Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Does adjuvant chemotherapy dose modification have an impact on the outcome of patients diagnosed with advanced stage ovarian cancer? An NRG Oncology/Gynecologic Oncology Group study☆

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HIGHLIGHTS

- Chemotherapy dose modification is common in ovarian cancer treatment.
- Patients requiring dose modification are more likely to require growth factor.
- Dose modified patients are at a higher risk of worse treatment outcome.

ARTICLE INFO

Article history:
Received 20 April 2018
Received in revised form 24 July 2018
Accepted 29 July 2018
Available online xxxx

ABSTRACT

Purpose. To determine the relationship between chemotherapy dose modification (dose adjustment or treatment delay), overall survival (OS) and progression-free survival (PFS) for women with advanced-stage epithelial ovarian carcinoma (EOC) and primary peritoneal carcinoma (PPC) who receive carboplatin and paclitaxel.

Methods. Women with stages III and IV EOC and PPC treated on the Gynecologic Oncology Group phase III trial, protocol 182, who completed eight cycles of carboplatin with paclitaxel were evaluated in this study. The

☆ This study was supported by National Cancer Institute grants to the Gynecologic Oncology Group (GOG) Administrative Office (CA 27469), the Gynecologic Oncology Group Statistical Office (CA 37517), NRG Oncology SDMC (1U10 CA180822) and NRG Operations (U10CA180868). The following Gynecologic Oncology Group member institutions participated in the primary treatment studies: University of Alabama at Birmingham, Oregon Health Sciences University, Duke University Medical Center, Abington Memorial Hospital, University of Rochester Medical Center, Walter Reed Army Medical Center, Wayne State University, University of Minnesota Medical School, University of Southern California at Los Angeles, University of Mississippi Medical Center, Colorado Gynecologic Oncology Group P.C., University of California at Los Angeles, University of Washington, University of Pennsylvania Cancer Center, University of Miami School of Medicine, Milton S. Hershey Medical Center, Georgetown University Hospital, University of Cincinnati, University of North Carolina School of Medicine, University of Iowa Hospitals and Clinics, University of Texas Southwestern Medical Center at Dallas, Indiana University School of Medicine, Wake Forest University School of Medicine, Albany Medical College, University of California Medical Center at Irvine, Tufts-New England Medical Center, Rush-Presbyterian-St. Luke's Medical Center, University of Kentucky, Eastern Virginia Medical School, The Cleveland Clinic Foundation, Johns Hopkins Oncology Center, State University of New York at Stony Brook, Eastern Pennsylvania GYN/ONC Center, P.C., Southwestern Oncology Group, Washington University School of Medicine, Memorial Sloan-Kettering Cancer Center, Columbus Cancer Council, University of Massachusetts Medical School, Fox Chase Cancer Center, Medical University of South Carolina, Women's Cancer Center, University of Oklahoma, University of Virginia Health Sciences Center, University of Chicago, University of Arizona Health Science Center, Tacoma General Hospital, Eastern Collaborative Oncology Group, Thomas Jefferson University Hospital, Case Western Reserve University, and Tampa Bay Cancer Consortium.

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https://doi.org/10.1016/j.ygyno.2018.07.021
0090-8258/

Please cite this article as: A.B. Olawaiye, et al., Does adjuvant chemotherapy dose modification have an impact on the outcome of patients diagnosed with advanced stage ovarian cance..., Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.07.021

Keywords:
Ovarian cancer
Chemotherapy
Dose reduction
Dose modification
Progression
G-CSF

patients were grouped per dose modification and use of granulocyte colony stimulating factor (G-CSF). The primary end point was OS; Hazard ratios (HR) for PFS and OS were calculated for patients who completed eight cycles of chemotherapy. Patients without dose modification were the referent group. All statistical analyses were performed using the R programming language and environment.

Results. A total of 738 patients were included in this study; 229 (31%) required dose modification, 509 did not. The two groups were well-balanced for demographic and prognostic factors. The adjusted hazard ratios (HR) for disease progression and death among dose-modified patients were: 1.43 (95% CI, 1.19–1.72, $P < 0.001$) and 1.26 (95% CI, 1.04–1.54, $P = 0.021$), respectively. Use of G-CSF was more frequent in dose-modified patients with an odds ratio (OR) of 3.63 (95% CI: 2.51–5.26, $P < 0.001$) compared to dose-unmodified patients.

Conclusion. Dose-modified patients were at a higher risk of disease progression and death. The need for chemotherapy dose modification may identify patients at greater risk for adverse outcomes in advanced stage EOC and PPC.

1. Introduction

Worldwide, 205,000 new ovarian cancer cases are diagnosed leading to 125,000 deaths annually making it the most lethal gynecologic malignancy [1]. In the United States there were 22,280 new cases and 14,240 deaths in 2016 [2]. The standard approach utilized in treating patients with advanced stage epithelial ovarian carcinoma (EOC) is primary cytoreductive surgery followed by adjuvant chemotherapy, or neoadjuvant chemotherapy with interval cytoreductive surgery [3]. Chemotherapy with carboplatin and paclitaxel remains the standard of care for patients with a new diagnosis of advanced stage EOC, in spite of extensive investigation of alternative treatment approaches and combinations.

Despite the excellent response rates and major advances made in the treatment of EOC and primary peritoneal carcinoma (PPC), the five-year overall survival (OS) is a modest 46% [4]. The reasons for this poor outcome is due to patients presenting with advanced stage disease and the fact that the majority of patients with advanced stage EOC and PPC will experience disease relapse after achieving an initial remission. Also, following recurrence, the vast majority of patients eventually develop chemoresistance. An adjustment of chemotherapy dose and schedule has been investigated in previous clinical trials. Increasing the number of cycles or the dose of chemotherapy per cycle has not resulted in any significant therapeutic advantage in terms of progression-free survival (PFS) or OS [5]. It has been previously shown that similar outcomes were seen in patients treated with 5 versus 12 cycles of chemotherapy [6–9]. Nonetheless, there are reasons to believe that completing the number of prescribed chemotherapy cycles on schedule without dose reduction may be associated with improved clinical outcomes. It is believed that only a proportion of malignant cells in a tumor are dividing and therefore vulnerable to chemotherapy at any given time. If these cells are not treated on schedule or are treated with a lower dose of chemotherapy, only sub-lethal damages are inflicted on the cancer cells. Theoretically, further chemotherapy dose delay and/or reduction allow such sub-lethal damages to be repaired. This concept has been evaluated in patients with breast cancer and studies have shown that completion of chemotherapy on schedule and above relative dose intensity thresholds improve patients' outcomes [10–12]. Also, Rabbie Hanna et al. in a multicenter retrospective study investigated the impact of relative dose intensity in ovarian cancer patients, the commonest regimen in their study was carboplatin and paclitaxel, despite adjustments for established prognostic factors, reduced relative dose intensity was associated with reduced overall survival [13].

During the period of this analysis, the most common chemotherapy regimen used for advanced stage EOC and PPC was intravenous carboplatin, typically at an area under the curve (AUC) of 6, and paclitaxel at 175 mg/m^2 body surface area. This combination therapy was administered every three weeks for a total of six to eight cycles. The primary objective of this study was to evaluate the impact, if any, of dose modification on the outcome of ovarian cancer treatment in terms of PFS and OS. Patients treated on the control arm of the GOG-182 served as the subjects of this study [14]. Dose modification in this study is described as chemotherapy dose reduction (≥15% of cycle 1 dose) or cycle delay (≥3 weeks) or both. We also compared PFS and OS in patients who required granulocyte colony stimulating factor (G-CSF) with those of patients who did not.

2. Patients and methods

2.1. Patient selection

Eligible patients for this study were women diagnosed with International Federation of Gynecologists and Obstetricians (FIGO) stages III and IV EOC or PPC who enrolled into GOG-182, a randomized controlled phase III trial. These women underwent optimal or sub-optimal cytoreductive surgery and were subsequently randomized to one of five treatment arms of intravenous platinum doublet or triplet chemotherapy regimens [14]. We embarked on this study following approval of the GOG Ancillary Data Committee.

The reference arm for GOG-182 was carboplatin (AUC of 6) and paclitaxel (175 mg/m^2). The intended number of cycles in all arms was eight. Patients who experienced significant toxicity were to be initially managed with chemotherapy dose modification (DM) consisting of dose reduction and/or cycle delay. Growth factors (mainly G-CSF) were utilized if toxicity persisted despite dose modification (DM). Some patients received G-CSF prophylactically and therefore a subgroup of patients who had no DM were treated with G-CSF.

The subjects of this study were patients who completed eight cycles of chemotherapy with or without DM. This group was chosen to allow for statistically valid comparison of treatment outcome in patients who required DM versus those who did not. For the purposes of this study, dose reduction was defined as a change of dose to 0.85 or less of that given in the first cycle whereas chemotherapy dose delay was defined as a protraction of the eight cycles of chemotherapy beyond 24 weeks; the expected duration of eight chemotherapy cycles without delay was 21 weeks. Chemotherapy DM is defined as dose reduction or cycle delay or a combination of both.

The selected study population was then divided into two main groups; group 1(dose-unmodified) consisted of patients who completed all the assigned eight cycles of chemotherapy with full dose administered on-schedule, and group 2 (dose-modified) consisted of patients who completed all eight cycles but required DM. Further subgrouping was done to evaluate the potential impact of G-CSF as follows; group 3 had no DM and no G-CSF, group 4 had no DM but received G-CSF, Group 5 had DM but no G-CSF and group 6 had both DM and G-CSF.

Regarding platelets nadir and absolute neutrophil count nadir, we have only limited and noisy data, these limited data doesn't integrate well into the time-varying survival models we created.

Statistical Design.

Categorical variables were compared between groups by the Pearson chi-square test, and continuous variables by the Wilcoxon–Mann–

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