Cytoreductive Surgery and HIPEC for the Prevention and Treatment of Colorectal Peritoneal Metastases: Lessons Learnt from Three Recent Randomized Trials

Dario Baratti[1*], Luca Sorentino[1], Marcello Guagliò[1]

[1]Peritoneal Surface Malignancy Program, Colo-rectal Cancer Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, via Venezian, 1 20133 Milano, Italy.

EDITORIAL

Please cite this paper as: Baratti D. Cytoreductive surgery and HIPEC for the prevention and treatment of colorectal peritoneal metastases: lessons learnt from three recent randomized trials. Journal of Investigative Oncology 2020; 1(1): 11-15.

***Corresponding Author:**

Dr. Dario Baratti, Peritoneal Surface Malignancy Program, Colo-rectal Cancer Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, via Venezian, 1 20133 Milano, Italy; Tel: +390223903441; Fax: +390223903228;

E-mail: dario.baratti@istitutotumori.mi.it

ABSTRACT

The final results of three large randomized trials that have recently addressed the role of Hyper thermic Intraperitoneal Chemotherapy (HIPEC) in the management of colorectal cancer peritoneal metastases (CRC-PM) are presented and critically appraised. Prodige-7 trial randomized patients with established CRC-PM after optimal cytoreductive surgery (residual tumor <1mm) to no HIPEC vs. oxaliplatin-based HIPEC. COLOPEC randomly assigned patients who had curative-intent surgery for pT4a/b or perforated CRC to oxaliplatin-based HIPEC given either at primary resection, or staged 5-8 weeks later, and followed by adjuvant systemic chemotherapy (s-CT), vs. standard adjuvant s-CT only. ProphyloCHIP trial randomized HIPEC combined with second-look surgery after adjuvant s-CT vs. standard surveillance in high-risk patients, defined as history of peritoneal or ovarian metastases or perforated primary CRC.

Key Words: Cytoreductive surgery; Colorectal cancer; Hyper thermic Intraperitoneal chemotherapy (HIPEC); Peritoneal metastases; Randomized trials

EDITORIAL

Peritoneal surfaces represent one of the most common sites for metastatic spread of colorectal cancer (CRC). In recent population-based studies, peritoneal metastases (PM) are detected in 3.8-4.3% of patients at primary diagnosis, and another 3.5-4.2% after curative primary surgery. [1-3] However, these incidence rates are likely underestimated because PM are more difficult to detect than liver or lung metastases.

CRC-PM have been historically associated with poor prognosis. Median survival was only about 6 months with supportive care or 5-fluoruracil-based systemic chemotherapy (s-CT). [4] Treatment results have improved with highly effective chemotherapy and biologically targeted agents. Nevertheless, prognosis peritoneal metastatic CRC is still worse than non-peritoneal metastatic CRC, even if it is treated with these modern combinations. [5]

Aggressive cytoreductive surgery (CRS) associated with hyper thermic intraperitoneal chemotherapy (HIPEC) to control the microscopic residual tumor has recently resulted in survival improvements over historical controls, and a successful randomized trial. [4,6] In this trial, 105 CRC-PM patients were randomly assigned to 5-fluorouracil-

based s-CT with or without palliative surgery (control group), or CRS plus mitomycin-based HIPEC, followed by the same s-CT (experimental group). Median overall survival was 12.6 and 22.3 months in control and experimental arm, respectively (P=0.032). [6]

The final results of three randomized trials of HIPEC in colorectal PM have been recently presented: Prodige-7 trial assessed HIPEC in the treatment of established PM, [7] and both COLOPEC and PropyloCHIP trials in the adjuvant setting. [8-9] Here, the main findings of these important studies will be discussed.

TREATMENT OF COLORECTAL PERITONEAL METASTASES

Criticisms to the first Dutch trial have centred on the use of out-dated 5-fluoruracil-based s-CT (even though a number of patients received irinotecan), and the impossibility to determine the benefit associated with HIPEC in addition to CRS. [6] The Prodige-7 trial was designed to investigate the specific value of HIPEC after complete CRS and s-CT. Patients with histologically proven, low-to-moderate extent CRC-PM were randomized after optimal surgery (residual tumor <1mm) to either no HIPEC or oxaliplatin-based HIPEC. All patients received six months of oxaliplatin or irinotecan-containing s-CT, either preoperatively, postoperatively, or both. The primary endpoint was overall survival. [7]

Over a six-year period (2008-2014), 265 patients were randomized in 17 French centres. After a 64-month median follow-up, median overall survival was 41.7 months in HIPEC arm, and 41.2 months in non-HIPEC arm (hazard ratio [HR]=1.00; 95% confidence interval [CI]=0.73-1.37; P=0.995). In the two groups, disease-free survival was 13.1 versus 11.1 months (HR=0.91; 95%CI=0.69-1.19; P=0.486), respectively. Sixty-day severe morbidity was higher in HIPEC group (24.1% vs. 13.6%; P=0.030). An unplanned subset analysis revealed a survival advantage in patients with medium tumor load (defined as peritoneal cancer index of 11 to 15): median survival was 41.6 months in 28 patients who had HIPEC, and 32.6 months in 18 controls with no HIPEC (P=0.003).

A relevant finding of the French trial is the unexpectedly high survival rate in CRS alone arm, that highlights the leading role of surgery in patients' outcome. It has not to be forgotten that until a couple of decades ago these patients were regarded to as terminally ill patients only to be palliated. Today, awareness that PM may represent a local-regional disease stage, and standardization of peritonectomy procedures to remove tumor implants have radically changed their treatment paradigm.

Conversely, HIPEC had no effect on overall and recurrence-free survival. This lack of benefit may have several explanations. First of all, the study design: Prodige-7 trial was designed to demonstrate an overall survival increase from 30 (non-HIPEC arm) to 48 months (HIPEC arm), with a two-sided 5% significance level and 80% power. At the time of Prodige-7 drafting, the only available literature data to estimate survival of patients treated with complete CRS, s-CT and no HIPEC were a small group of 19 patients from a randomized trial prematurely closed in the year 2000.[10] However, those patients were treated with out-dated 5-fluorouracil-based s-CT. Presumably, this has resulted in underestimation of survival in controls, and overestimation of the desired treatment effect. In comparison, the expected median overall survival improvement in s-CT trials is usually around 5 months. [11] Second, patients were not stratified taking into account biological determinants, such as RAS/RAF mutations, microsatellite instability and primary tumor side. Even though the randomized study design should have balanced potential prognostic factors between arms, no information about the molecular characterization of patients is available. Third, the cross-over of 16 patients who relapsed after CRS alone and underwent second CRS with HIPEC may have resulted in increased survival for non-HIPEC group.

Fourth, a growing body of literature suggests a possible prognostic impact of s-CT timing, as preoperative (neoadjuvant) s-CT seems to give greater benefit.[4] Timing of chemotherapy administration and median number of preoperative cycles were similar between arms, but this may have affected the interpretation of results. Preoperative s-CT is often administered to test tumor

chemosensitivity and biologic aggressiveness. In Prodige-7 trial, progression under preoperative s-CT was not among formal exclusion criteria, but it is possible that the investigators have excluded patients with progressive disease. Unfortunately, data on response to treatment are not available, and the high level of patient selection might not only explain the lack of HIPEC efficacy but also limit the external validity of the trial and generalization to the overall CRC-PM population.

Finally, it has been speculated around the uncertain efficacy of intraperitoneal oxaliplatin. Although oxaliplatin is one of the drugs of choice for metastatic CRC, factors such as previous oxaliplatin-based s-CT may induce alterations in chemosensitivity. Also, exposure time is a major determinant of platinum compounds efficacy. A recent study has demonstrated that 50% maximal inhibitory concentration (IC50) in SW620 colon cancer cell line treated for 30 minutes was significantly higher than a 2-hour treatment (10.6 vs. 2.8 mg/mL. P=0.02), suggesting that 2-hour duration is superior to 30 minutes. [11]

The only comparative nonrandomized series assessing the added value of mitomycin-C-based HIPEC is a study by our group. We compared 48 patients treated by perioperative s-CT and CRS with no HIPEC with 48 matched controls treated by s-CT and CRS/HIPEC. Analogously to the Prodige-7 trial, survival was not different between groups (34.8 vs. 39.3 months; P=0.702) but, unlike the French trials, severe morbidity was also not different (29.2% vs. 27.1%; P=1.000). Our results further support the leading role of surgery in patients' outcome, but mitomycin-C alone or combined with cisplatin was not associated with a significant survival difference.

PREVENTION OF COLORECTAL PERITONEAL METASTASES

Strategy involving local-regionally delivered chemotherapy to prevent the outgrowth of occult peritoneal seeding into macroscopic metastases is supported by a strong rationale: CRS/HIPEC improve CRC-PM patients' survival, but most of them are not suitable for this demanding treatment due to extensive peritoneal involvement, systemic metastases, and/or poor clinical conditions. Also, CRS/HIPEC is maximally effective and safe when small-volume disease is treated. Finally, the absence of symptoms, as well as current limitations of imaging, hampers early diagnosis and treatment. [4]

On these bases, the use of HIPEC for the prevention or early treatment of CRC-PM has been tested at different time-points, either simultaneously with primary surgery,[13-15] at the time of second-look surgery after adjuvant s-CT,[9] or as a staged procedure at 5-8 weeks postoperatively.[8] In the COLOPEC trial, Dutch investigators randomly assigned 204 patients who had curative-intent surgery for pT4a/b or perforated CRC to oxaliplatin-based HIPEC given either at primary resection in 9% of patient, or 5-8 weeks later in the remaining 91%, and followed by adjuvant s-CT. The control arm received standard adjuvant s-CT only. All patients showing no recurrent disease at 18 months underwent diagnostic laparoscopy. There was no difference in 18-month peritoneal-free survival between groups: 80.9% (95%CI=73.3-88.5) for the experimental arm vs. 76.2% (95%CI=68-84.4) for the control arms (P=0.28).[8]

Between 2008 and 2014, the French trial ProphyloCHIP enrolled 150 patients who had curative intent surgery for primary CRC associated with risk-factors for metachronous PM, defined as history of ovarian or low-volume PM resected with the primary, or perforated primary.[9] After 6-month adjuvant s-CT, and an additional 6-month follow-up, patients who were clinically, radiologically and biochemically disease-free were randomized between systematic second-look surgery plus oxaliplatin-based HIPEC vs. standard surveillance.

During the second-look laparotomy, CRC-PM was diagnosed in 52% of patients. After a median follow-up of 51 months, 3-year disease-free survival was 44% (95%CI=33-56) in second-look group and 51% (95%CI=40-62) in surveillance group (P=0.75). Peritoneal relapse occurred in 25 (33%) patients in surveillance group and 24 (32%) patients in second-look group. Three-year OS was 80% [95%CI=69-88] and 79% [95%CI=68-87] in surveillance and second-look groups, respectively.

Investigators in Rome and Milan have completed two pilot studies to test HIPEC at the same time as primary resection. [13-14] Among patients with pT4a/b or perforated CRC (the same population as in COLOPEC trial), PM occurred in one of 7 patients treated in Rome (median follow-up 48 months), [4] and one of 14 patients treated in Milan (median follow-up 128.0 months).[Baratti D, unpublished data] A further series of simultaneous HIPEC is the study by Tentes, that report no PM in 15 patients (median follow-up of 17 months). [15] In total, PM occurred in 2 of 36 patients (5.6 %) of three series of adjuvant HIPEC simultaneous with primary surgery., [13-15] This rate compares favourably with the peritoneal failure rates of COLOPEC trial: 19% in experimental arm receiving staged adjuvant HIPEC, and 23% in controls. [7]

The simultaneous time setting is further supported by a pharmacological rationale, namely better exposure to antiblastic agents before viable tumor cells are entrapped in postoperative adhesions. [13] Also, 9% of patients in COLOPEC trial were found with PM at surgical exploration preceding intentional adjuvant HIPEC, and these patients could have been potentially cured by HIPEC at primary surgery.[8] On the other hand, the simultaneous setting may be hampered by logistic issues, difficult preoperative/intraoperative identification of T4 tumors, and potential toxicity of HIPEC. However, three independent studies have demonstrated that HIPEC at primary surgery is feasible in specialized centres. [13-15] Regarding safety issues, five anastomotic leaks (5.7%) and three HIPEC-related toxicities (3.4%), namely two transient renal failures, and one grade 2 pancreatitis, were observed in the total of 87 patients from the three series, that included also pT3 primaries and completely resected ovarian or low-volume peritoneal metastases. Such a complication rate has to be seen not only in light of the potentially adverse impact of HIPEC, but also of the extensive surgery performed in patients with advanced disease. The balance between the potential benefit and risks does not appear to be radically different from that of preoperative radiation in rectal cancer.

FUTURE PERSPECTIVES

Both the Dutch and French investigators have to be congratulated for having completed randomized trials in a complex clinical setting such as CRC-PM. However, many questions remain unanswered. The Prodige-7 trial failed to demonstrate a statistical survival benefit associated with HIPEC. On this base, the exclusion of HIPEC from CRC-PM treatment has been advocated. In our opinion, the study conclusions should be reformulated as follows: 30-minute oxaliplatin-based HIPEC did not improve survival in highly selected patients treated with s-CT and complete CRS.

Furthermore, the study can only answer according to the sample size calculation, as randomized trials do not actually tell us if a given therapy is more effective than another. They just tell us if a predetermined survival difference between arms can be achieved. Thus, the correct conclusion is that CRS/HIPEC failed to produce an 18-month survival advantage over CRS alone, a quite unrealistic end-point. Therefore, future trials should not be discouraged, and should be ideally aimed at identifying which patients, if any, might take advantage from HIPEC administration, investigating the most active drugs and drug combinations, and determining how the treatment components (treatment duration, temperature, drug concentration, type of perfusate medium) affect patient outcomes.

As adjuvant HIPEC is concerned, future trials must address the question whether staged vs. simultaneous adjuvant HIPEC impact outcomes, and the role of prophylactic resection of target organs. Accordingly, the PROMENADE (NCT02974556) trial is open in seven Italian high-volume centres to randomize patients with cT3c/d CRC (depth of invasion beyond the outer border of the muscularis propria >5 to 15 mm, and >15 mm, respectively), and cT4a/b CRC (any N, M0) to standard surgery vs. proactive surgical management (greater omentectomy, appendectomy, liver round ligament resection, bilateral adnexectomy in post-menopausal women) and oxaliplatin-based simultaneous HIPEC. The primary study endpoint will be peritoneal recurrence at 36 months. The Spanish collaborative study HIPECT4 (NCT02614534) is actively enrolling patients with cT4a/b CRC to test mitomycin-based

adjuvant HIPEC plus resection of target organs at primary surgery.

REFERENCES

1. Segelman J, Granath F, Holm T, et al. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. Br J Surg. 2012; 99: 699–705.

2. van Gestel YR, Thomassen I, Lemmens VE, Pruijt JF, van Herk-Sukel MP, Rutten HJ, et al. Metachronous peritoneal carcinomatosis after curative treatment of colorectal cancer. Eur J Surg Oncol. 2014; 40: 963-969.

3. Lemmens VE, Klaver YL, Verwaal VJ, Rutten HJ, Coebergh JW, de Hingh IH. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study Int. J. Cancer, 2011; 128: 2717-272

4. Baratti D, Kusamura S, Pietrantonio F, Guaglio M, Niger M, Deraco M. Progress in treatments for colorectal cancer peritoneal metastases during the years 2010-2015. A systematic review. Crit Rev Oncol Hematol. 2016; 100: 209-22.

5. Franko J, Shi Q, Meyers JP, Maughan TS, Adams RA, Seymour MT, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. Lancet Oncol. 2016; 17: 1709-1719.

6. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003; 21: 3737-3743.

7.http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.18_suppl.LBA3503?af=R

8. Klaver CEL, Wisselink DD, Punt CJA, et al. Adjuvant hyperthermic intraperitoneal chemotherapy in patients with locally advanced colon cancer (COLOPEC): a multicentre, open-label, randomised trial. Lancet Gastroenterol Hepatol 2019; 4: 761-770.

9.https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.3531

10. Elias D, Delperro JR, Sideris L, Benhamou E, Pocard M, Baton O, Giovannini M, Lasser P.Treatment of peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in conducting randomized trials. Ann Surg Oncol. 2004; 11: 518-21.

11. Ceelen W. HIPEC with oxaliplatin for colorectal peritoneal metastasis: The end of the road? ELSO 2019; 45: 400-2.

12. Baratti D, Kusamura S, Azmi N, Guaglio M, Montenovo M, Deraco M. Colorectal Peritoneal Metastases Treated by Perioperative Systemic Chemotherapy and Cytoreductive Surgery With or Without Mitomycin C-Based HIPEC: A Comparative Study Using the Peritoneal Surface Disease Severity Score (PSDSS). Ann Surg Oncol. 2020; 27: 98-106.

13. Baratti D, Kusamura S, Iusco D, et al. Hyperthermic Intraperitoneal Chemotherapy (HIPEC) at the Time of Primary Curative Surgery in Patients with Colorectal Cancer at High Risk for Metachronous Peritoneal Metastases. Ann Surg Oncol. 2017; 24: 167-175.

14. Sammartino P, Sibio S, Biacchi D, et al. Long-term results after proactive management for locoregional controlin patients with colonic cancer at high risk of peritoneal metastses. Int. J Colorectal Dis 2014; 29: 1081-1089.

15. Tentes AA, Spiliotis ID, Korakianitis OS, Vaxevanidou A, Kyziridis D. Adjuvant perioperative intraperitoneal chemotherapy in locally advanced colorectal carcinoma: preliminary results. ISRN Surg 2011; 2011: 529876.

PEER REVIEW

Not commissioned. Externally peer reviewed.