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Geriatric Oncology

Chemotherapy for Ovarian Cancer in the Older Adult

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Opinion statement

The treatment of epithelial ovarian cancer in the older adult presents many challenges. The standard of care is cytoreductive surgery with the aim of achieving minimal residual disease. Surgery is then usually followed by six cycles of platinum–taxane chemotherapy. Older patients often have comorbidities which limit treatment choice and increase the risk of major surgical procedures. Platinum-based chemotherapy is generally well tolerated in fit elderly patients but can result in more toxicity in patients of increasing age. Results of a recent randomized trial of neoadjuvant platinum-based chemotherapy vs upfront surgery reveal decreased toxicity and equivalent survival in patients who receive chemotherapy prior to surgery. Treatment strategies to reduce the toxicity of chemotherapy include the use of single agent carboplatin, dose reduction, and weekly scheduling. Comprehensive geriatric assessment (CGA) of older patients prior to treatment may predict for toxicity of therapy and even survival. While comprehensive assessment may be desirable, it is impractical in the clinic. A simplified screening tool to detect geriatric problems and the further need for a formal assessment is more feasible. Prospective clinical trials of therapy in the elderly patient population are needed to guide treatment decisions.

Prognostic factors in patients with epithelial ovarian cancer

- The standard of care for patients with advanced epithelial ovarian cancer is cytoreductive surgery, also known as optimal debulking, and six cycles of platinum–taxane based chemotherapy [1]. Optimal debulking surgery is the strongest independent prognostic factor for survival, and an attempt should be made to offer full cytoreductive surgery to all the patients with advanced epithelial ovarian cancer [2]. Other prognostic factors include initial stage, histologic type, high tumor grade, and the amount of residual disease after debulking surgery. Molecular markers such as the mutations in the excision repair cross-complementation group (ERCC) genes, especially ERCC1 and ERCC5 have been shown to predict for response to platinum therapy and correlate with progression-free and overall survival [3, 4].
- Increased age at diagnosis is also considered a poor prognostic factor [5–13]. The reason for the apparent decrease in survival with

increasing patient age is not clear. Epidemiological studies suggest that elderly patients with advanced ovarian cancer present at a more advanced stage and receive less aggressive surgery [9]. Older patients are less likely to be referred to a gynecological oncologist [14] or a specialist referral center [13]. Increasing age is associated with a decreased likelihood of receiving any form of chemotherapy [7, 15] or of platinum–taxane chemotherapy [16, 17].

- It has been suggested that inferior survival is seen in older patients due to changes in tumor biology and inherent resistance to chemotherapy [18, 19]. This has not been established in clinical trials; however, it is known that older patients have less diagnostic assessment, a higher proportion of tumors with an unknown histology, and inadequate staging procedures [20].

The effect of comorbidity on survival in patients with advanced ovarian cancer

- Elderly patients are more likely to have comorbidities which will influence the type of treatment offered and may have an impact on survival. The effect of comorbidity on prognosis has been explored in population-based analyses from the USA [21], Denmark [22], and Holland [13] with slightly differing results.
- In an effort to clarify the effect of comorbidities on outcome, Janda *et al.* performed a large population-based analysis using the SEER database (from 1992 to 1999 with follow-up to 2002) on a group of 3994 women over the age of 65 years with stage III or IV ovarian cancer [21]. As expected, increasing patient age, FIGO stage IV, and the presence of comorbidities were associated with decreased survival at 12 months. In addition, survival was lower in patients treated outside large treatment facilities. A risk score based on patient age and the number of comorbidities was derived and applied to a validation data set. Patients were divided into low-, medium-, or high-risk groups based on this score.
- The Janda risk score needs to be validated prospectively before widespread application, but analysis of outcome according to patient comorbidity, stage, and treatment facility allowed a better prediction of survival at 12 months than that based on age alone. One-year survival for patients in the low-risk group who received surgery and chemotherapy was 89% with a median survival of 37 months (range 34–40) regardless of age. In contrast, patients with multiple comorbidities had a 1-year survival of 62% and median survival of 18 months even if they were treated with both modalities. Patients over the age of 80 years without comorbidity were allocated into the low-risk group and had a median survival of 23 months if they received both surgery and chemotherapy. The study found 38 patients over the age of 85 who received both therapeutic modalities and demonstrated a 1-year survival of 63% (median survival 22 months—range 12–33).
- The comprehensive database of all the patients treated in Denmark between 1995 and 2005 was used to describe the outcome of treatment for ovarian cancer based on comorbidities and tumor stage [22]. The Charlson comorbidity index [23] was applied to a cohort of 5213 patients with ovarian cancer over the age of 15 years. Out of these, 3727 (72%) had no comorbidity recorded, 1116 (21%) had a Charlson score 1–2, and 370 (7%) had a Charlson score 3+. This study found a higher prevalence of comorbidity in patients with an advanced stage of ovarian cancer. The 1- and 5-year

mortality was almost double in patients with severe comorbidity compared to those without registered comorbidity, even after adjustment for stage [22].

- These findings are contradicted by the results of an earlier and smaller study from Holland [13]. Using a dataset of 1116 patients with epithelial ovarian cancer, increased age, FIGO stage, and presence of comorbidity were independent predictors of failure to receive combined treatment with surgery and chemotherapy. The presence of comorbidities was not an independent prognostic factor; however, increasing age and treatment with surgery and platinum-based chemotherapy did predict survival.

Implications for undertreatment of elderly patients

- The consequences of undertreatment have been analyzed in a number of retrospective studies in women with ovarian cancer [20]. Most such trials conclude that undertreatment could explain the poorer prognosis of elderly women with this disease [9, 13, 16, 24, 25]. The reason for the difference in prognosis is multifactorial however, it has been documented that undertreated women with ovarian cancer do have a poorer prognosis. As most studies are retrospective and observational, the magnitude of the effect of undertreatment is difficult to quantify [20] but older patients are at especially at risk given the prevalence of age bias in the medical community.

Chemotherapy in older adults with ovarian cancer

First line

- Chemotherapy significantly prolongs survival in patients with advanced epithelial ovarian cancer [26]. Despite many years of searching for an improvement, the standard regimen remains a platinum–taxane combination. The doublet of carboplatin (area under the curve (AUC) = 5–7.5) and paclitaxel (175 mg/m^2 over 3 hours), both given 3 weekly for a total of 6 cycles, remains the standard arm of phase III clinical trials in 2009.
- Clinical trials specific to the elderly population have mostly been small prospective phase II trials or retrospective analyses. There are no published large randomized trials of chemotherapy in older women with ovarian cancer. The main reason for this is that carboplatin and paclitaxel is generally well tolerated and has established efficacy in older patients [27]. Despite the relative tolerability of carboplatin and paclitaxel, a significant proportion of elderly patients do not receive combination chemotherapy [7]. The reasons for this are multifactorial including patient choice, presence of comorbidities, physician age-bias, and failure to regain fitness after initial cytoreductive surgery. Alternative strategies to improve the tolerability of first-line chemotherapy include giving single agent carboplatin [28, 29], reducing the dose [30], and giving treatment in a weekly schedule [31].
- Carboplatin remains the backbone of any first line therapy if one considers the results of the ICON3 trial [29]. In this trial, 2074 patients were randomized to either the control arm (platinum therapy without a taxane) or to the combination of carboplatin and paclitaxel. As 948 patients were randomized to receive single agent carboplatin, this remains one of the largest trials ever conducted in this patient population. The study concluded that single-agent carboplatin and the combination of cyclophosphamide, doxorubicin and cisplatin (CAP)

are as effective as paclitaxel plus carboplatin as first-line treatment for women requiring chemotherapy for ovarian cancer. Given the fact that treatment with carboplatin alone results in significantly less toxicity than combination therapy it is logical that this regimen is an acceptable first-line strategy in women with comorbidities or of advanced age. However, the ICON3 study was not a trial conducted in an elderly patient population. Only 29% (n = 591) of patients were over the age of 65 and the median age of all patients was 58.9 years. Thus, as is the case with all large studies in this patient group it is difficult to generalize the results to elderly patients. Despite this, single agent carboplatin has been advocated as the treatment of choice by some authors [28] and it remains the "alternative" treatment with the least toxicity and with the most evidence to justify its use.

- The addition of paclitaxel to carboplatin is considered the standard of care but also significantly adds toxicity such as alopecia and peripheral neuropathy. There is prospective trial evidence that the clearance of paclitaxel decreases with increasing age and that this causes increased hematological toxicity [32]. However, this increased hematological toxicity did not lead to an increase in clinically significant adverse events.
- The reduction of the dose of 3 weekly carboplatin and paclitaxel on the basis of increased age is a strategy that is employed by some medical oncologists despite the lack of clinical trial evidence. In a multicenter retrospective analysis of 100 patients over the age of 70 years who received either standard dose therapy (carboplatin AUC 5–6 and paclitaxel 175 mg/m^2) or reduced-dose treatment (carboplatin AUC 4–5 and paclitaxel = 135 mg/m^2) investigators failed to find a difference in progression-free or overall survival [30]. Multivariate analysis revealed that only the administration of standard dose therapy predicted increased toxicity despite the performance status being worse in the standard dose cohort. This study can only be considered preliminary and requires prospective confirmation but it may provide some evidence for a dose reduction strategy in our more frail patients.
- Delivering both carboplatin and paclitaxel in a weekly schedule has been studied in phase II clinical trials. In a small series of 26 patients with ovarian cancer over the age of 70 years, carboplatin (AUC = 2) and paclitaxel (60 mg/m^2) were given weekly for 3 weeks in a 28 day cycle [31]. Despite a high incidence of comorbidities in this patient population, the toxicities were relatively mild. Only two patients (8%) reported peripheral neuropathy. Unfortunately the response rate in this trial was disappointing as only 5 of 13 patients (38.5%) with measurable disease gained a partial response. The median overall survival was 32 months. Other investigators have studied the weekly schedule in patients of all ages. In a large phase II trial 129 patients (mean age 59 years) were given weekly carboplatin (AUC = 2) and paclitaxel (100 mg/m^2) [33]. Response rates were comparable to the 3 weekly regimen as the Ca125 response rate was 78% and objective response rate in patients with measurable disease was 55%. Despite the relatively high dose of paclitaxel, the rate of peripheral neuropathy appeared to be modest (Grade 3 = 2.3%), but the weekly regimen caused significant hematological toxicity [33].
- The administration of "dose dense" weekly paclitaxel (80 mg/m^2) in conjunction with 3 weekly carboplatin (AUC = 6) was reported in a randomized phase III trial of over 630 patients by Isonishi and colleagues in abstract form at the American Society of Clinical Oncology (ASCO) annual scientific meeting in 2008 [34]. In comparison with

3 weekly carboplatin and paclitaxel (180 mg/m^2), weekly paclitaxel treatment appeared to result in a significant improvement in progression-free survival (PFS). The suggested benefit in overall survival at 2 years (83.6% vs 77.7% P = 0.05) remains to be confirmed. This seemed to come at the cost of higher hematological toxicity; specifically anaemia. There was no statistically significant difference in the rates of motor or sensory neuropathy between the two arms. The median age of the patients in this study was 57 years (range 25–87) [34]. These results appear tantalizing and require validation before being applied in the general patient population however, given that weekly paclitaxel is now the schedule of choice in patients with breast cancer, this regimen may have merit and should be studied in future clinical trials.

- Despite the desire to improve tolerability, a number of retrospective analyses have suggested that the combination of carboplatin and paclitaxel remains the treatment of choice in women over the age of 65 [27] or 70 [35, 36] who have undergone cytoreductive surgery. The most recent of these reviews involved 292 patients with stage IIIc or IV disease, all of whom were fit enough to undergo debulking surgery. The cohort of women over the age of 65 (n = 108 (37%)) did not exhibit an increased rate of toxicity however the starting dose of carboplatin was reduced more commonly in this age group [27]. Despite this, there was no significant difference in response rate, platinum sensitivity at 6 months, progression free or overall survival in the older patient group.

Elderly patients, renal function and the dose of carboplatin

- Carboplatin is completely excreted by the kidneys. As glomerular filtration rate (GFR) declines with increasing age, it is vital to estimate the GFR in all patients prior to using drugs which are renally excreted [37, 38]. The dose of carboplatin is either obtained using the Calvert formula [39] or the Chatelut equation [40]. When the Calvert formula is used, the patient's creatinine clearance (CrCl) can be estimated using a formula based on the serum creatinine. The most commonly used formulae are the Cockcroft–Gault [41] and the Jelliffe [42] formulae. The Jelliffe formula has been adopted for use by the Gynecological Oncology Group (GOG) in clinical trials. This formula was derived from 128 observations in 15 patients after renal transplantation and was intended as a quick bedside estimate. A feature of this formula is that the patient's height and weight are not required, however it yields an estimate of "standardized" CrCl in mL/min/1.73 m^2 and technically should be "uncorrected" to give a result in mL/min. The Wright [43] formula was derived in a population of cancer patients and has been found to be more accurate and precise in an elderly population [44]. Use of these equations allows for the individualization of dose, enables the prediction of toxicities and renders carboplatin a relatively safe drug to use in elderly patients.

Intraperitoneal chemotherapy

- The publication of the GOG 0172 trial by Armstrong and colleagues [45] led to an increased interest in intraperitoneal chemotherapy. The demonstration of a survival benefit in comparison with intravenous

platinum–paclitaxel has increased the use of intraperitoneal chemotherapy in patients who have been optimally cytoreduced. The median age of patients in the GOG 172 trial was not reported but only 13% of patients who received IP chemotherapy were over the age of 70 years. Less than 50% of patients of any age were able to complete the IP therapy due to toxicity. The principle toxicities related to complications with the catheter however, significantly more patients in the intraperitoneal-therapy group had grade 3 or 4 fatigue, pain, or hematologic, gastrointestinal, metabolic, or neurologic toxic effects [45]. While it is important not to deny elderly patients optimal therapy, the toxicity of the published IP regimen has led to variations being used in clinical practice. Further studies using IP carboplatin in place of cisplatin will need to be performed and toxicity in the elderly measured before this regimen is widely adopted in older women with ovarian cancer [46].

Neoadjuvant chemotherapy

- The term "neoadjuvant" was first used in 1982 by Emil Frei III in his Karnofsky lecture [47] at the American Society of Clinical Oncology meeting. It was used to describe chemotherapy given prior to definitive therapy. The aim of neoadjuvant therapy is to "ensure early treatment of micrometastases: and/or regression of the primary tumor to a size (stage) where surgical resection is more effective" [47].
- Arguments in support of neoadjuvant chemotherapy for ovarian cancer include
  - Increased rate of "optimal" cytoreduction
  - Less extensive surgery
  - Less blood loss, lower morbidity, decreased hospital stay
  - Ability to select patients with platinum-resistant disease
  - Decreased tumor bulk in truly inoperable patients
  - Chemotherapy is an effective treatment for malignant bowel obstruction.
- The evidence regarding the use of neoadjuvant chemotherapy has been based on retrospective case series and metaanalyses. Until recently, there have been no randomized clinical trials of this approach.
- The Cochrane systematic review [48] published in 2007 was able to find only one randomized clinical trial in the literature of neoadjuvant chemotherapy in ovarian cancer [49]. This trial involved the use of intraarterial cisplatin and ovarian artery embolization in a small number of patients and its results are not applicable to the general patient population.
- The much-awaited EORTC/NCIC-CTG 55971 trial has recently been presented [50]. This trial randomized 718 women to either upfront debulking surgery or three cycles of carboplatin and paclitaxel chemotherapy prior to "interval" debulking surgery (IDS). The primary endpoint was overall survival. The trial was powered to demonstrate non-inferiority. With a median follow up of 4.8 years, the trial demonstrated that neoadjuvant chemotherapy yielded equivalent progression-free survival (12 months vs 12 months; HR for IDS = 0.99 (0.87–1.13)). Overall survival was also equivalent (29 months vs 30 months (HR for IDS 0.98 (0.85–1.14)).

- Importantly, neoadjuvant chemotherapy prior to surgery resulted in a significant decrease in toxicity. The immediate postoperative mortality (<28 days) was 2.7% in the upfront surgery arm vs 0.6% in the neoadjuvant chemotherapy arm. There were less postoperative complications in patients who received neoadjuvant therapy.
- Given the lower morbidity and equivalent survival, the principal investigator, Ignace Vergote concluded that "neoadjuvant chemotherapy can be considered as the preferred treatment in patients with stage IIIc and IV epithelial ovarian cancer".
- Neoadjuvant chemotherapy is a strategy that is often employed in patients who may be deemed unfit for upfront surgery such as the elderly or patients with comorbidities. The population of patients in the EORTC 55971 trial were all deemed fit enough for surgical debulking. The median age of the patients in the study was 62 years (range 25–86 years) including 151 patients (21%) over the age of 70 years.
- This study did not directly address the issue of the best treatment in the very old (patients over the age of 80 years). A number of retrospective studies have reported that the routine use of up front debulking surgery in patients over the age of 80 results in unacceptable morbidity and mortality [21, 51, 52]. Given the reduced rate of postoperative complications in the neoadjuvant chemotherapy arm of the EORTC 55971 trial, the mantra that upfront surgery should be offered to all patients can now be challenged. Use of neoadjuvant platinum-based therapy can be considered a reasonable option in elderly patients with stage IIIC and IV ovarian cancer.

Second-line therapy

- Despite the impressive initial response rate with platinum-based chemotherapy, most patients with epithelial ovarian cancer will relapse and die from their disease. Patients who relapse less than 6 months after first line chemotherapy are considered platinum resistant. Patients are usually rechallenged with platinum therapy if they relapse after 6 months. Randomized trials have confirmed that treatment with carboplatin in combination with either paclitaxel [53] or gemcitabine [54] improves outcomes in comparison with carboplatin alone. The ICON4 trial [53] demonstrated an improvement in overall survival in patients who were treated with carboplatin and paclitaxel. Over 75% of patients on this study had relapsed more than 12 months after initial chemotherapy, and the median age of patients was only 60 years. The combination of gemcitabine and carboplatin resulted in an improvement in progression-free survival but not overall survival in a patient population of whom 40% had relapsed between 6 and 12 months [54]. The median age in this study was 58 years. Results from the recently completed CALYPSO trial of carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel are awaited.
- The decision to use combination chemotherapy in an elderly patient with potentially platinum-sensitive disease is therefore based on clinical trial data from younger patients. In most patients, the presence of comorbidity and the toxicity profile of the planned treatment will determine which palliative chemotherapy regimen is appropriate. In patients with multiple comorbidities, single-agent carboplatin may give palliative benefit. Fit patients with lingering peripheral neuropathy should be given the option of treatment with gemcitabine and carboplatin. The combination of carboplatin and paclitaxel remains an option in patients without significant neuropathy.

- Immediately after the disease becomes platinum resistant, single-agent chemotherapy is most often employed. The drugs with a demonstrated response rate include pegylated liposomal doxorubicin [55], topotecan [55, 56], gemcitabine [57], weekly paclitaxel [58], and oral etoposide [59]. Pegylated liposomal doxorubicin (PLD) is often the first choice in this setting as it has proven efficacy and relatively mild toxicity. The main side effect of this drug is cutaneous palmar–plantar erythrodysesthesia. Despite containing doxorubicin, there is no evidence that cardiac toxicity occurs with prolonged use. A number of authors have described use of this drug for protracted courses with no evidence of cardiac damage [60–62]. O'Brien *et al*. reported a randomized clinical trial of PLD vs conventional doxorubicin as first-line therapy in 509 women with metastatic breast cancer [63]. The use of conventional doxorubicin was associated with a significantly increased risk of cardiac toxicity as defined by a decrease in ejection fraction (LVEF) of ≥20% if the resting LVEF remained in the normal range, or ≥10% if the LVEF became abnormal. Forty-eight patients (18%) who received conventional doxorubicin experienced a cardiac event by these criteria. Although 10 patients (4%) who received PLD did experience a decrease in ejection fraction, no patient experienced symptoms of cardiac failure. Ten patients (4%) who received conventional doxorubicin developed symptomatic cardiac failure. None of the 78 patients aged over 65 years, who received PLD, experienced a decrease in ejection fraction. The mean decrease in LVEF in the patients who received PLD was 3% [63].
- While there is little evidence to support the use of PLD in patients with preexisting cardiac disease, this drug is relatively safe in elderly patients and is probably the best initial treatment option for patients with platinum resistant disease. Topotecan is sometimes used after PLD but has an increased toxicity profile. The weekly schedule of topotecan has not been formally studied in phase III clinical trials, but there is a suggestion from phase II data that this schedule is more tolerable than when the drug is given over 5 days once a month [56].
- Gemcitabine as a single agent has demonstrated activity and relatively low toxicity and is therefore another treatment option in patients who progress after receiving PLD. This drug is well tolerated in the elderly population, but myelotoxicity may be more common in this population.
- In all patients with relapsed disease, any treatment is palliative, and enhancing quality of life becomes the principal objective. Care must be taken not to cause harm. This is especially important in the elderly patient population. There is no published evidence to support the treatment of asymptomatic patients with rising tumor markers. This may be especially important in the elderly patient in whom the prevention of toxicity is important.

Comprehensive geriatric assessment

- The holistic management of elderly patients with cancer requires assessment of the various issues which may have an impact on treatment choice and tolerability of therapy. The comprehensive geriatric assessment (CGA) takes into account patients' comorbidities, mobility, cognitive function, the ability to perform activities of daily living, and psychological and nutritional status, and monitors for

polypharmacy and records social functioning and supports. While a CGA may be desirable in all elderly patients, it is considered to be impractical and time consuming in a busy oncology clinic [19]. A screening test or abbreviated assessment such as the Vulnerable Elders Survey [64] (VES-13) is, therefore, a recommended option for older patients if it is followed by a comprehensive assessment when problems are uncovered. However, the CGA is only useful if the clinical service has the ability to intervene when elderly-specific problems are found.

- The results of a CGA performed prior to treatment may predict for toxicity or even survival [65]. In a prospective study performed in 83 patients with ovarian cancer all over the age of 70 years, the presence of depression, FIGO stage IV disease, or the use of more than six prescription medications per day were independent predictors of decreased survival [65]. All the patients received combination chemotherapy with carboplatin and cyclophosphamide. Significant toxicities were more likely in patients with depression at baseline, dependence in activities of daily living, and poor-performance status (≥2). The incorporation of CGA in clinical trials will lead to a better understanding of the effects of treatment on elderly patients with ovarian cancer.

Future treatment options

- The incorporation of antiangiogenic molecules such as bevacizumab into chemotherapy regimens is becoming standard of care in the treatment of patients with solid tumors such as colorectal cancer. The randomized trials using bevacizumab in women with ovarian cancer are ongoing, and its use cannot be recommended outside of a clinical trial. Caution must be taken prior to the use of antiangiogenic therapy in elderly patients as there is the suggestion of increased toxicity such as thromboembolic events [66].

Summary

- The successful treatment of older women with ovarian cancer depends on adequate assessment of comorbidities and use of appropriate chemotherapy. While the use of standard therapy is justified in the fit elderly, modifications to treatment are possible in patients who are deemed to be frail or unlikely to tolerate full dose therapy. The use of neoadjuvant therapy prior to definitive surgery has been shown to reduce the overall toxicity of therapy in women with advanced disease and is now a justifiable approach in elderly patients. Clinical trials of therapy in older adults incorporating comprehensive geriatric assessment will educate us more about this increasingly common patient group.

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