Published in final edited form as:

Gynecol Oncol. 2017 March ; 144(3): 459–467. doi:10.1016/j.ygyno.2016.11.033.

Chemotherapy Completion in Elderly Women with Ovarian, Primary Peritoneal or Fallopian Tube Cancer – An NRG Oncology/Gynecologic Oncology Group Study

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Presented at Gynecologic Oncology 45th Annual Meeting on Women's Cancer presentation March 22–25, 2014 at the Tampa Convention Center in Tampa, FL.

The following Gynecologic Oncology Group member institutions participated in the primary treatment studies: University of Oklahoma Health Sciences Center; Women and Infants Hospital; Memorial Sloan Kettering Cancer Center; Foretdert and the Medical College of Wisconsin; University of Pittsburgh Cancer Institute (UPCI); Stony Brook University Medical Center; Case Western Reserve University; Cooper Hospital University Medical Center; Women's Cancer Center of Nevada; University of Chicago; Carolinas Medical Center/Levine Cancer Institute; Roswell Park Cancer Institute; Duke University Medical Center; University of Alabama at Birmingham; Ohio State University Comprehensive Cancer Center; University of Wisconsin Hospital and Clinics; University of North Carolina at Chapel Hill; University of Iowa Hospitals and Clinics; Cleveland Clinic Foundation; Fox Chase Cancer Center; Mayo Clinic; Yale University; UCSF-Mount Zion; University of Minnesota Medical Center-Fairview; University of Massachusetts Memorial Health Care; The Hospital of Central Connecticut; Saint Joseph's Hospital and Medical Center; Northwestern University; University of New Mexico; Moffitt Cancer Center and Research Institute; Aurora Women's Pavilion of Aurora West Allis Medical Center; and Kansas City CCOP.

CONFLICTS OF INTEREST

All other co-authors have no conflicts of interest to report.

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Abstract

PURPOSE—A simple measure to predict chemotherapy tolerance in elderly patients would be useful. We prospectively tested the association of baseline Instrumental Activities of Daily Living (IADL) score with ability to complete 4 cycles of first line chemotherapy without dose reductions or more than 7 days delay in elderly ovarian cancer patients.

PATIENTS AND METHODS—Patients age ≥ 70 along with their physicians chose between two regimens: CP (Carboplatin AUC 5, Paclitaxel 135 mg/m²) or C (Carboplatin AUC 5), both given every 3 weeks either after primary surgery or as neoadjuvant chemotherapy (NACT) with IADL and quality of life assessments performed at baseline, pre-cycle 3, and post-cycle 4.

RESULTS—Two-hundred-twelve women were enrolled, 152 selecting CP and 60 selecting C. Those who selected CP had higher baseline IADL scores ($p < 0.001$). After adjusting for age and PS, baseline IADL was independently associated with the choice of regimen ($p = 0.035$). The baseline IADL score was not found to be associated with completion of 4 cycles of chemotherapy without dose reduction or delays ($p = 0.21$), but was associated with completion of 4 cycles of chemotherapy regardless of dose reduction and delay ($p = 0.008$) and toxicity, with the odds ratio (OR) of grade 3+ toxicity decreasing 17% (OR: 0.83; 95%CI: 0.72–0.96; $p = 0.013$) for each additional activity in which the patient was independent. After adjustment for chemotherapy regimen, IADL was also associated with overall survival ($p = 0.019$) for patients receiving CP.

CONCLUSION—Patients with a higher baseline IADL score (more independent) were more likely to complete 4 cycles of chemotherapy and less likely to experience grade 3 or higher toxicity.

Keywords

chemotherapy; elderly women; ovarian cancer

INTRODUCTION

With the aging of a large cohort of baby boomers, it is anticipated that the frequency of age-related cancers such as ovarian cancer will grow, and we will be treating more elderly patients with the disease, including the “oldest of old” [1]. It has been claimed that many elderly women with ovarian cancer are not being provided with “appropriate” care, including standard doses and schedule of chemotherapy, and that this may partially account for their inferior cancer outcomes [2]. However, it is also known that older patients suffer more toxicity from chemotherapy, and that there is great heterogeneity in ability of patients of a given chronological age to tolerate treatment. There would be great value in a simple assessment to help the clinician predict the ability of a patient to tolerate chemotherapy as well as to potentially allow some comparison of functional status among elderly patients treated on clinical trials.

Numerous studies have demonstrated that chronological age does not equal physiological age. A geriatric assessment and patient reported outcomes (PROs) can be utilized to assess for the heterogeneity of functional abilities among older patients with cancer. A geriatric assessment includes an evaluation of functional status, comorbid medical conditions, psychological state, social support, nutritional status, and cognition [3]. An assessment of functional status includes evaluating the patient’s ability to perform Instrumental Activities of Daily Living (IADLs) which are self-care skills that allow independent functioning within the community and Activities of Daily Living (ADLs) which are basic self-care skills such as the ability to bathe and dress. PROs are questionnaires used in a clinical setting or trial where the responses are collected directly from the patient [4]. The most commonly used PRO tools assess symptoms, functional status, and quality of life (QOL).

The primary objective of this study was to explore the association between pre-treatment instrumental activities of daily living (IADL) and the patient’s ability to complete 4 cycles of chemotherapy without dose reduction or more than 7-day treatment delay for patients aged 70 years and older with primary ovarian, peritoneal, or fallopian tube cancer. Four cycles were chosen to allow patients to receive chemotherapy before or after surgery. Secondary objectives included exploring whether age, geriatric measures and patient-related outcomes (PROs) were correlated with toxicity or completion of chemotherapy. Translational research objectives included exploring the relationship between actual and calculated carboplatin AUC and the relationship between pharmacokinetic parameters and toxicity.

METHODS

Patients

Eligible patients were 70 years of age with stage I–IV epithelial cancer of the ovary, peritoneum, or fallopian tube. The cancer diagnosis was to be histologically or cytologically confirmed by surgery, biopsy, fine needle aspiration or paracentesis. A diagnosis of a mucinous cancer could be made by biopsy only. Patients were required to have received no previous treatment for the malignancy, a Gynecologic Oncology Group (GOG) performance status (PS) of 0 to 3, normal blood, renal and hepatic function. All patients gave written

informed consent according to institutional and federal guidelines before enrollment and the institutional review board at each participating site granted approval.

Patients could be registered either before primary chemotherapy or after cytoreduction surgery, prior to adjuvant chemotherapy. At study entry and before each treatment, a physical examination, medical history, and laboratory measurements were recommended. Patient-reported assessments (PROs) and physician assessment of PS were required prior to cycle 1 and 3, then 3–6 weeks after completion of cycle 4.

Treatment Plan

Patients and physicians selected between two chemotherapy options. There was no randomization. CP was carboplatin AUC 5 plus paclitaxel 135mg/m² plus pegfilgrastim or filgrastim (G-CSF) every 3 weeks. The G-CSF was initially required, but was changed to optional in February 2013. C was single agent carboplatin AUC 5 on day 1, every 3 weeks. Patients on either arm for whom the treating physician felt a carboplatin AUC of 5 to be unsafe could be started with a carboplatin AUC of 4. Standard dose modifications and parameters for treatment were suggested, but not required. After 4 cycles of chemotherapy, interval surgical cytoreduction (for patients who did not have prior primary surgery), and/or further chemotherapy were at the discretion of the treating physician.

Quality of Life and Other Assessments

The Functional Assessment of Cancer Therapy — Ovary (FACT-O), is a multi-dimensional PRO used to measure quality of life (QoL) [5]. It is composed of 4 subscales (physical well-being, social well-being, emotional well-being, and functional well-being). A higher score represents better QOL. The FACT/GOG-Ntx-4 subscale was used to assess peripheral neuropathy [6]. The Instrumental Activities of Daily Living (IADL) assessment used is a subscale of the Older American Resources and Services tool (OARS) [7]. This assessment provides a profile of the level of functioning and need for services in community-dwelling older adults. A higher IADL score indicates more independence. Activities of Daily Living (ADL) were measured using a subscale of the Medical Outcomes Study (MOS) Physical Health assessment [8]. Higher scores indicate more independence in ADL. The social activities subscale from the MOS was used in measuring social activity. Higher scores indicate less limitation in social activities. Medical comorbidity was measured with the Charlson Comorbidity Index [9]. The calculation for % unintentional weight loss was calculated = (weight lost in last 6 months/baseline body weight) × 100.

Pharmacokinetic Methods

Blood samples for quantitation of platinum concentrations were obtained at baseline and at 24 hours after carboplatin infusion. Blood samples for quantitation of paclitaxel were obtained at baseline, 1, 6, and 24 hours after infusion. At each time point, 7–10 mL of EDTA anticoagulated blood was drawn, inverted 5–10 times and placed on ice. Blood was then centrifuged at 1000 × g for 10 min at 4°C, and plasma was aliquoted in cryovials and frozen at –70°C or colder. Concentrations of total platinum were quantitated by atomic absorption spectrophotometry [10]. Concentrations of paclitaxel were determined using an established assay [11]. The AUC of ultrafilterable platinum was estimated utilizing the total platinum

concentration at 24 hour [12]. Paclitaxel AUC and time above 0.05 μM were also estimated with a previously published formula [13].

Statistical Analysis

The primary objective of this study was to explore the association between patient-reported IADL at baseline and the ability to complete 4 cycles of chemotherapy without dose reduction or more than 7 days treatment delay (tolerance of chemotherapy). A sample size of 185 patients was planned to provide an 80% statistical power at a 5% significant level to detect a 10% increase in the tolerance when a patient's baseline IADL is one standard deviation higher than the mean score (two-tailed test). It was assumed that approximately 70% would complete 4 cycles of treatment without delay and dose reduction and the r^2 achieved when IADL is regressed on other covariates was no larger than 0.3. The study was initially targeted to elderly patients who were at least 75 years old. Due to concerns about slow accrual, the age criteria for this study were altered from 75 to 70 years in April 2012. To ensure that the study sample was representative of elderly patients in all age groups we limited the patients aged 70–74 to approximately 25% of the total enrolled.

The completion status of 4 cycles was summarized for all eligible patients ($n=207$) who received at least 1 cycle. The analysis of the association between baseline PROs and tolerance was based on patients who completed baseline assessments. The analysis of the PROs over time was based on patients who completed baseline and at least 1 follow up assessment. A logistic regression was used in evaluating the likelihood of completing 4 cycles, the type of chemotherapy, and the development of grade 3+ toxicities.

The baseline IADL score was examined first as a continuous variable for its association with tolerance of chemotherapy. We also explored the IADL based on the number of activities, which was considered supportive to the primary analysis. The number ranged 0–7 with 0=dependent and 7=independent. The association between baseline IADL and overall survival (OS) was explored with Cox proportional hazards model. A linear mixed model was used in exploring the change of PRO and QOL over assessment time. Subgroup analysis based on the chemotherapy regimen chosen was conducted for exploratory purposes.

The primary endpoint of this study was the IADL score as a continuous variable and its association with the completion of 4 cycles of chemotherapy without dose reduction and >7 days delay was tested at a pre-designed significant level of 5%. Other analyses were considered exploratory and were not corrected for multiple testing. The p values for the exploratory analyses were provided to aid interpretation but must be interpreted conservatively. We considered p values of 0.01–0.05 to reflect a modest association and $p < 0.01$ to reflect a significant association.

RESULTS

Patient Population

Between August 15, 2011 and August 12, 2013, a total of 212 patients selected between 2 treatment options and were enrolled on study. Five were excluded from the analysis, due to protocol violation (Appendix Figure A1, online only). The characteristics of the 207

evaluable (CP, n=148; C, n=59) patients are summarized in Table 1. The average age was 77 years (70–89) for regimen CP and 84 (71–98) for regimen C. There were no significant differences in race and stage between the cohorts. Patients selecting CP were younger ($p<0.001$) and had better PS ($p=0.001$); higher IADL ($p<0.001$), ADL ($p<0.001$), QoL ($p=0.04$) and less comorbidity ($p=0.08$). After adjusting for age and PS, baseline IADL score was independently associated with the choice of regimen ($p=0.035$). There were 73 patients in the CP cohort and 35 in C cohort who were treated initially with chemotherapy. Of these 52% in the CP cohort and only 6% in the C cohort had surgery after chemotherapy.

Chemotherapy Completion and Adverse Events

Seventy-four percent of patients completed 4 cycles without dose reduction or more than a 7-day treatment delay and 87% completed 4 cycles of chemotherapy regardless of reduction or delay (Figure 1). Eighty-two percent in CP and 54% in C completed 4 cycles of chemotherapy without either reduction or more than 7-day delay. A total of 92% in the CP arm and 75% in C eventually completed 4 cycles. Choice of CP was significantly correlated ($p<0.001$) with the likelihood of completing 4 cycles of chemotherapy without dose reduction or more than 7-day delay. After adjusting for chemotherapy regimen, age and stage were not found to be associated with likelihood of completing 4 cycles without dose reduction or delay.

The median treatment delay was 7 days with a range of 1–28 days. Paclitaxel hypersensitivity (n=7) was the major reason for dose reduction in CP while hematologic toxicity was the primary reason in regimen C. In CP, 3 discontinued chemotherapy for side effects and 5 for other issues. In the C cohort, 5 discontinued for disease progression, 1 for side effects and 6 for other issues.

Significantly more patients who received CP had adverse events (Appendix Table A1, online only). For CP the most common grade 3 side effect was decreased neutrophil count (13%), followed by anemia, diarrhea, and dehydration. For C, the most common grade 3 side effect was anemia (12%), followed by fatigue and thrombocytopenia. There were 7 deaths on study, 4 on CP and 3 on C. One death on the CP regimen was attributed to treatment, 1 to treatment and disease, 1 to cardiac arrest, and 1 to aspiration. The patient who died due to treatment had extensive disease with questionable progression along with bone marrow and gastrointestinal toxicity and she was not given GCSF. The 3 deaths on regimen C were secondary to disease.

Association between Baseline IADL and Completion of Chemotherapy

There were 205 patients who completed PROs at baseline. The mean baseline IADL score was 12 (SD: 2.6; range: 2–14) for those who completed 4 cycles without dose reduction or more than 7-day delay and 11 (SD: 2.9; range: 3–14) for those who did not, which was not a significant difference ($p=0.208$), (Figure 2). However, patients with a higher IADL ($p=0.008$), ADL ($p=0.002$), social activities score ($p=.001$) and QoL score ($p=.002$), were more likely to complete 4 cycles of therapy regardless of dose reduction and delay (Figure 3). The odds ratio was 1.21 for completion of 4 cycles (95% CI: 1.05–1.4; $p=0.008$) for each

additional activity in which the patient was independent. Subgroup analysis by the chemotherapy cohort showed similar trends in both cohorts.

At baseline, 32% (65/205) of patients (36% in CP and 20% in C) reported being independent in all 7 IADLs. Patients with higher IADL scores were more likely to select or advised by their physician to receive CP than those with more dependency ($p<0.001$). The odds ratio for selection of CP was 1.31 (95% CI: 1.06~1.61; $p=0.011$) for each additional independent instrumental activity.

Association between Baseline IADL and Development of grade 3+ Toxicities

IADL score was found to be associated with development of grade 3+ toxicities during treatment after adjustment for chemotherapy choice. The rate of grade 3+ toxicity decreased 17% (OR: 0.83; 95% CI: 0.72~0.96; $p=0.013$) for each additional activity in which the patient was independent.

Association between other assessments and chemotherapy completion

Baseline scores on other assessments were explored for their association with the tolerance after adjusting for the chemotherapy regimen. The completion of 4 cycles without more than 7-day delay or dose reduction was found to be associated with ADL ($p=0.002$), and social activities ($p=0.019$) in patients on CP (Figure 2). Completion of 4 cycles of therapy regardless of dose reduction and delay was significantly associated with ADL ($p=0.015$) and QoL ($p=.002$) in CP, and with social activities score ($p=.001$) in both cohorts (Figure 3).

Patient-reported outcomes over time

Of the 207 patients, 190 (139 on CP and 51 on C) completed baseline and at least 1 subsequent PRO. After adjusting for age, PS, and treatment choice, ADL ($p=0.02$), social activity ($p=0.04$), and FACT-O ($p<0.001$) improved over time, but the IADL score did not change ($p=0.7$). The changes in IADL, ADL, social activities and FACT-O scores exhibited similar trends in both cohorts (Figure 4). Neurotoxicity worsened significantly for those on CP ($p<0.001$) but not for those on C ($p=0.8$).

Association between baseline IADL and overall survival

After adjustment for chemotherapy, the number of IADLs was associated with OS ($p=0.019$), (Figure 5). Subgroup analysis showed this association was only present among patients who received CP ($p=0.013$). In the CP arm, 45 patients had the ability to independently perform ≤ 4 IADLs while 101 patients had the ability to independently perform ≥ 5 IADLs at baseline. The patients with ≤ 4 independent IADLs were more likely to be non-Hispanic black (20% vs 3%), have worse performance status (as measured with the GOG performance status score) (≥ 2) (29% vs 5%), and have stage IV disease (29% vs 16%) compared to those reporting ≥ 5 independent IADLs.

Pharmacokinetic Analysis

A total of 167 eligible patients (120 in CP and 47 in C) submitted plasma specimens. Specimens from 114 patients on CP were adequate for analysis of paclitaxel and the specimens of 146 patients were adequate for carboplatin levels (Figure A2). The estimated

carboplatin AUC of patients who were intended to receive AUC 5 centered on AUC 5 (mean 5.6), although there was large variability of exposures with a standard deviation of 2.1 (Appendix Table A3, online only). Despite BSA-based dosing of paclitaxel, the observed AUC and clearance covered an almost 10-fold range centered on means of 14.8 (± 4.8) $\mu\text{M}\cdot\text{h}$ and 31.7 (± 10.2) h, respectively. After adjustment for baseline ANC and PLT counts, none of the pharmacokinetic properties of paclitaxel and carboplatin was found to be associated with the declined ANC or PLT post cycle 1 (prior to cycle 2). None of the estimated paclitaxel PK parameters correlated with severity of neurotoxicity (Appendix Table A2, online only).

DISCUSSION

Our trial was negative for the primary hypothesis of an association of a patient's baseline IADL with the ability to complete 4 cycles of chemotherapy without either dose reduction or more than 7 days delay. However, there was a significant correlation between IADL score and completion of chemotherapy regardless of reduction or delay, as well as with development of grade 3 or higher toxicity. In addition, in patients receiving CP, there was an association between IADL and OS. Hence, it may be useful to assess IADLs when prescribing chemotherapy both in clinical practice and in trials. Our findings of significant association of other PROs like social activities and QoL with outcomes is similar to what has been found by other investigators [14,15].

The protocol allowed physician and patient choice of regimen and flexibility of dosing. The majority of the frailer patients eventually completed 4 cycles of chemotherapy, and, importantly, improvement in QoL with chemotherapy was seen in both cohorts, likely reflecting the efficacy of platinum-based therapy in this disease. Prior research has shown that ovarian cancer patients' QoL (encompassing the social domain) is associated with OS [16].

Several studies of older patients with cancer have demonstrated that there is a relationship between results of a geriatric assessment, chemotherapy toxicity, subsequent functional decline, and OS [17–19]. However, only a few of these studies have been performed among patients with ovarian cancer [20]. In a study of carboplatin and cyclophosphamide, the GINECO group found that toxicity was associated with pre-treatment functional status and depression [21]. The GINECO group recently performed a pooled analysis on 3 phase II studies and found a correlation between overall survival and decreased functionality with the IADL tool [22]. In a second report, evaluating 2 sequential trials of carboplatin/cyclophosphamide and carboplatin/paclitaxel, older age, stage IV disease, use of paclitaxel and depression were associated with lower OS [23]. The importance of incorporating geriatric tools in clinical trials has been stressed by the IOM, ASCO, and the Cancer and Aging Research Group [24–28]. As demonstrated in this present study, PROs can aid in understanding the heterogeneity of the study population, choice of treatment, and risk factors for toxicity.

Debate continues in regards to relative benefits of treatment with primary chemotherapy versus primary surgery in women with ovarian cancer, however, it is clear that more primary

chemotherapy is being used in the elderly population [29,30]. Less surgery is being performed in the oldest of old [31–33]. Patients receiving neoadjuvant chemotherapy do not always eventually receive surgical debulking [34]. In the CP cohort approximately 50% of patients received primary chemotherapy with 25% not having surgery while on trial. In the C arm, almost 60% had primary chemotherapy and over 50% of these did not receive surgery during the study.

The mean observed carboplatin AUC in the current study was close to the target value of AUC 5, while the variability around this value was quite large [35]. These results may be explained by our approach of estimating the AUC value from a single value of total platinum at 24 hours [36,37]. The observed paclitaxel exposure of 14.8 (± 4.8) $\mu\text{M}\cdot\text{h}$ is very similar to previously reported values of 13.1 (± 4.4) $\mu\text{M}\cdot\text{h}$ at the same dose level [38]. The lack of an observed correlation between paclitaxel PK parameter values and neurotoxicity may be explained by the lower dose of 135 mg/m² compared to studies that did observe such a relationship [39].

A weakness of the study includes a non-randomized design. The GOG considered randomization, however, was very concerned with the ability to accrue patients and the potential for grade 3–4 toxicity. This was the first elderly-patient specific trial conducted by the GOG, therefore, much discussion was held in regarding the clinical trial approach. In addition, it was the group's first trial using a battery of PROs. We used PROs for IADLs, ADL, social activities and QoL, however, not for the measurement of co-morbidity. In retrospect, using a PRO for co-morbidity might have been useful.

Identifying populations with decreased tolerance to chemotherapy should allow appropriate starting dose reductions and design of interventions to decrease toxicity in these frailer groups. IADL is a very easily administered tool that should be useful for this purpose.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This project used the University of Pittsburgh Cancer Institute (UPCI) Cancer Pharmacokinetics and Pharmacodynamics Facility (CPPF), supported in part by award P30CA047904. 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 (1U10 CA180822) and NRG Operations (U10CA180868).

Dr. Jan Beumer receives grant monies from MCI as well as support for travel to meetings for the study or other purposes.

Dr. Thomas Herzog is on the Advisory Board for AstraZeneca, Roche and Johnson and Johnson.

Dr. Arti Hurria serves as a board member for ASCO Board of Directors as well as SIOG Board. Dr. Hurria receives compensation for board membership from ASCO Cancer.net Editorial Board and JGO Editorial Board. He also receives monies for consultancy services from Boehringer Ingelheim Pharmaceuticals, Carevive, Sanofi, and GTx, Inc. Dr. Hurria's institute receives researching funding from Cellegene, Novartis and GSK.

Dr. Robert Higgins receives grant monies from Carolinas Medical Center.

Dr. Angeles Alvarez Secord received personal fees for serving on the advisory board for Janssen, Clovis Oncology, Genentech, and AstraZeneca. She also received grant funding from Genentech, Amgen, Endocyte and Exelixis. Dr. Secord received grant money and personal fees for serving on an advisory board at Astex Pharmaceuticals, Inc., and Boehringer Ingelheim. Dr. secord received grant funding from Prima Biomed, Tesaro, Eisai Morphotek, Bristol Myers Squibb and Incyte. She received personal fees from Glasko Smith Klein and Precision Therapeutics while serving on an advisory board, and also received grant money from Abbie-Vie.

References

1. Tew WP, Muss HB, Kimmick GG, von Gruenigen VE, Lichtman SM. Breast and ovarian cancer in the older woman. *J Clin Oncol*. 2014; 32:2553–2561. [PubMed: 25071129]
2. Joseph N, Clark RM, Dizon DS, Lee MS, Goodman A, Boruta D Jr, et al. Delay in chemotherapy administration impacts survival in elderly patients with epithelial ovarian cancer. *Gynecol Oncol*. 2015; 137:401–405. [PubMed: 25839911]
3. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, Falandry C, Artz A, Brain E, Colloca G, Flamaing J, Karnakis T, Kenis C, Audisio RA, Mohile S, Repetto L, Van Leeuwen B, Milisen K, Hurria A. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol*. 2014; 32(24):2595–603. [PubMed: 25071125]
4. Deshpande PR, Rajan S, Lakshmi Sudeepthi B, Abdul Nazir CP. Patient-reported outcomes: A new era in clinical research. *Perspect Clin Res*. 2011; 2(4):137–144. [PubMed: 22145124]
5. Basen-Engquist K, Bodurka-Bervers D, Fitzgerald MA, Webster K, Cella D, Hu S, et al. Reliability and validity of the functional assessment of cancer therapy-ovarian. *J Clin Oncol*. 2001; 19:1809–1817. [PubMed: 11251013]
6. Calhoun EA, Welshman EE, Chang CH, Lurain JR, Fishman DA, Hunt TL, et al. Psychometric evaluation of the functional assessment of cancer therapy/gynecologic oncology group — neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. *Int J Gynecol Cancer*. 2003; 13:741–748. [PubMed: 14675309]
7. Fillenbaum GG, Smyer MA. The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. *J Geront*. 1981; 36:428–434. [PubMed: 7252074]
8. Stewart, AL., Ware, JE. Measuring functioning and well-being: The Medical Outcomes Study Approach. Durham, NC: Duke University Press; 1992.
9. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J of Clin Epidem*. 1994; 47:1245–1251.
10. Colville H, Dzadony R, Kemp R, Stewart S, Zeh HJ 3rd, Bartlett DL, et al. In vitro circuit stability of 5-fluorouracil and oxaliplatin in support of hyperthermic isolated hepatic perfusion. *J Extra Corpor Technol*. 2010; 42:75–79. [PubMed: 20437796]
11. Parise RA, Ramanathan RK, Zamboni WC, Egorin MJ. Sensitive liquid chromatography-mass spectrometry assay for quantitation of docetaxel and paclitaxel in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2003; 783:231–236.
12. Ghazal-Aswad S, Calvert AH, Newell DR. A single-sample assay for the estimation of the area under the free carboplatin plasma concentration versus time curve. *Cancer Chemother Pharmacol*. 1996; 37:429–434. [PubMed: 8599865]
13. Kearns CM, Gianni L, Vigano L, et al. Validation of paclitaxel limited sampling strategies. *Proc Am Soc Clin Oncol*. 1997 abstr 720.
14. Kroenke CH, Quesenberry C, Kwan ML, Sweeney C, Castillo A, Caan BJ. Social networks, social support, and burden in relationships, and mortality after breast cancer diagnosis in the Life After Breast Cancer Epidemiology (LACE) study. *Breast Cancer Res Treat*. 2013; 137:261–271. [PubMed: 23143212]
15. Wenzel LB, Huang HQ, Armstrong DK, Walker JI, Cella D. Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2007; 25:437–443. [PubMed: 17264340]
16. von Gruenigen VE, Huang HQ, Gil KM, Frasure HE, Armstrong DK, Wenzel LB. The association between quality of life domains and overall survival in ovarian cancer patients during adjuvant

chemotherapy: a Gynecologic Oncology Group Study. *Gynecol Oncol.* 2012; 124:379–382. [PubMed: 22119995]

17. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol.* 2014; 32:2595–2603. [PubMed: 25071125]
18. Puts MT, Hardt J, Monette J, Girre V, Springall E, Alibhai SM. Use of geriatric assessment for older adults in the oncology setting: a systematic review. *J Natl Cancer Inst.* 2012; 104:1133–1163. [PubMed: 22851269]
19. Puts MT, Santos B, Hardt J, Monette J, Girre V, Atenafu EG, et al. *Ann Oncol.* 2014; 25:307–315. [PubMed: 24256847]
20. Falandry C, Weber B, Savoye AM, Tinquaut F, Tredan O, Sevin E, et al. Development of a geriatric vulnerability score in elderly patients with advanced ovarian cancer treated with first-line carboplatin: a GINECO prospective trial. *Ann Oncol.* 2013; 24:2808–2813. [PubMed: 24061628]
21. Freyer G, Geay JF, Touzet S, Provençal J, Weber B, Jacquín JP, et al. Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. *Ann Oncol.* 2005; 16:1795–1800. [PubMed: 16093275]
22. Tinquaut F, Freyer G, Chauvin F, Gane N, Pujade-Lauraine E, Falandry C. Prognostic factors for overall survival in elderly patients with advanced ovarian cancer treated with chemotherapy: Results of a pooled analysis of three GINECO phase II trials. *Gynecol Oncol.* 2016; 143(1):22–26. [PubMed: 27045777]
23. Tredan O, Geay JF, Touzet S, Delva R, Weber B, Cretin J, et al. *Ann Oncol.* 2007; 18:256–262. [PubMed: 17082510]
24. Hurria A, Naylor M, Cohen HJ. Improving the quality of cancer care in an aging population: recommendations from an IOM report. *JAMA.* 2013; 310:1795–1796. [PubMed: 24193075]
25. Hurria A, Levit LA, Dale W, Mohile SG, Muss HB, Fehrenbacher L, et al. *J Clin Oncol.* 2015; 33:3826–3833. [PubMed: 26195697]
26. Hurria A, Cirrincione CT, Muss HB, Kornblith AB, Barry W, Artz AS, et al. Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401. *J Clin Oncol.* 2011; 29:1290–1296. [PubMed: 21357782]
27. Dale W, Mohile SG, Eldadah BA, Trimble EL, Schilsky RL, Cohen HJ, et al. Biological, clinical, and psychosocial correlates at the interface of cancer and aging research. *J Natl Cancer Inst.* 2012; 104:581–589. [PubMed: 22457474]
28. Hurria A, Dale W, Mooney M, Rowland JH, Ballman KV, Cohen HJ, et al. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. *J Clin Oncol.* 2014; 32:2587–2594. [PubMed: 25071116]
29. Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIc-IV ovarian cancer. *N Engl J Med.* 2010; 363:943–953. [PubMed: 20818904]
30. Lin JJ, Egorova N, Franco R, Prasad-Hayes M, Bickell NA. Ovarian cancer treatment and survival trends among women older than 65 years of age in the United States, 1995–2008. *Obstet Gynecol.* 2016; 127:81–89. [PubMed: 26646132]
31. Uyar D, Frasure HE, Markman M, von Gruenigen VE. Treatment patterns by decade of life in elderly women (> or =70 years of age) with ovarian cancer. *Gynecol Oncol.* 2005; 98:403–408. [PubMed: 16000216]
32. Hightower RD, Nguyen HN, Averette HE, Hoskins W, Harrison T, Steren A. National survey of ovarian carcinoma. IV: Patterns of care and related survival for older patients. *Cancer.* 1994; 73:377–383. [PubMed: 8293403]
33. Langstraat C, Aletti GD, Cliby WA. Morbidity, mortality and overall survival in elderly women undergoing primary surgical debulking for ovarian cancer: a delicate balance requiring individualization. *Gynecol Oncol.* 2011; 123:187–191. [PubMed: 21794902]
34. Thrall MM, Gray JH, Gaston Symons RG, Weiss NS, Flum DR, Goff BA. Neoadjuvant chemotherapy in the Medicare cohort with advanced ovarian cancer. *Gynecol Oncol.* 2011; 123:461–466. [PubMed: 21945309]

35. Bookman MA, McGuire WP 3rd, Kilpatrick D, Keenan E, Hogan WM, Johnson SW, et al. Carboplatin and paclitaxel in ovarian carcinoma: a phase I study of the Gynecologic Oncology Group. *J Clin Oncol.* 1996; 14:1895–1902. [PubMed: 8656258]
36. Panday VR, van Warmerdam LJ, Huizing MT, Rodenhuis S, Schellens JH, Beijnen JH. A single 24-hour plasma sample does not predict the carboplatin AUC from carboplatin-paclitaxel combinations or from a high-dose carboplatin-thiotepa-cyclophosphamide regimen. *Cancer Chemother Pharmacol.* 1999; 43:435–438. [PubMed: 10100601]
37. Peng B, Boddy AV, Cole M, Pearson AD, Chatelut E, Rubie H, et al. Comparison of methods for the estimation of carboplatin pharmacokinetics in paediatric cancer patients. *Eur J Cancer.* 1995; 31:1804–1810.
38. Ohtsu T, Sasaki Y, Tamura T, Miyata Y, Nakanomyo H, Nishiwaki Y, et al. Clinical pharmacokinetics and pharmacodynamics of paclitaxel: a 3-hour infusion versus a 24-hour infusion. *Clin Cancer Res.* 1995; 1:599–606. [PubMed: 9816021]
39. Lichtman SM, Hollis D, Miller AA, Rosner GL, Rhoades CA, Lester EP, et al. Prospective evaluation of the relationship of patient age and paclitaxel clinical pharmacology: Cancer and Leukemia Group B (CALGB 9762). *J Clin Oncol.* 2006; 24:1846–1851. [PubMed: 16567769]

RESEARCH HIGHLIGHTS

- IADL was correlated with completion of 4 cycles of chemotherapy
- ADL, social activity, and QoL improved over time
- IADL was associated with overall survival in those receiving CP

Completion Status of Four Cycles of Study Chemotherapy

Figure 1.

Completion status of four cycles of chemotherapy. Carboplatin Paclitaxel = CP, Carboplatin =P. Numbers equal %

Figure 2.

Subgroup analysis of the association between other geriatric measures and tolerance of chemotherapy. Independent activities of daily living (IADL), activities of daily living (ADL), The Functional Assessment of Cancer Therapy — Ovary (FACT-O), body mass index (BMI).

Figure 3.

Subgroup analysis of the association between geriatric measures and four cycles of chemotherapy regardless of dose reduction or treatment delay.

Figure 4. Patient reported PROs over Time by chemotherapy. Independent activities of daily living (IADL), activities of daily living (ADL), The Functional Assessment of Cancer Therapy — Ovary (FACT-O), Functional Assessment of Cancer Treatment — Neurotoxicity -FACT/GOG-Ntx 4 subscale

Figure 5.
Overall Survival by number of Independent Instrumental Activities. Carboplatin Paclitaxel = CP, Carboplatin = P

Table 1

Patient Characteristics at Baseline

Characteristic	Category	CP (n=148)		C (n=59)		Total (n=207)	
		No.	%	No.	%	No.	%
Age categories	70–74	51	34	4	7	55	27
	75–79	59	40	12	20	71	34
	80–84	30	20	20	34	50	24
	85	8	5	23	39	31	15
Race	Non Hispanic Black	12	8	2	3	14	7
	Non Hispanic White	133	90	55	93	188	91
	Other	3	2	2	3	5	2
Performance Status	0	67	45	17	29	84	41
	1	62	42	21	36	83	40
	2	14	9	13	22	27	13
	3	5	3	8	14	13	6
Stage	I	8	5	1	2	9	4
	II	13	9	5	8	18	9
	III	98	66	44	75	142	69
	IV	29	20	9	15	38	18
Neoadjuvant Chemo	No	75	51	24	41	99	48
	Yes	73	49	35	59	108	52
Carboplatin Dosage	AUC 4	8	5	6	10	14	7
	AUC 5	140	95	53	90	193	93
GCSF use	Start with Cycle 1	118	80	–	–	–	–
	Start post Cycle 1	9	6	–	–	–	–
	No	21	14	–	–	–	–
Geriatric and QOL Assessment at Baseline		Mean (Range)		Mean (Range)		Mean (Range)	

Characteristic	Category	CP (n=148)		C (n=59)		Total (n=207)	
		No.	%	No.	%	No.	%
Instrumental Activities of Daily Living(IADL)		12 (4–14)		10 (2–14)		12 (2–14)	
Activities of Daily Living (ADL)		46 (0–100)		38 (0–100)		42 (0–100)	
No. of Falls in Last 6 Months		0.4 (0–7)		0.4 (0–4)		0 (0–7)	
No. of Medical Morbidities		0.7 (0–4)		1.0 (0–6)		1 (0–6)	
Social Activities		54 (6–94)		47 (5–94)		52 (6–94)	
BMI		27 (16–40)		27 (18–49)		27 (16–49)	
% Weight loss in last 6 months		6 (–23–33)		3 (–17–30)		5(–23–33)	
Quality of Life measured with FACT-O		111 (54–151)		106 (66–145)		110 (54–151)	

Carboplatin Paclitaxel = CP; Carboplatin =P. AUC = Area under the curve, QOL = quality of life, BMI = body mass index, FACT-O = The Functional Assessment of Cancer Therapy — Ovary