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Insights into Immunotherapy Administration During the COVID-19 Pandemic: Experience from an Indian Tertiary Care Center

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ABSTRACT

The COVID-19 outbreak has been a scourge for cancer patients. The absence of knowledge and ignorance in addressing cancer patients throughout this epidemic has deteriorated their illnesses. Gathering information about patients undergoing immunotherapy during the COVID-19 pandemic was the study's goal. The information gathered covered the diagnosis, some research, and the effects of the immunotherapy medications as well as their adverse effects. To examine the actual situation, we looked at 13 patients who received immunotherapy during the COVID-19 epidemic and attempted to determine whether they experienced any severe side effects. This pilot project would serve as a foundation for larger research projects in the future. Immunotherapy medications including nivolumab, pembrolizumab, and atezolizumab were administered to our patients regularly during the COVID outbreak, which lasted from March 20 to June 20. Six individuals received nivolumab, six received pembrolizumab, and one received atezolizumab. Four patients were getting immunotherapy for lung cancer, three for head and neck cancer, two for recurrent lymphoma, and one each for hepatocellular carcinoma, renal cell cancer, malignant melanoma, and soft-tissue cancer among the 13 patients who continued to receive immunotherapy during the COVID pandemic. After taking pembrolizumab, one of the patients on atezolizumab improved. The majority of our patients remained in stable illness or partial remission, and there was no Grade 3 or 4 toxicity to these medications. One patient passed away shortly after starting a nivolumab cycle. For both the patients and the treating oncologist, the COVID-19 infection has presented an unexpected dilemma. It is extremely challenging to treat cancer patients when there is no prior evidence and the treatment is believed to be harmful. In this modest attempt, we hope to raise awareness that immunotherapy may continue throughout the COVID-19 epidemic as long as all necessary safeguards are taken.

Keywords: Immunotherapy, Nivolumab, Pembrolizumab, COVID-19

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Introduction

Cancer treatment consists of three pillars: surgery, radiotherapy, and chemotherapy. Nevertheless, during the last 20-25 years, we have established the fourth critical foundation in the shape of immunotherapy, which has resulted in a paradigm change in oncological care. Several immunotherapy medications, including atezolizumab, pembrolizumab, and nivolumab, are often utilized in oncological medicine. The axis between programmed death-1 (PD-1) and its ligand (PD-L1), which are found on both tumor and immune cells, is the focus of these medications. The several checkpoints that regulate our immune cells are inhibited by these medications. When these checkpoints are blocked, the immune cells proliferate quickly and eliminate the tumor cells. Over the past

ten years, the use of these medications has drastically altered the prognosis and course of therapy for several cancers. For high PD-L1 tumors, they can be administered as monotherapy or in combination with other chemotherapeutic medications, which significantly increases overall survival [1].

This post has been produced with the only goal of sharing our experience of employing immunotherapy medications in the current outbreak of the coronavirus.

A class of positive-sense, encapsulated, single-strand RNA viruses known as coronaviruses is responsible for moderate to severe acute respiratory syndrome. For this reason, it was called coronavirus 2 [2].

In December 2019, Wuhan, in China's Hubei Province, reported several pneumonia cases brought on by a new coronavirus. It quickly led to an outbreak in China and a worldwide epidemic. The coronavirus illness 2019 (COVID-19) was officially recognized by the World Health Organization in February 2020 [1].

A syndrome known as "cytokine storm" is caused by immunological dysregulation, which is the most well-understood etiology for morbidity and death in COVID-19 patients. In individuals with severe COVID-19, the body's immunological reaction becomes uncontrollable. Increasing levels of pro-inflammatory cytokines like IL6 and IL10 and overproduction of chemokines like CXCL10, CCL2, CCL3, and CCL4 are the main causes of this [3]. Given that COVID-19 infection modifies the immune environment, it is hard to say if administering immunotherapy would make infections worse or increase the likelihood of side effects [4].

Data regarding the use of immunotherapy in a COVID scenario are currently unavailable. This post was produced in light of this history to describe our experience treating cancer patients during the COVID-19 pandemic with immunotherapy (nivolumab, pembrolizumab, and atezolizumab).

Objectives

1. Enumerate the investigations and diagnosis of patients receiving immunotherapy.
2. Enumerate the adverse effects of immunotherapy.
3. Study the outcome after reassessment based on iRECIST criteria.

Inclusion criteria

1. All patients receiving immunotherapy drugs at our day-care center during the past 2 months.

Exclusion criteria

1. All cancer patients who were not receiving immunotherapy drugs were admitted to our ward.

Ethical clearance

The institutional review board granted ethical clearance following a discussion of the benefits and drawbacks of continuing immunotherapy for our patients during the COVID-19 pandemic.

Data collection

a. All patients undergoing immunotherapy had their age, sex, diagnosis, stage, and number of immunotherapy medication cycles documented.
b. The Arogya Setu app was used to assess patients before immunotherapy was administered. The Government of India released this questionnaire-based software that uses a person's symptoms, travel history, and proximity to any COVID-19-positive patients to determine if they are at high risk of contracting the virus or not. Aarogya Setu app at www.mygov.in
c. To check for any adverse events (AEs), routine examinations and examinations were carried out. For example, baseline ECG, thyroid evaluation/serum cortisol, dermatological assessment, full physical assessment, and contrast-enhanced computed tomography chest if an X-ray result in a symptomatic patient suggests pneumonitis.
d. The evaluation of the answer was conducted using the iRECIST standards.

Statistical analyses

Information on the individuals undergoing immunotherapy will be examined in this observational trial to determine its effectiveness and side effects.

Results and Discussion

We have been routinely administering immunotherapy medications, including nivolumab, pembrolizumab, and atezolizumab, as a second-line treatment to our cancer patients during this COVID-19 pandemic period, which began on March 20 and ended in June. Six individuals received nivolumab, six received pembrolizumab, and one received atezolizumab **(Figure 1)**.

Of the 13 patients who continued receiving immunotherapy during the COVID-19 pandemic, four had been given immunotherapy for lung cancer, three for head and neck cancer, two for relapse lymphoma, and one each for malignant melanoma, renal cell cancer (RCC), hepatocellular carcinoma (HCC), and other malignant soft-tissue tumors. After taking pembrolizumab, one of our patients with lung cancer who was getting atezolizumab improved.

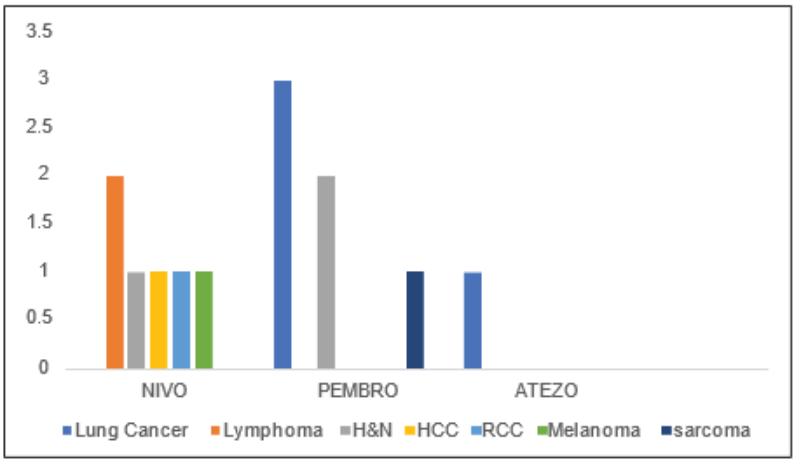

Figure 1. Distribution of immunotherapy

Nivolumab

There was only one female patient among the six receiving nivolumab **(Table 1)**, with the other five being male. A patient passed away while receiving treatment. He was a 65-year-old man with metastatic malignant melanoma. The condition began in 2019 when he developed a foot ulcer that was not healing. After receiving one cycle of nivolumab, he passed away on April 24, 2020, as a result of his illness progressing. Nivolumab is being administered to the majority of our patients in the second line or higher.

Our first patient, a 32-year-old woman, has Hodgkin's lymphoma that has relapsed. After receiving treatment with adriamycin, bleomycin, vinblastine, and dacarbazine, she underwent autologous stem-cell transplantation (ASCT), gemcitabine with oxaliplatin, and the BeGV protocol. After undergoing the COVID outbreak, she made improvements and is currently taking nivolumab, which she tolerated for six cycles.

Our patient (S No. 4) is a 39-year-old man with a known case of non-Hodgkin lymphoma (diffuse large B-cell lymphoma). His disease began in September 2017, and he has been treated with R-CHOP and ISRT 45 Gy/25 # until April 2018. He experienced an early relapse within 4 months, after which he received a salvage regimen of gemcitabine and carboplatin, followed by ASCT. After his transplant, he had a disease-free period for nearly a year before relapsing again in March 2020. He is currently receiving injections of nivolumab, and he has completed six cycles and is in partial remission.

After receiving pazopanib for over a year, our patient's metastatic RCC (clear cell) worsened, and nivolumab was prescribed. Instead of the required 240 mg every two weeks, he was given a dosage of 3 mg/kg. The patients had severe weariness and anemia; thus, this was done. Nivolumab had been tolerated by him. He could receive four nivolumab cycles until the middle of May, after which he was unable to report because of the lockdown.

An 80-year-old man with multicentric HCC who was unable to take sorafenib was put on nivolumab; after five weeks, his condition was stable and there were no side effects.

The patient was a 39-year-old man with recurrent nasopharyngeal cancer. Before receiving two further rounds of chemotherapy (cisplatin/cetuximab and TIP regimen), he underwent concomitant chemoradiation. Following these therapies, he made improvements and is currently on nivolumab.

Table 1. Details of patients receiving nivolumab

Sex	Age	Diagnosis	Dose	PD1/PDL1	Chemotherapy	Response	AE
Female	32	HL	180 mg	Not known	1. POST 4# ABVD	PR	
					2. POST 8# ABVD - PD	PD	
					3. DHAP 3# - PDRT 30 GY/10# - 13/03/2017 TO 21/03/2017	PD	
					4. GEM+OX 2# - SD	SD	
					5. BeGVP 2# - PR	PR	
					6. BeEAM 2# - ASCT in PR (14/10/2017)	PR	
					7. Nivolumab 6# AFTER COVID-19	iCR	
Male	56	RCC	180 mg	Unknown	Tablet pazopanib for last year injection of nivolumab 4# till mid-May	PD Response awaited	Anemia Fatigue
Male	80	HCC	240 mg	Unknown	Sorafenib for 1 month nivolumab 5#	Did not tolerate iSD	NO
Male	39	NHL	240 mg	Unknown	1. RCHOP - OCT 2017 (CIVIL)	CR	Neutropenia
					2. GDP/RGDP - JAN 2018 BMT DONE - FEB 2019	PD	
					3. Nivolumab - 17/04/2020 TO TILL DATE	iCR	
Male	39	CA nasopharynx	240 mg	Unknown	Pst CCRT + Adjuvant Nivolumab 4#	PD Awaiting response	
Male	61	Malignant melanoma	240 mg	> 1%	Death May 12, 2020, after receiving a single dose ON 24/04/2020	Died	

PDL1: Programmed death ligand 1, PD1: Programmed death 1, AE: Adverse event, iSD: Immune stable disease, iCR: Immune complete response, PR: Partial response, HCC: Hepatocellular carcinoma, RCC: Renal cell cancer, CA: Cancer, CCRT: Concurrent chemo-radiotherapy, NHL: Non-Hodgkin's lymphoma

Pembrolizumab

Six patients were getting pembrolizumab as part of immunotherapy **(Table 2)**. Three of the six were undergoing treatment for lung cancer with pembrolizumab. One of them had a 70% PDL1 status, while the other two had a 5% PDL1 state. Immunotherapy produced a response in nearly all of them. The majority of them reacted symptomatically, and they are now doing better.

A young woman, 44 years old, had soft tissue sarcoma that had spread. While undergoing therapy, she improved and was given six cycles of the mesna, doxorubicin, ifosfamide, and dacarbazine protocol (MAID). She was put on pembrolizumab since her PDL1 status was greater than 1%. She has barely finished two cycles and is awaiting an evaluation of her reaction.

Two head and neck cancer patients were treated with pembrolizumab: one was a recurrent case of oral cavity carcinoma, and the other was a recurrent case of nasopharyngeal carcinoma.

Table 2. Details of patients receiving pembrolizumab

Rel	Age	Diagnosis	PDL1	Line of chemotherapy	Response
Female	59	Carcinoma	5%	Pembrolizumab + carboplatin	PD
		lung		3# Pembrolizumab	iSD
Female	44	STS with	1%	MAID 6#	PD
		METS		2 # Pembrolizumab	Awaiting response
Male	21	Carcinoma	Unknown	1. Docetaxel + CIS + 5FU + Cetuximb - 30/03/2019 TO 24/08/2019 WBPET - PD	PD
		oral cavity		2. Pembrolizumab 6# - 25/02/2020 TO 17/03/2020 AFTER COVID-19	iSD
Male	74	NSCLC	70%	1. PEMEXTED + CDDP - 21/06/2019 TO 27/08/2019 08/11/2019	PD

				2. Pembrolizumab 6#	iPR
Self	40	MET	5%	NACCRT	PD
		Carcinoma lung		1. Paclitaxel + Carboplatin 2# - 06/09/2018 TO 12/10/2019	PD
				2. Paclitaxel + Carboplatin - 6#	PD
				3. Pembrolizumab + PEMXTED - 04/09/2018 TO 03/2020	PD
				4. Atezolizumab- 19/03/2020 TO TILL DATE	iPR
Self	39	Carcinoma nasopharynx	Not known	1. DOXCE+Carboplatin 3# 14/06/2013 TO 27/07/2013 WBPET FEB 2016 - MILD	PD
				2. ADJ CETUXI + CIS 5# - 26/08/16 TO 23/03/2016	PD
				3. CETUXI + CDDP+5FU 6# - 09/12/2016 TO 04/04/2017	PD
				4. Paclitaxel + Carboplatin 5# - 13/09/2017 TO 27/12/2017	PD
				5. TIP 6# - 02/09/2019 TO 18/12/2019	PD
				6. Pembrolizumab 8# - 1	iPR
				7. Nivolumab 4# - 01/05/20 TO TILL DATE	

PDL1: Programmed death ligand 1, iSD: Immune stable disease, iPR: Immune partial response, CA: Cancer

Atezolizumab

During this COVID pandemic, atezolizumab was administered to just one patient **(Table 3)**. He has a case of lung cancer and is 41 years old. In August 2018, he received a diagnosis. In the beginning, he had a questionable skeletal lesion.

He had six rounds of adjuvant paclitaxel and carboplatin after definitive CCRT, nevertheless, to cure him. In addition, he was given bisphosphonate and radiation to the bone area. He experienced a worsening illness during a nearly one-year treatment-free interval (TFI). There was no actionable mutation in his EGFR/ALK/Ros 1. PDL1 was 5%. He began on pembrolizumab and pemetrexed. He was given 8# till February 2020, when the illness worsened once more. Despite the lack of evidence supporting the use of further immunotherapies after progressing on one, he was initiated on a combination of gemcitabine, bevacizumab, and atezolizumab. After six rounds, response evaluation revealed a partial remission. The patient, who has Garde 2 neutropenia, is currently at ease. There were no additional negative effects observed.

Table 3. Detail of patient receiving atezolizumab

Sex	Age	Diagnosis	PD1/PDL1	Chemotherapy	Cycles	Response
Male	41	Metastatic	5%	CCRT		PD
		lung cancer		Paclitaxel + Carboplatin	6	PD
				Pemetrexed + Pembro	8	PD
				Atezolizumab + Bevacizumab + gemcitabine	6	iPR

PDL1: Programmed death ligand 1, PD1: Programmed death 1, iPR: Immune partial response, CCRT: Concurrent chemo-radiotherapy

Medical oncologists worldwide have faced significant challenges in managing cancer patients during the COVID-19 epidemic. Oncologists throughout the world have been on the defensive because of the concern that having chemotherapy might cause immunosuppression. Fewer people were visiting hospitals because of concern that they might become infected, which made the problems worse. In the current situation, it has taken us some time to comprehend and be ready to administer chemotherapy.

There is no data to back up or direct us at this time; this has never happened before. Confusion increased when we wanted to start or continue immunotherapy in the current environment. It was observed that serious COVID-19 patients had immunological dysregulation. Cytokine storm was the name given to this harmful immune reaction [5]. Biopsies from patients with COVID-19 showed tumor necrosis factor, interferon-gamma, and macrophages

and monocytes infiltrating the area. Irreversible lung damage and pulmonary edema are caused by these pro-inflammatory cells [6].

The goal of all immunotherapy is to increase the generation of immune cells capable of killing tumor cells. The primary way by which they do so is to disrupt the checkpoints that were put in place to regulate the overproduction of these immune cells. Using immunotherapy for COVID-19 patients was expected to have its issues. Another major issue was the most prevalent side effect of immunotherapy, pneumonitis. If any immunotherapy patient suffered respiratory abnormalities, it would be difficult to determine whether it was due to medication toxicity or COVID-19 infection. Another noteworthy limitation is the usage of steroids in the present context.

One kind of immunoglobulin seen on the surface of activated T cells is called PD1 (CD 279) [7]. Our patients received atezolizumab, pembrolizumab, and nivolumab as immunotherapy medications. Checkpoint inhibitors are the name given to these medications. PD1/PDL1 receptors are where they work. PD-1 and atezolizumab PD-L1 blockers are inhibited by pembrolizumab and nivolumab.

The immune checkpoint inhibitor ipilimumab was authorized for use in melanoma in March 2011. Pembrolizumab was authorized by the US FDA in September 2014 for the treatment of metastatic melanoma. Since then, these immunotherapy medications have been used to treat a variety of cancers, including non-small cell lung cancer (NSCLC), bladder cancer, RCC, head and neck cancer, hepatocellular cancer, gastric cancer, Hodgkin's lymphoma, and triple-negative breast cancer. More recently, these medications have been approved, usually as second-line treatments. While PDL1 status testing was required before immunotherapy could begin in NSCLC, it is not required in the majority of other illnesses for its use in a second-line context [8].

Platinum-ineligible metastatic urothelial carcinoma (mUC) requires tumor PDL1 expression before single-agent therapy can begin, among other genitourinary cancers. But for platinum-refractory mUC or metastatic RCC, there is no such necessity [9].

There were six individuals receiving nivolumab in our research. Malignant melanoma, recurrent lymphoma, RCC, HCC, and head-and-neck cancer were among the patients. There is just one female among the six; the other five are all male. The majority of our patients receive nivolumab in a second-line or higher situation.

Pembrolizumab was administered to six individuals. Out of the six, three had lung cancer, while the other two had sarcoma and head and neck cancer.

Lung cancer patients were the only ones receiving atezolizumab.

Before the COVID outbreak, all of these patients were prescribed these medications. They had all handled these medications rather well. Since the majority of them were hospitalized patients, it was decided to keep treating them.

They were not tested for COVID-19 infection since the majority of the patients were ward-admitted patients who had not displayed any symptoms of the virus. These immunotherapies were continued at the same frequency and dose intensity. Since the majority of our patients were admitted to the hospital for the full term, this was feasible in our environment.

Immuno-related adverse events (irAEs) are the special side effects of these medications [10]. Hepatotoxicity, endocrinopathies, diarrhea/colitis, and pneumonitis dermatologic are the most frequent and significant adverse drug events. The main problem with immunotherapy during a COVID-19 pandemic is that respiratory symptoms and imaging images from medication toxicity and COVID-19 infection might overlap. According to several studies, imaging characteristics of typical COVID-19 pneumonia include mixed consolidation and GGO (65%), vascular enlargements in the lesion (72%), and ground-glass opacities (GGO) (87%). Traction bronchiectasis symptoms were present in nearly half of the individuals. Nearly 80% of cases feature bilateral involvement and lower lung involvement, and the lesions are distributed peripherally [11].

Similarly, according to NCCN recommendations, immunotherapy medicines' pulmonary toxicities are categorized into four groups based on the intensity of the symptoms.

They are as follows:

1. Grade 1 – Asymptomatic/pneumonitis confined to < 25% of lung parenchyma or a single lobe
2. Grade 2 – Symptomatic with fever, cough, chest pain, and shortness of breath (moderate pneumonitis)
3. Grade 3 – Severe pneumonitis involves all lobes of the lung or > 50% of lung parenchyma
4. Grade 4 – Life-threatening pneumonitis involving difficulty in carrying out activities of daily living.

Thankfully, none of our patients experienced any respiratory issues, thus neither COVID tests nor HRCT were necessary.

Steroid usage and medication withholding are the primary therapy strategies for these issues. None of our patients had any gastrointestinal, rheumatological, hepatic, endocrine, or dermatological adverse effects. There was no need to change the dosage for the two individuals who experienced tiredness (Grade 1). Three patients were found to have mild neutropenia. The fact that these individuals had extensive treatment with several lines of chemotherapy may be the cause of their neutropenia. No more assessment was carried out since they reacted to granulocyte-stimulating substances.

The evaluation of the replies was conducted using the iRECIST standards, which were initially derived from RECIST 1.1 [12]. The replies are categorized according to these standards as immune complete response, immune partial response (iPR), immune stable disease (iSD), immune unconfirmed progressive disease, or immune-confirmed progressive disease (iCPD).

Two out of six nivolumab-treated patients were in CR, one had stable disease, two had not yet had a reevaluation, and one passed away from an advancing illness. Three of the six patients who received pembrolizumab had stable illness, two of the six experienced partial remission, and one has not yet undergone a reevaluation. An iPR was present in one patient on atezolizumab.

Role of programmed death 1/programmed death ligand-1 testing before the use of immunotherapy

Globally, immunotherapy medications that use monoclonal antibodies to target PD1 and PDL1 have revolutionized the treatment of cancer. PDL1 receptors are found on tumor cells, while PD1 receptors are found on activated T and B cells [13]. The tumors with higher PDL1 expressions have responded better to these checkpoint inhibitors in practically all of the cancers when they are administered. Thus, in all, four PD-L1 IHC assays employing four distinct PD-L1 antibodies (22C3, 28–8, SP263, and SP142) on two distinct IHC platforms (Dako and Ventana) and scoring systems are registered with the FDA. For every medication and cancer type for which it is prescribed, companion diagnostic tests have been established. Nivolumab usage in melanoma was contingent upon PD-L1 expression as determined by the PD-L1 IHC 28-8 pharmDx test [14]. The FDA has authorized the VENTANA PD-L1 (SP142) assay as a companion diagnostic test for atezolizumab in urothelial malignancy [15]. Knowing these platforms helps us determine which one was utilized in the clinical trial that resulted in the drug's approval in a certain scenario. **Table 4** lists the specifics of the illnesses and the function of the PDL 1 status test. In addition to PDL1 status, additional indicators include alterations in the DNA repair pathway, increased neoantigen load, and molecular smoking signature [16].

Only one of the six patients in our research who were taking nivolumab had a PDL1 status of more than 1%. The medication was given to other patients following ASCT or in a second or third-line context. During this time, six patients were still receiving pembrolizumab. Three out of six patients had PDL1 expression, and one of them had more than 70% expression. The expression was less than 70% in the single patient on atezolizumab.

Table 4. Details of malignancy and role of programmed death ligand 1 testing

Malignancy	Drugs	Target	Indication	Requirement of PDl1 testing
Melanoma	1. Pembrolizumab	PD1	Unresectable/metastatic	No
	2. Nivolumab	PD1		
	3. Nivo + Ipi	PD1 + CTLA4		
Non-small cell lung cancer	1. Nivolumab	PD1	Metastatic disease/PD	No
	2. Atezolizumab	PDL1	first-line monotherapy	No
	3. Pembrolizumab	Pd1	Second-line monotherapy	Yes
				Yes
RCC	Nivolumab	PD1	Advanced disease second-line	No
Gastric cancer	Pembrolizumab	PD1	Recurrent/metastatic disease after two lines of appropriate therapy	Yes
HCC	Nivolumab	PD1	Second line postsorafenib	No
Bladder cancer	Nivolumab	PD1	Second-line locally advanced/metastatic disease (post-platinum-based therapy)	No
	Atezolizumab	PDL1		
	Durvalumab	PDL1		
	Avelumab	PDL1		

	Pembrolizumab	PD1		
Head and neck cancer	Pembrolizumab Nivolumab	PD1 PD1	Recurrent/metastatic with progressive disease	No
MSI H/dMMR deficient solid tumors	Pembrolizumab	PD1	Second line on progression after adequate treatment	No
Classical Hodgkin's lymphoma	Nivolumab Pembrolizumab	PD1 PDL1	post ASCT/fourth line Post 3 lines	No No
MSI H/dMMR deficient colorectal tumor	Nivolumab	PD1	Metastatic colorectal cancer post5FU/Platinum/irinotecan	No

PDL1: Programmed death ligand 1, PD1: Programmed death 1, HCC: Hepatocellular carcinoma, RCC: Renal cell cancer

Limitations of the study

An army hospital served as the site of this investigation. Due to the lockdown, the majority of the patients who were admitted to the wards stayed there. Their exposure to COVID-19 infection was either little or nonexistent. Therefore, there was very little probability that these individuals would have any major infections during this period.

This was a research constraint since real-world patients are not allowed to stay in a hospital for three months; thus, they are often at a higher risk of contracting an infection.

Conclusion

The COVID-19 infection has presented an unexpected dilemma for the treating oncologist as well as the patients. Using immunotherapy medications in the current context is extremely challenging because of the lack of any prior data. The severity of the COVID-19 infection was believed to be increased by any overstimulation of immunity. To describe our experience with immunotherapy medications during the COVID-19 epidemic, this essay was prepared. During the COVID-19 pandemic, we had a positive response from our patients using immunotherapy. This is an attempt to modestly raise awareness that immunotherapy may continue throughout the COVID-19 epidemic as long as the necessary safeguards are taken.

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Ethics Statement: None

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