Editorial Commentary

Adjuvant hyperthermic intraperitoneal chemotherapy in patient with locally advanced colon cancer

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For colon cancer, one of the risk factors identified to develop peritoneal carcinomatosis is the trans-serosal invasion of the tumour (pT4a-b). This feature represents a significant risk factor for survival by itself, in this way, the prognosis of pT4 becomes similar to patients with N2 and M1 stages with a 5 years overall survival of 20% (1). Local relapse and peritoneal recurrence for T4 patients is estimated in 15.6% and 36.7% for 12 and 36 months respectively from surgical resection (2).

When an oncologic surgeon has to deal with a locally advanced colon carcinoma, he always thinks that there should be an additional treatment for his patient to avoid a future loco-regional relapse. Most of the times, an oncologic resection in a locally advanced colon carcinoma means an aggressive surgery that includes multi-visceral resections and a hard postoperative course. After this great effort made for the patient and doctors, the likelihood of a local relapse might rise up to 36% (2).

One of these additional treatments is the administration of intraperitoneal chemotherapy in hyperthermic conditions (HIPEC), although we thought that it will be useful for this type of patients, we must be cautious and wait for the evidence to use it as a prophylactic treatment. In that sense, recently has been published the COLOPEC study (3), which has failed to demonstrate an improvement in the survival with the use of 30 minutes of HIPEC with oxaliplatin as adjuvant treatment in locally advanced colon cancer.

This study was based on the excellent results from previous studies performed. They delivered HIPEC after primary resection with oxaliplatin or mitomycin C. A significant reduction in peritoneal relapse and an improvement of survival were demonstrated (4,5). The main problem was that these studies had multiple bias to use them as an evidence to use HIPEC as standard prophylactic treatment. COLOPEC has been the first randomized controlled trial that has analysed the use of adjuvant HIPEC in the treatment of locally advanced and perforated colon cancer. Briefly, the experimental arm has been treated by primary resection and HIPEC (primary clinically T4) or delayed additional HIPEC after emergent surgery or confirmed pathological T4 (up to 8 weeks after surgery) by laparoscopic or open approach. A bidirectional HIPEC protocol was used: fluorouracil (400 mg/m^2) and leucovorin (20 mg/m^2) were delivered intravenously followed by HIPEC using oxaliplatin (460 mg/m^2) in a single dose for 30 min at a temperature of 42–43 ℃.

Some troubles were found on this trial that the authors added in the discussion. The regimen of HIPEC used in this trial as prophylactic therapy had not demonstrated efficacy when it was used as adjuvant therapy in peritoneal carcinomatosis from colon cancer in the French multicentre trial PRODIGE 7 (6) where the authors considered the possibility that the time of HIPEC is too short to see the effect of the intraperitoneal oxaliplatin, or the drug was not effective for intraperitoneal delivery. This trial meant the change in the peritoneal carcinomatosis from colon management performing the cytoreductive surgery without HIPEC or using mitomycin C. Another question is the administration of HIPEC in a second stage could increase

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Table 1 Active randomized controlled trial in prophylactic HIPEC for colon carcinoma

Study	Patients	N	Treatment	Endpoint
Promenade Trial (8), Italy (recruitment)	Colon carcinoma T4, T3 mucinous	130	Experimental: Cytoreductive surgery and target organs + HIPEC with oxaliplatin 30 min	Disease free survival
University Zhejiang (9), RCT (recruitment)	High risk patients colon carcinoma: minimal carcinomatosis, ovarian metástasis, perforated and T4	300	Experimental: HIPEC with mitomycin C (30 mg/m^2); Closed technique: 60 min, 43 ℃	Disease free survival
HIPECT4 (7), Spain (recruitment)	Colon carcinoma cT4N0-2, M0	200	Experimental: Cytoreductive surgery +HIPEC mitomycin C 30 mg/m^2, 60 min, 43 ℃	Locoregional relapse

the morbidity and length of stay of these patients, as well as the potential delay of the usual adjuvant systemic treatment. The last trouble is that the endpoint was evaluated at 18 months after treatment, maybe this time of follow-up was too short to demonstrate a reduction in the rate of peritoneal relapse or survival benefits.

A Spanish clinical trial is on going, called HIPECT4 (7). This trial is still in a recruitment phase. This trial includes patients diagnosed of locally advanced colon carcinoma by radiological tests. The patient defined as cT4a/b N 0-2 M0 colon cancer are included on it. For the experimental arm the patient is treated by complete cytoreduction associating resection of target organs and HIPEC with mitomycin C 30 mg/m^2 during 60 min. Open or laparoscopic approach are allowed. The primary endpoint is the rate of loco-regional relapse or peritoneal carcinomatosis with a follow-up of 36 months. This trial avoids a second stage surgery, its follow-up is longer and the drug used is mitomycin C instead of oxaliplatin (*Table 1*).

PROMEDANE study (8) is other randomized study where in its experimental arm the patients will receive oxaliplatin 460 mg/m^2 and before the beginning of HIPEC an intravenous infusion of 400 mg/m^2 of 5-FU and 20 mg/m^2 of leucovorin will be administered, the primary endpoint is the incidence of peritoneal recurrence at 36 months. This study is not yet recruiting.

The third one comes from the Zhejiang University (9) where in the experimental arm the patients will receive HIPEC with mitomycin C (30 mg/m^2 of body surface area), closed technique, as preferred. Duration: 60 minutes. Mean Intra-abdominal Temperature: 43 ℃. This study is yet recruiting.

In spite of the belief of the benefits that the HIPEC could offer on these patients to avoid the metachronous peritoneal carcinomatosis or peritoneal relapse, we have to wait until the evidence says that the HIPEC gives a substantial benefits for these patients as a prophylactic treatment before considering its systematic use.

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