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NSCLC Immunotherapy and Related Rare Toxicities: A Monocentric Real-Life Experience

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ABSTRACT

BACKGROUND

In the last years immunotherapy has revolutionized the treatment of non-small cell lung cancer (NSCLC) not supported by a driver mutation. Immunotherapy related adverse events (irAEs) have a unique toxicity profiles distinct from the toxicities of classical chemotherapy treatment relating to their mechanism of action. We analyzed some serious and uncommon life-threatening irAEs, needing a change in the therapeutic strategy.

METHOD

Between October 2018 and October 2020, 63 NSCLC patients underwent immunotherapy. Thirty-eight patients underwent first-line Pembrolizumab, 200 mg every 21 days (Group A). Twenty patients were treated in second line with Pembrolizumab 200 mg every 21 days or Nivolumab 240 mg every 14 days or Atezolizumab 800 mg every 14 days (Group B). Five stage III patients treated after radio chemotherapy with Durvalumab 1500 mg every 14 days (Group C).

RESULTS

We experienced: a) 2 bowel perforations (3.2%), necessitating Hartmann's resection. Only one of the two patients restored immunotherapy; b) 1 chronic renal insufficiency (1.6%, creatinine up to 8 mg/dL) and 2 severe hypertransaminasemias (3.2%, up to 65 U/L), requiring the immediate and definitive interruption of ICIs; c) 2 pericardial effusions (3.2%), of which one needed subxiphoid pericardiocentesis for cardiac tamponade. Patient restored immunotherapy after resolution of the acute event.

CONCLUSIONS

Immunotherapy include monoclonal antibodies reducing the suppression of effector T cells and improving the tumor-specific immune responses. Most common irAEs are evident in mild and reversible form, but sometimes life-threatening irEAs show up. Therefore, further clinical trials needed to increase knowledge of drugs and prevent unexpected irAEs.

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KEYOWRDS

Non-small cell lung cancer; Immunotherapy; Toxicity; Adverse events

INTRODUCTION

Lung cancer is the most common cancer worldwide, showing an incidence of 11.6% and mortality of 18.4% [1] among all malignancies. Non-small cell lung cancer (NSCLC), including three main subtypes (adenocarcinoma, ADC, squamous cell carcinoma, SCC, and large cell carcinoma, LCC), accounts for 85% of bronchogenic carcinoma [2]. Prognosis of NSCLC cancer stage III and IV is poor, and standard treatments with cytotoxic anticancer drugs have limited therapeutic or life-threatening side effects. In the last few years, the advent of immune checkpoints inhibitors (ICIs) revolutionized the natural history and treatment algorithm of NSCLC not harboring a driver mutation.

To date, different monoclonal antibodies (pembrolizumab and nivolumab) have been approved targeting programmed death-ligand 1 (PD-L1) and the ligand PD-L1 (atezolizumab) in the first [3] and the second line treatment [4-6] of stage IV NSCLC. Moreover, in stage III NSCLC has been adopted a targeting ligand PD-L1 compound (durvalumab) after concomitant or sequential chemoradiotherapy [7].

Most recently, immunotherapy has been ratified with concomitant platinum-based chemotherapy in NSCLC first-line treatment [8]. All these studies show a great impact in NSCLC due to an improvement in overall survival (OS) and progression-free survival (PFS). However, although ICIs stimulate the immune system against tumor activity, may cause overwhelming inflammation, tissue damage, and autoimmunity activity based on the immune-related adverse events (irAEs). These irAEs were reported in patients up to 70% after treatment with inhibitors of the PD-1 axis [9]. Through our data examination, we evaluate the acute severe toxicities or toxicities not frequently reported in literature linked to immunotherapy treatments.

PATIENT AND METHODS

Over a period of 24 months, from October 2018 to October 2020, we evaluated 63 patients with inoperable non-small cell lung cancer (NSCLC) who underwent immunotherapy treatment. Fifty-eight patients (92.1%) were in metastatic stage involving single or multiple sites and 5 patients (7.9%) in unresectable advanced stage III. Immunotherapy was proposed in the first or second line and only who underwent at least 3 courses of administration were considered in the study. Three Groups have been defined: 1) Group A, 38 patients (60.3%) underwent first-line treatment with Pembrolizumab 200 mg every 21 days; 2) Group B, 20 patients (31.8%) who, after first-line platinum compound based chemotherapy, in second line underwent Pembrolizumab 200 mg every 21 days or Nivolumab 240 mg every 14 days or Atezolizumab 800 mg every 14 days; 3) Group C, 5 patients (7.9%) in advanced stage III (T3a-b N2-3) treated after concomitant or sequential radio chemotherapy with Durvalumab 1500 mg every 14 days. Forty-seven patients (74.6%) were males and 16 (25.4%) females, with an average age of 70 years (range: 39-88 years). Of these, only 6 (9.5%) have never been smokers, 17 (27%) have stopped smoking for variable time and 40 (63.5%) are habitual smokers. According to the Eastern Cooperative Oncology Group (ECOG) scale [10], 25 patients (39.7%) were in state 1, 33 (52.4%) in state 2 and only 5 (7.9%) in state 3. The histologically predominant lung cancer is non-squamous type (42 patients, 66.7%) while the squamous type was found in 21 patients (33.3%). The most affected metastatic site was the bone (27 patients), followed by the liver (10 patients) and brain (9 patients). Clinical data were summarized in Table 1.

Clinical Data	N	%	Mean	Interval	SD
Gender					
Male	47	74.6			
Female	16	25.4			
Age			68.9	39-88	10.4
ECOG					
1	25	39.7			
2	33	52.4			
3	5	7.9			
Smoking Status					
Current	40	63.5			
Former	17	27			
Never	6	9.5			
Histology					
Squamous	21	33.3			
Non Squamous	42	66.7			
Metastasis Sites (Including multi-sites)					
Brain	9	14.3			
Liver	10	15.9			
Bone	27	42.8			
Others	45	71.4			
Stage III	5	7.9			
Previous Chemotherapy					
Previous	35	55.6			
None	28	44.4			
Treatment duration (Months)			8.55	2-39	7.61
Number of administrations			12.4	3-63	13.1

Table 1: Clinical Data of patients treated with immunotherapy.

RESULTS

We observed 42 any grade immune-related adverse events (66.7%), 33 G1-G2 irAEs and 9 G3-G4 irAEs. No irEAs leading to death was experienced. Toxicity classification and related treatment was performed due to common good clinical practice, according to AIOM guidelines [11]: 1) G1 irAEs did not include discontinuation of ICIs; 2) G2 irAEs expected the addition of low dose steroids therapy; 3) G3 irAEs were addressed with discontinuation of immunotherapy, the introduction of high-dose steroids and of specific dysfunction organ treatments. Once the resolution of irAEs toxicities and after adequate clinical, laboratoristic and radiological revaluation, ICIs treatment was resumed with an average period of 2 weeks. The most frequent (19.0%) irAEs were observed in the gastrointestinal site with 6.4% diarrhea, 9.5% gastritis and 3.2% stomatitis. The second frequent irAEs (17.5%) were dermatological, with 2 events of severe toxicity (3.2%). The third frequent irAE was iperthyroidsm (11.1%); no G3-G4 thyroid immuno-related toxicity was observed. Other irAEs were neurological (1.6%), pyrexia after infusion (1.6%) and pneumonitis (1.6%).

Complications	Any grade	G1-G2	G3-G4
Diarrhea	4 (6.4%)	4 (6.4%)	
Gastritiis	6 (9.5%)	6 (9.5%)	
Stomatitis	2 (3.2%)	1 (1.6%)	1 (1.6%)
Pyrexia after infusion	1 (1.6%)	1 (1.6%)	
Increasing creatinine level	3 (4.7%)	2 (3.2%)	1 (1.6%)
Neurological	1 (1.6%)	1 (1.6%)	
Iperthyroidism	7 (11.1%)	7 (11.1%)	
Pneumonitis	1 (1.6%)	1 (1.6%)	
Skin reaction/dermatitis	11 (17.4%)	9 (14.2%)	2 (3.2%)
Bowel perforation	2 (3.2%)		2 (3.2%)
Pericardial effusion	2 (3.2%)	1 (1.6%)	1 (1.6%)
Hypertransaminasemias	2 (3.2%)		2 (3.2%)
Total Number	42	33	9

Table 2: All toxicities following immunotherapy.

One patient affected by IV stage NSCLC, after 13 administering of Nivolumab, developed a G4 pericardial effusion evidenced as cardiac tamponade. Immunotherapy was stopped and patient underwent pericardiocentesis. After resolution of emergency, patient was re-staging and ICIs wasn't resumed. The second patient with pericardial effusion was positively treated with medical therapy and re-started ICIs. Other patient affected by IV stage NSCLC, after 11 administering of Pembrolizumab, showed multi irEAs (severe hypercarotenemia, severe skin toxicity, stomatitis and hypertransaminasemias) associated with moderate symptoms like anemia, asthenia and diarrhea. ICIs was interrupted and patient was hospitalized for pharmacological support. After 2 months, we observed complete resolution of almost all toxicities except kidney failure and we decided not to restore ICIs. We observed two bowel perforations (3.2%). The first was related to a IIIB stage NSCLC patient. After 9 Durvalumab administrations due to a progressive onset of severe constipation, vomiting and abdominal pain and increasing of transaminases level, patient underwent Hartmann's resection. After 1 month patient resumed Durvalumab treatment based on excellent performance status and computed tomography evaluation (stability of NSCL and good resolution of colon irAEs). The second was related to a metastatic patient, that displayed severe abdominal pain

due to bowel obstruction after 8 Nivolumab administration. Patient underwent Hartmann's procedures and ICIs was interrupted for progression disease. Finally, we observed a case of hypertransaminasemias as a single hepatic toxicity, after 6 administering of Pembrolizumab. Despite an adequate organ support and the steroids treatment, patient discontinued ICIs for progression disease. Table 2 shows the toxicities linked to immunotherapy.

DISCUSSION

The arising of immunotherapy revolutionized NCLSC treatments, thanks to an immune reactivation against cancer cells. However, ICIs can also stimulate the immune system against specific organ or tissue leading to an immune-related adverse events. IrAEs is becoming more clearly defined: skin, gut, endocrine, lung and musculoskeletal irAEs are relatively common. Cardiovascular, hematologic, renal, neurological and ophthalmologic irAEs are well-recognized but occur much less frequently. These irAEs were reported up to 70% patients after treatment with inhibitors of the PD1 axis [9], in line with our experience (66.7%). Most frequent irAEs evidenced were G1-G2 toxicity, according to the main studies regarding ICIs treatment. Gastrointestinal, skin and thyroid's irAEs required continuing ICIs with possible addition of low dose of steroids. We experienced 9 patients developing G3-G4 irAEs, some of which (4 in total) are not clearly focused in literature. The first irAEs was a severe kidney failure. Renal damage due to ICIs is a rare event. A recent meta-analysis by Wang et al [12] highlighted the very low (less than 1%) incidence of renal toxicity due to anti PD-L1 regardless of the treatment type. There were reports of acute renal failure and renal failure only with nivolumab treatment, although the incidence was only ~2% for all grade and ~1% for severe grade. Therefore, kidney failure should be better taken into account in the management of immunological therapies, possibly by carefully weekly monitoring renal function. The second irAEs was the pericardial effusion with cardiac tamponade, event not well decoded in the literature. The possible explanation for heart involvement in ICI-related autoimmune response could be the presence of PD-1 and PD-L1 proteins on cardiomyocytes. In fact, an animal study demonstrated that PD-1 deletion can determine autoimmune damage [13]. Salem et al [14] displayed a specific association between pericardial disease and ICIs with a possible real incidence higher than expected. Proper cardiac evaluation strategies during ICIs treatment should be a part of a tailored follow-up. The last severe and unusual irEAs were two bowel perforations. This complication was not reported in retrospective or prospective studies, but only as case report evidence [15,16]. It has been previously described that prolonged ICIs therapy may induce colitis although there is no knowledge regarding the mechanism of gastrointestinal perforation linked to ICIs. Therefore, physicians should be aware of the risk of this complication during prolonged immunotherapy treatment. In conclusion, immunotherapy has positively changed the natural history of advanced lung cancer but it can trigger autoimmune responses against specific organs or tissues causing serious adverse events. Therefore, physicians should improve and modify common indications of pharmacological surveillance in relation to these new toxicities especially in prolonged treatment with ICIs.

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