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Publication Date

2023-06-01

DOI

10.1016/j.ygyno.2023.03.018

Peer reviewed

HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2024 June 01.

Published in final edited form as:

Gynecol Oncol. 2023 June ; 173: 130–137. doi:10.1016/j.ygyno.2023.03.018.

The effect of older age on treatment outcomes in women with advanced ovarian cancer receiving chemotherapy: An NRG-Oncology/Gynecologic Oncology Group (GOG-0182-ICON5) ancillary study

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Clintrials.gov: NCT00011986

Declaration of Competing Interest

Each coauthor must complete an icmje form so that this page can be completed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2023.03.018.

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Abstract

Objective.—To assess the effect of age on overall survival (OS) in women with ovarian cancer receiving chemotherapy. Secondary objectives were to describe the effect of age on treatment compliance, toxicities, progression free survival (PFS), time from surgery to chemotherapy, and rates of optimal cytoreduction.

Methods.—Women enrolled in GOG 0182-ICON5 with stage III or IV epithelial ovarian cancer (EOC) who underwent surgery and chemotherapy between 2001 and 2004 were included. Patients were divided into ages <70 and ≥ 70 years. Baseline characteristics, treatment compliance, toxicities, and clinical outcomes were compared.

Results.—We included a total of 3686 patients, with 620 patients (16.8%) ≥ 70 years. OS was 37.2 months in older compared to 45.0 months in younger patients (HR 1.21, 95% CI, 1.09–1.34, $p < 0.001$). Older patients had an increased risk of cancer-specific-death (HR 1.16, 95% CI, 1.04–1.29) as well as non-cancer related deaths (HR 2.78, 95% CI, 2.00–3.87). Median PFS was 15.1 months in older compared to 16.0 months in younger patients (HR 1.10, 95% CI, 1.00–1.20, $p = 0.056$). In the carboplatin/paclitaxel arm, older patients were just as likely to complete therapy and more likely to develop grade ≥ 2 peripheral neuropathy (35.7 vs 19.7%, $p < 0.001$). Risk of other toxicities remained equal between groups.

Conclusions.—In women with advanced EOC receiving chemotherapy, age ≥ 70 was associated with shorter OS and cancer specific survival. Older patients receiving carboplatin and paclitaxel reported higher rates of grade ≥ 2 neuropathy but were not more likely to suffer from other chemotherapy related toxicities.

1. Introduction

Ovarian cancer is one of the deadliest malignancies, ranking fifth in female cancer deaths and first in cancer deaths related to the female reproductive system. It predominantly affects older women, with a median age of diagnosis of 63 years [1]. As the world population ages and life expectancy increases, the number of women diagnosed with ovarian cancer is also expected to increase. Older age is correlated not only with increased rates of frailty and comorbidities, but also is associated with lower rates of enrollment into clinical trials, completion of staging surgery, and receipt of recommended chemotherapy regimens [2–6].

Based on several landmark trials, standard treatment for epithelial ovarian cancer (EOC) includes a combination of cytoreductive surgery and chemotherapy, typically containing a taxane in conjunction with a platinum-based agent [7–9]. Prior studies have shown that

older adults can tolerate chemotherapy at similar dose intensities compared to younger patients [10,11]. In ovarian cancer, older patients are more likely to undergo neoadjuvant chemotherapy and less likely to undergo surgery of any sort [12–14]. Although two recently published studies, GOG 273 and EWOC-1, have investigated the tolerability of various chemotherapy regimens in older patients, this field remains relatively understudied [15,16].

In an effort to improve outcomes in women with advanced ovarian cancer, GOG 0182-ICON5 studied the efficacy of the addition of topotecan, gemcitabine, or liposomal doxorubicin to carboplatin and paclitaxel against eight cycles of just carboplatin (AUC 6) and paclitaxel (175 mg/m^2) every 3 weeks [17]. Each of these agents had previously demonstrated activity against recurrent epithelial ovarian cancer but had not previously been well studied in the primary setting. The study found no statistically significant difference in either progression free survival (PFS) or overall survival (OS) associated with any of the experimental regimens compared to eight cycles of carboplatin and paclitaxel. Though the trial did not change the standard of care for patients with advanced ovarian cancer, it was one of the largest ovarian cancer upfront chemotherapy clinical trials (N = 4312) and provided valuable information about chemotherapy efficacy, tolerability, and toxicities.

We performed a secondary analysis of the Gynecologic Oncology Group 0182-ICON5 Trial to assess the effect of age on baseline characteristics, treatment compliance, toxicities, and clinical outcomes in women with ovarian cancer receiving chemotherapy.

2. Materials and methods

2.1. Objectives

The primary objective was to assess the effect of age on overall survival (OS) in women with ovarian cancer receiving chemotherapy. Secondary objectives included the effect of age on baseline characteristics, treatment compliance, toxicities, PFS, time interval from surgery to initiation of chemotherapy, and rates of optimal cytoreduction. Patients provided written informed consent consistent with federal, state and local requirements and gave authorization permitting the release of personal health information. The protocol was approved by the local institutional review board at each participating institution.

2.2. Study design

Full details of the GOG 0182-ICON5 trial design were previously published [17]. In summary, GOG 0182-ICON5 was a multicenter, international, randomized, phase 3 trial involving patients with International Federation of Gynecology and Obstetrics stage III or IV epithelial ovarian cancer or primary peritoneal carcinoma with either optimal (≤ 1 cm) or suboptimal residual disease. It remains the largest ovarian cancer trial for first line treatment. Patients were required to have an absolute neutrophil count ≥1500/μL, platelets ≥100,000/μL, creatinine ≤1.5× institutional upper limit normal (ULN), bilirubin ≤1.5 x ULN, AST and alkaline phosphatase ≤2.5 x ULN, and baseline sensory or motor neuropathy grade 1 or lower according to National Cancer Institute Common Toxicity Criteria version 2.

Eligible patients were recruited between 2001 and 2004. They were stratified by center, residual tumor, and intent for interval cytoreduction. They were then randomly allocated

to one of five arms that incorporated gemcitabine, liposomal doxorubicin or topotecan compared with a control arm with carboplatin plus paclitaxel (C + P) (Fig. 1). Each arm included eight cycles of triplet or sequential-doublet chemotherapy, which provided a minimum of four cycles that incorporated experimental treatments while maintaining at least four cycles with carboplatin and paclitaxel.

Additional chemotherapy, including maintenance or consolidation, was not permitted until there was evidence of progressive disease. However, Gynecological Cancer Intergroup (GCIG)-based international criteria for determination of progression that used serial measurements of serum CA-125 were permitted, which allowed initiation of secondary therapies before large-volume or symptomatic recurrence [18].

The primary trial objectives were OS and PFS. OS and PFS were assessed from the date of random assignment in all patients based on an intent-to-treat principle, and death due to any cause was considered a failure event. The date of last contact was used to calculate a censored time at risk for patients without documented progression (PFS) or for those who had no reported death (OS). All other patients were followed for 100 months after randomization.

Adverse events considered at least possibly related to treatment were categorized, graded, and reported according to National Cancer Institute Common Toxicity Criteria version 2.0. For the purpose of this report, only patients who received at least some of their assigned treatments are included in the summaries of adverse events.

2.3. Statistical design

The patient cohort was divided into two groups: age < 70 years and age ≥ 70 years based on studies that have suggested increased adverse events and vulnerability during the seventh decade of life [19,20]. Additional subgroup analyses comparing outcomes of patients aged 70–79 and 80–89 were also performed. All analyses were performed on the intent-to-treat (ITT) population. Baseline characteristics, treatment compliance, toxicities, and clinical outcomes were compared using the Pearson’s Chi-Squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Observed chemotherapy toxicity rates were computed by age group and the rates were compared using Pearson’s Chi-Squared test. Unadjusted Kaplan-Meier analyses were performed by age group for overall survival (OS) and progression free survival (PFS). The Cox proportional hazards models were performed by age group and adjusted for histology, performance status, treatment, stage, residual disease and grade. All statistical tests were performed at an alpha level of 0.05. All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

A total of 3686 patients were included in this analysis [17]. The median age was 59 years. Of these, 620 patients (16.8%) were 70 and older, with 549 (89%) patients between the ages of 70–79 and 71 (11%) patients between the ages of 80–89. Most women had a performance status of 0 (47.1%), followed by 1 (43.6%). Only a minority of patients had a performance status of 2 (6.7%) or 3 (0.08%). The proportion of older women was similar between the

control arm and each experimental treatment arm (Table 1). Older patients were more likely to have a GOG performance status of 2–3 (11.9% vs 5.8%), primary peritoneal cancer (21.5% vs. 12.3%), serous histology (85.6% vs. 81.5%), and higher tumor grade compared to younger patients ($p < 0.001$ for all comparisons). Older patients required a median of 29 days from completion of surgery to the start of adjuvant chemotherapy (range 21–37 days) compared to younger patients (median 26 days, range 19–24 days, $p < 0.001$). However, time from surgery to start of chemotherapy did not differ significantly between patients ages 70–79 (median 29.8 days) and patients 80–89 (median 31.1 days) ($p = 0.573$). Age was not associated with FIGO stage, rates of optimal debulking, BMI, or baseline CA-125 (Table 1). Older patients with suboptimal residual disease were less likely to undergo interval cytoreduction between the fourth and fifth cycles of adjuvant chemotherapy (2.4 vs 3.4) but this difference was not statistically significant ($p = 0.20$) [17].

By 100 months, a total of 2878 death events (78.1%) had occurred, with 2361 events (77.2%) occurring in the younger patient cohort and 517 events (83.4%) occurring in patients 70 and older. The estimated median time to progression or death for women with advanced-stage EOC who were receiving carboplatin and paclitaxel was 15 months, and estimated median overall survival was 36 months. For all arms, OS was a median of 37.2 months (95% CI, 33.6–40.3 months) in older patients aged 70 years and up compared to 45.0 months (95% CI, 42.6–46.9 months) in younger patients under the age of 70 (HR 1.21, 95% CI, 1.09–1.34, $p < 0.001$) (Table 2, Fig. 2). Subgroup analyses within the older patient cohort demonstrated increased risk of allcause mortality in patients aged 80–89 with a median OS of 29.2 months compared to 37.9 months in patients aged 70–79 (HR 1.38, 95% CI 1.05–1.83, $p = 0.012$) (Supplementary Fig. 1). Death due to non-cancer causes was more frequent in patients ages 70 and older (13% vs 7%, $p < 0.001$, HR 2.78, 95% CI, 2.00–3.87). Older patients also had an increased risk of cancer-specific death (HR 1.16, 95% CI, 1.04–1.29). An additional analysis was performed to assess survival over 9 more years of follow up (for a total of 17 years of follow up); however, in this period only 60 additional OS events occurred and data were limited due to censoring. As survival outcomes did not differ with the addition of the 9 additional years of follow-up due to a relatively small number of additional events, a more formal analysis was not performed.

PFS was a median of 14.8 months (95% CI, 13.1–17.7 months) in patients 70 and older compared to 16.3 months (95% CI, 15.2–17.5 months) in patients under 70 (HR 1.18, 95% CI, 0.95–1.46) (Table 2, Fig. 3). Subgroup analyses comparing patients between the ages of 80–89 to patients between the ages of 70–79 demonstrates equal PFS between groups (HR 1.10, 95% CI, 0.84–1.43, $p = 0.39$) (Supplementary Fig. 2).

Patients who were 70 and older were less likely to complete 8 cycles of triplet or sequential-doublet chemotherapy compared to patients younger than 70 (71.9% vs. 82.4%, $p < 0.001$). This trend was seen in all arms except for the arm with 8 cycles of carboplatin and paclitaxel, which showed that a roughly equal percentage of patients completed all 8 cycles (Supplemental Table 1). Reasons for treatment discontinuation, designated as disease/death, toxicity, or other, did not differ between the two age groups (Supplementary Table 2). Chemotherapy toxicity data were compiled and collected for all arms and demonstrated higher rates of Grade 3 and 4 leukopenia, thrombocytopenia, neutropenia, and peripheral

neuropathy in older patients, though size of differences between groups were small (Supplemental Table 3). Younger patients reported increased rates of pain and hepatic toxicity, though again, actual percentage differences between groups were small.

As patients who had a performance status of 2 or 3 made up 7% of the cohort, subgroup analyses were performed to assess the effect of performance status alone on outcomes. On univariate analyses, performance status of 2 or 3 was also associated with decreased OS compared to performance status of 0 or 1 (HR 1.39, 95% CI, 1.20–1.61) (Supplementary Fig. 3). On univariate analyses, performance status of 2 or 3 was associated with worsened progression free survival compared to performance status of 0 or 1 (HR 1.29, 95% CI, 1.12–1.48) (Supplementary Fig. 4). When analyzing chemotherapy-related toxicities by performance status, PS 2 or 3 was associated with higher rates of grade 3 or higher thrombocytopenia (41 vs 23%, $p = 0.004$) as well as grade 3 or higher anemia (22 vs. 11%, $p = 0.029$) (Supplemental Table 4). When limiting analyses to patients with a performance status of 0 or 1, age ≥ 70 still had a detrimental effect on all-cause mortality with a HR of 1.27, 95% CI 1.14–1.42.

As carboplatin and paclitaxel remain the standard of care chemotherapy for ovarian cancer, a sensitivity analysis was performed to analyze treatment outcomes just in the control arm (8 cycles of carboplatin with AUC 6 on D1 and Paclitaxel 175 mg/m^2 on D1). This group contained 115 patients aged 70 and older (15.6%) and 623 patients under the age of 70 (84.4%). Age had no effect on median PFS (14.8 vs. 16.3 months, $p = 0.05$) (Table 2). However, older age was associated with decreased overall survival, with a median OS of 36.6 months (95% CI, 31.4–43.4 months) for older patients compared to 45.2 months (95% CI, 40.4–51.7) months for younger patients (HR 1.28, 95% CI, 1.01–1.62, $p = 0.041$) (Table 2). There were no differences in treatment completion or cause for treatment discontinuation when stratified by age (Supplemental Tables 1, 2). In the control arm, older patients were more likely to develop grade 2 or higher peripheral neuropathy (35.7% vs 19.7%, $p < 0.001$), but risk of other toxicities remained equal between groups (Table 3). Rates of chemotherapy-related toxicity did not differ significantly between elderly patients aged 70–79 and 80–89.

4. Discussion

Ovarian cancer is highly chemotherapy sensitive and standard treatment involves a combination of surgery and chemotherapy. There is a lack of data regarding the tolerability and efficacy of various chemotherapy regimens in the primary treatment setting for an older population. GOG 0182-ICON5 remains the largest randomized controlled trial studying first-line chemotherapeutic agents in ovarian cancer patients. This group also included patients with poor performance status and who received standard dose treatment (Carboplatin AUC 6 (d1) + Paclitaxel 175 mg/m^2 (d1)). Though the original study predates more recent advancements in treatment such as the addition of bevacizumab and poly adenosine diphosphate ribose polymerase (PARP) inhibitors which have significantly changed outcomes for patients with advanced EOC, the results of the trial have shown that triplet therapy does not result in improved OS or PFS, and that the control arm utilizing a carboplatin and paclitaxel doublet remains the standard of care treatment for newly diagnosed patients [7–9,17,21–25].

In this secondary analysis of data, including extended follow-up of 100 months from randomization, we found that older women were more likely to have primary peritoneal cancer and higher-grade tumors than younger women. Furthermore, older patients required a longer period and had a larger range of days between surgery and start of postoperative chemotherapy. Age ≥ 70 was associated with shorter OS (37.2 months vs. 45.0 months) as well as increased rates of both non-cancer and cancer-related death. When limiting our analysis to just patients receiving carboplatin and paclitaxel ($N = 738$), we found that advanced age was still associated with decreased OS, with no effect on PFS or rates of treatment completion. Furthermore, older patients reported higher rates of Grade 2 and higher neuropathy but were not more likely to suffer from other chemotherapy related toxicities.

When considering an older patient cohort, measurement of performance status to determine how cancer impacts a patient's daily level of functioning is key. Although age is not necessarily indicative of one's functional status, older age has been correlated with increased vulnerability. In our cohort, age ≥ 70 was associated with worse performance status, with 12% of patients over the age of 70 reporting a GOG PS of 2–3 compared to only 6% of patients under 70. Though it is rare that patients with a PS of 3 are able to participate in clinical trials, their inclusion in this patient cohort provides important information regarding unfit patients. Additional analyses comparing outcomes by PS showed worse survival outcomes with worse PS, as well as higher rates of cytopenias.

Regarding surgical outcomes, older patients had similar optimal debulking rates but had longer post-operative recovery times prior to chemotherapy initiation. This is an important finding because while frailty has been associated with worse perioperative outcomes, such as increased rates of postoperative complications, requirement for ICU level of care, non-home discharge, and readmission which can delay receipt of adjuvant chemotherapy [26–30], age alone does not necessarily portend worse prognosis. As treatment for most epithelial ovarian cancers includes a combination of cytoreductive surgery with adjuvant chemotherapy, completion of the optimal chemotherapy regimen is a key part to prolonging OS. As elderly patients frequently require dose reductions and delays, several methods to improve tolerability of first-line treatment including weekly dosing, dose reductions, and additional supportive measures (IV hydration, granulocyte colony-stimulating factor analogs, thrombopoietin analogs) are undergoing investigation in the older ovarian cancer patient population [4,31]. Since publication of the original trial, neoadjuvant chemotherapy has also become a frequent option for patients with advanced disease who are not ideal candidates for primary cytoreductive surgery. Rates of neoadjuvant chemotherapy have increased yearly in patients with advanced epithelial ovarian cancer, from 17.6% of patients in 2004 to 45.1% of patients in 2016 [32]. However, all patients in this study underwent primary cytoreductive surgery followed by adjuvant therapy, had no difference in residual disease, and only a minimal difference of 3 days between surgery and start of chemotherapy. Our results suggest that age alone should not be used as a deciding factor to determine primary treatment, and that a thorough assessment of the patient's functional status needs to be considered.

Since the publication of GOG 0182-ICON5, several other studies have reported on the effects of various chemotherapy regimens in older patients. GOG 273 was a prospective non-randomized study of the association between pre-chemotherapy instrumental activities of daily living (IADL) and older patients' ability to complete 4 cycles of chemotherapy with a physician's choice of two different regimens: Carboplatin (AUC 5) with Paclitaxel (135 mg/m^2) and Carboplatin (AUC 5) alone, both administered every 3 weeks [15]. The study found that patients' IADL scores were correlated with completion of 4 cycles of chemotherapy regardless of reduction or delay, as well as development of grade 3+ toxicities. Greater independence was also associated with improved OS in patients receiving carboplatin and paclitaxel [15]. Their chemotherapy completion rates ranged from 92% in the carboplatin-paclitaxel group to 75% in the single agent carboplatin group. Comparatively, our data shows that in older patients over the age of 70, carboplatin and paclitaxel is tolerable and has relatively high rates of completion of 8 cycles (81.5% under 70yo completed vs 73.9% over 70yo completed) compared to younger patients.

The Elderly Women with Ovarian Cancer (EWOC-1) Trial compared feasibility, efficacy, and safety outcomes in vulnerable elderly women with advanced stage ovarian cancer randomized to receive either 6 cycles of either carboplatin (AUC 5) with paclitaxel (175 mg/m^2) every 3 weeks (control arm), single agent carboplatin (AUC 5–6) every 3 weeks, or weekly carboplatin (AUC 2) and paclitaxel (60 mg/m^2) [16]. This randomized controlled trial included patients 70 years and older with a Geriatric Vulnerability Score of 3 or greater. Completion rates were 65%, 47%, and 60% for the control arm, single agent carboplatin, and weekly carboplatin and paclitaxel arms, respectively. Fewer patients completed the single agent carboplatin regimen due to disease progression, and 20% of patients were unable to complete treatment with q3 week carboplatin and paclitaxel regimen due to toxicity [16]. As single agent carboplatin was associated with significantly worse PFS and OS, the trial was prematurely closed. Similarly, in our cohort of patients ≥70 years, 10.4% of patients receiving carboplatin and paclitaxel every 3 weeks reported treatment discontinuation due to toxicity, with most patients developing severe neuropathy. This finding is an important consideration as peripheral neuropathy interferes with daily activities and can lead to decreased proprioception, increased risk of falls, and subsequent injury, particularly in the elderly population. Despite peripheral neuropathy being an often a dose-limiting and long-lasting chemotherapy related adverse event, numerous interventions have been trialed without much success at limiting toxicity [33]. Several strategies aimed at prevention have been implemented, such as identification of patients who have medical conditions that may worsen symptoms such as diabetes, hypothyroidism, renal failure, or malnutrition. Icing extremities during infusions has also been beneficial, as has ensuring good nutritional status and avoiding vitamin deficiencies. Numerous neuroprotective therapies have been trialed, including carbamazepine, glutathione, or nimodipine, without any conclusive data supporting their benefit. Thus far duloxetine has been the only drug to demonstrate moderate evidence for the treatment of painful chemotherapy induced peripheral neuropathy. Current management strategies include dose reductions, modification of agent, or discontinuation of taxanes altogether especially in this more vulnerable cohort.

Strengths of our study are that we included data from one of the largest randomized controlled phase III trials in ovarian cancer, providing information on >620 patients over

the age of 70 with advanced ovarian cancer. However, participants in clinical trials are not representative of all cancer patients, thus limiting generalizability and ability to apply findings to a real-world population. Furthermore, given the retrospective nature of this analysis, we are limited by the variables that were collected at the time. For example, although patient age and PS were reported, specific data regarding patient comorbidities, geriatric variables (i.e. frailty score), as well as germline pathogenic variant status are lacking. Additionally, patients underwent 8 total cycles of chemotherapy, which now would be considered nonstandard [34–36]. We argue that toxicity and tolerability outcomes may still be extrapolated to a modern-day cohort receiving a total of 6 cycles. Furthermore, since the publication of GOG 0182-ICON5 in 2009, additional studies have reported improved outcomes with the addition of new systemic therapies such as bevacizumab and PARP inhibitors, which were not studied in the trial. However, these agents are often added in addition to, or as maintenance therapy after, and standard treatment remains carboplatin and paclitaxel in the first-line setting. Therefore, the findings of our study remain impactful.

Our paper reports on outcomes of older patients with advanced stage ovarian cancer receiving chemotherapy. Though older patients demonstrate shorter OS as well as shorter cause specific survival compared to younger patients, carboplatin and paclitaxel are associated with high rates of treatment compliance albeit at the higher risk of at least grade 2 peripheral neuropathy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This study was supported by National Cancer Institute grants to NRG Oncology (1 U10 CA180822), NRG Operations (U10CA180868) as well as NIH/NCI Cancer Center Support Grant P30 CA008748, SWOG (U10CA180888).

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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HIGHLIGHTS

- Age ≥ 70 years was associated with an increased risk of both cancer-related and non-cancer related death.
- Carboplatin and paclitaxel administration is well tolerated regardless of age.
- Older age was associated with higher rates of grade 2 or higher peripheral neuropathy.
- Risks of other chemotherapy related toxicities were equal between older compared to younger patients.

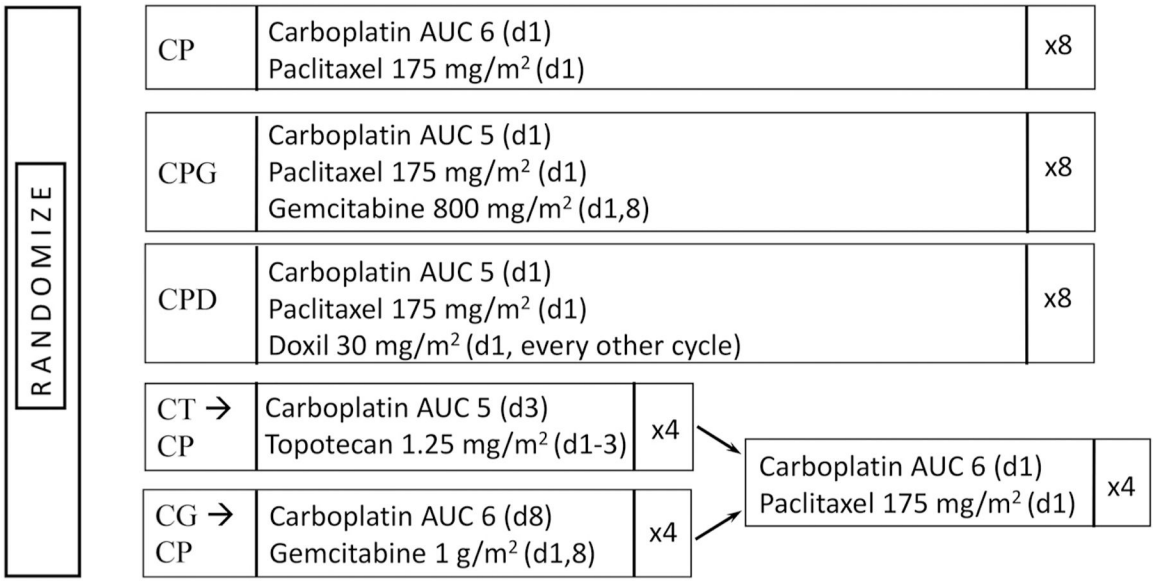

Fig. 1.
Clinical Trial Schematic for GOG 0182-ICON5.

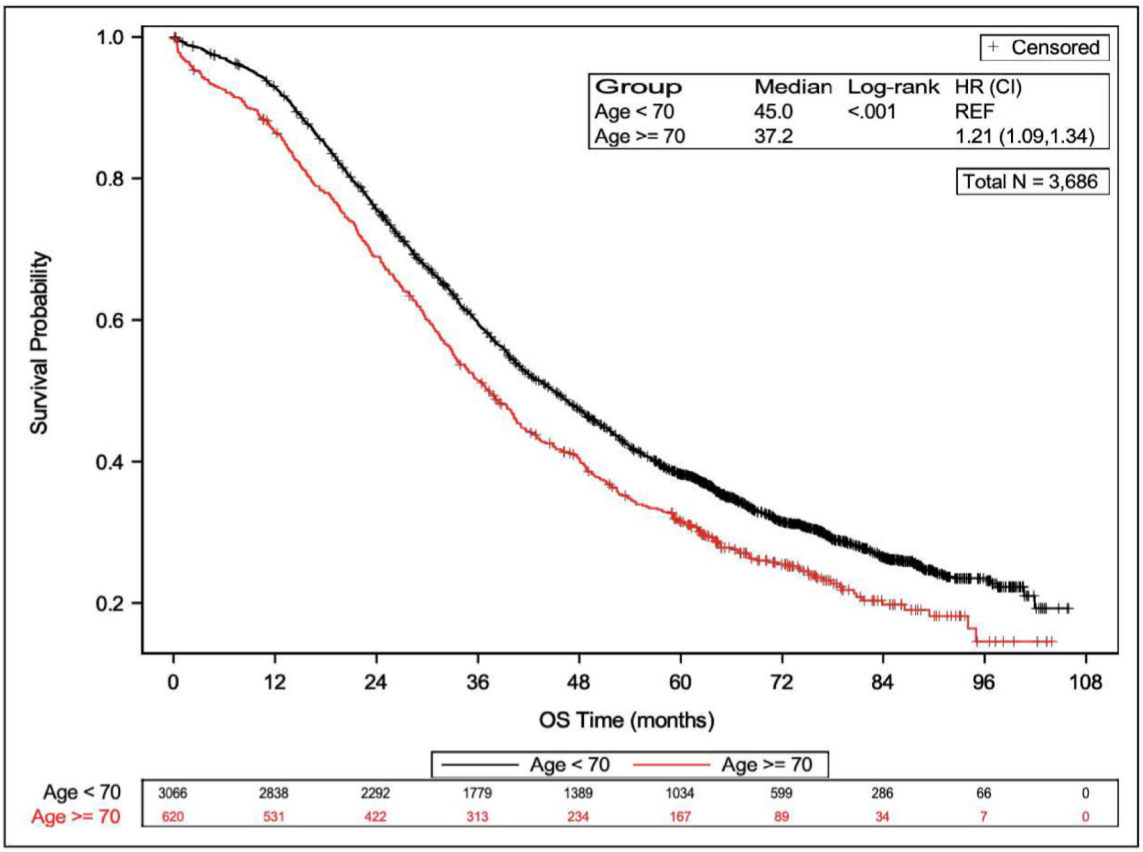

Fig. 2.

For all arms, OS was a median of 37.2 months (95% CI, 33.8–40.5 months) in older patients compared to 45.0 months (95% CI, 42.6–46.9 months) in younger patients. OS: overall survival.

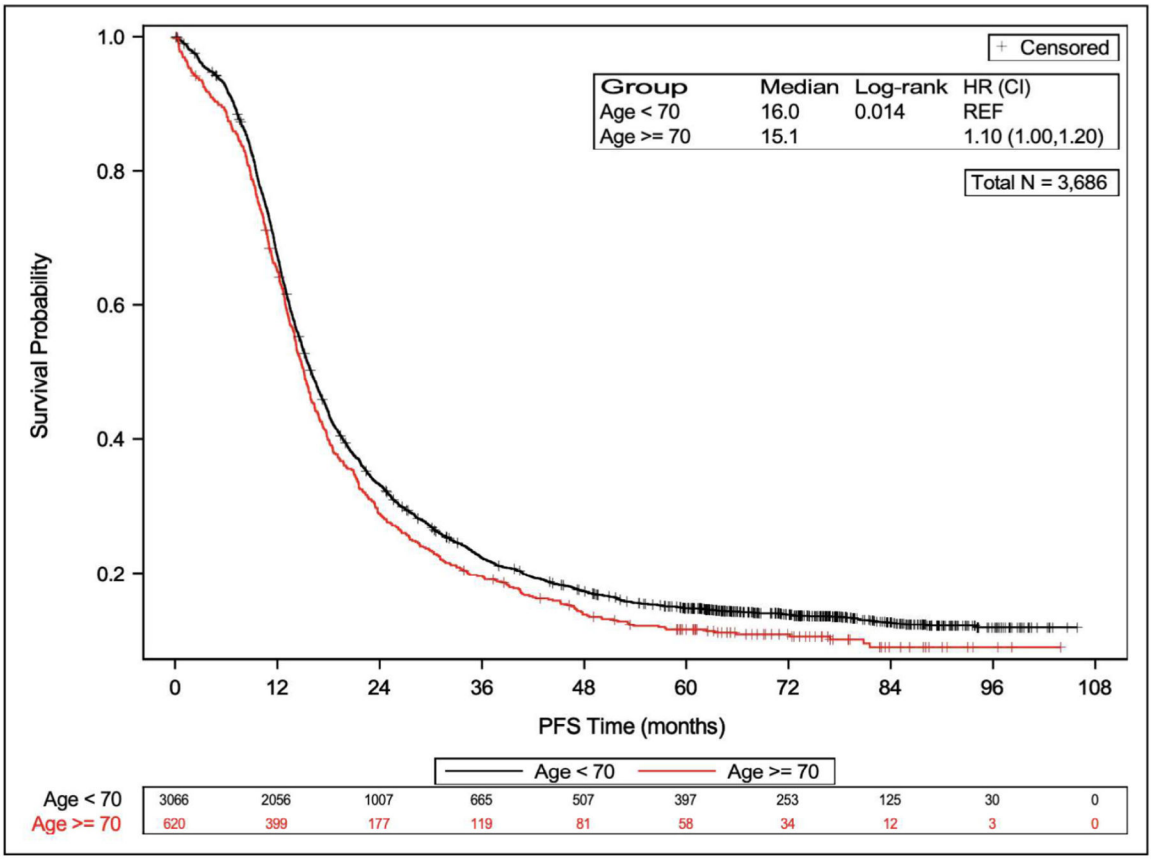

Fig. 3.

For all arms, PFS was a median of 15.1 months (95% CI, 14.2–15.9 months) in patients 70 and older compared to 16.0 months (95% CI, 15.4–16.6 months) in patients under 70. PFS: progression free survival.

Table 1

Baseline characteristics of patient cohort.

	Age < 70 N (col %)	**Age ≥ 70 N (col %)**	***P***
Total Patients	3066	620	
Treatment			0.89
Carboplatin + Paclitaxel x8C	623 (20.3)	115 (18.6)	
Carboplatin + Paclitaxel + Gemcitabine x8C	610 (19.9)	124 (20.3)	
Carboplatin + Paclitaxel + Doxil x8C	613 (20.0)	129 (20.8)	
Carboplatin + Topotecan x4C → Carboplatin + Paclitaxel x4C	612 (20.0)	125 (20.2)	
Carboplatin + Gemcitabine x4C → Carboplatin + Paclitaxel x4C	608 (19.8)	127 (20.5)	
Performance Status			<0.001
0	1513 (49.3)	224 (36.1)	
1	1306 (42.6)	302 (48.7)	
2–3	177 (5.8)	74 (11.9)	
Missing	70 (2.3)	20 (3.2)	
FIGO Stage			0.33
III	2614 (85.3)	538 (86.8)	
IV	452 (14.7)	82 (13.2)	
Tumor Site			<0.001
Primary Ovarian	2689 (87.7)	487 (78.5)	
Peritoneal	377 (12.3)	133 (21.5)	
Histology			p < 0.001
Serous	2499 (81.5)	530 (85.6)	
Endometrioid	161 (5.3)	21 (3.4)	
Clear cell	114 (3.7)	6 (1.0)	
Mucinous	36 (1.2)	3 (0.5)	
Mixed	177 (5.8)	36 (5.6)	
Other	79 (2.6)	24 (3.9)	
Tumor Grade			<0.001
1	199 (6.5)	27 (4.4)	
2	1015 (33.1)	221 (35.6)	

	Age < 70 N (col %)	**Age ≥ 70 N (col %)**	***P***
3	1737 (56.7)	366 (59.0)	
Not graded	115 (3.8)	6 (6.0)	
Tumor Residual			0.06
Microscopic	759 (24.8)	127 (20.5)	
Optimal	1455 (47.5)	303 (48.9)	
Suboptimal	852 (27.8)	190 (30.7)	
	Median (lower, upper quartile)	Median (lower, upper quartile)	
Time Between Surgery and Start of Chemotherapy (days)	26 days (19, 24)	29 days (21, 37)	< 0.001
BMI (kg/m2)	26 (22, 30)	25 (23, 29)	0.56
CA-125 (baseline)	205 (86, 543)	218 (93, 520)	0.41
Interval Cytoreduction	105 (3.4)	15 (2.4)	0.20

FIGO: International Federation of Gynecology and Obstetrics.

BMI: body mass index.

Characteristics were compared using the Pearson's Chi-Squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

Table 2

Disease progression and survival.

Treatment		Age < 70 Median in months (95%CI)	Age ≥ 70 Median in months (95%CI)	P	Adjusted Hazard Ratio (95%CI, P)
Carboplatin + Paclitaxel x8C	PFS	16.3 (15.2, 17.5)	14.8 (13.1, 17.7)	0.052	1.18 (0.95,1.46, 0.13)
	OS	45.2 (40.4, 51.7)	36.6 (31.4, 43.4)	0.014	1.28 (1.01, 1.62, 0.041)
All arms	PFS	16.0 (15.4, 16.6)	15.1 (14.2, 15.9)	0.014	1.10 (1.00, 1.20, 0.056)
	OS	45.0 (42.6, 46.9)	37.2 (33.6, 40.3)	<0.001	1.21 (1.09, 1.34, <0.001)

Cox proportional hazards models were performed by age group and adjusted for histology, performance status, treatment, stage, residual disease and grade.

Table 3

Reported chemotherapy toxicities for Carboplatin + Paclitaxel x8C subgroup, by age.

Toxicity Category	Age < 70 (%)	Age ≥ 70 (%)	*P*
Leukopenia (≥G3)	52.9	53.9	0.84
Thrombocytopenia (≥G3)	24.4	25.2	0.86
Neutropenia (≥G4)	62.2	67.8	0.25
Anemia (≥G3)	12.1	12.2	0.97
GI (≥G3)	9.5	13.9	0.15
GU/renal (≥G2)	5.8	4.3	0.54
Peripheral neuropathy (≥G2)	19.7	35.7	<0.001
Pain (≥G3)	5.5	4.3	0.63
Pulmonary (≥G3)	2.4	2.6	0.90
Hepatic (≥G2)	4.7	4.3	0.89
Infection (≥G3)	8.8	11.3	0.40
Auditory (≥G2)	2.7	3.5	0.66

GI: gastrointestinal.

GU: genitourinary.

Chemotherapy toxicity rates were computed by age group and the rates were compared using Pearson's Chi-squared test.