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Contribution of age to clinical trial enrollment and tolerance with ovarian cancer☆

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HIGHLIGHTS

- Older patients with ovarian cancer are less likely to enroll on clinical trial.
- Women ≥ 70 tolerated chemotherapy on trial as well as their younger counterparts
- Age ≥ 70 is an independent predictor of shorter overall survival in ovarian cancer.

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ABSTRACT

Introduction. Increasing age has been correlated with shorter survival in ovarian cancer patients, a finding attributed to diminished tolerance of standard therapy. Elderly patients, however, are less likely to enroll on clinical trials; thus, limited data exists to evaluate their response to front line treatment. This study describes how elderly patients on trial fared, with respect to toxicity and response, compared to younger women.

Methods. A retrospective cohort study was performed of ovarian cancer patients enrolled in front line chemotherapy trials at our institution between 2000 and 2013. Patients were dichotomized by age: <70 and ≥70 years. Clinical, pathologic, and treatment characteristics were recorded and analyzed using SAS version 9.3.

Results. 336 patients were enrolled. Of these, 79 (23.5%) were ≥70 yrs. Demographics were similar between the two groups. Compared to patients <70, those ≥70 completed a comparable number of chemotherapy cycles ($p = 0.16$) and had similar numbers of dose modifications ($p = 0.40$) and delays ($p = 0.26$). Both hematologic and non-hematologic toxicities occurred at similar rates as well. Age ≥ 70 (HR 1.8, 95% CI 1.27–2.54, $p = 0.0009$), stage III/IV (HR 3.44, 95% CI 1.08–10.95, $p = 0.036$), and residual disease (HR 2.63, 95% CI 1.82–3.78, $p < 0.0001$) were independently predictive of shorter overall survival.

Conclusion. Our data continues to support reports of shorter survival for older women with ovarian cancer. With physician bias removed and similar chemotherapy tolerance noted, our study suggests that inherent tumor biology may be a significant contributor. Further research is needed to identify the mechanisms which contribute to the inequality that age imposes on outcomes.

1. Introduction

In 2016, there are projected to be 22,280 new cases of ovarian cancer and over 14,000 deaths attributed to this disease [1]. Historically, >50% of these cases have been diagnosed in women 65 years old and older [2,3]. Additionally, between 2010 and 2030, the incidence of cancer in patients aged ≥65 years old is expected to increase by 67%, compared with only an 11% increased incidence in patients <65 years old [4]. Further compounding the increasing cancer burden in older women, there is a recognized association between increasing age and poorer outcomes with ovarian cancer. Vercelli et al. demonstrated that, in ovarian cancer, overall survival (OS) at 1 year for women <65 years old was 72%,

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compared to 33% in women 80–84 years old [5]. Gynecologic Oncology Group (GOG) protocol 182 also noted an 8 month shorter overall survival in women ≥70 years old [6]. Several hypotheses attempt to explain the disparity that age imposes. Proposed explanations include 1) older patients harboring an inherently more aggressive or resistant tumor biology; 2) older patients being diagnosed with more advanced stage and higher grade disease; 3) older patients receiving sub-standard surgical and chemotherapeutic interventions due to physician bias; and 4) a belief that older patients have a diminished ability to tolerate standard therapy [7,8].

The relationship between age and cancer related outcomes remains poorly understood as older patients are historically underrepresented in cancer clinical trials, making extrapolation of study findings to older and/or performance challenged individuals difficult. In a review of 59,300 patients enrolled onto 495 clinical trials sponsored by the National Cancer Institute (NCI), the overall proportion of patients aged ≥65 years old was only 32%, whereas this age group comprised 61% of incident cases in the US cancer population [9]. This trend is also noted in ovarian cancer specific research where older women (≥70) represented only 10–23% of all subjects enrolled (GOG 182, GOG218, GOG 158, AGO-OVAR, ICON7) [10–15].

Greenwade et al. looked to address factors that might influence overall clinical trial enrollment. They evaluated enrollment during a timeframe in which any woman, newly diagnosed with ovarian cancer, could be eligible for participation in a clinical trial. Factors considered included age, race, performance status, distance lived from the cancer center, as well as tumor and treatment characteristics. At a site where the NCCN statement that the best way to treat a cancer patient is on clinical trial is paramount, only 65% of eligible patients who presented with a new diagnosis of EOC were enrolled. Of these patients, older age was one of the few factors associated with decreased likelihood of trial enrollment.

As the U.S. population continues to age and cancer burden in this group grows, optimal management of elderly women becomes exceedingly important. At our institution, clinical trials are offered to every eligible patient. We sought to evaluate the reported toxicities, dose modification and treatment termination among older women (defined as ≥70) with ovarian cancer who participated on front-line chemotherapy clinical trials and compare this data to a younger cohort who were also enrolled on clinical trials. Additionally, we aimed to describe factors that influence clinical trial enrollment in the setting of newly diagnosed ovarian cancer.

2. Methods

This is an IRB-approved retrospective chart review of patients who underwent front-line treatment on a clinical trial for ovarian cancer at The University of Oklahoma from 2000 to 2013. Particular focus was paid to the time frame October 2009 to April 2013 as there was a trial available to all primary epithelial ovarian cancer patients, allowing for evaluation of factors contributing to enrollment. A total of eight trials were included between 2000 and 2013, one of which was a phase 2 pharmaceutical study, 3 of which were phase 3 cooperative group studies, and 4 of which were phase IB cooperative group studies. GOG 273 was not included in this analysis however, as we aimed to analyze tolerance to standard of care regimens. Women with stage II–IV, primary epithelial ovarian cancer, receiving either adjuvant or neoadjuvant therapy were considered for this study. Additionally, patients had to have a baseline performance status ≤2. Women with tumors of low malignant potential or non-epithelial tumors were excluded. For each case, demographic and clinical data were collected including age, race, stage, performance status, baseline CA-125, number of cycles completed on trial, number of dose delays, and number of dose modifications. Toxicities were recorded as the highest grade documented throughout the entirety of treatment and were collected for absolute neutrophil count (ANC), thrombocytopenia, anemia, peripheral sensory and motor neuropathy, and other non-hematologic toxicity. Data pertaining to recurrences and disease related status was also collected for survival analysis.

Patients were then dichotomized by age into <70 or ≥70 years old. Mean (SD)/median (range) was used to summarize continuous variables. Count (percentage) was used to summarize categorical data. For comparisons between the 2 age groups, Wilcoxon rank-sum/two-sample *t*-test for continuous variables or Chi-square/Fisher's exact test for categorical variables was used. The association between patient age (≥70 years old vs. <70 years old) and the overall survival was examined using the Kaplan-Meier plot with the log-rank test (unadjusted analysis) and the Cox proportional hazards model, adjusting for potential confounding factors. Two-way interactions involving patient age group were assessed. Statistical significance was defined as a 2-sided *p*-value of <0.05. The SAS software (version 9.3, Cary NC) was used for all analyses.

3. Results

During the study period of 2000–2013, 336 patients were enrolled on clinical trials for primary treatment of ovarian cancer. Of these, 79 (23.5%) were ≥70 yrs. Demographics were similar with respect to ethnicity ($p = 0.57$), stage ($p = 0.057$), and histology ($p = 0.088$). Grade varied between the age groups due to differences in grade 1 and unknown grade ($p = 0.018$), but high grade (grade 2/3) disease was similar between age groups. Additionally, performance status at initial visit was slightly worse for women ≥70, ($p = 0.017$). Baseline laboratory evaluation revealed comparable CA125 (median 240 U/mL vs 348 U/mL, $p = 0.28$), pretreatment white blood cell count (median 8100 cells/μL vs 7950 cells/μL, $p = 0.85$), and pretreatment platelet count (median 355,000 cells/μL vs 390,500 cells/μL, $p = 0.35$) in those ≥70 vs. <70, respectively. (Table 1)

The vast majority of patients in both age groups underwent primary debulking surgery and thereafter received adjuvant platinum-based chemotherapy (92.4% for ≥70 vs 94.2% for <70, $p = 0.71$). Patients ≥ 70 were less frequently enrolled on trials with a maintenance component (27.9% vs 44.4%, $p = 0.009$). Patients ≥ 70 completed a comparable number of cycles during their first-line chemotherapy (mean 5.9 vs 6.2, $p = 0.16$), had similar number of dose modifications (mean 0.7 vs 1.0, $p = 0.40$) and dose delays (mean 1.7 vs 2.1, $p = 0.26$), as compared to patients <70. (Table 2) Hematologic toxicities were not significantly different between ≥70 and <70 with grade 4 ANC in 62.2% vs 54.5% ($p = 0.36$) and grade 4 thrombocytopenia in 24.4% vs 14.3% ($p = 0.11$). Grade 2 or higher neuropathy (22.2% vs 23.8%, $p = 0.82$) and other non-hematologic toxicities (≥grade 3: 42.2% vs 32.7%, $p = 0.24$) were also not statistically different. (Table 3) Despite similar rates of chemotherapy completion and tolerance, older patients had a significantly shorter overall survival (45.3 vs 71.9 months, $p = 0.0013$). (Fig. 1) This correlation remained true when only patients with high grade serious carcinoma (HGSC) pathology were considered (44.4 vs 66.4 months, $p = 0.0009$), however no difference in overall survival was demonstrated between older and younger women with non-HGSC (0.7066). Additionally, use of bevacizumab maintenance therapy did not provide a survival benefit when comparing age groups ($p = 0.204$). However, in those women who did not receive bevacizumab maintenance, older women had a significantly shorter overall survival ($p = 0.0034$). Upon multivariate analysis adjusting for potential confounding factors identified through a series of univariate analyses, age ≥ 70 (HR 1.8, 95% CI 1.27–2.54, $p = 0.0009$), stage III/IV (HR 3.44, 95% CI 1.08–10.95, $p = 0.036$), and residual disease (HR 2.63, 95% CI 1.82–3.78, $p < 0.0001$) were independently predictive of a shorter overall survival. (Table 4)

4. Discussion

Limited trials have been conducted focusing on older women with ovarian cancer. The cooperative group GINECO in France has run the

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