Gynecologic Oncology 140 (2016) 36–41

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

A comparison of the toxicity and tolerability of two intraperitoneal chemotherapy regimens for advanced-stage epithelial ovarian cancer

Geneviève Bouchard-Fortier [a], Barry Rosen [a,b], Iryna Vyarvelska [b], Mark Pasetka [c], Allan Covens [a,d], Lilian T. Gien [a,d], Rachel Kupets [a,d], Katherine Pulman [a], Sarah E. Ferguson [a,b], Danielle Vicus [a,d,*]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Toronto, Toronto, ON, Canada
[b] Division of Gynecologic Oncology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada
[c] Department of Pharmacy, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada
[d] Division of Gynecologic Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

HIGHLIGHTS

- Randomized controlled trials have demonstrated significant survival benefits with intraperitoneal cisplatin.
- Intraperitoneal carboplatin has less gastroinstinal, neurologic and hematologic toxicities than intraperitoneal cisplatin
- High quality studies are evaluating the role of intraperitoneal carboplatin in optimally cytoreduced advanced ovarian cancer.

ARTICLE INFO

Article history:
Received 28 July 2015
Received in revised form 21 October 2015
Accepted 3 November 2015
Available online 4 November 2015

Keywords:
Ovarian cancer
Intraperitoneal chemotherapy
Carboplatin
Cisplatin
Primary cytoreductive surgery
Toxicity

ABSTRACT

Objectives. Randomized controlled trials (RCTs) in optimally cytoreduced epithelial ovarian cancer (EOC) patients have demonstrated an impressive survival benefit of intraperitoneal (IP) platinum over intravenous (IV), but its use has been limited by significant toxicity from cisplatin. The aim of this study was to compare the toxicity and tolerability of IP cisplatin to IP carboplatin in women with optimally cytoreduced EOC.

Methods. Retrospective analysis of 141 women with EOC who underwent optimal surgical cytoreduction followed by IV paclitaxel and IP cisplatin or IP carboplatin was performed. Toxicities of the two treatment regimens were compared. As a secondary outcome, overall survival (OS) and progression-free survival (PFS) probabilities were obtained using the Kaplan–Meier estimate; the log-rank test was used to compare survival curves.

Results. Of the 141 patients, 77 (54.6%) received IP cisplatin and 64 (45.4%) received IP carboplatin. Eighty-six percent received at least 4 cycles of IP chemotherapy. IP cisplatin was associated with significantly more grade 3 nausea and vomiting (10.4% vs 1.6%, $p = 0.033$), grade 3 neuropathy (7.8% vs 0%, $p = 0.013$) and grade 2–3 neutropenia (22.1% vs 9.4%, $p = 0.042$). No difference in PFS ($p = 0.602$) or OS ($p = 0.107$) was found between the groups.

Conclusion. IP chemotherapy had a high completion rate in both groups of patients. IP carboplatin required a less resource intense protocol and was tolerated better than IP cisplatin with less gastrointestinal, neurologic and hematologic toxicities.

1. Introduction

Epithelial ovarian cancer (EOC) is the leading cause of gynecologic cancer related-death in developed countries [1]. The 5-year overall survival (OS) is poor ranging from 30 to 40% as patients often present at an advanced-stage of the disease [2]. The standard treatment for advanced-stage EOC is a combination of cytoreductive surgery followed by platinum- and taxane-based chemotherapy; however the optimal route of administration remains controversial. Multiple randomized controlled trials have demonstrated an impressive survival benefit with intraperitoneal (IP) cisplatin in comparison to intravenous (IV) administration of platinum based regimens in optimally cytoreduced (<1 cm residual disease) advanced-stage ovarian cancer patients [3,4,5]. The instillation of IP cisplatin directly into the peritoneal cavity can enhance its effect by exposing the malignant cells to a high concentration of drug for an extended period of time therefore achieving a "local AUC" (area under the curve) that is greater than can be tolerated when the drug is administered systemically [5,6]. Grade 3 and 4 hematologic and nonhematologic toxicities including myelosuppression, nausea and vomiting, neuropathy, and abdominal pain are more

* Corresponding author at: Odette Cancer Centre, 2075 Bayview Ave. T2018, Toronto, ON M4N 3M5, Canada.
E-mail address: danielle.vicus@sunnybrook.ca (D. Vicus).

http://dx.doi.org/10.1016/j.ygyno.2015.11.005
0090-8258/

common when cisplatin is infused regionally. Cisplatin-associated toxicities, catheter-related failures and the complexity of administering IP chemotherapy have resulted in earlier discontinuation of treatment and limited its use as first-line treatment for advanced-stage EOC [3].

Studies have demonstrated that IV carboplatin has fewer chemotherapy-related toxicities than IV cisplatin with equivalent efficacy [7]. Hence, the combination of IV carboplatin and paclitaxel has become the first-line regimen in advanced stage EOC. Unfortunately, this data was unavailable when the IP chemotherapy trials were designed and initial studies demonstrated conflicting findings in regard to the potential efficacy of carboplatin when instilled regionally [8,9]. Subsequently, the majority of experience published to date involves IP cisplatin and there is a paucity of data on the efficacy of IP carboplatin. High quality studies are currently underway comparing IP cisplatin and IP carboplatin and will hopefully provide a definitive answer [10].

The National Comprehensive Cancer network issued a statement in 2008 recommending the use of IP chemotherapy in optimally cytoreduced advanced-stage EOC (regimen: paclitaxel 135 mg/m^2 IV infusion over 24 h on day 1, cisplatin 75–100 mg/m^2 IP infusion on day 2 and paclitaxel 60 mg/m^2 IP on day 8, based on the results of GOG 172) [11]. Despite strong evidence supporting the benefits of IP chemotherapy, its widespread use has been limited by the complexity of administering the intraperitoneal regimen and the toxicity concerns of IP cisplatin. Small retrospective studies have suggested that IP carboplatin has less toxicity than IP cisplatin while achieving similar oncologic outcomes [12]. The aim of this study was to compare the toxicity and tolerability of IP cisplatin to IP carboplatin in women with optimally cytoreduced advanced EOC.

2. Methods

In this retrospective cohort study, we identified all patients treated at two tertiary-care academic centers in Toronto, Canada with advanced EOC who received at least one cycle of IP chemotherapy after optimal surgical cytoreduction (defined as residual disease ≤ 1 cm) between 2005 and 2014. Each center used a different platinum-based IP chemotherapy regimen in a similar patient population allowing a comparison of these regimens. The two IP treatments were: (1) IP cisplatin 75–100 mg/m^2 and IV paclitaxel 175 mg/m^2 (3-hour infusion) on day 1 every 21 days or (2) IP carboplatin AUC 6 and IV paclitaxel 135 mg/m^2 (3-hour infusion) on day 1 every 21 days. Both centers used standard pre-chemotherapy medication to prevent nausea, vomiting and hypersensitivity reaction to paclitaxel (Table 1). All patients in the IP cisplatin regimen arm also received home hydration (1000 mL normal saline) for 3 days post-chemotherapy in addition to ondansetron, dexamethasone and aprepitant to prevent severe nausea and vomiting often associated with IP cisplatin (Table 1). At both centers, IV carboplatin was used as a substitute for IP cisplatin or IP carboplatin when patients discontinued IP chemotherapy due to toxicity or catheter-related complications. The treating gynecologic oncologist decided when the IP catheter (Bard 9.6) was to be inserted i.e. either at the time of primary cytoreductive surgery or after the first post-operative clinic visit by interventional radiology.

Table 1
Pre- and post-chemotherapy supportive medications.

	IP carboplatin regimen	IP cisplatin regimen
Pre-chemotherapy	Ondansetron 8 mg PO Dexamethasone 20 mg IV Diphenhydramine 50 mg IV Ranitidine 50 mg IV	Ondansetron 16 mg PO Dexamethasone 10 mg IV Aprepitant 125 mg PO Diphenhydramine 50 mg IV Famotidine 20 mg IV
Post-chemotherapy	Ondansetron 8 mg PO BID for 2 days Prochlorperazine 10 mg PO q4 h PRN	Ondansetron 16 mg PO OD for 2 days Prochlorperazine 10 mg PO q6 h PRN Dexamethasone 4 mg PO BID for 2 days Aprepitant 80 mg PO for 2 days Home hydration 1 L normal saline for 3 days

All patients with a histologically confirmed diagnosis of high-grade EOC (serous, endometrioid, clear cell, mucinous, and mixed histologies) or carcinosarcoma who had undergone primary cytoreductive surgery with less than 1 cm of visible residual disease followed by at least one cycle of IP chemotherapy were included. Patients with stage II, III or IV (malignant pleural effusion only) were eligible. We excluded patients with early-stage EOC (stage 1), low-grade and borderline histologies, patients who received neoadjuvant chemotherapy, or patients who were suboptimally cytoreduced with residual disease more than 1 cm and patients for whom no follow-up data was available. We also excluded patients who received IP paclitaxel on day 8. Nine patients in the IP cisplatin group received IP paclitaxel on day 8 during the study period, because funding for IP paclitaxel became available only in 2014; therefore we excluded those patients from the study.

Medical records were thoroughly reviewed including outpatient clinic notes, pharmacy notes, operative and pathology reports, imaging reports, and admission notes. Reasons for dose changes or delays of IP chemotherapy were documented. The following baseline and treatment characteristics were abstracted from the charts: age, FIGO stage, histology, amount of residual disease (≤1 cm or no macroscopic disease), time to initiation of IP chemotherapy from surgery, and number of cycles of IP chemotherapy and/or IV chemotherapy completed. Patients were seen prior to each chemotherapy cycle (every 21 days) in the outpatient clinic to evaluate the toxicity and tolerability of the assigned treatment. Routine blood work including a complete blood count, electrolytes and creatinine was done prior to every cycle of chemotherapy. Data on recurrence, site of recurrence and death were collected.

The primary objective of this study was to compare the toxicity of the two IP chemotherapy regimens. The secondary objectives were to compare the tolerability and outcomes of patients with advanced-stage EOC treated with two different chemotherapy regimens with regard to the number of IP chemotherapy cycles completed, overall survival (OS), progression-free survival (PSF), and rate of recurrence. Common Terminology Criteria for Adverse Events (version 4.0) was used to grade treatment toxicity as mild (grade 1), moderate (grade 2), severe (grade 3) and life-threatening (grade 4). Treatment toxicity was graded by the same investigator at both centers (GBF), using a combination of outpatient clinic notes and pharmacy notes. Categories of treatment-related toxicities included: nausea/vomiting, neuropathy, neutropenia, thrombocytopenia, abdominal pain, intraperitoneal catheter issues (occlusion or infection) or tinnitus. Overall survival (OS) was defined as the interval from the date of diagnosis (histologic confirmation of malignancy) until the date of death or date of last follow-up. Progression-free survival (PFS) was defined as the interval from date of diagnosis until date of recurrence or date of last follow-up.

Statistical analysis was done using Stata™ version 11.2 (StataCorp, College Station, Texas). Descriptive statistics were performed for baseline characteristics. The chi-square test and the Mann–Whitney test were used, where appropriate, to compare baseline and treatment characteristics between patients who received the IP cisplatin regimen to those who received the IP carboplatin regimen; p-value < 0.05 was considered statistically significant. OS and PFS probabilities were obtained using the Kaplan–Meier estimate and the log-rank test was used to compare survival curves. Power analysis for comparing OS and PFS was performed using Power Analysis and Sample Size (PASSv2005) software and applying a two-sided log-rank test with type I error of 0.05. Univariate and multivariable analyses were performed using the Cox proportional hazards regression model. Factors such as age at diagnosis, stage, histologic type, time to initiation of IP chemotherapy and number of IP cycles completed were evaluated on univariate analysis. On multivariate analysis, the backward stepwise selection procedure