Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Safety of mRNA-COVID-19 Vaccines in Patients With Thoracic Cancers

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ABSTRACT

This is a prospective trial of 207 patients with thoracic cancer receiving anticancer treatments and COVID-19 vaccines. After long follow-up, there were no safety signals of concern and only 0.5% of patients experienced grade 3 vaccine-related adverse events. Our study supports the current vaccine prioritization, third and/or fourth dose of all lung cancer patients with active treatment.

Background: Pivotal trials of COVID-19 vaccines did not include cancer patients with questions remaining in this population. Particularly in patients with thoracic malignancies receiving anticancer treatments, the safety of these vaccines has so far been little investigated. **Methods:** This is a prospective trial of patients with thoracic cancer receiving anticancer treatments and COVID-19 vaccines at the Division of Thoracic Oncology of European Institute of Oncology between February and September 2021. **Results:** A total 207 patients affected by thoracic cancers (199 lung cancers and 8 mesotheliomas) had received Covid-19 vaccines (206 mRNA vaccines and 1 virus-vectored vaccine). The majority of patients had at least one comorbidity (76.3%). They were concomitantly treating with targeted therapy (TT) (45.9%), immunotherapy (IO) (22.7%), and chemotherapy (CT) (14%). A total of 64 AEs (15.6%) were observed after administration of Sars-Cov-2 vaccine. The majority of AEs were grade 1 [G1] (6.3%) and G2 (8.8%), only two events were G3 (0.5%). The median follow-up was 9 months (range 1-22 months), during this follow-up 21 patients (10.1%) had a positive nasal swab, most of the patients were asymptomatic (67%) and the symptomatic ones (33%) had mild symptoms and fewer complications and hospitalizations. **Conclusions:** COVID-19 m-RNA vaccines appear to be safe in the cohort of patients with thoracic malignances in active treatment, including those receiving immunotherapy. Considering the high morbidity and mortality associated with COVID-19 in patients with lung cancer receiving active treatments, our study supports the current vaccine prioritization, third and/or fourth dose, of all cancer patients with active treatment.

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Introduction

Since its outbreak in December 2019 from Wuhan (China), coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (Sars-Cov-2) has rapidly spread all around the World,[1,2] leading the World Health Organization (WHO) to declare coronavirus disease 2019 (COVID-19) a pandemic on March 11, 2020.[3] After two years of pandemic, at the time of writing, a total of 546 million of cases and about 6.3 million of deaths have been recorded worldwide (mortality rate 1.15%).[4] In Italy, 19.3 million of cases and 169.062 deaths for COVID-19 have been documented (mortality rate 0.8 %).[5] Beyond the known flu-like mild symptoms (fever, anosmia, dysgeusia, diarrhea, fatigue, myalgia, cough), in some cases the clinical evolution of the COVID-19 can degenerate in an acute distress respiratory syndrome, with a potential fatal outcome.[6]

Advanced age (≥65 years) and comorbidities (mainly cardiovascular disease, diabetes mellitus, and obesity) are the main factors associated with worse outcome. However, severe cases have occurred also in individuals without known risk factors.[6] Moreover, patients with cancer are at high risk of developing COVID-19 related life-threating complications; indeed, the mortality rate in patients suffering from cancer and from lung cancer (LC) was 13% and 35.5%, respectively.[7-9]

Since the first genome sequencing of Sars-Cov-2,[10] several therapeutic attempts have been developed, namely protease inhibitors and monoclonal antibodies. The protease inhibitors (Nirmatrelvir

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and Molnupiravir) and monoclonal antibodies (REGN-COV2 and LY-CoV555) are limited for the management of patients at high risk of complications in the early phases of the COVID-19.[11-14] In order to prevent the infection of Sars-Cov-2 and limit the spread of the pandemic, a worldwide effort has led to the development of several vaccines, consisting of nucleoside-modified RNA vaccine, recombinant DNA or via virus-vectored vaccine, and a recombinant spike protein nanoparticle vaccine.[15] At the time of writing, the Italian Medicine Agency (AIFA) has authorized the use of five vaccines in Italy: two nucleoside-modified RNA vaccine (BNT162b2 vaccine, BioNTech/Pfizer; mRNA-1273 vaccine, Moderna),[16,17] two chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19 vaccine, NIHR Oxford Biomedical Research Centre/AstraZeneca; Ad26.COV2.S, Johnson & Johnson/Janssen),[18,19] and an adjuvanted, recombinant spike protein nanoparticle vaccine (NVX-CoV2373, Novavax).[20]

The pivotal clinical trials of COVID-19 vaccines have shown efficacy in 70-90% of enrolled subjects, with an overall favorable safety profile in healthy individuals, as well as in elderly or affected by chronic diseases.[16-20] Although cancer patients represent a priority population for vaccination, they were initially excluded from these studies.[21] To date, available data of immunogenicity and safety for this population derives mainly from non-randomized prospective studies.[22-40]

The purpose of our work is to describe the safety profile of COVID-19 vaccines in patients affected by thoracic malignancies receiving antineoplastic drugs.

Materials and Methods

Patient recruitment and data collection

We conducted a prospective trial, including all vaccinated patients with diagnosis of thoracic cancers at any stage undergoing treatment or follow-up in our department (Division of Thoracic Oncology, European Institute of Oncology, IRCCS) between February and September 2021.

We have included patients who received at least one boost of one of the COVID-19 vaccines authorized in Italy in this period (ie, Pfizer-BioNTech [BNT162b2], Moderna [mRNA-1273], AstraZeneca [ChAdO × 1 nCoV-19] and Johnson & Johnson [Ad26.COV2.S]). Patients were included regardless type of anticancer therapy. Patients refusing the COVID-19 vaccination or postponing its administration were excluded.

Patient demographic, pathological, and clinical characteristics (age, gender, performance status, smoking habits, comorbidities, type of cancer, TNM stage, type of ongoing anticancer treatments, previous anticancer therapy, and prior Sars-Cov-2 contagious) were extracted from outpatient/inpatient medical records.

All enrolled patients were vaccinated in vaccination centers according to the Italian national vaccination campaign. After 1 week (±1 day), patients were contacted by telephone to collect information on early adverse events (AEs). During scheduled follow-up visits for continued cancer treatment, new AEs were investigated through a differential diagnosis. Both local (ie, pain, erythema, edema, induration at the injection site, and locoregional reactive lymphadenopathies) and systemic AEs (ie, fever, chills, headache, fatigue, myalgia, arthralgia, nausea, vomiting, and others) related to vaccination per investigator's evaluation were collected and graded according to Common Terminology Criteria for AEs (CTCAE) version 5.0.[41] Finally, post-vaccination Sars-Cov-2 infection and related symptoms were recorded.

Endpoints and Outcomes

The principal purpose of this study was to describe the safety profile of COVID-19 vaccines in a cohort of patients with thoracic cancers receiving anticancer treatment. The primary outcome was to investigate the incidence of COVID-19 vaccine-related AEs reported by patients over the telephone one week after vaccination and during scheduled clinical visits. The secondary outcome was to assess the number of patients with post-vaccine SARS-Cov2 infections reporting the type and frequency of symptoms and complications.

Ethics statement

The study was conducted based on the prescriptions and recommendations of the Helsinki declaration for studies including human subjects, and aligns with the European, national and institutional policies for prospective data collection intended for medical research.

This study was approved by the Institutional Review Board (IRB) of the European Institute of Oncology, Milan, Italy, and referenced with the IRB number UID 3519.

Data were anonymized and collected with data minimization. Only the investigators are aware of the de-codification encryption to re-identify patients. The data are stored in the institutional dataset of medical records for research, protected with a password, and accessible only from hospital-based computers, provided an identification as a doctor or data management personnel of our clinical department.

Statistical Analysis

Clinical and pathological features were characterized using descriptive statistics. Quantitative variables were described using the usual statistics: *n*, mean, median, interquartile range, minimum and maximum. Qualitative variables were described using numbers and percentages. Missing values were not counted for percentage calculations.

Statistical analysis was performed using R Statistical Software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Of the total 214 patients, 207 (96.7%) adhered to the COVID-19 vaccination and were included in this study. Particularly, four patients had refused the vaccination and three patients had decided to postpone its administration, all of them were excluded from this trial. Clinical features of 207 patients affected by thoracic cancers enrolled in the study are summarized in Table 1. Just over half (51,2%) of the patients were male. The median age was 67 years (IQR: 60-73 years). Most of the patients were former smoker (50.2%) and had ECOG PS of 1 (66.6%). The majority of patients had at least one comorbidity (76.3%). Most patients

Table 1 Principal Characteristics of the Study Population.

Total patients	N 207	% 100%
Sex		
Male	106	51.2%
Female	101	48.8%
age, median (IQR) yr	67	(60-73)
Smoking status		
Never	78	37.7%
Former	104	50.2%
Current	25	12.1%
Comorbidities		
No	49	23.7%
Yes	158	76.3%
PS ECOG		
0	59	28.5%
1	138	66.6%
2	10	4.8%
Subtype		
Adenocarcinoma	181	87.4%
Squamous cell carcinoma	6	2.8%
LCNEC	1	0.5%
SCLC	11	5.4%
Mesothelioma	8	3.9%
Stage at diagnosis		
early-stage	106	51.2%
advanced-stage	101	48.8%
Current stage		
I-IIIA	7	3.4%
IIIB	9	4.3%
IV	191	92.3%
Local therapy received in T/N in early stage		
Surgery	68	32.9%
RT	29	14.0%
CT+RT	9	4.3%
None	101	48.8%
Number of previous systemic treatment		
0	106	51.2%
1	72	34.8%
2	21	10.1%
≥ 3	8	3.9%
Ongoing treatment		
CT	29	14.0%
IO	47	22.7%
TT	95	45.9%
CT+IO	20	9.7%
CT+anti-VEGF	4	1.9%
IO+TT	3	1.4%
IO+IO	2	1.0%
None	7	3.4%

Abbreviations: anti-VEGF = antibodies against Vascular Endothelial Growth Factor; CT = chemotherapy; ECOG = Eastern Cooperative Oncology Group; IQR = inter-quartile range; IO = immunotherapy; LCNEC = large cell neuroendocrine carcinoma; N = absolute number of patients; N = locoregional lymph nodes; RT = radiotherapy; SCLC = small cell lung cancer-; T = primary tumor; TT = targeted therapy; Yr = years; % = percentage.

were affected by hypertension (27%), cardiovascular disease (27%), obesity (14%), hypothyroidism (13%), diabetes (9%), rheumatological disease (5%), chronic obstructive pulmonary disease [CORPD] (5%) and other lung diseases (4%) as reported in Table A1. Thoracic tumors were distributed as follows: 181 (87.4%) lung adenocarcinoma (ADC), 6 (2.8%) squamous-cell lung carcinoma (SSC), 11 (5.4%) small cell lung cancer (SCLC), 1 (0.5%) large cell neuroendocrine carcinoma (LCNEC) and 8 (3.9%) mesothelioma. At the diagnosis, 101 (48.8%) patients have a stage IV cancer while 106 (51.2%) have an early-stage cancer. However, the majority of patients (92.3%) were metastatic at time of vaccination. Regarding treatment, most patients were receiving targeted therapy (TT) (45.9%), immunotherapy (IO) (22.7%), and chemotherapy (CT) (14%) and combination therapies in approximately 14% of cases, of these 1.9% received anti-(vascular endothelial growth factor) VEGF drugs. Only 3.4% of patients were not receiving any therapy. Table A2 provides more details of ongoing treatments during COVID-19 vaccination.

Nine patients (4.4%) were previously infected with Sars-Cov-2 as reported in Table A3. Of these, only one (11%) was asymptomatic and eight patients (89%) were symptomatic. The most common symptoms were cough (75%), fever (50%), dyspnea (38%) followed by dysgeusia (23%), anosmia (25%) and diarrhea (13%). Three patients (38%) had radiologically diagnosed pneumonia. Four patients (44%) were hospitalized and one patient (11%) was admitted to the ICU. Table A3 also reports the type of therapy received by these patients.

Type of COVID-19 vaccine

Most patients received mRNA-based vaccine (n = 206, 99.5%), of these 143 patients (69.1%) received BNT162b2/BioNTech/Pfizer vaccine and 63 patients (30.4%) received mRNA-1273/Moderna vaccine. Only one patient (0.5%) received chimpanzee adenovirus-vector vaccine, ChAdOx1 nCoV-19/AstraZeneca. Overall, 411 doses of vaccine were administered to 207 patients. All patients received at least one dose (D1) and 204 (98.6%) completed the vaccination course with the second dose (D2) (Table 2), three patients did not receive the booster for various reasons but not for serious AEs at D1.

Safety

Forty-three patients (20.7%) experienced an AE after Sars-Cov-2 vaccines administration. A total of 64 AEs (15.6%) were observed after the administration of Sars-Cov-2 vaccine D1 (n = 207) and

Table 2 Characteristics of COVID-19 Vaccine and Adverse Events (AEs).

Type of COVID-19 Vaccine	N	%
Pfizer (BNT162b2)	143	69.1%
Moderna (mRNA 1273)	63	30.4%
Astra-Zeneca (AZD1222)	1	0.5%
Doses		
D1	207	100%
D2	204	98.6%
AEs after vaccine injection		
Total	64	15.6%
Local Symptoms	17	4.2%
Systemic Symptoms	47	11.4%
Grade of AEs		
G1	26	6.3%
G2	36	8.8%
G3	2	0.5%

Abbreviations: AEs = adverse events; D1 = first dose; D2 = second dose (or boosted dose); G = grade (sec. CTCAE v.5.0); G1 = grade one; G2 = grade two; G3 = grade three; N = absolute number; % = percentage.

D2 (n = 204). The majority of AEs were grade 1 [G1] (6.3%) and G2 (8.8%), only two events were G3 (0.5%). No grade 4 or higher AEs were observed. The majority of patients experienced systemic symptoms (n = 47; 11.4%) rather than local symptoms (n = 17; 4.2%) (Table 2).

For the total of 64 AEs reported (Figure 1A), the most common G1 AEs in patients receiving Sars-Cov-2 vaccine were local pain at injection site (n = 10; 15.6%), fever (n = 6; 9.4%), fatigue (n = 2; 3.1%), headache (n = 2; 3.1%), and diarrhea (n = 2; 3.1%). Instead, the most common G2 events were fever (n = 8; 12.5%), local pain (n = 7; 10.9%), myalgia (n = 7; 3.1%), fatigue (n = 6; 9.4%) headache (n = 2; 3.1%), and chills (n = 2; 3.1%). The two G3 AEs were fever and dyspnea.

Most AEs (n = 62; 96.9%) started within 7 days of vaccination (Figure 1B). Regarding the duration of the AEs, most resolved within 3 days (n = 61; 95.3%), the symptom that persisted beyond 15 days in two cases was fatigue (Figure 1C). Thirty-two AEs required systemic pharmacologic intervention: local pain (n = 7), fever (n = 9), myalgia (n = 7), headache (n = 2), chills (n = 2), joint pain (n = 1), nausea (n = 1), diarrhea (n=1) and other (n = 2) (Table A4). One patient was hospitalized due to AEs vaccination for G3 fever.

We reported in Table A5 the AEs according the different treatments in progress: there were differences in AE (we do not know if also of efficacy) between TKI, ICI and cytotoxic chemotherapy. A lower incidence of adverse events (10.5%) was recorded in the 28 patients receiving chemotherapy.

No new safety concerns after the third boost of RNA vaccine (data not shown).

COVID-19 infection after vaccination

After a median follow up of 9 months (range 1-22 mos), we collected data on SARS-CoV-2 infection post-vaccination (Table A3). Twenty-one patients (10.1%) had a positive nasal swab, and specularly to the pivotal studies, we can consider a vaccine efficacy of 89.9%. COVID-19 infection was symptomatic in the majority of the cases (14 patients, 67%). The most common symptoms were fever (71%), cough (71%) and dysgeusia (29%) in symptomatic patients. In general, symptoms were mild, with a shorter course. Compared to patients with SARS-COV2 infection before vaccine, fewer cases of pneumonia occurred after vaccine (n = 1 vs. n = 3) as well as hospital admissions (n = 1 vs. n = 4) and median number of days of hospitalization (5 days vs. 15 days); moreover, none intensive care unit (ICU) access was recorded (n = 0 vs. n = 1). However, in this rough comparison we must admit the presence of significant confounding factors and the most important is the different prevalence of the various Sars-Cov2 variants and subvariants between the time before the vaccination (original virus and Beta Variant, B.1.351) and the time frame of the study (the Delta variant, B.1.617.2, the Omicron variant, B.1.1.529 and its variants) in Italy.[42]

During this follow-up, 22 patients (10.6 %) died due to disease progression (no correlation with COVID-19 vaccine side effects was found).

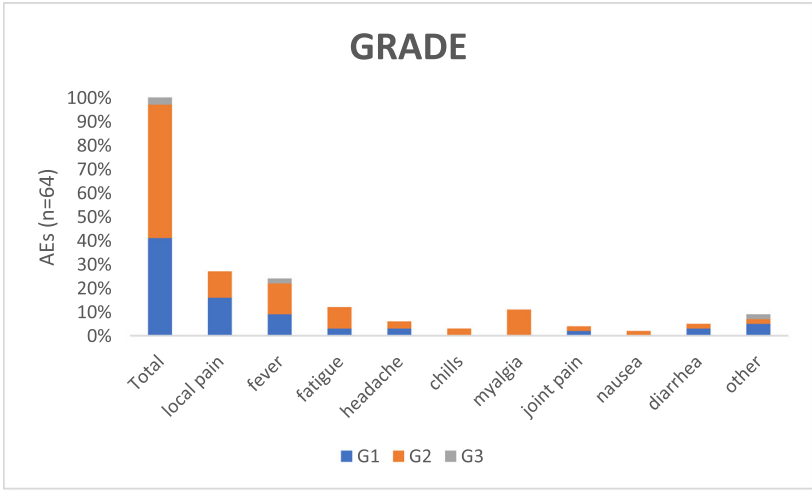
Discussion

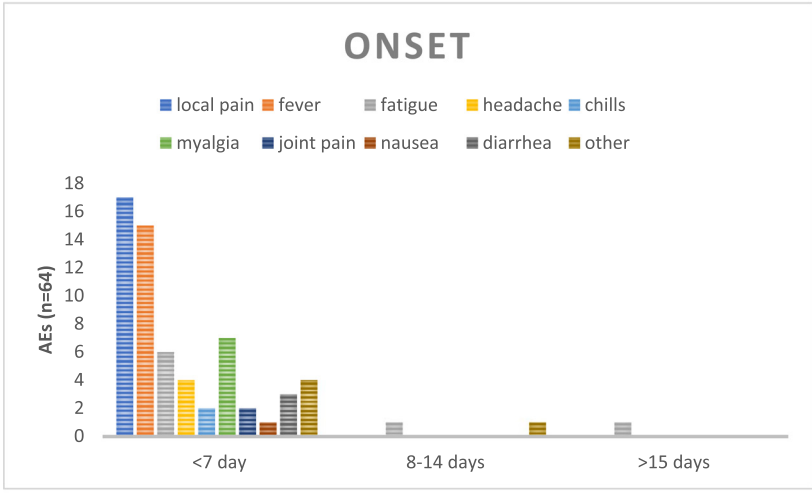
Our study was a prospective observational evaluation of patients affected by thoracic neoplasms (mainly LC) in active oncological treatment, undergoing vaccination against Sars-Cov-2 during active oncological treatment, in order to describe safety and efficacy of these vaccines in this population. Two-hundred and seven patients have been enrolled into this trial and followed for a period of 9 months (range 1-22 months). We observed 89.9% of efficacy as a protection against post-vaccine SARS-CoV2 infection. Around 10% of the patients contracted Sars-Cov-2 during the fourth epidemic wave in Italy without any experience of Covid-19 severe complications. The safety profile was manageable, causing less than 1% of G3-4 toxicity and only one case of hospitalization. We did not record any interfering with oncological treatments, including immunotherapy. All these results support the feasibility and the safety of these vaccines, helping the clinicians to confidently recommend also third and fourth dose if indicated per local guidelines.

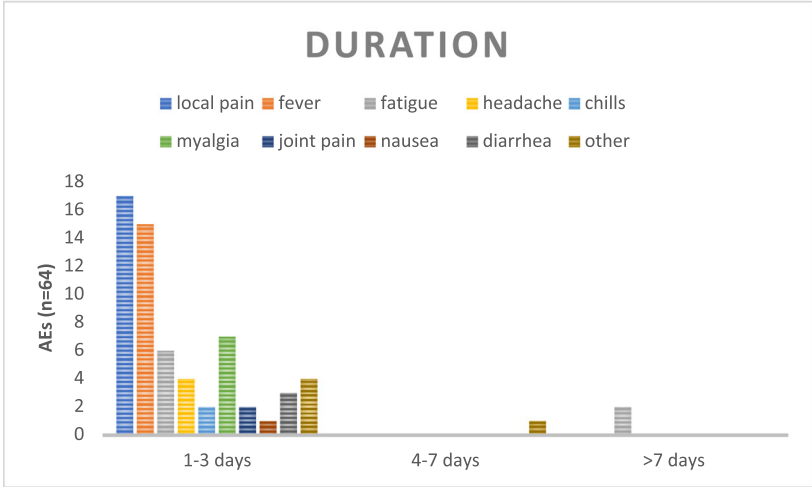
LC patients harbor a higher risk of COVID-19-related mortality (30% of infected patients) without vaccination, as previously reported.[8,9,43] Thus, cancer patients represent a priority category for SARS-CoV-2 vaccination.[19] In Italy, vaccination against COVID-19 has been made available since December 27, 2020. Initially, no evidence was available about the efficacy and safety of COVID-19 vaccination in cancer patients because of their exclusion from pivotal clinical trials.[16-20]

To date, published data of cancer patients vaccinated against COVID-19 derive from prospective observational studies (Table A6). Many of these studies have reported that immune response after COVID-19 vaccination are less effective in cancer patients than in healthy controls.[22,23,25-27,29,31-33,40] In particular, various studies have shown that good efficacy is not achieved after just one dose of the vaccine.[29-31,40] A pronounced delay in antibody production compared to healthy controls has been observed, and seroconversion

Figure 1 Incidence of adverse events (AEs) after COVID-19 vaccination in all patients. (A) Grade of AE, according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. (B) Days from vaccination to onset of AE. (C) Duration of AE.







occurred in most patients after the second dose,[20] therefore, second boost dose is needed to reach a satisfactory humoral response.[23]

In these studies, the median IgG titer in cancer patients was reported to be lower than in health controls.[20,28-31,40] However, the elicitation of the immune response was stronger after the second boost and the effect was even stronger after the third dose.[32-34] Furthermore, data on the duration of protection after vaccination are limited for healthy participants[44,45] and are very lacking for cancer patients.[28] Eliakim-Raz et al demonstrated that there is a negative linear correlation of IgG titer and time after the second dose for both patients ($R = -0.34$, $P < .001$) and controls ($R = -0.70$, $P < .001$).[27]

However, the maximum interference was observed in patients with hematological malignancies respect to patients with solid tumors,[23,28,30,34-36,39,40] and in details patients with hematologic cancers could elicit inadequate humoral and cellular responses while patients with solid tumors obtain excellent humoral response but inadequate cellular response.[28,34]

Another factor that could influence the immune response is advanced age, due to immunosenescence; studies are conflicting in this sense and few have found a true correlation between advanced age and poor response at multivariate analyzes.[38] Instead, Iacono et al. confirm adequate seroconversion in old patients with cancer (>80 years).[46] On the other hand, regarding young cancer patients (AYA), one very small study demonstrated 90% efficacy after the second dose.[47]

In previous studies, a significant difference in seroconversion rate was noted between the various anti-cancer treatment modalities. Patients who no received therapy (ie, clinical surveillance) or on endocrine therapy (ET) were reported the best outcomes with high seroconversion rates (98-100%) and excellent median antibody titers, compared to those patients who received cytotoxic chemotherapy alone or in combination with IO or biological treatments that had significantly lower levels of antibody titers.[35] Some data suggest that cancer therapy hinders immune responses to vaccines, particularly chemotherapy.[22,23,25,29,33,40] Also, patients with solid tumors receiving chronic use of steroids could elicit poor immune response.[25,38]

Concerning immunotherapy, particularly immune checkpoint inhibitors (I-CIs), contrasting studies have been reported, some studies reported equal and non-interfering efficacy[22,34] and other studies reported low effectiveness.[27,28,37] Regarding the safety, a debated topic previously, it appears to be safe. Waissengrin et al. observed a similar side-effect profile in healthy controls and in cancer patients treated with IO and no new immune-related side effects or exacerbation of existing immune-related side effects were observed.[22] In our study, no specific safety concerns were observed in ICI-treated patients, particularly with regard to immune-related adverse effects, as reported in previous cases.[21,22] In particular, our study confirms the safety profile of vaccines during immunotherapy with approved antagonists of programmed cell death protein 1 (PD-1) and its ligand PD-L1.[24] Furthermore, it appears to be safe in their combination with other investigative agents, as reported by previous studies.[48] However, perhaps these events may be too rare to be captured in our analysis and would require longitudinal pharmacovigilance.

When reported, AEs of any grade ranged from 18.9% to 74% after the first dose and from 23.1% to 72% after the second dose.[22-24,31,34,36,37,40,47-49] Very few G3 or higher AEs were recorded[25,34,36] and vaccine doesn't seem to augment oncological treatment toxicity.[24,49] A curious finding reported by one study is that AEs after booster predicted a higher likelihood of vaccine response ($P = .003$).[23]

In these prospective studies, LC were mixed with the other types of cancers. To our knowledge, only one prospective study concerning only thoracic tumors has been published so far. This study reported efficacy and safety profile in 306 patients with thoracic cancer (93% received two vaccine doses). The efficacy of mRNA COVID-19 vaccines reported was 98.4%. Serological conversion was also reported with only 6.3% of patients negative after the second dose. In multivariate analysis, only age ($P < .01$) and long-term corticosteroid treatment ($P = .01$) were significantly associated with a lack of immunization. In this study 30 patients received a third vaccine dose, with only three patients showing persistently negative serology thereafter, whereas the others exhibited clear seroconversion. Safety data were available for 90.1%, without significant safety concerns. No anaphylactic reaction occurred and no vaccine-related death occurred.[38] Similarly, our study reports a median follow-up of 9 months of a group of patients with thoracic cancers (mainly LC) in active treatment boosted with mRNA vaccines recording neither vaccine safety alerts or oncological treatment interferences. Also, we observed an excellent post-vaccine protection.

In fact, during the follow-up, around 10% of our patients were contaminated with Sars-Cov-2 without developing serious complications from Covid-19. This could be considered indirect evidence of the efficacy of mRNA-COVID-19 vaccines in this subset of frailty patients. Some observational studies have also shown that these vaccines are highly effective against asymptomatic infections and suppress viral load in breakthrough infections.[50] However, it should be emphasized that the development of immunogenicity alone does not mean absolute protection from COVID-19 infection, in fact, it is necessary to continue with social norms (social distancing, masks, hand disinfection, etc.) to avoid contagion.

Some highly transmissible SARS-CoV-2 variants of concern that partially evade antibody responses are suspected to have arisen following prolonged evolution within immunocompromised patients.[51-53] We have seen how compared to individuals not on immunosuppressive therapy, the magnitudes of vaccine-induced antibody and T cell responses induced by the vaccine is substantially reduced in cancer patients. These reduced levels can be particularly problematic in the face of variants (from beta to omicron subvariants) that possess some neutralizing mutations that evade antibodies. Indeed, the level of protection of the different COVID-19 vaccines against the different variants of SARS-CoV-2 is still poorly understood. There are studies that investigates the effectiveness of COVID-19 vaccination in preventing infection by the newly discovered SARS- CoV-2 variants. One study evaluated the effectiveness of the mRNA- 1273 vaccine against SARS-CoV-2 variants and assess its effectiveness by time against the delta variant since vaccination in 8153 cases and obtained an effectiveness after two doses of 86.7% against infection with the delta variant, 98.4% against alpha, 96-

98% against other identified variants, and 79.9% against unidentified variants.[54]

Our study presents several limitations. First of all, humoral (anti-S IgG) and cellular (specific anti-SARS-CoV2 CD4+/CD8+ T cell) immune responses were not evaluated for logistical and financial reasons. Our population was heterogeneous, confounding factors such as cancer type, cancer treatment, and vaccine type could not be accounted reliably in our statistics. In addition, the small cohort limited the potential identification of rare events, for example, the occurrence of exceptional toxicities of special interest, and their delayed occurrence. This is a general issue with vaccine development. Most of patients in our series received mRNA vaccines, with possible problems of generalizability for viral-vector or inactivated vaccine.[37] The choice of mRNA vaccines for patients with cancer was determined by the national policy-makers, recommending this type for the most vulnerable populations. Finally, the monocentric nature of the study may hinder its external validity.

The strengths of this study are that, for the first time, the safety profile of COVID-19 vaccines was investigated in a cohort of patients with thoracic malignances particularly, in patients receiving immunotherapy and targeted therapies with a median follow-up of 9 months (one of the longest reported so far, to our knowledge).

Conclusion

The safety profile of COVID-19 vaccines in patients with thoracic malignancies, including those in treatment with immune checkpoint inhibitors and specific target therapies, does not seem to differ from that of the general population of patients. Considering the high morbidity and mortality associated with COVID-19 in patients with lung cancer receiving active treatments, our study supports the current vaccine prioritization of all cancer patients with active treatment. Taken together our data with those from literature, that observed that immune response after COVID-19 vaccination is less effective in cancer patients than in healthy controls, we strongly recommend the booster dose (4th administration) for the patients with thoracic malignancies especially those who are in active treatment.

Authors Contribution

Conceptualization: GS; Data curation; GS, PTA; Formal analysis: GS, PTA; Funding acquisition: FdM; Investigation: GS, PTA, CC, EDS, AI, CS, FG, PPMBG, GC, AP, FdM; Methodology: GS, PTA; Project administration: GS, FdM; Resources: GS, PTA; Supervision: FdM; Validation: GS, FdM; Visualization: GS, PTA; Roles/Writing - original draft: GS, PTA; Writing – review and editing: GS, PTA, CC, EDS, AI, CS, FG, PPMBG, GC, AP and FdM.

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Clinical Practice Points

Although cancer patients represent a priority population for vaccination, they were initially excluded from these studies. To date, available data of immunogenicity and safety for this population derives mainly from non-randomized prospective studies. The purpose of our work is to describe the safety profile and efficacy of COVID-19 vaccines in patients affected by thoracic malignancies receiving antineoplastic drugs.

We found out that the safety profile of COVID-19 vaccines in patients with thoracic malignancies in active treatment (including immune checkpoint inhibitors and specific targeted therapies) was manageable, causing less than 1% of G3-4 toxicity and only one case of hospitalization.

Considering the high morbidity and mortality associated with COVID-19 in patients with lung cancer receiving active treatments, our study supports the current vaccine prioritization, third and/or fourth dose, of all cancer patients with active treatment.

Disclosure

GS served as advisor for Takeda outside the submitted work. CC served as advisor for AstraZeneca outside the submitted work. GC served as consultant or advisor for Roche, Lilly and Bristol-Myers Squibb, served on the speaker's bureau for Roche, Pfizer and Lilly, received travel funding from Pfizer and Roche, and received honoraria from Roche, Pfizer, Lilly, Novartis, AstraZeneca and SEAGEN, all outside the submitted work. AP served as consultant or advisor for AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Pfizer and Roche/Genentech; received speaker bureau from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Jansenn, Eli Lilly, Merck Sharp & Dohme, eCancer and Medscape, all outside the submitted work. FdM receiving advisory fees from Roche, Bristol-Myers Squibb, and AstraZeneca and consulting. fees from Merck Sharp & Dohme, all outside the submitted work. Other authors do not report potential conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2022.10.004.

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