Doublet Chemotherapy in the Elderly Patient With Ovarian Cancer

MIN Y. TEO,^a DEREK G. POWER,^a WILLIAM P. TEW,^b STUART M. LICHTMAN^c

^aDepartment of Medical Oncology, Cork/Mercy University Hospitals, Cork, Ireland; ^bGynecologic Medical Oncology Service and ^cDepartment of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

Key Words. Ovarian cancer • Elderly • Geriatrics • Chemotherapy

Disclosures: The authors indicated no financial relationships.

Section Editors: **Dennis Chi:** None; **Peter Harper:** Sanofi, Roche, Imclone, Pfizer, GlaxoSmithKline, Lilly, Genentech (C/A); commercial symposia for Lilly, Novartis, Sanofi, and Roche (H)

Reviewer "A": Roche, Janssen (C/A)

Reviewer "B": None

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Summarize trends in the treatment of older women with ovarian cancer.
2. Describe the potential value of performing a geriatric assessment prior to treatment in older women with ovarian cancer.

CME

This article is available for continuing medical education credit at CME.TheOncologist.com.

ABSTRACT

The aging of the population has focused on the need to evaluate older patients with cancer. Approximately 50% of patients with ovarian cancer will be older than age 65 years. Increasing age has been associated with decreased survival. It is uncertain whether this relates to biologic factors, treatment factors, or both. There is concern that undertreatment may be associated with decreased survival. Older patients with ovarian cancer have been underrepresented in clinical trials. Therefore, the evidence base on which make decisions is lacking. Clinicians need to be aware of the currently available data to aid in treatment decisions. Doublet therapy is the most common standard treatment in epithelial ovarian cancer. It usually consists of a taxane and a platinum compound. A series of cooperative

group studies in both the United States and Europe established intravenous paclitaxel and carboplatin as the most common standard in optimally debulked patients. The recent introduction of intraperitoneal therapy has complicated decision making in terms of which older patients would benefit from this more toxic therapy. In relapsed patients, the issue of platinum sensitivity is critical in deciding whether to reutilize platinum compounds. It is unclear whether single agents or combinations are superior, particularly in older patients. Geriatric assessment is an important component of decision making. Prospective studies are needed to develop strategies to determine the optimal treatment for older patients with ovarian cancer. *The Oncologist* 2012;17:1450–1460

Correspondence: Stuart M. Lichtman, M.D., Memorial Sloan-Kettering Cancer Center, 650 Commack Road, Commack, New York 11725, USA. Telephone: 631-623-4100; Fax: 631-864-3827; e-mail: lichtmas@mskcc.org Received April 5, 2012; accepted for publication July 25, 2012; first published online in *The Oncologist Express* on August 22, 2012. ©AlphaMed Press 1083-7159/2012/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2012-0155>

INTRODUCTION

Epithelial cancer of the ovary arises from malignant transformation of the epithelium of the ovarian surface, which is contiguous with the peritoneum [1] and accounts for more than 85% of all ovarian neoplasms [1, 2]. Ovarian cancer is the eighth most common cancer in women, but it is the fifth leading cause of cancer death [3]. Ovarian cancer accounts for more than 20% of all gynecologic malignancies and is invariably associated with the worst outcome [2]. It is estimated that 21,880 women were diagnosed with ovarian cancer in the United States in 2010 and another 13,850 died from it [4]. Even though there has been a steady improvement in the survival of women with ovarian cancer over the last three decades, patients older than 60 years have a worse prognosis [5].

Ovarian cancer is primarily a disease of postmenopausal women. From age 45 years, the incidence of ovarian cancer rises rapidly until the eighth decade of life, with its incidence rate peaking at 54 per 100,000 in women aged between 75 and 79 years of age, compared to 3.0 per 100,000 in women under 30 years [6]. Close to half of all women with ovarian cancer will be older than 65, but these women account for more than two-thirds of cancer-related deaths [6]. This age group is more likely to be diagnosed at the advanced stage, accounting for at least 45% of all stage III and IV disease [6, 7].

Most epithelial cancers of ovary remain relatively asymptomatic until tumor enlargement leads to symptoms associated with compression of pelvic structures, ascites, abdominal distention, bowel obstruction, or distant metastases [2]. The probability of diagnosis at a localized and potentially curable stage decreases with age [8]. In one Gynecologic Oncology Group (GOG) study, 82% of patients older than 65 years presented with stage III and IV disease compared to 67% of patients younger than 65 years [9]. Some studies have reported age as an independent poor prognostic factor [10]. The age-standardized survival rate at 1 year is 57% for patients age 65–69 years, 45% for 70–74 years, 43% for 75–79 years, 33% for 80–84 years, and 25% for age 85 and above [11]. Cumulative analyses from six GOG trials showed that every 10-year increase in age was associated with 6% increase in risk of disease progression and 12% in risk for death from ovarian cancer [12].

FIRST-LINE CHEMOTHERAPY

Ovarian cancer is one of the most chemosensitive malignancies. Combination platinum-based chemotherapy is a mainstay of treatment in International Federation of Gynecology and Obstetrics (FIGO) stage II–IV disease; it has also been shown to confer a survival benefit in resected stage IB and IC disease [13].

First-line treatment in advanced ovarian cancer has evolved significantly since the 1980s [14]. Phase III trials are summarized in Table 1. The GOG-111, GOG-132, and European Canadian Intergroup OV-10 trials have established the combination of paclitaxel-cisplatin regimen as first-line treatment for advanced ovarian cancer [14–17]. The GOG-111 and OV-10 trials compared cisplatin-paclitaxel combination to the heretofore standard treatment of cisplatin and cyclophosphamide [15, 17]. Despite differences in inclusion criteria and

study design, both studies concordantly demonstrated the superiority of paclitaxel over cyclophosphamide in combination with cisplatin. The GOG-132 trial was a three-arm study with a patient population similar to the GOG-111 trial; it compared single-agent high-dose cisplatin with single-agent paclitaxel or cisplatin-paclitaxel doublet. High-dose cisplatin and the cisplatin-paclitaxel combination yielded identical but superior response rates and progression-free survival compared to paclitaxel alone [16]. Overall survival did not differ significantly between the groups. Early crossover to paclitaxel in the cisplatin arm was postulated to explain the relative lack of an overall survival benefit between the arms. The median age for patients in the GOG-111 trial was 60 years, with a range of 20 to 84 years of age; the OV-10 cohort had a median age of 58 years, ranging between 22 and 85 years. The proportion of older patients was not reported in these trials, whereas less than 20% of patients in the GOG-132 were over the age of 70 years.

Cisplatin is frequently associated with significant neurotoxicity, ototoxicity, nephrotoxicity, gastrointestinal toxicity, and myelosuppression [18]. Carboplatin was introduced in 1985; its role in ovarian cancer was soon supported by a meta-analysis of 37 randomized trials that showed superiority of platinum-based chemotherapy over non-platinum regimens, as well as equivalence of cisplatin and carboplatin [14]. Three phase III trials sought to further explore the efficacy and tolerability of carboplatin and paclitaxel compared to cisplatin and paclitaxel. One of the first randomized studies comparing paclitaxel-carboplatin with paclitaxel-cisplatin was a Dutch/Danish combined study, which randomized 208 patients to receive paclitaxel 175 mg/m² intravenously as a 3-hour infusion with either cisplatin (75 mg/m²) or carboplatin (area under the curve [AUC] 5), every 3 weeks. Overall response rates of 62% and 66% were achieved for the cisplatin and carboplatin arms, respectively. Median overall survival times were 30 and 32 months for the cisplatin and carboplatin arms, respectively. The paclitaxel-carboplatin arm produced significantly less nausea and vomiting, less peripheral neurotoxicity, but more thrombocytopenia and granulocytopenia. Overall, 17% of patients from the cisplatin arm discontinued treatment secondary to toxicities compared to 5% on the carboplatin arm [19]. Univariate analysis of trial data showed equivalent efficacy in both patients above and below 56 years [19].

The phase III GOG-158 trial [20] randomized 792 patients with small-volume, resected stage III disease to receive either 75 mg/m² cisplatin with 24-hour infusion of paclitaxel at 135 mg/m² or carboplatin (AUC 7.5) with 175 mg/m² of paclitaxel over 3 hours. Higher frequencies of both hematological and nonhematological toxicities were seen in the cisplatin arm. Median progression-free survival and overall survival times were 19.4 and 48.7 months for cisplatin arm compared with 20.7 and 57.4 months for carboplatin arm, respectively ($p > .05$). Only 12% of patients included in this trial were aged 70 years and above.

The Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) trial enrolled 798 patients in a design similar to the two prior studies. Median progression-free survival times were 17.2 and 19.1 months for the carboplatin-taxane arm and cis-

Table 1. Overview of phase III clinical trials for the first-line treatment of epithelial ovarian cancer, including the proportion of elderly patients examined

Trial	Year	Arms	n of patients	Definition of elderly	n of elderly patients	% of elderly patients	PFS (mos)	OS (mos)	PFS in elderly (mos)	OS in elderly (mos)
GOG 111 [15]	1996	CDDP-C vs. CDDP-P	386	NR	NR	NR	18 vs. 13	38 vs. 24	NR	NR
GOG 132 [16]	2000	CDDP vs. P vs. CDDP-P	614	60–69; ≥70	194, 108	32%, 18%	16.4 vs. 11.2 vs.	23 vs. 26 vs. 26.6	NR	NR
OVA-10 [17]	2000	CDDP-P vs. CDDP-C	680	NR	NR	NR	15.5 vs. 11.5	NR	NR	NR
Dutch/Danish study [19]	2000	CP vs. CDDP-P	208	NR	NR	NR	NS	NS	HR (>56 vs. ≤56): >1.01	NR
GOG 158 [20]	2003	CP vs. CDDP-P	792	61–70; 71–80; 81–90	215, 85, 10	27%, 11%, 1%	20.7 vs. 19.4	57.4 vs. 48.7	NR	NR
AGO OVAR [22, 24]	2003	CP vs. CDDP-P	798	≥70	103	12.90%	17.2 vs. 19.1	43.3 vs. 49.4	NR	NR
ICON2 [29]	1998	C vs. CAP	1,526	>65	482	32%	15.5 vs. 17.0	33 vs. 33	NR	NR
ICON3 [30]	2002	CP vs. C/CAP	2,074	>65	591	29%	17.3 vs. 16.1	36.1 vs. 35.4	NR	NR
JGOG [50]	2009	Dose-dense CP vs. CP	631	>60	263	41.7%	28.0 vs. 17.2	At 2 yrs: 83.6 vs. 77.7%	HR 0.74 (95% CI: 0.55–1.00)	NR
GOG 218 [27]	2011	CP + Bev + maintenance Bev vs. CP + Bev vs. CP	1,873	>70	430	23.0%	14.1 vs. 11.2 vs. 10.3	NR	HR 0.68; 0.84	NR
ICON7 [28]	2011	CP + Bev vs. CP	1,528	>70	150	10.0%	19.0 vs. 17.3	NR	HR 0.82 (95% CI: 0.51–1.30)	NR
GOG 182 [51, 52]	2009	CP ± gem/PLD/topo	3,686	≥70	620	16.80%	15.4 vs. 16.4	39.6 ~ 44.2	15	37
Alberts et al. [69]	1996	Cy + IP CDDP vs. CDDP-C	654	NR	NR	NR	NR	49 vs. 41	NR	NR
GOG 114 [71]	2001	CDDP-P vs. C > P + IP CDDP	523	61–70; >70	114, 49	22%, 9%	23 vs. 28	52 vs. 63	NR	NR
GOG 172 [70]	2006	CDDP-P vs. IP CDDP-P	415	61–70; >70	109, 48	26%, 12%	18.3 vs. 23.8	49.7 vs. 65.6	NR	NR

Abbreviations: AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; Bev, bevacizumab; CAP, cyclophosphamide/doxorubicin/cisplatin; CC, carboplatin/cyclophosphamide; CDDP, cisplatin; CDDP-C, cisplatin/cyclophosphamide; CDDP-P, cisplatin/paclitaxel; CP, carboplatin/paclitaxel; Cy, cyclophosphamide; gem, gemcitabine; GOG, Gynecologic Oncology Group; ICON, International Collaborative Ovarian Neoplasm; IP, intraperitoneal; NR, not reported; NS, not statistically significant; OS, overall survival; P, paclitaxel; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; topo, topotecan.

platin-taxane arm, respectively ($p > .05$); overall survival times were 43.3 and 44.1 months for the carboplatin-taxane arm and cisplatin-taxane arm, respectively ($p < .05$) [21]. However, mean global quality-of-life scores at the end of treatment were significantly better in the carboplatin-paclitaxel arm [22].

These pivotal phase III trials have prompted the Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference to adopt carboplatin and paclitaxel as the standard comparator arm for future first-line trials [23]. Nevertheless, the data on the feasibility of combination chemotherapy in elderly patients remain sparse. Only the AGO subsequently reported tolerability of carboplatin-paclitaxel in older patients; 13% percent of patients in the AGO study were over the age of 70 years [24]. These elderly patients received more than 96% of recommended chemotherapy doses in both arms of the study. Rates of early discontinuation were higher, at 26% ver-

sus 13% for the older (>70 years old) and younger groups, respectively. The most common causes for early treatment discontinuation were patient preference (10% vs. 3%, $p < .001$) and toxicities (19% vs. 8%, $p < .001$). No significant differences in rate of cycle delay, dose reduction, or granulocyte colony-stimulating factor and/or prophylactic antibiotics use were noted. Quality-of-life measurements and nonhematological toxicities were comparable. The rate of febrile neutropenia was higher in the older versus younger age groups (5% vs. <1%, $p < .005$) [24].

In recent years, the role of angiogenesis in the biology of ovarian cancer has been extensively studied. Vascular endothelial growth factor (VEGF) is expressed by ovarian cancer cell lines, and a reduction in VEGF levels is associated with increased cell survival [25]. Phase II trials of bevacizumab, a monoclonal antibody against circulating VEGF, in ovarian cancer have shown favorable response rates and delayed dis-

ease progression [26]. Two recent large phase III studies have examined the effect of bevacizumab combined with first-line chemotherapy in women with advanced ovarian cancer [27, 28]. With over 1,500 and 1,800 patients recruited to both International Collaborative Ovarian Neoplasm (ICON) 7 and GOG-218, respectively, the addition of bevacizumab as concurrent and maintenance therapy demonstrated significant but clinically restricted gain in progression-free survival. Overall survival data are incomplete. ICON7 enrolled 1,578 patients, with 479 patients (31%) between ages 60 and 69 years, and 150 patients (10%) over 70 years of age [28]. The median age was 57 years. GOG-218 enrolled 822 patients (44%) between ages 60 and 69 years, and 430 (23%) over 70 years [27]. Subgroup analyses suggested activities of bevacizumab across all age groups, with a greater effect seen in those patients with poor prognosis disease. GOG-218 reported increased incidence of hypertension in the bevacizumab arm while patients who received bevacizumab in ICON7 appeared to experience higher rate of mucocutaneous bleeding, hypertension, thromboembolic events, and gastrointestinal perforation. Neither study reported whether older patients experienced higher rate of toxicities.

It is evident that data to guide the medical treatment of older women with advanced ovarian cancer are lacking. Most available studies contain either small numbers of older patients or were retrospective in nature; therefore, the applicability to the older population is unclear. The ICON2 trial showed equivalence of single-agent carboplatin compared to cyclophosphamide-doxorubicin-cisplatin with better toxicity profile [29]. In the follow-up study, ICON3, which enrolled more than 2,000 patients, the carboplatin-paclitaxel was compared to either cyclophosphamide-doxorubicin-cisplatin or single-agent carboplatin. The authors found comparable overall survival (36.1 vs. 35.4 months, $p = .74$) and progression-free survival (17.3 vs. 16.1 months, $p = .16$), with favorable toxicity profile for single-agent carboplatin [30]. Even though only approximately 30% of patients were over the age of 65 in these two studies, the results have prompted Pignata et al. to advocate monotherapy in older patients with ovarian cancer [31], whereas others have proposed less toxic chemotherapeutic regimens, such as carboplatin and mitoxantrone [32].

As previously mentioned, there is an age-related decrease in survival in older patients compared with comparably staged younger patients. Various hypotheses have been proposed to explain this discrepancy, including the fact that older patients receive a less aggressive approach compared to younger patients, tolerance of chemotherapy is less, and disease is invariably more advanced and aggressive at presentation [33–35]. We will discuss each of these separately.

LESSER TREATMENT RECEIVED?

Analysis of National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database of over 22,000 patients with ovarian cancer diagnosed between 1973 and 1987 showed that only 1.6% of patients younger than 45 years were not treated, compared to 8.4% in 65–74 year age group, 22% in 75–84 year age group, and more than 47% in above 85 years.

The 5-year survival rates differed substantially between age groups, at 46.3% for patients younger than 45 years and 8.3% for patients older than 85 years [36].

Despite guidelines, significant numbers of women with ovarian cancer were not being provided with appropriate care, especially older women. When treatment patterns for women with ovarian cancer diagnosed in the early 1990s were analyzed, a greater percentage of women older than 65 years of age did not receive surgery (7.2% vs. 0.7%) or received only biopsies compared to younger women after controlling for disease stage at diagnosis and comorbidities [37]. Women older than 65 years were significantly less likely to receive recommended therapies. In fact, only 30.4%–34.1% of women over 75 years of age received guideline therapies, compared with 55%–75% of younger women [38].

In another review of patients with ovarian cancer diagnosed between 1992 and 1996, chemotherapy use in patients surviving beyond 4 months from diagnosis increased from 80% to 86%. However, an inverse correlation with age was seen, with 88% of patients aged 65–69 years receiving chemotherapy compared to 43% for patients older than 85 years. Using the age group of 65–69 years as reference, the odds ratio for receiving treatment was 0.96 for 70–74 years, 0.65 for 75–79 years, 0.24 for 80–84 years, and 0.12 for patients 85 years and older [39]. Despite only half of patients older than 65 years receiving platinum-based chemotherapy, improvement in overall survival of around 38% was observed in treated patients. This is comparable to results from randomized controlled trials among patients younger than 65 years [40].

European studies also revealed similar trends in age and chemotherapy use. A review of the Geneva Cancer Registry with 736 diagnoses of ovarian cancer reported some interesting observations. Patients older than 70 years had less screened detected tumors ($p < .001$), received less optimal cytoreductive surgery (20% vs. 43%, $p < .001$), and received chemotherapy less frequently (52% vs. 73%, $p < .001$), compared to patients younger than 70 years [41]. The 5-year disease-specific survival rates were significantly different between both groups, at 18% compared to 53% for older and younger groups, respectively (hazard ratio: 1.8, 95% confidence interval: 1.4–2.4). A Dutch population-based study reported similar conclusions. More than 1,100 patients were diagnosed with FIGO stage II and III ovarian cancer and only 45% of patients older than 70 years of age underwent optimal treatment in the form of combined surgery and chemotherapy, compared to more than 80% in the younger cohort, despite a relative absence of comorbidities in the older group [42]. Older women were also less likely to be enrolled into clinical trials [7, 9] and were less likely to be seen by gynecologic oncologists [43].

It has been reported that older patients with breast and colon cancers were less likely to be referred to an oncologist [44] or to receive optimal adjuvant chemotherapy [45], even after controlling for comorbidities and functional status. Few studies investigate clinicians' attitudes towards treatment in older patients with ovarian cancer. In a survey of all practicing gynecological oncologists in Australia and New Zealand, respondents considered age to be the second most frequent non-

disease-related barrier to optimal debulking of advanced ovarian cancer [46]. Literature on medical oncologists' attitude to chemotherapeutic intervention for ovarian cancer is limited. In advanced colorectal cancer, for example, a majority of U.S. community-based oncologists recommend combination therapy for younger patients, whereas nearly one in four choose lower-intensity therapies for older patients [47]. It is most likely that a similar preference would be seen in ovarian cancer.

TOLERABILITY

The probability of older patients tolerating aggressive standard treatment has been the subject of numerous investigations. Older patients receiving chemotherapy have been reported to experience a greater rate of hematological and nonhematological (mucosal, cardiac, and neurological) toxicities [48]. However, evidence regarding toxicities in older patients treated for ovarian cancer remains contradictory.

Some recent retrospective studies have shown that older patients were able to tolerate standard-dose paclitaxel-carboplatin combination chemotherapy [49–52]. Ceccaroni et al. reported a 44% rate of grade 3/4 hematological toxicities, but discontinuation rate was low at 6.8% [49]. Kotani et al. found that only 65% of patients completed the prescribed course of treatment and found grade 3/4 peripheral neuropathy (42%) to be the most common treatment-limiting toxicity [52]. In a combined analysis of two Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO) studies, Trédan et al. found that the carboplatin-paclitaxel regimen resulted in more hematological and neurotoxicities but remained a feasible regimen, with 68.1% of patients managing to receive six cycles of scheduled chemotherapy compared to 75.6% of those patients receiving carboplatin-cyclophosphamide [34].

Bruchim et al. reported a retrospective study of 143 patients with advanced ovarian cancer, in which 46% were over the age of 70 years. Elderly patients were more likely to receive neoadjuvant chemotherapy (43.3% vs. 13.4%, $p < .01$) and hematological toxicity was significantly more common (75% vs. 36.3%, $p = .001$), although no significant difference was noted in grade 3/4 toxicities. The older patients were more likely to have dose reductions and treatment delays but they had similar overall response (80% vs. 87.6%) and complete response rates (60% vs. 71.9%) compared to younger patients [53]. Penson et al. treated 12 elderly patients with a median age of 82 years (range, 75–86 years) with standard dose chemotherapy. Ten patients had an Eastern Cooperative Oncology Group (ECOG) score of 0–1. Only three patients were able to complete treatment, and there were three deaths during the study [54]. Other studies have demonstrated that reduced-dose chemotherapy allowed for better compliance and greater tolerability while maintaining equivalent efficacy [55, 56].

MORE AGGRESSIVE DISEASE?

When older patients undergo aggressive surgical and chemotherapeutic management, survival is reported to be significantly decreased compared to younger patients. It is unclear if underlying tumor biology or inherent histologic differences contribute to this observation.

Certain histologic subtypes of epithelial ovarian cancer, such as mucinous and clear cell variants, have been suggested to demonstrate a chemoresistant phenotype [57, 58]. A study based on a Japanese population-based cancer registry showed that in women older than 50 years, an increasing trend in clear cell, mucinous, and endometrioid adenocarcinomas was observed over a 24-year period from 1983 to 2007. In fact, the authors noticed a significant 3.1-fold increase in clear cell adenocarcinoma among women older than 50 years during the past two decades [59]. Nevertheless, the actual incidence of these histologic variants remains low. In a meta-analysis of seven randomized trials for advanced ovarian cancer with more than 8,700 patients, only 2.5% and 3.0% had clear cell and mucinous histology, respectively [57]. Data obtained from the SEER database between 1988 and 2001 showed that clear cell and mucinous variants constituted 5% and 9.7% of epithelial ovarian cancer [60]. The low incidence is less likely to contribute to poorer outcomes in older patients.

Older women are more likely to be diagnosed at an advanced stage. For example, only 11% of women older than 85 years of age were diagnosed with stage I disease, compared to 45% of women younger than 45 [6]. In a retrospective exploratory analysis of six GOG protocols between 1976 and 1990 [33] involving 2,123 patients. Five hundred and twelve patients were above 65 years and 173 patients were above 70 years of age. Older patients had a worse prognosis even though age itself did not adversely affect dose intensity of treatment. In a smaller series, Marchetti et al. [61] reported a median overall survival of 22 months in patients older than 65 years compared to 36.7 months in younger patients, despite equivalent rate of optimal debulking surgery and chemotherapy dosing intensity. Analysis of a phase III Southwestern Oncology Group trial comparing cisplatin-cyclophosphamide with carboplatin-cyclophosphamide showed a statistically significant difference of 3.8 months in overall survival in older patients despite similar tolerability of chemotherapy and planned dose received [62]. In contrast, two other trials [63, 64] did not find age to be a poor prognostic indicator, although older patients appeared to have higher rate of residual disease (67% vs. 39%) [64] and received lower percentage of planned dose [63]. However, it is important to note that these trials were all carried out before carboplatin-paclitaxel was accepted as the standard treatment.

Survival data from the platinum-paclitaxel doublet era in older patients with ovarian cancer are sparse. A single institution retrospective review reported that older patients demonstrated similar rates of initial response, platinum resistance, progression-free survival, and overall survival compared with younger patients [50]. In a study involving 53 women receiving carboplatin-paclitaxel for stage II to IV ovarian cancer, Higgins et al. [51] found no significant difference in clinical response rates between women older and younger than 60 years of age. Hershman et al. found that overall survival in older women improved by 38% when treated with platinum-based chemotherapy and was greatest when combined with paclitaxel, similar to the benefits described in randomized trials in younger patients [40]. The Hellenic Oncology Coopera-

tive Group reported their experience with 1,748 patients, of which 282 were older than 70 years and over two-thirds received paclitaxel-platinum chemotherapy. Older patients had significantly worse median survival of 33 months compared to 118.5 months for younger patients ($p < .001$) [10].

Various efforts have been undertaken to improve on survival benefit of the current carboplatin-paclitaxel regimen. A Japanese Gynecologic Oncology Group study randomized 631 patients to receive dose-dense weekly paclitaxel and thrice-weekly carboplatin or standard regimen [65]. Overall survival at 3 years was significantly higher in the experimental arm (72.1% vs. 65.1%, $p = .03$). The hazard ratio for progression-free survival for patients older than 60 years was 0.74 (confidence interval: 0.55–1.00). This study did not formally report effects on older patients, so it is difficult to extrapolate to this population.

The GOG-182 was a five-arm trial investigating the benefit of incorporating a third agent to carboplatin-paclitaxel. More than 3,000 women were enrolled to receive the standard doublet in addition to gemcitabine, topotecan, and pegylated liposomal doxorubicin. The addition of a third agent failed to improve progression-free or overall survival times [66]. Around 17% of patients enrolled were over the age of 70 years. These older patients had lower complete rates of prescribed treatments, shorter survival, and increased toxicity [67].

INTRAPERITONEAL CHEMOTHERAPY

The peritoneal cavity is a common site of disease in advanced ovarian cancer. Intraperitoneal (IP) administration of high-dose chemotherapy allows higher local drug concentration, prolonged tumor exposure, and reduced systemic toxicities [68]. Four large phase III randomized trials have demonstrated significant survival advantage with intraperitoneal chemotherapy [68–71].

The GOG-114 trial randomized 523 patients to compare standard-dose cisplatin-paclitaxel with two cycles of carboplatin (AUC 9) followed by six cycles of paclitaxel (135 mg/m²) and intraperitoneal cisplatin (100 mg/m²). In all, 29% of all patients in the experimental arm received less-than-prescribed cycles of intraperitoneal treatment as a result of toxicities. Despite this, patients randomized to the experimental arm had superior progression-free survival (28 vs. 23 months, $p = .01$) and borderline improvement in overall survival (63 vs. 52 months, $p = .05$). Of note, 60 (26%) and 22 (9%) of patients in the experimental arm were in the 61–70 year age group and over-70 years age group, respectively [71].

A total of 429 patients in the GOG-172 trial received intravenous paclitaxel and were randomized to either intravenous or intraperitoneal cisplatin. Overall, 26% of patients were older than 60 years of age, 12% were older than 70 years, and 1% were older than 80 years [70]. Only 42% of patients were able to complete the assigned treatment secondary to significant toxicities and patient discomfort. Quality-of-life assessment was significantly worse in the IP arm but improved over time. Progression-free survival time (23.8 vs. 18.3 months, $p = .05$) and overall survival time (65.6 vs. 49.7 months, $p = .03$) were significantly improved in the experimental arm.

Kothari et al. retrospectively analyzed 109 patients who received intraperitoneal chemotherapy for ovarian cancer. Patients older than 70 years were less likely to complete all planned cycles of therapy (odds ratio: 0.33, confidence interval: 0.13–0.83; $p = .01$), but age did not increase complication rates or affect progression-free survival [72]. Investigators from Memorial Sloan-Kettering Cancer Center recently reported their experience of 118 patients with median age of 70 years (range: 65–83 years). In all, 55% of patients completed all planned cycles and 18% of patients required switching to intravenous therapy. Overall, 14% of these older patients had treatment delays and 32% required dose reduction. Median progression-free interval was 1.2 years, and toxicity rates were comparable to published data [73].

From published data, it appears that with adequate support and dose reduction, intraperitoneal could be safely administered to older patients. However, there are many challenges involved in administering intraperitoneal chemotherapy to older patients, such as insertion and maintenance of the IP catheter, risk of peritonitis, and increased risk of nephrotoxicity and myelosuppression with cisplatin and paclitaxel, respectively [74–76].

RECURRENT DISEASE

The majority of patients who undergo treatment for epithelial ovarian cancer experience disease recurrence. Second-line chemotherapy is invariably the only treatment option in the relapsed setting. Choice of salvage therapy is based on timing of relapse and performance status. Because platinum is always considered in the relapsed setting, patients with recurrent ovarian cancer are divided into those who relapse within 6 months (i.e., platinum-resistant disease) and those who relapse after six months (i.e., platinum-sensitive disease) [77]. The relapse-free period correlates highly to subsequent cisplatin response rates, ranging from 20%–30% in the case of a platinum-free period of 6–12 months to more than 60% for platinum-free interval of 12–18 months [68].

Recurrent ovarian cancer has historically been treated with single-agent chemotherapy due to a lack of evidence for combination regimen and fear of cumulative toxicity [78]. The landmark ICON4 trial investigated the role of paclitaxel plus platinum-based chemotherapy compared to conventional carboplatin monotherapy in platinum-sensitive relapsed ovarian cancer. Rechallenge with paclitaxel-platinum combination compared to platinum-only therapy showed a 3-month and 5-month gain in median progression-free survival and overall survival, respectively [79]. In all, 30% of the 560 enrolled patients were over the age of 65 years and they derived the same benefit as younger patients. Overall, 20%–30% of patients experienced grade 3/4 hematological and neurological toxicities. It is not known if the rates were higher in the older patient subgroup.

An intergroup trial of the European Organization for Research and Treatment of Cancer, National Cancer Institute of Canada Clinical Trials Group, and Arbeitsgemeinschaft Gynäkologische Onkologie, Studiengruppe Ovarialkarzinom groups compared the combination of carboplatin and gemcit-

abine to carboplatin alone; it demonstrated a superior response rate (47.2% vs. 30.9%, $p < .0016$) and prolonged progression-free survival time (8.6 months vs. 5.8 months, hazard ratio: 0.72, 95% confidence interval: 0.58–0.90; $p = .0031$). However, no survival advantage was seen [80]. Subgroup analysis showed that age older than 60 years is not adversely associated with poorer progression-free survival.

The recently reported Ovarian Cancer Evaluation of Avas-tin and Safety (OCEANS) trial aimed to improve upon the carboplatin/gemcitabine doublet [81]. Overall, 484 patients were randomized to chemotherapy with either bevacizumab or placebo. Unlike outcomes in first-line setting, patients who received the carboplatin/gemcitabine/bevacizumab triplet had superior progression-free survival of 12.4 months versus 8.4 months ($p < .0001$) and an improved response rate of 78.5% versus 57.4% ($p < .0001$). The median age of the entire cohort was 60–61 years of age, with 35.1%–38.4% of patients being 65 years of age or older. Subgroup analysis showed that older patients experienced comparable benefit from the addition of bevacizumab at 12.3 versus 8.4 months, although it was not reported if older patients endured higher rates of toxicities [81].

To address the cumulative risk of neurological toxicities when rechallenged with paclitaxel-platinum, the large phase III Caelyx in Platinum Sensitive Ovarian Patients (CALYPSO) trial was designed to compare the noninferiority of carboplatin in combination with pegylated liposomal doxorubicin to carboplatin-paclitaxel. A total of 976 patients were recruited. Numbers of cycles received and dose intensity were identical between older and younger patients. Progression-free survival was statistically superior in the pegylated liposomal doxorubicin arm, at 11.3 months versus 9.4 months [82]. Sixteen percent of patients were older than 70 years of age, and this group completed more than six cycles of planned treatment at the same rate as younger patients with no significant differences in rates of hematologic toxicities. The therapeutic index for elderly and younger patients was similar. Less hypersensitive reactions and more neuropathy were observed in elderly patients. Carboplatin-pegylated liposomal doxorubicin was thought to be the preferable treatment option in older patients [83].

Trials have explored the utility of non-platinum chemotherapy combinations in relapsed ovarian cancer [84]. Trabectedin is a marine-derived antineoplastic agent that induces cell cycle arrest and apoptosis. Monk et al. randomized 672 patients to receive trabectedin plus pegylated liposomal doxorubicin or trabectedin alone. Response rates, progression-free, and overall survival were superior in the combination arm in the overall population and in the platinum-sensitive subgroup. In all, 27% of patients were over 65 years. However, age carried no prognostic role in multivariate analysis.

Treatment for platinum-resistant disease generally consists of single non-platinum agent chemotherapy, with response rates in the range of 10–25% and duration of disease control from 4–8 months [68, 77, 85]. Few studies have been reported in the elderly population. Bicher et al. reported a series of 48 patients treated with 250 mg/m² of paclitaxel every 3 weeks. Median age of the cohort was 55 years, with 29% of the pa-

tients aged 62 years or greater and 8% of patients 70 years of age or greater. Dose intensity, cycles administered, and toxicities were comparable for the older and younger patients [35]. Grondlund et al. treated 57 recurrent ovarian cancer patients with topotecan and found that overall performance status was a better prognostic marker than chronologic age for treatment response and survival [86]. However, results from the Study of an Ovarian Cancer cohort Recurred After First Line Treatment: a Retrospective Survey (SOCRATES) found that elderly patients with platinum-sensitive disease had a worse outcome. Older patients received less surgery and chemotherapy and experienced lower response rates compared to younger patients [87].

AGE AND GERIATRIC ASSESSMENT

The definition of an “older” population is often discordant between datasets. The selection of 65 years of age is an arbitrary definition based on conventional cutoff for medical, social, and economic purposes [6]. Gerontologic literature generally labels individuals from 65 through 74 years of age as “early elderly” and those older than 75 years as “late elderly” [6, 88]. Cutoffs for elderly patients in oncologic studies are often highly variable, ranging from 45 years [89] to over 75 years [90] or older [91].

Advanced chronologic age is often an obstacle to enrollment in a clinical trial [43] or receipt of optimal treatment [9, 36, 39, 92]. However, the older patient subgroup is not homogeneous and life expectancy differs within the same age groups in an elderly population [93]. For example, 25% of women aged 75 years will live more than 17 years, 50% will live at least 11.9 years, and 25% will live less than 6.8 years [93]. Studies in patients with cancer have shown that chronological age is not a determinant of tolerability to treatment in various tumor types [94–96]. Performance status and comorbidities appear to be more predictive of patients’ outcome [53]. Approximately 8% of the elderly cancer population suffer from cancer alone, 37% have one or two additional comorbidities, and 55% have three or more comorbidities [49]. In one study of 269 elderly patients with normal performance status, 13% had two or more comorbidities; 9.3% and 37.7% had limitations in activities of daily living (ADLs) and instrumental ADLs, respectively, and 30% had limitations in mental or emotional status [97].

Multidimensional assessment has been proposed to evaluate various age-related factors in the elderly patients with cancer because the ECOG score is not sufficient and does not truly reflect an older patient’s true functional status [97, 98]. The comprehensive geriatric assessment (CGA) was initially devised to provide geriatricians with a multidisciplinary comprehensive evaluation of an older individual’s functional status, comorbid medical conditions, cognition, psychological state, nutritional status, and social support (Table 3) [99]; it has been proven useful in gerontologic practice in randomized and controlled studies [48]. In recent years, the potential benefits of geriatric assessment in care of elderly patients with cancer have been actively studied. Advantages include assessment of comorbidities and functional dependence, which may render a person more susceptible to complications of treatment [100];

Table 2. Overview of phase III clinical trials in first-line treatment of epithelial ovarian cancer, including proportion of elderly patients examined												
Trial	Phase	Year	Arms	n of patients	Definition of elderly	n of elderly patients	% of elderly patients	PFS (mos)	OS (mos)	PFS in elderly (mos)	OS in elderly (mos)	
ICON4 [79]	III	2003	CP vs. C (71%), CAP(17%), others	802	>65	239	30%	12 vs. 9	29 vs. 24	NR	NR	
Intergroup [80]	III	2006	CG vs. C	356	>65	100	28%	8.6 vs. 5.8	18 vs. 17.3	Compared to <65, $p = .28$	NR	
OCEANS [81]	III	2012	CG ± Bev	484	>65	178		12.4 vs. 8.4	NR	12.3 vs. 8.4		
CALYPSO [82, 83]	III	2010	C-PLD vs. CP	976	>70	157	16%	11.3 vs. 9.4	NR	11.6 vs. 10.3	NR	
Monk et al. [84]	III	2010	PLD-T vs. PLD	672	>65	179	27%	7.3 vs. 5.8	NR	6.3 vs. 5.8	NR	
Abbreviations: Bev, bevacizumab; C, carboplatin; CAP, cyclophosphamide/doxorubicin/cisplatin; CG, carboplatin/gemcitabine; CP, carboplatin/paclitaxel; ICON, International Collaborative Ovarian Neoplasm; NR, not reported; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PLD-T, pegylated liposomal doxorubicin/trabectedin.												

evaluation of emotional, cognitive, and socioeconomic conditions, which could interfere with compliance; and gross estimate of life expectancy [48]. It has been shown that the CGA can significantly influence treatment decisions [101] and estimate the probability of increased mortality risk and inability to complete prescribed treatment [102]. Components of a proposed CGA are shown in Table 2.

To date, only a few trials have incorporated a geriatric assessment of some form in the ovarian cancer literature. The Multicenter Italian Trial in Ovarian Cancer study, which assessed tolerability of weekly paclitaxel and carboplatin in elderly patients, recorded ADLs, instrumental ADLs, and comorbidities at baseline [103]. The overall patient number was too small to make any meaningful correlation, however. In a GINECO study in which 83 patients older than age 70 years received carboplatin and cyclophosphamide, Freyer et al. reported that comprehensive geriatric assessment was able to predict severe toxicities and overall survival [104].

CONCLUSION

Ovarian cancer is predominantly a disease of postmenopausal women in which incidence rises rapidly from age 45 onwards. Approximately 50% of all patients with ovarian cancer are older than age 65, and these women account for over two-thirds of cancer-related deaths despite advances and improvement in survival achieved with modern chemotherapeutic agents.

There is a greater propensity for older women to be diagnosed with more advanced stage ovarian cancer and therefore poorer outcomes and survival. However, studies have shown that older women were less likely to receive optimal debulking surgery, per-protocol chemotherapy, referrals to gynecologic oncologists, or even enrollment in clinical trials. Subgroup analyses of randomized clinical trials and retrospective studies have demonstrated that platinum-based doublet chemotherapy might give rise to higher rate of toxicities in older patients, but a significant proportion is able to complete prespecified ther-

apies, some with minor dose modification. This is exemplified by the large international ICON4 study, in which up to 30% of study participants were over the age of 65, with no evidence of intolerance of platinum-doublet chemotherapy in a second-line setting.

It is now recognized that the older patient subgroup is not

Table 3. Comprehensive geriatrics assessment	
Parameters assessed	Elements of the assessment
Function	Performance status Activities of daily living Instrumental activities of daily living
Comorbidity	Number of comorbid conditions Severity of comorbid conditions Charlson comorbidity index
Socioeconomic conditions	Living conditions Presence and adequacy of a caregiver
Cognitive	Folstein's mini-mental status Other tests
Emotional conditions	Geriatric depression scale
Pharmacy	Number of medications Appropriateness of medications Risk of drug interactions
Nutrition	Mini-nutritional assessment
Geriatric syndromes	Dementia, delirium, depression, falls, neglect and abuse, spontaneous bone fractures
Adapted from Balducci L, Extermann M. Management of cancer in the older person: A practical approach. <i>The Oncologist</i> 2000;5:224–237, with permission.	

homogenous and age per se is a poor surrogate for outcomes. This is reflected by the highly varied and conflicting results from various studies examining tolerance of chemotherapy in older patients. Adoption of multidimensional geriatric assessment might offer more accurate estimation of treatment tolerance in older patients.

In conclusion, platinum-based chemotherapy is efficacious and tolerable in well-selected older patients. Optimal management of older patients with ovarian cancer is dictated by their desire for treatment with the potential for long-lasting remission or cure, as well as their willingness to accept potential toxicities. Future studies should routinely include components of comprehensive geriatric assessment to predict efficacy and tolerance of treatment. The preponderance of an older patient group in this disease mandates such studies and the exclusion

of the elderly from clinical trials is no longer acceptable. Cancer-specific mortality is often higher than noncancer mortality in this group of patients, and investigators should not discriminate against older patients when drafting protocols for new treatments. The changing population demographics mandates this.

AUTHOR CONTRIBUTIONS

Conception/Design: Min Y. Teo, Derek G. Power, William P. Tew, Stuart M. Lichtman

Provision of study material or patients: Min Y. Teo, Derek G. Power

Collection and/or assembly of data: Min Y. Teo, Derek G. Power

Data analysis and interpretation: Min Y. Teo, Derek G. Power

Manuscript writing: Min Y. Teo, Derek G. Power, William P. Tew, Stuart M. Lichtman

Final approval of manuscript: Min Y. Teo, Derek G. Power, William P. Tew, Stuart M. Lichtman

REFERENCES

- Cannistra SA. Cancer of the ovary. *N Engl J Med* 2004;351:2519–2529.
- Merino MJ, Jaffe G. Age contrast in ovarian pathology. *Cancer* 1993;71:537–544.
- Jemal A, Siegel R, Ward E et al. Cancer statistics, 2008. *CA: Cancer J Clin* 2008;58:71–96.
- American Cancer Society. Cancer Facts & Figures, 2010. Atlanta, GA: American Cancer Society; 2010.
- Barnholtz-Sloan JS, Schwartz AG, Qureshi F et al. Ovarian cancer: Changes in patterns at diagnosis and relative survival over the last three decades. *Am J Obstet Gynecol* 2003;189:1120–1127.
- Yancik R. Ovarian cancer. Age contrasts in incidence, histology, disease stage at diagnosis, and mortality. *Cancer* 1993;71:517–523.
- Markman M, Lewis JL, Saigo P et al. Epithelial ovarian cancer in the elderly. The Memorial Sloan-Kettering Cancer Center experience. *Cancer* 1993;71:634–637.
- Grover SA, Cook EF, Adam J, Coupal L, Goldman L. Delayed diagnosis of gynecologic tumors in elderly women: Relation to national medical practice patterns. *Am J Med* 1989;86:151–157.
- Moore DH, Kauderer JT, Bell J et al. An assessment of age and other factors influencing protocol versus alternative treatments for patients with epithelial ovarian cancer referred to member institutions: A Gynecologic Oncology Group study. *Gynecol Oncol* 2004;94:368–374.
- Pectasides D, Fountzilas G, Aravantinos G et al. Epithelial ovarian carcinoma in younger vs. older women: Is age an independent prognostic factor? The Hellenic Oncology Cooperative Group experience. *Int J Gynecol Cancer* 2007;17:1003–1010.
- Vercelli M, Capocaccia R, Quaglia A et al. Relative survival in elderly European cancer patients: Evidence for health care inequalities. The EURO CARE Working Group. *Crit Rev Oncol Hematol* 2000;35:161–179.
- Winter WE, Maxwell GL, Tian C et al. Prognostic factors for stage III epithelial ovarian cancer: A Gynecologic Oncology Group Study. *J Clin Oncol* 2007;25:3621–3627.
- Trimbos JB, Parmar M, Vergote I et al. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: Two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst* 2003;95:105–112.
- Aabo K, Adams M, Adnitt P et al. Chemotherapy in advanced ovarian cancer: Four systematic meta-analyses of individual patient data from 37 randomized trials. Advanced Ovarian Cancer Trialists' Group. *Br J Cancer* 1998;78:1479–1487.
- McGuire WP, Hoskins WJ, Brady MF et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996;334:1–6.
- Muggia FM, Braly PS, Brady MF et al. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: A gynecologic oncology group study. *J Clin Oncol* 2000;18:106–115.
- Piccart MJ, Bertelsen K, James K et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: Three-year results. *J Natl Cancer Inst* 2000;92:699–708.
- McGuire WP, Markman M. Primary ovarian cancer chemotherapy: Current standards of care. *Br J Cancer* 2003;89(Suppl 3):S3–S8.
- Neijt JP, Engelholm SA, Tuxen MK et al. Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. *J Clin Oncol* 2000;18:3084–3092.
- Ozols RF, Bundy BN, Greer BE et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group study. *J Clin Oncol* 2003;21:3194–3200.
- du Bois A, Luck HJ, Meier W et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst* 2003;95:1320–1329.
- Greimel ER, Bjelic-Radisic V, Pfisterer J et al. Randomized study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group comparing quality of life in patients with ovarian cancer treated with cisplatin/paclitaxel versus carboplatin/paclitaxel. *J Clin Oncol* 2006;24:579–586.
- du Bois A, Quinn M, Thigpen T, et al. 2004 consensus statements on the management of ovarian cancer: Final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference. *Ann Oncol* 2005;16 (Suppl 8):7–12.
- Hilpert F, du Bois A, Greimel ER et al. Feasibility, toxicity and quality of life of first-line chemotherapy with platinum/paclitaxel in elderly patients aged ≥ 70 years with advanced ovarian cancer: A study by the AGO OVAR Germany. *Ann Oncol* 2007;18:282–287.
- Yoneda J, Kuniyasu H, Crispens MA et al. Expression of angiogenesis-related genes and progression of human ovarian carcinomas in nude mice. *J Natl Cancer Inst* 1998;90:447–454.
- Garcia AA, Hirte H, Fleming G et al. Phase II Clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: A trial of the California, Chicago, and Princess Margaret Hospital Phase II Consortia. *J Clin Oncol* 2008;26:76–82.
- Burger RA, Brady MF, Bookman MA et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011;365:2473–2483.
- Perren TJ, Swart AM, Pfisterer J et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011;365:2484–2496.
- ICON Collaborators. ICON2: Randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. International Collaborative Ovarian Neoplasm Study. *Lancet* 1998;352:1571–1576.
- International Collaborative Ovarian Neoplasm G. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: The ICON3 randomised trial. *Lancet* 2002;360:505–515.
- Pignata S, Monfardini S. Single agents should be administered in preference to combination chemotherapy for the treatment of patients over 70 years of age with advanced ovarian carcinoma. *Eur J Cancer* 2000;36:817–820.
- Nicoletto MO, Artioli G, Donach M et al. Elderly ovarian cancer: Treatment with mitoxantrone-carboplatin. *Gynecol Oncol* 2001;80:221–226.
- Thigpen T, Brady MF, Omura GA et al. Age as a prognostic factor in ovarian carcinoma. The Gynecologic Oncology Group experience. *Cancer* 1993;71:606–614.
- Trédan O, Geay JF, Touzet S et al. Carboplatin/cyclophosphamide or carboplatin/paclitaxel in elderly patients with advanced ovarian cancer? Analysis of two consecutive trials from the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. *Ann Oncol* 2007;18:256–262.
- Bicher A, Sarosy G, Kohn E et al. Age does not influence taxol dose intensity in recurrent carcinoma of the ovary. *Cancer* 1993;71:594–600.
- Ries LA. Ovarian cancer. Survival and treatment differences by age. *Cancer* 1993;71:524–529.
- Munoz KA, Harlan LC, Trimble EL. Patterns of care for women with ovarian cancer in the United States. *J Clin Oncol* 1997;15:3408–3415.
- Harlan LC, Clegg LX, Trimble EL. Trends in sur-

gery and chemotherapy for women diagnosed with ovarian cancer in the United States. *J Clin Oncol* 2003;21:3488–3494.

39. Sundararajan V, Hershman D, Grann VR et al. Variations in the use of chemotherapy for elderly patients with advanced ovarian cancer: A population-based study. *J Clin Oncol* 2002;20:173–178.

40. Hershman D, Jacobson JS, McBride R et al. Effectiveness of platinum-based chemotherapy among elderly patients with advanced ovarian cancer. *Gynecol Oncol* 2004;94:540–549.

41. Petignat P, Fioretta G, Verkooijen HM et al. Poorer survival of elderly patients with ovarian cancer: A population-based study. *Surg Oncol* 2004;13:181–186.

42. Maas HA, Kruitwagen RF, Lemmens VE et al. The influence of age and comorbidity on treatment and prognosis of ovarian cancer: A population-based study. *Gynecol Oncol* 2005;97:104–109.

43. Carney ME, Lancaster JM, Ford C et al. A population-based study of patterns of care for ovarian cancer: Who is seen by a gynecologic oncologist and who is not? *Gynecol Oncol* 2002;84:36–42.

44. Krzyzanowska MK, Regan MM, Powell M et al. Impact of patient age and comorbidity on surgeon versus oncologist preferences for adjuvant chemotherapy for stage III colon cancer. *J Am Coll Surg* 2009;208:202–209.

45. Hurria A, Naeim A, Elkin E et al. Adjuvant treatment recommendations in older women with breast cancer: A survey of oncologists. *Crit Rev Oncol Hematol* 2007;61:255–260.

46. Brand AH. Ovarian cancer debulking surgery: A survey of practice in Australia and New Zealand. *Int J Gynecol Cancer* 2011;21:230–235.

47. Foster JA, Salinas GD, Mansell D et al. How does older age influence oncologists' cancer management? *The Oncologist* 2010;15:584–592.

48. Balducci L, Extermann M. Management of cancer in the older person: A practical approach. *The Oncologist* 2000;5:224–237.

49. Ceccaroni M, D'Agostino G, Ferrandina G et al. Gynecological malignancies in elderly patients: Is age 70 a limit to standard-dose chemotherapy? An Italian retrospective toxicity multicentric study. *Gynecol Oncol* 2002;85:445–450.

50. Eisenhauer EL, Tew WP, Levine DA et al. Response and outcomes in elderly patients with stages IIIC-IV ovarian cancer receiving platinum-taxane chemotherapy. *Gynecol Oncol* 2007;106:381–387.

51. Higgins RV, Naumann RW, Gardner J, Hall JB. Is age a barrier to the aggressive treatment of ovarian cancer with paclitaxel and carboplatin? *Gynecol Oncol* 1999;75:464–467.

52. Kotani N, Katsumata N, Yonemori K et al. P61 Feasibility, efficacy and toxicity of carboplatin and paclitaxel as a first-line treatment in elderly patients with ovarian cancer. *Crit Rev Oncol Hematol* 2009;72:S40.

53. Bruchim I, Altaras M, Fishman A. Age contrasts in clinical characteristics and pattern of care in patients with epithelial ovarian cancer. *Gynecologic Oncol* 2002;86:274–278.

54. Penson RT, Kornblith B, Lee J, et al. Phase II study of carboplatin and paclitaxel in elderly women with newly diagnosed ovarian, peritoneal, or fallopian tube cancer. *J Clin Oncol* 2008;26(15 suppl):5590.

55. Fader AN, von Gruenigen V, Gibbons H et al. Improved tolerance of primary chemotherapy with reduced-dose carboplatin and paclitaxel in elderly ovarian cancer patients. *Gynecol Oncol* 2008;109:33–38.

56. Furini L, Artioli G, Lombardi G et al. P49 Chemotherapy in older women with ovarian cancer. *Crit Rev Oncol Hematol* 2009;72:S36.

57. Mackay HJ, Brady MF, Oza AM et al. Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer. *Int J Gynecol Cancer* 2010;20:945–952.

58. Bamias A, Psaltopoulou T, Sotiropoulou M et al. Mucinous but not clear cell histology is associated with inferior survival in patients with advanced stage ovarian carcinoma treated with platinum-paclitaxel chemotherapy. *Cancer* 2010;116:1462–1468.

59. Yahata T, Banzai C, Tanaka K. Histology-specific long-term trends in the incidence of ovarian cancer and borderline tumor in Japanese females: A population-based study from 1983 to 2007 in Niigata. *J Obstet Gynaecol Res* 2012;38:645–650.

60. Chan JK, Teoh D, Hu JM et al. Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers. *Gynecol Oncol* 2008;109:370–376.

61. Marchetti DL, Lele SB, Priore RL et al. Treatment of advanced ovarian carcinoma in the elderly. *Gynecol Oncol* 1993;49:86–91.

62. Alberts DS, Dahlberg S, Green SJ et al. Analysis of patient age as an independent prognostic factor for survival in a phase III study of cisplatin-cyclophosphamide versus carboplatin-cyclophosphamide in stages III (suboptimal) and IV ovarian cancer. A Southwest Oncology Group study. *Cancer* 1993;71:618–627.

63. Edmonson JH, Su J, Krook JE. Treatment of ovarian cancer in elderly women. Mayo Clinic-North Central Cancer Treatment Group studies. *Cancer* 1993;71:615–617.

64. Gershenson DM, Mitchell MF, Atkinson N et al. Age contrasts in patients with advanced epithelial ovarian cancer. The MD Anderson Cancer Center experience. *Cancer* 1993;71:638–643.

65. Katsumata N, Yasuda M, Takahashi F et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009;374:1331–1338.

66. Bookman MA, Brady MF, McGuire WP et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: A Phase III Trial of the Gynecologic Cancer Intergroup. *J Clin Oncol* 2009;27:1419–1425.

67. Tew W, Java J, Chi D, et al. Treatment outcomes for older women with advanced ovarian cancer: Results from a phase III clinical trial (GOG182). *J Clin Oncol* 2010;28(15 suppl):5030.

68. Guarneri V, Piacentini F, Barbieri E, Conte PF. Achievements and unmet needs in the management of advanced ovarian cancer. *Gynecol Oncol* 2010;117:152–158.

69. Alberts DS, Liu PY, Hannigan EV et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 1996;335:1950–1955.

70. Armstrong DK, Bundy B, Wenzel L et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006;354:34–43.

71. Markman M, Bundy BN, Alberts DS et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: An intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol* 2001;19:1001–1007.

72. Kothari R, Nagel C, Koopmeiners JS et al. The effect of age on the tolerability of intraperitoneal chemotherapy, complication rate, and survival in patients with ovarian cancer. *Gynecol Oncol* 2010;119:491–495.

73. Tew W, O'Cearbhaill R, Zhou Q et al. Intraperitoneal

chemotherapy (IPC) in older women with epithelial ovarian cancer (EOC). *J Clin Oncol* 2009;27(15 suppl): 5541.

74. Launay-Vacher V, Spano JP, Janus N et al. Renal insufficiency and anticancer drugs in elderly cancer patients: A subgroup analysis of the IRMA study. *Crit Rev Oncol Hematol* 2009;70:124–133.

75. Lichtman SM, Wildiers H, Launay-Vacher V et al. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. *Eur J Cancer* 2007;43:14–34.

76. Lichtman SM, Hollis D, Miller AA 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.

77. Tew WP, Lichtman SM. Ovarian cancer in older women. *Semin Oncol* 2008;35:582–589.

78. Markman M, Bookman MA. Second-line treatment of ovarian cancer. *The Oncologist* 2000;5:26–35.

79. Parmar MK, Ledermann JA, Colombo N et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: The ICON4/AGO-OVAR-2.2 trial. *Lancet* 2003;361:2099–2106.

80. Pfisterer J, Plante M, Vergote I et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: An intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol* 2006;24:4699–4707.

81. Aghajanian C, Blank SV, Goff BA et al. OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012;30:2039–2045.

82. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E et al. Pegylated liposomal Doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol* 2010;28:3323–3329.

83. Kurtz J, Hilpert F, Dorum A, et al. Can elderly patients with recurrent ovarian cancer (ROC) be treated with a platinum-based doublet? Results from the CALYPSO trial. *J Clin Oncol* 2010;28(15 suppl):5031.

84. Monk BJ, Herzog TJ, Kaye SB et al. Trabectedin plus pegylated liposomal Doxorubicin in recurrent ovarian cancer. *J Clin Oncol* 2010;28:3107–3114.

85. Markman M. Pharmaceutical management of ovarian cancer: Current status. *Drugs* 2008;68:771–789.

86. Gronlund B, Høgdall C, Hansen HH, Engelholm SA. Performance status rather than age is the key prognostic factor in second-line treatment of elderly patients with epithelial ovarian carcinoma. *Cancer* 2002;94:1961–1967.

87. Pignata S, Ferrandina G, Scarfone G et al. Poor outcome of elderly patients with platinum-sensitive recurrent ovarian cancer: Results from the SOCRATES retrospective study. *Crit Rev Oncol Hematol* 2009;71:233–241.

88. Orimo H, Ito H, Suzuki T et al. Reviewing the definition of "elderly." *Geriatr Gerontol Int* 2006;6:149–158.

89. Chan JK, Loizzi V, Lin YG et al. Stages III and IV invasive epithelial ovarian carcinoma in younger versus older women: what prognostic factors are important? *Obstet Gynecol* 2003;102:156–161.

90. Cress RD, O'Malley CD, Leiserowitz GS, Campleman SL. Patterns of chemotherapy use for women with ovarian cancer: A population-based study. *J Clin Oncol* 2003;21:1530–1535.

91. Moore KN, Reid MS, Fong DN et al. Ovarian cancer in the octogenarian: Does the paradigm of aggressive

cytoreductive surgery and chemotherapy still apply? *Gynecol Oncol* 2008;110:133–139.

92. Hightower RD, Nguyen HN, Averette HE et al. National survey of ovarian carcinoma. IV: Patterns of care and related survival for older patients. *Cancer* 1994;73:377–383.

93. Walter LC, Covinsky KE. Cancer screening in elderly patients: A framework for individualized decision making. *JAMA* 2001;285:2750–2756.

94. Pentheroudakis G, Fountzilas G, Kalofonos HP et al. Palliative chemotherapy in elderly patients with common metastatic malignancies: A Hellenic Cooperative Oncology Group registry analysis of management, outcome and clinical benefit predictors. *Crit Rev Oncol Hematol* 2008;66:237–247.

95. Uyar D, Frasure HE, Markman M, von Gruenigen VE. Treatment patterns by decade of life in elderly women (≥ 70 years of age) with ovarian cancer. *Gynecol Oncol* 2005;98:403–408.

96. Vilella JA, Chaudhry T, Pearl ML et al. Comparison of tolerance of combination carboplatin and paclitaxel chemotherapy by age in women with ovarian cancer. *Gynecol Oncol* 2002;86:316–322.

97. Repetto L, Fratino L, Audisio RA et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: An Italian Group for Geriatric Oncology Study. *J Clin Oncol* 2002;20:494–502.

98. Monfardini S, Ferrucci L, Fratino L et al. Validation of a multidimensional evaluation scale for use in elderly cancer patients. *Cancer* 1996;77:395–401.

99. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol* 2007;25:1824–1831.

100. Hurria A, Togawa K, Mohile SG et al. Predicting chemotherapy toxicity in older adults with cancer: A prospective multicenter study. *J Clin Oncol* 2011;29:3457–3465.

101. Chaïbi P, Magné N, Breton S, et al. Influence of geriatric consultation with comprehensive geriatric assessment on final therapeutic decision in elderly cancer patients. *Crit Rev Oncol Hematol* 2010;79:302–307.

102. Aaldriks A, Maartense E, le Cessie S, et al. Predictive value of geriatric assessment for patients older than 70 years, treated with chemotherapy. *Crit Rev Oncol Hematol* 2010;79:205–212.

103. Pignata S, Breda E, Scambia G et al. A phase II study of weekly carboplatin and paclitaxel as first-line treatment of elderly patients with advanced ovarian cancer. A Multicentre Italian Trial in Ovarian cancer (MITO-5) study. *Crit Rev Oncol Hematol* 2008;66:229–236.

104. Freyer G, Geay JF, Touzet S 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.

Nudibranch: Arminid

Gar Waterman