Journal of Cancer Research and Clinical Oncology (2021) 147:2789–2800
https://doi.org/10.1007/s00432-021-03610-w

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Immune-related adverse events and immune checkpoint inhibitor tolerance on rechallenge in patients with irAEs: a single-center experience

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Received: 12 September 2020 / Accepted: 18 March 2021 / Published online: 28 March 2021

Abstract

Background Given the widespread use of immune checkpoint inhibitors (ICIs), newer immune related adverse events (irAEs) have come to light, including flare-ups of preexisting autoimmune disorders (AIDs) and delayed immune-related events. We aimed to identify the frequency and severity of new IRAEs, including AID flares in cancer patients treated with ICIs at our institution. We also studied the tolerability of ICIs upon rechallenge in patients with irAEs and hospital admissions due to irAEs in a community setting in rural Maine.

Methods We conducted a retrospective chart review analysis of all patients with cancer who received anti-PDL1/PDL1 inhibitors nivolumab, pembrolizumab, atezolizumab, and durvalumab at our tertiary care center from November 2015 to March 2019. Demographic data, cancer type and stage, irAEs, hospital admissions due to irAEs, and drug treatment information was extracted.

Results We included 465 patients who received ICIs, 115 (out of 465 25%) developed new irAEs. Preexisting AID were identified in 47 (out of 465) (10%), AID flares were observed in 12 patients (25% of 47). 17 (out of 47 36%) were on immunosuppression for underlying AID, 5 (out of 17, 29%) developed flares. Overall, 148 (32% of 465) irAEs occurred, as some patients had multiple toxicities. Majority were treated for Lung cancer (63%), followed by melanoma and genitourinary cancers. Due to irAE severity, treatment was permanently discontinued in 15% (out of 465) patients. Hospital admissions due to irAEs were required for 34 patients (7.3% of 465). ICI rechallenge was performed in 27 patients (6% of 465), and majority tolerated well.

Conclusion Our study shows that ICIs were generally well tolerated and can be used safely even in patients with preexisting AIDs; it is encouraging to see majority tolerated rechallenge with ICIs well.

Keywords Anti-PD1/PDL1 inhibitors · Immune checkpoint inhibitors · Immune-related adverse events · Preexisting autoimmune disorders · Delayed immune-related events · Hospital admissions due to irAEs · Rechallenge with ICIs

Introduction

Immune responses are tightly regulated by multiple co-stimulatory and co-inhibitory pathways. Evasion of these pathways is one way through which a tumor can spread. To date, exceptional research has enabled us to better understand these pathways and identify potential therapeutic targets. Subsequently, monoclonal antibodies targeting these co-stimulatory and co-inhibitory molecules have been developed, which enabled us to enhance the immune system to restore anti-tumor activity and substantially improve the prognosis of patients with advanced malignancy. The two major classes of these antibodies include cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) and programmed death cell 1 (anti-PD-1) antibodies. CTLA4 is a negative regulator of T cell activation present on CD4+ and CD8+ T cells, which has higher affinity for co-stimulatory receptors, CD80 and CD86 required for T cell activation. Binding to these co-stimulatory molecules decreases

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proliferation and downregulates T-cell responses and antigen-presenting cell function, resulting in a decreased immune response and immune tolerance to cancer cells (Tarhini et al. 2010). Ipilumab was the first anti-CTLA4 antibody approved by the FDA based on its ability to prolong survival in patients with metastatic melanoma (Hodi et al. 2010).

Programmed cell death 1 (PD1), a transmembrane protein expressed by T cells, is an inhibitory receptor that serves as an immunological checkpoint to limit bystander tissue damage and to prevent the development of autoimmunity. Binding of PD-1 with its ligands PD-L1 and PD-L2 induces an inhibitory signal, resulting in reduced T-cell proliferation, cytokine production, and cytotoxic activity (Brown et al. 2003), thereby leading to cancer evasion from the immune response. PDL1 is present on multiple tissue types, including many tumor cells. The FDA has approved pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab based on the results of phase 3 trials. Currently, ICI use is FDA-approved for the treatment of melanoma, renal cell cancer, head and neck cancer, urothelial cancer, Hodgkin's lymphoma, merkel cell cancer, gastric cancer, colorectal cancer, hepatocellular cancer, and microsatellite instability-high or mismatch repair-deficient solid tumors (Gong et al. 2018).

Despite the clinical benefits, ICIs have been associated with irAEs, which can affect multiple systems and are sometimes fulminant. The exact incidence of AID flares is unknown in patients with preexisting AIDs, as they were largely excluded from clinical trials. In our study, we report the frequency of new irAEs, including preexisting AID flares, in cancer patients treated with ICIs. We also studied the tolerability of ICIs upon rechallenge in patients with irAEs and hospital admissions due to irAEs in a community setting in rural Maine.

Methods

We conducted a retrospective chart review analysis of all patients with cancer who received single agent ICIs nivolumab, pembrolizumab, atezolizumab, and durvalumab at Northern Light Cancer Institute from 2015 to March 2019. All consecutive patients were included. We did not have any patients who received Avelumab at our institution. We excluded patients who received combination therapy and who were on clinical trials. Approval was obtained from the Northern Light Eastern Maine Medical Center institutional review board. We conducted a detailed chart review analysis of each patient in the study and identified the patients who developed irAEs.

We identified patients with preexisting AIDs, excluding those with preexisting autoimmune thyroid disease who received ICIs and developed a disease flare. Demographic data, including age, sex, cancer type and stage, history of preexisting AIDs, labs, imaging, and treatment, were all obtained through chart review.

Results

We included 465 patients who received ICIs, 298 received nivolumab; 121, pembrolizumab; 26, atezolizumab; and 20, durvalumab. 55% were male and 45% female. IrAEs were observed in 115 (25%) patients. Preexisting AIDs and flares were detected in 47 and 12 patients, respectively. Overall, 148 (32% of 465) irAEs were observed, as some patients had multiple toxicities. Nivolumab was administered either every 2 or 4 weeks, pembrolizumab and atezolizumab were administered every 3 weeks, and durvalumab was administered every 2 weeks. The average age of patients who developed irAEs was 65 years. Majority (56%) were treated for lung cancer, followed by melanoma and genitourinary

Table 1 Details of underlying malignancies in treated patients

Underlying cancer in treated patients who developed irAEs	Patients receiving nivolumab	Patients receiving pembrolizumab	Patients receiving durvalumab	Patients receiving atezolizumab
NSCLC[a]	34	15	7	2
Melanoma	20	0	0	0
Genitourinary cancers	12	2	0	3
Gastrointestinal cancers	6	2	0	0
Small-cell lung cancer	6	0	0	0
Head and neck cancers	3	1	0	0
Hodgkin's Lymphoma	1	0	0	0
Adeno carcinoma of unknown primary	1	0	0	0

[a]Non-small-cell lung cancer

cancers (see Table 1 for full details). Gastrointestinal (GI) irAEs were the most common (35%), followed by endocrine (25%) and pulmonary irAEs (20%). The most common irAE requiring permanent discontinuation of treatment and hospitalization was pneumonitis, followed by GI irAEs. Treatment was permanently discontinued in 57 patients (50% of 115) and held in 30 (26% of 115) due to initial irAEs. Upon rechallenge in 27 patients in whom treatment was held, 18 tolerated the drug well, and the remaining 9 did not. In 12 patients who had AID flares, 5 required permanent discontinuation of the drug. Overall treatment was permanently discontinued in 71 patients (15% of 465), including those who did not tolerate rechallenge and had flares of preexisting AIDs (see Table 2 for irAEs per system).

Individual systems with irAEs

Gastrointestinal (GI) irAEs were the most common irAEs observed in our study population. In total, 40 of 115 patients (35%) developed GI irAEs. Of these 30 patients received nivolumab, 17 had immune-mediated colitis; 11, immune-mediated hepatitis; and 2, immune-mediated pancreatitis. In the six pembrolizumab recipients, five developed immune-mediated colitis and one had immune-mediated hepatitis. One patient each in the atezolizumab and durvalumab groups developed immune-mediated colitis. The average development time of these irAEs was 20 weeks.

Immune-mediated colitis was seen in 24 patients (17 receiving nivolumab; 5, pembrolizumab; 1, atezolizumab; and 1, durvalumab), of which 14 were high grade and 10 were low grade. Treatment was discontinued in 13 and held in 7 patients for 8 weeks on average due to colitis severity. In patients whose treatment was held, on rechallenge with the same drug and dose, five tolerated well and two did not. Patients with severe symptoms required infliximab and intravenous steroids, but most were treated with oral prednisone, budesonide, and anti-diarrheal medication, which improved symptoms. Immune-mediated hepatitis was observed in 13 patients (11 receiving nivolumab; 1, pembrolizumab; and 1durvalumab), of which 5 were high grade and 8 were low grade. The drug was permanently discontinued in seven patients due to hepatitis severity. Treatment was held in five patients for 9 weeks on average, four of whom tolerated the rechallenge with the same drug and dose. The treatment was with systemic steroids. Immune-mediated pancreatitis was observed in two patients. Drug treatment was permanently discontinued in one and held in the other for 28 weeks; following rechallenge with the same drug and dose, it was well tolerated.

Endocrine irAEs were the second most common in our patient population, occurring in 29 of 115 patients (25%). Of these patients, 16 received nivolumab; 9, pembrolizumab; 3, durvalumab; and 1, atezolizumab. Immune-mediated primary thyroid disorders were the most common, followed by primary adrenal insufficiency, immune-mediated diabetes, hypopituitarism, hypophysitis, and hypogonadism. In total, 20 patients developed new-onset immune-mediated hypothyroidism with an average development time of 18 weeks. Treatment was discontinued in 1 patient due to preference and held in another for 1 week; in the remaining 18, the drug was continued without interruption. Treatment was with levothyroxine, which improved the symptoms.

Table 2 The number of patients with irAEs by system, grade, time of onset of irAEs, and held or discontinued treatment

Type of irAE[a]	Number and percentage ($n=465$)	High grade (grade 3–4)	Low grade (grade 1–2)	Time of onset (weeks)	Treatment discontinued	Treatment Held
Gastrointestinal	40 (9%)	20	20	20.5	16	12
Endocrine	29 (6%)	Not graded		26.2	3	4
Pneumonitis	23 (5%)	14	9	21	17	3
Dermatological	19 (4%)	12	7	25	8	4
Rheumatological and musculoskeletal	11 (2.4%)	6	6	17	5	3
CNS[b]	6 (1.3%)	3	1	8.5	3	1
CVS[c]	2 (<1%)	2	0	6.5	2	0
Nephritis	2 (<1%)	0	2	23	1	1
Hematological	2 (<1%)	1	1	54	1	0
Uveitis	2 (<1%)	1	1	2	1	1
Autoimmune flares	12 (2.6%)	7	5	3–18	5	2

[a]Immune-related adverse event

[b]Central nervous system

[c]Cardiovascular system

Immune-mediated primary adrenal insufficiency developed in four patients, three received nivolumab, whereas the fourth received atezolizumab. Treatment was discontinued in one patient, continued without interruption in one, and held in two patients. On average, the treatment was held for 2 weeks and was tolerated well upon rechallenge with the same drug and dose. Treatment was with hydrocortisone, which improved the symptoms. Pan-hypopituitarism developed in one patient, requiring permanent discontinuation of nivolumab as well as long-term hormone replacement therapy. Hypophysitis developed in one patient on nivolumab after 28 weeks of treatment, resulting in permanent discontinuation of the drug and long-term prednisone use. Two patients on pembrolizumab developed autoimmune diabetes, one of whom required hospitalization due to diabetic ketoacidosis (DKA) requiring long-term insulin. Treatment was held for 8 weeks and tolerated well upon rechallenge with the same drug and dose. All patients were referred to an endocrinologist.

Pulmonary*:* Checkpoint inhibitor pneumonitis (CIP) was the most common irAE in our study population, requiring hospitalization and permanent drug discontinuation. In total, 23 of 115 patients (20%) developed CIP, 14 were high grade and 9 were low grade. Of these 23 patients, 19 were nivolumab recipients, 2 received pembrolizumab and 1 each received atezolizumab and durvalumab. In the 19 patients who received nivolumab Eight and 11 patients were on 4- and 2-week-cycle regimens, respectively. The average time of CIP development in our patient population was 22 weeks. Non-small-cell lung cancer (NSCLC; 48%) was the most common underlying cancer, followed by small-cell lung cancer (22%). Moreover, 5 of the 23 patients (22%) had underlying chronic obstructive pulmonary disease.

Treatment was permanently discontinued in all 14 patients with high-grade CIP, and hospitalization was required in all. Four patients were admitted to the intensive care unit (ICU); one required intubation and the other three received high-flow oxygen, they were treated with intravenous steroids and infliximab. Patients who did not require ICU treatment was administered oral prednisone. In the remaining nine patients, who developed low-grade immune-mediated pneumonitis, nivolumab was continued without interruption in one, permanently discontinued in four, and held in four for an average duration of 6 weeks. Upon rechallenge with the same drug and dose, three tolerated well; and the remaining patient did not with recurrence of CIP.

Dermatological irAEs were observed in 19 patients (16.5% of 115) 10 were high grade and 9 were low grade. The average time of irAE development was 25 weeks. Moreover, 13, 4, and 2 patients received nivolumab, pembrolizumab, and durvalumab, respectively. Treatment was permanently discontinued in 8 patients with high-grade side effects. In the remaining 2 patients, nivolumab was held for an average of 30 weeks; upon rechallenge with the same drug at a reduced dose, recurrence of high-grade irAEs occurred, necessitating permanent discontinuation of the drug. In patients with low-grade irAEs, treatment was discontinued in one patient due to preference and held in another for 4 weeks, who tolerated well upon rechallenge with the same drug and dose. The treatment was administered with systemic steroids.

Rheumatic irAE: We had 11 patients (9.5% of 115) that developed rheumatological irAEs. Nine received nivolumab, one each received pembrolizumab and atezolizumab respectively. Average time to develop irAE is 15 weeks. Inflammatory arthritis was observed in 3 Nivolumab recipients, treatment was permanently discontinued in 1, held in the other two for an average of 3 weeks. Recurrence of high-grade inflammatory arthritis necessitated permanent discontinuation of drug in one and the other patient tolerated the rechallange well with same dose of Nivolumab. Six developed myalgias and arthralgias, 4 were Nivolumab recipients and 1 each received Pembrolizumab and Atezolizumab. Drug was permanently discontinued in 2 out of 4 patients who received nivolumab and in those received pembrolizumab and atezolizumab due to high grade irAE. Sjogren's was diagnosed in one patient on Nivolumab based on the symptoms and serological testing (anti Ro/SSA and ANA positive, in the setting of history of rheumatoid arthritis) treated with steroid rinses and artificial saliva, the remaining patient on nivolumab developed sicca syndrome. Most patients were referred to rheumatologist and were treated with oral steroids, which improved the symptoms.

Neurological: Six patients (5%) developed immune-related neurological side effects: five received nivolumab, and one was on pembrolizumab. Among nivolumab recipients, two developed Lambert-Eaton myasthenic syndrome, one had a flare of underlying multiple sclerosis, one developed optic neuritis, and one developed immune cervical radiculopathy. The patient on pembrolizumab developed Guillain-Barré syndrome. The average duration to develop neurological irAEs was 8 weeks. The drug was discontinued in five patients; for the patient with immune-mediated cervical radiculopathy, the drug was held for 4 weeks followed by rechallenge at the same dose, which was well tolerated. Treatment consisted of steroids and/or intravenous immunoglobulins (IVIG).

Other irAEs: Two patients had cardiac irAEs. One patient on pembrolizumab developed myocarditis at 3 weeks, and the other, who received durvalumab, developed cardiomyopathy at 10 weeks. The drug was permanently discontinued in both, which improved the symptoms. Both were seen by a cardiologist.

Hematological irAEs were observed in two patients on nivolumab, who experienced aplastic anemia and

immune-mediated thrombocytopenia. Drug treatment was permanently discontinued in the former patient and continued without interruption in the latter.

Immune-mediated nephritis was seen in two patients; one received nivolumab, and the other, atezolizumab. Atezolizumab was permanently discontinued in one patient; for the patient receiving nivolumab, treatment was held for 4 weeks and tolerated well upon rechallenge with the same dose.

Uveitis developed in two patients on nivolumab within 2 weeks upon initiating drug treatment. One required permanent discontinuation; and in the other, the drug was held for 2 weeks and was well tolerated upon rechallenge at the same dose. Both patients were seen by an ophthalmologist and treated with oral prednisone.

Flare-up of preexisting AIDs: We had 47 patients with preexisting AIDs; 26 received nivolumab, and 21 received pembrolizumab. A total of 17 (out of 47, 36%), 10 pembrolizumab recipients and 7 nivolumab recipients were on immunosuppression for preexisting AID. 3 were on Methotrexate only, 2 were on Plaquenil only, 3 were on prednisone only, 1 was on Methotrexate and Rituximab, 1 was on Methotrexate, Rituximab and Prednisone, 2 were on Budesonide, 1 was on Sulfasalazine, 1 was on Secukinumab, 2 were on topical steroids, 1 was on Belatacept and Prednisone for kidney transplant. Over all 5 (out of 17 29%) were on prednisone and 5 (out of 17 29%) were on methotrexate. We excluded patients with preexisting thyroid AIDs. Majority were females. The average age was 62 years. The most common preexisting AIDs in our patient population were rheumatoid arthritis (RA), psoriasis and psoriatic arthritis (PA), inflammatory bowel disease (IBD), sarcoidosis, and systemic lupus erythematosus (see Table 3 for a full list of the preexisting). The most commonly treated malignancies were Lung cancer (53%), followed by melanoma (20%).

Table 3 Shows the type of underlying autoimmune disorder and no of patients with the specific preexisting AID

Preexisting auto immune disorder (AID)	Number and % of patients (total 47)
Rheumatoid Arthritis	12 (25%)
Psoriasis and Psoriatric arthritis	10 (21%)
IBD[a]	5 (11%)
Sarcoid	4 (8.5%)
SLE[b]	3 (6%)
Sjogren's	2
Lichen planus	2
Raynaud's	2
Multiple sclerosis	2
Wegener's	1
Uveitis	1
Ankylosing spondylitis	1
Polymyalgia Rheumatica	1
Kidney transplant on immunosuppression	1

[a]Inflammatory bowel disease

[b]Systemic lupus erythematosus

Overall, 12 patients (26% of 47) developed flares of preexisting AIDs, as follows: three RA, two PA, two lichen planus, two IBD, one multiple sclerosis, one uveitis, and one polymyalgia rheumatica. Of these 12 patients, treatment was permanently discontinued in five, continued without interruption for five, and held in two patients for 6 weeks and 8 months, respectively, who tolerated well upon rechallenge with the same drug and dose to complete the course. The majority of patients (81%) developed a flare within the first 3 cycles (6–18 weeks) of treatment initiation. Hospital admission was required for three patients due to the severity of the symptoms. Most patients were treated with systemic steroids, which improved the symptoms.

In patients who were on immunosuppression 3 out of 10 pembrolizumab recipients developed flares one had flare up of ulcerative colitis, one had flare of crohns disease, both required permanent discontinuation of treatment and other patient developed flare of Psoriasis which resolved with prednisone and tolerated pembrolizumab well. In nivolumab recipients, 2 out of 7 developed flares of preexisting AID. One had flare up of RA and other had flare up of Lichen planus, both were treated with steroids and tolerated nivolumab well. All these were flares of preexisting AID, not new irAEs. See Table 4 for further details.

Delayed immune-related adverse events (DIREs): Three patients developed DIREs, all of whom were on nivolumab (see Table 5 for full details). The average development time of DIREs was 5.5 months.

Discussion

ICIs are associated with a broad spectrum of irAEs affecting different systems of the body. The incidence of irAEs of any grade reported in large clinical trials is 50–80%, and high-grade irAEs constitute 15–20% (Chuzi et al. 2017). The most common irAEs associated with ICIs reported in clinical trials are GI (colitis, diarrhea), dermatological (rash, pruritis), and endocrine (hypo and hyperthyroidism) (Robert et al. 2015; Borghaei et al. 2015; Herbst et al. 2016; Eggermont et al. 2018; Rittmeyer et al. 2017; Garassino et al. 2018). The incidence of irAEs is higher with combination therapy than with monotherapy alone (Motzer et al. 2018; Hellmann et al. 2018; Wolchok et al. 2017). In general, the onset of irAEs occurs quite early, mostly within weeks to 3 months after initiating ICI treatment; it is sometimes delayed up to 1 year after treatment initiation, especially for pulmonary and hepatic toxicities (Remon et al. 2018). The incidence of

Table 4 List of patients who were on immunosuppression at the time of initiation of ICI

Preexisting AID	Immunosuppressant medication patients on	ICI	Developed flare yes/no	ICI discontinued yes/no	Rx of flare
Rheumatoid Arthritis	Methotrexate	Pembrolizumab	No	No	
Rheumatoid Arthritis	Methotrexate	Pembrolizumab	No	No	
Rheumatoid Arthritis	Methotrexate + Rituximab + prednisone	Pembrolizumab	No	No	
Rheumatoid Arthritis	Methotrexate + Plaquenil	Nivolumab	No	No	
Rheumatoid Arthritis	Plaquenil	Nivolumab	No	No	
Rheumatoid Arthritis	prednisone	Nivolumab	Yes	NO	High dose prednisone + Intra lesion steroid injection
Rheumatoid Arthritis	prednisone	Nivolumab	No	No	
Ulcerative colitis	Budesonide	Pembrolizumab	Yes	YES	IV solumedrol
Chrons Disease	Sulfasalazine	Pembrolizumab	YES	YES	Iv solumedrol
Ulcerative colitis	Budesonide	Nivolumab	No	No	
Sjogrens syndrome	Methotrexate + rituximab	Pembrolizumab	No	No	
Psoriatic arthritis	Secukinumab	Pembrolizumab	No	No	
Psoriasis	Topical steroid Clobetasone	Pembrolizumab	Yes	No	Prednisone
Psoriasis	Topical steroid Triamcinolone	Pembrolizumab	No	No	
Lichen planus	Topical steroid clobetasone	Nivolumab	Yes	No	Prednisone
Discoid lupus	Plaquenil	Pembrolizumab	No	No	
Kidney transplant	Belatacept + prednisone	Nivolumab	No	No	

Table includes the underlying AID, immunosuppressive medication the patients are on, type of ICI received, treatment received for flare

Table 5 Shows–hospital admissions and ICU admissions due to irAEs

irAE due to ICIs	Number of patients required hospital admission	Number of patients required ICU[a] admission	IRAE treatment	Outcome
Pneumonitis	14	4	Prednisone oral for non-ICU, IV solumedrol and Infliximab for ICU	3 out of 4 patients requiring ICU died. Remaining had improved
Colitis	5	1	Solumedrol and Infliximab for patients requiring ICU admission, prednisone for non-ICU	All patients improved with the IRAE treatment
Hepatitis	2	0	Prednisone	Improved
Pancreatitis	1	0	Prednisone	Improved
Bullous pemphigoid	1	0	Prednisone	Improved
Diabetic ketoacidosis	1	1	IV insulin for rx of DKA	Improved
Adrenal Insufficiency	1	0		
Pan hypopituitarism	1	0		
Guillain–Barre syndrome	1	0	IVIG and long-term oral prednisone	Improved
Multiple sclerosis flare	1	0	High dose IV solumedrol	Improved
Myocarditis	1	0	Conservative management, ICI were discontinued	
Lambert Eaton myasthenic syndrome	1	0		
Cardiomyopathy	1	0	ICI discontinuation	Improved
Aplastic anemia	1	0	ICI discontinuation	Improved

[a]Intensive care unit

irAEs is higher in older patients (> 65 years) (Sattar et al. 2019; Muchnik et al. 2019). The pathophysiology of irAEs is not well understood; they are hypothesized to involve upregulation of the immune system and activation of T cells, leading to the production of proinflammatory cytokines that potentiate inflammation and autoimmunity (Calabrese and Velcheti 2017; Euw et al. 2009; Uemura et al. 2016). NCCN, ASCO, ESMO and SITC (Thompson et al. 2019; Brahmer et al. 2018; Haanen et al. 2018; Puzanov et al. 2017) has laid out guidelines regarding grading and management of irAEs.

In our study, we present real-world data on irAEs occurring due to the PD1/PDL1 inhibitors nivolumab, pembrolizumab, atezolizumab, and durvalumab in our patient population treated at a tertiary care center in rural Maine with particular focus on hospital admissions, tolerability of ICIs in patients with underlying AIDs, DIREs, and rechallenge.

Hospital Admissions: The literature offers limited data regarding hospitalizations due to irAEs from ICIs. Most irAEs were managed on an outpatient basis, but some required hospitalization in view of their severity. One study showed that 41% of patients on ICIs were admitted to the hospital for suspected irAEs, and 23% had confirmed irAEs (Balaji et al. 2019). Another study showed that 11% of patients receiving ICIs required hospital admission due to irAEs (Ahern et al. 2020). In our study of the 115 patients who developed irAEs, 34 required hospital admission, of which CIP was the most common cause, followed by colitis; 14 of the 23 patients (61%) with CIP required hospitalization (see Table 6 for full list of irAEs requiring hospitalization). ICU level of care was required for five patients (four for CIP and one due to colitis). Of the four patients with CIP requiring ICU admission, three succumbed to the disease. Overall, most patients requiring hospital admission improved with discontinuation of the drug and administration of systemic steroids. Some patients required infliximab, IVIG, and long-term immunosuppressive agents. The incidence of CIP in our patient population was 5% (23 out of 465), which is similar to the incidence of pneumonitis in clinical trials (Brahmer et al. 2015; Motzer et al. 2015; Khoja et al. 2017). Overall, 7% (34 out of 465) of patients who received ICIs required hospital admission in our study.

Data regarding preexisting AID flares due to ICIs are limited, their incidence is largely unknown. Consequently, the lack of knowledge regarding the safety of ICIs in these patients poses a major challenge. A systematic review of 123 patients showed a 50% incidence of preexisting AID flares. RA and PA flares were the most common and were more likely to occur with anti-PD1/PDL1 inhibitors than with anti-CTLA4 antibodies (Abdel-Wahab et al. 2018; Gutzmer et al. 2017). Two retrospective studies have evaluated the toxicities of ICIs in patients with advanced-stage melanoma and a history of AIDs (Johnson et al. 2016; Menzies et al. 2017), indicating that the use of ICIs in these patients is generally safe. Another retrospective study in 2018 evaluated the safety of PD1 inhibitors in patients with NSCLC with underlying AIDs and revealed that patients who were symptomatic due to underlying AIDs at the time of treatment initiation were significantly at higher risk of developing flares compared to those who were initially asymptomatic. The flares were mild and manageable without discontinuation of the drug (Leonardi et al. 2018). A study from Italy also showed that these patients are increased risk for low grade irAEs and anti PD1 ICI are usually well tolerated in cancer patients with preexisting AID (Cortellini et al. 2019). Initiation of ICI in patients with preexisting AID can be considered if the underlying AID is under good control and if the patient is on no or low level of immunosuppression and to be avoided in patients with underlying poor control of the AID or requiring high doses of immunosuppressants, those with life threatening AID and neurologic or neuromuscular AID (Kennedy et al. 2019). Another approach is a personalized two step risk-based prevention strategy, first to lower the risk of compromising ICI efficacy before their initiation, nonselective immunosuppressants could be replaced by specific selective immunosuppressant drugs and subsequently combining ICI with the selective immunosuppressant to prevent flare of AID (Haanen et al. 2020).

In our study population, 47 patients (10% of 465) had preexisting AIDs. The average patient age was 61 years. Almost half of the patients had RA, psoriasis, and PA. Flares of preexisting AIDs were observed in only 26% of our patients with underlying AIDs. Treatment discontinuation was required in only 5 (10.6% of 47). Most flares subsided with discontinuation of the drug and systemic steroids. In patients who were on immunosuppressants for preexisting AID 5 out of 17 (29%) developed flare and others tolerated

Table 6 Delayed immune related adverse event

	Age in years	Gender	Underlying Primary cancer	Treatment	Type of DIRE*	Time to develop DIRE* (in months after completion of ICI (months)
1	66	Female	Melanoma	Nivolumab	Colitis	3
2	72	Male	Melanoma	Nivolumab	Hypogonadism	8
3	72	Male	Melanoma	Nivolumab	Temporal arteritis	8

*Delayed immune related adverse events

Table 7 Shows data on rechallange with ICI

	Age in years	Sex	Underlying malignancy	Treatment (rx)	Initial irAE due to which ICI are held	Time to develop initial irAE (in weeks)	Treatment held (in weeks)	Rechallenged	Tolerated rx Yes/no	Recurrence of iRAEs Y/N and type of irAE recurrence
1	57	M	NSCLC	Nivolumab 4 wk regimen	Dermatitis grade 3	108	12	Yes with 2 wk regimen	No–1 cy	Yes–high grade rash
2	64	M	NSCLC	Nivolumab 2 wk regimen	Hepatitis and Pancreatitis both grade 2	28	25	Yes – 2wk regimen	Yes	No
3	49	M	NSCLC	Nivolumab 2wk regimen	Colitis grade 3	154	14	Yes–2wk regimen	Yes	No
4	57	F	NSCLC	Nivolumab 2wk regimen	Dermatitis grade 2	10	4	Yes–2wk regimen	Yes	No
5	68	F	NSCLC	Nivolumab 2wk regimen	Rash grade 3	10	52	Yes–at 4 wk regimen	No–2 cy	Yes–high grade rash
6	64	M	NSCLC	Nivolumab 2wk regimen	Hepatitis grade 2	12	8	Yes–at 2wk regimen	Yes	Yes–Low grade pneumonitis
7	76	M	Small cell lung ca	Nivolumab 4wk regimen	Pneumonitis grade 2	16	5	Yes–at 2wk regimen	No–1cy	Yes–high grade Pneumonitis
8	69	F	Melanoma	Nivolumab 4wk regimen	Hepatitis grade 2	54	4	Yes–at 4wk regimen	No–1cy	Yes–aplastic anemia
9	71	F	Renal cell cancer	Nivolumab 2wk regimen	Pneumonitis grade 2	8	2	Yes–at 2wk regimen	Yes	No
10	60	M	RCC	Nivolumab 4wk regimen	Inflammatory arthritis grade 3	32	4	Yes- at 2wk regimen	No–1cy	Yes–arthritis
11	66	M	NSCLC	Nivolumab 4wk regimen	Colitis grade 2	18	4	Yes–at 4wk regimen	Yes	No
12	51	M	RCC	Nivolumab 2wk regimen	Seropositive Rheumatoid Arthritis grade 3	8	2	Yes–at 2wk regimen	Yes	No
13	74	F	RCC	Nivolumab 2wk regimen	Hepatitis grade 2	18	2	Yes–at 2wk regimen	Yes	No
14	59	F	Small cell Lung ca	Nivolumab 4wk regimen	Pneumonitis grade 2	80	10	Yes–at 4wk regimen	Yes	No
15	45	M	RCC	Nivolumab 2wk regimen	Nephritis grade 2	10	4	Yes–at 2 wk regimen	No–4cy	Yes–high grade nephritis
16	56	M	Anaplastic thyroid ca	Nivolumab 4wk regimen	Colitis grade 3	40	10	Yes–at 2 wk regimen	Yes	No
17	71	M	Melanoma	Nivolumab 2wk regimen	Adrenal Insufficiency	12	1	Yes–at 2wk regimen	Yes	No
18	55	M	Small cell lung ca	Nivolumab 2wk regimen	Pneumonitis grade 2	8	6	Yes–at 2wk regimen	Yes	No
19	54	F	Melanoma	Nivolumab 2wk regimen	Radiculopathy	20	4	Yes–at 2wk regimen	Yes	No

Table 7 (continued)

	Age in years	Sex	Underlying malignancy	Treatment (rx)	Initial irAE due to which ICI are held	Time to develop initial irAE (in weeks)	Treatment held (in weeks)	Rechallenged	Tolerated rx Yes/no	Recurrence of iRAEs Y/N and type of irAE recurrence
20	56	M	Melanoma	Nivolumab 2wk regimen	Arthralgias grade 2	32	2	Yes–at 2wk regimen	Yes	NO
21	59	F	Melanoma	Nivolumab 2wk regimen	Uveitis	2	2	Yes–at 2wk regimen	yes	NO
22	71	M	NSCLC	Pembrolizumab	Colitis grade 2	15	8	Yes–at same dose	No–1cy	Yes–high grade colitis
23	70	F	NSCLC	Pembrolizumab	Colitis grade 3	27	3	Yes–at same dose	Yes	Yes–low grade colitis
24	63	F	NSCLC	Pembrolizumab	Thyroiditis	15	1	Yes–at same dose	Yes	No
25	57	F	Thymic ca	Pembrolizumab	Autoimmune diabetes	30	6	Yes–at same dose	Yes	No
26	56	F	NSCLC	Durvalumab	Hepatitis grade 2	6	8	Yes–at same dose	Yes	No
27	49	M	NSCLC	Atezolizumab	Adrenal Insufficiency	27	2	Yes–at same dose	Yes	No

NSCLC non small cell Lung cancer, *RCC* renal cell cancer

the immunotherapy well, treatment had to be permanently discontinued in 2 out of 5 who developed flare and in the remaining 3 treatment was continued without interruption. Overall, in our study, ICI treatment was well tolerated by our patients with preexisting AIDs.

DIREs comprise an emerging spectrum of irAEs due to ICIs, which has not been defined in large clinical trials. The exact incidence of DIREs is unknown. DIREs are defined as new irAEs manifesting ≥ 90 days after discontinuation of immunotherapy (Abdel-Wahab et al. 2018) and can occur up to 2 years after completing the treatment. A literature review identified 23 DIRE cases in the largest known study of DIREs so far, which showed that the median off-treatment interval time for the development of DIREs was 6 months (Couey et al. 2019); which was similar to that reported in our study (5.5 months).

ICI Rechallenge: Early recognition and prompt treatment are vital for managing irAEs due to Immunotherapy. Current guidelines focus on decisions about holding or discontinuing therapy as well as the use of immunosuppressants to treat irAEs. The recommendation is to permanently discontinue ICI therapy for grade 3 or grade 4 irAEs (Thompson et al. 2019; Brahmer et al. 2018; Haanen et al. 2018; Puzanov et al. 2017). Currently, there is little data on rechallenge following improvement from an irAE, which is a frequent clinical scenario. Available data regarding rechallenge with ICIs from studies on NSCLC, renal cell cancer, melanoma, lymphoma, and solid tumors indicated that 40–50% of patients developed irAEs upon rechallenge, including recurrence of the initial irAE or the occurrence of a new, different irAE (Pollack et al. 2018; Niki et al. 2018; Giaj et al. 2020; Santini et al. 2018; Simonaggio et al. 2019; Abou et al. 2020). Most irAEs occurred early in the course after rechallenge, majority were low-grade and can be managed with standard treatment algorithms. Thus, resuming ICI`s can be considered in selected patients with close monitoring. In our study, treatment was held in 30 patients due to irAEs, most of whom received nivolumab (see Table 7 for full details). ICIs were held for an average of 8 weeks. On rechallenge with the same drug in 27 patients, 18 (67%) tolerated well, and the remaining 9 did not. Most patients who did not tolerate the rechallenge had recurrence of the initial irAE (7 out of 9, 78%), and two had a new, distinct irAE.

Of the 27 patients who were rechallenged, 21 were in nivolumab group, 16 were resumed on their previous regimen (same dose and interval), while in the remaining 5 the regimen was adjusted (4 patients changed from a 4-week to a 2-week regimen, and in 1 changed from 2-week to 4-week regimen). 16 of the 21 patients tolerated the rechallenge well. Changes in drug dosages did not affect tolerability, as four of five patients (80%) did not tolerate the drug following the dose change (i.e., they had recurrence of the initial

irAE). Rechallenge with the same dose was tolerated well in the pembrolizumab, atezolizumab, and durvalumab groups.

In the subgroup of patients who were rechallenged, 7 (out of 27, 26%) had grade 3 initial irAE and 20 (out of 27, 74%) had grade 2 that necessitated immunotherapy to be held. We did not rechallange anyone with grade 4 irAE. In the 7 with grade 3 initial irAE recurrence was seen in 4 (out of 7, 57%), 3 were high-grade requiring permanent discontinuation of drug. Whereas in the 20 patients with low grade initial irAE recurrence was seen in 4 (out of 20, 20%), 3 were high-grade requiring permanent discontinuation of drug. Overall, rechallenges were tolerated well by majority of our study population.

Our study has numerous strengths, as it was a highly comprehensive study with a detailed chart review, which provided information about various types of irAEs patients developed due to ICIs, including the effects on preexisting AIDs. We reported our data on DIREs, hospitalizations due to irAEs and rechallenge of ICI in patients who developed irAEs due to ICIs. This is real-world data was obtained from a community setting in rural Maine. However, there are certain limitations as well, this is a retrospective study in nature and included data from a single.

Center, there is no control group, no randomization, no external validation, no standardized management as there was variability in management of irAE and further monitoring & clinical practice. Moreover, we only included patients on PD1/PDL1 inhibitors and not anti-CTLA4 inhibitors. Some patients were noted to have mild symptoms that were not documented as irAEs and were never referred to specialists. Additionally, patients may not have reported mild symptoms, such as self-limiting diarrhea, rash, arthralgias, and soon. Thus, it is possible that irAEs were underreported in our study.

Conclusion

Due to the increased use of ICIs, clinicians are challenged with both common and uncommon irAEs such as flares of preexisting AIDs and DIREs. Our study showed that ICIs are generally well tolerated and can be used safely even in patients with preexisting AIDs. Most irAEs can be managed on an outpatient basis with multidisciplinary efforts between oncologists and other specialists, especially if they are involved earlier in the course. Hospital admissions due to irAEs were required for 7% of patients. It is very encouraging to see that ICI rechallenges were tolerated by majority in our study population, which could be particularly important in patients with advanced cancer and limited therapeutic options apart from ICIs. It is important that these patients should be monitored closely, and early referral to specialists can help to manage irAEs and avoid hospital admissions in some cases. Moreover, appropriate awareness must be raised among clinicians for early diagnosis and effective management strategies. Further research is necessary to identify the risk factors that increase patient susceptibility to developing irAEs and to develop strategies for prevention, early detection, and effective management.

Declarations

Conflict of interest None.

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