

In-depth characterisation of the immune response upon COVID-19 vaccination in cancer patients

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SUMMARY

COVID-19 vaccination in cancer patients is complicated by underlying disease and treatment related immunosuppression, which is associated with attenuated vaccine responses and increased risk of severe COVID-19 after SARS-CoV-2 infection. In addition, due to their immunosuppressed status, cancer patients were excluded from pivotal COVID-19 vaccine trials, leaving critical knowledge gaps regarding vaccine safety, immunogenicity, and long-term outcomes in this vulnerable population. This thesis investigates how COVID-19 vaccination shapes humoral and cellular immunity in cancer patients. Across three prospective Belgian studies (B-VOICE, Tri-VOICE, REAL-V) including 760 cancer patients on active anti-neoplastic treatment, mRNA vaccines elicited higher IgG and IgA antibody responses than adenoviral vector vaccines, with responses that were particularly impaired in patients receiving chemotherapy or B-cell depleting therapy. However, administration of an mRNA booster dose after initial dual-dose vaccination with a viral vector vaccine restored IgG antibody levels to those seen with schedules including three mRNA vaccination doses and elicited enhanced T-cell responses. An IgG antibody-based correlate of protection of 20.42 BAU/mL was identified for the pre Omicron period, but this association disappeared once Omicron variants predominated, underscoring the limitations of antibody centric metrics and the growing relevance of cellular immunity. Functional T-cell analysis and T-cell receptor sequencing showed that COVID-19 vaccination induces polyfunctional SARS-CoV-2-specific T-cells and durable CD4 clonal memory, while natural infection predominantly expanded CD8 clonotypes, indicating complementary vaccine versus infection induced cellular immunity. Overall, this work supports personalised vaccination strategies that prioritise mRNA vaccines, systematic booster administration, and combined monitoring of humoral and cellular immunity, while emphasising the long-term supportive needs of cancer patients in the evolving COVID-19 landscape. (BELG J MED ONCOL 2026;20(2): 85–88)

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INTRODUCTION

Cancer patients are considered immunocompromised due to both the malignancy and its treatment, resulting in impaired infection control and suboptimal vaccine responses.¹ Early in the COVID-19 pandemic, they were identified as a high risk group for severe disease,² yet they were excluded from pivotal vaccine efficacy trials, leaving oncologists without evidence based guidance on vaccine safety and effectiveness in this population.³ At the same time, SARS-CoV-2 continued to evolve with variants capable of immune escape and waning post vaccine immunity, necessitating booster campaigns and updated vaccine formulations.^{4,5} This thesis⁶ addresses this knowledge gap by systematically characterising humoral and cellular responses to different COVID-19 vaccine platforms and booster schedules in cancer patients, as well as defining antibody based correlates of protection and characterising long term clinical and psychosocial consequences of COVID-19.

BODY

VACCINE SAFETY IN CANCER PATIENTS

A total of 760 cancer patients under active anti-neoplastic treatment was included across three major prospective clinical trials: B-VOICE, Tri-VOICE plus and REAL-V (EudraCT nos. 2021-000300-38, 2021-003573-58 and BUN nr. B3002021000069). These patients received up to four vaccine doses over a period of one year (initial dual-dose vaccination plus two subsequent boosters) and were longitudinally followed-up, starting before first vaccination until six months after second booster administration. During these studies, blood samples were collected every one to six months from every patient, starting before first vaccine dose administration until 28 days after second booster. In the blood samples, different immunological parameters were assessed including quantification of humoral antibodies, neutralising antibodies and specific T-cells. Initial findings demonstrated that both mRNA-based BNT162b2 and adenoviral vector-based ChAdOx1 were safe for vaccination of cancer patients receiving active anti-neoplastic treatment.⁷ Local and systemic adverse events were mostly mild to moderate, with severe events reported in only 1–3% of patients. All adverse events resolved within a few days after vaccine administration.

VACCINE EFFICACY: MRNA VERSUS ADENOVIRAL VECTOR VACCINES AND BOOSTER STRATEGIES

While cancer patients, and especially patients with solid tumors receiving chemotherapy and patients with hema-

tological malignancies, mounted significantly lower IgG antibody responses compared to healthy controls following initial dual-dose BNT162b2,⁷ initial dual-dose BNT162b2 vaccination induced both higher IgG and IgA antibody titers than dual-dose ChAdOx1 vaccination.^{8,9} The reduced antibody responses after ChAdOx1 raised questions about compensatory immune mechanisms, urging analysis of T-cell responses and booster effects. When BNT162b2 boosters were administered, both homologous (BNT162b2/BNT162b2/BNT162b2) and heterologous (ChAdOx1/ChAdOx1/BNT162b2) vaccination schedules significantly enhanced antibody titers. Moreover, heterologous boosting was able to close the initial gap in antibody response, achieving titers comparable to homologous mRNA schedules, while eliciting a more robust T-cell response. In contrast, homologous mRNA boosting resulted in superior neutralisation against the BA.1 Omicron variant, illustrating variable immunological outcomes based on vaccination schedule.¹⁰

CORRELATE OF PROTECTION AND VARIANT IMPACT

Despite multiple vaccine doses, breakthrough infections were still reported by approximately 20% of cancer patients. A correlate of protection (CoP), defined as an antibody threshold protective against SARS-CoV-2 infection, was identified at 20.42 BAU/mL for the pre-BA.1 (Omicron) period.¹¹ However, when Omicron became the dominant circulating variant, the relationship between antibody titers and clinical protection faded and no robust CoP could be established, highlighting Omicron's immune escape and the increasing importance of cellular immunity for adequate protection.

T-CELL FUNCTION AND TCR REPERTOIRE DYNAMICS

Beyond humoral immunity, COVID-19 vaccination in cancer patients was shown to affect T-cell populations. Vaccination was shown to induce a shift in T-cell populations from a predominantly monofunctional phenotype (single cytokine production) to polyfunctional cells that have the capacity to simultaneously produce multiple cytokines. This enhances the quality and durability of the immune response. This T-cell polyfunctionality, especially in CD8+ T-cells, is essential for sustained long-term protection, particularly as antibody levels decline over time. In addition, longitudinal T-cell receptor (TCR) sequencing revealed that CD4+ T-cell clonotypes expanded significantly after primo-vaccination and were reactivated upon booster administration, indicating a durable memory response. In contrast, CD8+ T-cell expansions were more prominent after a natural SARS-CoV-2

KEY MESSAGES FOR CLINICAL PRACTICE

1. Prioritise the use of mRNA vaccines over viral vector vaccines and ensure booster administration to sustain protection against COVID-19
2. Implement regular monitoring of immune responses, including both antibody and T-cell responses, to evaluate vaccine efficacy
3. Use TCR sequencing for personalized immune profiling to enable tailored vaccination and follow-up strategies for cancer patients
4. Integrate long COVID screening and psychological support in post COVID cancer care to address the broad impact of SARS-CoV-2 infections

infection. These findings underscore the distinct, yet complementary roles of vaccine induced and infection-induced cellular immunity.

LONG COVID AND QUALITY OF LIFE

Among cancer patients infected during the study, nearly 80% report persistent symptoms - fatigue, myalgia, sleep disturbances, cognitive complaints - beyond four weeks after infection. This long COVID syndrome impacted the patient's quality of life and mental health. Although similar symptoms have been reported in non-cancer populations, the prevalence is remarkably higher.¹² During a focus group interview, patients described feelings of isolation, insufficient information, and lack of structured support regarding long COVID support, emphasising the need for better integration of long COVID care within oncology follow-up services.

CONCLUSION

Cancer patients under active anti-neoplastic treatment can be safely vaccinated against COVID-19. However, their immune response is often diminished in comparison to healthy individuals, especially under chemotherapy and B-cell depleting therapy. Repeated booster immunisations, especially those including mRNA vaccines, effectively enhance both humoral and cellular immunity, partially overcoming initial response deficits. The disappearance of a correlate of protection with the emergence of the Omicron variant underscores the ongoing challenge created by viral evolution and highlights the importance of cellular immunity in maintaining protection. Furthermore, the high prevalence of long COVID symptoms emphasises the

need for post COVID care within oncology departments. Altogether, these findings advocate for a personalised, multidimensional vaccination approach that integrates vaccine platform choice, booster scheduling, and immunomonitoring with attention for long COVID and psychosocial care in cancer patients to ensure durable protection and improved quality of life.

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