İLERİ EVRE/REKÜREN OVER KANSERİ NEDENİYLE HİPERTERMİK İNTRAPERİTONYAL KEMOTERAPİ (HIPEC) UYGULADIĞIMIZ HASTALARDAKİ PEROPERATİF TECRÜBEMİZ

Our Peroperative Experience in Patients who Underwent Hyperthermic Intraperitoneal Chemotherapy (Hipec) For Advanced Stage/Recurrent Ovarian Cancer

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ÖZET

Amaç: İleri evre/reküren over kanseri nedeniyle sitoredüktif cerrahi ve Hipertermik İntraperitonyal Kemoterapi (HIPEC) uyguladımız hastalardaki peroperatif morbidite ve mortaliteyi araştırdık.
Yöntem: Ocak 2016-Aralık 2018 tarihleri arasında HIPEC uyguladığımız hastaların elektronik dosyaları ve takipleri retrospektif olarak incelendi.
Bulgular: Nihai patolojisi musinöz apandiks tümörü gelen 1 vaka dışlandığında peritonyal karsinomatozis nedeniyle toplam 18 hastaya ileri cerrahi ve HIPEC uygulandı. Hastaların ortalama yaşı 54,6 (aralık, 22-76 yaş) idi. Median preoperatif CA125 değeri 64 U/ml (aralık, 6-4756 U/ml) idi. 3 hasta rekürens nedeniyle, 15 hasta (11 interval, 4 first-look cerrahi) ise primer olarak opere edildi. Hastaların hepsine peritonektomi prosedürü, 4 hastaya ise beraberinde barsak rezeksiyonu uygulandı. Ortalama operasyon süresi 323,5 dakika (aralık, 180-495 dakika) idi. En sık gözlenen dahili morbidite, kan transfüzyonu (83.3%, 15/18); cerrahi morbidite ise yara yeri enfeksiyonu (%16.6, 3/18) bulundu. Hastaların ortalama hastanede yatış süresi 10,3 gün (aralık, 5-32 gün) idi. Peroperatif mortalite gözlenmedi.
Sonuç: HIPEC, yoğun bakım koşulları iyi olan ve multidisipliner kliniklerde uygulandığında peroperatif ciddi morbidite ve mortaliteye neden olmayan bir yöntemdir.

Anahtar Sözcükler: *HIPEC; Peroperatif; Morbidite.*

ABSTRACT

Objective: We investigated peroperative morbidity and mortality in patients who underwent cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for advanced stage/recurrent ovarian cancer.
Methods: Between January 2016 and December 2018, electronic files and follow-up of patients who underwent HIPEC were reviewed retrospectively.
Results: After one case of mucinous appendiceal tumor was excluded, a total of 18 patients underwent advanced surgery and HIPEC due to peritoneal carcinomatosis were detected. The mean age of the patients was 54.6 years (range, 22-76 years). The median preoperative CA125 value was 64 U/ml (range 6-4756 U/ml). Fifteen patients (11 interval surgeries, 4 first-look surgeries) were operated primarily while 3 patients were operated due to recurrent disease. Peritonectomy procedure was performed in all patients and bowel resection was performed in 4 patients. The mean operative time was 323.5 minutes (range, 180-495 minutes). The most common medical morbidity was blood transfusion (83.3%, 15/18) while most common surgical morbidity was wound infection (16.6%, 3/18). The mean length of hospitalization was 10.3 days (range, 5-32 days). No peroperative mortality was observed.
Conclusion: HIPEC is a method that does not cause severe morbidity and mortality when well intensive care conditions are applied in multidisciplinary clinics.

Keywords: *HIPEC; Peroperative; Morbidity.*

INTRODUCTION

Ovarian cancer (OC) represents the fifth most common cause of cancer-related death for women and is the most frequent cause of death from gynecological malignancies in the industrialized countries (1). Overall prognosis is poor with the five-year survival rate is only %30. This is related to absence of the screening tools in OC and %75 of patients are detected at advanced stage. At the time of diagnosis, disease mainly spreads to serosal surfaces, but also lymph nodes and parenchymal metastases could be seen. The standard treatment of primary OC is comprehensive cytoreductive surgery (CRS) and systemic chemotherapy. Despite these efforts most of the patients recur (1,2).

Since twenty years, comprehensive CRS combined with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for the management of some rare peritoneal surface malignancies (PSM) like pseudomyxoma peritonei or mesothelioma and also for selected patients with colorectal carcinomatosis are accepted as standard of care (3-5). But in the issue of epithelial ovarian cancer (OC) data are conflicting. Although some data suggested benefit of CRS and HIPEC in selected group of OC, most of the literature could not show its survival advantage besides reporting high morbidity and mortality (6-8).

In our study; we investigated peroperative morbidity and mortality in patients who underwent CRS and HIPEC for advanced stage/recurrent ovarian cancer.

MATERIALS AND METHODS

In this retrospective, single-center, descriptive study; records of the patients between January 2016 and December 2018 who underwent CRS and HIPEC for the indication of peritoneal carcinomatosis (PC) were detected at the Department of Obstetrics and Gynecology, Tepecik Research and Teaching Hospital. All the patients had provided written informed consent. File charts, follow-up reports, pathology and laboratory results, consultations were reviewed. Collected data included patient's age, preoperative serum CA 125 level, operative procedure, HIPEC procedure, final pathologic diagnosis, peroperative morbidity and mortality. To exclude bias, the cases which were operated by the same gyne-oncologist (Dr.Mehmet Gökçü) were chosen for the analysis. Peroperative period was defined as the time within 2 months after the operation was performed. CRS was distinguished as 1-Primary surgery: This was also as subdivided as "first look", if the patient has not received peroperative chemotherapy or "interval surgery", if the patient has received neo-adjuvant 3-4 cycles of chemotherapy 2-Recurrent surgery: If the disease has recurred in more than 6 months of time after the CRS and standard first-line systemic chemotherapy was done. The assessment of the completeness of the cancer resection was performed with the CC-score: CC-0 correspond to no macroscopic residual disease, CC-1 to residual tumour nodules less than 2.5 mm, and CC-2 to residual tumour nodules more than 2.5 mm (9).

Patients whose final pathologic diagnosis were non-epithelial ovarian cancer were excluded from the study. Survival analysis was not done as this was not the aim of the study.

RESULTS

After one case of mucinous appendiceal tumor was excluded, a total of 18 patients underwent advanced surgery and HIPEC due to peritoneal carcinomatosis was detected. The mean age of the patients was 54.6 years (range, 22-76 years). The median preoperative CA125 value was 64 U/ml (range 6-4756 U/ml). Fifteen patients (11 interval surgeries, 4 first-look surgeries) were operated primarily while 3 patients were operated due to recurrent disease. Peritonectomy (either on upper or lower abdomen) procedure was performed in all patients and bowel resection was performed in 4 patients. Of these bowel resections, only one anastomosis was performed. The mean operative time was 323.5 minutes (range, 180-495 minutes). Following maximal effort at comprehensive surgery, 77.7% of patients (14/18) were considered a CC-0 resection, and 22.2% of patients (4/18) were considered a CC-1.

Open technique was used in all HIPEC procedures with a median duration of

90 minutes (range, 60-120 min), with median intraperitoneal temperatures

of 42 oC (range, 40-42 oC). Paclitaxel was the drug most

commonly preferred during HIPEC (%55.5, 10/18). Mean overall and intensive care unit hospitalization times were 10.3 (range, 5-32 days) and 1.5 days (range, 1-6 days), respectively.

In the peroperative period, the most common medical morbidity was blood transfusion (%83.3, 15/18) followed by electrolyte disturbance (%72, 13/18) while most common surgical morbidity was wound infection (%16.6, 3/18). No peroperative mortality was observed. Descriptive data of the study cohort was shown in Table 1.

DISCUSSION

Ovarian cancer is the leading cause of death from a gynecological cancer in the world (2). The high rate of death is contributed to the extra-ovarian spread of the disease at the time of diagnosis. Despite the standard extensive CRS plus combinated platinum analogue and taxane chemotherapy, most of the patients recur and die of the disease (10).

In recent decades, HIPEC appeared as a promising method in OC treatment due to the peritoneal cavity is the main site of the disease spread and peritoneum is a resectable organ. In accordance, GOG 172 demonstrated that as compared with intravenous paclitaxel plus cisplatin, intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel improves survival in patients with optimally debulked stage III ovarian cancer (11). Unfortunately, only %42 of the patients in the intraperitoneal group received the planned six cycles of therapy. The primary reason for discontinuation of intraperitoneal therapy was catheter-related complications. Secondarily, more patients in the intraperitoneal-therapy group than in the intravenous-therapy group had severe or life-threatening (grade 3 or 4) fatigue, pain, or hematologic, gastrointestinal, metabolic, or neurologic toxic effects (P≤0.001). To overcome the problems associated with multiple course outpatient intraperitoneal chemotherapy, could HIPEC be a way out as it was for once used immediately after the CRS? In the issues of morbidity and mortality, data are conflicting. In their systematic review, Hotouras et al. investigated the impact of HIPEC in patients with recurrent ovarian cancer and found that HIPEC-related morbidity (between %13.6-100) was mainly minor and not significantly different from that experienced by patients who only underwent cytoreduction (12). Similarly, in our cohort most of the peroperative morbidities were minor and resolved without serious intervention. By contrast, in the systematic review made by Chiva et al., higher rates of severe surgical morbidity (25% in the primary and 19% in the recurrent patients) and mortality (ranges of 0–7% in both groups),
were found than those found in the literature, which are approximately %10–12 for both primary and recurrent disease without HIPEC (13).

As anastomotic leakage is one of the most common reasons of the mortality in patients with CRS and HIPEC was done, authors mostly prefer ostomy although there is no evidence that HIPEC for ovarian cancer is associated with a higher rate of anastomotic leakage than the rate without HIPEC (14). In the study of van Driel et al., among the patients who underwent bowel resection, a colostomy or ileostomy was performed more commonly among patients in the surgery-plus-HIPEC group (21 of 29 patients [72%]) than among those in the surgery group (13 of 30 patients [43%]) (P = 0.04) (7). Similarly, we performed just one anastomosis (%25, 1/4) among patients we resected the bowel. And leakage was not observed in that patient.

In our series no mortality was observed but most of the patients (%72-80) suffered blood transfusion and electrolyte disturbance that required close follow-up of the kidney functions but did not require dialysis. In the study of Bakrin et al., fifty one patients (8%) had postoperative renal insufficiency with 15 patients (2%) that developed chronic renal insufficiency and 6 patients (1%) that required long-term dialysis (15). The effect on the kidney functions could be affected by the HIPEC procedure (duration, temperature, chemotherapy regimen) and the different study populations among these studies.

In conclusion, HIPEC is a method that does not cause severe morbidity and mortality when well intensive care conditions are applied in multidisciplinary clinics.

TABLE 1. Descriptive data of the study cohort

No	Age	CA125	Indication	Surgery	Op time (min)	Hospital-ization time (days)	Morbidity	HIPEC
1	63	25	Recurrent	peritonectomy+residual omentec-tomy	215	9	Blood transfusion,electrolyte disturbance	100 mg/m2 taxol, 42oC, 90 min
2	61	8	Interval	tah+bso+total omentectomy+peritonectomy+lnd	285	8	Blood transfusion,electrolyte disturbance	100 mg/m2 taxol, 42oC, 90 min
3	48	698	First look	tah+bso+total omentectomy+peritonectomy+lnd	330	6	Blood transfusion,electrolyte disturbance	100 mg/m2 taxol, 42oC, 90 min
4	22	4756	First look	tah+bso+total omentectomy+peritonectomy+lnd	320	18	Ileus,elevated liver enzymes,neuropathy	100 mg/m2 taxol, 40oC, 90 min
5	63	155	First look	tah+bso+low anterior resection+end ostomy+total omentectomy+peritone ctomy+apendectomy+lnd	380	21	Blood transfusion,electrolyte disturbance,wound infection,dehiscence	100 mg/m2 taxol, 42oC, 90 min
6	51	12	Interval	tah+bso+total omentectomy+peritonectomy+lnd	320	7	Blood transfusion	100 mg/m2 taxol, 41oC, 90 min
7	43	20	Interval	tah+bso+total omentectomy+periton ectomy+apendectomy+lnd	445	6	Blood transfusion	100 mg/m2 taxol, 42oC, 90 min
8	56	64	Interval	tah+bso+total omentectomy+peritonectomy	345	10	Blood transfusion	100 mg/m2 taxol, 41oC, 60 min
9	66	12	Interval	tah+bso+total omentectomy+perito nectomy+lnd+colon resection+end ostomy	465	12	Blood transfusion,electrolyte disturbance	100 mg/m2 taxol, 42oC, 90 min
10	59	129	Interval	tah+bso+total omentectomy+peritonectomy+lnd	490	7	Blood transfusion,electrolyte disturbance	100 mg/m2 taxol, 42oC, 90 min
11	51	520	First look	tah+bso+total omentectomy+peritonectomy+lnd	240	5	Blood transfusion,electrolyte disturbance	50 mg/m2 cisplatin, 42oC, 90 min
12	76	24	Interval	tah+bso+total omentectomy+peritonectomy+lnd	300	9	Blood transfusion,hypoxia	50 mg/m2 cisplatin, 120 min
13	64	96	Interval	tah+bso+total omentectomy+peritonectomy	225	7	Blood transfusion,electrolyte disturbance	50 mg/m2 cisplatin, 42oC, 90 min
14	67	25	Recurrent	tah+bso+total omentectomy+periton ectomy+lnd+splenectomy	180	9	Blood transfusion,electrolyte disturbance	50 mg/m2 cisplatin, 42oC, 90 min
15	65	6	Interval	tah+bso+low anterior rezection+end-to-end anastomosis+total omentec tomy+peritonectomy+apendectom y+lnd	300	32	Electrolyte disturbance,h ypoxia,atelectesia, wound infection,dehiscence	50 mg/m2 cisplatin, 120 min
16	52	66	Interval	tah+bso+total omentectomy+periton ectomy+lnd+splenectomy+cholecyste ctomy+total colectomy+end ostomy	495	9	Blood transfusion,electrolyte disturbance,ileus,wound hematoma	50 mg/m2 cisplatin, 41oC, 90 min
17	39	35	Recurrent	peritonectomy+residual omentec-tomy	225	5	Blood transfusion,electrolyte disturbance	50 mg/m2 cisplatin, 41oC, 90 min
18	38	34	Interval	tah+bso+total omentectomy+peritonectomy+lnd	265	6	Blood transfusion,electrolyte disturbance	50 mg/m2 cisplatin, 41oC, 90 min

tah+bso: Total abdominal hysterectomy and bilateral salpingo-oophorectomy
lnd: Lymph node dissection

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