CO06

EARLY INTRA-ABDOMINAL ADHESIONS: CAN WE STILL PRETEND THEY WON'T SPOIL OUR CLOSED-ABDOMED HIPEC?

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Objectives

The early onset of intra-abdominal adhesions during closed-abdomen HIPEC was first documented in 2016, by means of the Laparoscopy-Enhanced HIPEC technique (LE-HIPEC). A pilot study, conducted after cytoreductive surgery in 10 patients, demonstrated that 70% of the closed-abdomen HIPEC procedures are affected by the formation of early adhesions that can hamper the circulation of the perfusion fluid. This study provided a valid explanation for the non-uniform distribution of the methylene blue dye that was previously reported with the closed-abdomen HIPEC technique, thus giving further support to the evidence that the closed-abdomen technique results in the incomplete treatment of the peritoneal cavity.

Methods

Our case series of LE-HIPEC was updated to 28 patients. Laparoscopic exploration of the abdominal cavity was done every 15–20 minutes during the 90 minutes of the closed-abdomen perfusion time, and data about the finding of adhesions were prospectively recorded.

Results

At first laparoscopic exploration, intra-abdominal adhesions were found in 18 patients (64%). Adhesions between the bowel and the abdominal wall were found in 14 patients (50%), involving two or more abdominal regions in 9 of them. Adhesions among the loops of the bowel with creation of closed recesses of the mesentery were observed in 6 patients (21,4%). All these adhesions were not liable to be divided nor weakened by means of massaging the abdominal wall or changing the position of the patients: their complete division was achieved by means of a laparoscopic palpator. After complete division, at the following laparoscopic explorations recurrence of some weak adhesions was observed in 7 patients. Beyond 60 minutes of perfusion, no adhesions recurred after division.

Conclusion

Our case series confirms that, after cytoreductive surgery, early intra-abdominal adhesions are formed in more than half of the patients, soon after the closure of the abdominal wall. These adhesions are resistant to abdominal massage and create closed spaces that are virtually not reached by the perfusion fluid. The LE-HIPEC technique provides the tool for the complete division of the early intra-abdominal adhesions that occur after cytoreductive surgery, thus regaining the complete exposure of the abdominal cavity during a closed-abdomen perfusion. The statement that a standard closed-abdomen HIPEC is an adequate treatment of the peritoneal surface after cytoreductive surgery should be called into question.

CO08

BIOSYNTHETIC MESH INCREASES PERITONEAL METASTASIS GROWTH IN ANIMAL MODEL, THE BIOLOGICAL MESH DOES NOT!

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Objectives

After parietal trauma from peritoneal surgery 1/3 of the patients could develop recurrences on parietal scars or trocars. The severity of the excision in case of extensive parietal localization of peritoneal metastasis (PM) may require mesh. The aim of this project is to analyze the possible pro-tumoral effect of implanting of different types of intraperitoneal (IP) meshes on the PM growth in a murine model of colorectal carcinomatosis.

Methods

Firstly, a murine model of limited colorectal PM was created in Balb/c mouse after an IP injection of increasing concentrations of luciferase-labeled CT-26 tumoral cells (CT-26 luc+). Then, 3 types of meshes were placed in the peritoneal cavity: biosynthetic (Phasix $^{\text{TM}}$ ST Mesh) in the first group of mouse (n = 10), biological (Strattice $^{\text{TM}}$ Reconstructive Tissue Matrix) in the second group (n = 10) and synthetic (Vicryl) in the third group (n = 10). No mesh was placed in the control group (n = 10). Meshes were kindly provided by industries without any grant. Two protocols were established: implantation model: mesh was placed after a short laparotomy and normal peritoneal removal; 7 days after, an IP injection of CT-26 cells was realized; cytoreduction model: tumoral cytoreduction and mesh pose were realized 7 days after an IP injection of CT-26. The presence and growth of PM were observed by bioluminescence. The primary endpoint was the extent of PM evaluated by the PCI (Peritoneal Cancer Index) score.

Results

In the implantation model, the PCI average of biosynthetic, biological, synthetic and control groups was 13.1, 5, 8.3 and 4.4 respectively. A statistical difference was observed between the groups biosynthetic vs biological (p < 0.0002), biosynthetic vs synthetic (p < 0.04) and biosynthetic vs control (p < 0.0001). In the cytoreduction model, the PCI average of PhasixTM, StratticeTM, VicrylTM and control groups was 17.5, 15.5, 12.7 and 13.1 respectively (p = ns).No mortality was observed during the study.

Conclusion

The presence of IP mesh seems to promote the tumoral development of the colorectal PM. In the implantation model the PCI score is increased by biosynthetic mesh compared to the others meshes. In case of large abdominal wall injury, after extensive cytoreductive surgery for PM, use of biological meshes may be recommended compared to biosynthetic one.

CO09

NOVEL TREATMENT WITH INTRAPERITONEAL MOC31PE IMMUNOTOXIN IN COLORECTAL PERITONEAL METASTASIS: LONG-TERM OUTCOME FROM THE IMMUNOPECA TRIAL

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Objectives

Outcome following CRS-HIPEC for colorectal peritoneal metastasis (PM-CRC) is highly variable and most patients will experience disease recurrence, illustrating the need for improved treatment. MOC31PE immunotoxin, composed of the monoclonal antibody MOC31 and pseudomonas exotoxin A (PE), was developed to kill cells expressing the tumor-associated epithelial cell adhesion molecule (EpCAM), which is highly expressed in CRC. In the ImmunoPeCa trial we investigated the use of intraperitoneal (i.p.) MOC31PE as a novel treatment for PM-CRC.

Methods

This was a dose-finding phase I/II trial to evaluate the safety and tolerability (primary endpoint) upon a single dose of i.p. MOC31PE in PM-CRC undergoing CRS-HIPEC. MOC31PE was administered through indwelling abdominal drainage catheters on the first postoperative day. Pharmacokinetic profile, neutralizing antibody response, overall survival (OS) and disease-free survival (DFS) were secondary endpoints. 21 patients were treated at four dose levels (2.5 (n = 3), 5.0 (n = 3), 7.5 (n = 3) and 10 (n = 12) μ g/kg).

Results

There was no major toxicity, the maximum tolerated dose was not reached and systemic drug exposure was low. MOC31PE in peritoneal fluid samples retained cytotoxic capacity, suggesting that the drug is very stable under physiological conditions. With a 32 month follow-up, the median OS was not reached and the estimated 3-year OS was 85%. Median DFS was 20 (95%CI 7–34) months and the 3-year DFS 38%, with a follow-up of 25 months. Median PCI was 7 (0–20). Low levels of MOC31PE in peritoneal fluid samples following study treatment was associated with shortened DFS, also after adjusting for PCI in multivariable analysis (HR 4.5, p = 0.03). Although very encouraging, the results may reflect the selection of the cohort, and investigation in a larger cohort would be necessary to study efficacy.

Conclusion

I.p. MOC31PE following CRS-HIPEC for PM-CRC was safe and well tolerated. The promising long-term outcome combined with the low systemic uptake and retained cytotoxic activity in peritoneal fluid samples support further clinical testing.

CO10

ROLE OF LIQUID BIOPSY AS A PROGNOSTIC FACTOR IN PERITONEAL CARCINOMATOSIS. PRELIMINARY RESULTS IN A PERSONALIZED COHORT

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Objectives

Positive cytology is an independent poor prognostic factor in Peritoneal Carcinomatosis of Colorectal Origin (PCCR). The objective of this study is to evaluate the presence of free tumor-DNA in the blood and peritoneal fluid (PF) before and after undergoing Complete Cytoreduction (CCR-0) + Hyperthermic intraperitoneal chemotherapy (HIPEC), as a prognostic factor

Methods

In our prospective longitudinal study we exclusively selected patients with PCCR and pseudomyxoma peritonei with primary tumor KRAS mutated to be able to identify tumor DNA unambiguously. Blood and PF were collected from 11 patients. After double centrifugation, plasma and peritoneal fluid supernatant were stored at -80°C until analysis. Cell-free DNA was extracted and KRAS mutations detected by droplet digital PCR.

Results

27.27% of patients presented positive preHIPEC cytology and 9.09% suspicious. PostHIPEC cytology and at 24 and 72 hours were negative in these four cases.

In all patients, in PF total DNA levels increased after HIPEC.

Three patients with acellular PMP were analyzed, two had positive preHIPEC peritoneal-DNA that turned negative. None presented the mutation in the blood. All remain free of disease.

Of the 5 patients with established PCCR, 4 had cell-free tumor DNA in preHIPEC PF. In 2 of the 5 patients levels tended to neutralize after HIPEC; but in the cases in which levels increased, the three presented relapse, two at the peritoneum. These 5 patients had positive tumor DNA in the blood, in four of them the levels decreased but remained positive, 4 of them presented systemic relapse.

Of the three cases of second-look, all of them with negative findings, one with suspicious preHIPEC cytology, all had negative DNA levels in liquid and in plasma, except one with doubtful level; this patient presented a single pulmonary relapse. Currently all patients remain free of disease.

Conclusion

CRS+HIPEC neutralizes tumor cells in PF, but not free cell-free tumor DNA. Positive levels of tumor DNA in both PF and plasma seem to correlate to peritoneal and systemic relapses. Further studies are guaranteed to evaluate the potential of this liquid biopsy as a prognostic factor of future peritoneal and systemic relapses.