Infusion-related Reactions with Nivolumab and Pembrolizumab: A Case Series Analysis

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BACKGROUND

- Infusion-related reactions with immune-checkpoint inhibitors (ICI) are uncommon, with an incidence of ~6% and ~1.5% in clinical trials for nivolumab and pembrolizumab, respectively.[1,2] Incidences of severe reactions are reported in <1% of patients.
- Most ICI-related infusion reactions are mild and occur during the second or third administration of the ICI.[3,4]
- A retrospective study demonstrated similar frequencies of infusion-related reactions when nivolumab was infused over 30 minutes versus over 60 minutes.[5] Early phase studies with pembrolizumab supported the safety of a 30-minute infusion.[6]
- The University of Kansas Health System (TUKHS) has five infusion centers and administers ICI therapy to ~1,675 patients annually.
- With expanding indications and expected new drug approvals, we anticipate more patients will receive ICI therapy in the future, and, therefore, we may see ICI-related infusion reactions more frequently.

OBJECTIVE

- To analyze reported cases of infusion-related reactions with pembrolizumab and nivolumab

METHODS

- We identified patients who experienced an infusion-related reaction to nivolumab or pembrolizumab by reviewing safety events submitted between January 1, 2021, and January 1, 2023.
- Demographic and clinical information were collected through retrospective chart review, including cancer type, line of therapy, type of ICI, the dose of ICI, cycle length, and cycle number.
- Progress notes and medication administration records were reviewed to document the administration time of the ICI, types of infusion-related reactions, reaction onset and resolution time, and medications administered.
- US National Cancer Institute (NCI) Common Terminology Criteria of Adverse Events version 5 (CTCAE v5) was used to grade infusion-related reactions and allergic reactions
- Data regarding infusion-related reactions for the cycle following the cycle of the first infusion-related reaction were collected, including the addition of premedications, the extension of administration time, and whether the patient reacted again.
- Demographic information was summarized using descriptive statistics. Nominal data were summarized using Chi-Square. Alpha was 0.05.

RESULTS

- Over the two years, 1,968 patients received at least one dose of pembrolizumab (n=1297) or nivolumab (n=671) at one of the TUKHS infusion centers. Seventeen patients experienced an ICI-related infusion reaction—15 received nivolumab and 2 received pembrolizumab. As such, infusion-related reactions were 2.2% with nivolumab and 0.15% with pembrolizumab.
- Baseline characteristics are summarized in Table 1. The median age was 59 years (range 26-83). Nine patients were male and eight were female. Sixteen were White and one was Asian. Patients had melanoma (n=7), renal cell carcinoma (n=3), hepatocellular carcinoma (n=2), head and neck cancer (n=1), bladder cancer (n=1), colorectal cancer (n=1), mesothelioma (n=1), and cancer of unknown primary (n=1). Lines of therapy included neoadjuvant (n=1), adjuvant (n=6), and advanced/metastatic (n=10).
- Two patients (11.8%) received weight base dosing; fifteen (88.2%) received flat dosing. The median dose of nivolumab was 360 mg (range 240-480 mg), and the median dose of pembrolizumab was 300 mg (range 200-400 mg). All doses were given over 30 min.
- Twelve patients (70.6%) experienced the first infusion-related reaction during the second dose of ICI. The average time from starting therapy to the first infusion reaction was 43 days (range 0-251 days).

RESULTS (cont'd)

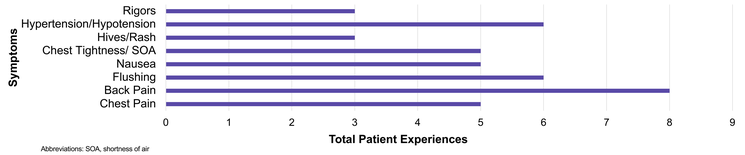
Table 1. Baseline Characteristics

Patient	Age (y)	Sex	Race	Malignancy	Line of Therapy	ICI	Additional Agent(s)	Dose of ICI Administered (mg)	Cycle Length (days)	Cycle and Day of 1st Infusion-Related Reaction
1	73	M	White	RCC	2L advanced	Nivolumab	-	480	28	C2D1
2	26	F	White	Melanoma	Adjuvant	Nivolumab	-	480	28	C1D1
3	83	M	White	HCC	2L advanced	Nivolumab	-	240	14	C2D1
4	59	M	White	Melanoma	Adjuvant	Nivolumab	-	480	28	C9D1
5	66	F	White	Melanoma	Adjuvant	Nivolumab	-	240	14	C2D1
6	51	M	White	Melanoma	1L advanced	Nivolumab	-	240	14	C3D1
7	81	F	White	HCC	Neoadjuvant	Nivolumab	-	240	14	C2D1
8	50	F	White	RCC	1L advanced	Nivolumab	Ipilimumab	284*	21	C2D1
9	53	F	White	Melanoma	Adjuvant	Nivolumab	-	480	28	C6D1
10	71	M	White	H&N	Adjuvant	Nivolumab	Radiation	240	14	C2D1
11	54	F	White	Malignant pleural mesothelioma	2L advanced	Nivolumab	Ipilimumab	360	42	C1D22
12	74	M	White	RCC	3L advanced	Nivolumab	Ipilimumab	300*	21	C2D1
13	52	M	White	Melanoma	1L advanced	Nivolumab	-	480	28	C2D1
14	55	M	White	Colorectal	3L advanced	Nivolumab	Regorafenib	480	28	C2D1
15	81	M	Asian	Bladder	Adjuvant	Nivolumab	-	480	28	C2D1
16	76	F	White	CUP	1L advanced	Pembrolizumab	Carboplatin, paclitaxel	200	21	C1D1
17	35	F	White	Melanoma	1L advanced	Pembrolizumab	-	400	42	C2D1

Abbreviations: 1L, first line; 2L, second line; 3L, third line; CUP, cancer of unknown primary; F, female; H&N, head and neck; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; M, male; RCC, renal cell carcinoma
*weight-based dosing

- All infusion-related reactions occurred during the infusion time. No delayed reactions occurred. All patients experienced multiple reaction symptoms (Figure 1), with back pain, flushing, and hypertension/hypotension being the most common. The severity of reactions was grade 1 (n=1), grade 2 (n=15), and grade 3 (n=1).

Figure 1. Symptoms of ICI-related Infusion Reactions



Abbreviations: SOA, shortness of air

- Infusions were paused for all patients after the reactions. All patients received at least one hypersensitivity medication, such as diphenhydramine, famotidine, methylprednisolone, and intravenous fluids. Four patients experienced rigors and were given meperidine. None were given epinephrine.

Table 2. Reaction Management (n=17)

Time from first dose to first infusion-related reaction, days (range)	28 (1-251)
Continued infusion after reaction, no. (%)	13 (76)
Discontinued infusion after reaction, no. (%)	4 (24)
Reaction medications given, no. (%)	
• Diphenhydramine	11 (65)
• Epinephrine	0
• Famotidine	13 (76)
• Intravenous fluids	14 (82)
• Meperidine	4 (24)
• Methylprednisolone	7 (41)
Continued original ICI therapy in subsequent cycles, no. (%)	14 (82)
If ICI therapy continued, changes made to future cycle(s), no. (%)	
• Premedications added	10 (71)
• Administration time extended	6 (42)
• Reduced ICI dose	0
• No changes	2 (14)

- Following the resolution of the infusion reaction, 13 patients resumed the infusion (Patient 2, Patient 3, Patient 4, and Patient 9 did not resume). Patient 1 resumed the infusion but experienced chest pain after restarting and the infusion was stopped.
- Two patients were hospitalized after the infusion-related reaction. Admission for Patient 7 could have been associated with the reaction, but admission for Patient 3 was unrelated. No patients died from the reaction.

- Fourteen patients continued therapy with the initial ICI. During the cycle following the cycle of the first infusion-related reaction, changes were made to the treatment plans for three patients. Ten patients had premedications added, and 6 had administration time extended. No dose changes were made. Two patients (Patient 3 and Patient 5) received subsequent treatment without any modifications, and neither experienced reactions with the subsequent doses.

RESULTS (cont'd)

- Five of the fourteen patients who continued ICI therapy reacted again despite modifying their subsequent plans. Four of these 5 patients reacted with the next dose but tolerated all future doses. Patient 11 did not receive future doses of nivolumab after reacting twice.
- Patient 1 changed from nivolumab to pembrolizumab and tolerated infusions without incidence. Patient 4 discontinued nivolumab because of disease progression, and Patient 16 stopped treatment because their cancer diagnosis changed from cancer of unknown primary to bladder cancer.
- Table 3 summarizes the Chi Squares of select variables.

Table 3. Chi Square of Select Variables

Variable 1	Variable 2	χ^2	p	Comments
Risk of infusion-related reaction				
Nivolumab	Pembrolizumab	22.3685	<0.001	Risk of infusion-related reaction was dependent on type of ICI received
White	Non-white	0.8033	0.37	Risk of infusion-related reaction was independent of race
Females	Males	0.0103	0.92	Risk of infusion-related reaction was independent of sex
Risk of subsequent infusion-related reaction				
Diphenhydramine added	Diphenhydramine not added	3.111	0.08	Risk of subsequent infusion-related reaction was independent of adding diphenhydramine to premedications
Famotidine added	Famotidine not added	2.8	0.09	Risk of subsequent infusion-related reaction was independent of adding famotidine to premedications
Administration time extended	Administration time not extended	0.0344	0.85	Risk of subsequent infusion-related reaction was independent of extending administration time
Critical value for all comparisons = 3.8415; alpha = 0.05				

DISCUSSION

- Infusion-related reactions occurred in 2.2% of patients that received nivolumab and 0.15% in patients who received pembrolizumab. Reactions were significantly higher with nivolumab.
- Most patients reacted during the second cycle of ICI. This is consistent with previous studies.
- There is no standard in the management of subsequent cycles for patients that previously reacted to an ICI. Prevention strategies such as adding premedications or extending the infusion time are provider- and patient-specific decisions. Based on our data, we cannot make concrete recommendations for preventing future reactions.
- None of the patients that experienced an infusion-related reaction to an ICI had lung cancer.
- Previous studies have seen a higher incidence of infusion-related reactions with higher ICI doses; however, our data do not support this correlation.
- When given with other agents, nivolumab and pembrolizumab are given first at our institutions. All patients who reacted tolerated the other treatments following the resolution of the ICI-related reaction.
- Weaknesses
  - Single center and retrospective
  - Data were collected from reported safety events. We cannot guarantee that all reactions were reported. Another option for data collection would be to run a report through the electronic medical record to identify patients with documented reactions in their charts. However, we found that 6 patients that experienced a reaction did not have documented reactions in their chart, so this method would not have identified all patients.
  - Pembrolizumab and nivolumab were the only ICIs evaluated. Other ICIs likely have different incidences of reactions.

CONCLUSIONS

- ICIs are associated with a low risk for infusion-related reactions. Between nivolumab and pembrolizumab, infusion-related reactions are more common with nivolumab.
- More studies are required to identify potential risk factors and best mitigation strategies.

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