

Bidirectional Intraoperative Chemotherapy Using Cisplatin and Ifosfamide for Intraperitoneal Mesothelioma in Severe Renal Impairment: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ADEF 1 **Razan K. Almesned**
ADE 2,3 **Ayman Z. Azzam**
E 4 **Ayman Aldeheshi**
ADE 2 **Tarek M. Amin**

1 Department of Urology, King Faisal Specialists Hospital and Research Center, Riyadh, Saudi Arabia
2 Department of Surgical Oncology, Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
3 Department of General Surgery, Faculty of Medicine, Alexandria University, Alexandria, Egypt
4 Anatomical Pathology Section, Department of Pathology & Lab Medicine, King Faisal Specialists Hospital and Research Center, Riyadh, Saudi Arabia

Corresponding Author: Razan K. Almesned, e-mail: razanalmesned@hotmail.com
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Patient: Female, 46-year-old
Final Diagnosis: Malignant peritoneal mesothelioma
Symptoms: Asymptomatic
Clinical Procedure: —
Specialty: Oncology





Objective: Unusual clinical course
Background: Malignant peritoneal mesothelioma (MPM) is an aggressive neoplasm with a poor prognosis. Bidirectional intraoperative chemotherapy (BDIC) using concurrent intraperitoneal and intravenous chemotherapy in combination with cytoreductive surgery (CRS) is an emerging treatment option for selected cases of MPM. It is a locoregional treatment that involves intraoperative chemoperfusion of heated chemotherapy. The administration of systemic along with intraperitoneal chemotherapy allows for a bidirectional chemotherapy gradient in peritoneal tumor cells. The aim of this treatment is eradication of microscopic residual cancer cells after major removal of macroscopic tumor nodules. To date, there is no consensus on the chemotherapeutic regimen that can be used in BDIC to manage MPM in patients with severe renal impairment. Administering intravenous ifosfamide with hyperthermic intraperitoneal cisplatin and doxorubicin is a promising regimen in treating peritoneal mesothelioma. Nephrotoxicity is a dose-limiting adverse effect of cisplatin and ifosfamide. Therefore, dose adjustment is required in patients with renal impairment.

Case Report: In this report, we describe a 46-year-old female patient with recurrent MPM and severe renal impairment. Her treatment was managed with hyperthermic intraperitoneal cisplatin and doxorubicin along with intravenous ifosfamide following CRS. The cisplatin dose was reduced to 50% and the ifosfamide dose was reduced by 25%. The patient tolerated the procedure well, without deterioration in her renal function. At her 9-month follow-up, she did not report experiencing chemotherapy-related adverse effects, and her kidney function remained stable.

Conclusions: Severe renal impairment might not be a contraindication to using potentially nephrotoxic chemotherapeutic agents in CRS-BDIC.

Keywords: Cytoreduction Surgical Procedures • Hyperthermic Intraperitoneal Chemotherapy • Mesothelioma, Malignant • Renal Insufficiency, Chronic

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Background

Malignant peritoneal mesothelioma (MPM) is a rare neoplasm, with an overall prevalence of 1 to 2 cases per million [1]. It is associated with rapid fatality and a mean symptoms-to-survival time of 345 days [2]. Treatment options for MPM are limited. Initially, cases were managed with palliative systemic chemotherapy alone or in combination with palliative surgery, with which median survival did not exceed 7 months [3]. Modern treatment of MPM includes the use of hyperthermic intraperitoneal (i.p.) chemotherapy (HIPEC), a locoregional treatment that involves the intraoperative chemoperfusion of heated chemotherapy to eradicate microscopic tumor cells after the major removal of macroscopic tumor nodules [4]. Many studies reported survival benefits favoring cytoreductive surgery (CRS) plus HIPEC over systemic chemotherapy with palliative surgery [5-7]. A meta-analysis of various studies on MPM demonstrated a 5-year predicted overall survival of 42% [7]. These positive outcomes of CRS and HIPEC encouraged clinicians to use intraoperative intravenous (i.v.) ifosfamide concurrently with HIPEC after CRS in treating MPM. [8,9]. The i.v. administered chemotherapeutic agents reach the residual disease through the capillaries feeding the tumor nodules. The administration of systemic chemotherapy along with i.p. chemotherapy allows for a bidirectional chemotherapy gradient in peritoneal tumor cells [10,11]. The chemotherapy dose used in HIPEC is usually a single-shot treatment and in lower doses than the corresponding systemic treatment.

CRS-BDIC using i.v. ifosfamide and i.p. cisplatin plus doxorubicin is an aggressive therapeutic approach that entails morbidity and mortality risks [8]. Among the reported nonsurgical complications is nephrotoxicity, which could be precipitated by the use of cisplatin and ifosfamide. The reported incidence of nephrotoxicity with cisplatin use in HIPEC ranges from 3.7% to 36% [12-14]. Two retrospective studies of BDIC using a systemic ifosfamide and i.p. cisplatin-doxorubicin regimen reported 0% and 33.3% rates of nephrotoxicity [8,15].

Herein, we report a case of a patient with MPM who was known to have stage 5 chronic kidney disease (CKD), and underwent CRS-BDIC using an i.v. ifosfamide and i.p. cisplatin-doxorubicin regimen.

Case Report

A 46-year-old woman was referred to our tertiary care center as a case of recurrent mesothelioma with liver metastasis. In 2019 in another center, she underwent CRS, including pelvic exenteration, hysterectomy, oophorectomy, partial peritonectomy, omentectomy, partial resection of the right diaphragm, resection of the rectosigmoid colon, resection of segments 6 and 7 of the liver, ileal conduit urinary diversion, and colostomy

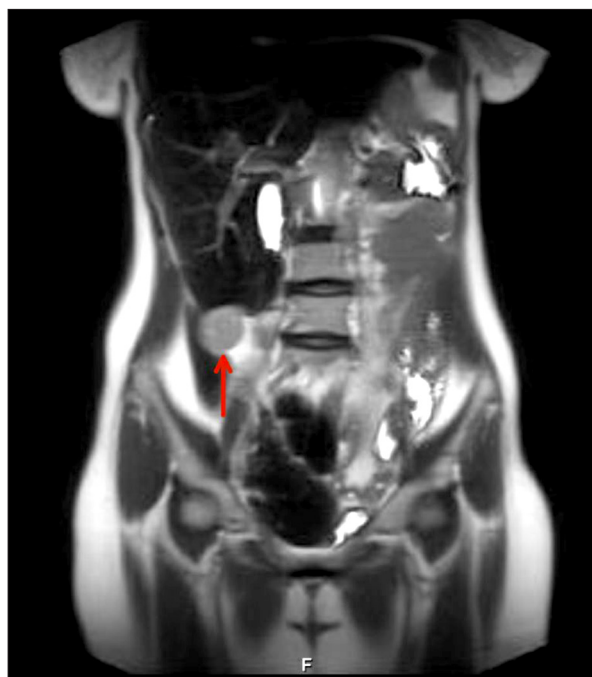


Figure 1. T1-weighted magnetic resonance imaging in the coronal plane of the abdominal and pelvis shows a subhepatic tumor (arrow).



Figure 2. Post-contrast T2-weighted magnetic resonance imaging in the transverse plane of the abdominal and pelvis shows a subhepatic tumor (arrow).

creation, followed by HIPEC. In March 2020, she had a recurrence and underwent exploratory laparotomy, local peritonectomy, resection of segment 5 of the liver, and reversal of colostomy, with a loop ileostomy elsewhere. The second operation was complicated by acute kidney injury attributed to a high-output stoma, which progressed to CKD. After that, she received 4 cycles of carboplatin with pemetrexed, which was complicated by multiple admissions due to dehydration and acute kidney injury episodes that mandated withholding of chemotherapy.

Magnetic resonance imaging (Figures 1, 2) and positron emission tomography (Figure 3) showed a peripheral subhepatic lesion in segment 7, measuring 0.7×1.3 cm.



Figure 3. A whole-body positron emission tomography scan shows a hypermetabolic subhepatic tumor (arrow).

The patient was not exposed to any of the well-known risk factors of mesothelioma, including radiation exposure, asbestos, erionite, or silicate exposure.

Her preoperative eGFR ranged between 5 and 8 mL/min/m², and her creatinine level ranged between 734 and 484 μmol/L (**Table 1**). In our center on November 21, 2021, she underwent CRS and HIPEC using 50% of i.p. cisplatin 25 mg/m² (37.5 mg) plus doxorubicin 7.5 mg/m² (22.5 mg) infused over 60 min concomitantly with a 75% i.v. ifosfamide dose of 1040 mg/m². Both i.p. and i.v. chemotherapy were started simultaneously after completing the resection of the subhepatic mesothelioma, partial wedge liver resection, colostomy closure, and appendectomy. Intraoperatively, continuous monitoring was performed using standard ASA and EV1000 hemodynamic monitoring systems (**Table 2**). A dialysis catheter was inserted in the left internal jugular vein, and a continuous renal replacement therapy machine was present on standby in case the patient became overloaded or developed chemotherapy-related adverse events. Close monitoring of the urine output was done during the operation hourly and every 15 min during the BDIC phase. Her intraoperative urine output was between 2 and 3 mL/kg/h, and mean arterial pressure was between 70 and 90 mmHg. The procedure was completed successfully without immediate complications, and the patient was moved to the Intensive Care Unit in a stable condition. She maintained adequate blood pressure, without the need for inotropes or vasopressors. In the Intensive Care Unit, her mean arterial pressure was maintained above 65, without inotropic support. Her renal function was monitored closely after surgery by a nephrologist. She did not require intraoperative or postoperative hemodialysis.

Table 1. Perioperative parameters.

| | Intravenous fluids (mL/h) | Creatinine (μmol/L) | eGFR (mL/min/m ²) | Mg (mmol/L) | Blood transfusion (mL) | BNP (pg/mL) |
|-------------------|------------------------------|------------------------|----------------------------------|----------------|---------------------------|----------------|
| Preop | 75 | 578 | 7 | 0.64 | | |
| Preop | 75 | 556 | 7 | 0.83 | 300 | |
| 0 Nov 21, 2021 | 100 | 415 | 10 | 0.65 | 600 | |
| POD 1 | 100 | 485 | 8 | 0.93 | | 1590 |
| POD 2 | 100 | 546 | 7 | 0.91 | 300 | 5481 |
| POD 3 | 100 | 553 | 7 | 0.93 | | 7041 |
| POD 4 | 100 | 538 | 7 | 0.88 | | |
| POD 5 | 100 | 554 | 7 | 0.83 | | |
| POD 6 | 100 | 507 | 8 | 0.83 | | |

BNP – brain natriuretic peptide; Mg – magnesium; POD – postoperative day.

Table 2. Intraoperative data.

| Characteristics | Value |
|---|-------|
| Maximum MAP, invasive (mmHg) | 103 |
| Minimum MAP, invasive (mmHg) | 50 |
| Maximum SBP, invasive (mmHg) | 138 |
| Minimum SBP, invasive (mmHg) | 99 |
| Drop in systolic blood pressure below 60 mmHg | None |
| Blood loss (mL) | 400 |
| Total fluids intake (mL) | 6600 |
| Packed red blood cells (mL) | 600 |
| Fresh frozen plasma (mL) | 500 |
| Total urine output (mL) | 1400 |
| Mean urine output (mL/kg/h) | 2-3 |
| Norepinephrine (mg) | 9.47 |

MAP – mean arterial pressure; SBP – systolic blood pressure.

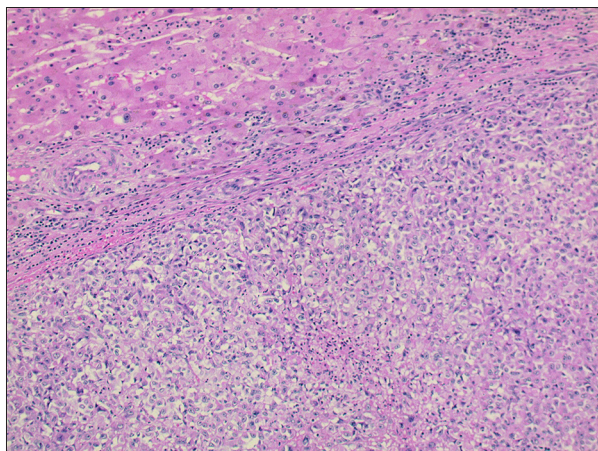


Figure 4. Medium-power view showing the sheets of tumor cells adherent to the liver capsule with no parenchymal invasion (hematoxylin and eosin, $\times 100$).

Histologic sections showed diffuse sheets and nests of epithelioid cells adherent to the liver and bowel wall, with no invasion into the liver parenchyma or bowel mucosa. Multiple foci of necrosis with micro-abscess formation were seen. The tumor cells were medium to large, with irregular contours, abundant eosinophilic cytoplasm, and visible nucleoli. By immunohistochemistry analysis, the tumor cells were positive for Pan-CK, CK 5/6, and Calretinin, confirming the diagnosis of mesothelioma (Figures 4-7).

Her postoperative course was complicated with pelvic collection, which was managed with drainage and i.v. antibiotics. The patient was followed up 9 months after the procedure. Her kidney function was stable, and she did not experience

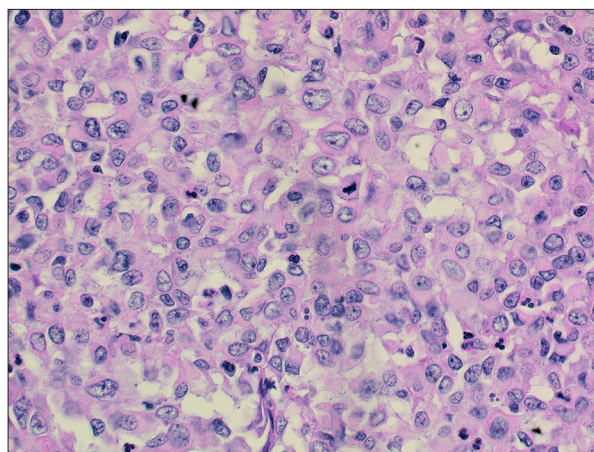


Figure 5. High-power view of the epithelioid tumor cells with scattered inflammatory cells along with a mitotic figure (hematoxylin and eosin, $\times 200$).

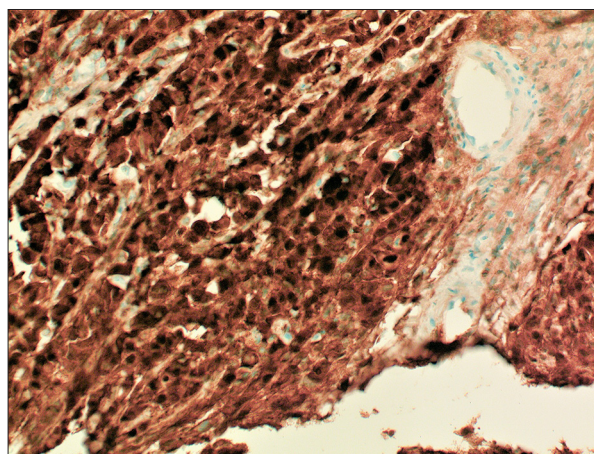


Figure 6. Calretinin immunohistochemistry study showing positive nuclear and cytoplasmic staining.

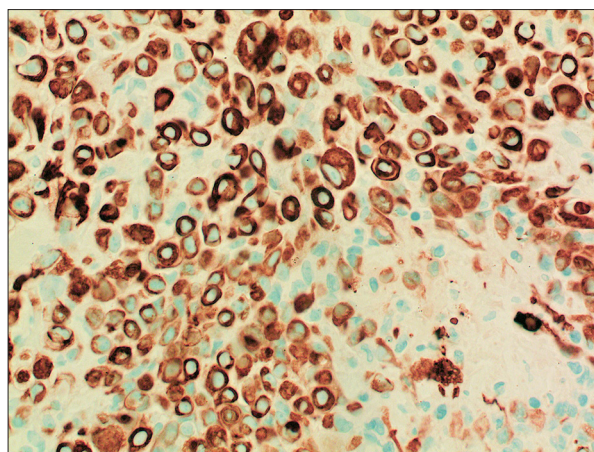


Figure 7. CK 5/6 immunohistochemistry. Strong cytoplasmic positive staining for CK 5/6 is also noted.

chemotherapy-related adverse effects. Her serum creatinine level was 478 $\mu\text{mol/L}$, and her eGFR was 8 mL/min/m^2 .

Discussion

Cisplatin is a valuable chemotherapeutic agent used in treating various solid organ malignancies. Nephrotoxicity is a dose-limiting adverse effect of cisplatin that can manifest as acute kidney injury, chronic kidney injury, electrolyte disturbances, and anemia [16]. Using i.v. cisplatin in patients with renal impairment places them at increased risk for further deterioration of their renal function. A retrospective study that reviewed 821 patients who received i.v. cisplatin and survived for at least 5 years showed <2% of patients with CKD stage 1 and 6% of patients with CKD stage 3 before treatment progressed to have an eGFR <29 $\text{mL/min per } 1.73 \text{ m}^2$; and <2% of patients with CKD stage 2 progressed to CKD stage 4 [17]. However, none of the patients required hemodialysis [17]. A study that included 113 patients who received cisplatin reported that 19 (12.1%) patients developed new-onset stage 3 CKD; this increase in risk was observed to be directly proportional to the dose administered and the number of cycles [18]. In the same study, the incidence of stage 2 CKD after receiving cisplatin increased from 18.6% to 40.7% [18].

Studies that examined the pharmacokinetics of cisplatin use in HIPEC demonstrated the systematic absorption of cisplatin [19]. When 50 mg/m^2 of cisplatin is given i.p., around 46% got absorbed from the peritoneal cavity into the plasma [19]; thus, nephrotoxicity was frequently described after HIPEC using cisplatin at various rates [12,13,16].

Multiple measures have been suggested to prevent cisplatin-induced nephrotoxicity. Hydration with isotonic fluid is the primary approach used to reduce cisplatin nephrotoxicity; however, despite aggressive hydration, the risk of cisplatin nephrotoxicity is not eliminated [20,21]. Prior to the introduction of hydration regimens, initial studies showed a 50%

incidence of nephrotoxicity [22,23]. After the introduction of various hydration methods, the incidence of nephrotoxicity lowered to levels reaching 3.7% in some reports [13]. There are no randomized clinical trials investigating the effectiveness of different hydrations regimens.

Ifosfamide is one of the few chemotherapeutic agents that demonstrated heat synergy in pharmacokinetic studies [8]. Ifosfamide and its metabolites have been found in the tumor nodules when it was administered continuously in BDIC [8]. There are available recommendations on the use of reduced doses of chemotherapeutic agents including ifosfamide in the setting of renal impairment [24,25]. Aronoff et al recommend a 25% reduction of the usual dose for patients with eGFR <10 mL/min and full dose for patients with eGFR between 10 and 50 mL/min [24]. Kintzel and Dorr, on the other hand, recommend a 25% dose reduction in creatinine clearance of 45 mL/min and 30% reduction in creatinine clearance of 30 mL/min [25]. There are only 2 reports in the literature on ifosfamide-induced nephrotoxicity when used in BDIC, which showed 0% and 33.3% [8,15]. The discrepancy between the 2 rates could be explained by the percentage of elderly patients (>65 years of age) included, which was 0% and 27.7%, respectively [8,15].

Conclusions

This case report highlights the success of CRS-BDIC using potentially nephrotoxic chemotherapeutic agents in a patient with renal impairment. However, further studies on this group of patients are needed to aid in patient selection, choice of chemotherapeutic agents, dose adjustment, method of administration, and perioperative care to establish the best practice.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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