Review Article on New Technologies

Systemic therapy in addition to cytoreduction and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastases: recent insights from clinical studies and translational research

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Abstract: There is a lack of randomized or high-quality intention-to-treat cohort studies addressing the role of systemic therapy in addition to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) as part of the treatment of colorectal peritoneal metastases (PM). Therefore, the choice whether or not to treat patients with systemic therapy is currently mainly based on expert opinion. As a result, treatment with neoadjuvant and/or adjuvant systemic therapy is implemented in various ways around the world. The aim of this review was to provide an overview of recent insights with regard to the systemic treatment of PM of colorectal origin obtained from clinical studies and translational research.

Keywords: Systemic therapy; cytoreductive surgery (CRS); hyperthermic intraperitoneal chemotherapy (HIPEC); peritoneal metastases (PM); colorectal cancer

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Introduction

The peritoneum is the second most prevalent metastatic site of colorectal cancer (CRC). As a result of intraperitoneal seeding of cancer cells, peritoneal metastases (PM) can develop throughout the abdominal cavity. In about 5% of CRC patients, PM are diagnosed at time of diagnosis of the primary tumor (synchronous metastases) (1,2). In another ~5% of CRC patients, PM will develop after curative resection of the primary tumor (metachronous metastases) (3-5). These numbers are probably an underestimation of the real incidence, as PM are difficult to be diagnosed with imaging studies and indeed, autopsy studies report much higher incidences (6).

Nowadays, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is considered standard treatment in patients with limited intraperitoneal disease in most countries (7,8). Unfortunately, locoregional and/or systemic recurrence occurs in most patients, even after aggressive and complete cytoreduction and HIPEC. In 35–41% of all patients, this even occurs within 1 year after treatment (9,10). In an effort to prevent or delay recurrence and thus prolong overall survival (OS), various experts have advocated systemic treatment in these patients either in a neoadjuvant setting, adjuvant setting or a combination of both. Others have questioned this strategy as compelling evidence to support systemic treatment in addition to CRS-HIPEC is currently lacking and side-effects may be severe. In the absence of consensus amongst experts, there is a wide

variation in systemic treatment protocols of these patients. The aim of the current review was to provide an overview of recent clinical and translational data with regard to systemic treatment of patients with PM of colorectal origin treated with CRS-HIPEC.

The rationale of (neo)adjuvant systemic therapy

There are various hypotheses that support the efficacy of systemic therapy in the context of CRS-HIPEC. Firstly, systemic therapy may eradicate micro metastases. With a high risk of systemic spread in advanced primary colorectal tumors, the addition of systemic therapy may lower the risk of distant metastases during and after treatment (1,11,12). Secondly, neoadjuvant systemic therapy may lower the intraperitoneal tumor-load prior to surgery (13,14). If the extent of disease decreases, the extent of surgery needed for complete resection is likely to decrease too. Besides a possible greater chance of complete resection, less extensive surgery may also lead to fewer post-operative complications (15,16). Finally, administration of systemic chemotherapy prior to CRS-HIPEC may select patients that will respond more favorable to CRS-HIPEC (17-19). Response to neoadjuvant treatment provides insight in tumor behavior and might be helpful in surgeon's decision making on whether or not to continue with CRS-HIPEC (20-22).

Interestingly, similar arguments have been used in the past to treat patients undergoing surgery for colorectal liver metastases (LM) with perioperative systemic therapy. This strategy was investigated in the EPOC-trial and compared with surgical treatment alone (23,24). Although this trial showed a significant improvement in progression-free survival (PFS) in patients treated with perioperative systemic treatment as compared to patients who underwent surgery alone, there was no difference in OS between both groups.

Potential risks of (neo)adjuvant systemic therapy

Besides the listed possible benefits of adding systemic therapy to CRS-HIPEC, it may also involve risks. Most importantly and most concerning is the potential effect on patients' general condition, particularly in the neoadjuvant setting. Systemic treatment with chemotherapy (± targeted therapy) and its consequent toxicity may significantly deteriorate patients' general condition (25). However, it is unknown to what extent this might lead to inoperability in patients with colorectal PM intended to undergo CRS-HIPEC, as only one small study has investigated this in an intention-to-treat setting (26). Another risk is that selection of patients by response to neoadjuvant treatment may improve survival of those patients that will eventually undergo CRS-HIPEC, but patients that progress during systemic treatment may have been denied a potential beneficial treatment with CRS-HIPEC.

Furthermore, systemic treatment may lead to an increased risk of post-operative morbidity. The main concern in this is the addition of VEGF-inhibitors in the neoadjuvant setting, as one study demonstrated that the administration of neoadjuvant VEGF-inhibitors increased the risk of post-operative complications by its possible anti-angiogenetic effects on healing processes such as anastomotic healing and wound healing (27). Finally, the addition of (neo)adjuvant systemic therapy to the treatment of patients with colorectal PM prolongs and intensifies treatment. This may temporarily or permanently affect quality of life (QoL). Currently, the effect of the addition of systemic treatment to CRS-HIPEC on QoL and costs is unknown (28).

Insights from clinical studies

In 2017, two systematic reviews addressing the role of (neo) adjuvant systemic therapy in patients with colorectal PM undergoing CRS-HIPEC were published. Both Rovers *et al*. (20) and Waite *et al*. (29) concluded that available evidence on the value of (neo)adjuvant systemic therapy as part of the treatment of colorectal PM was limited. There were no randomized controlled trials (RCT's) available and heterogeneity within the listed prospective and retrospective observational cohort studies was evident. None of the cohort studies were performed according to an adequate intention-to-treat design. Rovers *et al*. concluded that, despite the absence of high-level evidence, neoadjuvant systemic therapy might result in improved survival in selected patients. The value of adjuvant systemic therapy was questioned. However, Waite *et al*. concluded that there is some low-level evidence suggesting that adjuvant chemotherapy prolongs OS. Both study groups concluded that high-quality data investigating this topic are urgently needed.

Since the publication of these two systematic reviews, only one prospective study on this subject has been published: the COMBATAC trial (26). In this multicenter, open-label, single-arm study, patients with synchronous and metachronous colorectal or appendiceal PM were included and were treated with neoadjuvant systemic

therapy (doublet chemotherapy and cetuximab), followed by CRS-HIPEC. Unfortunately, the study was prematurely terminated because of insufficient accrual. However, results of this study are very interesting since this trial is the first to provide insight in the neoadjuvant treatment of patients with colorectal PM in an intention-to-treat setting. In this trial, a significant drop-out rate of patients during neoadjuvant systemic therapy was observed: of 25 patients undergoing neoadjuvant treatment, eventually only 14 patients underwent CRS-HIPEC. This is an interesting finding as most studies only report on patients that received systemic treatment and subsequently underwent CRS-HIPEC. By doing so, a selection bias is introduced and the reported survival results usually do not reflect the true impact of systemic therapy and CRS-HIPEC, as the outcomes of patients that drop-out during neo-adjuvant therapy are not taken into account. Such selection bias is probably also partially underlying the remarkably long survival (about 42 months) in both arms of the recently presented PRODIGE-7 trial (30). In this trial, patients were only included if they underwent at least 6 cycles of systemic treatment and underwent CRS-HIPEC. This phenomenon questions the external validity of this trial as no data were presented on the intention-to-treat group, consisting of all patients that were diagnosed with PM before undergoing (any) treatment.

To investigate the effect of systemic treatment in an RCT, the Dutch CAIRO6 trial was initiated in 2017 and is currently recruiting patients in all HIPEC-centers in the Netherlands. In this trial, patients with resectable synchronous or metachronous colorectal PM are randomized (1:1) for upfront CRS-HIPEC without (neo)adjuvant systemic therapy (group A) or CRS-HIPEC, preceded by neoadjuvant systemic therapy and followed by adjuvant systemic therapy (group B). In group B, the neoadjuvant systemic treatment comprises four cycles of capecitabine with oxaliplatin (CAPOX) or six cycles of 5-fluorouracil/leucovorin with oxaliplatin (FOLFOX) or six cycles of 5-fluorouracil/leucovorin with irinotecan (FOLFIRI), with bevacizumab. In the adjuvant setting, another 4–6 cycles of systemic therapy (without bevacizumab) are administered if patients are considered suitable (31). This intention-to-treat trial is subdivided in a phase II and a phase III study. The phase II study focuses on safety and feasibility of perioperative systemic treatment and was completed early 2019. The primary endpoint of the phase III trial, which is currently recruiting patients, is 3-year OS, with the hypothesis of a 15% increase in OS in group B, as compared to group A.

Insights from translational studies

There is a growing understanding that both the indication for and the type of systemic treatment in CRC patients should no longer be based on traditional clinical parameters such as tumor stage and lymph node status alone. Other factors such as the mutational status of the tumor, microsatellite (in)stability, sidedness of the tumor (left versus right), age and gender of the patient should be considered as well. Recent studies have shown that tumor specific properties may be of importance in the treatment of PM as well.

Consensus molecular subtypes in CRC

In 2015, a collaboration of six study groups who had previously developed a methodology for CRC classification based on gene-expression was established (32). Combining the six subtyping algorithms resulted in the "Consensus Molecular Subtype classification". This classification comprises 4 subtypes in total (CMS1-4), each of which having specific biological behavior and subsequent implications for optimal treatment and prognosis. The CMS4 subtype, also known as the Mesenchymal subtype, is considered the most difficult to treat and most lethal subtype. This subtype is characterized by stromal infiltration, overexpression of extracellular matrix proteins and high mixture with non-cancer cells. Furthermore, it is associated with the activation of transforming growth factor β (TGF β) signaling, angiogenesis, matrix remodeling pathways and complement inflammatory system activation. All of these features correlate with aggressive tumor behavior resulting in poor disease control and prognosis (33). Based on its characteristics, the CMS4 subtype is the most likely subtype to metastasize to distant organs.

Ever since the development of this new classification system, much research on the clinical implications of this CMS classification is performed. Linnekamp *et al*. investigated *in vitro* and *in vivo* drug response to different CMS subtypes and demonstrated that the CMS4 subtype was significantly less sensitive to 5-FU as compared to the other CMS subtypes (34). The same applied to oxaliplatin: CMS4 cell lines were more resistant to oxaliplatin-induced apoptosis compared to other cell lines. This implicates that CMS4 tumors are (partially) chemotherapy-resistant. A clinical study investigating the effects of adjuvant oxaliplatin-

based chemotherapy demonstrated that patients with CMS4 subtype tumors showed worse prognosis as compared to patients with other subtypes, regardless of clinical tumor stage (35). Hence, both translational and clinical studies have shown that CMS4 tumors are less sensitive to oxaliplatin-based chemotherapy as compared to other subtypes.

CMS4 subtype in the context of peritoneal metastases

A recent study demonstrated that the CMS4 subtype was highly prevalent in primary tumors of patients presenting with PM (60%), which was significantly higher than the incidence of CMS4 in all patients with stage I-IV CRC, (23%, P=0.002) (36). More importantly, the majority of PM (75%) were classified as CMS4. This is significantly higher as compared to the incidence of CMS4 in LM as reported in two other studies (47%, P=0.004 and 46.4%, P=0.007) (37,38).

Consequences of the overrepresentation of CMS4 for the treatment of colorectal PM

The finding that CMS4 is the predominant subtype in PM plus CMS4 being relavitely resistand to oxaliplatin, as described above, needs to be confirmed in larger future studies. These findings would indeed confirm the longstanding notion amongst experts that PM are resistant to systemic chemotherapy. Interestingly, recent in-vitro studies using patient-derived organoids of colorectal PM also showed oxaliplatin-resistance in doses that are currently used in HIPEC-regimens (39). Besides a very promising tool for individual-patient level testing of drug efficacy prior to HIPEC, this suggests that oxaliplatin might be inefficient during HIPEC.

If overrepresentation of oxaliplatin-resistant CMS4 in colorectal PM will be further confirmed, it may have profound consequences for the treatment of PM. Firstly, the systemic treatment of these patients should be re-evaluated as most regimens are currently oxaliplatin-based. Secondly, it would provide—at least in part—an explanation why recent RCTs investigating the efficacy of HIPEC may have failed to show such an effect. In both the French PRODIGE-7 trial and the Dutch COLOPEC-trial, an oxaliplatin-based HIPEC-regimen was used (30,40). This may indeed not be effective in intrinsic oxaliplatin-resistant CMS4-type PM. Thus, not the HIPEC-procedure by itself as tested in these trials but the chemotherapeutic agent used during HIPEC may be ineffective. Future research in the treatment of PM, both systemically and intraperitoneally during HIPEC, should focus on investigating cytotoxic agents specifically towards CMS4-subtype tumors.

The importance of the KRAS/BRAF pathway

Besides CMS4, mutations occurring in the genome of the PM may be important when considering systemic treatment in these patients. Recently, mutations in the KRAS/BRAF pathway have been investigated. The BRAF and KRAS proteins act as downstream secondary messengers of the epidermal growth factor receptor (EGFR), which regulates cancer-cell proliferation, apoptosis and tumor-induced neoangiogenesis (41). Anti-EGFR therapy prevents intracellular tyrosine kinase activation and, in that way, it counteracts the activation of KRAS and BRAF proteins. The application of these regimens is proven to be effective in metastatic CRC patients, resulting in improved OS, most effectively in combination with standard cytostatic regimens (42-45). As such, anti-EGFR may also be considered in patients with PM.

However, mutations in these signaling pathways downstream from EGFR may induce pathway activation which is independent of EGFR. As a result, EGFR blockage at the cell surface by EGFR-targeted regimens is ineffective in patients having such mutations (46).

KRAS gene mutations are present in 35–45% of patients with metastatic CRC (47,48). Furthermore, in patients with the KRAS wildtype, another 40–60% of patients are non-responders to EGFR-targeted therapy (49). Previous studies suggest this insensitivity could be due to mutations in other genes, like BRAF (46). BRAF mutations are present in 5–10% of metastatic colorectal tumors (50,51). However, most studies on this subject included mainly patients with colorectal LM (52-58).

A recently published study by Graf *et al*. (59) demonstrated that KRAS mutations were present in 46% of patients with colorectal or appendiceal PM. BRAF mutations were present in 11% of these patients and were associated with worse OS compared to BRAF wildtype tumors. KRAS mutations were not associated with worse OS in this study. Another study presented a higher percentage of BRAF mutations in patients with isolated colorectal PM, compared to patients having systemic metastases of colorectal origin (18% *vs*. 9%) (60). Moreover, in this study, BRAF mutations were not associated with worse OS, as compared to wildtype BRAF patients. A third study also demonstrated impaired OS in KRAS/

BRAF mutated tumors as compared to wildtype tumors, and this was regardless the administrated therapy (61). Taken together, mutations in the cancer genome such as in KRAS and BRAF have an important prognostic effect in colorectal PM. Future research should elucidate the mechanisms by which these mutations impair survival, potentially identifying targets for more effective treatment.

Conclusion and future perspective

There is currently no consensus regarding the value of systemic therapy either in a neoadjuvant setting, adjuvant setting or both in patients with colorectal PM undergoing CRS-HIPEC. Two systematic reviews concluded there is no high-level evidence to support either of the strategies. As such, the decision whether or not to add systemic treatment to CRS-HIPEC remains a matter of expert opinion, resulting in multiple protocols around the world. Ideally, this question should be answered with data from an RCT. Currently, such an RCT is recruiting patients in the Netherlands. The recently published COMBATAC-trial illustrated the importance of intention-to-treat analysis to avoid selection bias given the high number of patients that did not proceed to CRS-HIPEC after neoadjuvant treatment. Studies investigating the effect of systemic treatment in combination with CRS-HIPEC that only report on postoperative patients are probably subject to (severe) selection bias, as for instance the recently presented PRODIGE7-trial.

The notion that the majority of PM are probably of the CMS4-subtype and that this subtype is relatively resistant to various cytostatic drugs, including oxaliplatin, sheds new light on currently available systemic and intraperitoneal treatment regimens containing oxaliplatin. New cytotoxic agents specifically targeting CMS4 may further improve treatment of patients with colorectal PM.

Further analysis of specific mutations in the cancer genome of PM may provide important information on the efficacy of modern treatments (e.g., anti-EGFR treatment), may give prognostic information and may identify new targets for treatment.

In the future, systemic treatment of patients with PM will probably become individualized, based on their specific cancer genome and the consensus molecular subtype of their metastases. Advanced in-vitro testing of drug sensitivity prior to start of treatment, such as patient derived organoid technologies, may help to further enhance tailored treatment.

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Footnote

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