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STANDARDIZATION OF INTRAPERITONEAL CHEMOTHERAPY: PHARMACOLOGIC GUIDANCE TOWARDS AN OPTIMAL DOSIMETRY METHOD IN COLORECTAL PERITONEAL SURFACE MALIGNANCY TREATMENT

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Objectives

The combination therapy of CRS and HIPEC should be considered standard of care to treat colorectal peritoneal surface malignancy (PSM). Although, there is a near universal standardization regarding CRS, we lack a much-needed standardization amongst the IP chemotherapy treatment modalities, including the HIPEC dosing regimen. We should rely on pharmacologic evidence supporting standardization. The current dosing regimens of IP chemotherapy can be divided into concentration-based and BSA-based. Using the concept of dose intensification, we report on the pharmacologic advantage (PA), i.e. the area-under-the-curve (AUC) ratio of the peritoneal exposure over the IV exposure after IP chemotherapy administration.

Methods

The dosing regimens were clinically and pharmacologically evaluated in a randomized clinical trial, the COBOX trial. Patients diagnosed with colorectal PSM were randomized to concentration-based or BSA-based HIPEC. Oxaliplatin was administered at a dose of 460 mg/m² (BSA-based) or 460 mg/m^2 in 2 L/m 20.9% NaCl (concentration-based) during a 30-minute HIPEC. During HIPEC, blood, urine, peritoneal fluid and tumor nodules were sampled every 5 minutes for platinum quantification using a validated ICP-MS method. Primary endpoint was the evaluation of pharmacologic parameters.

Results

At present, 29 patients were randomized to concentration-based HIPEC (n = 14) and BSA-based HIPEC (n = 15). Both the AUC plasma, plasma ultrafiltrate ($p = 0.005$) and the AUC of the peritoneal fluid compartment ($p < 0.001$), reflecting toxicity and efficacy, were significantly higher in patients receiving concentration-based HIPEC. There was no difference in PA between the two groups ($p = 0.687$). At 30 minutes, 64.51% of the drug remained in the chemotherapy solution, 37.73% was retained in the body, and 0.61% was excreted in the urine.

Conclusion

There is no difference in PA between concentration-based and BSA-based HIPEC, using oxaliplatin as chemotherapeutic agent, which confirms our preclinical results.

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PHARMACOLOGICAL EFFECTS OF CARRIER FLUIDS ON THE HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY USING OXALIPLATIN IN VITRO AND IN VIVO

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Objectives

Carrier solutions play an important role in the distribution, plasma absorption, chemical stability, and solubility of anticancer agents during hyperthermic intraperitoneal chemotherapy (HIPEC). This study aimed to evaluate pharmacological effects of carrier fluids and to determine the most effective carrier fluid for HIPEC using oxaliplatin in vitro and in vivo.

Methods

In vitro study, we evaluated the degradation rates of oxaliplatin at the temperature 25°C, 37°C, and 43°C during 72 hours for six carrier fluids, which has different chloride concentration: normal saline, half saline, 5% dextrose, phosphate buffer saline, Dianeal® PD-2 peritoneal dialysis solution, and non-chloride Dianeal solution. In vivo study was performed HIPEC to use Sprague-Dawley rats, which were divided according to the kinds of carrier fluids, which contained different concentration of chloride ions: 5% dextrose solution, Normal saline, half saline, 20% lipid solution, Dianeal® PD-2 1.5% peritoneal dialysis solution, and non-chloride Dianeal® solution. The plasma area under the curve (AUC; AUC_{plasma}), peritoneal AUC (AUC_{fluid}), and peritoneal/plasma AUC ratios were compared among HIPEC carrier solutions.

Results

In vitro study, the degradation rates of oxaliplatin were increased in proportion to the concentration of chloride ions in the carrier fluids at the temperature of 25°C, 37°C, and 43°C. In addition, the degradation rates of oxaliplatin were acceptable that they were less than 15% during in-vitro study during 30 minutes at 43°C. In vivo study, plasma drug concentrations were significantly different among carrier solutions, varying by time. On the other hand, peritoneal drug concentrations did not change with carrier solution. The oxaliplatin AUC ratios of chloride-containing carrier fluid, which are both normal saline and Dianeal®, were higher than non-chloride containing carrier fluids. Although the oxaliplatin AUC_{fluid} of carrier fluids were not significantly different ($p = 0.941$), the AUC_{plasma} of a lipid solution was lower than that of 5% dextrose solution ($p = 0.039$).

Conclusion

The most important condition to get pharmacological efficacy during HIPEC is to make it to decrease plasma absorption rates of anticancer drug. It is expected that chloride-containing carrier fluids are more beneficial to increase pharmacological efficacy than hypotonic carrier fluids such as dextrose solution for oxaliplatin-based HIPEC.

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THERE IS NO DIFFERENCE IN PHARMACOLOGIC ADVANTAGE BETWEEN BSA-BASED AND CONCENTRATION-BASED HIPEC AFTER CRS IN COLORECTAL PERITONEAL CARCINOMATOSIS' TREATMENT: AN EXPERIMENTAL STUDY

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Objectives

At present, the combination therapy of CRS and HIPEC is considered standard of care for colorectal peritoneal surface malignancy (PSM) treatment. Although, there is a near universal standardization regarding the CRS, we are still lacking a much-needed standardization amongst the various IP chemotherapy treatment modalities, including the HIPEC dosing regimen. We should rely on pharmacologic evidence supporting such a standardization. The current dosing regimens of IP chemotherapy can be divided into body surface area (BSA)-based and concentration-based. Using the concept of dose intensification, we report on the pharmacologic advantage (PA), i.e. the area-under-the-curve (AUC) ratio of the peritoneal exposure over the IV exposure after IP chemotherapy administration.

Methods

Sixty-three WAG/Rij rats were IP injected with the rat colonic carcinoma cell line CC-531. Animals were randomized into three groups: CRS alone, CRS combined with BSA-based HIPEC (oxaliplatin, 150 mg/m^2 in 0.9% NaCl carrier solution) and CRS combined with concentration-based HIPEC (oxaliplatin, 150 mg/m^2 in 2L/m^2 0.9% NaCl as carrier solution). Primary and secondary endpoint were difference in PA and survival, respectively.

Results

Both the AUC plasma and the AUC of the peritoneal fluid compartment, reflecting toxicity and efficacy, were significantly higher in rats receiving concentration-based HIPEC compared to the BSA-based group ($p < 0.001$). However, there was no difference in PA between the two groups ($p = 0.274$), with a median PA of 19.61 (16.84–27.25) in the concentration-based group and a median PA off 19.58 (15.32–22.41) in the BSA-based group. Rats receiving HIPEC showed a significant lower tumor load ($p < 0.001$) at autopsy when compared to rats receiving CRS alone.

Conclusion

There is no difference in PA between concentration-based and BSA-based HIPEC, using oxaliplatin as chemotherapeutic agent.

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PHASE I STUDY ASSESSING SAFETY OF INTRAPERITONEAL CHEMOTHERAPY IN THE NEOADJUVANT TREATMENT OF PERITONEAL CARCINOMATOSIS OF COLORECTAL ORIGIN (NIPOX)

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Objectives

Peritoneal carcinosis in colorectal cancer is an advanced stage of disease where improved survival can be attained whenever the resection is possible. In unresectable cases, systemic chemotherapy is proposed in order to obtain conversion to resectability but results are not clearly evaluated. Local chemotherapy in the neoadjuvant setting was proved useful in several similar situations. We performed a phase I modified 3 + 3 dose escalation study to evaluate the safety and activity of intraperitoneal oxaliplatin in association with systemic FOLFIRI.

Methods

Patients were given fixed dose systemic FOLFIRI plus increasing doses of intraperitoneal oxaliplatin. Toxicity, response, and pharmacokinetics were analysed in order to identify the maximum tolerated dose (MTD) as well as the Recommended Phase II Dose (PR2D). The dose levels of oxaliplatin were 85 mg/m², 100 mg/m², 110 mg/m², and 130 mg/m², respecively.

Results

The study enrolled 11 patients with unresectable peritoneal carcinomatosis of colorectal origin previously treated with at least one line of systemic chemotherapy alone in the metastatic setting. Patients with neurotoxicity grade > 2 were not eligible. A dose limiting toxicity was not observed before the 4th dose level. Further results will be communicated.

Conclusion

The combination of intraperitoneal oxaliplatin with systemic FOLFIRI is safe, well-tolerated, and has activity in advanced peritoneal carcinomatosis of colorectal origin.

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PHASE 1 STUDY OF PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) WITH OXALIPLATIN FOR PERITONEAL CARCINOMATOSIS

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Objectives

Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) is a novel laparoscopic intraperitoneal chemotherapy delivery technique, with certain advantages such as homogeneous distribution of aerosol and deeper tissue penetration. Thus far, PIPAC Oxaliplatin has been administered at an arbitrary dose of 92 mg/m^2.

We aim to determine the dose-related safety profile and tolerability of PIPAC oxaliplatin. The secondary aim is to evaluate the clinic-pathologic response and to identify the pharmacokinetic profile of PIPAC oxaliplatin.

Methods

This is a Phase I 3+3 dose escalation study for gastric and colorectal cancer patients with predominant peritoneal metastasis starting at a dose of 45 mg/m^2. Safety is assessed according to Clavien-Dindo Classification and National Cancer Institute – Common Terminology Criteria for Adverse Events (version 4.0). Clinico-pathologic response is assessed using the Peritoneal Regression Grading Score, Peritoneal Cancer Index and Response Evaluation Criteria In Solid Tumour criteria (version 1.1). Pharmacokinetic analysis is performed using Inductively Coupled Plasma-Mass Spectrometry assay. This trial is registered on ClinicalTrials.gov (NCT03172416).

Results

As of April 2018, eight patients (11 PIPAC procedures) have been recruited (three with colorectal cancer). The median age is 57 years (range 51–65), with a mean PCI score of 15 (range 2–28). There were no intraoperative complications with a median operative time of 100 min (range 68–118 min). Patients stayed a minimum of 4 days after PIPAC for monitoring. One patient stayed for 21 days post PIPAC due to nutritional issues. Two patients developed pancreatitis (grade 2 and 3) on day 6 and day 9 after PIPAC administration. The patient with grade 3 pancreatitis demised 9 days after. Thus, the dose cohort at 45 mg/m^2 was expanded to 6 patients. No further dose limiting toxicity (grade 3 or worse) was noted.

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Conclusion

PIPAC oxaliplatin administered at 45 mg/m^2 may be associated with acute pancreatitis. The study is ongoing and is currently recruiting patients for the dose cohort of 60 mg/m^2.