

# Advances in the Antineoplastic Drug Management of Ovarian Cancer

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## Abstract

Despite recognized improvement in the survival and quality of life for patients with advanced ovarian cancer, over the past two decades there have been very few new antineoplastic agents specifically introduced for the management of this malignancy. An important exception to this otherwise most unfortunate situation is the demonstrated clinical activity of bevacizumab when delivered with standard cytotoxic chemotherapy in the primary, recurrent, platinum-sensitive, and platinum-resistant settings.

## Introduction

This review will briefly highlight relatively recent advances in the systemic management of ovarian cancer, with a specific focus on commercially available agents (in the United States) and data from phase III randomized trials. For those not well versed in ovarian cancer management or aware of the history of drug development in this area, what will be most evident is the rather striking paucity of new drugs or strategies introduced into routine clinical practice over the past decade. The status of data in this area is even more striking when one considers the rather substantial number of innovative agents introduced into the management of a variety of solid tumors and hematologic malignancies over the past 5 to 10 years.

In fact, from the perspective of an impact on overall survival (OS; still considered by some to be the only appropriate endpoint for drug registration purposes), the last “major” antineoplastic drug advance in ovarian cancer was the introduction of paclitaxel into the primary systemic management of the malignancy. The initial evidence-based trial to report a survival advantage associated with the substitution of paclitaxel for cyclophosphamide appeared in the peer-reviewed literature in 1996, 18 years ago.<sup>1</sup>

It is critical to note here that over this extended period of time there have been other highly clinically relevant chemotherapeutic advances in the management of ovarian cancer, but these have resulted from a modification in the strategy for delivery of an existing antineoplastic agent or from the use of an agent in the same class, rather than the introduction of a novel drug (Table 1).<sup>2,7</sup>

In addition, while one additional antineoplastic agent, pegylated liposomal doxorubicin (PLD), has been approved for second-line use in ovarian cancer based on evidence of an OS advantage compared with topotecan when employed as second-

line treatment, a strong argument can be advanced that this conclusion represents an unfortunate misinterpretation of the study results (Table 2).<sup>8,9</sup> In fact, the impact on OS observed in this trial in favor of PLD was substantially greater than the impact on progression-free survival (PFS). This suggests that a much higher percentage of individuals treated with PLD compared with topotecan likely received carboplatin following the completion of this study. Since topotecan is more myelosuppressive than PLD, fewer patients were able to get adequate doses of salvage carboplatin following topotecan—which may explain the OS benefit from PLD that was out of proportion to the PFS benefit associated with PLD.

**TABLE 1. Chemotherapeutic Advances in Ovarian Cancer Resulting From Modification in Delivery of an Established Class of Antineoplastic Agents**

1. Substitution of carboplatin for cisplatin (reduced toxicity, <i>no impact on survival</i> ) <sup>2</sup>
2. Intraperitoneal administration of cisplatin ( <i>improved OS</i> ) <sup>3</sup>
3. Use of an alternative taxane (docetaxel versus paclitaxel; change in toxicity profile; <i>no impact on survival</i> ) <sup>4</sup>
4. Weekly delivery of paclitaxel ( <i>improved OS, reduced toxicity, or both</i> ) <sup>5,6</sup>
5. Delivery of platinum-based chemotherapy (neoadjuvant) prior to definitive surgery (reduced surgery-related morbidity in selected patients; <i>no impact on survival</i> ) <sup>7</sup>

*OS = overall survival.*

## PFS Versus OS as a Primary Outcome in Ovarian Cancer Studies

With the availability of an increasing number of antineoplastic agents with demonstrated biological and clinical activity in ovarian cancer (even if not approved by the drug regulatory agencies for this clinical indication), there has been considerable discussion in the gynecologic cancer literature regarding the most appropriate endpoint for clinical studies in advanced, recurrent, or

resistant disease. It is well recognized that the large majority of patients with ovarian cancer (at least in the United States) receive multiple agents during the natural history of their disease process. This results from well-considered knowledge by oncologists of the unquestionable utility of a rather large number of commercially available antineoplastic agents with biological and clinical activity (based on data published in the peer-reviewed oncology literature) when employed as a second-line treatment approach in ovarian cancer.<sup>8-16</sup>

Further, existing theoretical evidence strongly supports the argument that it will be extremely difficult to demonstrate a statistically significant improvement in OS in any clinical setting when there is an anticipated prolonged, uncontrolled (as regards the approaches utilized in individual study patients) post-trial survival, and where a number of useful strategies are potentially available.<sup>17</sup>

### Current Noninvestigational Antineoplastic Drug Strategies Demonstrating Improved PFS in Advanced Ovarian Cancer

In any setting where an alternative endpoint to OS (eg, PFS) is utilized for regulatory approval, it will be critical to consider whether that endpoint is associated with meaningful clinical benefit. For example, an evaluation of the utility associated with extending the time until progression of signs or symptoms of the cancer is documented will need to consider both the toxicity of the program and the impact of the strategy on a patient's quality of life.

Recognizing the ongoing debate regarding study endpoints in ovarian cancer, it is important to acknowledge a number of trials that have revealed an improvement in PFS associated with the addition of an antineoplastic agent (other than a platinum agent or a taxane) in the management of ovarian cancer (Table 2).<sup>8-21</sup>

Few would argue with the observation that the most impressive recent results with the chemotherapeutic management of ovarian cancer have come from the introduction of antiangiogenic agents into approaches for disease management.<sup>18-21</sup> A total of four phase III randomized trials have been reported employing bevacizumab as a component of primary therapy<sup>18,19</sup> or for management of recurrent potentially platinum-sensitive<sup>20</sup> and platinum-resistant disease (Table 2).<sup>21</sup> In each of these trials, there was a statistically significant improvement in PFS, but not OS.

As previously discussed, the failure to convert a favorable impact on PFS into an OS benefit is not unexpected. Unfortunately, in the current environment of the drug regulatory world, this result likely means the agent will not be approved for use in ovar-

**TABLE 2. Commercially Available Antineoplastic Agents Demonstrating Improved Survival (PFS or OS) in Ovarian Cancer in Phase III Randomized Trials**

Agent	Comparator	Setting	Outcome
Cisplatin + paclitaxel <sup>1</sup>	Cisplatin + cyclophosphamide	Primary treatment of advanced ovarian cancer	Improved PFS and OS
Pegylated liposomal doxorubicin <sup>8,9</sup>	Topotecan	Platinum-resistant and recurrent platinum-sensitive ovarian cancer	Improved PFS and OS
Gemcitabine + carboplatin <sup>10</sup>	Single-agent carboplatin	Recurrent platinum-sensitive ovarian cancer	Improved PFS only
Platinum-paclitaxel therapy <sup>11</sup>	Non-paclitaxel-containing platinum-based therapy	Recurrent platinum-sensitive ovarian cancer	Improved PFS and OS
Carboplatin + pegylated liposomal doxorubicin <sup>12</sup>	Carboplatin + paclitaxel	Recurrent platinum-sensitive ovarian cancer	Improved PFS only
Paclitaxel maintenance therapy <sup>13,14</sup>		Following the attainment of a clinical complete response to primary platinum-paclitaxel chemotherapy	Improved PFS only
Bevacizumab <sup>18-21</sup>		Employed as a component of a regimen in primary, recurrent platinum-sensitive, and resistant ovarian cancer	Improved PFS only

PFS = progression-free survival; OS = overall survival.

ian cancer, although based on the impressive observed impact of bevacizumab on PFS, the drug is widely included in ovarian cancer treatment guidelines. Particularly noteworthy is the favorable impact on PFS associated with adding bevacizumab to one of several standard cytotoxic chemotherapeutic drugs in platinum-resistant disease, a setting where there had been no prior phase III trial data to demonstrate that any particular investigational strategy could improve a survival outcome.<sup>21</sup>

It is relevant to acknowledge that the optimal utilization of bevacizumab in the management of ovarian cancer remains to be defined. Further, it is uncertain whether the agent might appropriately be employed as a component of several different regimens during the clinical course of treatment for an individual patient. Finally, the role of maintenance bevacizumab following the attainment of a clinical response in a number of settings is an open question that will hopefully be addressed in future clinical trials.

## Conclusion

While substantial progress in the management of ovarian cancer has been made over the past several decades,<sup>22</sup> including improvement in both survival and quality of life, there has been a most unfortunate paucity of new agents introduced specifically for treatment of this difficult illness. Hopefully, this situation will change in the relatively near future as data strongly support the clinical utility of additional novel agents in well-defined settings (eg, olaparib as second-line maintenance therapy).<sup>23,24</sup>

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**Disclosure:** Dr. Markman has been a consultant or a member of a paid advisory board for Amgen Inc., Celgene Corporation, Caris Life Sciences, Ltd, Novartis Corporation, sanofi-aventis U.S., LLC., Takeda Pharmaceutical Company, Limited, and Genentech, Inc.

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