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Chapter

Novel Indications of Epigenetic Therapy in Ovarian Cancer

Courtney Griffiths, Michelle Bilbao, Lauren Krill and Olga Ostrovsky

Abstract

Early diagnosis and intervention are some of the longstanding challenges associated with ovarian cancer, which is the leading cause of gynecologic cancer mortality. While the majority of patients who present with advanced stage disease at time of diagnosis will initially respond to traditional combination platinum and taxane-based chemotherapy in conjunction with cytoreductive surgery, approximately 70% will ultimately recur due to chemoresistance within the first two years. Intratumor heterogeneity is proposed to be a leading factor in the development of chemoresistance and resultant poorer outcomes for those with recurrent or advanced stage disease. Both inherent and acquired mechanisms of chemoresistance are postulated to be a result of alterations in gene expression, also known as epigenetic modifications. Therefore, epigenetic therapy is a pivotal avenue which allows for reversal of chemoresistance in cancer through the targeting of aberrant mutations. In this chapter, we discuss how these epigenetic modifications prove to be promising targets in cancer therapy leading to heightened drug sensitivity and improved patient survival outcomes.

Keywords: cancer therapy, epigenetics, histone deacetylase inhibitors (HDACis), DNA methyltransferase inhibitors (DNMTis), tumor microenvironment

1. Introduction

1.1 Chemoresistance causes failure of classic ovarian cancer treatment

Ovarian cancer, similar to other malignancies, is characterized by molecular changes in cells which result in unregulated proliferation and spread to other organs [1]. Normal regulatory processes are disrupted and therefore aberrant cells are able to bypass checkpoints and lead to widespread metastatic potential [2]. Malignant ovarian neoplasms contribute to the highest mortality rates among women with gynecologic cancers [3]. Among them, high grade serous histologic subtypes are the most aggressive with an estimated 21,410 new cases and 13,770 ovarian cancer deaths in the United States in 2021 according to the American Cancer Society [4]. Due to limited feasibility of screening modalities in low risk patients and vague generalized symptoms, many patients are diagnosed at advanced stages contributing to a higher rate of treatment failures and poorer prognosis [5]. Traditional initial therapy consists of a combination of cytoreductive surgical management and platinum/taxane based chemotherapy [6]. The recommended surgical procedure includes a total hysterectomy with removal of bilateral fallopian tubes and ovaries, lymph node evaluation

as well as evaluation and removal of all visible disease along the omentum and any peritoneal surfaces with full exploration of the abdomen and pelvis [7]. Despite the frequent initial success with the aforementioned approach, approximately 70% of patients develop recurrent disease either secondary to intrinsic or extrinsic causes of chemoresistance [8, 9]. Once the tumor is able to evade standard therapy, treatment options then become limited and the disease process is incurable [10]. As a result, chemoresistance is one of the leading causes of mortality among advanced stage and recurrent ovarian cancer patients. Multiple mechanisms are responsible for inducing chemoresistance, and a better understanding of these processes may lead to better treatment outcomes for patients with progressive disease [11].

1.2 Histologic subtypes and tumorigenesis

Ovarian cancer can arise from several different cell types including epithelial, germ cell and mesenchymal (stromal) origins. These histological classifications vary widely with regard to treatment options and prognosis likely secondary to unique molecular and biologic features among each subtype [12, 13]. Epithelial ovarian cancer (EOC) accounts for 90% of ovarian cancer and can be subdivided into high grade serous, low grade serous, endometrioid, clear cell, mucinous, transitional cell, among several other subtypes with over two-thirds comprising high grade serous histology [14, 15]. Among high grade serous lesions, p53 mutations are typically omnipresent as well as other important germline and somatic mutations (BRCA 1, BRCA 2, and additional homologous recombinant genes), and tend to lead to more favorable treatment outcomes [16]. Although these gene mutations may induce chemoresistant disease, it is predominantly epimutations and their associated changes in gene expression which are thought to drive tumorigenesis. As chemoresistance may be innate or acquired even after an initial positive response to platinum therapy, it is plausible that genes involved in epigenetic reprogramming are controlled by specific transcription factors, and therefore may serve as a potential target for treatment [17, 18].

As with most malignancies, the staging of ovarian cancer and concurrent optimal cytoreduction plays a pertinent role in determining prognosis [19]. Ovarian neoplasms are staged surgically and according to the International Federation of Gynecology and Obstetrics (FIGO) classification. The 5-year overall survival rate differs significantly between early and advanced stage disease at 90% for Stage I disease and approximately 15–40% for Stage III/IV disease [20]. As most ovarian cancers are diagnosed in advanced stages, an individual's response to standard platinum chemotherapeutic agents becomes a major prognosticator in determining outcomes [21, 22].

1.3 Can epigenetic therapy overcome ovarian cancer chemoresistance?

The mainstay approach to treatment of high grade serous carcinomas is with a platinum based chemotherapeutic agent whereas other histologic subtypes prove to be more chemoresistant [23]. As primary treatments involve a platinum and taxane chemotherapeutic agent, an important predictor of progression free and overall survival is the platinum-free interval [24]. Patients are classified as platinum sensitive should disease recurrence occur greater than 6 months from completion of therapy, platinum resistant if less than 6 months and refractory if progression occurs through therapy [25]. This subclassification is imperative to predicting which patients will likely recur after initial therapy and will require molecular analyses in order to determine a more targeted treatment approach. Unfortunately, only 15% of patients who develop chemoresistance respond to subsequent therapies and many

ultimately will succumb to their disease within one year [26]. Multiple mechanisms have been suggested for acquired chemoresistance such as mutations in the cancer cells themselves, DNA repair failures as well as epigenetic changes [27–29].

For example, cancer stem cells (CSCs) which are capable of self-renewal, differentiation and tumorigenicity have been indicated in the development of platinum resistance disease [30, 31]. One particular study demonstrated upregulated expression of stem cell markers CD44, CD133, and ALDH1A1 in recurrent ovarian cancer in comparison to primary tumors [32]. DNA repair failures may also occur in nucleotide excision, recombination, and mismatch repair pathways enabling cancer cells to exploit repair mechanisms and therefore induce an acquired chemoresistance [33]. Point of nonsense mutations in oncogenes such as Ras or ERK signaling and/or DNA repair genes such as p53, PARP, BRCA 1 and 2 have been evidenced to cause chemoresistance and subsequent failure in standard oncologic treatments [34]. All in all, cancer renewal and heterogeneity are the main reasons for the development of chemoresistance and subsequent failure in standard oncologic treatments [35].

Another important component includes epigenetic modifications which result in silencing as well as activation of gene expression without DNA sequence alteration [36]. The majority of cancers, including ovarian cancer, have aberrant epigenetic modifications which result in the promotion of cancer growth, metastasis and chemoresistance [37].

1.4 Epigenetics

The field of epigenetics has gained heightened interest in the field of oncology over the years. This new concept of study was first described by Conrad Waddington in 1942 where he demonstrated the inheritance of an acquired characteristic in a particular population [38]. Although the definition has evolved over the years, the overall essence of epigenetics involves the alterations in gene expression without modification of the DNA sequence itself [39]. In other words, these aberrant changes are maintained through cell division without producing a change in the overall genetic information [40]. As stated previously, epigenetic alterations affect chromatin structure through a variety of mechanisms, altering patterns of gene expression. Disruptions in these epigenetic processes can in turn lead to altered gene function and further, malignant transformation through oncogene activation or tumor suppressor gene silencing [41]. As human cancer cells harbor aberrant epigenetic abnormalities, cancer progression is then enabled and mechanisms of resistance develop, which creates an opportunity for targeted therapy using epigenetic inhibitors.

Promoter hypermethylation silences crucial genes including but not limited to p16, SPARC, CTGF, CDH1 and ICAM-1. Other genes involved in methylation dysregulation include PTEN (seen in type 1 ovarian cancers), and those involved with suppression of metastasis [42]. Several studies have utilized DNA methylation assays in order to identify potential epigenetic biomarkers in cell free DNA for ovarian cancer in order to improve on early screening challenges [43–45]. This method of identification and targeting of differentially methylated regions (DMRs) has the potential to identify populations of at-risk patients for the development of epithelial ovarian cancers.

Moreover, epigenetic agents have already proved effective in acting as chemotherapy sensitizers by essentially improving or re-establishing tumor sensitivity as well as reversing resistant disease in a multitude of studies [46–48]. Where patients may ultimately be classified as platinum resistant, the use of epigenetic agents have the potential to reinvoke a response to platinum agents with one study demonstrating

a 35% objective response rate after administration of decitabine followed by carboplatin among platinum resistant ovarian cancer patients [48]. Therefore, current research is concentrated on the development of treatment methodologies involving the use of classic chemotherapy in combination or sequentially with epigenetic regimens in order to overcome chemoresistance and improve outcomes.

2. Epigenetic aberrations in ovarian cancer

2.1 DNA methylation

One of the most common methods of epigenetic modulation is through DNA methylation. Modification of cytosine residues in CpG dinucleotides or CpG islands by methylation leads to transcriptional silencing in vertebrates, however, non-CpG methylation has also been identified in stem cells [49]. Typically, small amounts of CpG island promoters are methylated in normal cells, however, in the presence of hypermethylation, tumorigenesis is often incited [50]. The particular enzymes that are responsible for DNA methylation are DNA methyltransferases (DNMTs) which include DNMT1, DNMT3A, DNMT3A, DNMT3B, and DNMT3C. These enzymes are classified as either *de novo* or maintenance groups, of which *de novo* are more specific to stem cell expression (DNMT3s) whereas DNTM1 is involved in maintenance of DNA methylation during cell division [51].

Both DNA hypomethylation and gene promoter DNA hypermethylation are major oncogenic driving factors. Specifically, hypermethylation of promoters on tumor suppressor genes BRCA 1 and BRCA 2 lead to their silencing and subsequent inactivation of DNA repair driving the development of malignancies such as breast and ovarian cancers [51, 52]. However, the earliest methylation errors were of reduced activity resulting in increased mutation rates. Notably, transcription of repeats, transposable elements (TEs) and oncogenes occurred secondary to changes from hypomethylation through the loss of DNMT1 function [41, 53].

2.2 Histone acetylation

DNA is packaged as chromatin which is composed of nucleosomes. In turn, the nucleosome is comprised of histone proteins (H3, H4, H2A, H2B) which can similarly undergo many modifications and affect DNA transcription, replication and repair [54]. A "histone code" exists in order to regulate chromatin structure through several different histone modifications, which can lead to either activation or repression dependent on the residues and type of modification such as acetylation, ubiquitylation, sumoylation and phosphorylation [40, 55] (**Figure 1**). Dysregulation of any of these functions can lead to oncogenic activation or even the silencing of tumor suppressor genes.

In comparison to DNA methylation, errors in chromatin modification in the development of epithelial ovarian cancers is less understood but also pertinent. The overexpression of class I histone deacetylases (HDACs) has been identified in several cancers, with a prominent association identified in high risk ovarian of serous and clear cell subtypes. In addition, an unfavorable prognostic correlation was seen in patients with endometrioid histologies [56].

2.3 MicroRNA dysregulation

Along with histone modification and methylation dysregulation, cancer cells are prone to errors in microRNA (miRNA) regulation. MiRNAs are small non-coding

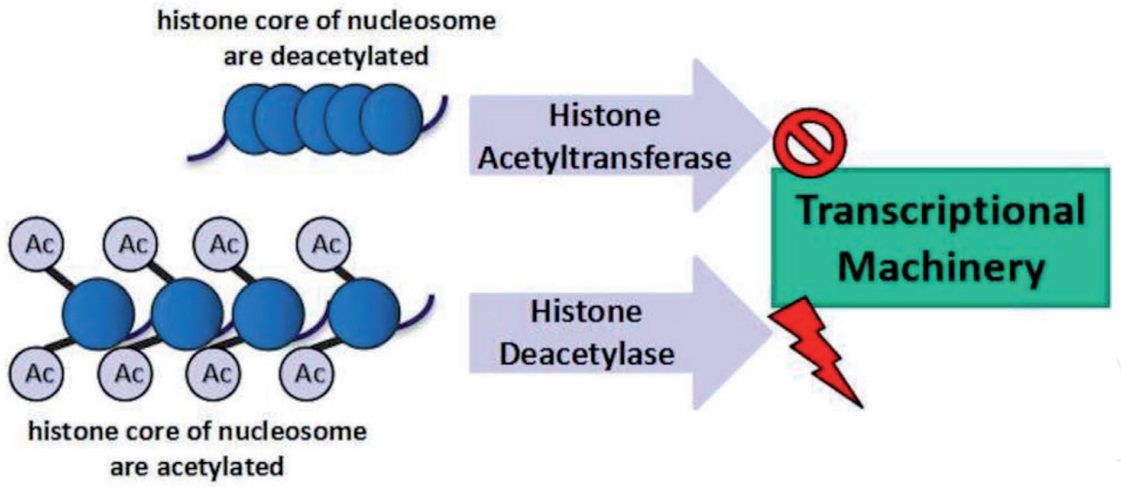

Figure 1.
The effect of histone acetylation and deacetylation on DNA transcription.

RNAs of 19–22 nucleotides in length which regulate the expression of certain genes either through degradation or inhibition of target mRNA [57]. The expression of epigenetic regulators (DNMTs and HDACs) are controlled by these miRNAs in a feedback loop of which when dysregulated, can lead to carcinogenic potential [58]. Genome analysis reveals condensed areas of miRNAs in cancer-associated genomic regions signifying that dysregulation of these particular areas could lead to aberrant expression [59]. With regard to epithelial ovarian cancer development, the aberrant expression of miRNAs can emulate oncogenic or tumor suppressor activity [60]. The overexpression of some types of miRNA as well as decreased activity of others were more closely correlated with ovarian cancer cells in comparison to healthy ovarian epithelial cells in several studies [61, 62], indicating another potential for early diagnostic screening and opportunity for intervention.

3. The clinical application of epigenetic therapies

3.1 DNA methylation inhibitors (DNMTis)

DNA methylation inhibitors (DNMTis) are deoxycytosine analogs. DNMTis prevent methyl group transfer by covalently binding to and trapping methyltransferases [63]. The simplest way to understand the effect of DNMTis is through their effect on oncogenes and tumor suppressor genes [64]. BRCA1 and BRCA2 are oncogenes that when hypermethylated, can lead to a variety of cancers including ovarian cancer [65]. In a similar way, demethylation of tumor suppressor genes like p53, MLH1, H1C1, p16, E-cadherin and APC, can also play a role in the genetic instability that leads to the development of ovarian cancer, its propagation and chemoresistance [64]. Indeed, both demethylation and hypermethylation of the genome have been associated with the development of platinum resistance in ovarian cancer [64]. Consequently, DNMTis have been shown in preclinical models to restore chemosensitivity and restore normal epigenetics [66].

The most commonly utilized DNA methyltransferase inhibitors are 5-azactidine (AZA) and decitabine (5-aza-2'deoxycytidine) [63]. Both were developed in the 1960s for the treatment of hematologic malignancies and are currently FDA approved for myelodysplastic syndromes. Both AZA and decitabine have demonstrated some efficacy in clinical and pre-clinical ovarian cancer studies, however, their dose-limiting myelotoxicity limits their practical use. As they can be toxic,

other DNMTis are currently under investigation: zebularine, procaine epigallocatechin-3-gallate (EGCG) (from green tea extracts), and RG 108 [64].

3.2 Histone deacetylase inhibitors (HDACis)

Histone deacetylase inhibitors (HDACis) act by targeting the zinc ion required for the catalytic function of the class I, II and IV HDACs [64]. The class III HDACs are not zinc dependent and are not inhibited by any of the current HDACis. HDACis are stratified by activity and chemical structure. There are pan-HDAC inhibitors, which affect classes I, II and IV, as well as class-specific inhibitors [67]. The chemical structure of HDACis include: hydroxamic acids, cyclic tetrapeptides, benzamides, and short-chain aliphatic acids [67]. They act on ovarian cancer in the alteration of gene transcription and chromatin remodeling [64]. In doing so, HDACis arrest cell growth, promote apoptosis, and inhibit angiogenesis [64].

The largest group of HDACis are the hydroxamic acids: vorinostat (suberanilohydroxamic acid or SAHA), belinostat, and panobinostat, all of which are pan-HDAC inhibitors FDA approved for hematologic malignancies [64]. Romidepsin, a tetrapeptide, has specific activity against Class I HDAC and is currently FDA approved for the treatment of cutaneous t-cell lymphoma [64]. Another HDACi in this group is etinostat [64]. Valproic acid is a short-chain aliphatic acid and is overall a weak HDACi with little clinical utility [64].

Since aberrant DNA methylation and histone acetylation contribute to the progression, metastasis and chemoresistance of high grade serous ovarian cancer, epigenetic drugs are thought to have the capability of reversing these effects (**Figure 2**).

3.3 Other epigenetic therapies

While DNMTis and HDACis have been more extensively studied, other epigenetic therapies are on the horizon. These drugs target methylation and

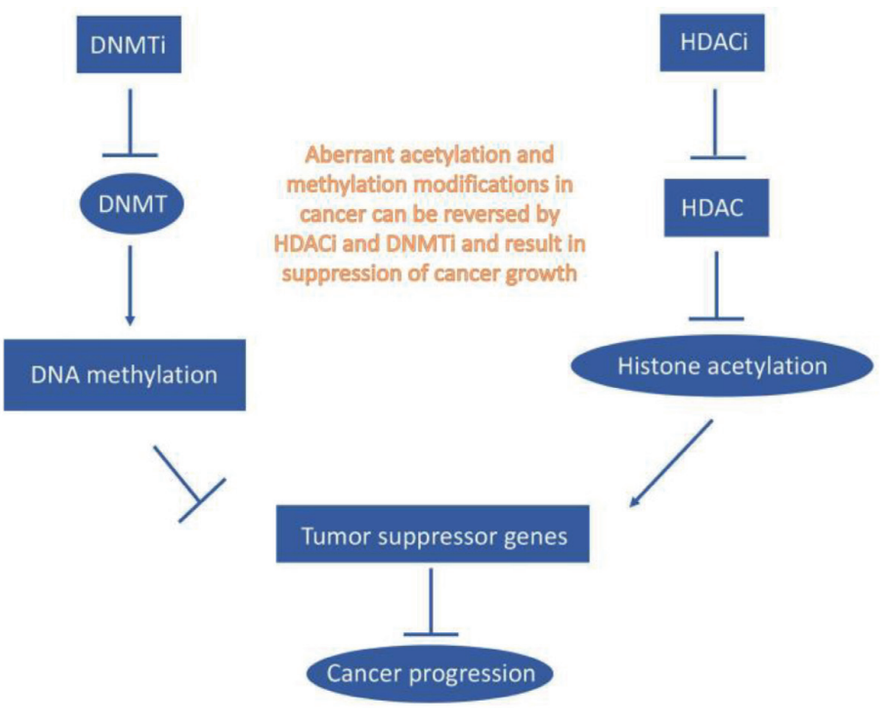

Figure 2.
The Role of DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis) in halting tumorigenesis.

phosphorylation of the cancer genome. Examples are small molecule inhibitors targeting the histone lysine methyltransferases EZH2 and inhibitors of bromodomain proteins, BET inhibitors [64]. G9A is one such target. It is a histone methyltransferase that demethylates H3K9 and is detected in 71.6% of metastatic high grade serous cancers [68]. JQ1 is an agent that targets the bromodomain and extraterminal (BET) protein BRD4 [68]. In preclinical models, JQ1 has suppressed BRD4 and restored cisplatin sensitivity in ovarian cancer [68]. Furthermore, JQ1 has been shown by other researchers to synergize with PARP inhibitors in ovarian cancer cells that are proficient in homologous recombination [68, 69]. These newer epigenetic therapies hold promise, but still need further investigation.

3.4 Efficacy of different inhibitors

It is important to note that in pre-clinical models, epigenetic therapies are more active against tumor cells, while normal cells appear to be resistant to their effects. [64] Yet, this is a double-edge sword. Because epigenetic regulators have a broad impact over the entire genome, there will be great anti-tumor effects, but also unintended nonspecific consequences [68]. These nonspecific effects explain the toxicities seen in the clinical trials done with epigenetic therapies.

4. Relevant clinical trials using epigenetic therapy in ovarian cancer

4.1 Success and failures

Clinical translation studies with epigenetic therapy have had mixed results, but the most success with epigenetic therapy appears to be when it is used in combination with other agents and at the lowest effective dose [64]. This was discovered with one of the first epigenetic clinical trials in 2008, when the Gynecologic Oncology Group learned that as a single agent, SAHA is not very effective. They conducted a phase II study of vorinostat (SAHA) in the treatment of 27 platinum resistant patients. While 9 of 27 patients had stabilization of their disease, only 1 of 27 had a partial response and only 2 patients had a progression free survival of greater than 6 months [70]. In 2013, Mendivil and colleagues conducted a study where vorinostat was given in combination with paclitaxel and carboplatin to 18 patients as upfront therapy. The investigators reported a 50 percent total response rate, however, the study was closed prematurely due to safety concerns. Patients suffered grade 3 and 4 neutropenia. Additionally, three bowel perforations effected closure of the study [71]. Matulonis et al. in 2015 conducted a phase 1 trial of platinum sensitive patients at their first recurrence again using vorinostat. In this trial, vorinostat was given with gemcitabine and carboplatin. This combination has also demonstrated some efficacy in the recurrent setting but had significant hematologic toxicity, namely, thrombocytopenia and neutropenia [72].

Fu and colleagues used azacitidine (AZA) to re-sensitize 17 platinum resistant patients to carboplatin in a phase Ib-II trial [73]. While the numbers were small, a partial response was noted in 70 percent of patients with an overall response rate of 22 percent [73]. Notably, these investigators gave their patients 5 days of AZA prior to carboplatin [73]. As it appears, epigenetic therapies may be most advantageous when used to augment classic chemotherapy and even immunotherapy, as opposed to being given in isolation or in combination with an existing regimen.

Oza and colleages recently conducted a larger study with 103 patients [74]. It randomized patients to guadecitabine and carboplatin versus investigator's choice

(topotecan, pegylated liposomal doxorubicin, paclitaxel or gemcitabine) until disease progression or unacceptable toxicity. Cross-over was allowed from the standard arm to the experimental arm and 27 patients crossed-over. The combination of guadecitabine and carboplatin was found to be effective, however the median progression free survival of 16 weeks when compared to the 9 weeks in the standard treatment arm was not found to be statistically significant [74].

4.2 The administration of epigenetic therapy – better together?

One approach to utilizing epigenetic therapy effectively up front is in alternating treatments of classic chemotherapy and epigenetic therapy. This method was found to be effective and less toxic in clinical translational studies [73, 74]. Sequential administration of classic chemotherapy and epigenetic drugs not only suppresses ovarian cancer growth *in vitro*, but also spares toxicity to normal cells and preserves the healing ability of stem cells [75]. Furthermore, chemotherapy and epigenetic therapy act synergistically allowing smaller doses of both to be administered. In turn, this decreases the toxicity of both chemotherapy and epigenetic therapy [69]. This methodology has yet to be broadly adopted in clinical trials involving epigenetic therapy.

For recurrent disease, epigenetic therapy may have utility. Epigenetic therapy restores platinum sensitivity as both hypermethylation and histone modification contribute to chemoresistance, reversing these epigenetic changes, should reverse the chemoresistance [64]. This has been borne out in the literature as less than 10 percent of platinum resistant patients would be expected to respond to platinum again, yet pretreatment with AZA yields a 22 percent response and decitabine, a 35 percent response [64]. Taxol resistance has not been as heavily explored in the literature as platinum resistance, however, epigenetic therapy, may re-sensitize ovarian cancer to paclitaxel as it does cisplatin. In one preclinical study, the HDACi panobinostat was used to re-sensitize ovarian cancer cell lines that had become resistant to paclitaxel [76]. These researchers were further able to demonstrate that when human ovarian cancer xenografts were implanted in a murine model, panobinostat in combination with cisplatin and paclitaxel was superior in efficacy to cisplatin-paclitaxel or panobinostat alone [76]. Thus, epigenetics may possibly be used upfront to "prime" or increase the efficacy of classic chemotherapy. Additionally, they may be sequenced in between classic chemotherapy and again when patients recur to re-sensitize them to platinum and taxol agents.

5. Future directions in improving patents care outcomes

5.1 Epigenetics and immunotherapy

There is biologic plausibility that epigenetic therapies can prime tumors for a better response to immunotherapy and turn "cold" tumors into "hot" ones [68]. For example, in one murine model, the combination of decitabine and anti-CTLA-4 significantly shrunk tumors and prolonged survival as compared to either agent alone [77]. There is additional preclinical data suggesting that AZA can upregulate T-cells in murine models [78]. Additionally, two clinical trials are currently underway. The results from one study of 75 patients are expected in March 2022 (NCT03206047). Its investigators are looking at AZA and atezolizumab with or without the anti-NY-ESO-1 vaccine (a biologic agent) in women with recurrent platinum resistant ovarian cancer. The other study is looking at guadecitabine with pembrolizumab for

recurrent ovarian cancer (NCT02901899). Thirty-five patients have been enrolled in this latter study and results are expected in March 2022.

5.2 Epigenetics and precision medicine

The heterogeneity of ovarian cancer is such that no two tumors are alike, however, tumors expressing similar genetic profiles, have been shown to respond to agents targeting their specific genetics. Recent clinical trials indicate that ovarian cancer patients with homologous recombination deficiency, for example, respond well to PARP inhibition [79, 80]. Newer epigenetic therapies like BET inhibitors, have the ability enhance PARP inhibition [69]. Another clinical challenge in ovarian cancer is the *ARID1A* mutation. Ovarian cancers with this mutation are associated with late-stage disease at diagnosis and early recurrence [81]. Roughly 50 percent of clear cell carcinomas, which are notoriously chemoresistant, harbor this mutation. In one murine model, the HDACi vorinostat was found to be highly effective against ARID1A mutated ovarian cancer [81]. Thus, epigenetics may help further precision medicine and the targeting of actionable mutations.

6. Conclusion

Platinum resistant and recurrent ovarian cancer patients have very little in the way of highly effective treatment. Chemotherapy may be effective for a period of months or a few years for these patients, but it is rarely if ever curable. Epigenetic therapies hold promise, especially in conjunction with other mechanisms, like PARP inhibitors and immunotherapy, but the timing, dosing and patient selection must be fine-tuned before they can enter the mainstream of treatment for ovarian cancer.

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Conflict of interest

The authors declare no conflict of interest.

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