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Research Article

Severe Hematologic Toxicity Following Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy

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Abstract

Background: To describe the kinetics of the blood cells and the appearance of severe hematologic toxicity following CRS-PIC. Analysis of the possible contributing factors with post-operative complications, principally hematologic, in order to establish recommendations based on the experience and results.

Patients and Methods: Retrospective revision of CRS-PIC cases performed between 2004 and 2015 on patients with diverse etiologies of peritoneal carcinomatosis. Analysis of clinical and surgical variables; a record of post-operative blood cell counts; univariate and multivariate analysis of possible risk factors associated with hematologic toxicity.

Results: 107 CRS-PIC procedures performed on 97 patients at the MD Anderson Cancer Center in Madrid. Types of PIC: a) HIPEC - 89 cases (51 bi-directional); b) HIPEC-EPIC - six cases; c) EPIC - two cases. Mitomycin C (MMC) is an independent risk factor for severe toxicity: 1. Medullary (OR 3.64, CI 95% 1.08 - 12.2; p = 0.037); 2. Neutropenia (OR 18.18, CI 95% 3.41 - 86.5; p = 0.001); 3. Thrombocytopenia (OR 4.71, CI 95% 1.10 - 20; p = 0.036). Neutropenia, use of G-CSF, the number of lines or cycles of systemic chemotherapy, iterative procedures, splenectomy, operating time, and PCI are not risk factors for severe hematologic toxicity. Days nine and 10 of the post-operative period are the nadir for major neutropenia and thrombocytopenia. HIPEC-EPIC presented severe toxicity in 33% of the cases, with two fatal outcomes.

Conclusion: HIPEC with MMC is an independent risk factor for severe hematologic toxicity. Daily monitoring of the blood cell count during the first two weeks of the post-operative period allows one to distinguish medullary toxicity from transient cytopenia secondary to the surgical procedure. HIPEC-EPIC must be performed with caution in selected cases, following its discussion in a multidisciplinary meeting, due to the high morbimortality rate for this combination. Knowledge of the implications of the types and protocols of HIPEC and of severe complications in the CRS-PIC post-operative period are fundamental for those involved in these procedures, principally those who are in training or developing emerging programs.

Keywords: *Toxicity; Cytoreductive Surgery; Perioperative Intraperitoneal Chemotherapy*

Abbreviations

CRS: Cytoreductive Surgery; PIC: Perioperative Intraperitoneal Chemotherapy; HIPEC: Hyperthermic Intraperitoneal Chemotherapy; EPIC: Early Post-Operative Intraperitoneal Chemotherapy; PCI: Peritoneal Cancer Index

Background

Cytoreductive surgery (CRS) combined with Perioperative Intraperitoneal Chemotherapy (PIC), when it is justified and performed by a multidisciplinary team specializing in oncology, is considered the gold standard for managing patient with confirmed peritoneal compromise of a gastrointestinal and gynecological oncological etiology [1-5]. Unfortunately, a high proportion of patients who have a malignant peritoneal pathology, and are possible candidates for this treatment option, do not have access to it for a variety of reasons (economic, cultural, lack of knowledge of the therapy, etc.). With new treatment centers emerging all over the world, it is imperative to foster education and specific training on these subjects [6,7].

For surgeons who are in training, or those who are already associated with an established Peritoneal Surface Oncology program, the systemic and intraperitoneal administration of chemotherapy agents, as well as the implications, benefits, adverse events and considerations during its perioperative application represent a great challenge. In addition, recognizing that the surgical procedure in itself presents its own morbidity and risk of mortality, which contribute in a summative manner with the possibility of post-operative complications, invites us to consider and analyze the variables related to the possible unfavorable outcomes [8-11]. One of these variables is the behavior of the types of blood sequences following the performance of the CRS-PIC procedure. Understanding the factors that influence the variability of the blood cell types, deciding when to perform relevant therapeutic interventions, and visualizing the implications regarding future complication stemming from its abnormality are all necessary [12-15]. However, the reality is that there is a scarcity of information on this in the literature.

Purpose of the Study

The purpose of the study is to describe the experience of a noted Surgical and Peritoneal Oncology center with respect to the behavior and kinetics of the different blood cell types following CRS-PIC. In addition, the aim is to present an analysis of the factors that may contribute to hematologic toxicity and produce recommendations based on the center's experience.

Patients and Methods

This is a retrospective study on a prospective database. The inclusion criteria were patients with peritoneal carcinomatosis with a primary peritoneal etiology (mesothelioma, primary serous papillary carcinoma of the peritoneum) and of a secondary peritoneal origin (colorectal, ovarian, gastric, small intestine, appendix), previously presented at the MD Anderson Cancer Center in Madrid, Spain, who were treated with CRS-PIC. The Perioperative Intraperitoneal Chemotherapy was administered in various ways: 1. Hyperthermic Intraperitoneal Chemotherapy (HIPEC); 2. HIPEC with concomitant Intravenous Chemotherapy (Bi-directional); 3. HIPEC with Early Post-Operative Intraperitoneal Chemotherapy (EPIC); 4. EPIC.

The evaluation, studies and integral treatment were performed at the MD Anderson Cancer Center in Madrid, Spain from 2004 to March of 2015. The demographic and clinical characteristics of the patients in the pre-operative period are recorded in table 1.

Cytoreductive surgery (CRS)

The surgical intention of cytoreduction is to resect the entire macroscopic peritoneal disease, with the aim of producing a complete extraction of the tumor. The performance of multivisceral resections, splenectomy, peritonectomies, and intestinal anastomosis depends on the individual requirements of each case, as well as institutional protocol [16,17]. Included were patients on whom an incomplete cytoreduction was performed if the intention of the PIC was palliative.

Procedures/Patients (n = 107/91)	
Mean age (range)	59 (22 - 81)
< 65 years	79 (74%)
≥ 65 years	28 (26%)
Male/female	34 (37%)/57 (63%)
Type of cancer	
Gastrointestinal	82 (76.6%)
Non Gastrointestinal	25 (23.4%)
Origin of peritoneal carcinomatosis	
Ovary	8 (7.5%)
Appendix	30 (28%)
Colon	30 (28%)
Rectum	7 (6.5%)
Gastric	13 (12.1%)
Bowel	1 (0.9%)
Mesothelioma	9 (8.4%)
Primary peritoneal	8 (7.5%)
Pancreas	1 (0.9%)
Previous systemic chemotherapy	83 (77.6)
Lines of chemotherapy (mean - range)	1,35 (0 - 5)
≤ 2	72 (86.7%)
> 2	11 (13.3%)
Cycles of chemotherapy (mean - range)	7.74 (0 - 41)
≤ 6	27 (32.5%)
> 6	56 (67.5%)
Severe neutropenia preoperatory[1]	11 (13.3%)
Preoperatory use of G-CSF	10 (12%)
PCI mean (range)	17 (0 - 39)[1]
≤ 20	63 (58,8%)
> 21	44 (41.2%)
Mean number of intestinal anastomoses	1 (1 - 4)
0,1	73 (68,2%)
≥ 2	34 (31,8%)
Splenectomy	32 (29,9%)

CCR	
Complete (0,1)	89 (83,2%)
Incomplete (2,3)	18 (16,8%)
Mean operatory time (minutes)	600 (240 - 960)
< 480 min	32 (29.9%)
> 481 min	75 (70,1%)
Post-operative blood transfusion	60 (56,1%)
Number of CRS-IPC	
1	74 (81,3%)
2	17 (18,7%)
Type of intraperitoneal chemotherapy	
Non EPIC	89 (83,2%)
With EPIC	18 (16,8%)
HIPEC protocols	
Not platin-based	40 (37,4%)
Platin-based	67 (62,6%)
Mean length of in-hospital stay (days)	24 (9-101)

Table 1: *Distribution of demographic, preoperative clinical characteristics, surgery and intraperitoneal chemotherapy. G-CSF: Granulocyte Colony Stimulating Factor; [1]: Previous hematologic toxicity grades 3 to 5 (CTCAE v.4.03[24]); HIPEC: Hyperthermic Intraperitoneal Chemotherapy; PCI: Peritoneal Cancer Index; CCR: Cytoreduction Index; IPC: Intraperitoneal Chemotherapy; EPIC: Early Postoperative Intraperitoneal Chemotherapy. [1]: The only patient with PCI 0 had a gastric cancer. She was in a clinical protocol for pre-operative intraperitoneal chemotherapy and after CRS-IPC.*

Description of intraperitoneal chemotherapy

The coliseum technique (open) [18] was implemented for the administration of the HIPEC. A volume of two liters per square meters of patient body surface was used, with a regular flow of 1,000 mL/min. The intraperitoneal temperature was maintained between 41.5 - 43.0 degrees Celsius for 30 to 90 minutes, according to the particular protocol used in each case. The chemotherapy medications, dosage, and perfusion time were selected in accordance with the following criteria: 1. Age (< 65 vs. ≥ 65) 2. Tumor histopathology; 3. Previous use of chemotherapy; 4. History of neutropenia following chemotherapy; 5. Previous use of granulocyte colony stimulating factors (G-CSF) for neutropenia; 6. Compromised renal function. The types of medication and perfusion times used changed over the course of the study in parallel to the advances and new discoveries regarding carcinomatosis over the same period. The 33% reduction in the chemotherapy dosage or the reduction of perfusion times during the HIPEC were subject to the surgeon's discretion.

EPIC was administered via intraabdominal catheters, with medications selected on an individual basis. It began on day one of the post-operative period, with a five-day projection. The protocol was modified if the patient presented signs of Systemic Inflammatory Response Syndrome (SIRS), hemodynamic instability, or confirmed hematologic toxicity. The bi-directional chemotherapy protocol used was 5-Fluorouracil (400 mg/square meter) and leucovorin (20 mg/square meter), administered endovenously, concomitant with the HIPEC.

Study parameters

The clinical and surgical variables used are presented in table 1.

The values for leukocytes, neutrophils, thrombocytes, and hemoglobin were recorded daily from the pre-operative period through 30 days following the CRS-PIC, or until the hospital discharge, whichever occurred first. The degree of toxicity was established according to the Common Terminology Criteria for Adverse Events (CTCAE) scale, v.4.03, June 2010 [19]. Medullary toxicity was defined as the combination of severe toxicities (severe neutropenia plus severe thrombocytopenia). Recorded for each patient were the day of the beginning of the toxicity, the nadir, the days of the normalization of values, and the duration of the abnormality. Leucopenia and anemia were excluded because their presentation involves a multifactorial etiology, and the relation of causality with each variable entailed by CRS-PIC is very difficult to establish.

The policies and direction of the management and treatment of severe hematologic toxicity were adopted from the American Society of Clinical Oncology (ASCO) [21] and European Society of Medical Oncology (ESMO) [22] guides.

Statistical analysis

The perioperative demographic and clinical variables, the cytoreduction details, the complications during hospitalization (hematologic, infectious, surgical) and the outcomes were all presented by way of descriptive statistics. A univariate analysis was developed with the Pearson chi-square test and the Fisher exact test regarding the potential risk factors for severe neutropenia, thrombocytopenia and medullary toxicity. A logistic regression model with multivariate analysis was used to determine the existence of a correlation between the clinical variables and the types of toxicity. The statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Statistics for Windows, Version 22.0, IBM Corp; Armonk, New York, U.S.A.).

Results

Between April of 2004 and March of 2015, 107 CRS-PIC procedures were performed on 91 patients. The types of PIC performed were: HIPEC (38 patients); HIPEC-BD, or low-dosage (51 cases); HIPEC-EPIC (16 patients); and EPIC (two patients).

Hematologic toxicity

Medullary toxicity was apparent in 24 cases (22.4%). The MMC-based protocol was an independent risk factor for medullary toxicity (OR 3.64, CI 95% 1.08 - 12.2; p = 0.037). In the development of an initial CRS-PIC, there was greater medullary toxicity than in iterative procedures (p = 0.038). Meanwhile, neutropenia following previous systemic chemotherapy, the need for an intraoperative blood transfusion, and the MMC-based HIPEC protocol presented a borderline significant correlation to medullary toxicity (p-values 0.084, 0.080, and 0.075, respectively).

Neutropenia

Neutropenia was apparent in 28 cases (26%), with severe neutropenia in 17 cases (16%). The cases of greatest severity presented themselves at the end of the first week of the post-operative period, with a median onset on day seven, a nadir on day 10, and a duration of four days. Two fatal outcomes occurred on these days. The HIPEC-EPIC combination, performed in 16 cases, was related to severe neutropenia in five cases (33%). The lowest neutrophil count corresponded to a patient treated with the Cisplatin/Doxorubicin HIPEC protocol (low-dosage), followed by EPIC with Paclitaxel. In the univariate analysis, the MMC-based HIPEC protocol was associated with severe neutropenia (p = 0.001). This association maintained its significance in the multivariate analysis, evincing that the MMC-based HIPEC protocol is an independent risk factor for severe neutropenia (OR 17.18, CI 95%, 3.41 - 86; p = 0.001) in this series.

Thrombocytopenia

Thrombocytopenia was apparent in 73 cases (68.2%), with severe thrombocytopenia in 14 cases (13%). The median onset was on day three, the nadir on day nine, normalization on day 14 and a duration of 11 days. The lowest platelet count was recorded in a patient who received the Cisplatin/Doxorubicin HIPEC protocol (low-dosage). Of the 37 HIPEC-BD (low-dosage) procedures, 31 (84%) presented thrombocytopenia and five (13.5%) of them developed severe toxicity (Table 1). Intraoperative blood transfusions were associated with thrombocytopenia, with a borderline significance ($p = 0.087$). The MMC-based HIPEC protocol was an independent risk factor for severe thrombocytopenia (OR 4.71, CI 95% 1.10 - 20; $p = 0.036$) in the multivariate analysis.

Morbidity and mortality following CRS-PIC

The severe morbidity rate was 44%. The principal complication was surgical in 25 cases (intraabdominal collection and/or digestive fistula); the second kind was infectious in 18 cases; seven (6.5%) of patients died during the post-operative period, within the 60 days following the CRS-PIC (two cases due to severe neutropenia, five cases due to infectious and surgical complications). The patients with severe neutropenia developed a progressive pancytopenia and medullary aplasia, with a fatal outcome on days eight and nine, respectively. The two cases were women aged 60 and the HIPEC-EPIC method was used. In the first case, the patient had colon cancer. She received the last systemic chemotherapy dose 17 days before the CRS-PIC procedure, evincing light neutropenia during the treatment. The protocol used was HIPEC with Mitomycin C (low-dosage) and EPIC with 5-Flourouracil for five days. The second case was diagnosed with PPSPC, without prior administration of systemic chemotherapy. The protocol used was HIPEC with Cisplatin/Doxorubicin (low-dosage) and EPIC with Paclitaxel for two days.

Discussion

The interest and knowledge regarding peritoneal carcinomatosis and its treatment with cytoreductive surgery and perioperative intraperitoneal chemotherapy for pathologies with neoplastic peritoneal compromise has grown exponentially around the world. This requires that the teams involved with the execution of the CRS-PIC procedure know about the evolution and normal presentation of the post-operative period, as well as the effects inherent to cytoreduction, in accordance with the number of organs resected, peritonectomies, intestinal anastomoses and other resections, as well as the possible complications derived from the use, type and protocol of intraperitoneal chemotherapy and its variants. These factors interact synchronously in a summative and sometimes unpredictable manner with respect to the physiological and clinical recuperation and the well-being of the patients. As such, knowledge of the indications, technical aspects, benefits, and possible complications, anticipation of the outcomes, and judicious monitoring of the patients during the post-operative period, as well as the opportune intervention in the event of complications, are the factors in which the true meaning of performing this type of procedure lies.

The results of a systemic revision regarding morbidity and mortality following CRS-PIC performed by Chua [10] allows one to establish that the 22.4% medullary toxicity figure presented in this study lies within the range of expected hematologic toxicity (0 - 28%), although it exceeds the median of 5.6% in all the series. The Chua study reported the findings of 24 authors from various centers around the world. Only 10 of these were programs under the direction and tutelage of surgeons with ample experience in developing CRS-PIC, with samples ranging between 103 and 460 patients. The other 14 institutions reported fewer than 50 patients on average. However, nine participating programs did not include data on hematologic toxicity.

Our primary objective was to establish the percentage corresponding to medullary toxicity in our findings, as well as to identify the possible factors related to its presentation: 1. The use of different modalities of administering Perioperative Intraperitoneal Chemother-

apy (HIPEC alone, HIPEC-BD (low-dosage), HIPEC-EPIC, and EPIC alone); 2. The dosage and protocols pertaining to the medications for different chemotherapies, due to the fact that their selection and use were adjusted progressively as time passed and the center gained experience; 3. The reported experience includes the data from the team's initial learning curve, and the consolidation of the results of the perfecting of the CRS-PIC procedure.

A logical and intuitive hypothesis is to consider that variables like the previous use of systemic chemotherapy, the number of cycles and lines of chemotherapy, the presentation of neutropenia during these period of previous systemic chemotherapy, and the use of granulocyte colony stimulating factors (G-CSF) in the treatment of severe neutropenia, are all potential and evident risk factors for the development of medullary toxicity, thrombocytopenia, and severe neutropenia in the post-operative period following CRS-PIC. However, what we witnessed in the results, and what is supported by other similar studies [23-25], is that this hypothesis has not been confirmed, and that there is no apparent significant correlation between hematologic toxicity and these variables. Our results evinced a borderline correlation with medullary toxicity following CRS-PIC in patients who presented severe neutropenia following systemic chemotherapy ($p = 0.084$).

Another intuitive hypothesis is to consider that there is a greater risk of clinical and hematologically toxic complications in patients who are repeating CRS-PIC or receiving iterative treatment. On the contrary, the results evince that the iterative procedures do not represent a greater risk for hematologic toxicity with respect to patients undergoing CRS-PIC for the first time. These results may be the consequence of the fact that the sample of patients undergoing iterative procedures was very small (17 cases, or 18.7%) and that the protocols used in these cases used lower doses of chemotherapy medications than the regular doses established in a first-time patient, by virtue of the consideration of CRS-PIC repeats.

Another aim of the study was to show the behavior of the cell counts for neutrophils and platelets following CRS-PIC in patients with severe thrombocytopenia and neutropenia. The idea resulted from the absence of descriptions of this kind of cellular kinetics, and its use in scenarios for emerging programs. While neutropenia is usually associated with medullary compromise and damage, compromising the cellular production of neutrophils, thrombocytopenia can also be produced by the surgical procedure if there is a significant amount of blood loss and the administration of blood transfusions is required. The nadir of major neutropenia was established on day 10 of the post-operative period, which allows us to suggest the daily monitoring of the blood cell count during the first two weeks following CRS-PIC.

With respect to the relationship between severe hematologic toxicity and the cytoreduction procedure, Votanopolous[24] reports the existence of a positive correlation between severe neutropenia and thrombocytopenia after CRS with the performance of a splenectomy and the use of the HIPEC with Oxaliplatin protocol. On the contrary, Becher [25] showed a negative correlation for hematologic toxicity in patients who underwent a splenectomy. Furthermore, out results showed no statistically significant association between a splenectomy and any of the forms of severe hematologic toxicity (neutropenia, thrombocytopenia, or medullary toxicity).

The performance of blood transfusions during the post-operative period presented a borderline significance in terms of the development of severe thrombocytopenia ($p = 0.087$). However, we are in agreement with the hypothesis presented by Chalret du Rieu [23] which explains that the development of severe thrombocytopenia as an event secondary to a significant loss of blood during the surgical procedure more than a real effect of medullary toxicity. The preceding can be explained by the fact that thrombocytopenia secondary to high blood loss during CRS does not imply that the bone marrow is compromised, and the production of blood cells should not be compromised. On the contrary, medullary toxicity is presented with a profound pancytopenia, which creates a predisposition toward the development of infectious complications and high morbidity-mortality. Using these already-established concepts and our presented morbidity rate (44%), we ratify the recommendation regarding the daily monitoring of blood cell counts during the first two weeks of the post-operative period.

The MMC-based HIPEC protocol represented an independent risk factor for medullary toxicity, neutropenia, and severe thrombocytopenia in our results. Lambert [14] showed a positive correlation between severe neutropenia (39%) following PIC and the use of

the HIPEC with Mitomycin C protocol. The median dosage of Mitomycin reported in Lambert's study was 55 mg/square meter, which is substantially greater that the maximum dosage we used (35 mg/square meter). In a comparative study of the HIPEC with Oxaliplatin versus HIPEC with Mitomycin C protocols in patients with peritoneal carcinomatosis of a colorectal origin, Hompes [26] shows a statistically significant rate of 26.8% above the hematologic toxicity through the use of MMC. The morbidity and total survival were similar in the two groups. Precaution regarding the potential toxicity of Mitomycin C is due to the fact that it remains one of the most frequently used medications within HIPEC protocols around the world.

We also described an alarming relationship between the combination of HIPEC-EPIC, the morbidity-mortality of the procedure and severe hematologic toxicity in the post-operative period, although this did not present any statistical significance. The use of HIPEC-EPIC was recorded in 16 cases and five (33%) of those resulted in the development of neutropenia and severe thrombocytopenia, with two fatal outcomes. McConnell [27] reported that the use of HIPEC-EPIC is an independent risk factor for the presentation and development of severe post-operative complications following CRS-PIC (OR 2.40, CI 95%, 1.24 - 4.66, p = 0.01). The results of McConnell's study describe a high rate of anastomotic leaks, intraabdominal abscesses, and reoperations. Elias [28] compared the effectivity and tolerance of the administration of HIPEC vs. EPIC used individually, following CRS-PIC in patients with peritoneal carcinomatosis of a colorectal etiology. Elias describes the presentation of a high rate of digestive fistulas and the need for surgical re-interventions in the EPIC group, without establishing statistical significance with his results. With the support of these authors' findings, which coincide with our observations and results, in cases where HIPEC-EPIC is used, we recommend paying special attention to and monitoring the high possibility of complications and morbidity-mortality in the post-operative period.

Conclusion

In conclusion, the specific knowledge of the effects produced by cytoreduction and the different PIC protocols regarding the different types of blood cells is essential for all involved with the CRS-PIC teams, particularly those in emerging programs. The daily monitoring and tracking of blood cell counts during the first two weeks of the post-operative period allow for the early diagnosis of severe complications, which will allow them to be treated in the best possible manner for each individual case. In addition, its characterization allows for the differentiation between true medullary toxicity when it presents a compromise of two or more cell lines and a transient cytopenia secondary to the surgical procedure itself.

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