Editorial Commentary

Demethylating agent as a platinum sensitizer in platinum-resistant ovarian cancer

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We have read Dr. Oza and colleagues' paper recently published with great interest (1). Given the fact that recurrence with acquired chemoresistance, so called platinum-resistant recurrence, accounts for the most of mortality in high-grade serous ovarian cancer (HGSOC), many researchers have been focusing on these resistant mechanisms on a molecular level and clinical trials have been conducted for these patients' population. However, the results were disappointing and there still are unmet needs for new treatments in patients with platinum-resistant HGSOC. Amid this challenging clinical scenario, the clinical trial done by Dr. Oza and colleagues gives us an evidence that targeting DNA methylation to restore platinum sensitivity may be a promising option in the treatment of patients with platinum resistant recurrent HGSOC.

Guadecitabine is a next-generation hypomethylating agent with a longer exposure time compared to previous ones such as azacitidine and decitabine (2). By demethylating certain tumor suppressor genes and reverting its decreased expression, the authors hypothesized that this hypomethylating agent would re-sensitize platinum-resistant ovarian cancer cells to carboplatin through the induction of apoptosis. This hypothesis was supported by preclinical research, which showed the treatment of platinum-resistant ovarian cancer xenografts with hypomethylating agents reversed the resistant phenotype (3). In the clinical trial by Dr. Oza and his colleagues, the progression-free survival (PFS) was longer in the experimental arm (guadecitabine + carboplatin q 28 days) than the conventional arm (single agent chemotherapy q 28 days, cross-over was allowed) showing 16.2 *vs.* 9.1 weeks (P=0.07), but it did not reach statistical significance, which means failure to meet the primary endpoint. Nevertheless, the 6-month PFS rate was significantly higher in the experimental arm than the conventional arm (37% *vs.* 11%, P=0.003). Adverse events were similar in both arms. Hypomethylating activity with guadecitabine was measured in peripheral blood mononuclear cells showing significantly decreased methylation of *MEGE-A2* and *MEAGE-A3*, but not for the tumor suppressor genes including *BRCA1*. As the authors mentioned, one could argue regarding the lack of single carboplatin control arm in the study design, the administration of conventional chemotherapy every 28 days rather than 21 days, and the schedule of topotecan administration. Nevertheless, the results are quite supporting the potential role of guadecitabine as a chemosensitizer in patients with heavily pretreated platinum resistant HGSOC.

It has been demonstrated that hypermethylation occurs in epithelial ovarian cancer and is associated with increasing stage, grade and mortality (4). Compared with normal ovarian surface epithelium, benign ovarian tumors, and borderline ovarian tumors, this aberrant methylation

of multiple CpG loci is more frequently observed in epithelial ovarian cancer (5). The patterns of altered DNA methylation in epithelial ovarian cancer were shown to be different across histology especially in regards to DNA hypermethylation as opposed to hypomethylation. For example, a report demonstrated that the incidence of global hypermethylation pattern was only in 1% of HGSOC which was lower than those of high grade endometrioid (16%) or clear cell carcinoma (71%) of the ovary. It therefore suggests that the lack of hypermethylation may be one of the HGSOC epigenetic features (6,7). There also was inconsistency in genes whose expressions were reduced by hypermethylation in HGSOC (8,9). Despite the aforementioned varying observations, numerous studies suggested that demethylating agents may reverse platinum sensitivity in platinum resistant HGSOC since DNA methylation changes were reported to play a role in driving acquired resistance to chemotherapy in epithelial ovarian cancer, regardless of histologic subtypes (10-12). This clinical trial partly demonstrated the proof of concept showing the 6-month PFS increased in patients with guadecitabine plus carboplatin compared with those treated with conventional single agent chemotherapy in platinum resistant HGSOC. The initial inclusion criteria of the study included patients with high grade endometrioid and clear cell carcinoma. However, only the patients with high grade serous histology were evaluated at the end. Therefore it remains unknown what the role of epigenetic priming with guadecitabine is in these different histology during either primary or recurrent treatment. The results of this trial warrant further studies with well-defined subgroups of patients with more precise predictive biomarkers.

Hypermethylation of the promoter regions of certain tumor suppressor genes may lead to gene silencing and inactivation of pathways such as DNA mismatch repair like the hypermethylation of *MLH1* in hereditary non-polyposis colorectal cancer (HNPCC) (13). In epithelial ovarian cancer, *BRCA1* promoter methylation is known as an important somatic driver in up to 11% of HGSOC (14). It was also reported that a patient with HGSOC who had had extensive promoter methylation and low *BRCA1* expression lost *BRCA1* methylation at the time of platinum resistant recurrence demonstrating the loss of *BRCA1* promoter as one of the molecular events associated with acquired resistance in HGSOC (9). Even though the authors did not find any loss of methylation in tumor suppressor genes including *BRCA1* in their study, there still remains a concern about the potential harmful effects of hypomethylating agents which may enhance resistance to chemotherapy by reducing methylation of tumor suppressor genes, especially for BRCA1. Furthermore, mutation of the *BRCA1/2* genes has been associated with good response to platinum-based chemotherapy (15), whereas reversion mutation at *BRCA2* is associated with platinum resistance (16). Methylation of the *FANCF* gene has also been associated with increased sensitivity to cisplatin. Accordingly, treatment with decitabine in cell line models led to demethylation of the *FANCF* gene and reduced sensitivity towards cisplatin (17). We agree the needs for identifying predictive biomarkers for patient selection as the authors said and the methylation patterns on specific genes may give an idea to solve this problem.

It was mentioned previously by the authors that demethylation of certain tumor suppressor genes may not be the sole consequence of the administration of hypomethylating agents. There are other possible mechanisms facilitated by hypomethylating agents with intricate network of regulatory effects. An important observation from previous studies relates to eliciting immune response pathways in ovarian tumors by guadecitabine. Studies have demonstrated that hypomethylating agents induced immune signaling in cancer cells by augmenting the viral response pathway and inducing re-expression of endogenous retroviral genes incorporated in the human genome, suggesting that other immunogenic pathways are also regulated epigenetically (18). These observations suggest that epigenetic modulators may serve as potent primers for immune-directed therapy. Understanding the effects of hypomethylating agents on these intricate relations of different mechanisms may be demanding but is an inevitable step towards the utilization of hypomethylating agents in cancer treatment.

As the authors noted in their report, the AURELIA trial demonstrated statistically significant improvement in PFS (HR, 0.48; 95% CI, 0.38 to 0.60) with the addition of bevacizumab to chemotherapy for platinum-resistant ovarian cancer (19). PFS benefit was seen consistently across all subgroups, providing robust evidence for the therapeutic effects of bevacizumab. The combination regimen of chemotherapy with bevacizumab has now been adopted as the standard treatment for platinum-resistant ovarian cancer patients. Consequently, it is unavoidable to ask whether the combination of hypomethylating agents with platinum-based chemotherapy surpasses the clinical efficacy of chemotherapy plus bevacizumab regimen. Performing comparative assessment of the clinical efficacy

of the two regimens remains a crucial assignment for future researchers. It is also important to evaluate the efficacy of the combination of hypomethylating agents with carboplatin against that of carboplatin alone, which was not included in the control arm of this study.

Hypomethylating agents such as azacitidine, decitabine and guadecitabine have been used to express genes silenced by DNA methylation, and have been used with success in patients with acute myeloid leukemia and other malignancies (20). The effects of these agents in epithelial ovarian cancer patients have also been investigated in an effort to provide solution for drug resistance. Such work has been worth the effort since the results from numerous preclinical studies provided optimistic results. However, the exact mechanisms and effects of those agents on epigenetic changes that occur in ovarian carcinogenesis still remain to be explored, highlighting the need for further studies with larger sample numbers and specific patient population groups. The comparative assessment of the effects of those agents against the current standard regimens in platinum-resistant ovarian cancer patients should also be performed.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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