FEATURE

Delivering immuno-oncology therapies in the community oncology setting

Introduction of anti-PD-1 therapy into two community oncology programs

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ABSTRACT

The increasing availability and wide spectrum of anti-tumour activity shown by immune checkpoint inhibitors, such as the anti-programmed cell death 1 (anti-PD-1) and anti-PD-1 ligand (anti-PD-L1) monoclonal antibodies, has produced considerable excitement in the oncology community. While use of these immuno-oncology (IO) agents may be correlated with good tolerability compared to traditional cytotoxic chemotherapy, their administration may also be accompanied by a different and expanded spectrum of clinical toxicities known as immune-related adverse events (irAEs). Community oncology programs often do not have access to the variety of subspecialty backup available in tertiary cancer treatment centres, and may have other significant operational constraints, including relatively low numbers of personnel. This article details the process undertaken to allow for the successful introduction of these agents into 2 separate community cancer care programs.

INTRODUCTION

Over the past few years, the introduction of immune checkpoint inhibitors has changed the landscape of advanced cancer treatment.[1,2,3] Blockade with antibodies against cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) increases the immunologic reaction against tumour cells in a variety of cancer types. Current tumour site approvals for anti-PD-1 include advanced melanoma, non-small cell lung cancer, renal cell cancer, Hodgkin lymphoma and, for anti-PD-1 ligand (PD-L1), bladder cancer*.

While the use of these immuno-oncology (IO) agents may be associated with somewhat better tolerability compared to conventional cytotoxic chemotherapy, immune-related adverse events (irAEs) may also occur as a consequence of the impaired self-tolerance that results from a loss of T-cell inhibition.[1,2,3] Such adverse reactions can potentially involve every organ system, however dermatologic, gastrointestinal, hepatic and endocrine toxicities have typically predominated.[2,3] Severe autoimmune side effects, grade 3 or greater, may be experienced by approximately 10% of patients treated with anti-PD-1 PD-L1 therapy.[1,2,3] Provided irAEs are detected early and dealt with appropriately, they are typically manageable; if not recognized and acted on in a timely fashion, they can be serious and even fatal.[1,4,5] The clinical management of irAEs is relatively new to many oncologists, and a recent collaborative position paper outlined 5 pillars for immunotherapy toxicity management (see **Figure 1**).[6]

There has also, in recent years, been a major shift in the delivery of cancer care in most areas in Canada. The current emphasis on patient-centred care, and the aim to provide therapy closer to home, has meant that a significant number of treatments that were previously only delivered in tertiary centers are now being administered in smaller

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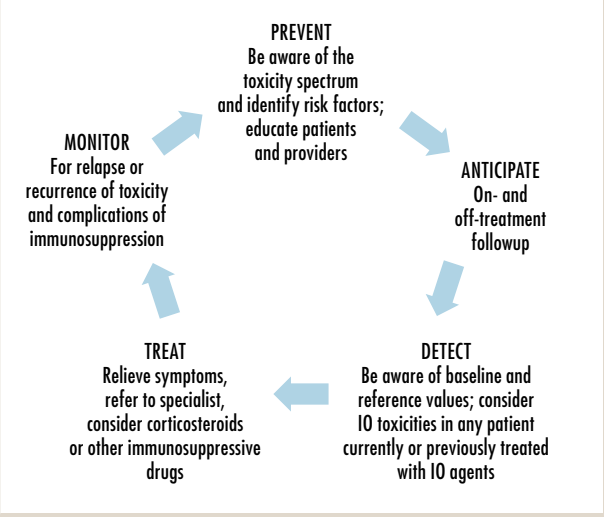
*Approved by the US Food and Drug Administration (FDA) but not by Health Canada. Two currently employed anti-PD-1 monoclonal antibodies are the agents nivolumab and pembrolizumab.[3,4,5]

FIGURE 1. Five pillars of immuno-oncology (IO) toxicity management



Adapted from Champiat S, Lambotte O, E. Barreau E. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Ann Oncol* 2016;27:559–74.

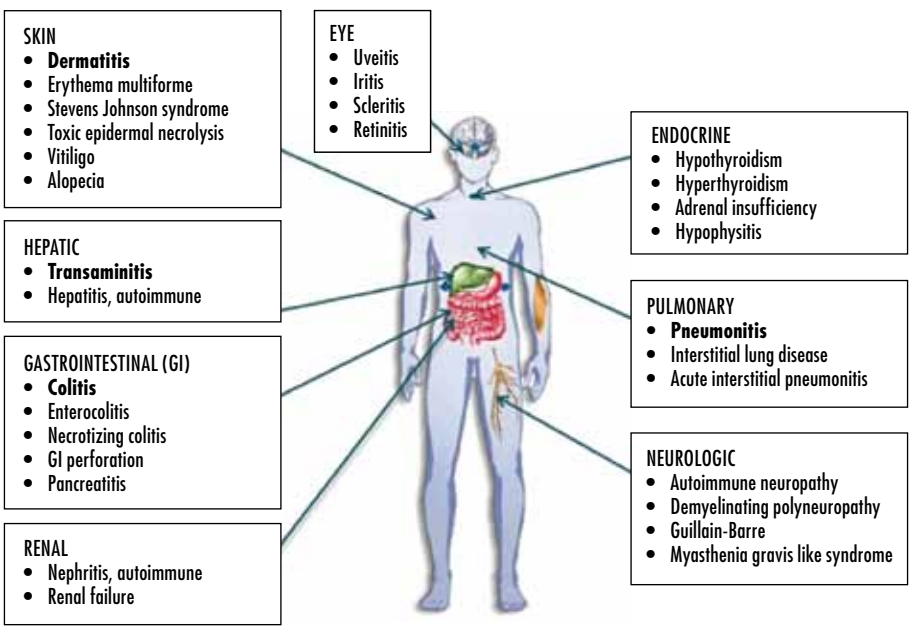
community-based cancer clinics. In some provincial jurisdictions, more than 50% of all cancer therapies are now delivered in the community setting.[7] Unfortunately, community cancer programs do not always have access to the subspecialty backup available in larger centres. Similarly, in the community setting, the point of first contact for cancer patients experiencing complications, especially on the weekends or after hours, may be a primary care physician, hospitalist or emergency room staff.[7]

The Jack Ady cancer program, which operates out of the Chinook Regional Hospital in Lethbridge Alberta, and the McMurtry and Baerg cancer program, which operates out of the Vernon Jubilee Hospital in Vernon, BC, are approximately the same size in terms of medical oncology staffing and patient population demographics. The clinic in Vernon first administered immunotherapy in 2012 with CTLA-4 monoclonal antibody therapy, and began providing anti-PD-1 monoclonal antibody therapy in late 2014. The immunotherapy program in Lethbridge was initiated in 2015. This paper describes the proactive approach undertaken in order to minimize complications in patients receiving IO therapies in these community settings.

SPECIFIC THERAPEUTIC CONCERNS WITH ANTI-PD-1 AGENTS

When an adverse event is noted with IO therapy, 3 scenarios must be considered: disease progression (the most common), a new complication unrelated to the disease or therapy, and finally, an irAE. **Figure 2** details some of the more common irAEs associated with use of the anti-PD-1 monoclonal antibodies, nivolumab and pembrolizumab.[4,5] Fortunately, most of these are relatively rare, with the commonest being rash/pruritus, transaminitis, diarrhea/colitis, and more rarely pneumonitis or endocrine toxicity.[1,5] Dermatologic toxicity usually manifests within the first few weeks on therapy, whereas diarrhea/colitis, transaminitis and pneumonitis tend to occur within 2 or 3 months of initiating therapy. While irAE's may transpire at any time, they most commonly occur within the first 3 to 4 months of therapy.[2,3] Skin rash may occur in up to 30% of patients, but is severe in less than 5% of those treated. Typically, incidence of diarrhea and transaminitis is in the range of 10%, though grade 3 or 4 effects present in less than 2%.[4,5] Pneumonitis is fortunately less common, with an overall incidence of all grades in the range of 3% and of grades 3 to 4 approaching 1%. Fortunately, hypophysitis is seen in < 1% of patients, but hypothyroidism may occur in up to 10%, so TSH needs to be checked periodically.[2,5] While we do not have prospective randomized controlled trial data to guide toxicity management, consensus guidelines have been established and

FIGURE 2. Some immune-related adverse events that may be associated with checkpoint inhibitor therapy



The more frequent serious complications appear in bold type.

have evolved over time based on clinical trial experience.[6]

Despite their relatively infrequent occurrence, because these irAEs can evolve quickly to life-threatening disease, the threshold for concern needs to be somewhat higher than with conventional chemotherapy.[1,2,3] For example, with diarrhea associated with conventional cytotoxic chemotherapy, concern become more acute when the threshold between grades 2 and 3 toxicity (greater than 6 bowel movements per day) is crossed. (**Table 1**) However, with anti-PD-1 therapy, any increase of 4 or more stools per day over baseline (grade 2 diarrhea), the appearance of blood or mucus in the stools, or any significant abdominal pain (grade 2 colitis), calls for immediate cessation of the IO agent, close monitoring, and initiation of corticosteroid treatment.[2,3] Similarly, with regard to pneumonitis, the detection of asymptomatic radiologic changes (grade 1) calls for consideration of holding anti-PD-1 therapy and close observation for development of symptoms (grade 2) that would warrant initiation of corticosteroids.[4,5] Any transaminase elevation of greater than 3 times the upper limit of normal, or bilirubin greater than 1.5 the upper limit of normal, also requires cessation of therapy, close observation and early steroid therapy intervention.[2,5] (**Table 1**)

THE COMMUNITY ONCOLOGY PROCESS

Given the increased sensitivity required for possible irAEs with nivolumab and pembrolizumab therapy, coupled with the possibility of an insidious presentation, it was felt that a comprehensive management protocol involving both the patients and any healthcare professionals who might be involved in their care was mandatory. In the community oncology setting, subspecialists in gastroenterology, pulmonology, dermatology, endocrinology and neurology are often not readily available.[7] Specialized consultant care in the community setting is more often a general internal medicine service. In addition, if certain subspecialists are available, they are more commonly generalists in their field and not, for example, neuroendocrinologists.

An algorithm detailing the steps required for safe program initiation was developed that fully recognized these limitations. Components included education, followup mechanisms and clear delineation of responsibilities, including most-responsible-person status. As noted in **Table 2**, this algorithm included not only physicians who were likely to come into contact with patients on IO agents (hospitalists, emergency room doctors, internists and primary physicians) but also nursing staff, pharmacy and the individual patients themselves. Detailed teaching for patients was accompanied by specially developed educational handouts (see **Table 3**).

As well, a protocol was put in place such that each patient would be contacted on a regular basis according to a predetermined schedule, especially during the first 3 months of therapy, when adverse events were most likely to occur. In addition, at one of the centres, an informal monthly cancer clinic team meeting was planned so that the entire team could discuss individual patients on IO therapy.

IMPLEMENTING THE ALGORITHM

The implementation process was somewhat different in each centre. At the Vernon community cancer program, a designated nurse undertook the initial IO patient teaching and weekly checkup telephone calls. As the program grew, a second nurse was added. Patient handouts/wallet cards were provided, and an immunotherapy letter (similar to an existing febrile neutropenia letter) was developed. Patients were also offered medical ID bracelets. Education updates in relation to the IO agents were directed at hospitalists, emergency room doctors, internal medicine specialists and pharmacists. Vernon was also able to designate local specialists who would be involved with specific IO toxicity management, including a gastroenterologist, an internist for endocrine side effects, a pulmonologist and a dermatologist. In addition to local physicians, education was targeted to physicians in the wider catchment hospitals where patients would be admitted if needed. Vernon planned for individual family physicians to be reached through the GP oncology network, since this constitutes one of the mandates of this physician group. In the first years of the IO program, the physician's cell phone was provided to patients; this is no longer considered necessary, as covering on-call medical oncologists are comfortable managing these patients according to the established algorithms. Work is now underway to develop treatment algorithms at the level of the regional health authority. Vernon has also adopted the monthly informal oncology staff review initiated in Lethbridge.

In the Jack Ady Program, patient teaching was undertaken by the treating physicians and clinic nurses (and it is hoped that advanced clinical pharmacists will soon be

TABLE 1. General management of immune-related adverse events

Grade*	Hospitalization	Corticosteroids	Immunotherapy
1	No	Not recommended	Continue (consider holding for pneumonitis)
2	No	Topical or oral	Suspend temporarily (if surface skin or endocrine, immunotherapy can be maintained)
3	Yes	Systemic, oral or intravenous (consider subspecialist referral)	Suspend, discuss risk/benefit with patient before resumption
4	Yes, possibly ICU	Systemic intravenous (subspecialist referral)	Discontinue permanently

*Grade: symptom severity (NCI CTCAE grade)
Adapted from: Champiat S, Lambotte O, E. Barreau E. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Ann Oncol.* 2016;27:559–74.

TABLE 2. Checklist for centre/program initiation of therapy with anti-PD-1 anti-PD-L1 ligand agents

Patient education materials developed
- ☐ patient handouts
- ☐ patient wallet card or drug ID identification

Patient educator clearly identified
- ☐ should be single consistent individual if at all possible

Patient educational process developed
- ☐ should be performed by a single consistent individual if at all possible
- ☐ periodic reinforcement reeducation process in place (e.g. every 3 months)

Photocopies developed and distributed for the algorithms to follow in the event of transaminitis, pulmonary toxicity, GI toxicity etc.
- ☐ all staff dealing with these patients should be educated and familiar with these materials

Followup process and single most responsible individual clearly identified
- ☐ protocol for checking the once weekly or biweekly blood counts, including more frequent monitoring if an abnormality is detected
- ☐ protocol for immediate followup if there is any grade 2 dermatologic, pulmonary or GI toxicity
- ☐ backup person for designated individual if sickness/vacation clearly identified

Backup community consultants for each of major toxicities identified and informed of new drugs and program
- ☐ ideally confirm in advance that these consultants agree to quickly co-consult for the minority of patients experiencing acute toxicity

General educational program for all clinic staff regarding new agents
- ☐ special emphasis on involvement in education with clinic pharmacists

Educational program for emergency room physicians/hospitalists/general internal medicine specialists (who may represent first point of contact for decompensating patients) planned/undertaken
- ☐ ideally confirm in advance that these consultants agree to quickly co-consult for the minority of patients experiencing acute toxicity

Monthly healthcare team conferences scheduled on status of each patient on these agents

PD-1=programmed cell death 1; PD-L1=PD-1 ligand.

involved as well), and patients were provided with individual information handouts. A nurse was designated to be involved with the IO program and also undertook weekly patient phone calls. Monthly informal oncology staff team meetings will begin soon. Specific in-depth educational sessions were directed at those who might be the first point of contact in the case of an irAE: emergency room doctors, hospitalists and internal medicine specialists. In addition, one medical oncologist was designated as principally responsible for the IO program. Since the Lethbridge medical oncology service has traditionally provided a 24/7 consultation service, it was not deemed necessary to provide patients with individual physician phone numbers.

Finally, a local subspecialty contact card was developed detailing each of the subspecialists who had agreed to be contacted in the event of system-specific toxicity: transaminitis/gastrointestinal-specific gastroenterologist, pulmonary toxicity-specific pulmonologist, neurologic toxicity-specific neurologist, endocrine toxicity-specific endocrinologist, and dermatologic toxicity-specific dermatologist.

The educational presentations provided for the various physician groups emphasized the potential subtle onset of irAEs, and focused intensively on 3 areas: diarrhea/colitis, pulmonary symptoms/pneumonitis and significantly abnormal liver function/transaminitis. Possible endocrine and neurologic toxicities, including hypophysitis, were also stressed. These medical groups were provided with specific management algorithms for these situations, and were reminded that immunotherapy can affect any organ system (see **Figure 2**).[8]

PROGRAM STATUS

To date, a combined total of approximately 45 patients have been started on anti-PD-1 therapy in these 2 centres. While irAEs have occurred, the systems put in place have generally worked well, and there have been no significant long-term adverse effects experienced to date. If anything, the rates of grade 3/4 toxicity are lower than might have been expected based on the literature, and we postulate that this is related to intensive appropriate education coupled with early intervention.

CONCLUSIONS

The introduction of IO therapies into the community oncology setting is in keeping with the current movement to deliver care closer to home. The unique immune toxicities of these agents and differing resources available in the community setting present challenges to their safe introduction. The programs described in this article have developed a detailed plan for the successful implementation of IO into the community setting.

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TABLE 3. Example of patient handout: diarrhea and pneumonitis teaching (nivolumab)

GENERAL:

Fortunately, significant diarrhea toxicity with this drug is experienced in less than 5% of patients.

However, it is somewhat unusual in that toxicity can evolve fairly quickly over the space of just a few days. Once you have started on this medication, one of our nurses will be calling you on a weekly basis for the first few months. If you experience any increase in diarrhea or abdominal symptoms, she will call twice weekly. Please take this sheet with you if you end up going to the emergency department after-hours.

DIARRHEA MANAGEMENT:

Nivolumab can cause diarrhea (due to drug-induced inflammation in the bowel). You may take probiotics. Probiotics can be found in certain brands of yogurt and as supplements.

When to report to nurse:

- Increased bowel movements/onset of diarrhea more than once a day
- There is special concern if you have more than 3 movements a day

When to report immediately to anyone (if outside of working hours, go to the nearest emergency department.
The on-call medical oncologist should be contacted by the emergency physician):

- Increase of 3 or more bowel movements above baseline
- Blood in stool
- Incontinence of stool
- Awakening at night due to stool urgency
- Abdominal pain, cramping or bloating
- Fever, sudden onset of severe abdominal pain

Your responsibilities at onset of diarrhea:

- Stop drugs with laxative properties.
- Start a stool chart: record frequency, volume, and associated symptoms.
- Drink 1.5-2 litres of water, electrolyte-containing drinks (e.g. Gatorade), or both daily.
- Monitor urine colour and volume. If your urine is dark yellow and decreased in volume, you may be dehydrated and should increase fluid intake.
- Eat potatoes, bananas, rice, apple sauce, toast, jello, plain pasta.
- Avoid all lactose-containing/dairy products and supplements, and fruits and vegetables.
- Use Imodium only under the guidance of a physician.

PNEUMONITIS (LUNG PROBLEMS):

- Nivolumab can cause pneumonitis (drug-induced inflammation in the lungs). This condition must be diagnosed and treated immediately.
- Report immediately any new or worsening respiratory symptoms such as new-onset cough, shortness of breath, or difficulty with breathing.
  If outside of working hours, go to the nearest emergency department and make sure to mention that you are taking this drug.
  The on-call medical oncologist should be contacted by the emergency physician.