Treating Older Patients With Ovarian Cancer: Another Perspective

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Dr. Piver presents a personal look at the issues he believes to be important in managing ovarian carcinoma in the elderly patient. He begins with an attempt to define elderly. His treatise then focuses on two major issues: the role of surgery in both early- and late-stage disease and the role of chemotherapy in the elderly patient. He then concludes with a suggested algorithm for decision-making in the elderly population. This commentary will look at each of these four areas.

Defining ‘Elderly’

With regard to the first of these topics, Dr. Piver is correct that the definition of elderly has evolved over time to the point where only those patients over the age of 70 are now considered to be elderly. Since 1990, however, data suggest that this definition is no longer adequate for purposes of informing treatment decision-making.[1,2]

An extensive examination of the age issue at a symposium sponsored by the National Institute on Aging in 1992 suggested that chronologic age is not an appropriate marker for patients that require an alteration in the standard approach to management of ovarian carcinoma. Cooperative group data on ovarian carcinoma demonstrated a marked drop in survival rates by decade of life as one goes from patients in their 30s to patients over the age of 70. The same data suggested, however, that the drop in survival rates correlated best with the tendency of physicians to use less aggressive therapy in older patients. The data further showed that older patients with no major comorbid conditions and good performance status tolerated treatment as well as and survived at similar rates to their younger counterparts with similar histologies and cellular differentiation. These observations argue for a treatment approach based on performance status and comorbid conditions rather than chronologic age per se. A subsequent prospective study of age and ovarian carcinoma by the Gynecologic Oncology Group confirms these observations.[3]

Role of Surgery

In his discussion of the role of surgery, Dr. Piver first addresses the importance of surgical staging in the patient with presumed stage I disease. This was evaluated in depth in a prospective surgical staging study of limited disease by the Ovarian Cancer Study Group (OCSS) and the Gynecologic Oncology Group (GOG) in the 1970s and 1980s.[4] By using careful surgical staging to eliminate patients who actually had microscopic or macroscopic disease outside the pelvis (stage III/IV disease) and by assessing relevant histopathologic features of the cancers, the OCSS and the GOG were able to categorize patients with stage I or II disease into those at low risk for recurrence (all of the following features: grade 1 or 2, no disease on the surface of the ovary, no disease outside the ovary, negative peritoneal cytology, and no ascites) and those at high risk for recurrence (any one of the following features: grade 3, disease on the surface of the ovary, disease outside of the ovary, positive peritoneal cytology, or ascites).

Those at low risk for recurrence have a recurrence rate of approximately 10% and, in general, have been managed with surgical resection and careful surgical staging followed by observation. Those at high risk for recurrence exhibit a recurrence rate of approximately 40% and demonstrate a significant decrease in recurrence rate with platinum-based adjuvant chemotherapy.[5,6] These observations in prospective trials support Dr. Piver’s contention that careful surgical staging is crucial to proper treatment decision-making in patients with limited-stage ovarian carcinoma. The role of surgery in patients with advanced disease is now established by a large number of retrospective studies as well as at least three prospective randomized trials. Retrospective data
strongly support the importance of surgical bulk reduction and, in particular, achievement of microscopic residual disease only.[7,8] Two prospective phase III trials of interval surgical bulk reduction after three cycles of chemotherapy show the importance of one but not two efforts at aggressive surgical bulk reduction in each patient.[9,10] More recently, the results of a randomized phase III comparison of upfront bulk reduction followed by chemotherapy vs neoadjuvant chemotherapy followed by bulk reduction show that the two approaches yield similar results.[11] The overall weight of evidence strongly supports the importance of aggressive bulk reduction at some point during the management of patients with advanced ovarian carcinoma. The theoretical rationale for bulk reduction argues in favor of upfront surgical cytoreduction (removal of resistant clones of cells and removal of large masses to which delivery of adequate drug via the intravascular compartment would be difficult).[12] Dr. Piver’s contention that bulk reduction is important is thus supported by the weight of evidence in the literature. His one further point that bulk reduction is best carried out by a trained gynecologic oncologist is supported by much higher rates of successful bulk reduction observed in patients who have their procedure done by a gynecologic oncologist.[13]

**Role of Chemotherapy**

With regard to the third topic, the role of chemotherapy, the most recent consensus conference of the Gynecologic Cancer Intergroup (GCIG) involving 13 international cooperative groups working with ovarian carcinoma unanimously defined the current standard of care for patients with advanced ovarian carcinoma to which any new approach must be compared as follows: an aggressive attempt at surgical bulk reduction followed by six cycles of paclitaxel/carboplatin.[13] Dr. Piver states that this standard was established by publication of the results of GOG Protocol 111 (by McGuire et al in 1996)[14] and has not changed since. This is incorrect. Dr. McGuire’s results were confirmed in 1997 by a second trial from a European/Canadian consortium,[15] which established the combination of paclitaxel/cisplatin as the evidence-based standard of care. It wasn’t until 7 years later that data were published to show that paclitaxel/carboplatin was in fact equivalent to paclitaxel/cisplatin and, because of a superior therapeutic index, was the appropriate standard of care.[16,17] Paclitaxel/carboplatin has thus been the evidence-based standard of care only since 2003, although it has been by far the most widely used regimen for advanced ovarian carcinoma since 1996.

While intraperitoneal chemotherapy was declared the standard of care for patients with small-volume residual advanced ovarian carcinoma in a Clinical Alert issued by the National Cancer Institute in January of 2006,[18] this approach has not been widely adopted outside of academic centers because of toxicity that prompted even the Clinical Alert authors to state that none of the tested intraperitoneal regimens could be recommended for routine clinical use. Dr. Piver’s statement to this effect is thus right on target. Dr. Piver’s most significant omission in the discussion of systemic therapy was his failure to address the emerging potential role of targeted or biologic agents in ovarian carcinoma. To date, despite phase II testing of a large number of these agents, only one has emerged as highly active and thus potentially a part of therapy for newly diagnosed disease. That agent is bevacizumab (Avastin), a monoclonal antibody directed against vascular endothelial growth factor (VEGF), which has shown substantial activity in recurrent ovarian carcinoma.[19] Bevacizumab is currently being evaluated in both newly diagnosed advanced disease and in patients with platinum-sensitive recurrent disease in four randomized phase III trials that should define the role, if any, of this agent. It is virtually certain that continued evaluation of targeted agents in ovarian carcinoma will add other targeted drugs to the list of agents to be tested in newly diagnosed disease.

**Treatment Decision-Making**

With regard to his final topic, Dr. Piver recommends an algorithm for treatment decision-making in ovarian carcinoma based on the comprehensive geriatric assessment (CGA). In short, he recommends treating with standard therapy in patients over age 70 who have a good performance status (GOG PS 0, 1, and selected 2) and no significant comorbid conditions. This is in essence what the symposium in 1992 recommended and is again right on target.

For patients with poorer performance status (most PS 2s as well as selected PS 3s) leading to dependence in their activities of daily living and/or significant comorbid conditions, he would modify the surgery to be less aggressive in the effort to achieve small-volume residual disease. For patients with even poorer performance status or with severe comorbidities, he recommends less aggressive chemotherapy or supportive care only. All of these recommendations fall in line with the concept that older patients in good shape should be treated without regard to their chronologic age—a
Final Thought

One final point is worth airing. Many physicians regard combination chemotherapy to be substantially more toxic than single-agent therapy and use this observation as a reason to use single-agent carboplatin in older patients with ovarian carcinoma regardless of performance status and comorbidities. Interestingly, the combination of paclitaxel/carboplatin may be the exception to this rule. While the doublet produces more neurotoxicity than single-agent carboplatin, it causes substantially less grade 3/4 myelosuppression, with all the associated risks.[20,21] It is clear that the doublet is more effective than single-agent carboplatin, and in the absence of substantially greater toxicity, the doublet should be considered the regimen of choice even in the elderly if they have no significant neuropathy from other causes.

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