

## Early COVID-19 booster is beneficial in cancer patients

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its corresponding coronavirus disease (COVID-19) was first reported as a cluster of pneumonia cases in Wuhan, China, on 31 December 2019<sup>1</sup> and led to an unprecedented pandemic in modern times. It quickly overwhelmed healthcare systems around the world, and rendered immunocompromised patients, such as those with cancer, particularly vulnerable to severe infections.

Also unprecedented was the rapid development of several highly effective vaccines, thanks to concerted global efforts. Once COVID-19 vaccinations were available, the Ministry of Health (MOH) in Singapore implemented a nationwide SARS-CoV-2 vaccination programme for healthcare staff in early January 2021, started a pilot for vaccinations for senior citizens in late January 2021, and progressively made the COVID-19 vaccine freely available for all Singaporeans and permanent residents. In line with emerging data thereafter, MOH offered a booster to immunocompromised patients as early as 2 months after the second dose. Currently, as of 7 November 2022, MOH encourages all eligible residents aged 18 years and above<sup>2</sup> to undergo a second COVID-19 booster or a fourth vaccination dose.

Other regulatory healthcare institutions recommended administering a COVID-19 booster within 3–6 months of the completion of the initial mRNA vaccination course and the Committee for Medicinal Products for Human Use approved an extra dose of the COVID-19 mRNA vaccines at least 28 days after the second dose.<sup>3</sup>

Against this background, the study by Lee et al. is timely. In their large, prospective observational study, the authors<sup>4</sup> presented real-world efficacy data in haematological (40/273) and solid cancer (233/273) patients in Singapore who received 2 doses of an mRNA vaccine, either BNT162b2 or mRNA1273, followed by a 3rd dose of BNT162b2 against SARS-CoV-2 during the COVID-19 pandemic. In total, 273 patients were recruited between July 2021 and March

2022 and about 3 quarters were treated with a real-world representative spread of available anti-cancer therapies in a wide range of cancer types. All patients were tested using the GenScript cPass SARS-CoV-2 Neutralization Antibody Detection Kit. Patients were seronegative at baseline and underwent blood tests after each vaccination, demonstrating seroconversion rates of 35.2%, 79.4% and 92.4%, respectively. The authors stated that after 3 doses, patients treated for haematological malignancies had lower antibodies (57.3%±46.2) compared to solid cancer patients on immunotherapy (94.1%±9.56,  $P<0.05$ ) and chemotherapy (92.8%±18.1,  $P<0.05$ ) confirming a lower antibody response in haematological malignancies. The solid cancer patient population comprised gastrointestinal cancers at 40.3%, followed by breast cancer (19%), lung cancers (9.5%) and others. Lee et al. considered patients not receiving anti-cancer therapy, or patients receiving radiotherapy or endocrine therapy only, as the control group. Patients with severe infections, defined as infections resulting in hospitalisation, intensive care unit (ICU) care, oxygen therapy or death, had significantly lower mean antibody levels than non-infected (28.3% versus 77.0%,  $P<0.05$ ) and mildly infected (28.3% vs 65.8%,  $P<0.05$ ) patients. Eighteen out of 77 patients with SARS-CoV-2 infection had severe COVID-19. Of these, 9 patients were haematology patients, and 5 were solid cancer patients, with both groups receiving respective active anti-cancer therapy. Patients on active anti-cancer therapy who received a third COVID-19 vaccine dose within 90 days of their second vaccination (early booster dosing), did not suffer severe COVID-19, underlining the effectiveness of early booster administration.

A systematic review of 30 published studies that reviewed data on the administration of a third COVID-19 vaccination<sup>5</sup> found that in cancer or immunocompromised patients, the mean seroconversion was 39.4% before and 66.6% after the third COVID-19

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Table 1. Risks of reduced antibody responses post-COVID-19 vaccination while on anti-cancer therapy

| Relevant reduction of antibody likely (>50%)                                                                                                                                                                               | Relevant reduction of antibody possible (<50%)                                                                                                                      | Relevant reduction of antibody uncommon                                                                                                                                                                                | Cellular therapy                                                                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• B cell depletion with monoclonal antibodies, BTK and/or BCL inhibitors</li> <li>• BCMA-targeted therapies</li> <li>• CD38-targeted therapies</li> <li>• JAK inhibitors</li> </ul> | <ul style="list-style-type: none"> <li>• Chemotherapy</li> <li>• Steroids</li> <li>• CDK4/6 inhibitors</li> <li>• Poly(ADP-ribose) polymerase inhibition</li> </ul> | <ul style="list-style-type: none"> <li>• Endocrine therapy</li> <li>• Tyrosine kinase inhibitors</li> <li>• Immune checkpoint inhibitors</li> <li>• Immunomodulatory drugs</li> <li>• Proteasome inhibitors</li> </ul> | <ul style="list-style-type: none"> <li>• Chimeric antigen receptor T cell therapy</li> <li>• Uncomplicated stem cell transplantation with stable engraftment</li> </ul> |

ADP: adenosine diphosphate; BTK: Bruton's tyrosine kinase; BCL: B cell lymphoma; BCMA: B cell maturation antigen; JAK: Janus kinase; CDK4/6: cyclin-dependent kinases 4 and 6

Adapted from Fendler A, de Vries EGE, Guerts van Kessel CH, et al. COVID-19 vaccines in patients with cancer: immunogenicity, efficacy and safety. *Nat Rev Clin Oncol* 2022;19:385-401.

vaccination. In October 2022, Youssra et al.<sup>6</sup> published a systematic review of a third COVID-19 vaccination in haematological and solid cancers. The authors described that the response after a third dose was reduced in haematological cancers as compared to solid cancers. They also reported that systemic anti-cancer therapy led to a poorer seroconversion in haematological cancers, likely driven by B cell depletion. The authors described that the interval between the second and the third vaccination ranged from 27 to 214 days, without a median range provided. Another difference to the study by Lee et al. was that some patients received a mix of mRNA and non-mRNA vaccinations, that is, heterologous vaccinations.

In terms of systemic anti-cancer therapy, a large retrospective cohort study in 29,152 vaccinated cancer patients suggested a clinical effectiveness of 57% (95% confidence interval [CI] 23–90) for patients on chemotherapy versus 76% (95% CI 50–91) for those on endocrine therapy and 85% (95% CI 29–100) without systemic therapy.<sup>7</sup> Fendler et al.<sup>8</sup> reviewed COVID-19 vaccines in cancer patients and categorised the risk of reduced antibody response after COVID-19 vaccinations into 4 groups. These groups were divided by their likelihood of relevant reduction of antibody being likely (>50%, B cell depletion), possible (<50%, chemotherapy), uncommon (hormone therapy), or treated with cell therapy (chimeric antigen receptor [CAR]-T cells) (Table 1). The data presented by Lee et al. concur well with this risk stratification, and the prospective observational design highlighted the differences in the risk of reduced antibody responses between haematological and solid cancers, although no patients treated with CAR-T cells and uncomplicated stem cell transplantation were enrolled.

The overall low risk of total COVID-19 infection in Lee et al.'s study population—77 out of 273—challenges the narrative that immunocompromised patients do not

mount a sufficient response to vaccinations, potentially negating the need to provide passive immunity and indicating that oral antiviral therapies should be prioritised instead. However, this overall low COVID-19 infection in the study population could also be due to the fact that, in September 2021, 76.6% of the Singapore population had completed 2 doses of vaccination.<sup>4</sup> At the same time, MOH announced that a third vaccination dose was offered to immunocompromised patients.<sup>4</sup> Additionally, risk mitigation measures were in place with mandatory mask-wearing, and this would also have contributed to a lower risk of COVID-19 infection in cancer patients, as well as in the Singapore population as a whole.

Lee et al. acknowledged the limitations of using antibody production to evaluate the immunogenicity of vaccinations, and that the duration is unknown for cancer patients to maintain levels necessary for an immune response. In line with many studies demonstrating waning immunity, the initial positive results of an early COVID-19 booster are likely to reduce over time. This waning immunity has led some countries, including Singapore, to offer a second COVID-19 booster.<sup>2</sup> Lee et al. further highlighted that cellular immunity against SARS-CoV-2 is of particular importance in patients who are unable to mount an adequate humoral response. They suggested that future studies, investigating the role of cellular immunity in conferring protection against SARS-CoV-2, will help to answer this question. With regards to different types of cancers, gastrointestinal cancer patients were predominant in Lee et al.'s study but compared to Shroff et al.,<sup>9</sup> the spread of cancer types did represent a real-world situation more closely.

Lee et al. added to the body of evidence that a third vaccination or first booster against SARS-CoV-2 clearly reduced the number of cancer patients with severe COVID-19. This study also added evidence that the

third booster ought to be given within 90 days from the second. During the study duration, the primary COVID-19 vaccination rate within the Singapore population rose from 51% to 89%<sup>10</sup>, indicating a successful Singapore-wide effort to fully vaccinate the population, protecting vulnerable patients, and reducing the healthcare burden in Singapore significantly. Lee et al. have shown that the administration of an early COVID-19 booster reduced severe COVID-19 infections in cancer patients further.

With this study, Lee et al. provided real-world evidence that an early third vaccination of an mRNA vaccine given while receiving anti-cancer therapy with targeted therapy and immunotherapy did not impair an immune response. In fact, the vaccine was effective, and an early SARS-CoV-2 booster reduced severe COVID-19 infections in all patients receiving chemotherapy. These findings showed that COVID-19-vaccinated cancer patients benefitted from an early booster in Singapore, and are likely too on a global level.

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