Author’s response to reviews

Title: BEV-IP: Perioperative chemotherapy with bevacizumab in patients undergoing cytoreduction and intraperitoneal chemoperfusion for colorectal carcinomatosis

Authors:

Wim Ceelen (wim.ceelen@ugent.be)
wouter willaert (wouter.willaert@ugent.be)
kurt van der speeten (Kurt.Vanderspeeten@zol.be)
gabriel liberale (gabriel.liberale@bordet.be)

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Author’s response to reviews:

We thank the reviewers for their insightful and constructive comments.

Reviewer #2: Wiliaert et al. present an interesting study protocol, but this paper should be revised with regard to some of the content.

Abstract

1. page 2, in the Methods/design, is "Oxaliplatin-based" a mistake of "oxaliplatin-based"?

We changed the spellign accordingly.

Background

2. page 4, Reference 10 is cited in the sentence of "In the CAIRO 2 study, which…". Is this a mistake?

This reference was mistaken, and is now corrected.

Methods/Design

3. page 9, in the paragraph of Study Objectives and Endpoints, why do the authors select IPC, not HIPEC?
Some centers (including our own) do not use hyperthermia (defined as a temperature >40°C), therefore we decided to use the more general term ‘IPC’.

4. page 9, in the paragraph of Study Objectives and Endpoints, why is the definition of PFS from date of surgery to disease progression or death, not from date of starting neoadjuvant chemotherapy to disease progression or death? Neoadjuvant chemotherapy is not the protocol treatment? Also about the definition of OS.

We agree, and the definition of PFS and OS has been changed (calculated from start of neoadjuvant therapy)

6. page 11, in the paragraph of Response assessment, why are patients with clinical signs or symptoms of disease progression excluded?

We assume that patients who progress under neoadjuvant chemotherapy are not good candidates for cytoreduction and IPC (but rather would benefit from a switch in chemotherapy).

7. page 12, in the paragraph of Surgery and Chemoperfusion, the authors wrote, "Oxaliplatin (200-460 mg/m2) in dextrose 5% (2 liter/m2) is administered IP…". Why is oxaliplatin not a constant dose?

The dose is calculated according to the body surface area. However, since perfusate volume is also calculated according to BSA, oxaliplatin concentration is constant.

8. page 13, in the paragraph of Follow-up, what is the regimen as adjutant chemotherapy?

Adjuvant therapy is identical to the neoadjuvant regimen. This was specified in the text.

9. page 15, in the paragraph of Statistical considerations, the authors wrote, "Thirty-day morbidity and mortality rates…", and based on the literature, the authors determined the sample size. Why was the sample size determined based on the three-month morbidity and mortality rates, which is the primary endpoint?

We have used the three month MM rate to calculate the sample size; this was corrected in the text.

10. page 15, in the paragraph of Statistical considerations, the authors wrote, "…, an interim analysis is planned after each cohort of 10 patients is included in the study". What kind of group does each cohort of 10 patients point to?

The analysis will be repeated after each additional 10 patients are included. This was specified in the text.

Reviewer #3: This is an interesting protocol looking at the utility and safety of bevacizumab peri-operatively for patients with peritoneal carcinomatosis from colorectal cancer.
The study protocol is well described and straightforward. Statistics are acceptable.

However, one revision is essential. The primary study outcome is assessment of morbidity and mortality following the cytoreductive surgery and preoperative chemotherapy. However, while some statistics are provided regarding "morbidity", what is being measured and assessed as morbidity is not defined anywhere in the protocol. This must be included. Everyone getting chemotherapy and extensive surgery has some degree of morbidity. What is being recorded for the protocol must be detailed very specifically. If it cannot, than morbidity cannot be utilized as an outcome. In the latter circumstance, if mortality is the only outcome, then the sample size would need to be drastically increased.

This was specified in the text. We will consider as an event (endpoint reached) whenever a Dindo-Clavien Grade IIIb or higher complication has occurred. Minor morbidity will be studied as a secondary endpoint.