


Impact of Therapy in Patients with Hematologic Malignancies on Seroconversion Rates After SARS-CoV-2 Vaccination

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Abstract

Introduction: The leading professional organizations in the field of hematology have recommended severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination for all patients with hematologic malignancies notwithstanding efficacy concerns. Here we report a systematic literature review regarding the antibody response to SARS-CoV-2 vaccination in patients with hematologic malignancies and its key determinants.

Methods: We conducted a systematic search of original articles evaluating the seroconversion rates with SARS-CoV-2 vaccines in hematological malignancies from the PubMed database published between April 1, 2021 and December 4, 2021. Calculated risk differences (RD) and 95% confidence intervals (CI) to compare seroconversion rates between patients with hematologic malignancies versus healthy control subjects used the Review Manager software, version 5.3.

Results: In our meta-analysis, we included 26 studies with control arms. After the first dose of vaccination, patients with hematologic malignancies had significantly lower seroconversion rates than controls (33.3% vs 74.9%; RD: -0.48%, 95% CI: -0.60%, -0.36%, $P < .001$). The seroconversion rates increased after the second dose, although a significant difference remained between these 2 groups (65.3% vs 97.8%; RD: -0.35%, 95% CI: -0.42%, -0.28%, $P < .001$). This difference in seroconversion rates was particularly pronounced for Chronic Lymphocytic Leukemia (CLL) patients (RD: -0.46%, 95% CI: -0.56, -0.37, $P < .001$), and for patients with B-lineage leukemia/lymphoma treated with anti-CD20 antibodies (RD: -0.70%, 95% CI: -0.88%, -0.51%, $P < .001$) or Bruton Tyrosine Kinase Inhibitors (BTKi; RD: -0.63%, 95% CI: -0.85%, -0.41%, $P < .001$). The RD was lower for patients under remission (RD: -0.10%, 95% CI: -0.18%, -0.02%, $P = .01$).

Conclusion: The seroconversion rates following SARS-CoV-2 vaccination in patients with hematologic malignancies, especially in CLL patients and patients treated with anti-CD20 antibodies or BTKi, were significantly lower than the seroconversion rates in healthy control subjects. Effective strategies capable of improving vaccine efficacy in these vulnerable patient populations are urgently needed.

Key words: antibody; COVID-19; hematological malignancies; SARS-CoV-2; vaccine.

Introduction

The vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as the primary strategy in the fight against the COVID-19 pandemic, and available vaccines have decreased COVID-19 mortality and morbidity worldwide.¹⁻⁴ Patients with hematological malignancies were prioritized for the vaccination against SARS-CoV-2,⁵ considering the high rate of mortality and morbidity of COVID-19 in these vulnerable patient populations.⁶ Early reports have suggested significantly decreased antibody responses to SARS-CoV-2 vaccination in patients with hematologic malignancies, although the sample sizes, treatment factors, and included patient cohorts were heterogeneous.⁷⁻⁹ Therefore, we systemically reviewed the available data on the antibody response to SARS-CoV-2 vaccination in patients with hematologic malignancies in the context of disease status and immunosuppressive therapy.

Methods

Literature Search

We conducted a systematic review from the PubMed database per the PRISMA guidelines¹⁰ with MeSH terms: “vaccine” OR “vaccination” AND “cancer” OR “malignancy” OR “neoplasms” OR “myeloid” OR “myeloma” OR “leukemia” OR “leukaemia” OR “lymphoma” OR “hematological” OR “myeloproliferative”. We included original articles evaluating the seroconversion rates with SARS-CoV-2 vaccines in hematological malignancies published between April 1, 2021 and December 4, 2021.

Study Selection and Meta-Analyses

Our systematic search retrieved a total of 5261 records and we included 26 studies with control arms in the analyses (12 studies for first dose and 22 studies for second dose) (Supplementary Fig. S1).

We performed meta-analyses via generic inverse-variance method with a random-effects model and reported heterogeneity with the I-square statistics. The principal summary measure was the risk difference (RD) with 95% 2-sided confidence intervals (CI). All analyses were done using the Review Manager software, version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The *P* values of <.05 were considered statistically significant.

Results

Seroconversion Rates After First Vaccination

Low seroconversion rates after the first vaccine dose as a consistent finding across all studies^{7,9,11-21} (Supplementary Table S1), represented a sharp contrast to over 80% seroconversion rates after the first vaccine dose in healthy control groups of most studies (8/12).^{9,11,13,15,16,18-20} In the pooled data from 12 studies, patients with hematologic malignancies had significantly lower likelihood of seroconversion after the first dose of vaccination (322/996, 33.3%) than healthy controls (856/1143, 74.9%; RD: -0.48%, 95% CI:

-0.60%, -0.36%, *P* < .001; Supplementary Table S1 and Fig. 1a). Significant variability existed among the studies (*I*² = 90%; Fig. 1a). Sensitivity analyses by subtracting individual studies from the equation showed a consistent negative effect.

Seroconversion Rates After Second Vaccination

In the pooled analysis of 22 studies encompassing 3187 patients,^{7,9,11,16-18,20-35} the possibility of an antibody response to 2-dose vaccination was 35% lower in patients with hematologic malignancies (97.8% in the control arms vs 65.3% in hematological malignancies) (RD: -0.35%, 95% CI: -0.42%, -0.28%, *P* < .001; Fig. 1b). Additionally, the antibody titers were consistently lower in patients with hematologic malignancies than healthy controls in most studies (Supplementary Table S2). The difference in seroconversion rates was most pronounced in Chronic Lymphocytic Leukemia (CLL) patients (RD: -0.46%, 95% CI: -0.56, -0.37, *P* < .001) (Fig. 2b), while the difference in seroconversion rates was lower in myeloma patients compared with controls (RD: -0.23%, 95% CI: -0.28, -0.18, *P* < .001) (Fig. 2a).

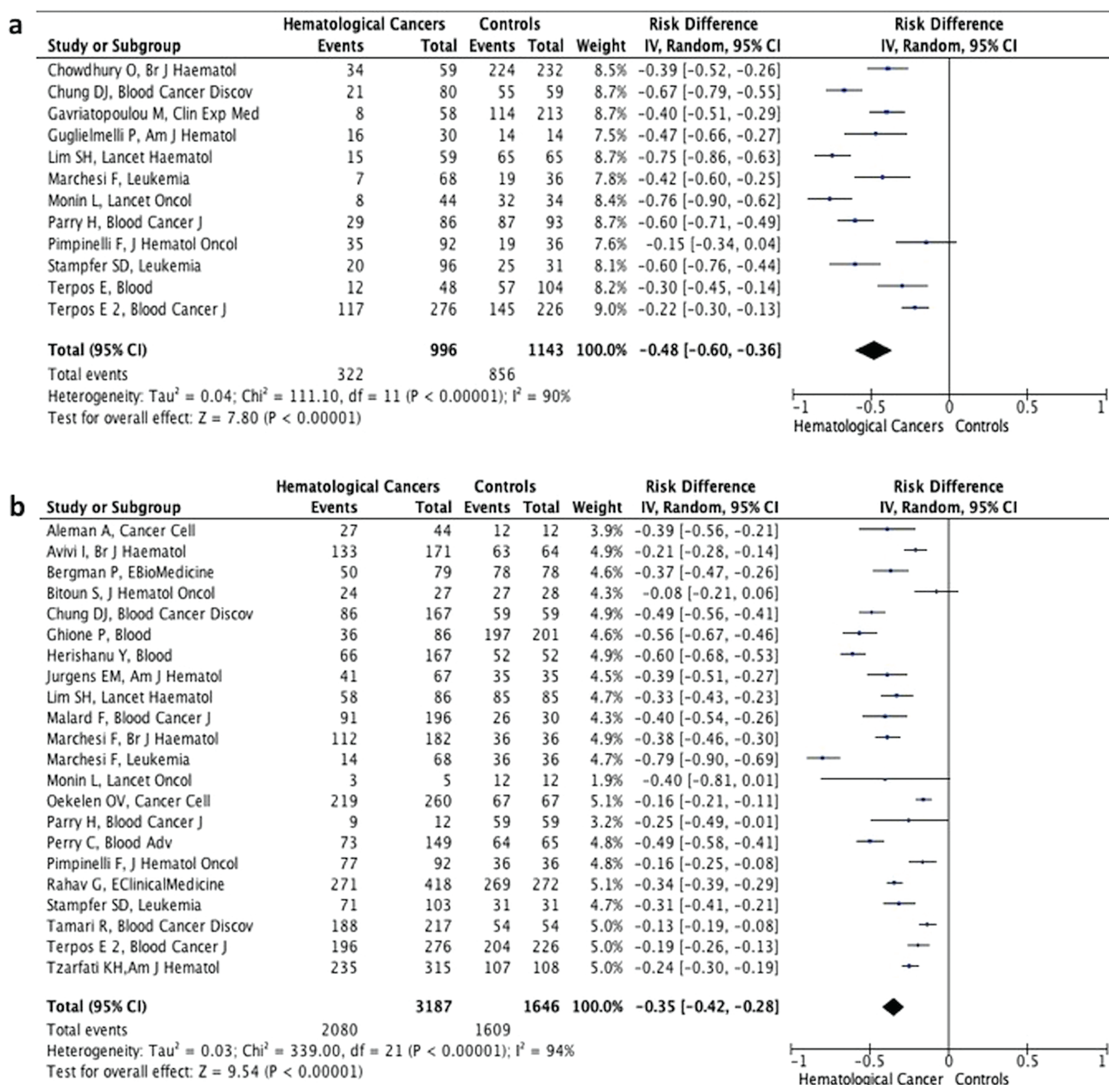


Figure 1. Forest plot illustrating the risk differences of seroconversion rates between patients with hematologic malignancies and healthy controls with first dose of vaccination (a) and second dose of vaccination (b).

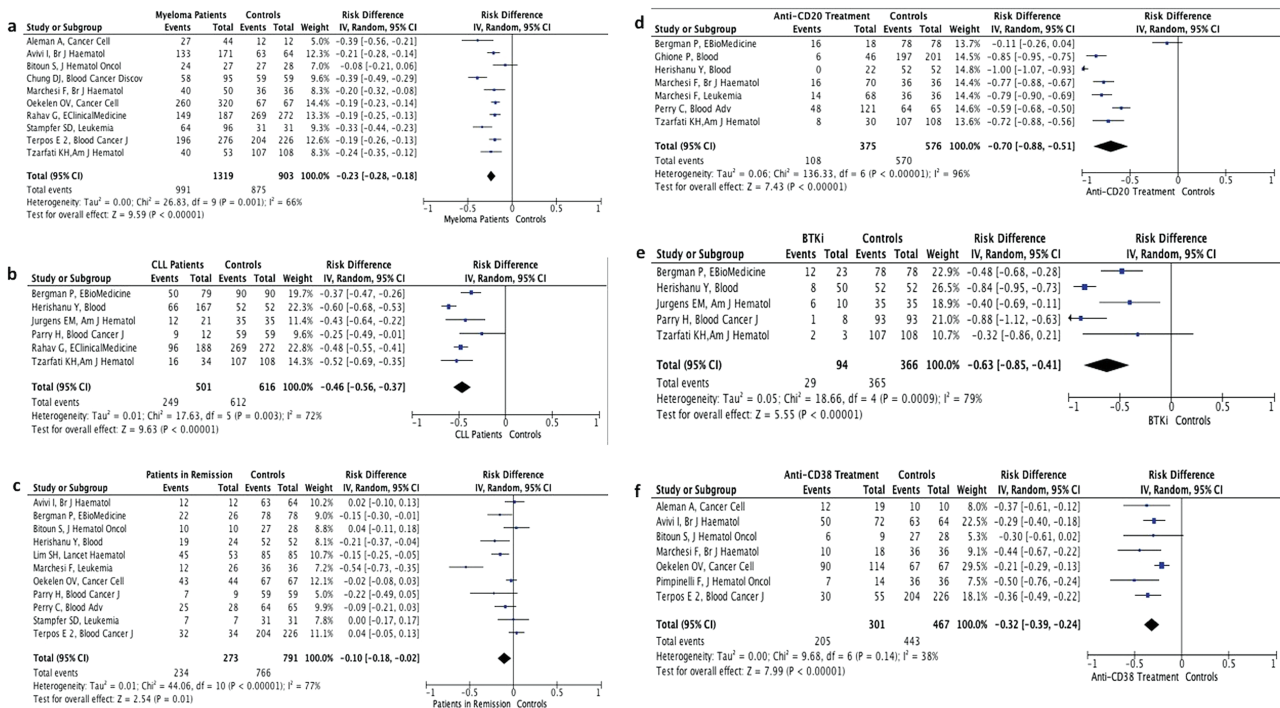


Figure 2. Forest plot illustrating the risk differences of seroconversion rates between multiple myeloma patients (a), CLL patients (b), patients in remission (c), hematologic malignancy patients treated with anti-CD 20 monoclonal antibodies (d), BTK inhibitors (e), anti-CD38 monoclonal antibodies (f), and healthy controls after second dose of vaccination.

The Effects of Treatments on Seroconversion Rates with 2-Dose Vaccination

Eleven studies reported specific outcomes for patients in remission^{11,16-18,21-25,30,31} (Supplementary Table S2). In the pooled analysis of these studies, the patients in remission had lower seroconversion rates than healthy controls, although with a smaller RD (RD: -0.10%, 95% CI: -0.18%, -0.02%, *P* = .01; Fig. 2c). In contrast, the seroconversion rates after 2-dose vaccination were strikingly lower in B-lineage leukemia/lymphoma patients treated with anti-CD20 antibodies (RD: -0.70%, 95% CI: -0.88%, -0.51%, *P* < .001; Fig. 2d) or Bruton Tyrosine Kinase Inhibitors (BTKi; RD: -0.63%, 95% CI: -0.85%, -0.41%, *P* < .001) compared with controls (Fig. 2e). Patients treated with an anti-CD38 antibody also had lower seroconversion rates with 2 dose vaccination (RD: -0.32%, 95% CI: -0.39%, -0.24%, *P* < .001; Fig. 2f). Significant heterogeneity was present in all analyses (Figs. 1a and b and 2a-f).

Discussion

In this meta-analysis, we consistently observed significantly lower seroconversion rates in patients with hematologic malignancies compared with healthy controls after 2-dose vaccination. Treatment with an anti-CD20 antibody or a BTKi appeared to accentuate this difference. However, several questions remain unanswered.

First, a consistently effective strategy for patients who remain seronegative after 2-dose vaccination is yet to be deciphered. In August 2021, FDA recommended a third-dose booster to immunosuppressive patients and later expanded this recommendation to individuals over 18 years of age with a high-risk of severe COVID-19 disease due to population level data. However, the efficacy of the third-dose booster is

relatively unknown in hematologic malignancies. In a recent study, 18 of 18 seronegative patients with lymphoid malignancies remained seronegative after a third vaccine dose.³⁶ Similarly, Marchesi et al observed only 4 seroconversions with a third-dose booster in 50 seronegative B-cell NHL patients.²¹ Likewise, whether the T-cell immunity correlates with antibody responses to vaccination is unknown. The observation of T-cell responses in the absence of seroconversion in approximately 25% of seronegative patients and a higher rate of T-cell responses than antibody responses in patients treated with anti-CD20 agents warrants measuring and reporting T-cell responses in addition to seroconversion in patients with hematologic malignancies.³⁷

Another vital question is the clinical efficacy of the COVID-19 vaccines. The clinical efficacy was the main endpoint of vaccine clinical trials, although real-life studies reported mostly seroconversion rates. Mittelman et al reported significantly higher risk of COVID-19 infection (RR 1.60, 95% CI: 1.12-2.37), severe COVID-19 infection (RR 2.27, 95% CI 1.18-5.19), and COVID-19-related deaths (RR 1.66, 95% CI 0.72-4.47) in vaccinated patients with hematologic malignancies compared with general population.³⁸ Similarly, Heudel et al reported significantly higher mortality rates in patients with hematologic malignancies in a cohort of 1503 patients with cancer.³⁹ These data further motivates applying additional boosters and prioritization of passive immunization strategies for patients with hematologic cancers.

Finally, the present study mostly reported outcomes with mRNA vaccines and the data on efficacy of vaccines other than mRNA vaccines are scarce. However, several regions of the World are using different vaccines. There is a need for additional studies evaluating the efficacy of other available vaccines in patients with hematologic malignancies.

Conflict of Interest

Fatih M. Uckun: Ares Pharmaceuticals (E, LLC), Aptevo Therapeutics, Reven Pharmaceuticals (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Author Contributions

Conception/design: D.C.G. and F.M.U. Collection and/or assembly of data: All authors. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors. D.C.G. and F.M.U. have planned the work. D.C.G., T.K.S., SA., and F.M.U. participated in data collection. All authors have made significant and substantive contributions to the reporting of the work, drafting of the manuscript, review, and revisions of the final draft. All co-authors qualify the criteria for authorship according to Vancouver protocol.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

References

- Baden LR, El Sahly HM, Essink B, et al Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2020;384:403-416.
- Polack FP, Thomas SJ, Kitchin N, et al Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383:2603-2615.
- Sadoff J, Gray G, Vandebosch A, et al Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med*. 2021;384:2187-2201.
- Voysey M, Clemens SAC, Madhi SA, et al Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397:99-111.
- Desai A, Gainor JF, Hegde A, et al COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials. *Nat Rev Clin Oncol*. 2021;18:313-319.
- Vijenthira A, Gong IY, Fox TA, et al Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood*. 2020;136:2881-2892.
- Pimpinelli F, Marchesi F, Piaggio G, et al Fifth-week immunogenicity and safety of anti-SARS-CoV-2 BNT162b2 vaccine in patients with multiple myeloma and myeloproliferative malignancies on active treatment: preliminary data from a single institution. *J Hematol Oncol*. 2021;14:81.
- Harrington P, de Lavallade H, Doores KJ, et al Single dose of BNT162b2 mRNA vaccine against SARS-CoV-2 induces high frequency of neutralising antibody and polyfunctional T-cell responses in patients with myeloproliferative neoplasms. *Leukemia*. 2021;35:3573-3577.
- Monin L, Laing AG, Muñoz-Ruiz M, et al Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. *Lancet Oncol*. 2021;22:765-778.
- Page MJ, McKenzie JE, Bossuyt PM, et al The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Br Med J*. 2021;372:n71.
- Lim SH, Campbell N, Johnson M, et al Antibody responses after SARS-CoV-2 vaccination in patients with lymphoma. *Lancet Haematol*. 2021;8:e542-e544.
- Terpos E, Trougakos IP, Gavriatopoulou M, et al Low neutralizing antibody responses against SARS-CoV-2 in older patients with myeloma after the first BNT162b2 vaccine dose. *Blood*. 2021;137:3674-3676.
- Chowdhury O, Bruguier H, Mallett G, et al Impaired antibody response to COVID-19 vaccination in patients with chronic myeloid neoplasms. *Br J Haematol*. 2021;194:1010-1015.
- Gavriatopoulou M, Terpos E, Kastritis E, et al Low neutralizing antibody responses in WM, CLL and NHL patients after the first dose of the BNT162b2 and AZD1222 vaccine. *Clin Exp Med*. 2021:1-5.
- Diefenbach C, Caro J, Koide A, et al Impaired humoral immunity to SARS-CoV-2 vaccination in non-hodgkin lymphoma and CLL patients. *medRxiv* 2021. <https://doi.org/10.1101/2021.06.02.21257804>.
- Parry H, McIlroy G, Bruton R, et al Antibody responses after first and second COVID-19 vaccination in patients with chronic lymphocytic leukaemia. *Blood Cancer J*. 2021;11:136.
- Terpos E, Gavriatopoulou M, Ntanasis-Stathopoulos I, et al The neutralizing antibody response post COVID-19 vaccination in patients with myeloma is highly dependent on the type of anti-myeloma treatment. *Blood Cancer J*. 2021;11:138.
- Stampfer SD, Goldwater MS, Jew S, et al Response to mRNA vaccination for COVID-19 among patients with multiple myeloma. *Leukemia*. 2021;35:3534-3541.
- Guglielmelli P, Mazzoni A, Maggi L, et al Impaired response to first SARS-CoV-2 dose vaccination in myeloproliferative neoplasm patients receiving ruxolitinib. *Am J Hematol*. 2021;96:E408-e410.
- Chung DJ, Shah GL, Devlin SM, et al Disease- and therapy-specific impact on humoral immune responses to COVID-19 vaccination in hematologic malignancies. *Blood Cancer Discov*. 2021;2:568-576.
- Marchesi F, Pimpinelli F, Giannarelli D, et al Impact of anti-CD20 monoclonal antibodies on serologic response to BNT162b2 vaccine in B-cell Non-Hodgkin's lymphomas. *Leukemia*. 2022;36:588-590.
- Perry C, Luttwak E, Balaban R, et al Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with B-cell non-Hodgkin lymphoma. *Blood Adv*. 2021;5:3053-3061.
- Herishanu Y, Avivi I, Aharon A, et al Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood*. 2021;137:3165-3173.
- Van Oekelen O, Gleason CR, Agte S, et al Highly variable SARS-CoV-2 spike antibody responses to two doses of COVID-19 RNA vaccination in patients with multiple myeloma. *Cancer Cell*. 2021;39:1028-1030.
- Avivi I, Balaban R, Shragai T, et al Humoral response rate and predictors of response to BNT162b2 mRNA COVID-19 vaccine in patients with multiple myeloma. *Br J Haematol*. 2021;195:186-193.
- Herzog Tzarfati K, Gutwein O, Apel A, et al BNT162b2 COVID-19 vaccine is significantly less effective in patients with hematologic malignancies. *Am J Hematol*. 2021;96:1195-1203.
- Ghione P, Gu JJ, Attwood K, et al Impaired humoral responses to COVID-19 vaccination in patients with lymphoma receiving B-cell-directed therapies. *Blood*. 2021;138:811-814.
- Rahav G, Lustig Y, Lavee J, et al BNT162b2 mRNA COVID-19 vaccination in immunocompromised patients: a prospective cohort study. *EClinicalMedicine*. 2021;41:101158.
- Aleman A, Upadhyaya B, Tuballes K, et al Variable cellular responses to SARS-CoV-2 in fully vaccinated patients with multiple myeloma. *Cancer Cell*. 2021;39:1442-1444.

30. Bergman P, Blennow O, Hansson L, et al Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunocompromised patients and healthy controls in a prospective open-label clinical trial. *EBioMedicine*. 2021;74:103705.
31. Bitoun S, Henry J, Vauloup-Fellous C, et al Response to COVID-19 mRNA vaccination in multiple myeloma is conserved but impaired compared to controls. *J Hematol Oncol*. 2021;14:166.
32. Jurgens EM, Ketas TJ, Zhao Z, et al Serologic response to mRNA COVID-19 vaccination in lymphoma patients. *Am J Hematol*. 2021;96:E410-e413.
33. Tamari R, Politikos I, Knorr DA, et al Predictors of humoral response to SARS-CoV-2 vaccination after hematopoietic cell transplantation and CAR T-cell therapy. *Blood Cancer Discov*. 2021;2:577-585.
34. Malard F, Gaugler B, Gozlan J, et al Weak immunogenicity of SARS-CoV-2 vaccine in patients with hematologic malignancies. *Blood Cancer J*. 2021;11:142.
35. Marchesi F, Pimpinelli F, Sperandio E, et al The 12-week kinetics of anti-SARS-CoV-2 antibodies in different haematological cancers after vaccination with BNT162b2. *Br J Haematol*. 2022;196:362-367.
36. Re D, Seitz-Polski B, Carles M, et al Humoral and cellular responses after a third dose of BNT162b2 vaccine in patients treated for lymphoid malignancies. *medRxiv*. 2021. <https://doi.org/10.1101/2021.07.18.21260669>.
37. Ehmsen S, Asmussen A, Jeppesen SS, et al Antibody and T cell immune responses following mRNA COVID-19 vaccination in patients with cancer. *Cancer Cell*. 2021;39:1034-1036.
38. Mittelman M, Magen O, Barda N, et al Effectiveness of the BNT162b2mRNA Covid-19 vaccine in patients with hematological neoplasms. *Blood*. 2021.
39. Heudel P, Favier B, Assaad S, et al Reduced SARS-CoV-2 infection and death after two doses of COVID-19 vaccines in a series of 1503 cancer patients. *Ann Oncol*. 2021;32:1443-1444.