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BNT162b2 mRNA Covid-19 Vaccine in AYA with cancer: a monocentric experience.

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Abstract:

Background and Aims: COVID-19 infection in pediatric cancer patients is severe or critical in 20% of the patients. It can therefore directly affect pediatric cancer patients and/or their care. We aimed at evaluating the safety and efficacy of BNT162b2 mRNA Covid-19 vaccine in AYA with solid tumor.

Methods: Retrospective analysis of safety and efficacy of BNT162b2 mRNA Covid-19 vaccine administered to patients, ≥ 16 years old, under treatment for a solid tumor or within 6 months' post-treatment from 15/2/2021 to 15/4/2021. Two administrations of the vaccine 3 weeks apart were given. Sera were tested for anti-SARS-Cov-2 IgG antibodies directed against the S1 domain of the spike protein. In case of positive serology, neutralization of SARS-Cov-2 was tested.

Results: Twenty-three patients with solid tumors were identified and proposed to get vaccinated. Nine patients refused and 1 previously developed COVID-19 infection with positive serology. At time of writing, 13 patients (10 M/2F); median age: 17) started vaccination. All patient received 2 injections except 2 patients who stopped vaccination because of tumor progression. Ten patients were under treatment (chemotherapy-7pts, immunotherapy-2 pts, targeted therapy-2 pts- follow-up 3 patients). Overall, vaccines were well tolerated. Five patients did not report any side-effect after the first injection and 4 after the second injection. Main local reactivity symptom was mild pain at the site of injection (6 and 2 pts). Fatigue (2pts and 5 pts) was the most frequent systemic symptom. One patient refused serology testing. All patients but 1 had pre-vaccination negative serology, 7/10 tested had positive serology before second vaccine injection, 9/10 had positive serology one month after the second injection. All patients with seroconversion had positive COVID-19 neutralization test. No patient developed COVID infections.

Conclusions: We report the good safety profile and good efficacy BNT162B2 vaccine in AYA with solid tumors. Larger series and monitoring of the kinetics of anti-Sars-Cov-2 IgG antibodies for several months are mandatory to confirm these preliminary results and to determine long-term vaccination.

Introduction:

Since its beginning, the COVID-19 pandemic has gradually directly and indirectly affected patients with chronic disease worldwide¹. Although children are at lower risk of developing severe form of COVID-19², children treated for malignancies may be at higher risk of developing severe forms as compared to their healthy counterparts²⁻⁵. The global registry of COVID-19 in Childhood Cancer⁶ reports 20% of severe and critical forms among 1500 patients. Direct and indirect consequences of COVID-19 such as delays in diagnosis or treatment can impact of outcome of these patients⁷. For children receiving experimental therapies, data are even rarer and physician have been very cautious. The ITCC have thus reported a 60% decrease of enrolment of patients in early phase clinical trials in Europe⁷

Despite initial hope in drug repurposing, medical treatments such as chloroquine have largely failed to help clearing the virus, although the use of heparin, steroids and oxygen have greatly helped to improve outcome of patients⁹⁻¹¹. As for today, beyond social distancing, vaccines are the main tools to prevent further spread of the pandemic and protect people from the infection¹².

We report here a monocentric retrospective monocentric experience with the RNAm vaccine in Adolescent and Young Adults (AYA) with solid malignancies under treatment or 6 months after completion of treatment treated in our department.

Patients & Methods:

Population: AYA older than 16 years old, under treatment for their malignancies or who had completed their treatment within 6 months and followed in the department of Pediatric Immunology, hematology and oncology, of the children hospital of La Timone, AP-HM were proposed to receive the BNT162b2 mRNA Covid-19 Vaccine.

Treatment: Patients were planned to receive two doses, 21 days apart, of the BNT162b2 vaccine (30 µg per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein¹²

Methods: Sera samples were tested for anti-SARS-Cov-2 IgG antibodies directed against the S1 domain of the spike protein of the virus using a commercial ELISA kit (Euroimmun®, Luebeck, Germany) as recommended by manufacturer. All samples with an ELISA ratio ≥ 0.7 , neutralizing antibodies against SARS-Cov-2 were detected using a virus neutralization test (VNT100), as previously described¹³. Serial dilutions of sera 1/10 to 1/160 were tested and specimen with VNT100 titer ≥ 40 were considered positive, those with titer at 20 indeterminate and < 20 , negative. Samples were taken before first administration (T0), before second administration (T1) one month after the second administration of the vaccine (T2).

Ethic: All data have been generated as part of the routine care at Assistance Publique-Hôpitaux de Marseille, and this study results from routine clinical management. The study was approved by the AP-HM, and access to the patients' biological and registry data issued from the hospital information system was approved by the data protection committee of Assistance Publique-Hôpitaux de Marseille (APHM PADS21-136). All patients signed informed consent.

Results:

Twenty-three patients were identified and proposed the BNT162b2 mRNA Covid-19 Vaccine. Out of these 23 patients, 9 refused to receive the vaccine. The reason for refusal were the fear of developing sides effect, the lack of long-term knowledge about tolerance for 8 patients and living too far from the hospital for 1 patient. One patient did not receive the vaccine as he already had developed COVID-19¹⁴ and still displayed positive serology and positive virus neutralization test. Therefore, 13 patients started vaccination (see Figure 1). The characteristics of these 13 patients are given in table 1. Patients were receiving chemotherapy (7 patients), targeted therapies (2 patients), or immunotherapies (2 patients) alone or in combination. Three patients were in follow-up.

Two patients did not receive the second injection because of tumor progression and also lived far away from our institution. They received palliative care only.

Overall, vaccines were well tolerated. Five out of 13 patients did not report any sides effect after the first injection and 4 out of 11 after the second injection. The most frequent side effect was a mild-to-moderate pain at the injection site (6 patients) that resolved within 1 to 2 days. The second administration seemed to be slightly less well tolerated with more frequent systemic reactions. Details of sides effects are reported in table 2. Systemic events including fever and chills were observed within the first 1 to 2 days after vaccination and resolved shortly thereafter. Aside from transient local and systemic reactions, no safety concerns were identified.

All patient but one were negative for COVID-19 serology before immunization. This patient did not previously develop COVID-19 symptoms and the second serology was negative. Overall, 3 weeks after the first the injection 8/10 tested patient developed seroconversion and one month after the second administration, the vaccine led to a seroconversion in 9/10 tested patients with positive COVID neutralization test in all. The only patient with negative serology 1 months after the second serology had a positive serology at the time of the second injection and positive seroneutralisation. No patients developed COVID after immunization.

Discussion

We report here, our experience with the immunization with a COVID-19 mRNA vaccine of AYA under treatment or shortly after completion of treatment for a solid tumor. Our results show a

high rate of refusal, a good tolerance and a high immunogenicity in a real life setting of immunocompromised pediatric patients. To the best of our knowledge, our results are the first reported in AYA with cancer, it is therefore impossible to compare it with other experiences. Adverse events are consistent with those previously reported in healthy AYA¹².

Preliminary studies reported that healthy children and adolescents under the age of 15 vaccinated against sars-Cov-2 have a very high rate of protection compared to a healthy adult. In cancer patients, only adult data is reported. Monin et al. recently reported that in 56 adult patients with solid tumors, one dose of the BNT162b2 vaccine yielded only poor efficacy at days 21 with 38% of the patients with positive anti-S IgG titres¹⁵. But in our study, almost all children with solid tumors seroconverted after the second dose of vaccine.

The series we report here has some limitations. We studied a small number of patients in a single center. Patients were limited to AYA with solid tumor and therefore, do not reflect the majority of the pediatric oncology patients. In addition, the study was conducted over a short period up to one month after the second dose of vaccine, it would be necessary to continue monitoring the kinetics of anti-sars-Cov-2 IgG antibodies for several in order to assess vaccine protection over time.

If our preliminary results are confirmed, such a vaccine could be proposed to AYA before the initiation of their treatment and during treatment to prevent severe forms of Covid-19 or additional complications related to the disease that may compromised their oncologic treatment and in turn their long-term outcomes.

Close follow-up remains mandatory to detect rare or unknown sides effect of the vaccine in this very specific population or interactions with oncologic treatment or procedures such as radiation recall¹⁶ or hypermetabolic lymphadenopathy on [(18)F]FDG PET-CT¹⁷.

Importantly, although both the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) have advocated for cancer patients a high priority status to get access to Covid-19 vaccines¹⁸, we have observed a high rate of refusal- much higher than recently reported by Di Noia et al. in a large italian adult series (904 patients) in which 11% refusal rate was observed¹⁹. Elsewhere, Barriere et al. performed a survey among adult cancer patients in France²⁰. Among the respondents, 536 (54%) reported their intent to be vaccinated, while 297 (30%) considered they were not ready yet but could change their mind and 166 (17%) patients reported to definitely refuse vaccination.

It is therefore crucial that adequate information and education is brought to pediatric cancer patients and their family to increase enrollment in vaccination programs and in turn the success of the campaign. Education strategies must be developed with respect to AYA specific needs and

habits, for example through social media ²¹ or webinars²² to make it happen as urged by Curigliano G and Eggermont ²³

Conclusion:

We report here a preliminary experience with RNA vaccines in AYA with solid tumors and report a good safety profile and excellent immunogenicity. Larger series and monitoring of the kinetics of anti-Sars-Cov-2 IgG antibodies for several months are mandatory to confirm these preliminary results and to determine long-term vaccination effect.

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Conflict of interest: none to declare

Acknowledgment: none

Figure Legends:

Table 1: Patients characteristics

Abbreviations used:

Pts: patients; ALCL : Anaplastic Large Cell Lymphoma, MGT: malignant germinal Tumors

Figure 1: Flowchart of patients

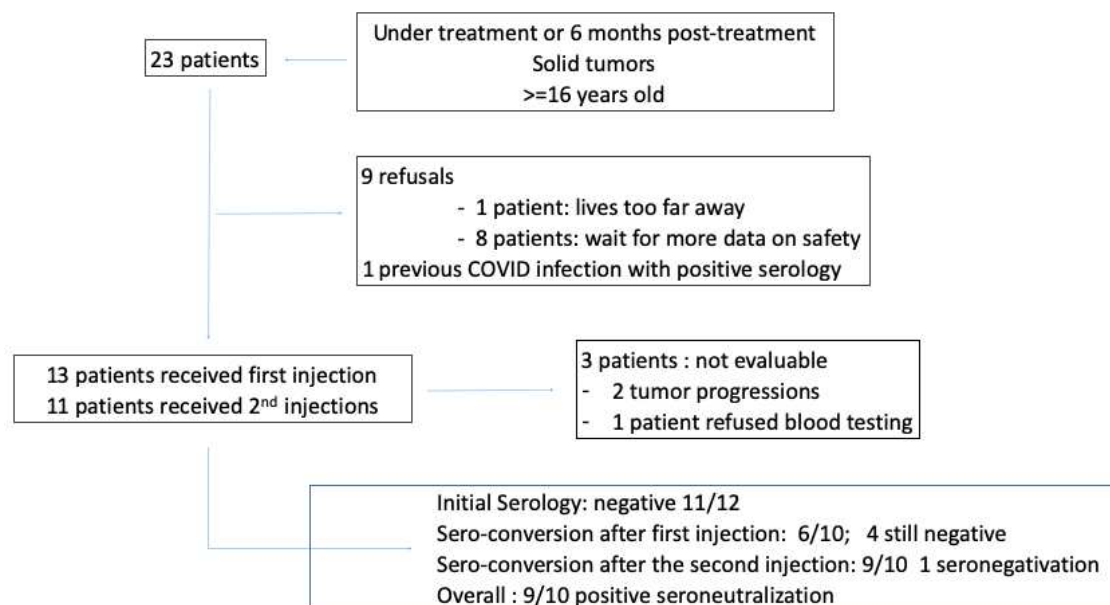
Table 2: Immunization of patients

ND: not done

1 patients refused serology to be performed.

1 patients stopped the vaccination program after tumor progression.

Table 3: Toxicity of vaccines



	Age (years)				Nb of previous
Patient	(at first injection)	Gender	Diagnosis	Ongoing treatment	line of treatment
1	21	M	B Cell Lymphoma	follow-up	2
2	16	M	Low Grade Glioma	trametinib	0
3	19	F	Ewing Sarcoma	metronomic cyclophosphamide	0
4	18	M	MGT	follow -up	2
5	17	M	Ewing Sarcoma	metronomic navelbine-cyclophosphamide	1
6	18	M	ALCL	vinblastine	4
7	17	M	Ewing Sarcoma	metronomic cyclophosphamide	1
8	16	F	Rhabdomyosarcoma	chemotherapy	0
9	17	M	Osteosarcoma	durvalumab-tremelimumab	2
10	17	M	Ewing Sarcoma	Nivolumab-Lirilumab	4
11	16	M	MGT	Follow-up	0
12	16	M	Desmoid Tumor	pazopanib-vinblastine	0
13	16	M	Rhabdoid tumor	metronomic chemotherapy + bevacizumab	0

	First administration	2nd Administration
	number of patients (13 patients)	number of patients (11 patients)
No toxicity	5	4
Sytemic Reactivity	3	5
- <i>Fever</i>	2	4
- <i>Asthenia</i>	2	5
- <i>Vomitting</i>	0	1
- <i>Headaches</i>	1	0
Local Reactivity	6	2
- <i>pain</i>	6	2

Patient	T0	T1	T2	Sero-neutralization
1	Neg	Neg	Pos	Pos
2	Neg	Pos	Pos	Pos
3	Neg	Pos	Pos	Pos
4	Neg	Pos	Pos	Pos
5	Neg	Neg	Pos	ND
6	Neg	Neg	Pos	Pos
7	ND	Pos	Pos	Pos
8	Pos	Neg	Pos	Pos
9	Neg	ND	ND	ND
10	Neg	ND	ND	ND
11	ND	ND	ND	ND
12	Neg	Pos	Pos	Pos
13	Neg	Pos	Neg	Pos