EDITORIAL

Modern management of peritoneal carcinomatosis of colorectal origin – Is hyperthermic intraoperative peritoneal chemotherapy the treatment of first choice?

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Abstract

Although cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is still considered as "experimental" by many, there is growing evidence that supports its general use in selective patients with peritoneal carcinomatosis of colorectal origin.

The selection of patients remains challenging but is the crucial key to achieve optimal oncological results. Recent studies have shown promising results of systemic chemotherapy with biological agents in the treatment of patients with peritoneal carcinomatosis. Thus, the combination of systemic chemotherapy with CRS and HIPEC could even improve overall survival in affected patients. Future studies are required to evaluate the effectiveness of multimodal therapy and to establish a standardized protocol for the treatment of patients with peritoneal carcinomatosis.

Key words

Colorectal cancer, Peritoneal carcinomatosis, Hyperthermic intraoperative peritoneal chemotherapy, Cytoreductive surgery, HIPEC

1 Introduction

Colorectal cancer (CRC) is the third most common cancer in the world and one of the leading causes of cancer-related deaths. Approximately 25% of all patients with CRC develop peritoneal carcinomatosis (PC) during the progression of their disease [1]. In addition, about 10% of patients with CRC already show peritoneal carcinomatosis at the time of initial diagnosis [2]. Peritoneal carcinomatosis is generally associated with poor prognosis with a mean survival rate of less than one year [3]. Peritoneal spread of tumour cells can develop by direct transcolonic tumour migration or by tumour cell seeding during surgical resection [1]. Systemic palliative chemotherapy has been considered the standard treatment for patients with advanced stage CRC and peritoneal carcinomatosis, in spite of having a limited benefit. Notably, modern chemotherapeutic regimens such as FOLFOX with or without antibodies have been shown to improve survival to a median of 15.7 months [4, 5].

2 Establishment of multimodal therapy in treatment of peritoneal carcinomatosis

In recent years, a new approach for treating patients with PC has evolved, which combines the removal of all visible tumour cells followed by hyperthermic intraoperative peritoneal chemotherapy (HIPEC). Although level Ia evidence to support cytoreductive surgery (CRS) and HIPEC in PC is still limited, there is an increasing number of studies that have shown promising results [6].

In contrast, this multimodal therapy is fully established in the treatment for pseudomyxoma peritonei resulting in a median survival duration of 196 months and a 10 year survival rate of 63% if complete tumour removal can be achieved [4].

The success of CRS and HIPEC relies on careful patient selection by a multidisciplinary team. This is crucial, as CRS and HIPEC can be associated with considerable morbidity and mortality, which could overcome the beneficial effect of the treatment per se and subsequently reduce quality of life significantly.

Admittedly, patient selection is sophisticated and depends on several factors, such as age, co-morbidities, evidence of extra abdominal disease, extent of disease according to scoring systems such as the peritoneal cancer index (PCI) and the feasibility of complete macroscopic cytoreduction. The PCI is the most commonly used prognostic indicator. It quantifies the extension of carcinomatosis by calculating the expansion of tumour in 13 regions of the abdomen in combination with the size of the tumour lesions. The score ranges from 0 to 39 points, with a higher score indicating an increased tumour load [7]. Elias et al. have found a 4-year survival rate of 44% if the PCI score is less than 6, 22% if the score is between 7 and 12, and only 7% if the score is >19. If the PCI score is above 20, multimodal therapy with CRS and HIPEC is generally not recommended [8].

Nevertheless, most available studies used different criteria for patient selection, as no defined standards exist. Thus, future studies will be of great importance to identify parameters which help to choose appropriate patients who will benefit from CRS and HIPEC. Non-clinical parameters, such as tumour infiltrating immune cells, have been shown to be strong predictors for survival in colorectal cancer patients [9]. Their role in patients with PC has not been investigated so far, but might play a role in the future.

There is no doubt that systemic chemotherapy regimens have improved in the last decades showing prolonged overall survival rates in a high number of studies [10-16]. Systemic chemotherapy regimens for metastatic colorectal cancer (MCRC) contain mainly 5-fluorouracil (5-FU) with folinic acid (FA) in combination with oxaliplatin or irinotecan [17]. In recent years, targeted therapy with antibodies against the vascular endothelial growth factor (VEGF) or the epidermal growth factor receptor (EGFR) have further improved patient outcome in advanced stage colorectal cancer. Recently, Klaver Yl et al. were able to demonstrate that the addition of biological agents in the treatment of selected patients with peritoneal carcinomatosis prolonged overall survival up to 22.4 months [18]. However, several studies found good or even better results, when surgical and systemic therapy modalities were combined, with a median survival of 48 and 63 months after complete macroscopic cytoreduction and HIPEC compared to 12 and 24 months with chemotherapy alone [3, 13]. This absolutely states the importance of the multimodal concepts and therefore should be incorporated into treatment protocols and guidelines. The ongoing COMBATAC trial represents an interesting prospective multicenter phase II study evaluating the feasibility and efficacy of the combined multidisciplinary treatment regimen consisting of perioperative systemic combination chemotherapy plus cetuximab and CRS plus bidirectional HIPEC with intraperitoneal oxaliplatin [1].

3 Conclusions and future analyses

Although CRS and HIPEC are still considered as “experimental” by many, there is increasing evidence that supports its general use in selective patients with PC. Careful patient selection is challenging but certainly crucial to achieve optimal

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results. Future studies are mandatory to focus on treatment protocols that combine CRS and HIPEC with systemic chemotherapy regimens including monoclonal antibodies. Further clinical and non-clinical parameters need to be identified to offer a tailored individual treatment strategy for affected patients.

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