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Long-term immunity after BNT162b2 mRNA COVID-19 vaccination in pediatric patients with cancer

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1. Introduction

Children with cancer have a higher morbidity and mortality following SARS-CoV-2 infection compared to the general pediatric population [1] and vaccination is recommended [2]. Recent studies demonstrate that 2–12 weeks after the 2nd vaccination the humoral immunity is lower in children under active cancer treatment compared to healthy children [3,4] or children off cancer treatment [5,6]. An additional 3rd vaccine dose increases antibody levels [5–7] and is recommended in children under active cancer treatment [5,6]. T-cell responses are also lower, although discordant results are reported in children with an adequate T-cell response in the absence of adequate antibody levels [3,6,7]. Currently, data on long term immunity induced by SARS-CoV-2 vaccination in children with cancer is scarce. In this study we investigate the antibody levels and T-cell response 1-year after the 2nd SARS-CoV-2 vaccination in children vaccinated during or after cancer treatment.

2. Methods

2.1. Study population and outcomes

This is a follow up study of our previous study on the immunogenicity after the primary COVID-19 vaccination series [6] (EudraCT number: 2021-003388-90). As previously described in detail [6], patients aged 5–17 years with a history of pediatric cancer or hematopoietic stem cell transplantation (HSCT) were enrolled. All children were vaccinated with a 2- or 3-dose series of BNT162b2 (Pfizer/BioNTech) mRNA COVID-19 vaccine. Blood was sampled 1 year after the 2nd vaccination and SARS-CoV-2 specific antibody-[6,8,9] and T-cell [6,10] responses were determined conform references.

2.2. Statistical analysis

Patients were categorized into 3 mutually exclusive groups, based on the number of immunizing events (2, 3, or 4; either a SARS-CoV-2 infection or a COVID-19 vaccination) they experienced. Treatment status (with active treatment defined as immuno- or chemotherapy < 6 weeks before an immunizing event) was used to further divide into 4

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different treatment groups: 1. patients under active treatment during each immunizing event (On Tx), 2. patients under active treatment during each immunizing event, except for the last immunizing event (On/Off Tx), 3. patients no longer under active treatment during each immunizing event (Off Tx) and 4. patients who never received chemo- or immunotherapy (No Tx). Descriptive statistics are presented. For a more detailed description of the methods see Supplementary material.

2.3. Ethical approval

This prospective, observational, cohort study was approved by the Medical Research Ethics Committee (MREC) Utrecht and Central Committee on Research involving Human Subjects (CCMO (NL78187.041.21, 21-430/D) and registered in the European Union Drug Regulating Authorities Clinical Trials database (EudraCT number: 2021-003388-90). Patients and parents/legal guardians were asked for informed consent before participating.

3. Results

Seventy-one children who provided follow-up samples 1 year after the 2nd vaccination were included (flowchart, Supplementary material). Supplementary Table 5 illustrates demographic and baseline characteristics for 66 patients (5 patients are described separately in Supplementary Table 8 as they did not match any of the 4 treatment groups). Hematological malignancies were most common (68.2 %). Fifteen patients (22.7 %) had a history of HSCT/CAR T-cell therapy. Seventy-nine percent experienced one or multiple SARS-CoV-2 infections before or after vaccination. None of these patients was admitted to the intensive care unit or died due to COVID-19. Median follow-up between last immunizing event and last blood sampling was 222 days.

In patients on treatment (On Tx), higher anti-SARS-CoV-2 spike 1 antibody levels were observed in children who had experienced more immunizing events. Median antibody levels increased from 56 (5–967) BAU/mL (2 immunizing events) to 533 (0.1–5097) BAU/mL and 905 (13–9360) BAU/mL (3- respectively 4 immunizing events). The corresponding number of good responders also increased from 25 % to 67 % (2- versus 4 immunizing events). In patients off treatment (Off Tx), median antibody levels in the 2-, 3-, and 4 immunizing events group were all within the good response range (> 300 BAU/mL). Compared to the On Tx group, median antibody levels and percentages of good responders in the Off Tx group were higher for all immunizing events groups (2-, 3- and 4 immunizing events) (Fig. 1A, Table 1).

T-cell responses (On Tx), expressed as median IFN-γ release, following 2nd -, 3rd -, or 4th vaccination were normal (> 200 mIU/mL). A modest increase in the percentage of good responders was seen with each subsequent immunizing events group (from 80 % in patients with 2- to 100 % in patients with 4 immunizing events). In the On/Off Tx- and Off Tx groups, all patients were good responders (Fig. 1B).

Supplementary Tables 6 and 7 depicts separate antibody- and T-cell responses for children with and without a history of COVID-19 infection. Supplementary Figs. 9 and 10 show antibody- and T-cell responses by length of follow-up after last immunizing event for children on treatment.

4. Discussion

In children under active cancer treatment during vaccination and/or infection, improved SARS-CoV-2 antibody responses were observed in those children that had experienced a higher number of immunizing events. When comparing the 2-, 3- and 4- immunizing events groups, each additional vaccination/infection suggests an increase in median antibody titers and the number of good responders. These results suggest that combining multiple vaccinations/infections effectively achieves long-term immunity, also in an immunocompromised population. This is promising as little is known about long-term effectiveness following COVID-19 vaccination in children [11]. Our results are in line with a recent small retrospective study that showed positive anti-S1 antibodies levels after 12-months follow up in 8 pediatric cancer patients [12]. Compared to the B-cell response, the percentage of adequate T-cell responders was higher (80–100 %). This discordance between antibody and T-cell response was also seen during short term follow-up [3,6,7]. Our observations of a robust T-cell response are important as T-cells play a vital role in protection against severe disease and different SARS-CoV-2 variants [13].

Because of break-through COVID-19 infections, median follow-up was 7 months. Shorter follow-up may result in differences in detected immunity between children, but Supplementary Figs. S9 and S10 indicate the number of immunizing events to be more important than length of follow-up. The high incidence of infections limited the possibility of doing a comparative analysis between patients with and without a history of COVID-19. We recognize that the clinical course of these infections and the possible relation to the immune status of a patient are important in determining the clinical relevance of COVID-19 vaccination. Unfortunately, detailed data on all COVID-19 episodes was limited available. However, as stated in the results, we did not observe any intensive care unit admissions or deaths due to COVID-19 vaccination in our population. Next to COVID-19 status, other subgroup analyses such as type of malignancy (e.g. hematological versus solid) or intensity and type of treatment (e.g. HSCT versus non-HSCT) would have been valuable but were not possible due to insufficient sample sizes. Previous research on influenza immunization in children with cancer showed a correlation between the immune response and different variables such as type of malignancy and absolute lymphocyte count [14]. Especially, the absolute CD4-positive T-cell count seemed to be predictive for an adequate vaccination response against H1N1 influenza [15]. Unfortunately we did not have data on lymphocyte counts or other immunologic determinants prior to SARS-CoV-2 infection or vaccination. Future research to identify risk factors for decreased immunity and longer follow-up on additional booster vaccinations are needed.

In conclusion, this study shows the immunogenicity of (re)vaccination in pediatric cancer patients. Currently data on vaccine effectiveness in general in pediatric cancer patients is limited [16]. We show that, despite their immunocompromised state and reduced vaccine response, vaccination is useful and that over 66 % of those patients can acquire long-term immunity. Furthermore, additional booster doses seem beneficial for maintaining long-term immunity. We recommend revaccination after 6–12 months for pediatric cancer patients who are vaccinated during anti-cancer treatment.

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CRediT authorship contribution statement

Peter M. Hoogerbrugge: Writing – review & editing, Methodology, Conceptualization. **Caroline A. Lindemans:** Writing – review & editing, Methodology, Conceptualization. **Stefan Nierkens:** Writing – review & editing, Methodology, Conceptualization. **Gaby Smits:** Writing – review & editing, Investigation, Formal analysis. **Rob S. van Binnendijk:** Writing – review & editing, Investigation, Formal analysis. **Marta Fiocco:** Writing – review & editing, Formal analysis. **Louis J. Bont:** Writing – review & editing, Methodology, Conceptualization. **Wim J. E. Tissing:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **K. L. Juliëtte Schmidt:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Noortje R. Severeijns:** Investigation. **Noël M. M. Dautzenberg:** Writing – review & editing, Investigation, Formal analysis.

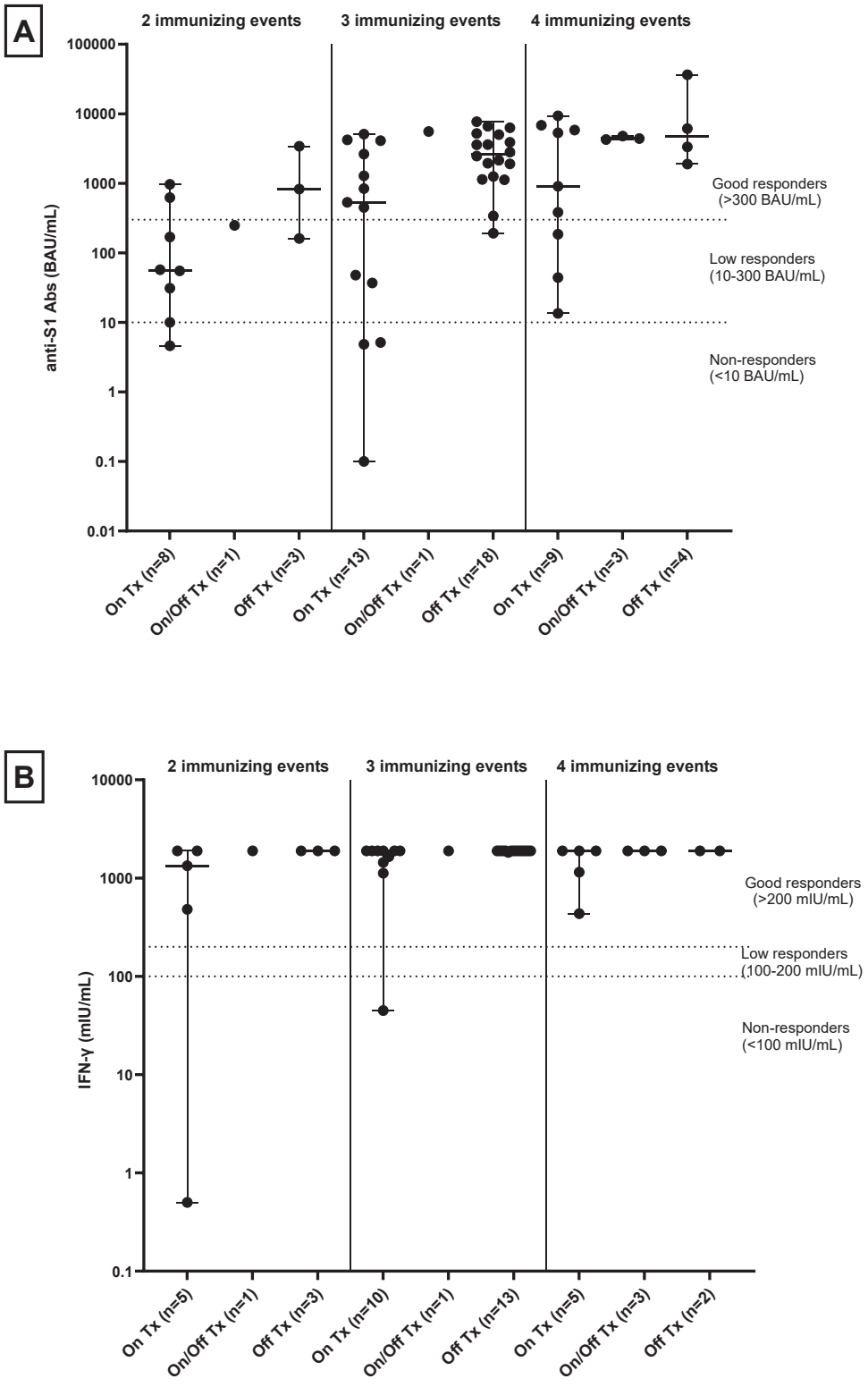

Fig. 1. Long-term SARS-CoV-2 specific antibody- and T-cell response in pediatric cancer patients who experienced 2-, 3- or 4 immunizing events (either a BNT162b2 mRNA COVID-19 vaccination or SARS-CoV-2 infection). Patients were categorized into three mutually exclusive treatment groups based on active treatment status (defined as immuno- or chemotherapy < 6 weeks before an immunizing event); On Tx (patients under active treatment during each immunizing event), On/Off Tx (patients under active treatment during each immunizing event, except for the last immunizing event during which they were no longer under active treatment), and Off Tx (patients no longer under active treatment during each immunizing event) **(A)** Anti-S1 antibody levels in binding antibody units per milliliter (BAU/mL) with non-responders < 10 BAU/mL, low responders 10–300 BAU/mL or good responders > 300 BAU/mL. **(B)** Amount of interferon gamma (IFN-γ) as released by SARS-CoV-2 specific T-cells in milli-international units per milliliter (mIU/mL) with non-responders < 100 mIU/mL, low responders 100–200 mIU/mL, and good responders > 200 mIU/mL.

Table 1
Long-term antibody response[a] following BNT162b2 mRNA COVID-19 vaccination and/or SARS-CoV-2 infection.

	On Tx[b]	On/Off Tx[b]	Off Tx[b]	No Tx[b]
2 immunizing events[c]				
Number of patients (n)	8	1	3	1
Median (range)	56 (5–967)	249	825 (161–3407)	4099
Non-responders, n (%)	1 (12.5)	0	0	0
Low responders, n (%)	5 (62.5)	1 (100)	1 (33.3)	0
Good responders, n (%)	2 (25)	0	2 (66.7)	1 (100)
3 immunizing events[c]				
Number of patients (n)	13	1	18	4
Median (range)	533 (0.1–5097)	5570	2643 (192–7717)	2143 (642–15,224)
Non responders, n (%)	3 (23.1)	0	0	0
Low responders, n (%)	2 (15.4)	0	1 (5.6)	0
Good responders, n (%)	8 (61.5)	1 (100)	17 (94.4)	4 (100)
4 immunizing events[c]				
Number of patients (n)	9	3	4	1
Median (range)	905 (13–9360)	4406 (4276–4788)	4728 (1888–36,463)	10,299
Non responders, n (%)	0	0	0	0
Low responders, n (%)	3 (33.3)	0	0	0
Good responders, n (%)	6 (66.7)	3 (100)	4 (100)	1 (100)

[a] Anti-SARS-CoV-2 spike 1 antibody response with antibody response groups defined as non-responders < 10 BAU/mL, low responders 10–300 BAU/mL, good responders > 300 BAU/mL.

[b] Patients were divided into four mutually exclusive treatment groups based on active treatment status (defined as immuno- or chemotherapy < 6 weeks before an immunizing event); On Tx (patients under active treatment during each immunizing event), On/Off Tx (patients under active treatment during each immunizing event, except for the last immunizing event during which they were no longer under active treatment), Off Tx (patients no longer under active treatment during each immunizing event) and No Tx (patients without a history of chemo- or immunotherapy).

[c] Immunizing event: a SARS-CoV-2 infection or a SARS-CoV-2 vaccination.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2024.100172.

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