Persistent immune-related adverse events after immune checkpoint inhibitor therapy

Cameron Giles[1], Carly Barron[2], Elaine McWhirter[3]
Faculty of Health Sciences, McMaster University[1], Department of Medicine, McMaster University[2], Department of Oncology, McMaster University[3]

Introduction

Treatment with immune checkpoint inhibitors (ICIs) leads to improved progression-free and overall survival in a number of cancers. However, the non-specific immune response induced by these agents may also lead to immune-related adverse events (irAEs).[1] There is emerging evidence, primarily in the form of case reports, describing persistent immunotherapy toxicities refractory to treatment with immunosuppressive/immunomodulating medications and/or withholding immunotherapy.[2,3] Thus, we have initiated a study to identify and characterize patients with persistent irAEs following treatment with ICIs.

Objectives and Methods

Study Design: Retrospective chart review of patients at the Juravinski Cancer Centre, Hamilton, ON

Objectives:

1. Identify patients who have experienced persistent toxicities after treatment with ICIs
2. Characterize the severity and duration of the irAEs
3. Understand the management approach to irAEs with immunosuppressive and/or immunomodulating medications
4. Identify serious adverse events related to the long-term toxicities of ICIs themselves or the therapies used to manage them

Population:

1. Adults with solid-organ cancer receiving ICI therapy
2. Developed irAE while on treatment or within 6 months of completing immunotherapy, which persisted for >6 months despite withholding treatment and/or initiating immunosuppressive/immunomodulating medications

Recruitment: Ongoing, 6 patients identified thus far

Results 1

Table 1. Baseline characteristics

Patient	Age	Sex	Cancer Type	Stage	Other/Previous Treatment
1	59	F	Pancreatic adenocarcinoma	IV	Gemcitabine, Nab-Paclitaxel (both concurrent with ICI therapy)
2	75	M	Melanoma	IV	None
3	76	F	Melanoma	IV	Interferon-Alpha, Vemurafenib
4	58	F	Lung adenocarcinoma	IV	Cisplatin, Pemetrexed, Docetaxel, Erlotinib, Afatinib
5	61	M	Melanoma	IIIC	None
6	67	F	Lung adenocarcinoma	IV	Cisplatin, Vinorelbine, Carboplatin, Gemcitabine, Maraba Virus-Vectored Vaccine (concurrent with ICI therapy)

Table 2. Checkpoint inhibitor and irAEs

Patient	Checkpoint Inhibitor	Doses to irAE	irAE (Grade)	irAE Duration (Days)	Time ICI Held (Days)
1	Tremilimumab, Durvalumab	3	Hepatitis (3)	432 (ongoing)	234 (discontinued)
2	Nivolumab	6	• Dermatitis (2/3) • Arthritis (3/4)	• 490 • 787 (ongoing)	56 (discontinued)
3	Ipilimumab, Nivolumab	3	Colitis (3)	851	108 (discontinued)
4	Nivolumab	3	Arthritis (2)	520	0 (discontinued)
5	Pembrolizumab	20	Peripheral neuropathy (3)	177 (ongoing)	68 (discontinued)
6	Pembrolizumab	3	• Mucositis (2) • Dermatitis (4)	• 292 • 397 (ongoing)	56 (discontinued)

Results 2

Table 3. irAE treatment with immunosuppressive/immunomodulating medications and associated morbidity/mortality

Patient	Immunosuppressant	Immunomodulator	Morbidity	Mortality
1	• Prednisone (13m, ongoing) • Methylprednisone (2wks)	Mycophenolate (12m, ongoing)	• Steroid-induced diabetes mellitus • Osteoporosis • Hepatic abscess	No
2	• Prednisone (9m) • Intra-articular methylprednisone (q3m for 12m, ongoing)	Sulfasalazine (2m)	Nausea/vomiting	No
3	• Prednisone (20m) • Methylprednisone (2 IV courses) • Budesonide (8m)	None	Non-disseminated herpes zoster	No
4	• Prednisone (8m) • Intra-articular cortisone (1 dose)	Hydroxychloroquine (8m)	Nausea	Yes*
5	Prednisone (3m, ongoing)	None	None	No
6	• Prednisone (13m, ongoing) • Topical clobetasol (3m, ongoing)	None	None	No

*Death not secondary to corticosteroid treatment

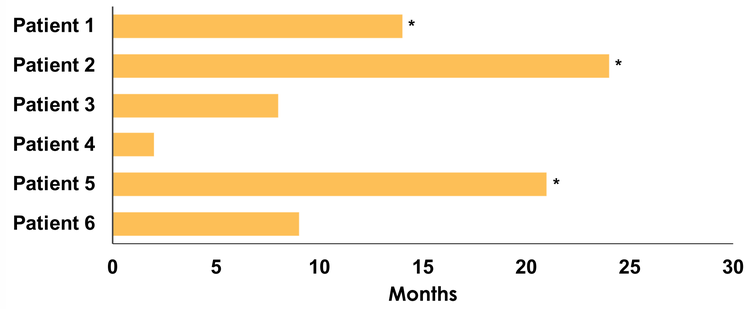

Figure 1. Progression-free survival in patients treated with ICIs who experienced persistent irAEs (* indicates no disease progression)

Conclusions

- **There is a subset of patients treated with ICIs who develop persistent irAEs (>6 months)**
- **ICI therapy had to be discontinued indefinitely in all patients with persistent irAEs**
- **Persistent irAEs may be refractory to or require prolonged courses of immunosuppressive/immunomodulating medications**
- **Majority of patients developed adverse side effects from medications used to treat irAEs**

Future Research

- Aim to identify patient factors and markers that will help predict patients at risk of irAEs – particularly persistent irAEs
- Compare patients that develop persistent irAEs versus patients with short-duration irAEs
- Plan is to expand this study to other centres in Canada and summarize the results in a national retrospective chart review

References

1. Esfahani K, Meti N, Miller Jr. WH, et al. Adverse events associated with immune checkpoint inhibitor treatment for cancer. *CMAJ* 2019;191:E40-6.
2. Iyoda T, Kurita N, Takada A, et al. Resolution of infliximab-refractory nivolumab-induced acute severe enterocolitis after cyclosporine treatment in a patient with non-small cell lung cancer. *Am J Case Rep* 2018;19:360-4.
3. De Jong C, Peters, BJM, Schramel FMNH. Recurrent episodes of nivolumab-induced pneumonitis after nivolumab discontinuation and the time course of carcinoembryonic antigen levels: a case of a 58-year-old woman with non-small cell lung cancer. *Chemotherapy* 2018; 63:272-7.