Given our prior knowledge about the impact of immunosuppression on response to non-COVID vaccines, it was unsurprising that patients with HM, especially those on lymphocytotoxic therapies, including anti-CD20 mAbs, were significantly less likely to develop adequate seroconversion after two doses of COVID-19 mRNA vaccination compared to those with solid malignancy.[3] Although patients may be independently protected by cellular immunity, the majority of the seronegative patients with HM did not elicit CD8+/CD4+ T cell responses after 2 doses.[4] How this blunted vaccine response translates to clinical outcomes following breakthrough infections in this vulnerable population is largely underexamined.

In a small, single-center retrospective cohort study of 70 HM patients with COVID-19, DeVoe et al. report no statistical difference in outcomes (hospitalization or COVID-19 severity based on the WHO scale) between vaccinated (15 fully vaccinated, one partially vaccinated) and unvaccinated groups (n=54).[5] Similar findings of comparable outcomes were reported by another registry-based study comparing breakthrough infections in 131 patients with any cancer (specifically, 19 fully vaccinated and 18 partially vaccinated HM patients) with infections in unvaccinated controls.[6] Both studies primarily included data before or during the Delta variant dominance and had considered receipt of 2 doses as "full" vaccination. We recommend extreme caution to interpret the results from these studies as just first insights into case fatality rates following primarily Delta breakthrough infections after two doses of mRNA vaccination, and not to be confused as vaccine effectiveness studies in patients with HM. A recent electronic health records study identified that the risk of breakthrough infections in 6,964 patients with HM was 14.5% after 2 vaccine doses; however, this study may have oversampled people with medical encounters at large academic medical institutions.[7] To understand COVID-19 vaccine effectiveness in patients with HM, we urgently need large-scale population-based studies with adequate representation of vaccinations records and mild COVID-19 cases from outside healthcare systems. Furthermore, with the 2nd booster recommendation for all patients with cancer, additional data are also needed to reflect how 3-dose or

4-dose vaccination series perform against the breakthrough Omicron infections and disease severity in this group.

Besides being biased toward sicker patients, the study by DeVoe et al.[5] is limited by too small a sample size to adjust for potential confounders that can distort the association between receipt of vaccination and COVID-19 severity. Interaction between multiple factors related to host (e.g., age, sex, Black race, Hispanic ethnicity, eastern cooperative oncology group performance status of 2 or more, pre-existing comorbidities, etc.), underlying disease and treatment (e.g., active and progressing cancer status, specific immunosuppressive treatments, lymphopenia, neutropenia, corticosteroids, etc.), and environmental factors (e.g., dominant viral strain, viral load, period, region, etc.) determine COVID-19 severity in patients with cancer.[1] Thus, future studies aiming to understand vaccine effectiveness against breakthrough infection and COVID-19 severity in patients with HM should be cognizant of these potential confounders when comparing vaccinated and unvaccinated groups using an appropriate sample size. Patients with cancer also have multiple ongoing complications, making hospitalizations, ICU admission, and mechanical ventilation subjective markers for COVID-19 severity. Future studies should consider reporting 30-d and all-cause mortality and long COVID or post-acute sequelae of COVID-19 (PASC) as outcomes for COVID-19 vaccine effectiveness in patients with HM.

The choice of the control group is also highly pertinent to the interpretation of these findings. DeVoe et al. combined patients with solid malignancy and those with HM in the control group;[5] however, this might have underestimated the effect estimate because patients with solid malignancy have been shown to have significantly better COVID-19 outcomes and vaccine response compared to HM.[1,3] Both studies also included unvaccinated controls from the Alpha and Delta wave, while the vaccinated cases were primarily from the Delta wave.[5,6] It is essential to underscore the need for selecting contemporaneous unvaccinated controls to account for the spatiotemporal variations during the pandemic. Availability of genome sequencing, viral load, antibody, and T cell repertoire is crucially needed to provide a comprehensive picture of the vaccine's effectiveness. DeVoe et al. should be commended for including whole-genome sequencing information, albeit for only 16% of the cohort.[5] Also, hospital- or registry-based reports have generally not been able to account for other environmental factors or social determinants of health between vaccinated and unvaccinated groups, all of which could have a direct impact on their COVID-19 exposure, immune response, access to healthcare, clinical trials, and latest anti-COVID therapies, and thus subsequent outcomes.

Finally, a persistent theme across studies has been the impact of immunosuppressive agents, i.e., anti-B cell therapies, such as anti-CD20 mAb rituximab, on decreasing the vaccine response and increasing COVID-19 severity in HM.[1-3] Although still lower than controls, patients with HM had a significant increase in antibody levels after 3rd dose of vaccination compared to 1st or 2nd dose; however, 67% of patients on anti-B cell therapies did not develop antibodies compared to 7.5% of those without anti-B cell therapy.[8] Thus, patients on anti-B cell therapies is one of the highest-risk group and thus it is imperative to understand the timing of treatment in relation to vaccination and planning of booster administration. Meanwhile, convalescent plasma has shown excellent promise in immunocompromised HM; however, has not been widely adopted. In a retrospective cohort study of 966 individuals with HM and COVID-19, convalescent plasma treatment was associated with improved 30-day mortality (HR, 0.60; 95%CI, 0.37-0.97).[9] Not specifically in cancer, but in a recent multicenter, double-blind, randomized, controlled trial administration of convalescent plasma within nine days after the onset of COVID-19 symptoms led to a 54% relative risk reduction in hospitalization compared to those who with control plasma.[10] DeVoe et al. reported 14.5% of patients

had received convalescent plasma;[5] however, did not provide distribution between the vaccinated and unvaccinated groups. Although clearly important in determining outcomes, antiviral therapies have neither been mentioned nor accounted for in majority of studies examining outcomes following breakthrough infections, which further makes inference difficult from these reports.[5-7]

In conclusion, patients with HM have a lower response to COVID-19 vaccine, higher rates of breakthrough infections, and subsequently worse outcomes than patients with solid malignancy. Compared to non-cancer patients, the vaccine effectiveness against symptomatic infections seems lower in patients with HM visiting academic centers (cumulative infection risk: 4.9% vs. 14.9%);[7] however, epidemiological studies are still needed to understand the effectiveness of mRNA vaccination, especially boosters, against COVID-19 severity in this group. Early administration with high-titer convalescent plasma or plasma from vaccinated individuals should be considered as an option in immunocompromised patients with breakthrough infections, especially those with anti-B cell therapies and low vaccine response. Continued surveillance in patients with HM is essential to assess the changes in vaccine effectiveness against evolving variants. In the meantime, vaccination including boosters, masking, and physical distancing are recommended for all high-risk HM patients to prevent infections and short- and long-term consequences of COVID-19.

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