Cervical Cancer: Open Access

Extended Abstract OMICS International 2017
Vol.2 No.3

Epigenetic Therapy should be in the Tool Box for Recurrent Ovarian Cancer

Olga Ostrovsky
Department of Surgery, Cooper
University Hospital, New Jersey, USA, Email: Ostrovsky-olga@cooperhealth.edu

Introduction
Ovarian cancer prematurely ends the lives of 13,980 women in the United States annually [1]. Metastatic, chemoresistant disease is the major reason for recurrent disease. With each passing year, there is increasingly more evidence that epigenetic therapy is not only extremely effective in treating recurrent metastatic ovarian cancer, but is able to reverse its chemoresistant properties [2].

Methods:
Ovarian cancer has aberrant epigenetics:
Ovarian cancer is known to exhibit hypermethylation of CpG islands within promoter regions of tumor suppressor genes [3]. High grade serous carcinoma with global hypomethylation of unstable satellite DNA sequences contributing to carcinogenesis is associated with advanced stage and poor prognosis [4]. Additionally associated with poor prognosis are histone deacetylase 1, 2, and 3 [4]. Histones, the proteins responsible for the winding and unwinding of DNA, and the subsequent transcription and translation resulting in gene expression, are critical in the immortalization of cancer cells. Histone deacetylation in ovarian cancer has been linked to increased cell proliferation, cell migration and metastasis, as well as the development of platinum resistance [4].
To complicate matters further, ovarian cancer cells are not a homogeneous population, even within the same patient [5]. Ovarian cancer cells often demonstrate dysregulation in gene expression as a result of variable DNA mutations, but also aberrant epigenetics [4]. This is the difficulty in treating ovarian cancer. The target is constantly moving. Ovarian cancer uses epigenetic modifications, chromatin methylation and acetylation to activate genes which drive proliferation and lead to chemoresistance. Yet, these epigenetic modifications also suppress oncogenes responsible for critical cell cycle check points [6]. However, the good news is that epigenetic profiles in normal and cancer tissues are different [4]. Therefore, epigenetic therapy may be preferable to classic chemotherapy because it can specifically target cancer cells affecting normal cell populations.

Epigenetic therapy and ovarian cancer:
Platinum refractory and platinum resistant patients have very little in the way of effective treatment [7]. Patients requiring three or more lines of chemotherapy demonstrate effectiveness of treatment as low as 11.9% in some studies [8]. Clinical translation studies on epigenetic therapy have had mixed results. One phase Ib-IIa trial using azacitidine resensitized some platinum resistant patients to carboplatin [9]. Phase I studies using vorinostat (suberanilohydroxamic acid) were terminated early due to unacceptable toxicities, namely, myelosuppression and gastrointestinal perforation [10,11]. Investigators need to fine-tune the administration of epigenetic drugs to maximize cancer damage and minimize toxicity.
Determining the optimal regimens and dosing of these therapies is critical due to the limited overall survival of patients following the identification of recurrent platinum resistant ovarian cancer. We are calling for the scientific community to develop novel treatment strategies that are capable of maintaining a balance between treating this aggressive disease and maintaining health and quality of life for ovarian cancer patients. One such approach, alternating treatments of classic chemotherapy and epigenetic therapy, demonstrated promising results in recurrent ovarian cancer cell lines in our lab (under review). Our preliminary studies demonstrate that sequential administration of classic chemotherapy and epigenetic drugs not only suppresses ovarian cancer growth, but also spares toxicity to normal cells and preserves the healing ability of stem cells. Taken together, the proper dosing and kinetics of epigenetic and classic chemotherapy treatments may offer a new approach for effective, minimally toxic treatment for platinum resistant ovarian cancer patients.

The role of the omentum in ovarian cancer:
As a modulator and moderator of DNA, epigenetic therapy can also act on other cells in the body that serve to support metastatic ovarian cancer. The omentum is the most common organ to which ovarian cancer metastasizes and has become an important point of ovarian cancer research [12]. To borrow from Stephen Paget's theory, every metastatic ovarian cancer "seed" only takes root because of fertile "soil" [13].
As such, the omental tumor microenvironment has rightfully garnered much attention in ovarian cancer research [12]. The omentum is composed of many different cell types and, indeed, ovarian cancer exploits the rich tumor microenvironment of the omentum for its own benefit [14]. The omentum not only aids in propagating ovarian cancer, but in feeding cancer its necessary growth factors, it provides for chemoresistance. In our research, we have focused on omental adipose stem cells (OASCs) and their effect on human recurrent ovarian cancer cell lines. Our lab has uncovered that conditioned medium from OASCs demonstrated up to a 27-fold increase in tumorogenic factors and promoted chemoresistance of Caov-3 against chemotherapy [2].

This work is partly presented at Joint Event on 24th World Congress on Pharmacology & 7th World Heart Congress, August19- 20, 2019 at Vienna, Austria

Cervical Cancer: Open Access

Extended Abstract OMICS International 2017 Vol.2 No.3

Furthermore, epigenetic therapy resulted in up to a 40-fold reversal in this chemoresistance [2]. Other investigators have had similar findings [15,16]. In one lab, conditioned medium from OASCs altered the proteomic profiles of epithelial ovarian cancer cell lines in vitro [15]. The net effect is increased ovarian cancer proliferation, migration and chemoresistance [16]. The secretome of OASCs serves as a driver of metastatic ovarian cancer [15,16].

Discussion:

Epigenetic therapy is novel in that it not only addresses metastatic ovarian cancer directly, but it also addresses the nutritive and supportive tumor microenvironment. Our paper demonstrates that the influence of tumorigenic omentum can be reversed by epigenetic intervention. The next logical question is, " Can epigenetic therapy convert the omentum from a tumorogenic organ to a cancer resistant organ? " To again reference Steven Paget, can we make the "soil" of the omentum inhospitable to ovarian cancer [13]? In treating OASCs within the omentum, we may alter the secretome which will then starve ovarian cancer of the growth factors necessary for metastasis and proliferation. In addition to adipose stem cells, the tumor microenvironment of the omentum also consists of a vast infiltration of lymphocytes which also can be utilized to eliminate ovarian cancer. Immune regulators like interferon gamma, tumor necrosis alpha, interleukin 2 and interleukin 1 are potent activators of lymphocytes and the immune response to cancer [17-19].

Can the secretome of OASCs be modified with epigenetic therapy to release these immune regulators and induce the immune response in the omentum, targeting metastatic ovarian cancer? Moreover, ovarian cancer is known to evade lymphocyte activity with checkpoint inhibitors like PD-L1 and B7 [20]. Can epigenetic therapy thus modify the omental secretome to upregulate immune activators and down regulate checkpoint inhibitors like PD-L1 and B7? As ovarian cancer is heterogenous, so, too, its treatment needs to be heterogeneous. The classic debulking surgery followed by six cycles of carboplatin and paclitaxel fails the 70% of women who recur after 3 years [21].

Newer drugs like bevacizumab, PARP inhibitors, and immunotherapeutic agents have changed the landscape, but there is still room for improvement [22].

Conclusion:

Epigenetic therapy can augment these novel approaches. Eventually, outcomes of this research can be translated into clinical studies and will hopefully give new, safer, and more effective alternatives to women with recurrent, chemoresistant, and metastatic ovarian cancer.