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Prognostic factors of hemorrhagic complications after oxaliplatin-based hyperthermic intraperitoneal chemotherapy: Toward routine preoperative dosage of Von Willebrand factor?

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Abstract

Background: Oxaliplatin-based hyperthermic intraperitoneal chemotherapy (HIPEC-ox) induces specific morbidity with hemorrhagic complications (HC). The aim of this study was to identify preoperative, intraoperative and postoperative HC predictive factors after HIPEC-ox.
Methods: A prospective single center study that included all consecutive patients treated with curative-intent HIPEC-ox, whatever the origin of peritoneal disease, was conducted. All patients underwent systematic blood tests exploring primary hemostasis and endothelial activation before surgical incision (D0) and on postoperative days 2 (POD2) and 5 (POD5).
Results: Between May 2012 and August 2015, 47 patients were enrolled in the study. The overall HC rate was 38%. Major morbidity was significantly higher in patients with HC. Patients presenting HC were significantly more often affected with pseudomyxoma peritonei and had less preoperative chemotherapy. Multivariate analysis showed that a higher plasmatic level of Von Willebrand factor antigen at D0 (D0 VWF:Ag) was a protective predictive factor for HC ($p = 0.049$, HR: 0.97 CI 95% [0.94–1.00]). A D0 VWF:Ag level below 138% had a sensitivity of 87.5%, a specificity of 67% and an area under the curve of 80.3% (CI 95% [66.5–94], $p < 0.01$) for predicting HC.
Conclusions: Through the identification of prognostic factors, this study highlighted a subgroup of patients with low risk of HC after HIPEC-ox. Based on these results, we propose a routine preoperative dosage of VWF that would help the surgeon to select the most suitable patients for HIPEC-ox.

Keywords: HIPEC; Oxaliplatin; Hemorrhagic complication; Chemotherapy; Von Willebrand factor

Introduction

Complete cytoreductive surgery (CCRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have become the standard of care for patients suffering from limited colorectal peritoneal metastasis (PM), pseudomyxoma peritonei (PMP), and malignant peritoneal mesothelioma (MPM), because these procedures have been associated with improved survival.[1–10] A matter that is still under debate is the type of drug that should be used for HIPEC. Mitomycin C (MMC) is the historical drug and is still recommended by the American Society of Peritoneal Surface Malignancies for PM of colorectal

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cancer.[11] Oxaliplatin-based HIPEC (HIPEC-ox), originally described by Elias et al.,[12] is nowadays also widely used for colorectal PM and PMP and is even preferred for MPM by several teams.[13] Many teams perform HIPEC-ox associated to intravenous intraoperative 5-fluorouracil (5-FU) because these are systemic drugs frequently used in adjuvant and metastatic situations. However, several studies suggested that the use of oxaliplatin for HIPEC significantly increases the rate of hemorrhagic complications (HC) compared to others drugs. For instance, the CHIPOVAC phase II trial, evaluating CCRS and HIPEC-ox in ovarian PM was early terminated because of high morbidity rates mostly related to HC.[14] A retrospective analysis of the 2008 Report of the French Association of Surgery concerning 701 patients with various peritoneal diseases indicated a rate of 15.7% for HIPEC-ox versus 2.6% for HIPEC performed with others drugs.[15] HC mostly corresponded to intraperitoneal hemorrhage and usually occurred around 9 days after HIPEC-ox. Nowadays, there are no clinical or biological factors explaining the higher incidence of HC after HIPEC-ox. Therefore, the aim of this study was to identify clinico-biological preoperative, peroperative or postoperative prognostic factors of HC after CCRS and HIPEC-ox.

Material, patients and methods

A prospective single center study was performed. All consecutive patients, whatever the origin of the peritoneal disease, curatively-treated with CCRS and HIPEC-ox between May 2012 and August 2015 in the Department of General and Digestive Surgery of the Strasbourg University Hospital (France) were included. All the patients gave informed consent for their inclusion in the study. The study received institutional review board approval. Indications for CCRS and HIPEC-ox were discussed during multidisciplinary meetings. Age, gender, characteristics of primary tumor, past history of HIPEC or systemic chemotherapy, use of systemic preoperative chemotherapy, blood type and anticoagulant/aggregant treatment were recorded at patient admission.

Study definitions

Preoperative systemic chemotherapy was defined as a period of time between the last chemotherapy cycle and HIPEC-ox of less than 2.5 months. A period superior to 2.5 months after the end of chemotherapy was considered as past history of chemotherapy. HC were defined as any unusual blood externalizing taking into account the surgical procedures performed. HC may be associated with anemia (Hemoglobin <10 g/dL) and/or thrombopenia (platelet $<80{,}000/mm^3$) requiring red blood cell or platelets units transfusions. Patients who experienced HC were classified in the “HC group” and those who did not were classified in the “NHC group” (No-HC).

Surgical procedure

The extent of peritoneal seeding was calculated for each patient using Sugarbaker’s PCI.[16] CCRS was performed with previously described peritonectomy techniques.[17] In case of resectable liver metastasis, radiofrequency ablation or minor hepatectomy (<3 liver contiguous segments according to the Couinaud definition[18]) may have been associated to CCRS. HIPEC-ox was administered using a closed technique with abdominal massage. Patients received an intravenous perfusion of 5-FU (400 mg/m^2) with leucovorin (20 mg/m^2) just before starting HIPEC. Oxaliplatin was administered at a dose of 360 mg/m^2 in iso-osmotic 5% dextrose for 30 min, with intraperitoneal temperature of 42 °C. Postoperative mortality and morbidity were evaluated with the Dindo–Clavien classification.[19] Grade 3 or more complications were considered as major morbidity.

Hemostasis protocol

All patients underwent blood tests exploring primary hemostasis and endothelial activation on Day 0 (D0), after the anesthetic induction and before the surgical incision of the CCRS and HIPEC-ox, and on postoperative days (POD) 2 and 5. The analyzes included a closure time (PFA-200, Siemens) in the presence of epinephrine (CT-EPI) and Adenosine diphosphate (CT-ADP), dosage of Von Willebrand factor antigen (VWF:Ag) levels by immunoturbidimetry, dosage of VWF-ristocetin cofactor activity (VWF:RCo) by turbidimetry and dosage of the plasminogen activator inhibitor (PAI) by chromogenic substrate assay. Platelet aggregation was performed with the light transmission assay (LTA) method, which consists in recording the transmission of a light beam across a suspension of constantly agitated platelets in a platelet-rich plasma (PRP) after stimulation by various agonists (ADP, collagen or arachidonic acid).[20]

Patients follow-up

All patients underwent clinical examination 1 month after surgery, then clinical examination, imaging studies, and tumor marker blood tests, every 3 months over a period of 2 years.

Statistical analysis

The cutoff date of survival analyzes was December 31st 2015 for the censored data analysis. Continuous variables are presented as mean (±standard deviation) or median values. The Gaussian nature of the quantitative variables was assessed graphically and using the Shapiro–Wilk test. Categorical variables were compared within groups using the Chi-squared and Fisher’s exact tests when appropriate, whereas Mann–Whitney tests were used for

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