Examining the Selection Criteria of Neoadjuvant Chemotherapy Patients

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Abstract

Objectives: To identify predictors of neoadjuvant chemotherapy (NAC) and to examine toxicities, dose reduction, interruptions, and second-line chemotherapy

Materials and Methods: A retrospective chart review of 391 patients with late-stage ovarian cancer diagnosed between January 1, 2004 and December 31, 2010 was conducted. Logistic regression was used to predict chemotherapy type. Cumulative incidence of toxicities, dose reduction, and treatment interruption were calculated using the Kaplan-Meier method. Overall survival was analyzed using time-varying Cox regression models. A competing risk model was used to predict second-line chemotherapy with death as a competing risk.

Results: Older patients were less likely to receive primary debulking (OR 0.710; 95% CI 0.55–0.92, $P = 0.0108$), as were patients with longer diagnostic intervals. Clear-cell, endometrioid, and mucinous carcinoma were more likely to receive adjuvant treatment than unclassified epithelial (OR 6.964; 95% CI 2.02–24.03, $P = 0.0021$). Adjuvant patients experienced higher incidence of chemotherapy toxicities ($P < 0.0001$) and treatment interruption ($P = 0.016$) at 3 months. There was no statistically significant difference in the incidence of chemotherapy dose reduction of >20% in the NAC and adjuvant populations ($P = 0.142$). Neoadjuvant patients were more likely to require more than one line of chemotherapy ([Subhazard Ratio] = 4.334; 95% CI 2.51–7.50, $P < 0.0001$).

Conclusion: Our study found that patients with shorter diagnostic intervals, more advanced age, and unclassified epithelial histotype were more likely to receive NAC. NAC patients did not experience a higher incidence of chemotherapy toxicities, treatment interruption, or dose reduction. There is treatment selection bias for sicker patients being treated with NAC.

Key Words: Neoadjuvant chemotherapy, ovarian cancer, chemotherapy toxicity, treatment interruption, dose reduction

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Résumé

Objectif : Identifier les facteurs permettant de prédire le recours à une chimiothérapie néoadjuvante (CNA) et examiner l'incidence de la toxicité, de la réduction de la dose, de l'interruption du traitement et du recours à la chimiothérapie de deuxième intention.

Matériaux et Méthodologie : Nous avons mené une étude rétrospective des dossiers de 391 patientes atteintes d'un cancer de l'ovaire de stade avancé diagnostiqué entre le 1er janvier 2004 et le 31 décembre 2010. Une régression logistique a été utilisée pour prédire le type de chimiothérapie reçue par les patientes. L'incidence cumulative de la toxicité, de la réduction de la dose et de l'interruption du traitement a été calculée à l'aide de la méthode de Kaplan-Meier. Le taux de survie global a été analysé au moyen de modèles de régression de Cox tenant compte des variables dépendantes du temps. Nous nous sommes servis d'un modèle de risques concurrents pour prédire le recours à une chimiothérapie de deuxième intention, et avons considéré le décès comme risque concurrent.

Résultats : Les patientes plus âgées étaient moins susceptibles de subir une réduction tumorale primaire (rapport de cote [RC] : 0,710; IC à 95 % : 0,55–0,92; $P = 0,0108$); il en va de même pour celles ayant connu un long intervalle diagnostique. Les patientes atteintes d'un carcinome à cellules claires, endométrioïde ou mucineux étaient plus susceptibles de recevoir un traitement adjuvant que celles atteintes d'une tumeur épithéliale non catégorisée (RC : 6964; IC à 95 % : 2,02–24,03; $P = 0,0021$). Les patientes recevant un traitement adjuvant présentaient une plus grande incidence de toxicité secondaire à la chimiothérapie ($P < 0,0001$) et d'interruption de traitement ($P = 0,016$) au troisième mois. Aucune différence statistiquement significative n'a été observée en ce qui a trait à l'incidence d'une réduction de plus de 20 % de la dose entre les groupes CNA et chimiothérapie adjuvante ($P = 0,142$). Les patientes du groupe CNA étaient plus susceptibles de nécessiter plus d'un traitement de chimiothérapie (rapport de sous-risque [SHR] = 4334; IC à 95 % : 2,51–7,50, $P < 0,0001$).

Conclusion : Notre étude a montré qu'un court intervalle diagnostique, un âge avancé et une tumeur épithéliale non catégorisée étaient associés à une probabilité accrue de CNA. Les patientes recevant une CNA n'ont pas présenté une incidence plus élevée de toxicité, d'interruption de traitement ou de réduction de la dose que celles recevant un autre traitement. Une préférence a été observée dans le choix du traitement administré aux patientes les plus malades, qui recevaient plus souvent une CNA.

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INTRODUCTION

Over the past 40 years, survival rates for women with epithelial ovarian cancer have not drastically changed despite the introduction of advanced surgical techniques and chemotherapy.[1–3] Ovarian cancers are typically treated by surgical cytoreduction of all disease in combination with chemotherapy.[1] Surgical cytoreduction followed by primary chemotherapy with a carboplatin-paclitaxel regimen is considered the gold standard for the management of ovarian cancer,[4] which is known as adjuvant therapy. By contrast, patients with bulky stage III/IV disease who are poor surgical candidates due to high-risk comorbidity conditions or disease factors should be considered for neoadjuvant chemotherapy (NAC) treatment.[5]

May et al. conducted a large multicentred observational study and found that late-stage ovarian cancer patients receiving NAC had poorer survival than patients receiving adjuvant therapy (under review 2017). This is in agreement with other observational studies[6–9] which showed poorer survival for neoadjuvant patients. However, Vergote et al. demonstrated in a RCT that NAC followed by interval cytoreduction is equivalent to primary cytoreduction followed by chemotherapy for late-stage disease (stages IIIc and IV).[7] Additionally, the CHORUS (Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer) trial demonstrated that in women with stage III or IV ovarian cancer, survival with NAC is not inferior to primary surgery followed by adjuvant chemotherapy.[8] Therefore, while randomized trials indicate the NAC is equivalent to primary debulking with adjuvant chemotherapy, observational studies indicate that survival is worse in NAC patients. These data indicate a possible selection bias in these observational studies. This prompted the members of the Manitoba Ovarian Cancer Outcomes (MOCO) study group to investigate the treatment of ovarian cancer in Manitoba in order to determine what, if anything, was affecting the survival of Manitoba ovarian cancer patients, including the impact of NAC and associated factors. The objectives of this study were: to examine predictors of receiving NAC; to examine the incidence of toxicities, dose reduction, and treatment interruption between NAC and adjuvant chemotherapy patients; and to compare the incidence of second-line chemotherapy between NAC and adjuvant chemotherapy patients to help determine factors that may predispose to bias in observational trials.

MATERIAL AND METHODS

Ethical Approval

Institutional research ethics board approval (HREB H2012:145) was obtained in 2012 prior to data collection.

Data Sources

Invasive ovarian cancer cases diagnosed between January 1, 2004 and December 31, 2010 were identified through the Manitoba Cancer Registry. Data extracted from the Registry included record type, histology codes, grade, age at diagnosis, American Joint Committee on Cancer (AJCC) staging, postal code, treatment, and death date. Postal codes were used to identify residence at diagnosis and were also converted into income quintiles[9] stratified into urban and rural. Data extracted from charts included physician encounters prior to and after diagnosis, diagnostic procedures, chemotherapy drugs administered and dates of administration, chemotherapy dose information, and dates of reported toxicities. Physician notes from encounters included symptom information, which identified the time of first presentation. The type of physician at each encounter was also identified. Type I and II ovarian cancers were determined using grade and histology information.[10] Unclassified histology included: carcinoma NOS, small cell carcinoma NOS, non-small cell carcinoma, adenocarcinoma NOS, neuroendocrine carcinoma NOS, adenocarcinoma with mixed subtypes, papillary adenocarcinoma NOS, and cystadenocarcinoma NOS. "Other" histology included: carcinoma undifferentiated NOS, carcinoma anaplastic NOS, papillary carcinoma NOS, transitional cell carcinoma NOS, mixed cell adenocarcinoma, mixed tumour malignant NOS, Mullerian mixed tumour, mesodermal mixed tumour, carcinoma sarcoma NOS, serous adenocarcinofibroma, neoplasm malignant, tumour cells malignant, malignant tumour spindle cell type, sarcoma NOS, giant cell sarcoma, and leiomyosarcoma NOS.

Administrative data from Manitoba Health (Physician Claims and Hospital abstracts data) were also included. Physician notes from encounters included symptom information, which