PARP Inhibitor Olaparib in BRCA-Deficient Advanced Ovarian Cancer
CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting more than 30,000 attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Summarize the efficacy and relative safety of two doses of olaparib monotherapy for patients with ovarian cancer and confirmed BRCA1 or BRCA2 mutations.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Deborah K Armstrong, MD
Associate Professor of Oncology
Associate Professor of Gynecology and Obstetrics
The Sidney Kimmel Comprehensive Cancer Center
The Johns Hopkins University
Baltimore, Maryland
Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology.

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Last review date: August 2009
Expiration date: August 2010
Click to go directly to our slides on gem/cisplatin in cervical cancer and three papers on ovarian cancer — earlier diagnosis with CA125, liposomal doxorubicin/carboplatin, and olaparib in patients with BRCA mutations.

I wonder if current medical oncology fellows know the strange and pretty sad history of chemotherapy? Do they realize that a generation or more of currently practicing oncologists were weaned on theoretical reasons why we just had to optimize the dose and schedule of chemo to eradicate this cruel disease?

There was a time when testicular cancer was the shining example of how to end the cancer problem, but thirty or more years later, not too many other chemo cures have shown up. Today we have personalized medicine — “molecular-targeted biologic therapy” or whatever you choose to call the current search for agents and regimens that provide solutions like imatinib in CML ... or is CML the new testicular cancer, and will we again find years from now that the catastrophe that is cancer has not abated?

The four ASCO gyn-onc papers profiled in this issue of 5MJC are emblematic of the current mix of old concepts and “new” ideas that defines the state of affairs in oncology research.

We begin with a rare gynecologic-oncology ASCO plenary paper demonstrating no benefit from earlier first-line chemo using CA125 screening for the 80 percent of patients with disease progression after surgery and chemo for primary ovarian cancer. The related massive current investment in adjuvant therapy of solid tumors (particularly but not restricted to breast, lung and colorectal cancer) represents perhaps one third of current medical oncology office visits, a sobering thought when one considers that most — perhaps two thirds or more — of the patients are deriving absolutely no benefit from treatment while experiencing not-inconsequential toxicity.

While this CA125 paper has critical clinical implications, it also is another example of the failed theories of legendary chemo/mouse investigators like Skipper and Schnabel and maybe a few current research icons.

The next two studies are examples of lame duck chemo alphabet comparison trials, in one case demonstrating a modest benefit from adding gemcitabine to cisplatin with radiation therapy for locally advanced cervical cancer, and in the other showing equal or greater efficacy of the combination of liposomal doxorubicin and carboplatin compared
to paclitaxel/carboplatin. While both these trials also have clinical relevance, neither is close to being a magic bullet story.

This brings us once again to PARP inhibition, and the oral agent olaparib that we profiled in the first issue of this series in an encouraging ASCO report on patients with advanced breast cancer and BRCA germline mutations. This related paper focuses on patients with ovarian cancer and BRCA, and again impressive antitumor activity is reported.

While this quartet of studies seems to portend a changing of the guard not only in gynecologic-oncology but also in solid tumors in general, I wonder if it also represents more of the same in that, conceptually, “molecular-targeted therapy,” like chemo, is an attempt at differential cytotoxicity, albeit with perhaps cleaner, safer and more effective agents. If we continue to put most of our eggs in this antimicrobial model, in 20 years will we once again find disappointment and more hospice care for our patients?

Please take our 30-second survey and voice your opinion, and click here for our slides and Dr Deborah Armstrong’s commentary on gem/cisplatin in cervical cancer, and three papers on ovarian cancer — earlier diagnosis with CA125, liposomal doxorubicin/carboplatin, and olaparib in patients with BRCA mutations.

Next up, for our final post-ASCO journal club, four GI cancer studies: one on gemcitabine with or without cisplatin for biliary cancer, two on oxaliplatin as part of neoadjuvant chemoradiation treatment of rectal cancer and a Memorial report on nonsurgical management for patients presenting with primary colorectal cancer and metastatic disease.

Neil Love, MD
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PARP Inhibitor Olaparib in BRCA-Deficient Advanced Ovarian Cancer

Presentation discussed in this issue:


Slides from the presentation and excerpts from a related interview with Deborah K Armstrong, MD (June 18, 2009)

Phase II Trial of the Oral PARP Inhibitor Olaparib (AZD2281) in BRCA-Deficient Advanced Ovarian Cancer

Audeh MW et al.

ASCO 2009; Abstract 5500. (Clinical Science Symposium)
**Introduction**

- Poly(ADP-ribose) polymerase (PARP) is a key regulator of the DNA damage repair process
- BRCA1/2-deficient cells are highly sensitive to PARP inhibition
- Olaparib is a novel, orally active PARP inhibitor
  - 400 mg BID identified as the maximum tolerated dose (Yap et al. ASCO 2007)
  - Phase I ORR (RECIST) = 28% in BRCA-mutated ovarian cancer (Fong et al. ASCO 2008)

**Current study objectives:**

- Evaluate the objective response rate (ORR), progression-free survival (PFS) and safety of single-agent olaparib 400 mg BID and 100 mg BID in patients with BRCA1 or 2 mutations who have recurrent ovarian cancer whose disease has progressed on at least one prior platinum-based chemotherapy

Source: Audeh MW et al. ASCO 2009; Abstract 5500.
**Mechanism of Cell Death from Synthetic Lethality Induced by PARP Inhibition**

- **A Normal Cells**
  - Base-excision repair
  - Homologous recombination
  - PARP1, BRCA
  - Repair

- **B Cells with BRCA Mutation**
  - Base-excision repair
  - Homologous recombination
  - PARP1, BRCA
  - Repair

- **C Cells with Drug-Induced PARP1 Inhibition**
  - Base-excision repair
  - Homologous recombination
  - PARP1, BRCA
  - Cancer drug
  - PARP1
  - BRCA
  - Repair

- **D Cells with BRCA Mutation and PARP1 Inhibition**
  - Base-excision repair
  - Homologous recombination
  - PARP1, BRCA
  - Cancer drug
  - PARP1
  - BRCA
  - No repair
  - Cell death

In normal cells, both base-excision repair (BER) and homologous recombination (HR) are available for the repair of damaged DNA (A). In cells that have lost either BRCA1 or BRCA2, HR is nonfunctional, and BER and other DNA-repair processes can compensate for the loss of HR (B). In cells that have lost BER function because of PARP1 inhibition but retain at least one functioning copy of BRCA1 and BRCA2, HR is intact and can repair DNA damage, including damage left unrepaired because of the loss of BER (C). In the cancer cells of mutation carriers, all BRCA1 or BRCA2 function is absent, and when PARP1 is inhibited, cancer cells are unable to repair DNA damage by HR or BER, and cell death results.

Source: With permission from Iglehart JD, Silver DP. NEJM 2009; 361(2):189-91. Copyright © 2009 Massachusetts Medical Society. All rights reserved.

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**Phase II Open-Label Single-Arm, Multi-Cohort Study**

**Cohort 1**
- Olaparib 400 mg BID (MTD) 28 day cycles
- (n = 33)

**Cohort 2**
- Olaparib 100 mg BID 28 day cycles
- (n = 24)

**Eligibility**
- Recurrent (Stage IIIB/C or IV) ovarian cancer after failure of ≥ 1 platinum-based chemotherapy
- Confirmed BRCA1 or 2 mutation

MTD = maximum tolerated dose (determined during Phase I evaluation)

Source: Audeh MW et al. ASCO 2009; Abstract 5500.
### Efficacy: Intent-to-Treat Analysis

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Olaparib 400 mg BID (n = 33)</th>
<th>Olaparib 100 mg BID (n = 24)</th>
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</thead>
<tbody>
<tr>
<td>Overall response rate (ORR) by RECIST</td>
<td>33%</td>
<td>13%</td>
</tr>
<tr>
<td>Complete response</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Partial response</td>
<td>27%</td>
<td>13%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>33%</td>
<td>29%</td>
</tr>
<tr>
<td>ORR by RECIST and/or GCIG criteria (≥50% reduction in CA-125)</td>
<td>61%</td>
<td>17%</td>
</tr>
<tr>
<td>ORR by platinum-sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum-sensitive (400mg n=7; 100mg n=8)</td>
<td>14%</td>
<td>25%</td>
</tr>
<tr>
<td>Platinum-resistant (400mg n=26; 100mg n=16)</td>
<td>38%</td>
<td>6%</td>
</tr>
<tr>
<td>Duration of response (DOR)*</td>
<td>290 days</td>
<td>269 days</td>
</tr>
<tr>
<td>Progression-free survival (median)</td>
<td>5.8 mos</td>
<td>1.9 mos</td>
</tr>
</tbody>
</table>

* DOR is underestimated, since some patients are still responding

Source: Audeh MW et al. ASCO 2009; Abstract 5500.

### Safety: Most Frequently Reported Adverse Events (AEs)*

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Olaparib 400 mg BID (n = 33)</th>
<th>Olaparib 100 mg BID (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>64%</td>
<td>63%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>52%</td>
<td>54%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37%</td>
<td>29%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33%</td>
<td>25%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>27%</td>
<td>17%</td>
</tr>
</tbody>
</table>

**Dose adjustments and discontinuations due to AEs**

<table>
<thead>
<tr>
<th>Event</th>
<th>Olaparib 400 mg BID (n = 33)</th>
<th>Olaparib 100 mg BID (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>Dose interruption</td>
<td>36%</td>
<td>17%</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>27%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* ≥ 25% reported in either cohort

Source: Audeh MW et al. ASCO 2009; Abstract 5500.
DEBORAH K ARMSTRONG, MD: There clearly is a lot of interest in using PARP inhibitors in ovarian cancer. We know that approximately 10 percent of ovarian cancer cases are related to germ-line BRCA mutations, and the BRCA proteins are important in repairing double-strand DNA damage. The PARP inhibitors actually inhibit single-strand DNA repair mechanisms, which are really the backup when the double-strand repair mechanisms don’t work. So interest has arisen in using them, for example, in combination with chemotherapy for patients with BRCA-deficient ovarian cancer.

Surprisingly, we have seen that these PARP inhibitors are active when used as single agents. That tells me that enough genetic changes occur in advanced cancer, including ovarian cancer, that they’re probably undergoing spontaneous DNA breaks at a fairly rapid rate and that normally these are repaired. By blocking the repair of these DNA breaks, you create some anticancer activity.

In the study reported by Audeh and colleagues, they used olaparib alone. They began with a dose of 400 milligrams BID. Preclinical data and other clinical trials suggested that pretty good inhibition could be achieved with 100 milligrams BID, so they added that dose to the trial as well. They actually saw responses — two out of 33 patients with CRs and nine out of 33 with PRs at the 400-mg BID dose. They saw more activity at the 400-mg BID dose, so that’s probably the one that they will take forward in clinical trials.
**DR LOVE:** It looked on their waterfall plot like most of the patients actually had some objective signs of tumor regression.

**DR ARMSTRONG:** Yes. Between two thirds and three quarters of the patients had some decline in CA125 levels. The take-home message is that the PARP inhibitors are active by themselves in patients with BRCA-associated ovarian cancer, and may work even better when used in combination with agents that damage DNA — and remember, that’s a phenomenon that’s almost exclusive to cancer cells, because normal cells still have functioning BRCA protein — thus selective toxicity for the cancer cell.

Dr Armstrong is Associate Professor of Oncology as well as Associate Professor of Gynecology and Obstetrics at The Johns Hopkins University’s Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland.