

Review

Regimens of Intraperitoneal Chemotherapy for Peritoneal Carcinomatosis from Colorectal Cancer

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Abstract. *Although systemic chemotherapy has been improved, peritoneal carcinomatosis remains a factor of poor prognosis in patients with colorectal cancer. In order to achieve a higher drug concentration in the peritoneal cavity, intraperitoneal chemotherapy has been performed. However, the optimal regimen for intraperitoneal chemotherapy has not been determined. In this review of intraperitoneal chemotherapy for colorectal cancer, we summarize regimens of hyperthermic intraperitoneal chemotherapy (HIPEC) and other intraperitoneal chemotherapy modalities, such as early postoperative intraperitoneal chemotherapy (EPIC) and sequential postoperative intraperitoneal chemotherapy (SPIC). Mitomycin C and oxaliplatin are the most common chemotherapeutic agents used for HIPEC. Some combination therapies such as those involving bevacizumab, H₂O₂, and amifostine have potential to increase HIPEC efficacy. 5-Fluorouracil is used mainly for EPIC and SPIC. Some new agents such as paclitaxel, melphalan, and various nanoparticles have been developed. These novel chemotherapeutic agents may achieve clinical implementation in the future.*

The frequency of peritoneal carcinomatosis is approximately 7.3-7.9% in patients with colon cancer at the time of primary resection, which is relatively low compared to other sites of

metastasis such as lung and liver (1). However, it is associated with a very poor prognosis, with a median survival of 6 months in untreated cases (1, 2). Although overall survival for treatment with systemic chemotherapy has improved, peritoneal carcinomatosis remains a factor of poor prognosis (3, 4).

In 1978, the intraperitoneal administration of chemotherapeutic agents was first described as a method to achieve higher drug concentration in the peritoneal cavity than by intravenous chemotherapy (5). Subsequently, the efficacy of intraperitoneal chemotherapy has been demonstrated for ovarian, gastric, and colorectal cancer (6, 7). In regard to colorectal cancer, Sugarbaker *et al.* stated that cytoreductive surgery (CRS) and intraperitoneal chemotherapy may potentially increase long-term survival (8, 9). After hyperthermic intraperitoneal chemotherapy (HIPEC) was introduced (10), this procedure has become widely implemented in clinical practice. One randomized controlled trial revealed a significant efficacy of CRS and HIPEC (11, 12).

However, due to the high morbidity (20-50%) and mortality (1-6%) of both CRS and HIPEC (11, 13-15), it is only performed in a limited number of Institutions. Moreover, the efficacy of CRS and HIPEC is limited in patients with highly advanced peritoneal carcinomatosis (16). The development of optimized intraperitoneal chemotherapy regimens may be important to reduce morbidity and mortality, and to improve the effectiveness in highly advanced cases.

In this review, we summarize the current status of intraperitoneal chemotherapy for colorectal cancer focusing on the treatment regimens.

HIPEC

The regimens of intraperitoneal chemotherapy consist of HIPEC, early postoperative intraperitoneal chemotherapy (EPIC), and sequential postoperative intraperitoneal

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chemotherapy (SPIC). HIPEC is the most common procedure for intraperitoneal chemotherapy. The temperature of the chemotherapeutic agent is maintained at 42-43°C to achieve a high drug concentration in the tumor tissue (17). Hyperthermic chemotherapy has been found to increase the concentration and efficacy of doxorubicin in animal models (18, 19). This synergistic effect was also demonstrated for mitomycin C (MMC), cisplatin, and oxaliplatin (17, 20, 21).

Chemotherapeutic agents for HIPEC. There are over 50 studies regarding the treatment of colorectal cancer with HIPEC. The major studies analyzing more than 100 patients are listed in Table I (11-13, 22-38). MMC and oxaliplatin are the most common chemotherapeutic agents used for HIPEC. There have been multiple retrospective studies examining the efficacy of MMC and oxaliplatin for HIPEC treatment. Leung *et al.* demonstrated that patients treated with HIPEC using oxaliplatin had better prognoses than those receiving MMC-based HIPEC (median survival: 56 vs. 26 months, respectively) (39). Conversely, Prada-Villaverde *et al.* reported that HIPEC with MMC may be superior to oxaliplatin-based HIPEC when patients have favorable histology or a low burden of peritoneal carcinomatosis (median survival: 54.3 vs. 30.4 months, respectively) (40). In regards to morbidity, despite the frequency of thrombocytopenia being slightly higher in patients receiving oxaliplatin-based HIPEC (41), the mean operative time, mean hospital stay, and the rate of grade 3/4 morbidities according to Common Terminology Criteria for Adverse Events v3.0 were not significantly different between HIPEC treatments using MMC/doxorubicin or oxaliplatin (42). At present there exists no prospective study that compares these two HIPEC regimens. Randomized controlled trials are necessary to standardize these chemotherapeutic regimens.

Irinotecan or cisplatin is sometimes administered in combination with MMC as shown in Table I. Quenet *et al.* attempted to demonstrate the effect of adding irinotecan to the treatment regimen of patients receiving HIPEC using oxaliplatin (26). However, the overall survival was not significantly different between treatment groups with and without the addition of irinotecan. A phase I study of HIPEC with MMC and irinotecan has been initiated (43). Some combination therapies may become a standard HIPEC regimen in the future.

Agents with potential to increase HIPEC efficacy. Bevacizumab, which targets vascular endothelial growth factor, may increase the efficacy of chemotherapy when administered in the perioperative setting. Bevacizumab was shown to increase the intraperitoneal concentration of oxaliplatin in a murine model (44). Ceelen *et al.* reported that patients receiving HIPEC therapy using either oxaliplatin or MMC, combined with preoperative

intravenous bevacizumab, showed a better prognosis than those without bevacizumab (median survival: 39 vs. 22 months, respectively) (34). Chia *et al.* reported an increase in treatment efficacy with an intraperitoneal administration of MMC, doxorubicin, or cisplatin combined with intraperitoneal bevacizumab (45). However, a rodent model of HIPEC with oxaliplatin found that efficacy was not improved when adding intraperitoneal bevacizumab (46). Moreover, in a retrospective study, the postoperative complication rate in patients treated by HIPEC in combination with bevacizumab was higher than in patients treated by HIPEC only (major morbidity: 33.8% vs. 18.6%, respectively) (47). In particular, the frequency of intra-abdominal abscess was significantly higher in the group using bevacizumab compared to the group not using bevacizumab (13.8% vs. 2.9%, respectively).

MMC in combination with H₂O₂ has been shown to increase HIPEC efficacy. Harrison *et al.* demonstrated the safety of this procedure in a phase I trial. H₂O₂ was found to increase the concentration of MMC in the peritoneal cavity and reduce the serum concentration of MMC, which may intensify antitumor effects and reduce MMC-related toxicity (48).

Agents with potential to reduce HIPEC-related adverse effects. HIPEC with cisplatin has an associated risk of renal dysfunction during treatment. Bouhadjari *et al.* investigated the effect of amifostine, which is free radical scavenger, for patients treated with HIPEC using oxaliplatin (49). Thirty-one patients receiving amifostine had a lower risk for renal dysfunction (which is defined as a creatinine clearance rate lower than 30 ml/min), compared to 21 patients not receiving amifostine (13% vs. 33%, respectively).

Postoperative Intraperitoneal Chemotherapy: EPIC and SPIC

Primarily, there are two types of regimens for postoperative intraperitoneal chemotherapy. EPIC is usually performed 4-6 days after surgery, while SPIC may continue for several months. A randomized control trial revealed that the prognosis of patients treated with intraperitoneal 5-fluorouracil (5-FU) and leucovorin for 6 months after surgery was better than that of patients receiving systemic chemotherapy (50). As shown in Table II (23, 27, 51-63), 5-FU is used mainly for EPIC and SPIC.

The overall survival with EPIC therapy was superior to that with HIPEC in a murine model (64). However, a clinical study found that the 5-year survival of patients treated using EPIC, as compared to HIPEC, was worse and was associated with a higher rate of digestive fistulas (55). Moreover, the median survival of patients treated with SPIC was worse than HIPEC in a retrospective study with a small sample size (median survival: 23.9 and 36.5 months, respectively) (15).

Table I. Hyperthermic intraperitoneal chemotherapy (IPC) for colorectal cancer (limited only to studies of more than 100 cases).

Author (Ref)	Year	n	Agent for IPC
Pestieau <i>et al.</i> (22)	2000	104	MMC
Verwaal <i>et al.</i> (11)	2003	105	MMC
Glehen <i>et al.</i> (23)	2004	506	MMC+cisplatin
Cavaliere <i>et al.</i> (24)	2006	120	MMC+cisplatin oxaliplatin
Verwaal <i>et al.</i> (12)	2008	105	MMC
Elias <i>et al.</i> (14)	2010	523	MMC±cisplatin Oxaliplatin±irinotecan
Chua <i>et al.</i> (25)	2011	294	MMC
Quenet <i>et al.</i> (26)	2011	146	Oxaliplatin±irinotecan
Cashin <i>et al.</i> (27)	2012	151	MMC Oxaliplatin+irinotecan
Passot <i>et al.</i> (28)	2012	120	MMC±irinotecan Oxaliplatin±irinotecan
Goere <i>et al.</i> (29)	2013	107	Oxaliplatin±irinotecan
Yonemura <i>et al.</i> (30)	2013	142	MMC+cisplatin
Kuijpers <i>et al.</i> (31)	2013	660	MMC
Esquivel <i>et al.</i> (32)	2014	1013	Oxaliplatin or MMC or other
Braam <i>et al.</i> (33)	2014	132	MMC
Ceelen <i>et al.</i> (34)	2014	152	Oxaliplatin or MMC
Levine <i>et al.</i> (35)	2014	232	MMC
Faron <i>et al.</i> (36)	2016	173	Oxaliplatin+irinotecan
Froysnes (37)	2016	119	MMC
Maillet <i>et al.</i> (38)	2016	231	Not described

MMC: Mitomycin C.

Table II. Summary of normothermic intraperitoneal chemotherapy (IPC).

Author (Ref)	Year	n	Method	Agent for IPC
Glehen <i>et al.</i> (23)	2004	506	EPIC±HIPEC	5-FU
Kecmanovic <i>et al.</i> (51)	2005	18	HIPEC+EPIC	5-FU
Da Silva <i>et al.</i> (52)	2006	70	HIPEC+EPIC	5-FU±MMC
Fuzun <i>et al.</i> (53)	2006	29	HIPEC+EPIC	5-FU
Bijelic <i>et al.</i> (54)	2007	49	HIPEC+EPIC	5-FU±MMC
Elias <i>et al.</i> (55)	2007	23	EPIC	5-FU+MMC
Piso <i>et al.</i> (56)	2007	32	HIPEC+EPIC	5-FU
Yan <i>et al.</i> (57)	2008	50	HIPEC+EPIC	5-FU
Bretcha-Boix <i>et al.</i> (58)	2010	20	HIPEC+EPIC	5-FU
Saxena <i>et al.</i> (59)	2010	63	EPIC±HIPEC	5-FU
Cashin <i>et al.</i> (60)	2012	57	SPIC	5-FU+leucovorin
Klaver <i>et al.</i> (61)	2012	24	EPIC±HIPEC	5-FU
Chua <i>et al.</i> (62)	2013	75	HIPEC+EPIC	5-FU
Huang <i>et al.</i> (63)	2014	62	HIPEC+EPIC	Docetaxel+carboplatin

HIPEC: Hyperthermic intraperitoneal chemotherapy, EPIC: early postoperative intraperitoneal chemotherapy, SPIC: sequential postoperative intraperitoneal chemotherapy, MMC: mitomycin C.

Combining EPIC or SPIC with HIPEC. Since there are few data supporting the superiority of either EPIC or SPIC treatment over HIPEC, the combination of postoperative intraperitoneal chemotherapy with HIPEC has been performed in several studies (Table II). Although the combination of

HIPEC with either EPIC or SPIC may improve survival, the frequency of postoperative complications was higher. Moreover, no survival benefit was observed when the combination of HIPEC using MMC and EPIC using 5-FU was compared with the oxaliplatin-based HIPEC alone (62, 65).

Other Therapeutic Agents and Methods for Intraperitoneal Chemotherapy

Melphalan. Sardi *et al.* reported the effect of melphalan, an alkylating agent, in second-line intraperitoneal chemotherapy for 25 patients with peritoneal carcinomatosis, who had poor response to CRS/HIPEC treatments using MMC or oxaliplatin (66). There was no postoperative mortality and grade III-IV morbidity was 23%, which is comparable to that with first-line HIPEC. The long-term overall survival was 89%, 45%, and 30% at 1, 3, and 5 years, respectively, which is acceptable for a second-line treatment.

Paclitaxel. The optimal intraperitoneal chemotherapeutic agent is considered to exhibit the property of retaining a high drug concentration in the peritoneal cavity for an extended period of time. Slowly absorbed agents can meet this aim. Since paclitaxel is water insoluble, it requires solubilization in polyoxyethylated castor oil, also called Kolliphor EL. Its large particle size (10-12 nm in diameter) enables high concentrations of agents to remain in the peritoneal cavity for a longer duration (21). Moreover, slow absorption leads to suppression of serum levels of paclitaxel, which is associated with a lower incidence of adverse effects (7, 67).

The clinical efficacy of paclitaxel was demonstrated for peritoneal carcinomatosis originating from primary ovarian or gastric cancer (67, 68). Although the effect of paclitaxel was only evaluated in an animal model of colorectal cancer, intraperitoneal administration was superior to intravenous administration in terms of the inhibitory effects on peritoneal tumor growth (69, 70). Taxane-based systemic chemotherapy failed to demonstrate efficacy in the treatment of colorectal cancer (71).

Pressurized aerosol. Pressurized aerosols, using oxaliplatin, cisplatin, or doxorubicin, are capable of increasing the local concentration of chemotherapeutic agents (72). Since only 10% of a typical systemic dose is enough to reach a high local concentration, side-effects may be reduced by maintaining a low serum concentration. Although major adverse effects were not reported according to several case series (73, 74), the efficacy of this chemotherapeutic regimen has not been demonstrated.

Low-molecular weight heparin. Reviparin, a low-molecular weight heparin, has shown some potential as an intraperitoneal chemotherapeutic agent in an animal study. Pross *et al.* demonstrated that the intraperitoneal administration of reviparin was able to reduce tumor weight as a dose-dependent effect (75). The suppression of tumor growth and metastasis is considered to be caused by a decrease in cell proliferation, cell adhesion, and cell invasion.

Nanoparticles. In an effort to achieve slow absorption of therapeutic agents, various nanoparticles have been developed. Nanoparticles are agents of 20-100 nm in molecular diameter which are suitable for absorption into tumor tissue through the enhanced permeability and retention effect (76).

Paclitaxel-loaded copolymer nanoparticles are able to maintain higher agent concentrations in the peritoneal cavity when compared to paclitaxel (77). Docetaxel-loaded biodegradable porous microspheres, 5-FU-loaded micelles, and cisplatin in a thermosensitive chitosan-based hydrogel have also shown an increase in tumor regression effects in a murine model (78, 79). For colorectal cancer, these therapeutic agents have only been investigated using animal models.

Adjuvant Intraperitoneal Chemotherapy to prevent Peritoneal Carcinomatosis

Adjuvant intraperitoneal chemotherapy has been examined for the prevention of peritoneal recurrence (80). Noura *et al.* reported that intraperitoneal chemotherapy with MMC prevented peritoneal recurrence in patients with colorectal cancer with positive peritoneal lavage cytology (81). Scheithauer *et al.* also demonstrated the efficacy of early postoperative intraperitoneal chemotherapy using 5-FU and leucovorin for 241 patients with stage III or T4 colon cancer (82). A randomized control trial demonstrated that peritoneal recurrence decreased when administering postoperative intraperitoneal 5-FU chemotherapy in patients with stage II colon cancer (83). However, in this trial the efficacy of adjuvant intraperitoneal chemotherapy was not observed in patients with stage III colon cancer.

HIPEC has also been performed as adjuvant chemotherapy (84). Tentes *et al.* reported that patients receiving HIPEC with MMC or oxaliplatin had a better prognosis than those receiving EPIC with 5-FU (85). Based on these results, a randomized control trial for HIPEC with oxaliplatin has been initiated for patients with T4 or intra-abdominally perforated colon cancer without distant metastases (86).

Conclusion

We reviewed the chemotherapeutic agents used in intraperitoneal chemotherapy for colorectal cancer. MMC and oxaliplatin are commonly utilized agents for HIPEC, with 5-FU typically used for both SPIC and EPIC. However, there have been few prospective studies investigating the optimal intraperitoneal chemotherapy regimen. Some drugs, such as bevacizumab, may increase the efficacy of intraperitoneal chemotherapy, while others, such as paclitaxel and nanoparticles, have the potential to be alternative chemotherapeutic agents. Moreover, intraperitoneal chemotherapy may prevent recurrence in patients with a high risk for

peritoneal carcinomatosis. In the future, it is necessary to develop safe and more effective chemotherapeutic regimens, as well as establish comprehensive criteria for intraperitoneal chemotherapy.

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