Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: July 31, 2023

Citation: de Witte P, Boerma D, et al., 2023. Risk of Acute Kidney Injury Following Mytomicin C Resorption during Hyperthermic Intraperitoneal Chemotherapy, Medical Research Archives, [online] 11(7). https://doi.org/10.18103/mra.v11i7.2.4181

DOI
https://doi.org/10.18103/mra.v11i7.2.4181

ISSN: 2375-1924

RESEARCH ARTICLE

Risk of Acute Kidney Injury Following Mytomicin C Resorption during Hyperthermic Intraperitoneal Chemotherapy

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ABSTRACT

Background: Surgical cytoreduction and simultaneous hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) is a common treatment for peritoneal carcinomatosis. During intraperitoneal chemotherapy, mitomycin C is frequently used. Mitomycin C is known to be nephrotoxic. Little is known about the effect of systemically absorbed mitomycin C on renal function during HIPEC surgery.

Methods: In twenty-two patients undergoing cytoreductive surgery and HIPEC for peritoneal carcinomatosis the systemic levels of mitomycin C were measured in plasma. The relation of plasma levels of mitomycin C with duration of surgery and complexity of surgery was evaluated.
Furthermore, we evaluated the relation between systemic mitomycin C levels with renal function.

Results Two patients of the total of 22 patients developed acute kidney injury. In these patients, preoperative creatinine level increased from (1) 109 µmol/L to maximum 890 µmol/L on the 6th postoperative day after which renal replacement therapy was started and (2) from 67 µmol/L to 213 µmol/L. Whereas maximum plasma levels of mitomycin C in these 2 patients were 145 µg/L and 280 µg/L compared to the levels in the other patients (167 µg/L ±80.8). Peak levels of plasma creatinine were on post operative day 2. None of the other patients needed renal replacement therapy. Eight patients showed significant increase of plasma creatinine levels, i.e. >20% increase from preoperative values. We did not observe a correlation between complexity of surgery, increased absorption of mitomycin C, higher mitomycin C plasma levels and signs of kidney injury.

Conclusions: Systemic absorption of mitomycin C during HIPEC surgery is independent to extension of cytoreductive surgery and duration of surgery. In this small study group, we observed an impairment of renal function which may be related to systemic absorption of mitomycin C. Further research is warranted to answer possible association of mitomycin C levels in patients at risk for development of AKI.

Keywords: Mitomycin; HIPEC; cytoreductive surgery; renal function; kidney injury; AKI

INTRODUCTION

Cytoreductive surgery (CRS) combined with HIPEC as a treatment option for selected patients with peritoneal carcinomatosis of gastrointestinal tumours is generally accepted.[1–4] Intraperitoneal free cancer cells from either spontaneous liberation from the primary tumour or by the traumatic injury during radical surgical curative resection is held responsible for the recurrence or dissemination of tumour cells into the peritoneal cavity. These cells are trapped in a relative hypoxic environment and therefore may be less sensitive to the effect of systemic chemotherapeutic drugs. [5,6] Cytoreductive surgery with HIPEC provides regional increased chemotherapeutic doses with a relative low systemic dose, with reduced risk of organ dysfunction. Furthermore, absorption of the drugs within the peritoneal cavity may lead to transportation to the liver by the portal venous circulation and may inhibit the development of micrometastasis. The hyperthermia impairs reparation of DNA and oxidative phosphorylation and on the other hand increases drug-sensitivity, penetration of the drugs into the tumour, and helps tumour lysis and cytotoxicity.[6,7]

So, systemic dose reduction may contribute to a decrease in toxicity with fewer negative side effects, such as primary or secondary organ damage and a consequent decrease in morbidity, while maintaining effectiveness and thereby improving survival.

During HIPEC, the abdomen is flushed with warmed chemotherapy. Mitomycin C (MMC) is a frequently used chemotherapeutic agent during this procedure. By administering chemotherapy locally instead of systemically, it is possible to administer higher dosages of the agents directly to the tumour site with reduced systemic effects. Systemic absorption of MMC is 1/100 of intraperitoneal levels. Systemic MMC might give general side effects of which neutropenia is the most common with an incidence between 28 and 83%. [8–11]

Administration of MMC systemically (iv and /or intra-arterially through a catheter in the superior part of the abdominal aorta) showed that the renal toxicity of MMC depended on the total dose. The acceptable cumulative dose of MMC was estimated approximately 50 mg/m^2, when the drug was given as 10- to 15-mg/m^2 doses at 8-week intervals, with the risk of serious renal complications < 2%. At doses >70 mg/m^2, there was an estimated 5% risk of acute kidney injury (AKI).[12] Whereas, the general preoperative condition of patients has independent influence both on morbidity and mortality. For instance, diabetes mellitus with an incidence of 18% among patient with cancer, led to a more than double length of ICU-stay (ICU-LOS), and major complications, e.g., infections, respiratory failure, thrombotic events, and kidney injury after cytoreductive surgery with HIPEC.[13,14] Therefore, our study describes our observational results of the presence and risk for AKI in patients scheduled for cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy.

METHODS

Study design

The aim of the original randomised trial was to evaluate if patients undergoing a HIPEC procedure received a more optimal fluid administration if FloTrac/Vigileo monitoring was used compared with patients receiving standard care.[15] After institutional review board approval and registered as R-11.33A/OPTIFLUID III, we prospectively evaluated 22 HIPEC-patients involving single agent chemotherapy with MMC 35 mg/m^2 body surface area, who were performed at our hospital by 2 surgeons between October 2011 and September 2013. For this study, we included adult patients scheduled for cytoreduction through open abdominal surgery prior to HIPEC administration. One patient in this study with profound AKI after HIPEC procedure brought the hypothesis of the possible role of MMC during HIPEC in the development of acute kidney injury. We re-analysed the samples for MMC-levels. Furthermore, we hypothesized that MMC absorption could be correlated to the surgical wound surface inflicted before hyperthermic intraperitoneal chemotherapy. Surgical wound surface was estimated by the surgeon (DB) after surgery, blinded for the changes in kidney function and graded 1 to5 (1= small wound surface with only small peritoneal resection, 5 = large wound surface with extensive debulking and multi-organ resections)

Patient population

All patients 18 years and older undergoing a HIPEC procedure for treatment of peritoneal carcinomatosis of colorectal cancer from January 2011 to January 2014 were asked to participate. The patients were screened for eligibility to participate in the study by preoperative assessment. Exclusion criteria were left ventricle ejection fraction under 40%, severe coronary artery disease and unwilling or unable to receive epidural anaesthesia. Patients with metastatic disease outside of the peritoneum, i.e. bone, liver, and lung were excluded. Eligible patients who approved to participate gave written informed consent.

HIPEC procedure

All participants underwent a median laparotomy. Extensive operative debulking with peritonectomy and, when needed, multi-organ resections, e.g., liver and spleen, were performed, as described by Sugarbaker et al.[16] and all the latter recommendations.[5] The purpose of the cytoreduction was to obtain a macroscopically complete cytoreductive surgery (R1) resection, which means that no macroscopically visible residual tumour was left at the end of the surgical resection. At the surgeon's discretion the intestines were anastomosed or locally repaired. After the cytoreduction, the open perfusion protocol of the abdominal cavity with MMC was performed.[17] The inflow temperature of the perfusate was 41–42 °C. As soon as this temperature was reached, MMC was added, 35 mg/m^2 body surface area, in three fractions (one half, one fourth, and one fourth of the total dose) with a 30 min dosing interval.

Anaesthesia

Before induction of general anaesthesia a median epidural catheter was placed in all patients. Epidural analgesia was initiated before incision with 10 ml of levobupivacaine 0.25% after which continuous administration was started with bupivacaine .125% with sufentanil 1 µg per mL (6 to 10 mL/h). Perioperative antimicrobial prophylaxis was routinely administered to all patients, i.e., 2 grams of cefazoline IV, at time of induction and repeated after 4 hours of surgery. Induction of general anaesthesia was performed with propofol (2mg/kg), fentanyl (3 µg/kg), and atracurium (0.5 mg/kg). After induction, anaesthesia was maintained with continuous administration of propofol. A tracheal tube was placed and the patients were ventilated with tidal volumes of 6 to 8 mL per kg body weight. A radial artery catheter and a central venous catheter (right internal jugular vein) were placed after induction of general anaesthesia and intubation. Muscle relaxation was maintained using continuous infusion of atracurium (0.3 mg kg^{-1} h-1) and was monitored with NMT-monitoring (Train of Four) with no twitches during surgery.[18] Possible hypothermia during cytoreductive surgery was prevented by forced air warming with blankets and warmed infusions in all patients. All patients received PONV-prophylaxis according to local protocol, i.e. combination of dexamethasone, ondansetron, and haloperidol, when necessary.

After the procedure the patients were admitted to the PACU or ICU for at least 24 hours.

Collection of blood samples

Blood specimens for haemoglobin, leukocytes, and platelet counts were collected into 4.5-mL glass Vacutainer ® tubes containing EDTA (Becton Dickinson, Franklin Lakes, USA). Blood samples were collected in 4.5-mL siliconized glass Vacutainer® tubes containing 3.8% trisodium citrate solution (0.105 M) (Becton Dickinson). Samples were collected via a radial artery catheter, centrifuged for 20 minutes at 1500 x g, and stored in aliquots at −80^{0}C until analysis. Blood samples were collected 1) after placement of radial artery catheter; 2) just before induction of hyperthermia; 3) thirty minutes after hyperthermia; 4) at the end of hyperthermia; 5) at arrival in the ICU; 6) after 12; and 7) after 24 hours postoperatively.

Biochemical analysis

Plasma samples were thawed and analysed for MMC in Strasbourg France.

Mitomycin C was measured using a liquid chromatography (LC) method with a photodiode array detector.[19,20] Briefly, samples were deproteinized by a mixture of tert-butyl methyl ether in basic pH. After centrifugation, the supernatant was evaporated under nitrogen flow and the dry extract was dissolved in the mobile phase. Mitomycin C was separated from coextracted compounds by reversed-phase liquid chromatography on a Kinetex® C18 column (15 x 4.6mm and 2.6 µM) and mobile phases were phosphate buffer at 10 mM and pH=7.0 with Methanol (60/40). A high detection sensitivity and selectivity was obtained by photometric measurements at 365 nm. The precision of the determinations was better than 5% relative standard deviation for plasma samples within the range 2–1000 ng/mL.[21]

Statistical Analysis

For data storage and statistical analysis, standard computer software (SPSS 26, IBM Corp, Armonk NY) was used. A 2-tailed P value < 0.05 was considered statistically significant in all tests. Continuous data are presented as mean and standard deviation (SD), if Gaussian distributed and as median and interquartile range (IQR), if not normally distributed. To compare independent continuous variables between groups, a student t test in case the values followed a Gaussian distribution or the Mann-Whitney U test was conducted otherwise, where appropriate. Categorical variables are given as frequencies and percentages. To compare dichotomous variables between groups, a χ2-test or Fisher's exact test was used.

RESULTS

Patient characteristics

Over a 2-year period, 37 patients undergoing HIPEC surgery gave informed consent to participate in the study. Thirteen patients were excluded during the operation in case of terminating surgery for inoperable tumours before starting with HIPEC. From one patient the blood samples were lost. Finally, one patient was treated with 5 FU leucovorin and Oxaliplatin instead of MMC. Patient characteristics of the remaining 22 patients are shown in Table 1.

Mean duration of surgery was 376 ± 68 minutes.

Kidney Injury

The patients had a preoperative plasma creatinine level of median 67 µmol/L, IQR 57-76 µmol/L. On the second postoperative day plasma creatinine levels were median 68 µmol/L, IQR 54-84 µmol/L. In 8 patients postoperative creatinine levels increased >20%, which ranged from 25 - 132%. Two patients of the total of 22 patients developed acute kidney of whom one required renal replacement therapy. In this patient preoperative creatinine level increased from 109 µmol/L to maximum 890 µmol/L on the 6th postoperative day after which renal replacement therapy was started. None of the other patients needed renal replacement therapy.

Moreover, we did not observe a possible association of the AKI with either the perioperative blood loss and the need for transfusion of red blood cells. Nine patients received transfusion red blood cells, i.e., 4 patients received 1 unit, 4 patients received 2 units and 1 patients received 4 units of packed red cells.

Mitomycin C

In the blood samples at t1 and t2 no MMC was detected as this was before starting open perfusion with MMC. At t5, MMC was detectable only in 2 patients, and at t 6 an 7 only in one patient. The patient in whom the MMC was still detectable at t6 and t7 was the patient who developed acute kidney injury requiring renal replacement therapy. This patient had normal liver functions. One patient had undetectable levels of MMC in all samples.

Mean MMC levels were 164 ± 77 µg/L at t3, decreasing to 54 ± 40 µg/L at t4.

Maximum plasma levels of MMC in the 2 patients who developed AKI were 145 µg/L and 280 µg/L, which was not significantly higher compared with the levels in the other patients (159 µg/L ±76, p= 0.6, figure 1).

We found no relation between the postoperative creatinine levels and the maximum MMC levels at t3 (figure 2).

There was no relation between mitomycin C levels at t3 and t4 and the development of AKI or increase in creatinine levels. Neither did we found a relation between extension of surgery and levels of MMC at t3 and t4 (figures 3a and b). There was no relation between duration of surgery and systemic levels of MMC at t3 (p=0.9) and t4 (p=0.9).

fig 1. levels of MMC at t3 for patients developing AKI vs no AKI

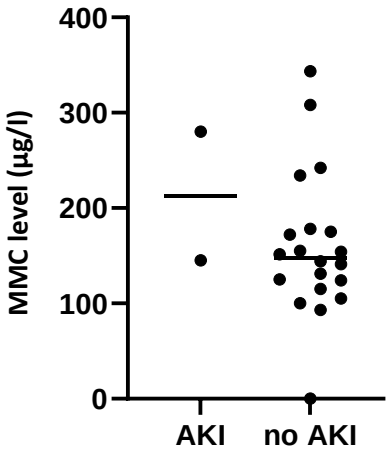

fig 2. MMC levels at t3 vs postoperative creatinine levels

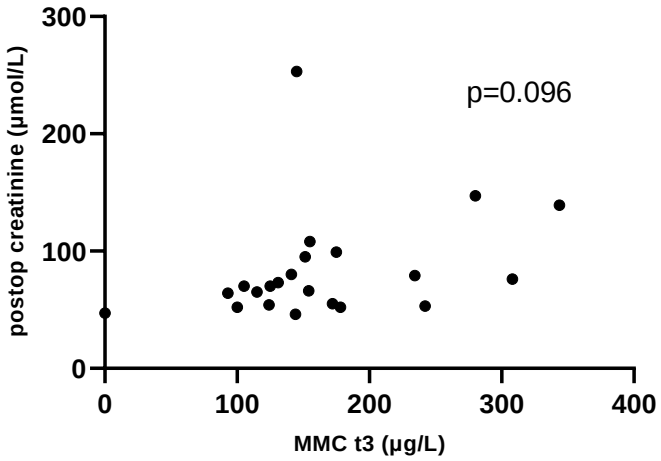

fig 3a. box plot of MMC levels vs surgical score 1-5 at t3

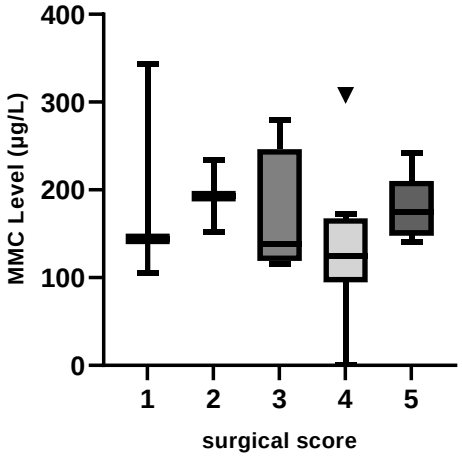

fig 3b. box plot of MMC levels vs surgical score 1-5 at t4

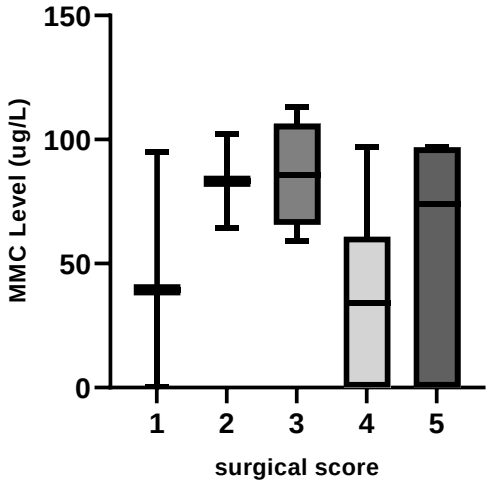

Table 1 patient characteristics

Variable	
Age (years)	61.0 ± 10.4
Sex male (%)	9 (41%)
Weight (kg)	77 ± 13
Height (cm)	172 ± 8.6
BSA (m2)	1.9 ± 0.2
BMI (kg/m2)	25.6 ± 2.9
Primary tumour	
Colon	20 (91%)
Small intestine	1 (4.5%)
Pseudomyxoma	1 (4.5%)
Comorbidity	
ASA 1-2	21 (95.5%)
ASA 3-4	1 (4.5%)
IDDM	1 (4.5%)
NIDDM	3 (13.6%)
COPD	1 (4.5%)
Hypertension	6 (27.3%)
Cerebrovascular disease	3 (13.6%)
Myocardial infaction	1 (4.5%)
CABG	1 (4.5%)
Medication use	
Coumadin	2 (9.1%)
beta blocker	5 (22.7%)
diuretic	4 (18.2%)
carbasalate calcium	3 (13.6%)
ace inhibitor	6 (27.3%)
statin	4 (18.2%)
calcium antagonist	4 (18.2%)
Surgical score	
1	3 (13.6%)
2	3 (13.6%)
3	4 (18.2%)
4	8 (36%)
5	5 (22.7%)

BSA: body surface area. BMI: body mass index. ASA: American Society of Anesthesiologists physical status classification system. NIDDM: non-insulin dependent diabetes mellitus. IDDM: insulin dependent diabetes mellitus. Surgical score is extension of surgical wound surface.
Data are expressed as mean (±SD) or absolute number (percentage), where appropriate.

DISCUSSION

To our knowledge, this is the first study evaluating the relation between systemic absorption of MMC during HIPEC surgery and correlated it with extensiveness of surgery and kidney function. In this small study, we found no relation between systemic absorption of MMC and the development of AKI or the increase in postoperative creatinine plasma levels. However, the only patient whose MMC levels remained detectable at 12 and 24 hours postoperatively was the patient requiring renal replacement therapy. Possibly our sample size was too small to find a

significant relation between systemic absorption of MMC and kidney injury.

Furthermore, we tried to evaluate the relation between extensiveness of surgery and absorption of MMC. We found no significant relation as the systemic absorption of MMC might be merely caused by absorption by the peritoneum instead of through the surgical wound bed. The score of surgical extensiveness to the discretion of the surgeon (DB) as used in present study is not a validated score.

Restriction of intravenous fluids perioperatively led to a significantly reduction of postoperative complications both cardiopulmonary and tissue-healing complications in a multicenter trial including 172 adult patients admitted for elective colorectal resection.[22] Positive salt and water balance sufficient to cause a 3 kg weight gain after surgery delays return of gastrointestinal function and prolongs hospital stay in patients undergoing elective colonic resection. We previously showed that the use of non-invasive CO monitoring by means of FloTrac/Vigileo did not lead to more optimal fluid administration in patients undergoing HIPEC surgery. All patients showed an inflammatory response during after HIPEC surgery.[15] We did not observe a relation between the changes in inflammatory mediators, such as IL-6 response and the occurrence of complications in this small group. However, change in kidney function by occurrence of change in plasma creatinine levels was present in 8 patients and led to AKI in 2 patients.

There is increasing consensus to quantify the accurate volume of free tumour cells in the abdominal cavity in patients with peritoneal metastasis.[23] Here, both the detection of free tumour cells through immunostaining method with the use of flowcytometry and counting the relative frequency of CD 326 (+) tumour cells against cd 45 (+) leukocytes showed a significantly higher tumour cells/leukocytes ratio which correlated with presence severity of peritoneal metastasis.

Secondly RT-PCR-mediated detection of micrometastasis were more prognostic in peritoneal than in omental washes for prediction of intraperitoneal recurrence of gastric carcinoma in patients undergoing elective laparotomy for cancer surgery[24]. At the same time, a search for a more optimal target for amplification is warranted. A combination of several mRNAs that excel in specificity at the expense of sensitivity may be one of the ways of establishing a reliable detection system, until an ideal target is found.

As all patients had peritoneal metastatic disease, we did not measure the number of tumour cells during the operation, but tried to quantity the severity of metastatic disease by both measurement of surgical effort and quantification of surface area of resection and related this to the duration of surgery, as time of peritoneal lavage was the same for all patients. Although all patients followed the same protocol one may imagine that there could be differences between patients, e.g. the combination of increased surgical lesions due to tumour resection especially in the posterior abdomen and continuous hydrostatic pressures of the MMC-peritoneal lavage fluid could lead to an increase of MMC absorption and successively higher increased MMC plasma levels.

Pharmacokinetics of intraperitoneal MMC has shown a 10-20 times higher concentration of MMC in the perfusate during HIPEC compared to the plasma concentration.[25] Previous studies have reported that maximum plasma concentrations of MMC are from 0.11 to 0.5 mg/L.

Neutropenia is one of the major complications with administration of MMC.[8] The onset and severity of neutropenia were proportional to the plasma concentration of MMC.[8,25] Although the neutropenia in the 45 patients studied did not influence mortality, infection or LOS. Female patients were more at risk than male regarding the occurrence of neutropenia.[11]

In a retrospective study among 935 patients Randle and colleagues observed an increased ICU-LOS and kidney failure (OR 4.2, 95% CI 1.9–9.1, $P = 0.002$).[14]

Although, in a retrospective study HIPEC was suggested as an independent risk factor for the development of kidney injury in patients who received the combination of cisplatin (50 mg/m^2) with doxorubicin (15 mg/m^2). Here the nephrotoxicity of platinum-based therapy in itself combined with hyperthermia, dehydration, inotropic support, and hypotension may have been responsible for the kidney injury.[26] A prospective study also with cisplatin

(90 mg/m^2) in 47 patients with ovarian cancer with peritoneal metastasis undergoing cytoreductive surgery combined with HIPEC showed an incidence of kidney injury of 9.4% with need for renal replacement therapy in 5.7% of patients.[27] Significant risk factors were age> 48 years, baseline creatinine >60 µmol/L, correlated with nine times the risk of kidney injury, postoperatively. Whereas, eGFR (Cockcroft–Gault formula), of <80.2 mL/min was 5.5 times more likely to result in AKI compared to higher creatinine clearance. Other noticeable risk factors were pre-operative albumin<40 g/L, number of preoperative carboplatin cycles >8, time interval between the

end of pre-operative chemotherapy and date of surgery less than 7 days, blood transfusion >2 units. There was indication of a trend towards higher probability of AKI if cisplatin dose during HIPEC was 70mg or higher.

Concerning the need for blood transfusion, Schmidt observed in a retrospective analysis that of 71 patients in total who underwent CRS-HIPEC, 50% received either packed cells and/or FFP during surgery and postoperatively in 28% of cases.[28] Furthermore, as 72% of patients received thoracic epidural analgesia, they observed both an opioid sparing effect and a reduced duration of postoperative ventilation by their strategy. Our observational study has limitations. Our study was neither designed nor powered to demonstrate the risk of kidney failure in HIPEC patients in e.g. a comparison of various doses, duration of surgery or patients with different preoperative renal function. For instance, with a known an estimated 5% risk of AKI (effect size) and a power of 80% at doses >70 mg MMC/m^2 >3000 patients would have to be studied.

In contrast, Ravish Kapoor and colleagues in 2019 observed no AKI in a group of patients who underwent laparoscopic CRS-HIPEC with intraperitoneally administration of fixed doses of MMC (30 mg) and cisplatin (200 mg).[29]

CONCLUSION

During surgical cytoreduction and simultaneous hyperthermic intraoperative intraperitoneal chemotherapy, mitomycin C is absorbed by the peritoneum in patients with gastrointestinal cancer

In present study two patients developed acute kidney injury of whom one needed renal replacement therapy. We were not able to find a correlation between absorption of mitomycin C during surgery and successive increase of mitomycin C-plasma levels to either increase of serum creatinine levels or development of acute kidney injury in this relative small group of patients. Interestingly the patient requiring renal replacement therapy was the only patient in whom mitomycin C was detectable in all postoperative samples despite a normal liver function. Possibly the impaired clearance of mitomycin C in this patient led to kidney failure.

Pre-existing chronic kidney disease is a significant risk factor for development of acute kidney injury, whereas acute kidney injury by itself may lead to chronic kidney disease. Patients with cancer and treated with chemotherapy for cancer such as in our group of patients appeared to be at risk for development of acute kidney injury. In this manuscript we aim to increase awareness of acute kidney injury as a serious complication in these vulnerable patients for whom future research is needed in order to facilitate recovery and minimize the risk of these complications.

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