Ovarian Cancer in Elderly Women

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By Nicholas C. Lambrou, MD and Robert E. Bristow, MD

The incidence of ovarian carcinoma increases with advancing age, peaking during the 7th decade of life and remaining elevated until age 80 years. Despite the high prevalence of ovarian cancer in the elderly, the management of these patients is often less aggressive than that of their younger counterparts. As a result, many elderly cancer patients receive inadequate treatment. However, data do not support the concept that age, per se, is a negative prognostic factor. In fact, the majority of elderly patients are able to tolerate the standard of care for ovarian cancer including initial surgical cytoreduction followed by platinum and taxane chemotherapy. Because functional status has not demonstrated a reliable correlation with either tumor stage or comorbidity, each patient’s comorbidities should be assessed independently. For elderly patients with significant medical comorbidity, the extent of surgery and aggressiveness of chemotherapy should be tailored to the extent of disease, symptoms, overall health, and life goals. In addition, enhanced cooperation between geriatricians and oncologists may assist the pretreatment assessment of elderly patients and improve treatment guidelines in this population.

ABSTRACT: The incidence of ovarian carcinoma increases with advancing age, peaking during the 7th decade of life and remaining elevated until age 80 years. Despite the high prevalence of ovarian cancer in the elderly, the management of these patients is often less aggressive than that of their younger counterparts. As a result, many elderly cancer patients receive inadequate treatment. However, data do not support the concept that age, per se, is a negative prognostic factor. In fact, the majority of elderly patients are able to tolerate the standard of care for ovarian cancer including initial surgical cytoreduction followed by platinum and taxane chemotherapy. Because functional status has not demonstrated a reliable correlation with either tumor stage or comorbidity, each patient’s comorbidities should be assessed independently. For elderly patients with significant medical comorbidity, the extent of surgery and aggressiveness of chemotherapy should be tailored to the extent of disease, symptoms, overall health, and life goals. In addition, enhanced cooperation between geriatricians and oncologists may assist the pretreatment assessment of elderly patients and improve treatment guidelines in this population.

Dramatic improvements in health care and a decrease in mortality have resulted in an increase in life expectancy among people living in developed countries. In Western countries, a woman's life expectancy was 81.1 years in 1991 and is expected to reach 90.4 years by 2020.[1,2] As a result, the number of cancer-bearing patients aged 70 years and older may also be expected to increase.[3-5] The incidence of ovarian carcinoma rises with advancing age, peaks during the 7th decade of life, and remains elevated until age 80 years. Malignant ovarian neoplasms manifest after age 65 in 30% to 40% of patients.[6,7] Despite the high prevalence of this disease in the elderly, the management of these patients is often less aggressive than that of their younger counterparts, with the result being that many elderly patients receive inadequate treatment.[8-12]

Standard Management for Ovarian Cancer

Approximately 75% of patients with epithelial ovarian cancer are diagnosed when their disease has spread throughout the peritoneal cavity. Most commonly, patients will present with abdominal discomfort or pain. This is generally followed closely by abdominal distention due to the presence of intra-abdominal masses and/or malignant ascites. Gastrointestinal symptoms are nonspecific but include nausea, early satiety, constipation or obstipation, and, less frequently, urinary symptoms.[13] If disease has progressed to involve the lungs by the presence of pulmonary metastases or malignant pleural effusions, the patient may complain of shortness of breath and lethargy.

Staging
TABLE 1

FIGO Staging for Carcinoma of the Ovary

The 5-year survival of patients with epithelial ovarian cancer correlates directly with tumor stage. The International Federation of Gynecology and Obstetrics (FIGO) staging system, revised in 1985, is presented in Table 1. With the exception of stage IV disease, which can be diagnosed by a cytologically positive pleural fluid, computed tomography-guided biopsy of intraparenchymal liver lesions, or other pathologic evidence of distant spread, the stage of disease is only accurately determined by an exploratory surgical assessment (ie, laparotomy or laparoscopy). Laparotomy should be performed through a vertical midline incision to allow access to the upper abdomen. Peritoneal lavage or aspiration of ascites is performed to obtain specimens for cytologic analysis. Suspicious areas throughout the abdomen and pelvis, including adhesions, should be biopsied with separate specimens obtained from the pelvis, right and left paracolic gutters, and the undersurfaces of the right and left hemidiaphragms. All intestinal surfaces should be evaluated, and an omentectomy with random peritoneal biopsies should be performed. Pelvic and aortic lymph node sampling is also required.

When the staging is thorough and methodical, a significant number of patients initially thought to have localized disease will be upstaged. In a report by Young and colleagues,[14] 31% of women thought to have stage I or II disease at initial surgery were upstaged at repeat surgical staging. Of these patients, 77% were upstaged to stage III. In a report by McGowan et al,[15] gynecologic oncologists performed adequate surgical staging in 97% of cases, compared to 52% of cases for obstetrician/gynecologists and 35% of cases for general surgeons. In this report, 46% of the 291 women evaluated, had been inadequately staged.

Surgical Cytoreduction

In addition to the prognostic importance of accurate staging, surgical cytoreduction (or debulking) has proven to be an integral component in the management of epithelial ovarian cancer. The volume of residual disease following cytoreductive surgery is inversely related to survival.[16-19] Current criteria for optimal cytoreduction imply residual tumor nodules no greater than 1 cm in diameter. Patients who have undergone optimal cytoreduction have approximately a 22-month median survival advantage compared to patients with suboptimal cytoreduction (residual disease > 1 cm in maximum diameter). Hoskins and colleagues analyzed data from the Gynecologic Oncology Group and noted a significant improvement in survival among patients with 1- to 2- cm residual disease compared to those with greater than 2-cm residual disease.[20] In addition to the survival benefits of cytoreductive surgery, recent reports also confirm that aggressive primary cytoreductions are associated with minimal morbidity and mortality when performed by experienced surgeons.[21] Most studies supporting the survival benefit of cytoreductive surgery have enrolled patients with both stage III and IV disease. Four recent retrospective reports have examined cytoreductive surgery separately in patients with stage IV disease and have consistently demonstrated a statistically significant improvement in survival when a small volume of residual disease remains.[22-24]

Chemotherapy

Surgery alone rarely produces cure in ovarian cancer patients. Chemotherapy agents from a wide variety of classes have demonstrated activity against ovarian cancer. With the establishment of platinum-based therapy and the introduction of the taxanes, the past 2 decades have seen dramatic improvements in response to chemotherapy and progression-free survival. Paclitaxel was reported to have significant activity in advanced ovarian carcinoma in 1989.[25] After a series of phase I and II trials established the activity of paclitaxel, two prospective randomized
trials comparing cisplatin plus paclitaxel vs cisplatin plus cyclophosphamide (Cytoxan, Neosar) demonstrated the superiority of the paclitaxel-containing regimen.[26,27] Subsequent prospective randomized trials compared paclitaxel/carboplatin (Paraplatin) vs paclitaxel/cisplatin, demonstrating decreased toxicity with the carboplatin regimen and no difference in efficacy.[28,29] With these results, paclitaxel plus carboplatin is now considered first-line treatment for most patients with advanced ovarian cancer.

Patterns of Care

In one of the earliest published reports to examine patterns of care among elderly patients with ovarian cancer, Ries[11] analyzed data for over 22,000 women diagnosed between 1973 and 1987 within the Surveillance, Epidemiology, and End Results (SEER) program. When stratified by stage, age was a significant determinant of survival. The 5-year survival rate for women less than age 45 was 45%, compared to 8% for those age 85 and over. Over 40% of women over 85 did not receive definitive treatment for their disease. In addition, when treatment was given, younger women received multimodality therapy more often than did their older counterparts, who received more single-modality treatments such as surgery, chemotherapy, or hormonal therapy alone. Further evidence that older women received less aggressive therapy and had poorer survival rates was published in 1994. Hightower and colleagues[12] analyzed data from the American College of Surgeons Cancer Commission to investigate differences in patterns of care among the elderly. This study compared survival and care in two patient groups—those age 80 or older vs those under 80. Of 12,316 patients diagnosed between 1983 and 1988, 1,115 were at least 80 years old. Survival was significantly lower among patients in the older group. Most elderly ovarian cancer patients were cared for by nononcologists such as general surgeons (31%) and obstetrician/gynecologists (29%). They also received fewer total abdominal hysterectomies, bilateral salpingo-oophorectomies, and omentectomies than their younger counterparts. Optimal tumor debulking rates were significantly lower for women age 80 or older, and these patients were less likely than younger patients to be given adjuvant chemotherapy (42% vs 69%, P < .0001).

Trial Enrollment

It was recently reported that, although 60% of cancers arise in people over age 65, only 20% to 40% of these patients are enrolled in phase II and III trials, and the majority of patients in these trials are less than age 70.[30,31] Markman et al.[32] reported on the Memorial Sloan-Kettering Cancer Center experience regarding enrollment of women with ovarian cancer into clinical trials after primary surgical therapy. A total of 46% of the younger patients were entered into an intensive initial chemotherapy trial, compared to 17% of older patients. The reported reason for the lower enrollment of older patients was an excessive prevalence of comorbid conditions such as heart disease. In addition, the rate of referrals to this institution for both initial treatment and salvage therapy was fourfold higher among younger women compared to their older counterparts. This observation suggests that older patients are less likely to be referred for secondary experimental programs. Recent reports have also demonstrated that older women with ovarian cancer are less likely to receive the standard recommended treatment[33] or be seen by a gynecologic oncologist in the course of their treatment.[34] Carney and colleagues[34] conducted a statewide population-based study in Utah between 1992 and 1998. Among the 848 cases of epithelial ovarian cancer identified, fewer than 25% of women over age 70 were seen by a gynecologic oncologist, compared to 55% of women aged 40 to 59 and 42.6% of those aged 60 to 69. In the same study, patients with advanced disease experienced a significant survival advantage when a gynecologic oncologist was involved in their care.

Surgery

Although several studies have reported that elderly patients undergo proportionally fewer surgeries and less aggressive surgery for primary treatment of ovarian cancer than their younger counterparts,[35,36] few data exist on the influence of age itself on surgical outcomes. Several large trials have shown that healthy elderly patients tolerate most oncologic treatments as well as younger patients,[30,37] despite the widely held belief that elderly patients cannot tolerate radical surgical intervention. One should also consider that the elderly patients in these studies may have been selected on the basis of performance status, age, and the absence of serious medical illnesses, and may not be representative of the elderly population at large.
In a recent series by Cloven et al.,[35] 16 of 18 ovarian cancer patients under age 80 underwent primary debulking surgery. In 25% of patients, tumors were optimally cytoreduced, and 38% experienced major postoperative morbidity. In addition, 75% spent time in the intensive care unit, but the majority were discharged home and received postoperative chemotherapy. Most patients in this group had one or more preexisting medical illnesses and an advanced American Society of Anesthesiologists (ASA) score.

In another recent report by Bruchim and colleagues,[36] patients with epithelial ovarian cancer were retrospectively reviewed and stratified according to age (< 70 or ≥ 70). The more elderly group of patients underwent fewer primary debulking surgeries and were more likely to receive neoadjuvant chemotherapy. However, age did not appear to be a limiting factor in achieving optimal debulking among those who did undergo surgery. Nearly 92% of the younger patients were entered into a first-line chemotherapy protocol, compared to 65% of the older patients. Notably, hematologic toxicity was more severe among the elderly patients who received chemotherapy.

**Chemotherapy**

Cooperative trials have shown that healthy elderly patients can tolerate most chemotherapy regimens as well as their younger counterparts. However, this observation may not necessarily apply to the subset of elderly patients with significant medical comorbidity. A recent review by Ceccaroni et al.,[5] suggests that a multidimensional geriatric evaluation may be useful in selecting elderly patients for chemotherapy. Similarly, Monfardini et al.[38] have published the Multidimensional Assessment of Cancer in the Elderly (MACE) comprehensive geriatric assessment (CGA) scale and have proposed its use in clinical trials. TABLE 2

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**Assessment of Aging**

Repetto and colleagues[39] recently published a review describing a clinical approach to the geriatric oncology patient. Table 2 summarizes the variety of current methods used to assess the effects of aging.[39] It is evident that many parameters may be used to assess elderly patients and that the majority of these are nonspecific. Cooperation between geriatricians and oncologists is a potential strategy to improve the pretreatment assessment.

In elderly patients, several pharmacodynamic changes may increase the toxicity and decrease the efficacy of cytotoxic treatments. Molecular changes associated with age that may lead to a higher prevalence of drug resistance include a reduction in the tumor growth rate and a resistance to apoptosis.[5,40-42] Theoretically, a reduction in lean body mass and an increase in body fat may occur with age, which can influence drug distribution. However, to date, no significant correlation has been found between age and drug clearance, dose, or toxicity.[5] Several studies have
demonstrated that despite an age-related decrease in patient's creatinine clearance of many drugs, total clearance does not change. This may be due to an increase in hepatic clearance.[5,43,44]

**Toxicity**

The most commonly encountered chemotherapy-related toxicity is myelotoxicity, which may occur more frequently in the elderly. An Eastern Cooperative Oncology Group review showed that commonly used chemotherapeutic agents (for nine disease sites) were significantly more myelotoxic in patients over age 70 than in those under 70.[45] However, the increased toxicity appeared to be mostly limited to methotrexate and semustine (methyl-CCNU). In the Mayo Clinic experience involving women with ovarian cancer in phase III trials, progressively larger dose reductions were required for continuation of treatment with advancing age; however, chemotherapy was generally well tolerated across all age groups.[37]

In a recent review of advanced ovarian cancer in the elderly by Chiara et al.[46] no significant difference in toxicity was evident between patients less than or greater than age 65 treated with cisplatin-based chemotherapy. Interruption of chemotherapy due to toxicity, however, was more frequent among the elderly. Thyss et al.[47] demonstrated that cisplatin can be safely administered (at doses ranging from 60 to 100 mg/m²) without excessive toxicity in patients over 80 with normal renal function.

In a recent Italian trial, carboplatin (230 mg/m² every 28 days) was administered intravenously with mitoxantrone (Novantrone) to 82 ovarian cancer patients who were greater than age 70 and was well tolerated.[48] Similar data in the setting of second-line treatment have shown no difference in toxicity between patients 65 years of age and their younger counterparts.[49]

### Italian Multicenter Trial

The largest study of chemotherapy tolerance in elderly oncology patients evaluated women with gynecologic malignancies treated between 1990 and 2000 in four Italian centers.[1] The median age of the 148 patients reviewed was 73 years (range: 70 to 84 yr), and 37% were greater than age 75. Nearly 70% were treated for ovarian cancer. One or more comorbid conditions were present in nearly 80% of patients. Of the patients who received first-line chemotherapy, 96 (64.9%) received a platinum-based regimen with no taxane (group 1), 42 (28.4%) received combined platinum/ paclitaxel regimens (group 2), and 10 (6.8%) received a taxane-based regimen with no platinum (group 3).

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<th>Grade 3/4 Toxicity Observed in Gynecologic Oncology Patients Aged 70 Years and Older During First-Line Chemotherapy</th>
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Table 3 summarizes the toxicity data stratified according to the type of first-line chemotherapy administered.[1] No significant differences in performance status before, during, and at the completion of first-line chemotherapy were observed. Of the 103 ovarian cancer patients, 74 (71.9%) received combination chemotherapy, and 38 (36.9%) received first-line treatment with a platinum and taxanes. Grade 3/4 hematologic toxicities were reported in 38.2% of patients, and 6.8% of the patients discontinued treatment due to toxicity. No significant association was seen between the number of comorbidities and toxicities.

This study confirms previous reports, which indicate that elderly patients with adequate renal and hepatic function tolerate standard chemotherapy regimens with equivalent toxicity profiles and no significant difference in treatment delays or discontinuations.[37,49-51]

### Summary

The most commonly encountered chemotherapy-related toxicity is myelotoxicity, which may occur more frequently in the elderly. An Eastern Cooperative Oncology Group review showed that commonly used chemotherapeutic agents (for nine disease sites) were significantly more myelotoxic in patients over age 70 than in those under 70.[45] However, the increased toxicity appeared to be mostly limited to methotrexate and semustine (methyl-CCNU). In the Mayo Clinic experience involving women with ovarian cancer in phase III trials, progressively larger dose reductions were required for continuation of treatment with advancing age; however, chemotherapy was generally well tolerated across all age groups.

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This study confirms previous reports, which indicate that elderly patients with adequate renal and hepatic function tolerate standard chemotherapy regimens with equivalent toxicity profiles and no significant difference in treatment delays or discontinuations.[37,49-51]
The treatment of elderly ovarian cancer patients should be individualized. Data do not support the premise that age, per se, is a negative prognostic factor. In fact, the majority of elderly patients are able to tolerate the standard of care for ovarian cancer including initial surgical cytoreduction followed by platinum and taxane chemotherapy. Because functional status does not demonstrate a reliable correlation with either tumor stage or comorbidity, each patient’s comorbidities should be assessed independently. For elderly patients with significant medical comorbidity, the extent of surgery and the aggressiveness of chemotherapy should be tailored to the individual’s extent of disease, symptoms, overall health, and life goals. Few clinical trials are specifically designed for older patients, and the number of elderly patients referred to existing trials is limited. A concerted effort should be made to enter older persons into treatment protocols. In addition, enhanced cooperation between geriatricians and oncologists may aid the pretreatment assessment of elderly patients and improve treatment guidelines in this population.

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