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Current Perspective

Current perspectives for SARS-CoV-2 vaccination efficacy improvement in patients with active treatment against cancer

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Abstract   A higher risk of death from coronavirus disease 19 has been shown for patients with solid cancers or haematological malignancies (HM). Thanks to the accelerated development of anti−SARS-SoV-2 vaccines in less than a year since the start of the global pandemic, patients with cancer were quickly prioritised in early 2021 for vaccination, however dependent on the very unequal availability at the global level. Impaired immunogenicity of SARS-CoV-2 mRNA vaccines in immunocompromised patients was rapidly reported as early as April 2021, although the vaccination fortunately appears to be generally effective without increasing the spacing. Worryingly, the humoral response of the SARS-CoV-2 vaccination is, however, considered insufficient in patients followed for HM, in particular when they are on anti-CD20 treatment.

Thus, improving vaccination coverage by strengthening immune stimulation should be evaluated in patients under active treatment against cancer. Here, we discuss three different

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boost vaccination;
Double-dose

approaches: a third dose of early vaccine (repeated immune stimulation), heterologous prime-boost vaccination (multimodal immune stimulation) and a double-dose strategy (maximisation of immune response). Dedicated therapeutic trials, currently almost non-existent, seem rapidly necessary.

As humanity confronted a viral pandemic since 2019 that will strikingly change our societies, the oncology community faced two major challenges. The first emergency was to make the oncology care setting safe, i.e. avoiding a risk of contamination by this new potentially deadly virus and precluding a loss of chance due to logistics failure, leading to inappropriate surgical delays, and therefore to significant negative impact on survival [1]. The second was, thanks to the accelerated development of anti−SARS-SoV-2 vaccines in less than a year since the start of the global pandemic, to prioritise patients with cancer for the vaccination, when available, by considering them as highly vulnerable patients [2−6]. Before even starting the anti−SARS-CoV-2 vaccination campaign, in a series of 1000 French patients followed for cancer, we had shown the desire of a majority of them to be vaccinated [7], contrasting with data available at the same time in the general French population. Only 166 patients declared categorically refusing vaccination (16.6%). The medical oncologist was the main source of reliable information, and the main source of motivation to accept vaccination was the fear about their health (76.9%), the desire to protect their loved ones (49.9%) (altruism), the duty of collective responsibility (45.6%) (citizenship) and finally the wish to return to a normal life (38.7%). Since then, in an Italian study of 914 patients eligible for vaccination, only 48 refused vaccination (11.2%, 95% confidence interval [CI] 9.1−13.2) [8]. This confirms the need for all caregivers in connection with cancer to respond to the willingness of patients of being vaccinated, by carrying out information campaigns promoting vaccination, while trying at the same time to reassure the undecided or even to convince the antivaccine patients [9].

In this review, we propose to make a brief synthesis of the main knowledge available on the subject of cancer and coronavirus disease 19 (COVID-19), starting with the data showing higher risk of hospitalisation or death in patients with cancer. Then, we will discuss the data currently available highlighting the vaccine efficacy in patients followed for cancer, without initial data because of their exclusion from initial registration studies [2,10,11]. The findings of a decrease in the humoral immune response compared with the general population will then allow us to address as a last resort the perspectives for vaccine optimisation, requiring specific strategic trials, which unfortunately are still not available.

1. Evidence of COVID-19−related risk of hospitalisation or death in oncology

Despite conflicting data coming from small series including solid cancer (SC) or haematological malignancies (HM) [12,13], larger population studies evidenced an increased mortality risk in these patients, compared with control groups [14−19]. As per the large national United Kingdom (UK)−National Health Service database reporting 10,926 deaths among more than 17 million patients, COVID-19−related death was associated to a cancer diagnosis of less than 1 year (Relative Risk (RR) 1.7), mainly in case of HM (RR 2.8) [17]. A retrospective case−control analysis of electronic records involved 73.4 million patients from 360 hospitals in 50 states in the United States, with more than 2 million having at least 1 of 13 common cancers, including 273,140 people with a cancer diagnosis within the last year [18]. These individuals diagnosed with recent cancer had a significantly increased risk of COVID-19 infection (adjusted overall risk [aOR], 7.14 [95% CI, 6.91−7.39]; $p < 0.001$), with the strongest association found for newly diagnosed leukaemia (aOR, 12.16 [95% CI, 11.03−13.40]; $p < 0.001$), non-Hodgkin lymphoma (aOR, 8.54 [95% CI, 7.80−9.36]; $p < 0.001$) and lung cancer (aOR, 7.66 [95% CI, 7.07−8.29]; $p < 0.001$). Compared with patients with a COVID-19 without cancer, or with a cancer without COVID-19, patients combining both had a higher risk of hospitalisation (47.46% versus 24.26% or 12.39%, $p < 0.001$) and death (14.93% versus 5.26% or 4.03%, $p < 0.001$). Finally, a study carried out in more than 66 million people in France during the Covid-19 first wave (February−June 2020) established an increased cancer-related morbimortality risk in SARS-CoV-2−infected patients, particularly in case of lung cancer (x3.6 times higher risk for hospitalisation and x5.7 times for death) [19].

2. Risk of a decreased vaccine efficacy against SARS-CoV-2 in oncology

Preliminary anti−SARS-CoV-2 vaccine efficacy in the oncology setting, recently published (April 2021), is reported in Table 1. Our team lately reported a decrease in the immunogenicity of the anti−SARS-CoV-2 vaccination with BNT162b2 (Pfizer/BioNTech) mRNA vaccine in 122 patients with SC under active

Table 1
Series reporting anti-S seroconversion rates after SARS-CoV-2 vaccination in patients with solid cancer (SC) or haematological malignancies (HM).

Cohort Technique	Patients	Seroconversion rate at w3–w4 N (%)	Seroconversion rate at w6–w8 N (%)
Barriere et al. [20]			
Seroconversion if total IgG, IgA, IgM against anti-S ≥ 0.8 IU/mL (Elecsys ® anti-SARS-CoV-2 immunoassay [Roche Diagnostics, France])	HV	13 (100.0%)	24 (100.0%)
	SC	58 (47.5%)	40 (95.2%)
	SC with CT	45 (42.9%)	37 (94.9%)
	SC with TT	13 (76.5%)	3 (100.0%)
Palich et al. [21]			
Seroconversion if anti-S IgG ≥ 50 IU/mL (Abbott SARS-CoV-2 IgG chemiluminescent microparticle immunoassay)	HV	25 (100.0%)	
	SC	52 (55%)	
Monin et al. [22]			
Seroconversion if neutralising anti-S IgG with a threshold of 70 EC_{50} dilution units	HV	32 (94%)	12 (100%)
	SC	21 (38%)	18 (95%)
	HM	8 (18%)	3 (60%)
Terpos et al. [23]			
Seroconversion if neutralising anti-S Ab inhibition titres ≥ 30% (ELISA, cPassTM SARS-CoV-2 NAbs Detection Kit; GenScript, Piscataway, NJ, USA)	HV	57 (54.8%)	
	Elderly MM pts	12 (25.0%)	
Herishanu et al. [24]			
Seroconversion if total IgG, IgA, IgM against anti-S ≥ 0.8 IU/mL (Elecsys ® anti-SARS-CoV-2 immunoassay [Roche Diagnostics, France])	CLL (total population) pts		66 (39.5%)
	CLL treatment-naïve pts		23 (55.2%)
	CLL actively treated pts		12 (16%)
	CLL pts treated with anti-CD20 Ab (n = 22) within the last 12 months		0 (0%)
	CLL pts exposed to anti-CD20 Ab ≥12 months before vaccination		25 (45.5%)

Ab: antibodies; Anti-S: anti-spike antibodies; pts: patients; w: week; HV: healthy volunteer; CT: chemotherapy; TT: targeted therapy; MM: multiple myeloma; CLL: chronic lymphocytic leukaemia SC: solid cancer;.

treatment [20]. These preliminary data showed that 47.5% of the patients presented anti-Spike (S) immunoglobulin (Ig) titres at the time of the booster at week 3–4 compared with 100% in the control group of healthy volunteers (HVs). At week 6–8, however, 95% (N = 40/42) of patients with SC had developed anti-S antibodies but at a lower median rate than the control group, with a noticeable heterogeneity (245.2 IU/mL range (0–5467) vs. 2517 IU/mL range (157.6–6318.0), respectively, in the HV group, p < 0.001). A better vaccine response was obtained in patients under targeted therapy (anti HER2, anti-angiogenic, anti-PD1/PDL1) without associated chemotherapy (CT) at week 3–4, showing 76.5% anti-S seroconversion versus 42.9% in patients under CT (p = 0.016). These preliminary data were strengthened by a second French series reporting a seroconversion rate of 55% at the time of the booster, again with a negative impact due to ongoing CT [21]. The Royal College of London team reported then a cohort of 151 patients with cancer (SOAP-02 vaccine study). They demonstrated a 38% seroconversion rate at day 21 after the first BNT162b2 dose in patients with SC, with a reassuring boost effect because 18 of 19 patients (so 95%; 95% CI 75–99) had positive anti-S IgG titres at week 6 [22].

Among patients with HM, vaccine efficacy seems even lower. In elderly patients with multiple myeloma, after the first dose of the BNT162b2 vaccine, a low neutralising antibody response against SARS-CoV-2 was reported [23]. In 167 patients with chronic lymphocytic leukaemia (CLL), the seroconversion rate was 39.5% after two doses [24]. A comparison between 52 patients with CLL and 52 sex- and age-matched healthy controls revealed a significantly reduced response rate among patients (52% vs 100%, p < 0.001). Response rate was highest in patients who obtained clinical remission after treatment (79.2%), followed by 55.2% in treatment-naïve patients and 16% only in patients under treatment at the time of vaccination. None of the patients exposed to anti-CD20 antibodies <12 months before vaccination

responded. In the SOAP-2 vaccine study preliminary report [22], the proportion of positive anti-S IgG titres at week 3 after a single vaccine dose was eight of 44 (18%) patients with HM and three of five (60%) patients after the booster, although limited number of patients so far to clinical conclusion.

All the preliminary data, which should be quickly confirmed, therefore objectify a reduction in the humoral immune response after mRNA vaccination among patients with cancer, in particular in patients undergoing CT, and more particularly under anti-CD20 therapy. The postponement of the second dose, proposed in some countries to allow as many people as possible to benefit from the first dose, appears to us to be at high risk in immunocompromised patients, given a large proportion of patients without seroconversion during the booster. What no one knows, however, is the level of protection of neutralising antibodies sufficient to confer clinical effective immune defence.

3. Hypothesised strategies to improve vaccination coverage in patients with cancer

Allowing a better vaccination coverage thus appears to be urgently needed, given the increased risk of hospitalisation or death for many patients with cancer and the lower or even the absence of vaccine efficacy in some of them with the current vaccination schedule. Thus, the improvement of the vaccine strategy by strengthening the immune stimulation should be evaluated. We specify here three different possible strategies, summarised in Fig. 1, based on putative immune mechanisms.

3.1. Third vaccine dose: repeated immune stimulation

The first option is to propose a third vaccine dose in the absence of seroconversion or early after a proper vaccination. Less than 10% of patients on active treatment for SC but almost 100% of patients with HM undergoing treatment with anti-CD20 or having stopped it for less than 1 year are eligible for this option. Apart, for patients followed for a SC, even if more than 90% of patients get a positive anti-S response, the median antibody level remains lower than the general population and close to the detection threshold at week 6−8 for some of them [20]. This raises the question of an insufficient vaccine protection in this population, particularly in the setting of variant spread.

Thus, patients on anti-CD20 treatment now or during the past year or followed for a SC with no or low anti-S Ig titre could be good candidates for a third dose.

The hypothesis of a benefit of an additional booster to improve vaccination response results firstly from data regarding the seasonal influenza vaccine booster in cancer. In this context, it significantly increases seroconversion in patients followed for cancer, as
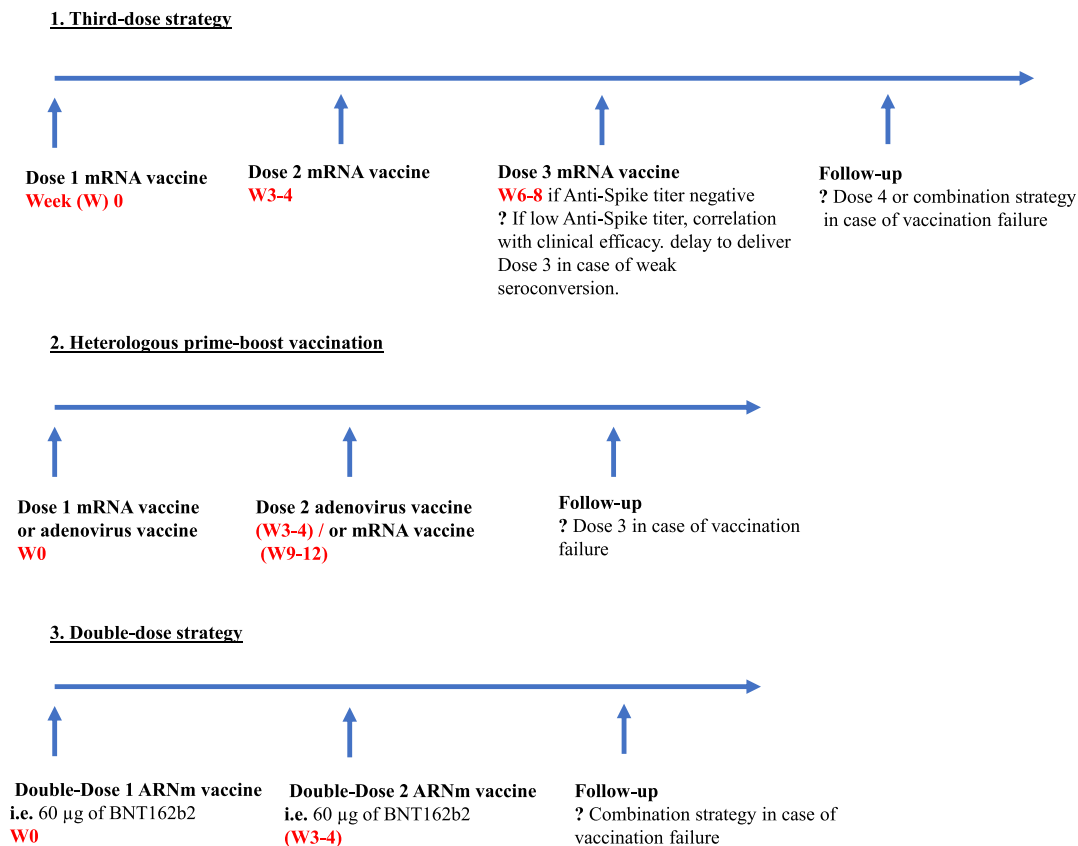

Fig. 1. Hypothesised strategies to improve vaccination coverage in patients with cancer.

reported for 65 patients vaccinated under CT with the 2009 H1N1 influenza vaccine: the seroconversion rates were 44% after one dose and 73% after the booster, suggesting that two doses may be needed for patients under CT [25]. In another study of 109 patients vaccinated against several types of influenza vaccines, the increase in the reported seroconversion rate did not, however, exceed 10%, which led to the conclusion that a probably limited effect of a second vaccine dose in the event of immunosuppression [26]. Among patients on anti-CD20 therapy for HM [27] or rheumatoid arthritis [28], the effectiveness of influenza vaccination is also strongly impaired, with a weak restored response 6—10 months after rituximab. Interestingly, despite the lack of a significant effect of 2009 H1N1 influenza booster vaccinations on the humoral immune response in B cell—depleted patients with autoimmune rheumatic diseases, an enhanced antiviral T cell response has been reported [29]. Considering that the T immune response could play an important role in the protective response against SARS-CoV-2 [30], the strategy of an early additional booster could allow a T cell immunity response, which could then compensate for the impaired humoral immunity. The limitation of this hypothesis relies on the altered T cell response reported in the event of COVID-19 occurring in patients with cancer under treatment [31]. In the preliminary report of the SOAP-2 vaccine study [22], the T cell response appeared to be greater in proportion after the first dose than the B immune response, again with a boost effect, but still a lower proportional response than the control group.

Besides the lack of dedicated clinical trials, cohort studies are underway to assess the effectiveness of this strategy.

3.2. Heterologous prime-boost vaccination: multimodal immune stimulation

Considering that several anti—SARS-CoV-2 vaccine types are available, a vaccine mixing strategy with a first mRNA dose and a second dose of vaccine vectorised by non-replicating adenovirus (or vice versa) could be suggested, expecting an improvement of the immune response. Data suggest that heterologous may be better than homologous prime-boost regimens for antiviral protection, currently studied in the anti—HIV 1 vaccine strategy [32].

On purpose, a large-scale trial (COVID-19 Heterologous Prime-Boost Study Com-Cov) is in progress in the UK and will involve more than 800 volunteers. Unfortunately, immunocompromised patients or patients under active treatment for cancer are excluded.

We should therefore consider a dedicated therapeutic trial by convincing either a collaborative group or manufacturers, which represents a major obstacle to this strategy. In addition, accessibility to several types of vaccines makes such a trial very complex to set up without support, not to mention patients' mistrust of adenovirus vaccines.

3.3. Double-dose strategy: maximising the immune response

Another approach could be firstly to target patients at risk of vaccine ineffectiveness, to vaccinate with a double dose of the mRNA vaccine.

The hypothesis of a double-dose strategy is based on literature data and current vaccination practices, particularly in immunocompromised HIV-positive patients vaccinated against hepatitis B [33]. Likewise, a double dose of the hepatitis B vaccine in oncology patients under CT allowed better vaccination coverage than the control group [34]. Similarly, an anti-influenza vaccination strategy at increased doses allowed better immunogenicity in patients followed for multiple myeloma [35]. Among 122 patients enrolled, 47 received single-dose standard-of-care vaccination and 75 received 2 doses of a high-dose vaccine. Rates of haemagglutinin inhibition titre against all 3 strains (H1N1, H3N2 and influenza B) were significantly higher for patients after tandem high-dose vaccination versus control (87.3% vs 63.2%; P = 0.003) and led to higher seroconversion at the end of the flu season (60.0% vs 31.6%; P = 0.04).

Concerning safety, HVs (N = 12) without comorbidity have already received a maximum dose of 100 μg (label dose 30 μg) in the original phase I trial of a first vaccine version BNT162b1 (Pfizer/BioNTech) with some local and systemic grade III transient effects [36]. The tolerance profile of the BNT162b2 version was reported to be better than the BNT162b1 [37]. Therefore, the BNT162b2 was chosen at a maximum dose of 30 μg, given a high expected level of immunogenicity, regardless of age, equivalent to the BNT162b1. The composition of the lipid nanoparticles, the components of the formulation or the sequence selection for the vaccine RNA could influence the side-effect profile. The reason for a better tolerance of BNT162b2 than BNT162b1 is not certain, as the two vaccine candidates share the same mRNA platform, RNA production and purification processes and formulation of lipid nanoparticles. They differ in the nucleotide sequences which encode the vaccine antigens and in the overall size of the RNA constructs. The number of mRNA molecules in 30 μg of BNT162b1 is approximately 5 times greater than that in 30 μg of BNT162b2 [37]. The nucleotide composition of RNA has been reported to affect its immune stimulating activity and reactogenicity profile, and this is a possible explanation for the differences between these candidate vaccines. Altogether, the available data allow us to assume that the risk of intolerance of 60 μg of BNT162b2 is low. In addition, the targeted population has a lower risk of side-effects given their immunosuppression. Finally, a phase I/II study is needed to evaluate this

strategy, which can be promising to improve the immune response earlier for immunocompromised patients, i.e. as soon as after the first vaccine injection.

4. Conclusion

Anti−SARS-CoV-2 vaccination in patients with SC seems globally effective after well-conducted vaccination without booster spacing. However, the level of the humoral response remains lower than the general population, and no data exist yet to establish a correlation between clinical efficacy and anti-S antibody titre, justifying the pursuit of observational monitoring of cohorts of vaccinated patients.

Worryingly, SARS-Cov2 vaccination results are considered insufficient in patients followed for HM, in particular when on anti-CD20 therapy. Thus, the implementation of cohort follow-up evaluating the impact of alternative strategies, such as an early third vaccine dose, a vaccine combination or, maybe more effective, a double vaccine dose at the first injection, is urgently needed in this group of patients, a call to action.

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Conflict of interest statement

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.

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