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Patterns of chemotherapy treatment for women with invasive epithelial ovarian cancer – A population-based study

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HIGHLIGHTS

- Medical records of all Australian women with ovarian cancer in 2005 were abstracted.
- Older women, those with high-grade/low-stage or mucinous cancers had less chemotherapy.
- Only 32% completed 6 cycles of carboplatin/paclitaxel without dose reduction/delay.

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ABSTRACT

Objective. Ovarian cancer five-year survival is poor at <40%. In the absence of effective screening or new treatments, ensuring all women receive optimal treatment is one avenue to improve survival. There is little population-based information regarding the primary chemotherapy treatment that women with epithelial ovarian cancer receive. This information is essential to identify potential gaps in care.

Methods. Cancer registries identified all women diagnosed with invasive epithelial ovarian cancer in Australia in 2005 (n = 1192). Histopathology, chemotherapy and comorbidity information was abstracted from medical records. Multivariable logistic regression was used to identify factors associated with chemotherapy commencement, regimen, and completion.

Results. Women >70 years ($p<0.0001$), those with high-grade, stage IA/IB cancers (vs. stages IC–IV, $p=0.003$) and those with mucinous cancers ($p=0.0002$) were less likely to start chemotherapy. Most treated women received platinum-based drugs (97%), but only 68% received combination carboplatin–paclitaxel and only half completed six cycles without treatment modification/delay. Approximately 19% received single-agent carboplatin: mostly those aged >70 ($p<0.0001$) and/or with co-morbidities ($p<0.0001$). Age was the strongest predictor of completing six cycles of combination therapy.

Conclusions. For specific patient groups, particularly older women, there is notable variation from standard treatment. Understanding how treatment variations affect survival and determining optimal regimens for these groups are research priorities.

Introduction

Most women with ovarian cancer have stage III or IV disease at diagnosis with five-year survival rates below 30% [1]. Screening strategies have not been shown to improve survival [2] and, whilst newer treatments are being trialled, at present the only avenue to improve

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survival from this disease is to ensure that all women receive optimal available evidence-based treatment.

Randomised controlled trials have shown consistently that platinum-based combination chemotherapy improves the survival of women with epithelial ovarian cancer [3] and recommended first line chemotherapy for advanced cancers (stages IIB–IV) has been carboplatin (at AUC 5–7.5) and paclitaxel (175 mg/m^2) given three-weekly for six cycles [4,5]. Evidence also supports adjuvant chemotherapy for early-stage cancers apart from low-grade, stage IA/IB cancers [6]. Outside the context of clinical trials conducted in highly selected populations, there is little evidence at the population level regarding the frequency with which women with ovarian cancer receive chemotherapy as recommended or the reasons for treatment variations. This information is essential to identify potential gaps in care and, thereby, to help ensure all women diagnosed with ovarian cancer receive optimal treatment.

Obtaining detailed population-based data on treatment practices is logistically challenging. Studies linking Surveillance, Epidemiology, and End Results (SEER) data with Medicare data for women aged 65 and over with advanced ovarian cancer [7–12] have produced useful information on predictors of chemotherapy commencement and completion in this age-group in the US, but data linkage does not allow for collection of detailed information on reasons for variation in commencement or completion of chemotherapy, or on treatment delays and dose reductions. Furthermore, US Medicare data only includes women over the age of 65 years. Few population-based medical record studies have been conducted [13–15] and only one of these [15] has reported detailed information on the ways in which chemotherapy is used and the reasons for treatment variations.

To address this lack of population-based data, we have analysed data from a comprehensive medical record study of all women diagnosed with invasive epithelial ovarian cancer in Australia over a one-year period.

Patients and methods

Australia has eight state-and territory-based Cancer Registries and Australian law requires that all hospitals, pathology laboratories, radiotherapy centres and death registries report all cancer cases and deaths to one of these. Many of these processes are automated and registration is considered to be close to complete. We used these registries to ascertain all women (aged ≥18 years) diagnosed with primary invasive epithelial ovarian cancer (including fallopian tube/primary peritoneal cancers) in Australia during 2005. This year was selected as it was one year after Australian clinical practice guidelines [16] were published and thus allowed us to compare actual treatment with guideline-recommended treatment.

After identifying all eligible women, the cancer registries collated information on women's age and postcode at diagnosis, and the histological subtype and grade of their cancer. They also provided details to study nurses who located women's medical records and abstracted information including histological subtype, grade, stage at diagnosis, surgical procedures and chemotherapy information including treatment dates; drugs and doses given; and reasons for delays, dose reductions or drug cessation. De-identified data were returned to the investigators. The study was approved by the Human Research Ethics Committees at the Queensland Institute of Medical Research and all participating hospitals and cancer registries.

A woman's postcode was used to classify her degree of accessibility to major urban centres (major cities, inner regional, outer regional, remote, very remote) using the Accessibility/Remoteness Index of Australia (ARIA+) classification for 2006 [17] and socioeconomic status (SES) using the Socio-Economic Indexes for Areas (SEIFA) index of advantage and disadvantage [18]. Information on race/ethnicity was not available. Australia has a publically funded universal health care system which means that public hospital treatment is provided free of charge to everyone. However, private health insurance is also available so that insured people can choose to have treatment provided in private facilities by private specialist doctors. We were interested to see if treatment patterns varied according to health insurance status so recorded this information from the clinical notes.

Coding of clinical information

Cancers were classified as serous, mucinous, endometrioid, clear cell (included any with a clear cell component), carcinosarcoma, other subtypes, and unspecified/undifferentiated epithelial cancers. The Australian guidelines recommend chemotherapy for women with stage IC+ cancers and for those with 'high-risk' stage IA/IB cancers (i.e. grade 3/poorly-differentiated or of clear cell histology) [16]. Women were thus classified into four groups for analysis: early-stage/low-risk cancers (stage IA/IB, grades 1–2 [well/moderately-differentiated], non-clear cell histology); early-stage/high-risk cancers; stage IC or above; or unknown stage/grade. As most early-stage cancers are also low-grade, women with stage IA/IB cancers without grade information (n=12) were assumed to have early-stage/low-risk cancers; conversely, most high-grade cancers are stage IC or higher thus women with high-grade cancers without stage information (n=87) were assumed to have at least stage IC disease.

As there is international variation in the recommended carboplatin dose, AUC 5 and 6 were considered standard for these analyses. Furthermore, women for whom dose information was missing were conservatively assumed to have started treatment at the standard dose. Although dose-dense regimens and intraperitoneal chemotherapy are increasingly considered acceptable alternatives, the guidelines current when the women in this study were diagnosed recommended that first line treatment should include a platinum compound and, ideally, should be carboplatin and paclitaxel given three-weekly for six cycles [16]. Women were therefore classified, firstly, according to whether they were treated with a platinum-based drug (carboplatin/cisplatin); secondly, as to whether they started treatment with combination carboplatin–paclitaxel; and, thirdly, whether they completed at least six cycles of combination treatment at approximately three-weekly intervals. Women who completed six cycles of combination treatment were further categorised according to whether administration of any cycle was delayed by over seven days (defined as 'delay') or if the dose of either drug had to be reduced. In order to highlight variations in treatment patterns we chose a strict definition of 'standard treatment' and thus women treated with single-agent carboplatin, other regimens of carboplatin and/or paclitaxel and other drugs were classified as not having 'standard' treatment, although these treatments are appropriate in specific clinical situations (e.g., Australian guidelines suggest single-agent carboplatin for patients unsuitable for combination treatment on the basis of concurrent medical conditions or poor performance status).

Using information from the clinical record, a comorbidity score was derived for each woman based on the Charlson Comorbidity Index [19]. If an index condition was not mentioned in the clinical record we assumed that a woman did not have that condition.

Statistical analysis

Continuous variables were compared across groups using t-tests and non-parametric tests. Categorical variables were compared using chi-squared tests and chi-squared tests for trend, with Fisher's exact test used when any expected cell numbers were less than five. Multivariable unconditional logistic regression was used to identify variables associated with a dichotomous outcome (for example, chemotherapy yes vs. no) after adjusting for potential confounding variables. All statistical tests were two-sided and $p<0.05$ was considered statistically significant.