

Review article

Epigenetic therapy for the treatment of epithelial ovarian cancer: A clinical review



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ABSTRACT

Despite a good initial response to chemotherapy, the majority of patients with epithelial ovarian cancer will eventually recur and die of their disease. The introduction of targeted therapies to traditional chemotherapy regimens has done little to improve overall survival in women with ovarian cancer. It has become increasingly apparent that the cancer epigenome contributes significantly to the pathogenesis of ovarian cancer and may play an important role in cell proliferation, metastasis, chemoresistance, and immune tolerance. Epigenetic therapies such as DNA methyltransferase inhibitors and histone deacetylase inhibitors have the potential to reverse these epigenetic changes; however, more research is needed to determine how to incorporate these agents into clinical practice. In this review, we discuss the common epigenetic changes that occur in epithelial ovarian cancer, the current epigenetic therapies that may target these changes, and the clinical experience with epigenetic therapy for the treatment of epithelial ovarian cancer.

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1. Introduction

With an estimated 22,280 new cases of ovarian cancer and 14,240 deaths projected in 2016, ovarian cancer remains the fifth-leading cause of cancer death in women (Siegel et al., 2016). While the majority of patients respond to primary platinum and taxane-based

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chemotherapy, recurrence rates are high with over 75% of patients ultimately relapsing (Ozols et al., 2003). Advances in cytotoxic chemotherapy and development of novel targeted therapies such as the poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors have improved progression-free survival (PFS) but have failed to significantly impact overall survival (OS) (Armstrong et al., 2006; Ledermann et al., 2012). As long-term prognosis for patients with epithelial ovarian cancer remains poor, there is a need for development of new therapies to augment or replace traditional cytotoxic chemotherapies. One such area of therapeutic potential involves the use of epigenetic therapy.

While germline and somatic mutations in tumor suppressor genes such as *BRCA1/2* have long been implicated in the development of ovarian cancer (Welch & King, 2001), it has become increasingly apparent that epigenetic changes also play a critical role. Epigenetic changes alter gene expression without affecting the underlying DNA sequence. The two most widely affected epigenetic pathways in cancer are DNA methylation and histone modification (Dawson & Kouzarides, 2012).

2. DNA methylation

DNA methylation occurs at the carbon-5 position of cytosine residues, usually in cytosine-phosphate-guanine (CpG) dinucleotide sequences, and inhibits gene transcription (Fig. 1). The process of DNA methylation is regulated by a family of enzymes known as the DNA methyltransferases (DNMTs), which consists of DNMT1, DNMT3a, and DNMT3b. DNMT1 maintains appropriate methylation between cell divisions, while DNMT3a and DNMT3b control *de novo* methylation during embryogenesis (Sarkar et al., 2013). Levels of all three DNMTs have been shown to be upregulated in cancer cells compared to normal cells (Kautiainen & Jones, 1986; Xie et al., 1999).

CpG islands are CpG-rich sequences associated with the promoters of widely expressed genes which are normally protected from methylation. Genome-wide mapping has confirmed that 5–10% of these CpG islands become abnormally methylated in cancer genomes, and this *de novo* methylation has been implicated in the silencing of multiple tumor suppressor genes, as well as other genes that are critical for regulation of cell growth, angiogenesis, and DNA repair (Dawson & Kouzarides, 2012).

A number of genes have been found to be silenced *via* hypermethylation in ovarian cancer, and the degree of abnormal methylation has been correlated with disease progression and decreased survival (Watts et al., 2008; Wei et al., 2002). *BRCA1* promoter hypermethylation with resultant decreased *BRCA1* protein expression has been identified in 15–35% of patients with sporadic ovarian cancer (Bai et al., 2014; Baldwin et al., 2000). The effect of *BRCA1* methylation on prognosis is unclear; it has been associated with improved survival in some studies and decreased survival in others (Bai et al., 2014; Chiang et al., 2006). *BRCA1* methylation has also been correlated with improved chemosensitivity and response to PARP inhibitors, suggesting that patients with *BRCA1* methylation have a similar phenotype to patients with germline *BRCA1* mutations (Chaudhry et al., 2009; Veeck et al., 2010). Hypermethylation has been found to contribute to silencing of multiple other tumor suppressor genes in ovarian cancer, including

p53, *MLH1*, *HIC1*, *p16*, *E-cadherin*, and *APC* (Strathdee et al., 2001; Makarla et al., 2005; Chmelarova et al., 2013), and both hypermethylation of multiple genes and increased expression of DNMTs have been associated with the development of platinum resistance (Li et al., 2009; Matei & Nephew, 2010).

While ovarian cancer is characterized by hypermethylation of numerous promoter CpG islands, the ovarian cancer genome is hypomethylated as a whole (Watts et al., 2008). Hypomethylation of unstable satellite DNA sequences has been shown to play an important role in carcinogenesis and is thought to contribute to genomic instability (Feinberg & Vogelstein, 1983; Widschwendter et al., 2004). Patients with ovarian cancer have significantly increased hypomethylation of satellite DNA compared to patients with benign or borderline ovarian tumors, and this extensive hypomethylation is strongly correlated with advanced stage and poor prognosis (Watts et al., 2008; Widschwendter et al., 2004).

3. Histone acetylation

Histones are proteins that package DNA into nucleosomes which are the functional unit of chromatin. Post-translational histone modification can occur through several mechanisms; acetylation at the ϵ -amino group of lysine residues on the amino-terminal tails of the histone proteins is the best understood (Dawson & Kouzarides, 2012). Histone acetylation converts chromatin to an open or transcriptionally permissive state and is regulated by a class of enzymes known as histone acetyltransferases (HACs). Conversely, deacetylation is regulated by the histone deacetylases (HDACs) and converts chromatin to a more condensed or transcriptionally repressive state due to increase in electrostatic interactions between the histones and DNA (Fig. 2) (Dawson & Kouzarides, 2012). HDACs are also involved in acetylation of lysine residues of several non-histone proteins, including the estrogen and androgen receptors, p53, c-Myc, and STAT3 (Kim & Bae, 2011).

Eighteen distinct HDACs have been identified and separated into four classes based on sequence homology with yeast (Dawson & Kouzarides, 2012). Classes I, II, and IV are zinc-dependent, while class III is characterized by NAD⁺ dependence. Class I HDACs are found only in the nucleus and are the most prevalent, while class II, III, and IV HDACs are found both in the nucleus and cytoplasm (Kim & Bae, 2011).

High levels of HDACs with resultant histone hypoacetylation have been identified in multiple cancers (Nakagawa et al., 2007). HDAC1, 2, and 3 are all class I HDACs that are expressed at high levels in ovarian cancer and are associated with poor prognosis (Khabele et al., 2007; Weichert et al., 2008). Expression of the class I HDACs has been shown to increase in a stepwise fashion when moving from benign to borderline to malignant ovarian tumors, indicating that these HDACs may play an important role in carcinogenesis. Specifically, HDAC1 and 2 expression correlate with increased cell proliferation in ovarian cancer cells, while HDAC3 expression inversely correlates with E-cadherin expression, suggesting a role in cell migration and metastasis (Hayashi et al., 2010). Additionally, HDAC overexpression has been correlated with development of platinum resistance in ovarian cancer (Kim et al., 2012).

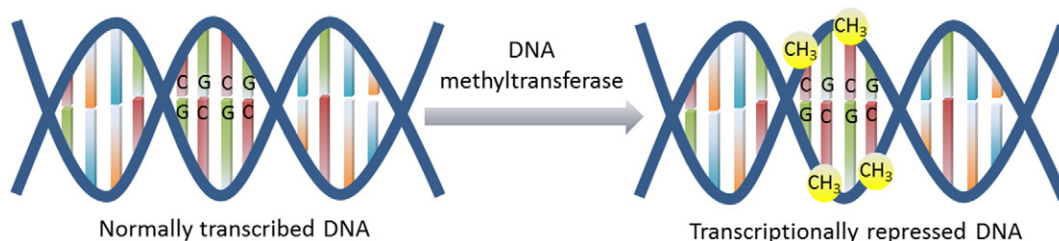


Fig. 1. The process of DNA methylation is mediated by a family of enzymes known as the DNA methyltransferases, which add a methyl (CH₃) group at the carbon-5 position of cytosine-phosphate-guanine (CpG) dinucleotide sequences. The addition of the methyl groups inhibits DNA transcription and can lead to silencing of various genes.

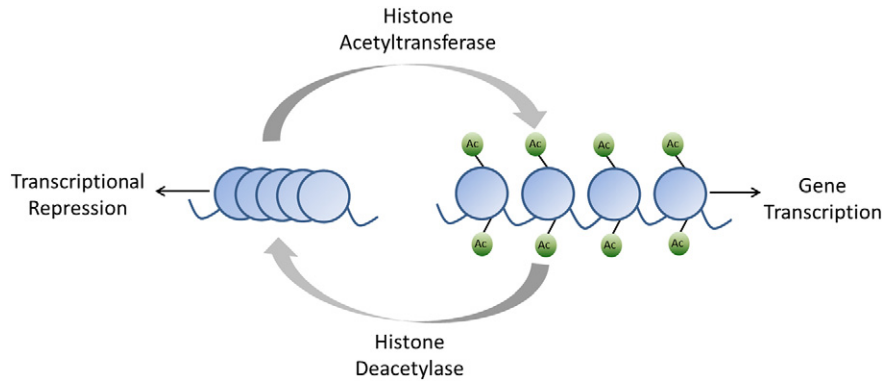


Fig. 2. Histone acetylation converts chromatin to an open or transcriptionally permissive state and is regulated by the histone acetyltransferases. Deacetylation is regulated by the histone deacetylases and converts chromatin to a condensed or transcriptionally repressive state.

4. Epigenetic therapy

4.1. DNA methyltransferase inhibitors

The DNMT inhibitors are cytosine analogues that are incorporated into DNA during replication and covalently bind to the DNMT enzymes inhibiting their function. At higher doses, these agents can also trap the DNMT enzyme leading to enzyme degradation and cytotoxicity (Heninger et al., 2015). 5-azacytidine (5-AZA) and decitabine (5-aza-2'-deoxycytidine) are the two most commonly used DNMT inhibitors and were initially developed in the 1960s as cytotoxic drugs for use in the treatment of hematologic malignancies. Their ability to inhibit DNA methylation was discovered later (Heninger et al., 2015). Both of these drugs are currently FDA-approved for the treatment of myelodysplastic syndromes, but they have been investigated in numerous solid tumors (FDA approval for decitabine for injection (Dacogen) to treat myelodysplastic syndromes. 2006 December 13, 2016; Kaminskias et al., 2005).

The major toxicity for 5-AZA and decitabine is myelosuppression which can be severe and dose-limiting (FDA approval for decitabine for injection (Dacogen) to treat myelodysplastic syndromes. 2006 December 13, 2016; Kaminskias et al., 2005). Given this substantial toxicity, several other DNMT inhibitors are currently being investigated, including less-toxic nucleoside inhibitors such as zebularine, non-nucleoside inhibitors such as the local anesthetic procaine, the main polyphenol compound from green tea epigallocatechin-3-gallate (EGCG), and the small-molecule inhibitor RG108 (Heninger et al., 2015; Stresemann et al., 2006).

4.2. Histone deacetylase inhibitors

In the 1970's, Riggs et al. discovered that the drug sodium butyrate was an effective and specific inhibitor of HDAC activity. Subsequently, sodium butyrate was found to induce cell differentiation and inhibit tumor cell growth, prompting the development of several HDAC inhibitors designed for clinical use (Lane & Chabner, 2009). All of the current HDAC inhibitors act by targeting the zinc ion required for catalytic function of the class I, II, and IV HDACs. The class III HDACs, which are not zinc dependent, are not inhibited by any of the available HDAC inhibitors (Lane & Chabner, 2009; Bolden et al., 2006).

HDAC inhibitors can be classified by their specificity (pan-HDAC inhibitors versus class-specific inhibitors) or by their molecular structure. Structurally, HDAC inhibitors can be divided into four classes—hydroxamic acids, cyclic tetrapeptides, benzamides, and short-chain aliphatic acids (Kim & Bae, 2011; Lane & Chabner, 2009). The hydroxamic acids are the largest class of HDAC inhibitors and include vorinostat, belinostat, and panobinostat; all are pan-HDAC inhibitors that have been FDA-approved for the treatment of hematologic malignancies (Mann et al., 2007; Lee et al., 2015; Laubach et al., 2015).

Romidepsin, a class I HDAC-specific cyclic tetrapeptide, is FDA-approved for the treatment of cutaneous T-cell lymphoma (Barbarotta & Hurley, 2015). While the class I specific benzamide entinostat (MS-275) is not currently FDA-approved, it has been granted a breakthrough designation when used in combination with exemestane for recurrent or metastatic estrogen-receptor positive breast cancer in postmenopausal women who have progressed after aromatase inhibitor therapy (FDA grants breakthrough therapy status to entinostat for advanced breast cancer, 2013). It is also being investigated in multiple other disease sites (Ngamphaiboon et al., 2015). The short-chain aliphatic acids, such as valproic acid, are relatively weak HDAC inhibitors making them less clinically attractive (Kim & Bae, 2011; Lane & Chabner, 2009).

The clinical activity of HDAC inhibitors, which includes arrest of cell growth (Bolden et al., 2006), promotion of cell differentiation and apoptosis (Rosato et al., 2003), and inhibition of angiogenesis (Kim et al., 2001), is achieved by selective alteration of gene transcription. This occurs through chromatin remodeling, changes in structure of transcription factor complexes, and regulation of multiple non-histone proteins (Bolden et al., 2006). HDAC inhibition alone does not result in transcriptional changes of all genes. It is estimated that 20% of known genes are affected by HDAC inhibitors, with approximately half of those being up-regulated and the remainder being downregulated (Peart et al., 2005). Importantly, when compared to tumor cells, normal cells are relatively resistant to the effects of HDAC inhibitors (Johnstone, 2002).

4.3. Other epigenetic therapies

While histone acetylation/deacetylation is the best understood pathway of histone modification, there are several other pathways that are important in regulating chromatin structure and gene transcription, including methylation and phosphorylation, which may represent additional therapeutic targets (Dawson & Kouzarides, 2012). One such example is the histone lysine methyltransferases EZH2, which mediates methylation of a lysine residue on histone H3. Its overexpression has been correlated with aggressive behavior, metastasis, and poor prognosis in multiple cancers, prompting development of small-molecule inhibitors that are currently being investigated in clinical trials (McCabe & Creasy, 2014).

The primary readers of acetylated lysine residues are the bromodomain proteins, which include the BET family (BRD2, BRD3, BRD4, and BRDt). These proteins play an important role in transcription elongation and cell-cycle progression by RNA polymerase II. Inhibition of the BET bromodomain family has been shown to inhibit MYC transcription, resulting in decreased cell proliferation and increased apoptosis (Fu et al., 2015). BET inhibitors have efficacy in several hematologic malignancies and are being studied in solid tumors as well (Chaidos et al., 2015).

5. Use of epigenetic therapy in ovarian cancer

Both HDAC inhibitors and DNMT inhibitors have been investigated in ovarian cancer as single agents and in combination with other therapies. The current clinical experience is summarized in Table 1.

5.1. Single agents

Similar to clinical findings in other disease sites, HDAC inhibitors have limited utility as single agents in ovarian cancer. Vorinostat and belinostat have been studied as single agents in patients with platinum-resistant ovarian cancer and while well-tolerated have minimal antitumor activity (Mackay et al., 2010; Modesitt et al., 2008). In a phase 2 study that enrolled 27 patients with recurrent, platinum-sensitive ovarian cancer, only two patients had a PFS longer than 6 months with single-agent vorinostat (Modesitt et al., 2008). Single agent belinostat was evaluated in a cohort of 32 patients with platinum-resistant recurrent disease, 18 with epithelial ovarian cancer and 14 with ovarian tumors of low malignant potential. For the patients with epithelial ovarian cancer, the median PFS was 2.3 months and the best response was stable disease in nine patients (Mackay et al., 2010). Given this lack of activity, attention has shifted to using these drugs in combination with other agents.

5.2. Restoration of platinum-sensitivity

Due to preclinical data indicating that both hypermethylation and histone modification may play an important role in the development of chemotherapy resistance (Li et al., 2009; Matei & Nephew, 2010), both DNMT inhibitors and HDAC inhibitors have been investigated as a means to mitigate platinum resistance in patients with recurrent disease.

While previously published data suggests that <10% of patients with platinum-resistant ovarian cancer will have an objective response to retreatment with platinum, pretreatment with azacytidine or decitabine produced objective response rates (ORRs) of 22% and 35%, respectively (Fu et al., 2011; Matei et al., 2012). Low-dose decitabine led to demethylation of multiple genes in pathways involved in Wnt signaling and apoptosis, as well as several individual genes including *MLH1*, *RASSF1A*,

HOXA10, *HOXA11*, and *BRCA1* (Matei et al., 2012; Fang et al., 2010). Although toxicity is a significant concern with these agents, both were well-tolerated in combination with carboplatin dosed for an area under the curve (AUC) of 5 [51–53]. While these studies were small, the results indicate that treatment with DNMT inhibitors may improve response to platinum in patients with platinum-resistant disease.

Experience with the HDAC inhibitors has been less encouraging in patients with platinum resistance. A phase 2 study of belinostat and carboplatin included 27 patients with platinum-resistant disease. The results were disappointing with an ORR of only 7.4%, and the study was terminated early due to lack of activity (Dizon et al., 2012a).

One phase 1 study has evaluated the combination of an HDAC inhibitor and DNMT inhibitor in patients with advanced malignancy refractory to standard treatment, including 10 patients with platinum-refractory or resistant ovarian cancer. 3 of the 10 ovarian cancer patients in this study had stable disease for >4 months; however, the combination was poorly tolerated with nearly 80% of patients experiencing grade 3 or higher adverse events (Falchook et al., 2013).

5.3. Combination with cytotoxic chemotherapy

Low-dose decitabine has been studied in combination with dose-reduced paclitaxel and platinum chemotherapy in patients with platinum-resistant/refractory ovarian cancer in a phase 1/2 study. The combination was well-tolerated and produced clinical benefit (either partial response or stable disease) in over 70% of the 17 patients included in the trial (Fu et al., 2011).

Attempts to combine vorinostat with cytotoxic chemotherapy have been unsuccessful due to toxicity. A phase 2 trial combining vorinostat with paclitaxel and carboplatin in the upfront setting was terminated early after gastrointestinal perforation occurred in 3 of 11 patients (Mendivil et al., 2013). Similarly, a phase 1 study of vorinostat in combination with carboplatin and gemcitabine in platinum-sensitive patients with a first recurrence was terminated early due to unacceptable hematologic toxicity (Matulonis et al., 2015).

Belinostat is better tolerated than vorinostat in combination regimens. In a phase 1b/phase 2 trial that included 19 patients with recurrent platinum-sensitive disease and 16 patients with platinum-resistant disease, belinostat in combination with paclitaxel and

Table 1
Clinical Experience with Epigenetic Therapy in Epithelial Ovarian Cancer.

Citation	1st Author	Year	Study Type	Regimen	# Pts	Population	Findings
HDAC Inhibitors							
(Modesitt et al., 2008)	Modesitt	2008	Phase 2	Vorinostat	27	Platinum-resistant	1 PR, 9 SD, only 2 patients had PFS > 6 months
(Mendivil et al., 2013)	Mendivil	2013	Phase 2	Vorinostat + paclitaxel/carbo	18	Primary therapy	7 CR, 2 PR, 2 SD, ORR 50%. Terminated early due to GI perforation in 3 patients
(Matulonis et al., 2015)	Matulonis	2015	Phase 1	Vorinostat + gemcitabine/carbo	15	1st recurrence, platinum-sensitive	6 PR, 1 SD. Terminated early due to hematologic toxicity
(Mackay et al., 2010)	Mackay	2010	Phase 2	Belinostat	32	Platinum-resistant EOC or LMP	LMP: 1 PR, 10 SD EOC: 9 SD
(Dizon et al., 2012a)	Dizon	2012	Phase 2	Belinostat + carbo	27	Platinum-resistant	ORR 7.4%. Terminated early due to lack of activity
(Dizon et al., 2012b)	Dizon	2012	Phase 1b/2	Belinostat + paclitaxel/carbo	35	Recurrent EOC	3 CR, 12 PR, ORR 43%
DNMT Inhibitors							
(Fu et al., 2011)	Fu	2011	Phase 1	5AZA + carbo	17	Platinum-resistant	1 CR, 3 PR, 10 SD. ORR 22%
(Falchook et al., 2013)	Falchook	2013	Phase 1	5AZA + VPA + carbo	32 (10 EOC)	Platinum-resistant	3/10 EOC patients had minor response or SD > 4 months
(Fang et al., 2010)	Fang	2010	Phase 1	Decitabine + carbo	9	Platinum-resistant	1 CR, 3 SD > 6 months
(Matei et al., 2012)	Matei	2012	Phase 2	Decitabine + carbo	17	Platinum-resistant	1 CR, 5 PR, 6 SD. 35% ORR
(Odunsi et al., 2014)	Odunsi	2014	Phase 1	NY-ESO-1 vaccine + decitabine + PLD	10	Recurrent EOC	5 SD, 1 PR

Carbo = carboplatin; 5AZA = 5-azacytidine; VPA = valproic acid; PLD = pegylated liposomal doxorubicin; EOC = epithelial ovarian cancer; LMP = low malignant potential; CR = complete response; PR = partial response; SD = stable disease; ORR = objective response rate; PFS = progression-free survival.

carboplatin produced an ORR of 43%. The combination was well-tolerated with the only grade 4 toxicity being neutropenia in 14% of patients. The most common toxicities were nausea/vomiting and fatigue (Dizon et al., 2012b).

6. Epigenetic therapy and immunotherapy

While immune checkpoint blockade, which includes monoclonal antibody targeted inhibitors of programmed cell death protein 1 (PD1) and its ligand (PDL1) or anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), has shown promise for patients with metastatic melanoma, the majority of patients with ovarian cancer do not respond to single-agent checkpoint inhibitors (Varga et al., 2015; Gaillard et al., 2016). Several strategies have been developed to enhance response to checkpoint inhibitors, including using these agents in combination with chemotherapy or using dual checkpoint inhibitor therapy (Gaillard et al., 2016). Another exciting possibility involves the use of checkpoint inhibitors in combination with epigenetic therapy.

Interest in combining epigenetic and immunotherapy was sparked after a group of patients with non-small cell lung cancer (NSCLC) progressed through low-dose DNMT inhibitor therapy and crossed over to a checkpoint inhibitor trial. 60% of those patients developed a durable response that persisted at least 2.5 years, significantly better than the patients in the same trial that did not receive prior epigenetic therapy (Chiappinelli et al., 2016; Juergens et al., 2011). Subsequently, NSCLC cell lines treated with 5-AZA were found to have significant upregulation of multiple immune pathways, including increased expression of cancer testis antigen, major histocompatibility complex class I (MHC1), and PDL1 (Wrangle et al., 2013). In diffuse large B cell lymphoma, HDAC inhibitors have been shown to upregulate major histocompatibility complex class II (MHCII) expression on tumor cells via the transcriptional regulator CIITA (Cycon et al., 2013), and increased MHCII expression has been associated with improved immunogenicity and tumor rejection in animal models of breast, prostate, and renal cell carcinoma (Hillman et al., 2004; Mortara et al., 2006). Additionally, MHCII expression has been associated with increased infiltration of CD8 lymphocytes and improved survival in patients with triple negative breast cancer and papillary serous ovarian cancer (Cycon et al., 2013; Forero et al., 2016).

The combination of epigenetic therapy and immunotherapy has shown promising results in preclinical studies. In syngeneic murine models of colorectal (CT26) and breast (4 T1) cancer, the addition of entinostat and 5AZA to anti-PD1 and anti-CTLA4 led to complete tumor regression in 10/11 CT26 tumor-bearing mice and 10/10 4 T1 tumor-bearing mice. This was in comparison to the dual checkpoint inhibitor therapy alone, which resulted in tumor eradication in 36% of the CT26 mice and 30% of the 4T1 mice (Kim et al., 2014). Similarly, in a syngeneic ovarian cancer model, the combination of decitabine and anti-CTLA-4 significantly reduced tumor growth and prolonged survival compared to either agent alone. The enhanced anti-tumor effect appeared to be related to increased recruitment and activation of cytotoxic T lymphocytes (Wang et al., 2015).

The only currently published clinical trial evaluating the combination of epigenetic therapy and immunotherapy in ovarian cancer is a phase 1 study with the cancer testis antigen NY-ESO-1 vaccine plus decitabine and liposomal doxorubicin in patients with recurrent epithelial ovarian cancer. Increased NY-ESO-1 antibodies and associated T cell response were seen in the majority of patients, and 6/10 evaluable patients had either a partial response or stable disease (Odunsi et al., 2014). The combination of entinostat and the PDL1 inhibitor avelumab is currently being evaluated in patients with recurrent epithelial ovarian cancer [NCT02915523], and may provide additional insight into clinical response to combination epigenetic therapy and immunotherapy.

7. Conclusions

Epigenetic alterations such as aberrant DNA methylation and histone modification play an important role in the pathogenesis of epithelial ovarian cancer, and may contribute to multiple cancer phenotypes, including cell proliferation, metastasis, chemoresistance, and immune tolerance. An increasing number of therapeutic agents targeting epigenetic alterations are available, and these therapies, which include DNMT inhibitors and HDAC inhibitors, represent an exciting area of research.

While response rates with single-agent epigenetic therapy have thus far been low, these agents have been able to at least partially mitigate platinum resistance and improve response to immunotherapy in preclinical studies and some early phase clinical trials in epithelial ovarian cancer, indicating that epigenetic agents may be best used in combination with other therapies. Pretreatment with low dose azacytidine or decitabine produced ORRs of 22–35% to carboplatin in patients with documented platinum-resistance ovarian cancer, which is an improvement over the 10% ORR typically seen with carboplatin in this population (Fu et al., 2011; Matei et al., 2012).

In diffuse large B-cell lymphoma, treatment with HDAC inhibitors has resulted in upregulation of the MHCII pathway, which is known to be associated with improved survival in both breast and ovarian carcinoma (Cycon et al., 2013; Forero et al., 2016). In our experience, treatment with the HDAC inhibitor entinostat has resulted in increased MHCII expression *in vitro* in human and murine ovarian cancer cell lines, as well as *in vivo* in both a patient-derived xenograft and a syngeneic mouse model (unpublished data). HDAC inhibitors have also been associated with improved response to immune checkpoint inhibitors in patients with NSCLC (Juergens et al., 2011). The results of an ongoing clinical trial (NCT02915523) combining entinostat with a PDL1 inhibitor in ovarian cancer should provide additional information on the best way to combine these two classes of therapy in epithelial ovarian cancer. More studies are needed to determine the best strategy to incorporate these agents into the treatment of ovarian cancer while minimizing toxicity and maximizing clinical benefit.

Conflict of interest statement

None of the authors have any conflicts of interest to disclose.

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