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Clinical efficacy and long-term immunogenicity of an early triple dose regimen of SARS-CoV-2 mRNA vaccination in cancer patients

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ABSTRACT

Introduction: Three doses of SARS-CoV-2 mRNA vaccines have been recommended for cancer patients to reduce the risk of severe disease. Anti-neoplastic treatment, such as chemotherapy, may affect long-term vaccine immunogenicity.

Method: Patients with solid or haematological cancer were recruited from 2 hospitals between July 2021 and March 2022. Humoral response was evaluated using GenScript cPASS surrogate virus neutralisation assays. Clinical outcomes were obtained from medical records and national mandatory-reporting databases.

Results: A total of 273 patients were recruited, with 40 having haematological malignancies and the rest solid tumours. Among the participants, 204 (74.7%) were receiving active cancer therapy, including 98 (35.9%) undergoing systemic chemotherapy and the rest targeted therapy or immunotherapy. All patients were seronegative at baseline. Seroconversion rates after receiving 1, 2 and 3 doses of SARS-CoV-2 mRNA vaccination were 35.2%, 79.4% and 92.4%, respectively. After 3 doses, patients on active treatment for haematological malignancies had lower antibodies (57.3%±46.2) when compared to patients on immunotherapy (94.1%±9.56, $P<0.05$) and chemotherapy (92.8%±18.1, $P<0.05$). SARS-CoV-2 infection was reported in 77 (28.2%) patients, of which 18 were severe. No patient receiving a third dose within 90 days of the second dose experienced severe infection.

Conclusion: This study demonstrates the benefit of early administration of the third dose among cancer patients.

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Keywords: Cancer, oncology, SARS-CoV-2, third dose, vaccination

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CLINICAL IMPACT

What is New

- This study is the first in Singapore to evaluate the real-world efficacy of a third SARS-CoV-2 vaccine in cancer patients.
- This study is among the first in the world to assess the effect of tumour-type and anti-neoplastic treatment in determining vaccine response.

Clinical Implications

- An early triple dose regimen of SARS-CoV-2 vaccination is effective in cancer patients.
- Targeted therapy and immunotherapy do not impair SARS-CoV-2 antibody production.
- More SARS-CoV-2 vaccine doses strongly correlate with reduced infection severity.

INTRODUCTION

The spread of the SARS-CoV-2 virus has led to the ongoing worldwide COVID-19 pandemic. Initial studies have reported an increased vulnerability of patients with solid and haematological malignancies to SARS-CoV-2 infections.[1,2] Global efforts to combat SARS-CoV-2 led to the unprecedented rapid development of multiple vaccines, with reported efficacies of 94–98% at preventing severe disease.[3-6] However, early trials evaluating immunogenicity were limited in immunosuppressed individuals, largely excluding cancer patients on active chemotherapy, transplant patients, and patients with immunodeficiencies. Subsequent studies demonstrated that while most patients with solid organ malignancies develop adequate anti-viral immunity, patients with haematological malignancies had significantly lower seroconversion rates.[7-9] In particular, patients who had received highly immunosuppressive therapies such as anti-CD20 monoclonal antibodies and stem cell transplantation were at the highest risk of reduced seroconversion.[8,10,11]

The increased vulnerability to SARS-CoV-2 infections in cancer patients, coupled with the blunted immune response to vaccination, has prompted a third, fourth and even fifth dose to be administered to immunosuppressed individuals. Furthermore, previous publications have reported waning immunity 6 months following the second dose of mRNA vaccine BNT162b2 in healthy subjects.[12] A similar decrease in humoral response was also reported in patients with solid tumours on active cancer treatment 3 months after the second dose,[13] supporting the recommendation for administering a third dose in immunocompromised patients. Small-scale studies have demonstrated encouraging results, with increased virus-neutralising antibody titres immediately post-third dose for cancer patients.[10,13,14]

However, existing studies primarily reported immunogenicity responses to SARS-CoV-2 vaccinations, focusing on seroconversion rates and neutralising antibody levels. Few studies have demonstrated the real-world efficacy of vaccination in association with the severity of SARS-CoV-2 infections. This is a significant gap to be addressed, especially given recent evidence suggesting that the blunted immune response by SARS-CoV-2 vaccines in oncology patients makes them more susceptible to breakthrough infections,[15] coupled with the rapid emergence of antibody-evading SARS-CoV-2 variants (Delta and Omicron).[16,17]

In September 2021, 76.6% of the Singaporean population had completed 2 doses of vaccination, compared to 63.1% in the UK, 59.5% in Israel and 54.4% in the US.[18] At the time, the Ministry of Health (MOH), Singapore announced a third dose of SARS-CoV-2 vaccination to be offered to immunosuppressed patients, as early as 2 months after the second dose.[19] By 31 March 2022, 91% of Singapore's population had received at least 2 doses of vaccine, and 72% received a booster or 3 doses. In addition, the country has a comprehensive and robust national database that accurately tracks the incidence and severity of SARS-CoV-2 infections.[20] By 6 May 2022, Singapore had a total of 1,212,337 COVID-19 cases (20.4%) out of its 5.9 million population.[21] From 1 May 2021 to 14 Apr 2022, 0.67% of fully vaccinated (without booster) and 0.24% of fully vaccinated (with booster) populations infected with SARS-CoV-2 ever required oxygen supplementation in the general ward, in intensive care unit (ICU) or died.[20] SARS-CoV-2 viral genome sequencing data showed that the Delta variant predominated in Singapore between May and December 2021, before being overtaken by the Omicron variant since January 2022.[22] The overarching national framework provides us with the opportunity to evaluate the real-world efficacy of SARS-CoV-2 vaccinations and correlating it with clinical severity of SARS-CoV-2 infections in our patients.

This study is among the first to assess the effect of tumour type and anti-neoplastic treatment in determining vaccine response to the third dose of vaccine in cancer patients, and provide real-world efficacy data on SARS-CoV-2 infections with

correlation to the neutralising antibody levels and humoral response. While there have been emerging data on the real-world efficacy of the third dose on cancer patients, the evidence is still sparse and confined to certain geographical regions.[23] This large prospective study adds to the literature on real-world efficacy of a third SARS-CoV-2 vaccine dose in patients with solid and haematological malignancies.

METHOD

Patients and sample collection

This is a prospective study using blood samples from patients with a personal history of malignancy, recruited from the 2 hospitals of the National University Cancer Institute, Singapore: the National University Hospital (NUH) and Ng Teng Fong General Hospital, Singapore, between July 2021 and March 2022. Included patients must be ≥21 years old and must have been deemed by their primary physician to be suitable to receive SARS-CoV-2 vaccination. Clinicopathological data (including age at diagnosis, sex, type of cancer, and anti-neoplastic treatment at enrolment) were collected, and de-identified. Haematological malignancies included leukaemias, myeloma and lymphomas. Types of anti-neoplastic treatments included targeted therapy, immunotherapy and chemotherapy (online Supplementary Table S1). Patients with cancer on surveillance, hormonal therapy or radiotherapy were also included and defined as the "control" group. All patients received mRNA vaccination with either the Pfizer BNT162b2 vaccine, or the Moderna mRNA1273 vaccine.

Subjects were matched with administrative data on SARS-CoV-2 vaccinations and infections reported to the Ministry of Health for the purposes of monitoring disease transmission and vaccination uptake under the Infectious Disease Act. Administrative data on vaccinations included the date and brand of vaccinations, while data on SARS-CoV-2 infections include notification date of infection, and whether cases required treatment in hospital, supplementary oxygen, ICU care and/or resulted in death.

Serology testing

Serology was tested using GenScript cPass SARS-CoV-2 Neutralization Antibody Detection Kits (GenScript Biotech Pte Ltd, Singapore), which performs rapid detection of total neutralising antibodies against SARS-CoV-2 viral spike protein receptor binding domain, with seroconversion defined as a detected output of 30% or more.[24] This form of immunoassay has been shown to perform similarly well as other commercially available immunoassays.[25]

Serology was performed by trained laboratory personnel at NUH. Blood draws were collected immediately before the first vaccine dose (T1), 3–8 weeks after the first vaccine dose or immediately before the second vaccine dose (T2), 3 months after the first vaccine dose or immediately before the third vaccine dose (T3), and 3 months after the third vaccine dose (T4) (Fig. 1).

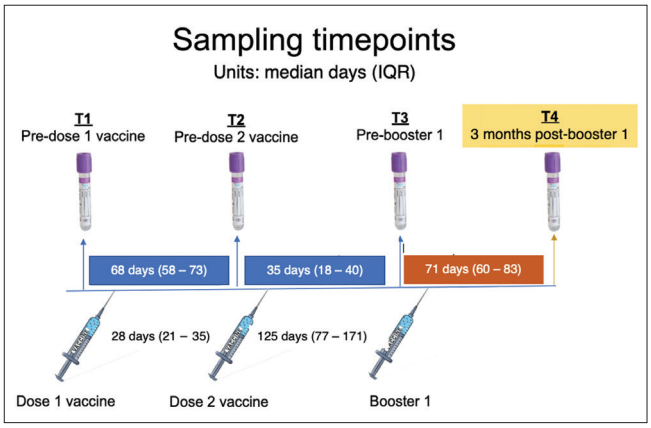

Fig. 1. Schematic of blood collection (draws) after vaccination.
IQR: interquartile range

Statistical analysis

Statistical analyses were performed using R version 4.0.1 (R Foundation, Vienna, Austria). Contingency tables and chi-square or Fisher's Exact tests (for categorical variables), t-test for comparison of means (2 means), one-way analysis of variance for comparison of means (more than 2 means) and Mann-Whitney U test for comparison of medians (for continuous variables) were used to investigate associations of serology results with clinicopathological characteristics and outcomes. A P value <0.05 was considered to indicate statistical significance unless otherwise stated.

Ethical approval

The National Healthcare Group Domain-Specific Review Board provided ethical approval for the use of patient materials in this study (reference number 2021/00523). All individuals enrolled in this study provided written informed consent as part of protocols approved by the Domain Specific Review Board of ethics and in compliance with the October 2013 Declaration of Helsinki principles. Enrolled individuals did not receive compensation for their participation in

the study. No patients nor members of the public were involved in the design of this study.

RESULTS

Patient baseline characteristics

In this prospective observational study, a total of 273 participants were recruited (Table 1). The median age of the patients was 63 years with 50.5% (138/273) female. Forty (14.7%) patients were diagnosed with haematological malignancies, 110 (40.3%) with gastrointestinal (GI) and hepatobiliary (HPB) cancers, and 123 (45.0%) with other malignancies (Table 1).

Of the participants, 204 (74.7%) were receiving active cancer therapy, including 49 (17.9%) on targeted therapies only, 23 (8.4%) on immunotherapy, 98 (35.9%) receiving systemic chemotherapy (with or without immunotherapy), and 34 (12.5%) on active treatment for haematological malignancy. Sixty-nine (25.3%) patients were not on active treatment or only receiving radiotherapy or hormone therapy. These patients were considered the "control" group in our analysis. (Table 1).

A total of 265 had completed the full 2-dose regimen with either BNT162b2 or mRNA1273 vaccine, and 216 received 3 doses of vaccination. The median duration

Table 1. Baseline characteristics of patients recruited, including types of cancer diagnosis and cancer treatment received

	Total patients recruited	Serology data for patients receiving 1 dose	Serology data for patients receiving 2 doses	Serology data for patients receiving 3 doses
	N=273	n=267	n=265	n=216
Median age (IQR), years	63 (15.3)	63 (15.5)	63 (15.0)	63 (14.0)
Median duration from previous dose (IQR), days	-	-	28 (14)	125.5 (94)
Sex, n (%)				
Male	135 (49.5)	131 (49.1)	131 (49.4)	115 (53.2)
Female	138 (50.5)	136 (50.9)	134 (50.6)	101 (46.8)
Cancer type, n (%)				
Haematological cancer (including lymphoma)	40 (14.7)	38 (14.2)	38 (14.3)	29 (13.4)
Gastrointestinal and hepato-pancreatobiliarycancers	110 (40.3)	108 (40.4)	108 (40.8)	93 (43.1)
Lung cancer	26 (9.5)	25 (9.4)	25 (9.4)	17 (7.9)
Breast	52 (19.0)	51 (19.1)	50 (18.9)	38 (17.6)
Gynaecological	17 (6.2)	17 (6.4)	16 (6.0)	14 (6.5)
Prostate	9 (3.3)	9 (3.4)	9 (3.4)	8 (3.7)
Renal	7 (2.6)	7 (2.6)	7 (2.6)	7 (3.2)
Others	12 (4.4)	12 (4.5)	12 (4.5)	11 (5.1)
Treatment received, n (%)				
Control No active treatment, radiotherapy or hormonal therapy only	69 (25.3)	68 (25.5)	68 (25.7)	56 (25.9)
Targeted therapy	49 (17.9)	48 (18.0)	47 (17.7)	36 (16.7)
Immunotherapy	23 (8.4)	23 (8.6)	23 (8.7)	19 (8.8)
Systemic chemotherapy	98 (35.9)	96 (36.0)	95 (35.8)	82 (38.0)
Active treatment for haematological cancer	34 (12.5)	32 (12.0)	32 (12.1)	23 (10.6)

IQR: interquartile range

between second and third dose of vaccine was 125 days for the entire cohort. Excluding those not on active treatment, the median duration was 113 days. Of those patients who received the third dose, 77 (35.6%) had the vaccine administered between 60 and 90 days post-second dose.

Higher antibody titres are associated with reduced severity of SARS-CoV-2 infection

We evaluated the real-world clinical efficacy of vaccination in our patient cohort. SARS-CoV-2 infection was reported in 77 of the 273 patients (28%); 36 (47%) were of the Delta variant, and 41 (53%) were of the Omicron variant, corresponding to the SARS-CoV-2 lineage prevalence in Singapore in 2021–2022.[22] Fifty-nine of the 77 patients developed mild infection, which we defined as either asymptomatic infection, or symptomatic without requiring hospital admission, such as home recovery or virtual ward care. Virtual ward care involved remote care by hospital doctors and nurses during patient isolation. Eighteen of the 77 patients suffered from severe SARS-CoV-2 infections, defined as infection resulting in hospitalisation, ICU care, oxygen therapy or death. We elected to use this distinction of infection severity to reflect the different levels of healthcare requirements and hospital facilities. Of note, only 1 patient required ICU care, and 1 death was reported in our cohort.

Last measured antibody levels prior to infection were correlated with infection severity (Fig. 2). Patients with severe infections had significantly lower mean antibody levels than non-infected (28.3% vs 77.0%, $P<0.05$) and mild infection groups (28.3% versus 65.8%, $P<0.05$). However, the mean differences between the non-infected and mild infection groups were not significant (77.0% vs 65.8%, $P=0.116$). This suggests that higher antibody titres may protect patients from severe disease, but not against mild infection.

Further analysis of patients of different infection severities (no infection, mild infection and severe infection) was performed based on the treatment modalities received. Patients on chemotherapy and on active treatment for haematological malignancies accounted for a greater proportion of severe infections. Of the 18 patients with severe SARS-CoV-2 infections, 9 were on active treatment for haematological malignancies and 5 were on active chemotherapy. Of the 77 patients who received their third dose of vaccine within 90 days of the second dose, none had severe infection.

Seroconversion and antibody responses to mRNA vaccination

Two doses of the SARS-CoV-2 mRNA vaccines (BNT162b2 or mRNA1273) were required to produce a significant antibody response. Seroconversion was 35.2% after the first dose, with median antibody output of 0% (0.0–60.5), compared to 79.4% seroconversion rate and median output of 85.0% (47.9–97.4) after the second dose. A third dose was able to increase antibody titres further, reaching a 92.4% seroconversion with a median output of 99.0% (91.5–99.4) (Fig. 3). Mean antibody output increased after the administration of the second dose (28.1±36.9 vs 69.5±34.9, $P<0.05$) and after the administration of a third dose (69.5±34.9 vs 87.3±26.5, $P<0.05$). Seroconversion stratified by key characteristics—including treatment type, cancer type and sex—is reported in the online Supplementary Tables S2–5.

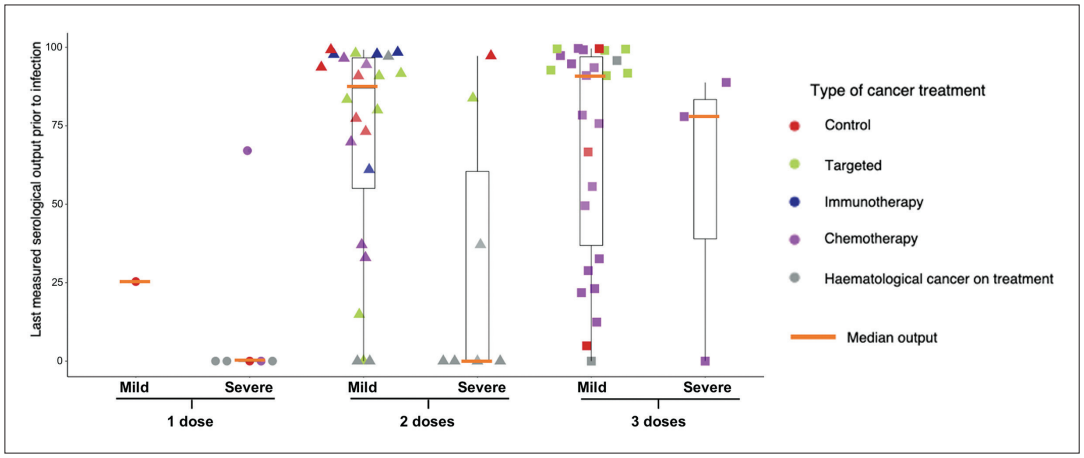

Fig. 2. Most recent antibody output level and severity of SARS-CoV-2 infection. Colours reflect the anti-neoplastic treatment modality received by patients. Shapes reflect the number of vaccine doses received (1, 2 or 3) doses when patients reported infections.

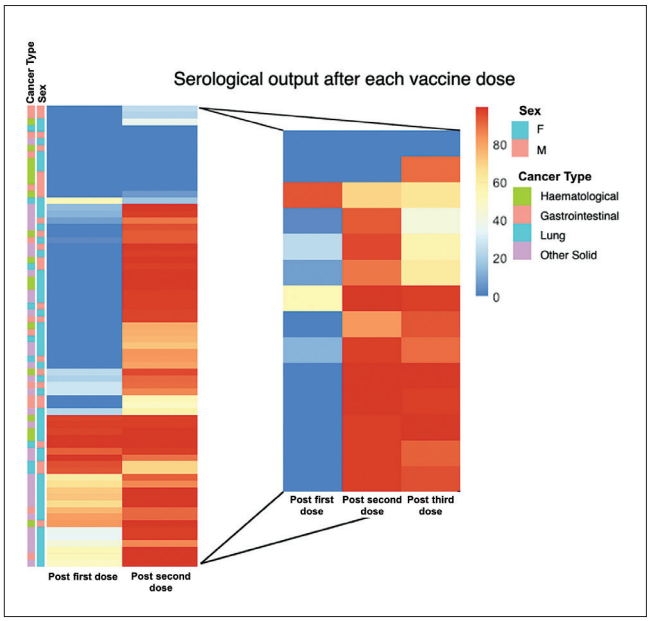

Fig. 3. Antibody responses of cancer patients to mRNA vaccination. Left: Heatmap of serological output after each dose in patients who received 2 doses of a SARS-CoV-2 vaccine. Right: Serological output of the subgroup of these patients who received 3 doses of a SARS-CoV-2 vaccine.

Association with anti-neoplastic treatment

Patients receiving different modalities of anti-neoplastic treatments demonstrated varying degrees of humoral responses and seroconversion (Fig. 4).

Serology output in patients in control group, receiving chemotherapy, targeted therapy, immunotherapy or treatment for haematological malignancy, after 1 dose, 2 doses and 3 doses of SARS-CoV-2 vaccination.

After 2 doses of SARS-CoV-2 vaccination, patients on active treatment for haematological malignancies had significantly lower mean antibody titres (46.8%) compared to patients on other forms of treatment: patients in the control group (75.4%, $P<0.05$), patients on targeted therapy (78.0%, $P<0.05$), immunotherapy (75.8%, $P<0.05$) or chemotherapy (68.1%, $P<0.05$).

After 3 doses of vaccination, patients on active treatment for haematological malignancy (57.3%) still showed significantly lower mean antibody titres compared to patients on immunotherapy (94.1%, $P<0.05$) and chemotherapy (92.8%, $P<0.05$).

Proportionally, patients on active treatment for haematological malignancy also showed lower seroconversion rates compared to other treatment groups (online Supplementary Table S2). After 2 doses of vaccination, seroconversion rates were higher in patients in the control group (83.0%), on targeted therapy (87.5%), on immunotherapy (94.1%), and on chemotherapy (79.5%), compared to 51.9% in patients with haematological malignancies on active treatment. After 3 doses of vaccination, seroconversion rates were higher in patients in the control group (92.3%), on targeted therapy (86.7%), on immunotherapy (100%), and on chemotherapy (96.9%), compared to 66.7% in patients with haematological malignancies on active treatment.

Association with tumour type

We compared the humoral response to 2 and 3 doses of the SARS-CoV-2 vaccine in patients with different tumour types. After 2 doses of vaccination, the mean antibody titres of patients with haematological malignancies (54.1%) were significantly lower than that of patients with other solid cancers (77.0%, $P<0.05$). However, other mean differences between the patients with other types of cancer (GI: 66.8%, lung: 78.1%) were not significant.

Proportionally, patients with solid organ tumours had higher seroconversion rates than patients with

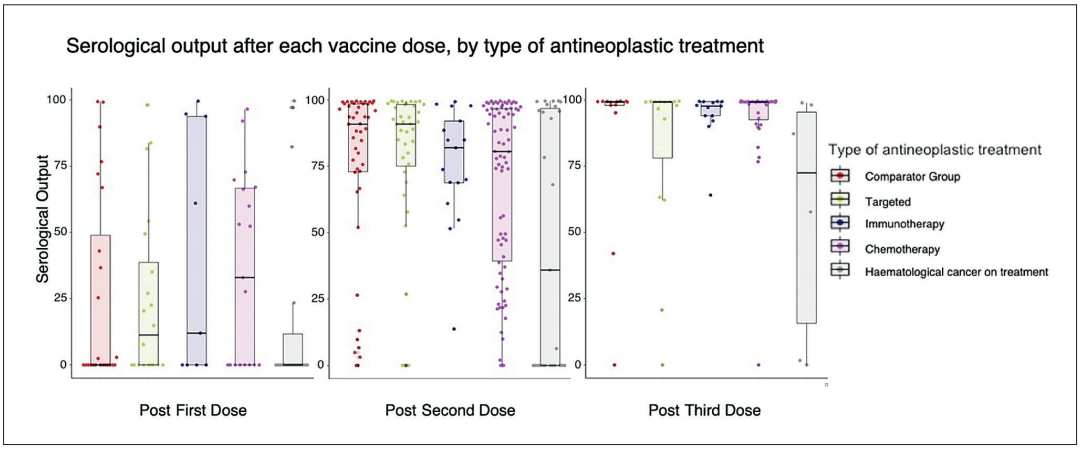

Fig. 4. Association of anti-SARS-CoV-2 antibodies with anti-cancer therapy received.

haematological malignancies (online Supplementary Tables S1–3). After 2 doses of vaccination, seroconversion rates were higher in patients with GI (78.3%), lung (89.5%) and other solid (86.7%) cancers, compared to 59.4% in patients with haematological malignancies. After 3 doses, seroconversion rates were still higher in patients with GI (93.9%), lung (100%) and other solid (96.3%) cancers, compared to 71.4% in patients with haematological malignancies. While limited by sample size, lymphoma patients appeared to perform worse than leukaemia and myeloma patients (online Supplementary Table S4).

Immunogenicity of third dose in previously seronegative patients

Forty-four (19.0%) of patients did not seroconvert after receiving a complete course of 2 doses of the vaccine. Of this group, 17 patients received the third dose, and seroconversion was successfully achieved in 13/17 (76.5%) of previously seronegative patients after the third dose. There were no significant differences in seroconversion rates or antibody levels in patients who received 3 doses of BNT162b2 (n=198), when compared to patients who received 2 doses of mRNA1273 followed by a third dose of BNT162b2 (n=6).

DISCUSSION

The SARS-CoV-2 pandemic had overwhelmed healthcare systems around the world, with immunosuppressed patients being particularly vulnerable to severe infections.[1,2] Despite the unprecedented speed of development of efficacious vaccines, oncological patients were at risk of blunted immune response to vaccinations, particularly if they are receiving immunosuppressive chemotherapy or anti-B-cell therapies.[26-29]

In accordance with other published studies,[8,14,27,28,30,31] patients on treatment for haematological malignancies demonstrated lower antibody titres and the greatest risk of non-seroconversion after 2 and 3 doses of vaccine, compared to patients receiving targeted therapy, immunotherapy or not on anti-neoplastic treatment. This is likely because patients with haematological cancer are on B -cell-depleting therapies, and it has been established that patients on therapies such as anti-CD19 and anti-CD20 therapy demonstrate a poor response to SARS-CoV-2 vaccines.[32,33] In addition, patients with B cell/plasma cell malignancies are known to have severe deficiencies in humoral immunity due to reduction in normal B/plasma cells, further contributing to reduced antibody response to vaccination.[34] Nevertheless, recent studies have demonstrated that a third mRNA-1273 vaccine is able to produce antibody concentrations comparable to healthy individuals after the standard 2-dose regimen,[35] particularly if the third dose is delayed to allow the immune system to "recuperate" after the second dose.[35]

There had been earlier concerns raised of immune checkpoint inhibitors impairing T cell function and hence possibly suppressing antibody response to SARS-CoV-2 vaccination.[36] However, our study demonstrated that patients on targeted therapy and immunotherapy seroconverted as effectively as control patients after 2 doses of SARS-CoV-2 vaccine. This provides real-world data that targeted therapy and immunotherapy did not blunt the immune system's ability to mount an effective antibody response to SARS-CoV-2 vaccination.

Singapore rolled out a rapid and comprehensive vaccination programme, with 76.6% of the population completing the full 2-dose regime by September 2021. This led to the majority of our immunosuppressed patients completing the 2-dose regimen when the Delta and Omicron variants hit the population on a background of a highly immunised general population. In our cohort, only 18 of 77 SARS-CoV-2-infected cancer patients (23%) suffered from serious infections requiring hospitalisation, with only 1 patient needing ICU-level care and another resulting in SARS-CoV-2-related mortality (1.3%). We demonstrate that low rates of severe infection can be achieved even in this highly vulnerable group of immunosuppressed patients. This is via (1) early and high rates of vaccination in cancer patients; (2) a background of a highly vaccinated general population; and (3) effective public health measures including meticulous and swift contact tracing, individual-level quarantine, as well as standard health advice such as wearing of face masks, hand-washing and social distancing. Vaccination against SARS-CoV-2 has been shown to result in milder and shorter illnesses in the general population,[37,38] and would likely confer similar protection in oncological patients who adequately seroconvert.

Most published studies to date focused on immunogenicity as a marker of vaccine efficacy, with few correlating antibody levels with the clinical severity of infection. Our study reported 77 out of 273 patients infected with SARS-CoV-2, of which 36 were presumed Delta variant, and 41 presumed Omicron variant, according to the SARS-CoV-2 lineage prevalence in Singapore from 2021–2022, comparable to the general population.[22] Singapore has a robust mandatory-reporting national database tracking each patient's infection status and progression. This permitted

accurate tracking of the clinical disease severity and correlation to the real-world efficacy of SARS-CoV-2 vaccinations in our patients.

Some countries, including Singapore, have proposed an additional fourth dose for susceptible patients to further boost the antibody response, citing waning immunity as a rationale.[12,39,40] The US Food and Drug Administration licensed the use of a fourth dose for immunocompromised individuals, and in March 2022, the UK had announced a fourth dose for all vulnerable adults. Israel was one of the first countries to administer a fourth dose of the BNT162b2 and mRNA1273 vaccines, with promising results and initial reports of an 8- and 10-fold increase in neutralising antibody titres against the Omicron variant (B.1.1.529) at 1 and 2 weeks after the additional booster dose, respectively, compared to 5 months after the third vaccine.[39]

There are limitations in our study that must be acknowledged. We assessed antibody production to evaluate the immunogenicity of vaccination. Longer follow-up is required to establish if, and for how long, cancer patients can maintain these levels of immune responses. We also assessed seroconversion using the GenScript cPASS surrogate virus neutralisation assay, which is an indirect measurement of antibody titres. Furthermore, not all neutralisation antibodies measured are necessarily receptor binding-domain (RBD) antibodies.[41] However, studies have shown that RBD-targeting neutralisation antibodies are immunodominant.[42] Despite the limitations of the assay, GenScript cPass has high specificity and sensitivity and is widely adopted.[24] Further studies may also seek to investigate the role of cellular immunity in conferring protection against SARS-CoV-2, particularly in patients who are unable to mount an adequate humoral response. Additionally, prevalence data were used to assume if patients had been infected by the Delta or Omicron variants. Future studies may want to rely on whole genomic sequencing to characterise the variants patients are infected with to better understand the relationship between levels of antibodies and sero-protection against vaccine escaping variants.

CONCLUSION

In our study, we demonstrated that each additional dose of vaccine further augmented the humoral response by increasing the seroconversion rates and antibody titres among cancer patients. This humoral response also differed depending on the tumour types and anti-neoplastic treatment. Patients on active treatment for haematological malignancies had the lowest antibody titres, followed by patients on chemotherapy. Patients receiving targeted therapy and immunotherapy had comparable differences in antibody response compared to those on radiotherapy, hormonal therapy, or no active treatment. Antibody titres were also shown to correlate with infection severity. Overall, the study shows that the early administration of third dose among cancer patients achieved high rates of seroconversion and prevented severe infection.

Data availability

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to patient confidentiality.

Disclosures

RS—honoraria (MSD, Eli Lilly, BMS, Roche, Taiho, AstraZeneca and DKSH), consulting or advisory role (Bristol Myers Squibb, Merck, Eisai, Bayer, Taiho, Novartis, MSD and GSK), travel (Roche, AstraZeneca, Taiho, Eisai, DKSH), and research funding (Paxman Coolers and MSD). SCL—grant support/research collaborations (Pfizer, Eisai, Taiho, ACT Genomics, Bayer, MSD and Adagene); Advisory Board/speaking engagement (Pfizer, Novartis, AstraZeneca, ACT Genomics, Eli Lilly, MSD and Roche); and conference support (Amgen, Pfizer and Roche).

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