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Letter

Immune responses following third COVID-19 vaccination are reduced in patients with hematological malignancies compared to patients with solid cancer

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Patients with cancer are at higher risk of severe COVID-19 (Grivas et al., 2021; Kuderer et al., 2020), and they are currently prioritized globally for a third COVID-19 vaccine dose. Humoral and cellular immune responses are detected after two primary COVID-19 vaccine doses in most patients with cancer (Ehmsen et al., 2021; Fendler et al., 2021; Oosting et al., 2021), although neutralizing responses against variants of concern (VOCs) are reduced. Neutralizing responses are frequently impaired in patients with hematological malignancies, especially those receiving B cell-depleting therapies (Ehmsen et al., 2021; Fendler et al., 2021; Thakkar et al., 2021). Because neutralizing antibody (NAb) responses are directly associated with vaccine efficacy (Gilbert et al., 2021; Khoury et al., 2021), these patients without a neutralizing response are at higher risk of breakthrough infections (Hippisley-Cox et al., 2021). Here, we report follow-up results from CAPTURE (NCT03226886), a longitudinal, prospective cohort study of vaccine response in patients with cancer, relative to the duration of response after two doses of either the BNT162b2 (Pfizer) or ChAdOx1 (AstraZeneca) vaccine; and following third vaccination with BNT162b2. We present data on NAb and T cell responses against whole live virus, including wild-type SARS-CoV-2 (WT), Beta, and Delta VOCs. We

specifically evaluated responses to Beta and Delta given their known immune-evasive capacity.

We assessed the durability of NAb responses in 353 patients (77% [n = 271] with solid cancer and 23% [n = 82] with hematological malignancies; Table S1) following two doses of COVID-19 vaccine (72% [n = 255] ChAdOx1 and 28% [n = 98] BNT162b2). NAbs against WT were undetectable after 14–28 days and up to 110 days (range 84–153) following the second dose in 4% (n = 12) of patients with solid cancer and 30% (n = 25) of patients with hematological malignancies. In those who initially had detectable post-second-dose NAb against WT (n = 316, 71% against Beta, and 62% against Delta), we observed a time-dependent decline in NAb titers (NAbT) during follow-up (median of 111 days, range 37–252 days after the second vaccine dose; Figure S1A). After an initial response to two vaccine doses, in patients with solid cancer (n = 259), 1% (n = 3) had undetectable NAbs against WT, 16% (n = 43) against Beta, and 18% (n = 47) against Delta; in patients with hematological malignancies (n = 57), 7% (n = 4) had undetectable NAbT against WT, 9% (n = 5) against Beta, and 16% (n = 9) against Delta. The proportions of those with waning NAb did not differ significantly among patients with solid cancer or hematological malignancies apart from WT (Chi^2 test: WT, p value = 0.02; Beta, p value = 0.16; Delta, p value = 0.67).

We previously reported that T cell responses, measured 14–28 days after the second dose, are comparable between patients with solid cancer and hematological malignancies and can also be detected in those without NAb responses (Fendler et al., 2021). During follow-up (median of 93 days [range: 63–171 days] after the second dose), we evaluated T cell responses in 55 patients. Patients without a detectable T cell response following the second dose remained negative. In those with an initial response (n = 43 with solid cancer and n = 12 with hematological malignancy; Figure S1B), it was maintained in 49% (n = 21) of patients with solid cancer and 42% (n = 5) with hematological malignancies (Wilcoxon signed rank test, p = 0.56).

During the course of routine clinical care, eight CAPTURE participants (n = 7 with solid cancer and n = 1 with hematological malignancies) were diagnosed with SARS-COV-2 following two vaccine doses between July and October 2021 (median time between second vaccine dose and infection: 118 days [range: 59–173]), and these were likely to have been caused by the Delta variant that was dominant in the UK at that time. The symptoms were either mild (n = 7 patients; WHO severity score 2–3; fever [n = 5], coryza [n = 4], anosmia [n = 4], and cough [n = 3]) or absent (n = 1 patient), no patient requiring hospital care, and all recovered. We evaluated immune responses prior to infection following two vaccine doses; although all patients had detectable NAbT against WT SARS-CoV-2, only one had detectable NAbT against Delta. Following infection, all patients mounted detectable neutralizing responses to Delta (Figure S1C). T cell responses were evaluable in five patients prior to infection and in seven patients following infection. Although only 1/5 patients had detectable T cell responses to WT prior to infection, 5/7 had a detectable T cell responses following infection, including 2/4 patients who had undetectable T cell responses before infection (Figure S1D).

We next evaluated 199 cancer patients (n = 115 [58%] with solid cancer) who received a third vaccine dose per UK guidelines. Patients who tested positive via RT-PCR for SARS-CoV-2 between their second and third doses were excluded from this analysis. All patients received a third dose of BNT162b2 following two doses of either BNT162b2 (33%) or ChAdOx1 (67%) (Table S1). The median time between second and third vaccine dose was 176 days (range 65–274 days), and immune responses were measured at a median of 23 days after the third dose (range: 11–47 days). Prior to the third dose, 88% (n = 176) had detectable NAb against WT, but given the dominance of Delta, we considered all patients with undetectable NAb against Delta to be "non-responders" to two doses (51% [n = 102]; 43% [n = 50] of patients with solid cancer and 62% [n = 52] of patients with hematological malignancy; Table S1).

Considering non-responders to Delta after two vaccine doses, in solid cancer patients (n = 50), following the third dose, 94% (n = 47) had detectable NAb against Delta and 88% (n = 44) against Beta (Figure S1E); in patients with hematological malignancy (n = 52), following the third dose, 54% (n = 28) had detectable NAb against Delta and 54% (n = 28) against Beta. The proportion of those with detectable NAb after third dose was significantly higher in patients with solid cancer (Chi^2 test: Beta, p value = 0.0002; Delta, p value < 0.0001). Finally, following the third dose, we observed an increase in median NAbT against all variants in initial responders (patients with detectable NAbs against Delta after two vaccine doses).

Our data indicate that a third vaccine dose can generate NAb in patients who are non-responders following two doses, and it further boosts NAbT against VOCs in responders. However, the proportion of patients with hematological malignancies who have undetectable NAbT against Delta following the third vaccine dose remains significant (46%).

Multivariable binary regression analysis showed that the presence of hematological malignancy was significantly associated with undetectable NAb against Beta or Delta after the third dose (variables included: cancer type, age, primary vaccine type, and sex). Considering patients with hematological malignancies in a further multivariable analysis (see Table S1 for included variables), primary vaccination with BNT162b2 (n = 17) versus ChAdOx1 (n = 35) was significantly associated with lack of neutralizing responses against Beta and Delta (BNT162b2: Delta, 29% [n = 5]; Beta, 35% [n = 6]. ChAdOx1: Delta, 66% [n = 23]; Beta, 63% [n = 22]), and these results suggest a benefit of the heterologous vaccination approach. Following the third vaccine dose, in patients who had received anti-CD20 in the 12 months prior to the first vaccine dose, 1/6 had detectable NAbT against Delta and 2/6 against Beta. In the group of patients who commenced anti-CD20 therapy between the second and third dose, 3/4 patients had detectable NAbT against Delta and Beta following the third dose.

Following stimulation with WT, Beta, and Delta spike-specific peptide pools, T cell responses were measured using IFN-γ ELISPOT (Fendler et al., 2021) in a subset of 48 patients (69% [n = 33] with solid cancer) who are representative of the cohort that received a third dose. Prior to third dose, 33% (n = 11) of patients with solid cancer and 40% (n = 6) of patients with hematological malignancies had

detectable T cell responses. Following the third vaccine dose, this rose to 73% (n = 24) and 73% (n = 11), respectively. The number of Spot Forming Units (SFU)/10^6 was significantly increased after the third dose relative to post-second dose (Figure S1F).

Our data show that a third dose of COVID-19 vaccine boosts NAb responses in patients with cancer, including those that had undetectable NAbT following two vaccine doses or for whom NAbT waned. We found that NAbT were higher in patients who received two doses of ChAdOx1 and a third dose of BNT162b2 compared to three doses of BNT162b2. Further, we show that T cell responses are amplified following the third vaccine dose, and this likely offers additional protection—especially in individuals with low or absent neutralizing responses. Encouragingly, the proportion of patients with solid cancer who had detectable responses after third vaccination is high and comparable to individuals without cancer. In contrast, a significant number of patients with hematological malignancies still had undetectable neutralizing responses following a third vaccine dose, especially against VOCs, and remain at risk of breakthrough infection. These findings are particularly pertinent given reports of reduced vaccine efficacy and NAb activity against the emerging Omicron VOC compared to Delta (Cele et al., 2021).

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2021.12.013.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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