Perioperative Management for Colorectal Peritoneal Metastases

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Introduction

Colorectal cancer (CRC) is the third leading cause of death in Europe owing to metastatic spread. Tumor dissemination occurs via 2 main routes: a systemic route through the bloodstream leading to liver or lung metastases and a local route through the peritoneal cavity. The current concept of potentially curative treatment for metastatic CRC (mCRC) combines the treatment of microscopic disease using chemotherapy with surgical resection of macroscopic disease. This combined modality approach offers long-term survival and even cures in some cases, and it represents the standard of care for mCRC.

The natural history of mCRC with peritoneal metastases is different from mCRC involving other systemic sites. Metastatic peritoneal disease is associated with worse survival when compared with other metastatic sites even after complete surgical resection, and this poor outcome is explained by a limited response to systemic chemotherapy. The COMBATAC trial (A prospective multicenter phase II study evaluating multimodality treatment of patients with peritoneal carcinomatosis arising from appendiceal and colorectal cancer) presented by Glockzin

This is the author's manuscript of the article published in final edited form as:

Kim, B. J., & Passot, G. (2018). Perioperative Management for Colorectal Peritoneal Metastases. *Clinical Colorectal Cancer, 17*(4), 249–250. https://doi.org/10.1016/j.clcc.2018.08.005

et al aimed to determine the impact of perioperative systemic chemotherapy plus targeted therapy using cetuximab on outcomes after potentially curative cytoreductive surgery for peritoneal metastases from CRC.

Discussion

The goal of this trial was noteworthy as it hoped to better define the most effective perioperative management for peritoneal mCRC. Unfortunately, despite an appropriate study design, the trial ended prematurely owing to poor patient enrollment. However, this report by Glockin et al is important as it highlighted once again the critical impact of multimodality treatment concept for potentially curative treatment of peritoneal metastases combining systemic chemotherapy and complete surgical resection.

Associated with surgery, systemic chemotherapy was shown to be a major positive prognostic factor for a curative outcome. However, the most appropriate chemotherapy regimen before and/or after surgery remains still in question. When proposed before surgery, pathologic response should be evaluated because it is an important prognostic factor. Another argument favoring preoperative chemotherapy is the morbidity associated with cytoreductive surgery, which could preclude or postpone return to adjuvant chemotherapy. With respect to perioperative chemotherapy, no regimen has demonstrated a clear clinical benefit, but oxaliplatin-based chemotherapy for 4 to 6 preoperative cycles has received the most attention. However, increased morbidity after cytoreductive surgery has been associated with anti-vascular endothelial growth factor therapy. For patients with response or stable disease after preoperative chemotherapy, cytoreductive surgery should be considered. Owing to the lower efficacy of systemic chemotherapy on peritoneal metastases, peritoneal progression is not a formal contra-indication for surgery, when systemic disease is controlled.

Postoperative adjuvant chemotherapy is also an important issue to consider, and the general recommendation is to resume the same chemotherapy within 8 weeks after surgery when feasible to complete a goal of 12 perioperative cycles. Randomized controlled trials are currently lacking to better determine the most appropriate perioperative management for patients with peritoneal metastasis of CRC. However, several arguments exist to consider perioperative chemotherapy as the standard of care.

When complete cytoreduction can be achieved, surgery is the only definitive treatment that offers a positive long-term outcome or even cures for patients with peritoneal metastasis from CRC. Cytoreductive surgery is a demanding treatment, and patient selection is pivotal. A recent colonoscopy is required before surgery in order to rule out the presence of second colon cancer localization (around 10% of patients). Peritoneal metastases must be proven either on pathology or from medical history with a typical lesion on imaging. A computed tomography is mandatory to allow for detection of both peritoneal and extraperitoneal disease. Considering the relatively low sensitivity of computed tomography and magnetic resonance imaging for the diagnosis of peritoneal metastases, an exploratory laparoscopy with peritoneal biopsies should be considered to confirm peritoneal metastases and evaluate resectability. The 2 main prognostic factors after cytoreductive surgery for peritoneal metastases of CRC are completeness of cytoreduction based on completeness of cytoreduction (CC) score (CC-0, no residual nodules; CC-1, residual nodes < 2.5 mm; CC-2, residual nodules < 25 mm; and CC-3, > 25 mm), and extent of peritoneal metastases based on Peritoneal Cancer Index (PCI). Improved outcomes are expected with complete cytoreductive surgery (CC-0), and PCI < 7. Moreover, when complete cytoreductive surgery is considered, the only surgical approach should be open laparotomy because laparoscopic exploration significantly underestimates the extent of peritoneal spread. In 1989,

Paul Sugarbaker proposed hyperthermic intraperitoneal chemotherapy (HIPEC) to treat microscopic peritoneal disease. The rationale for this approach was to increase peritoneal concentration of chemotherapy and improve its cytotoxic effects by hyperthermia. At the time, it was reasoned that peritoneal metastases presented with poorer prognoses than systemic metastases with a greater than 50% risk of peritoneal recurrence; HIPEC was implemented with the goal of improving local control. Since 1989, several retrospective studies and one randomized control trial demonstrated the positive effect of combined cytoreductive surgery and HIPEC on survival for patients with peritoneal metastases from CRC. However, the specific impact of HIPEC has not been clearly established. The French PRODIGE 7 trial (Perioperative outcomes of cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal carcinomatosis: PRODIGE 7 randomized trial; NCT00769405) recently presented the results of a multi-institutional randomized controlled trial to determine the impact of HIPEC using oxaliplatin in the management of peritoneal metastases from CRC.

The goal of this clinical study was to compare the clinical efficacy of complete cytoreductive surgery with complete cytoreductive surgery with HIPEC using oxaliplatin in patients with metastatic peritoneal disease. In this trial, 60-day morbidity was significantly higher in the HIPEC group (24.1% vs. 13.6%; $P = .030$), and this combined approach was associated with an increased length of hospital stay. In terms of clinical efficacy, the investigators reported 41.7 and 41.2 months of median overall survival in the HIPEC and non-HIPEC groups, respectively ($P = .995$). In a subset of patients with PCI between 11 and 15, HIPEC seemed to provide clinical benefit as recurrence-free survival was 13.1 and 11.1 months in the HIPEC and non-HIPEC groups, respectively ($P = .486$). This study concluded that the addition of oxaliplatin-HIPEC to

complete cytoreductive surgery did not influence survival. These results questioned the interest of oxaliplatin-HIPEC in the management of peritoneal metastases for CRC. Considering the high rate of peritoneal recurrence after complete cytoreductive surgery, the limited effect of systemic chemotherapy, and the poorer prognosis of peritoneal metastases from CRC, increasing local control is a major challenge! Based on the results provided in liver metastases by hepatic intra-arterial chemotherapy, intraperitoneal therapy should still be considered as part of the treatment algorithm.

Conclusion

Global efforts continue to focus on identifying the most appropriate management of peritoneal metastases from CRC, and it is critical that local therapy must be considered integral to improve local control. It is clear that the effectiveness and safety of complete macroscopic surgical resection of mCRC is becoming a reality in the modern era. However, the treatment of microscopic mCRC remains an on-going challenge both with respect to its diagnosis and treatment. Although there have been significant advances in the perioperative management and systemic therapy of mCRC, the same type of improvements continue to be urgently needed for metastatic peritoneal disease.

Disclosure

The authors have stated that they have no conflicts of interest.

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