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The relevance of intraperitoneal chemotherapy in preventing or treating neoplasms of the peritoneal surfaces - Peritoneal mesothelioma

English summary

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

Québec

SUMMARY

The relevance of intraperitoneal chemotherapy in preventing or treating neoplasms of the peritoneal surfaces - Peritoneal mesothelioma

Context

Peritoneal surface neoplasms (PSNs) comprise a heterogeneous group of cancers characterized by their location on the serous surfaces of the abdominal cavity. Peritoneal tumors are generally associated with a poor prognosis, particularly due to the difficulty of reaching effective cytotoxic concentrations in the peritoneal cavity with systemic chemotherapy.

Intraperitoneal (IP) chemotherapy is a therapeutic approach available in various forms, including hyperthermic intraperitoneal chemotherapy (HIPEC), normothermic intraperitoneal chemotherapy (NIPEC), and early postoperative intraperitoneal chemotherapy (EPIC), which allow cytotoxic agents to be delivered directly into the abdominal cavity to maximize their local concentration and promote tissue penetration while limiting systemic toxicity. This locoregional method has been used, following cytoreductive surgery, to treat various types of NSPs such as peritoneal mesothelioma and peritoneal metastases of colorectal, ovarian, gastric, and appendiceal origin. However, the appropriateness of IP chemotherapy in the management of these conditions, as well as its administration modalities, are not well defined.

In this context, the Direction de la cancérologie of the ministère de la Santé et des Services sociaux (MSSS) has mandated the Institut national d'excellence en santé et en services sociaux (INESSS) to assess the clinical relevance of IP chemotherapy for the prevention or treatment of PSNs and to issue recommendations, where appropriate, to support its optimal, equitable, and harmonized use across the Quebec healthcare network.

This report focuses specifically on the relevance of IP chemotherapy for the treatment of peritoneal mesothelioma, a rare primary cancer that develops from the mesothelial cells of the peritoneum.

Methodology

A systematic review of the scientific literature was conducted to identify available data regarding the clinical relevance of IP chemotherapy combined with cytoreductive surgery (CRS) for the management of peritoneal mesothelioma. The selected literature includes two retrospective studies meeting the selection criteria and nine additional retrospective studies, as well as international recommendations from clinical practice guidelines, expert group publications, and health technology assessment reports (12 publications from 9 different organizations).

Consultations were also conducted with clinicians experienced in this modality, as well as with the Comité de l'évolution des pratiques en oncologie (CEPO). A permanent deliberative committee supported the development of findings and recommendations following the completion of the work.

Findings

By integrating scientific, contextual, and experiential data, the following findings were identified:

Health needs

- Peritoneal mesothelioma is a rare primary cancer that is generally diagnosed at an advanced stage and has a poor prognosis.
- The World Health Organization has classified mesothelioma into three histological subtypes: epithelioid (80–90%), sarcomatoid (< 5%), and biphasic (10–20%).
- The median overall survival for people with peritoneal mesothelioma, regardless of histological subtype or treatment administered, is 19.5 months. Epithelioid histology is a predictive factor associated with a better prognosis.
- According to current international guidelines, the optimal treatment for resectable disease relies primarily on cytoreductive surgery combined with IP chemotherapy.
- However, due to the rarity of the disease, no randomized controlled trials have been conducted to support this practice, and the effect of IP chemotherapy as an adjunct to cytoreductive surgery remains unknown.
- In the absence of such evidence, standard treatment modalities have not been established, leading to some variation in clinical practice regarding the selection of eligible patients, the technical parameters of the perfusion, and the use of systemic chemotherapy.

Assessment of the level of scientific evidence

- Two primary studies were selected to evaluate the efficacy and safety of IP chemotherapy in combination with cytoreductive surgery for the treatment of patients with peritoneal mesothelioma. The quality of life of these patients was not assessed in the selected studies.
- The designs of these retrospective studies were deemed poorly suited for addressing the evaluation questions. The efficacy results are derived from multivariate analyses that included treatment (CRS+HIPEC *vs* CRS) as a variable. Significant methodological weaknesses limit the scope of the presented results, including heterogeneity in the treatments administered, the lack of adjustments for certain factors independently associated with overall survival, and errors in the presentation of the multivariate analysis results.

- The level of evidence regarding the efficacy and safety of HIPEC in combination with cytoreductive surgery was deemed low and insufficient, respectively.

Efficacy and et safety

- The included studies do not allow us to conclude that patients treated with HIPEC following cytoreductive surgery have an overall survival benefit compared to those treated with cytoreductive surgery alone.
- The available data do not allow for a comparison of the safety of HIPEC combined with cytoreductive surgery to that of cytoreductive surgery alone. However, some of the evidence reviewed indicates that the procedure carries significant risks of complications for the patient.
- Despite acknowledging the limited evidence available to support these recommendations, the majority of professional associations, evaluation agencies, and expert groups agree that IP chemotherapy (primarily in the form of HIPEC) combined with cytoreductive surgery should be the standard of care for a selected population of patients with peritoneal mesothelioma. The position of these organizations, which contrasts with the available evidence, is based on the following arguments:
  - the rarity of the disease, which limits the ability to conduct controlled studies;
  - the inequity that would result from assigning patients to a treatment (control) group whose efficacy is known from the outset, based on historical data, to be inferior to that of IP chemotherapy combined with cytoreductive surgery;
  - the poor prognosis of peritoneal mesothelioma;
  - the risk-benefit ratio, which would favor the intervention.

Perspective in the Quebec context

- It is impossible to paint a picture of HIPEC practice in Quebec based on medical-administrative data or local hospital registries. No centralized provincial registry exists for this purpose.
- Cytoreductive surgery combined with HIPEC for the treatment of peritoneal mesothelioma is performed in a few specialized PSN referral centers; the number of patients treated using this approach cannot be quantified from databases, but it is likely fewer than five cases per year per specialist performing this procedure.
- In current Quebec practice, perioperative systemic chemotherapy (usually neoadjuvant) is typically offered to patients with resectable peritoneal mesothelioma; HIPEC (cisplatin/doxorubicin) is administered after complete/optimal cytoreduction and is used for a limited number of patients who are rigorously selected based on prognostic factors—notably tumor histology, peritoneal carcinomatosis index, and Ki-67 positivity rate.

- The consulted clinicians believe that HIPEC should be considered after complete/optimal cytoreduction, despite the low level of evidence, due to the rarity of the disease—which limits the ability to conduct comparative studies—its poor prognosis, and the perceived curative potential of the intervention for certain selected patients.

Environmental considerations

- The available data on the environmental impacts of HIPEC remain very limited. To date, no life-cycle analysis of HIPEC in a hospital setting comparable to that of Quebec has been identified. Although the prolonged duration of surgery and the use of anesthetic gases are the main sources of greenhouse gas emissions associated with HIPEC, the specific environmental impact of HIPEC remains relatively marginal given the small number of patients treated and the limited number of hospitals performing this procedure.

INESSS position and recommendations

In light of all the scientific, contextual, and experiential data collected, the findings presented, and the deliberation process conducted, INESSS issues the following recommendations:

> For individuals with resectable peritoneal mesothelioma, the evidence is currently insufficient to determine the efficacy and safety of HIPEC following complete/optimal resection, as well as the quality of life of those who have undergone the procedure. Additional evidence is needed to take a position on the relevance of using the procedure, to specify the optimal modalities of use, and to identify individuals likely to benefit from it (if applicable).

In support of this position, INESSS makes a number of additional recommendations aimed at promoting optimal care:

- Patients with peritoneal mesothelioma (whether resectable or not) should be directed as soon as possible to a referral center with a multidisciplinary care team specializing in neoplasms of the peritoneal surfaces. The proposed comprehensive management (follow-up strategies, treatment options) should be discussed by the comité du diagnostic et du traitement du cancer (CDTC) (cancer diagnosis and treatment committee), regardless of whether locoregional treatment is being considered.
- The decision to use HIPEC should be made in an informed manner and shared with the patient based on complete and balanced information regarding the expected benefits, risks, and potential adverse effects, the uncertainties associated with the available evidence, as well as other relevant therapeutic

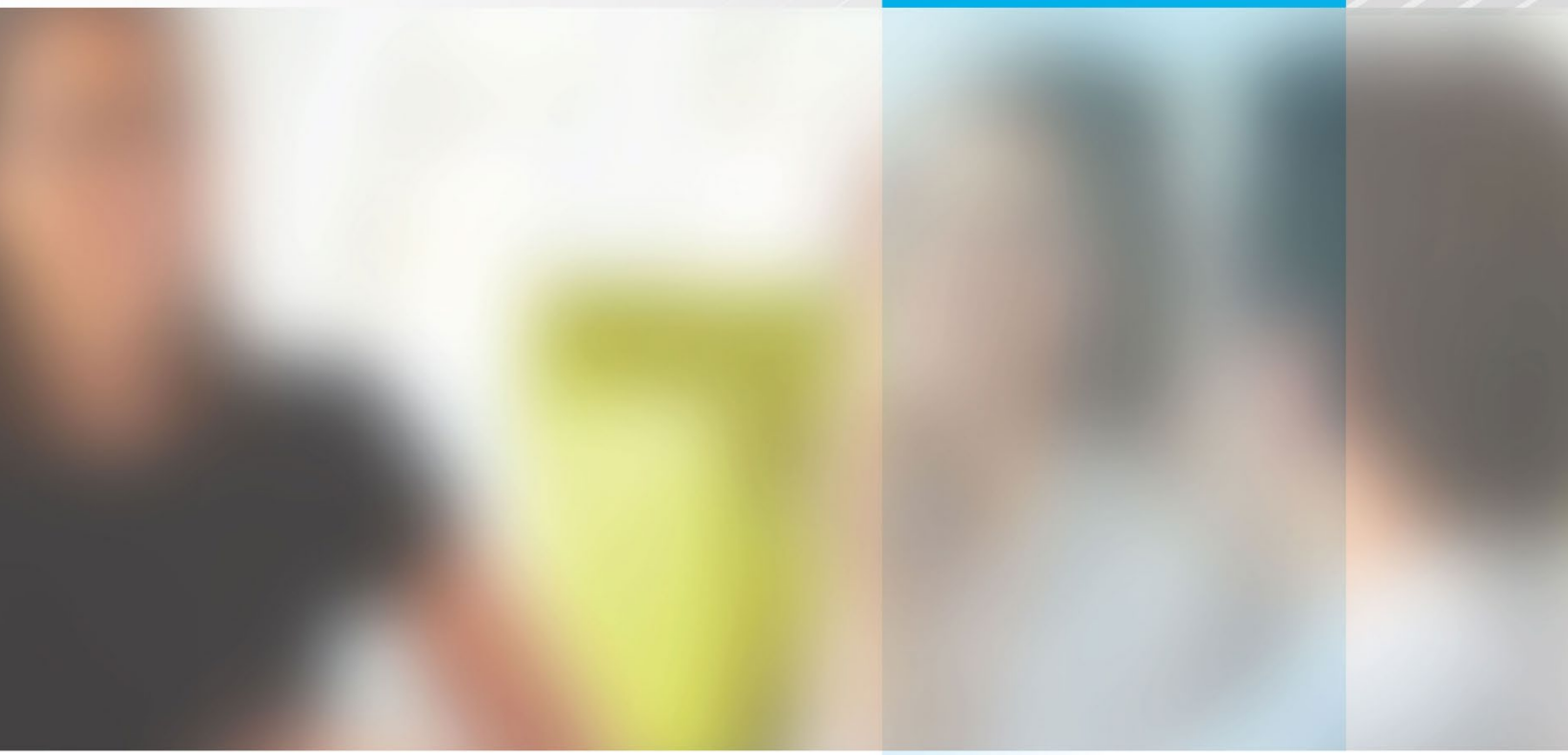
options. This approach aims to support a choice consistent with the patient's values, preferences, and clinical situation.

- Since HIPEC is a little-practiced procedure for which the evidence regarding its efficacy and safety is limited in methodological terms, the collection and sharing of clinical data from specialized centers offering the treatment (regardless of the indication) should be encouraged in order to support the development of knowledge and evidence in the real-world setting of healthcare in Quebec.

Recommendations update

The relevance of updating this opinion will be assessed and determined based on the availability of new data supporting any of the evaluated aspects, in particular the publication of studies, meta-analyses, recommendations from international organizations, or national regulations.

At the time of writing this report, no ongoing studies were being conducted to evaluate the efficacy and safety of IP chemotherapy in combination with cytoreductive surgery, compared with cytoreductive surgery alone.



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