INBRIEF | Summarizing the Evidence

Dosing and Timing of Immuno-Oncology Drugs

Key Messages

- For nivolumab:
  - There appears to be no relationship between dose and clinical effect at doses from 1 mg/kg to 10 mg/kg for the treatment of several types of cancer. Each dose within this range is considered both effective and safe, despite a lack of published evidence for every dosing scenario, because the established dosing schedule options are such that patients could be exposed to any dose in the range.
  - A fixed dose of 240 mg every two weeks appears to be more wasteful compared with the 3 mg/kg dose for patients weighing less than 80 kg, depending on a given site's volume of patients, sterile compounding procedures, and purchasing practices. An option to cap dosing at 240 mg for patients weighing more than 80 kg would be acceptable from a regulatory and clinical standpoint.
- For pembrolizumab, the dosage that would result in the least wastage appears to be 2 mg/kg every three weeks with a 200 mg dose cap for patients weighing 100 kg or more.
- Patients may be considered eligible to receive a second immuno-oncology treatment after a sufficient washout period based on the time it takes for the drug to leave the body — that is, 201 days for nivolumab, 237 days for pembrolizumab, and 209 days for durvalumab. However, there are caveats to this rationale, and no randomized clinical trial has demonstrated the effectiveness of re-treatment.

Context

Immuno-oncology (IO) drugs (also called immune checkpoint inhibitors or immunotherapy drugs) have transformed the field of medical oncology. Because these drugs impede the ability of a tumour to disrupt its detection by the immune system, they can elicit an exceptional therapeutic response, allowing for significant regression, and sometimes resolution, of several cancer types.

Technology

IO drugs that have been approved by Health Canada and recommended for reimbursement by CADTH's pan-Canadian Oncology Drug Review Expert Review Committee for a variety of indications include nivolumab, pembrolizumab, atezolizumab, durvalumab, and ipilimumab. IO drugs can be given either in the adjuvant or the consolidation setting (to prevent recurrence after surgery or as intensive therapy with a curative intent), or in the metastatic setting (after cancer has spread to other parts of the body).

Currently, IO drugs can be used in the metastatic setting for the treatment of melanoma, non–small cell lung cancer, squamous cell carcinoma of the head and neck, and renal cell carcinoma. Pembrolizumab and nivolumab are the only IO drugs that have been approved for adjuvant therapy, and specifically for melanoma. Durvalumab has been approved only for consolidation therapy following curative-intent chemo-radiation therapy for non–small cell lung cancer.

The dosing of IO drugs varies. It can be based on a patient's weight (e.g., 3 mg/kg every two weeks), it can be a fixed (or "flat") dose (e.g., 200 mg every three weeks), or it can be weight-based up to a fixed maximum dose. The timing of dosing (e.g., every three weeks versus six weeks) can also vary.

Issue

Fixed dosing of pembrolizumab and nivolumab, using exact multiples of commercial vial sizes, is often preferred over weight-based dosing because it is more convenient to prepare. However, it also means that many patients are given more of the drug than they need. Weight-based dosing up to a fixed maximum dose could potentially be a more cost-effective option.

If a patient's cancer has progressed during adjuvant IO therapy, it is generally not advised to treat the patient again with the same IO drug (or a similar one). But if a patient has relapsed while off treatment, re-treatment with the IO drug might be appropriate, as long as a sufficient amount of time has elapsed since the initial treatment to ensure that the patient has no remaining drug in their system. This amount of time, called the "washout period," is uncertain.

A review of the pharmacometric literature on nivolumab and pembrolizumab can help guide decisions regarding optimal dosing schedules, and a review of the evidence on the effectiveness and timing of immuno-oncology re-treatment after adjuvant IO can help guide decisions regarding re-treatment.

Methods

To obtain evidence related to IO drug dosing, CADTH searched the published literature and a researcher screened the results and selected articles for review. Full-text publications of population pharmacokinetics and modelling studies were evaluated for final article selection according to predetermined selection criteria (population, intervention, comparator , outcomes, and study designs). A separate search of the published literature for pharmacokinetics and clinical studies was conducted to find evidence on the timing of IO re-treatment.

Results

Dosing Strategies

The product monograph for nivolumab specifies a dose of 3 mg/kg every two weeks. However, the relatively wide efficacy and safety profiles of nivolumab (between 1 mg/kg and 10 mg/kg) allow for several possible dosing strategies to be considered.

Fixed doses of 240 mg every two weeks or 480 mg every four weeks have been proposed to improve ease of use and administration, as well as to reduce prescription errors. The fixed 240 mg dose would be less costly compared with the weight-based dose for patients weighing less than 80 kg. Therefore, an approach using weight-based dosing with a cap so that all patients weighing more than 80 kg receive the recommended fixed dose has been suggested as a way to improve cost-effectiveness.

A complementary approach is dose banding — using round doses based on weight ranges to facilitate calculations and preparation. One evaluation of such a strategy, using a dose of approximately 3 mg/kg with 40 mg and 100 mg vials, found that this approach could be more convenient and less expensive than fixed dosing while also reducing drug wastage.

Several clinical studies have shown that any dose of pembrolizumab between 2 mg/kg and 10 mg/kg every three weeks is safe and effective. An evaluation of exposure-response relationships and multiple dosing regimens of pembrolizumab suggests that, for patients of any weight, the most efficient dosage is 2 mg/kg every three weeks with a 200 mg upper dose cap. Where pembrolizumab is available as a 50 mg powder for solution and 100 mg/4 mL solution for infusion, capping the dosing regimen of this drug at 200 mg could limit wastage for patients weighing more than 100 kg; however, the 50 mg vial is discontinued in Canada.

For any dosing strategy, wastage and cost savings may vary from site to site based on patient numbers, sterile compounding procedures, and purchasing practices.

Timing of Re-treatment

No evidence on the effectiveness and timing of IO re-treatment was found. However, it can be assumed that patients can receive a second treatment after enough time has elapsed since the initial treatment for the drug to have left the patient's body (i.e., after a sufficient washout period). After this time, a patient is considered eligible for the same or similar treatment because their new tumour would have grown in the absence of exposure to the drug and, therefore, is not likely to be refractory (resistant) to it. Based on the substantive pharmacokinetic literature on pembrolizumab, nivolumab, and durvalumab, washout periods are calculated per the following table.

Table 1: Washout Periods

Drug	Half-Life	Washout Period[a]
Nivolumab	20.1 days	201 days (6.7 months)
Pembrolizumab	23.7 days	237 days (8 months)
Durvalumab	20.9 days	209 days (7 months)

[a] Calculated by multiplying the half-life of each drug by 10, in accordance with Canadian regulatory guidance.

From a policy and practice perspective, suggested washout values should be viewed as theoretical and somewhat arbitrary. The residual biological activity of the drug after the washout period is not known. The effectiveness of re-treatment after adjuvant immunotherapy is also unknown and, therefore, evidence from future well-conducted clinical studies is needed to confirm the effectiveness of re-treatment.

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