INESSS
LE SAVOIR PREND FORME

MARCH 2023

Update of the tool for choosing the dosage of monoclonal antibodies targeting PD 1 or PD-L1

English summary

Une production de l'Institut national
d'excellence en santé
et en services sociaux (INESSS)

Québec

SUMMARY

Update of the tool for choosing the dosage of monoclonal antibodies targeting PD-1 or PD-L1

Introduction

Atezolizumab, avelumab, cemiplimab, durvalumab, dostarlimab, nivolumab and pembrolizumab are monoclonal antibodies indicated for the treatment of several cancers. They act by preventing the interaction of the T-cell programmed cell death 1 (PD-1) receptor and its ligands, thereby removing the inhibition of the antitumour immune response. Several dosing regimens are proposed in the Canadian product monographs for these drugs, namely, the administration of a fixed dose, a weight-based dose or the choice between these two dosing strategies. The variety of the dosing strategies recommended in the Canadian product monographs raises questions for clinicians, and among other things, highlights certain pharmacoeconomic considerations.

Since the publication of the clinical tool on nivolumab and pembrolizumab dosage selection in 2020 by the Institut national d'excellence en santé et en services sociaux (INESSS), new indications for nivolumab and pembrolizumab and new anti-PD 1 and anti-PD L1 monoclonal antibodies have been approved by Health Canada and added to the Régie de l'assurance maladie du Québec (RAMQ)'s *Liste des médicaments - Établissements*. The objective of this work is to partially update the clinical tool on nivolumab and pembrolizumab dosage selection, adding to it as well the dosages for atezolizumab, avelumab, cemiplimab, dostarlimab and durvalumab in order to guide clinicians in choosing the doses to be administered for these drugs.

Methodology

To develop this tool, we examined scientific efficacy, safety and pharmacokinetic data from systematic reviews of primary studies, pharmacoeconomic data, and recommendations from clinical practice guidelines (CPGs). These data were enriched with information specific to the Québec context and with experiential knowledge provided by clinicians with different expertise and specialties. The search for scientific information was conducted in several databases from the date of their inception to June 2022 and was limited to items published in French or English, while the search for CPGs and guidance documents was limited to items published from January 2014 to June 2022. The grey literature was searched as well, as were the bibliographies in the selected publications. The official Canadian product monographs for Health Canada-approved anti-PD-1 and anti-PD-L1 monoclonal antibodies were consulted to supplement the search for the conditions of use of these drugs.

The results of this systematic review are presented in the form of a narrative synthesis. For each efficacy and safety endpoint, a summary statement of scientific evidence is provided, to which an overall level of scientific evidence was assigned. The recommendations were developed in collaboration with the advisory committee. The

information on contextual and experiential data is presented in narrative form and is summarized in tables.

Results

The search for scientific information conducted in 2020 yielded 31 documents that met the selection criteria (25 scientific articles and 7 items containing recommendations), while that conducted in 2022 yielded 45 (31 scientific articles and 14 items containing recommendations). It should be noted, however, that the data presented in several of these scientific articles were derived from mathematical models and that no data were available for several types of cancers for which some of these drugs are indicated for treatment in Canada.

The results of the systematic review suggest, with a level of evidence deemed low to moderate, that there is no statistically significant difference in efficacy or safety between the different weight-based doses of anti-PD-1 and anti-PD-L1 monoclonal antibodies tested in the studies. These results also suggest, with a level of evidence generally considered low, that there is no statistically significant difference in efficacy or safety between the fixed doses and weight-based doses, or between standard and extended-interval dosing, based on the identified studies that have evaluated these dosing regimens. In addition, the predicted pharmacokinetic endpoints for fixed doses versus weight-based doses are generally similar, while the predicted pharmacokinetic parameters for high doses administered less frequently suggest serum concentrations that remain within the established limits for each drug. Moreover, pharmacoeconomic analyses done for pembrolizumab and nivolumab show a likely increase in pharmacoeconomic ratios with the use of fixed doses, while a fixed dose of cemiplimab every 3 weeks would reduce costs compared to a weight-adjusted dose administered every 2 weeks. In addition, some dosage regimens recommended in the product monographs or clinical practice guidelines have not been compared with other doses or dosage regimens.

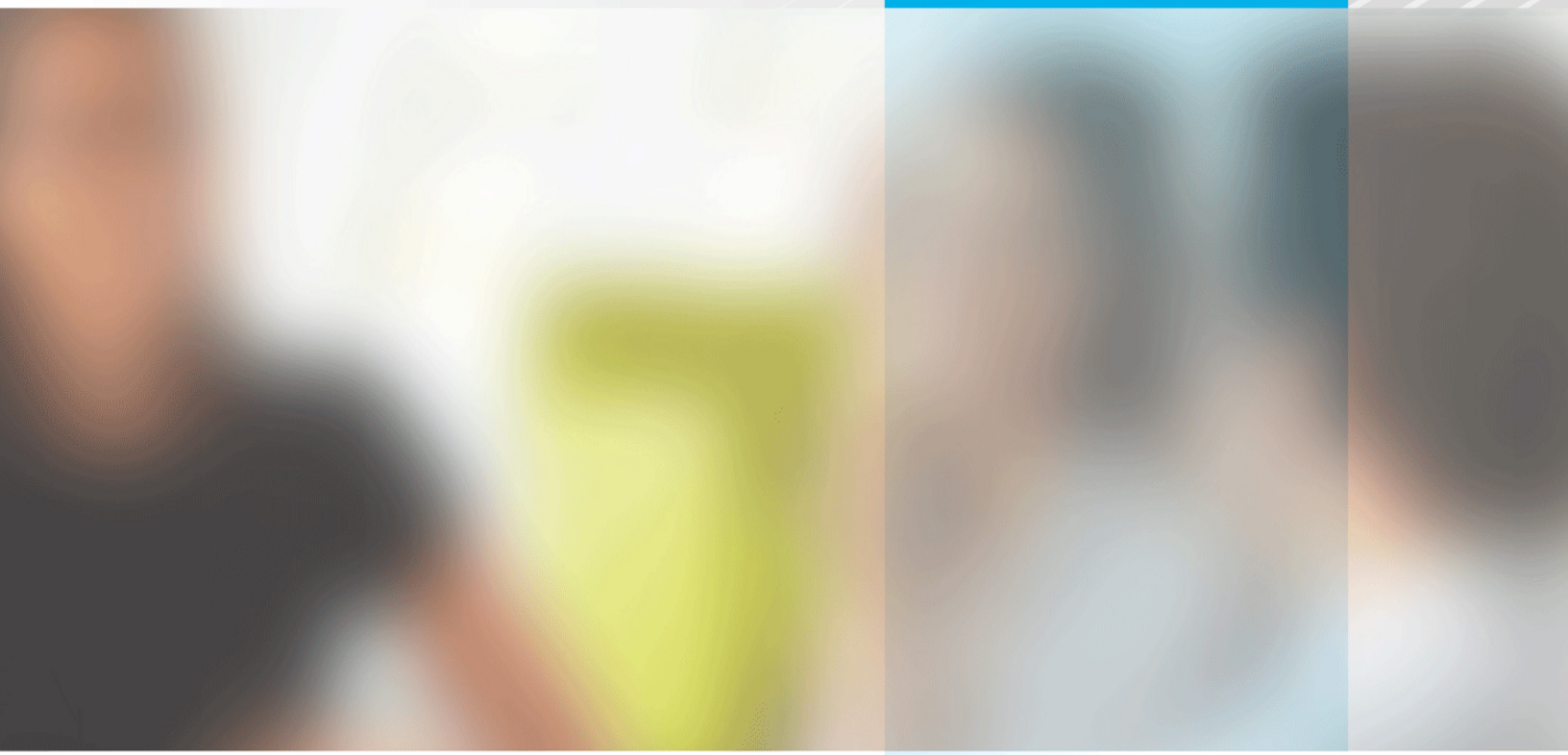
Since anti-PD-1 and anti-PD-L1 monoclonal antibodies do not directly target the tumour site, but rather the binding between T cells and a ligand, it was decided to propose in the decision support tool, for all Health Canada-approved indications, the use of a weight-based dose up to a maximum dose equal to the fixed dose for avelumab, durvalumab, nivolumab and pembrolizumab. However, it was decided to propose the fixed doses for atezolizumab, cemiplimab and dostarlimab, as recommended in the Canadian product monographs. It was also decided to propose all intervals, both standard and extended, for atezolizumab, durvalumab, nivolumab and pembrolizumab. When multiple dosing intervals are possible, the advisory committee’s members suggest that the choice of interval be left to the prescriber's discretion, based on the patient’s characteristics, the indication and the specific characteristics of the setting. Also, since they lower the frequency of administration, extended intervals could provide certain benefits to both the health-care system and patients, by reducing, among other things, costs associated with treatments. However, patients who receive a high dose at extended intervals could be offered a more frequent follow-up to monitor the adverse effects, therapeutic response

and hyperprogression, so as to be able to detect a problem early and adjust the therapy, if necessary, as soon as possible.

Lastly, it is pointed out that certain populations are more likely to experience adverse effects following the administration of anti-PD-1 and anti-PD-L1 monoclonal antibodies, such as patients with a pre-existing autoimmune disease and those who have undergone a solid-organ transplant or a hematopoietic stem cell transplant (HSCT). These persons could benefit from a more frequent medical follow-up at the start of treatment, whether the treatment was initiated using an extended interval or not. These precautions are also mentioned with regard to treating patients who previously discontinued treatment because of adverse effects due to immunotherapy and patients with a lower tolerance for adverse effects.

Conclusion

Development of the anti-PD-1 and anti-PD-L1 monoclonal antibodies dosing decision support tool required a collaborative approach that brought together scientific, contextual and experiential knowledge. This tool will serve to facilitate the prescribing of these drugs by reducing the confusion due to the multitude of dosage regimens proposed in the product monographs. The few points included in the tool for certain specific populations are important considerations when managing and following these patients.



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