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CURRENT RESEARCH AND THERAPEUTIC STRATEGIES IN EPITHELIAL OVARIAN CANCER

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Abstract
Ovarian cancer is the highly lethal tumours despite maximal therapy. Traditional treatments for these cancers which rely on non-specific, cytotoxic approaches that generally act through damaging DNA which have a marginal impact on patient survival. However, advances in the understanding of the molecular biology underlying ovarian cancer pathogenesis have revealed abnormalities in a set of common cellular pathways and functions among the majority of these tumours that are now being targeted by novel agents in preclinical and clinical development. Such molecularly targeted agents might offer the promise of improved tumour control without substantial toxicity. Still, significant challenges in their development remain, the inability to predict tumour response and limitations of drug delivery into the tumour. Currently the use of novel targeted agents, which reduce the morbidity and mortality from ovarian cancer associated with treatment by focusing on abnormal rather than normal tissues. Given the heterogeneity of this disease, increases in long-term survival might be achieved by translating recent insights at the molecular and cellular levels to personalize individual strategies for treatment and to optimize early detection.

Keywords: Review, Ovarian Cancer, Comprehensive Treatment for Ovarian Cancer, CA-125, Bevacizumab.

INTRODUCTION

Ovarian cancer is the most lethal gynecologic malignancy and it is the ninth most common cancer in women and lowest survival rate compared with all female cancer. More than 204,000 women globally diagnosed and 125,000 deaths each year (Parkin et al., 2005). In the USA the incidence of ovarian malignancies is one in 72, and every year about 22,000 women diagnosed with ovarian cancer. African-American women are mostly affected than white Americans. The World Health Organization has categorized (Tavassoli and Devilee, 2003) epithelial ovarian carcinoma represents 80% of ovarian cancers. The origin and pathogenesis of epithelial ovarian cancer (EOC) have long been investigated but still poorly understood. Studies have shown that epithelial ovarian cancer is not a single disease but is composed of a diverse group of tumors that can be classified based on distinctive morphologic and molecular genetic features (Kurman et al., 2010). The symptoms of ovarian carcinoma often are unclear or other conditions. High mortality rate is a result of the fact that the majority patients are diagnosed at a metastatic disease when it is more difficult to treat, and most of the patients diagnosed at the age of above 60 (Cannistra, 2004; National Cancer Institute (NCI), 2014). The developing and developed countries are correspondingly affected by the ovarian cancer. Since 1992 the occurrence of ovarian cancer has remained stable, and the mortality rates decreased by 1.9% per year from 2004 to 2008. The tumor growth produces the symptoms of pelvic ascites, abdominal distension and pain. Statistically a 45% of patients with ovarian carcinoma are possibly to live for five years. However the poor prognosis of ovarian carcinoma is the lack of symptoms in the early stages of disease (Munkarah et al., 2007; Hogdall, 2008), and the lack of scientifically available screening tools (Australian Institute of Health and Welfare and National Breast and Ovarian Cancer Centre (Australia), 2010).

Still there is no novel therapeutic agent are suggested for the treatment of ovarian cancer. Although the critical need of develop highly sensitive or specific screening tools for the early detection of disease. The most of current investigations focuses on the inhibition of signal transduction pathways and targeting DNA repair mechanisms. Currently the use of targeted agents, which reduce the morbidity and mortality from ovarian cancer associated with treatment by focusing on abnormal rather than normal tissues. However, this review deals with investigation of advances in biomarker and targeting agents in development for the treatment of ovarian cancer to improve the survival rate among the patient population.

TYPES OF OVARIAN CANCER

There are many types of ovarian cancer. Some types of ovarian cancer are extremely rare. The major three types are named for the cells where they start; *i) Epithelial:* Epithelial ovarian carcinoma (EOC) is the major ovarian cancer (90%), which start in the epithelial tissue (outside lining of the ovary). The World Health Organization histological typing of epithelial ovarian tumors distinguishes the following different subtypes. These types are divided into serous, mucinous, endometrioid,

clear cell, transitional and undifferentiated types. Clinical trials also have confirmed that the subtype has prognostic significance of progression (Mackay *et al*., 2010). Conversely the threat of EOC increased with age, particularly after above the age of fifty. *ii) Serous cancer***:** In ovarian cancer, serous carcinomas are the major common histological subtype accounting for up to 80% of diseases. Currently many data has been offered that high grade serous and low-grade serous ovarian cancers are two different disease entities (Vang *et al*., 2009). Patients with mild cytologicatypia and small mitotic rates are classified as low-grade, but patients with elevated cytologicatypia and high mitotic process are measured high grade serous tumors. Clinically, patients with low grade serous tumors, which report for 10% of serous cancers and consist of a longer survival compared with high-grade tumors (Diaz-Padilla *et al*., 2012). The low-grade serous tumors do not react to conventional chemotherapy regimens (Schmeler *et al*., 2008). *iii) Clear cell carcinoma:* The clear cell carcinoma of the ovary were considered by the origin of mesonephric or mesometanephric (Schiller, 1939), but at present these neoplasm are normally measured to be of the genital tract, of muillerian (Herbst and Scully, 1970; Kurman RJ, Scully, 1976). Clear-cell carcinomas report for 5% of ovarian cancers in the world. It develops more common in Japanese women. In stage 1 clear cell tumor prognosis is relatively high but in advanced stage with worse prognosis than serous ovarian carcinoma and resistant to the standard chemotherapeutic agents used. Clear cell carcinoma is also strongly related with endometriosis and important proportions carry ARID1A mutations (Wiegand *et al*., 2010). *Borderline tumors (tumors of low malignant Potential):* Borderline tumors consist of about 10%–15% of ovarian malignancies. As most borderline tumors is serous in origin. Borderline serous tumors form part of the low-grade serous tumors. They are controllable typically by surgery and poor responds to chemotherapy. *Ovarian germ cell tumors:* Germ cell tumours account for about less than 5% of ovarian carcinoma. Mostly ovarian germ cell tumors are benign, but a few are cancerous. Its start in the egg producing cells and which may arise in any age, but about 80% are affected at the age of 30. Normally, patients with germ cell tumor the 9/10 surviving as a minimum 5 years after detecting. There are several subtypes of germ cell tumors. The most common germ cell tumors are teratoma, dysgerminoma, endodermal sinus tumor and choriocarcinoma. Teratomas are germ cell neoplasm which arises in three layers of a developing embryo (the endoderm, mesoderm and ectoderm) which are almost all common ovarian germ cell tumor and it is a benign that generally women affected at reproductive age. Although it can be treated by removal of the cyst, after sometimes a new cyst develops in the other side of the ovary. Dysgerminoma is a rare ovarian germ cell tumor and usually women affected in their teens and twenties of age. *Sex cord stromal:* About 5% of ovarian cancers only affected by the sex cord stromal tumour, which arises in the connective tissue of the ovary which produce estrogens and progesterone hormones. Mostly women are diagnosed at advanced stage. Sub types of sex cord stromal tumors include granulosa, granulose theca and sertoli leydig cell tumors.

HOW IS OVARIAN CANCER STAGED?

Staging is very important because ovarian cancers have different prognoses at different stages and are treated differently. Staging is the process of finding out how widespread a cancer is. Most ovarian cancers that are not obviously widespread are staged at surgery. One of the goals of surgery for ovarian cancer is to take tissue samples fordiagnosis and staging. To stage the cancer, samples of tissues are taken from different parts of the pelvis and abdomen and examined under the microscope. There are four stages of ovarian cancer - Stage I (early disease) to Stage IV (advanced disease). Your treatment plan and prognosis (the probable course and outcome of your disease) will be determined by the stage of cancer you have.

i) Stage I: The neoplasm is only limited to the ovary (or ovaries) or fallopian tube(s). It has not spread to other organs.
Stage IA: Cancer has developed in one ovary and the tumor is confined to the inside of the ovary, and also spread only inside the fallopian tube
Stage IB: Cancer has formed in both ovaries and fallopian tubes but not on their outer surfaces.
Stage IC: Cancer is in one or both ovaries. It also on the surface of the ovary or in abdominal fluid or a fluid-filled capsule has burst.

ii) Stage II: The cancer is in one or both ovaries or fallopian tubes and has spread to nearby organs of uterus, bladder, the sigmoid colon, or the rectum but not in distant sites.
Stage IIA: The tumor has spread to the uterus, Fallopian tubes or both
Stage IIB: The tumor has spread to the pelvic organs such as bladder, rectum or colon.
Stage IIC: The tumor has spread to any of the above. Also, it is on the surface of the ovary, a fluid-filled capsule has burst or cancer cells are in abdominal fluid.

iii) Stage III: The cancer is in one or both ovaries. It has spread to nearby lymph nodes or other abdominal organs, not including the liver.
Stage IIIA: The cancer has spread to the lining of the abdomen and the cancer spread in the lymph nodes is 10 mm across or smaller.

Stage IIIB: cancer present in one or both ovaries or fallopian tubes, and it may have spread into close to organs in the pelvis. It may spread 2 cm or smaller across, are in the abdomen and may also deposits on the outside of the liver or spleen. Cancer may have also spread to the lymph nodes, but it has not spread to the inside of the liver or spleen or to distant sites.
Stage IIIC: the cancer may have also spread to the lymph nodes, except it has not spread to the inside of the liver or spleen or to distant sites.

iv) Stage IV: The cancer has spread to the lung, liver or other distant organs.

SYMPTOMS AND DIAGNOSIS OF OVARIAN CANCER

Symptoms of ovarian cancer is general abdominal discomfort or pain, bloating and/or a feeling of fullness, even after a light meal, nausea, diarrhea, constipation or frequent urination, unexplained weight loss or gain, loss of appetite, abnormal vaginal bleeding, unusual fatigue, back pain, pain during sex, menstrual changes, and this symptoms are occur more than 12 times a month.

Patients with ovarian cancer may have less number of symptoms, and making clinical early diagnosis is more difficult. Symptoms are most commonly seen with advanced stage. Recognized symptoms of all stages includes pelvic pain, constipation, diarrhea, urinary frequency, vaginal bleeding, abdominal distension and fatigue. In advanced ovarian cancer, ascites and abdominal masses lead to increased abdominal girth, bloating, nausea, anorexia, dyspepsia and early satiety. Extension of disease across the diaphragm to the pleural cavities can produce pleural effusions and the development of respiratory symptoms. Tissue biopsy is the only technique to find exact ovarian cancer is surgery, laparoscopy and fine needle aspiration (FNA) is the types of biopsy. Ultrasound evaluation is the largely valuable non-invasive diagnostic examination. The diagnosis of suspected ovarian carcinoma includes measurement of CA 125, which is elevated in most of the patients with metastatic disease of EOC (Cannistra, 2004) conversely it is also highest in serous and humble in mucinous EOC. However CA 125 is not only specific for EOC and it may be high in nonmalignant state (Bast *et al*., 1983).

Other Available Tools for Ovarian Cancer Diagnosis: CA-125

The CA-125 is a biomarker that may be higher in the blood of some patients with particular types of cancers. The CA-125 glycoprotein antigen is the mainly considered tumor marker for ovarian tumors, report for 85–90% of ovarian cancers. CA-125 is elevated in women with early and advanced stage of ovarian cancer is 47%:80–90% (American College of Obstetricians and Gynecologists, 2009). National Cancer Institute conducted CA-125 screening study there are 3692 women participated in a screening study and 2% of false-positive rate achieved in ovarian cancer (Skates *et al*., 2011). However CA-125 Clinically has been used for diagnosis with improve prognosis and surveillance of patients. The CA-125 is combination with other biomarkers and without combined imaging techniques and concurrent assessment of multiple markers may achieve the required sensitivity specificity.

Serum Biomarkers Are Under Evaluation beside CA-125: HE4

This protein has a four disulfide core and is encoded by the *WFDC2* gene (Galgano *et al*., 2006). It is higher in ovarian cancer and especially in different types of (EOC's) the HE4 mRNA level is high (Hough *et al*., 2000; Lu *et al*., 2004). Specifically HE4 is overexpressed in, endometrioid and serous ovarian cancer (Drapkin *et al*., 2005). Recently, two studies similarly concluded that HE4 is a valuable biomarker in the detecting of ovarian cancer (Wu *et al*., 2012; Yu *et al*., 2012). HE4 obtained US FDA approval for monitoring of disease recurrence or progression. Moore *et al*. reported that HE4 and CA-125 are combined to detect tumor, reported a sensitivity of 94.3% and specificity of 75% (Moore *et al*., 2009).

Mesothelin: Mesothelin is a cell surface molecule and expressed by mesothelial cells. Elevated serum mesothelin was detected in 60% of ovarian cancers (Mcintosh *et al*., 2004). Obulhasim found that mesothelin was highly expressed in serous cystadenocarcinoma and serous borderline tumors of the ovary. Combination of mesothelin and CA-125 detected more ovarian cancers than each marker alone. Early stage ovarian cancer the mesothelin was elevated in urine assays in comparison with serum assays and patients with 95% specificity (Badgwell *et al*., 2007).

Transferrin: Transferrin (79 kDa) is an iron binding blood plasma glycoprotein's responsible for transporting iron. Ahmed *et al*. previously reported that transferrin to be decreased in the serum of women with ovarian cancer (Ahmed *et al*., 2005). Its function as promoter of tumor development and survival via antiapoptotic effects (Koshkaryev *et al*., 2012). One combination study of CA-125, transferrin, TTR and ApoA1 gained a sensitivity and specificity (89%:92%) respectively for early detection screening (Su *et al*., 2007).

Osteopontin: Osteopontin (OPN) is an adhesive glycol-protein associated with bone remodeling and in addition to immune function and it is produced by vascular endothelial cells and osteoblasts. It inhibits apoptosis in ovarian tumor. Kim conducted a study which consisting of 107 plasma samples using cDNA array, resulted considerably elevated levels of OPN expressed in invasive ovarian cancer and borderline ovarian tumors (Kim *et al*., 2002). OPN is mostly used as a sole biomarker and it has a sensitivity of 81.3%, when it is combined with CA-125 the sensitivity is 93.8%, but a little specificity of 33.7% (Nakae *et al*., 2006). Combination study of osteopontin with leptin, prolactin and IGF, found that a sensitivity of 96% and a specificity of 94% (Mor *et al*., 2005).

Vascular Endothelial Growth Factor (**VEGF):** Vascular endothelial growth factor (VEGF) is a potent angiogenic factor and was first described as an essential growth factor for vascular endothelial cells. VEGF is up-regulated in many tumors and its contribution to tumor angiogenesis is well defined. In addition to endothelial cells, VEGF and VEGF receptors are expressed on numerous non-endothelial cells including tumor cells. VEGF is a glycosylated angiogenesis mediator, and the VEGF intensity in sera from patients with metastatic stage was higher than patients with localized ovarian tumors (Kraft *et al*., 2009). Although elevated level of VEGF in ascitic fluids to be considerably related with shorter overal survival. However VEGF is combined with CA-125 the sensitivity is and specificity is (77%:87%) respectively (Li *et al*., 2004). The inhibition VEGF has been revealed to inhibit tumor growth (Byrne *et al*., 2003).

miRNAs: Recently many studies focused on miRNAs for identify potential protein biomarkers. The miRNAs is a non-coding RNAs that negatively regulate gene expression by translation inhibition or messenger RNA (mRNA) degradation, through base-pair (Lopez *et al*., 2009; Mendell and Olson, 2012). The miRNA expression in ovarian cancer has defined differentially expressed miRNAs in ovarian cancer (Iorio *et al*., 2007; Zhang *et al*., 2008). Different miRNAs may represent potentially targets for detection, diagnosis, and therapy for ovarian cancer (Bartels and Tsongalis, 2009). A recent cancer genome atlas report revealed 487 samples had consequent miRNA data from 489 samples of serous ovarian adenocarcinomas (Integrated genomic analyses of ovarian carcinoma, 2011). Resnick *et al*. conducted a study on differences in serum miRNAs between normal and patients with ovarian cancer, resulted that among the 21 miRNAs, these five miRNAs were found to be over expressed miR-21, miR-29a, miR-92, miR-93 and miR-126, and 3 miRNAs (miR-127 and miR155 and miR-99) were lower expression in the sera of patients with ovarian cancer (Resnick *et al*., 2009). Currently several studies focused on establishing miRNA as novel molecular biomarkers for ovarian cancer (Kuhlmann *et al*., 2012).

Prevention and early detection: The identification of patients at increased genetic risk (genomic alterations) currently offers the most effective measure for prevention and early detection of disease. Most of the ovarian cancer is diagnosed at an advanced stage, and these women have significantly worse outcome than those with early stage disease. It is important to recognize that the extent of disease and the ability to remove the tumor surgically (Shih and Kurman, 2004). High grade serous ovarian carcinoma is the most common ovarian carcinomas and most patients present with advanced stage disease. However, there are many early detection tests should focus on identifying the precursors of advanced stage high grade serous ovarian tumors. Emerging insights into disease progression of high grade serous ovarian cancers now suggest that early detection of low volume advanced stage, rather than early stage. We are in need to develop early detection tools.

Tumor adaptation and resistance: Tumor resistance to chemotherapy is a well known clinical phenomenon.Cell line studies and immunohistochemical studies of tumors suggest that resistance is a selective process. The evolutionary models of clonal selection may elucidate drug resistance in carcinoma. Resistance in ovarian carcinoma and in particular whether heterogeneity may associate with primary platinum resistance, and needs further investigation. The plethora of research devoted to the mechanisms of platinum resistance. However, this translates to clinical practise. Most recent, studies provided some of the first insights into clonal variation and mechanisms of resistance *in vivo* (Cooke *et al*., 2010; Stronach *et al*., 2011).

Pathology and the Site of Origin: A clear etiologic factor responsible for the evolution of ovarian cancer has not been identified. Although many cycles of ovulation in ovary, and the ovarian surface epithelium undergoes repeated distraction and repair. The epithelial ovarian carcinoma represents 80% of ovarian cancers according to the major epithelial cell type (Tavassoli and Devilee, 2003). The high grade serous carcinoma is origin in three anatomical sites: the ovarian surface epithelium, the fallopian tube epithelium, and the mesothelium covering the surface of the peritoneal cavity. The repeated cycle of ovulation and surface repair, and the tendency of the ovarian epithelium to become trapped in addition cysts contribute to malignant conversion. Generally the pathologists were unable to find an in situ ovarian lesion. Currently the

high grade ovarian serous carcinoma is the only epithelial cancer without a recognized precancerous component. Presently, the fimbriael epithelium of the fallopian tube is a possible site of origin for ovarian cancer (Piek *et al*., 2001).

Treatment Strategies: Surgery

Surgery is mandatory for the diagnosis, staging, and treatment of ovarian cancer. While ovarian cancer can spread through the lymphatic system, the mass of the tumor growth will be found on peritoneal surfaces. This distinctive tumor spread within the peritoneal cavity has led to attempts at surgical resection. In the past three decades, almost every study has demonstrated that the initial surgery and overall survival (OS) for patients with ovarian cancer (Bristow *et al*., 2002). The main aim of debulking surgery is to make the patient entirely debulked and obviously with no evidence of disease. Patients with initial surgery performed by a gynecologic oncology surgeon are more likely to be diagnosis and staging of disease and to provide therapeutic benefit with cytoreduction. This specific histologic diagnosis and exact staging are necessary for before systemic treatment as well as prognosis, will be resolute by the surgical stage of disease. Ovarian cancers are surgically staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system (Benedet *et al*., 2000). After the debulking of stage III disease long term OS is approximately 25%; therefore, a small but women treated with aggressive initial surgery followed by some chemotherapy found significant cure rate.

Radiation therapy: Radiation therapy exploit high energy x-rays or particles to destroy malignant cells. In the earlier period radiation was used more regularly for ovarian cancer, now it is only rarely used for main treatment for this cancer. External beam radiation therapy is the main type of used for treatment of ovarian cancer and this given 5 days a week for several weeks. Radiation therapy also may be given as a brachytherapy (implant of radioactive materials) placed near the malignancy and is rarely done for ovarian cancer. The abdomino-pelvic radiation therapy used for the patients with minimal remaining disease after primary surgery. Mostly there are two moving-strip techniques commonly used for the treatment, in which a small part of the abdomen is irradiated every day in order; but in open-field method, in which the whole volume is treated every day (Dembo *et al*., 1983). However the long treatment practice may allow accelerate proliferation of neoplasm (Withers *et al*., 1988) and reseeding of tumor metastases from the untreated area to the treated area. The abdomino-pelvic radiation therapy for ovarian cancer is used in the past 15 years in all stages (Delclos and Smith, 1975). Randomized and nonrandomized studies of abdomino-pelvic radiation therapy, significantly data have defined the patients favorable outcome. Using abdomino-pelvic radiation therapy for advanced disease (stage III), patients with OS rate is 10 years and with less late morbidity. One nonrandomized study with the six cycles of cisplatin-based combination chemotherapy, followed by abdominopelvic radiation therapy prove improve their median survival time and less recurence rate significantly, compared to that achieved by radiation therapy alone (Schray *et al*., 1988).

Chemotherapy: Chemotherapy is the use of chemicals to kill rogue cells. Historically these cancer drugs worked almost indiscriminately on rapidly dividing cells, usually poisoning them through free-radical toxic action. The chemotherapy drugs used are decided according to the type of tumour and its state of advancement. Some chemicals work directly on the rogue cell´s DNA; others on the receptors at the cell surface, trying to stop the rogue secondary messages getting through. The risks are largely in the side effects. Pills taken orally, or drugs administered into veins, poison the whole body. Indeed, some drugs are themselves carcinogens. The liver and immune system do their best to remove the poisons, but both are weakened in the process.

Women with ovarian cancer may need chemotherapy after surgery to obliterate ovarian cancer cells. Chemotherapy (chemo) is the nutritional or pharmaceutical drugs to slow or converse the development of pre-malignancy to invasive cancer. Mostly it uses drugs that are injected into a vein (IV) or given by mouth. However some patients with ovarian cancer, chemotherapy may also be injected via a catheter (thin tube) directly into the abdominal cavity that is called intraperitonial (IP) chemotherapy. In this way the drugs are absorbed into the bloodstream. Chemotherapy drugs exterminate cancer cells at the same time it damage may some normal cells. Therefore, the oncology doctor will be considerate to avoid or reduce side effects, it depend on the type of drugs, the quantity taken, and the duration of treatment. It is most frequently a combination of two or more drugs, given IV every 3 to 4 weeks. Giving A single drug alone seems to be more effective than combinations of drugs in the initial treatment of ovarian cancer.

A recent meta-analysis of five large potential clinical experiments with platinum-based chemotherapy reveals that chemotherapy is more beneficial in patients with early stage ovarian cancer (Winter Roach *et al*., 2009). Patients who treated with platinum based adjuvant chemotherapy had improved OS and PFS than patients who did not treated with adjuvant chemotherapy. The only one randomised trial (GOG 157) which illustrated that patients treated with six phase of carboplatin

and paclitaxel were no longer PFS or OS (Chan JK *et al*., 2010). Currently there is no data to show that the addition of paclitaxel to carboplatin is better.

Specific Novel Targeted therapies: Cancer world have developed enormously. However, despite this advancement, many tumors develop resistance and novel approaches are needed. Recently, a greater understanding of cellular biology has translated into the development of novel anti oncogenic agents with varying mechanisms of action. The small molecule inhibitors has demonstrated activity in positive metastatic multiple cancer types and in the preoperative setting (Bast *et al*., 2009).

Antiangiogenic therapy: Angiogenesis plays a critical role in the growth and spread of cancer. A blood supply is necessary for tumors to grow beyond a few millimeters in size. Because tumors cannot grow beyond a certain size or spread without a blood supply, and scientists are trying to find ways to block angiogenesis. They are studying natural and synthetic angiogenic inhibitors, also called anti-angiogenic agents, with the idea that these molecules will prevent or slow the growth of cancer (Shih et al., 2006).

Bevacizumab: In Epithelial Ovarian Cancer (EOC), particularly the angiogenesis had a crucial role so it has been a key target in clinical research. Bevacizumab, is a monoclonal antibody that binds to the vascular endothelial growth factor (VEGF)-receptor ligand VEGF-A. In a Phase II trial of 62 ovarian cancer patients treated with bevacizumab, from this 13 patients 21% experienced clinical responses (two complete responses [CR] and eleven partial responses [PR]), and 25 patients 40.3% experienced survived progression-free for at least 6 months, with no gastrointestinal (GI) perforations (Burger *et al*., 2007). The International Collaborative Ovarian Neoplasm group (ICON) 7 found that the greatest benefit of adding bevacizumab was seen in population with advanced stage III–IV disease. Within this population, significantly median Overall survival (OS) is 28.8 and 36.6 months (Perren *et al*., 2011).

Aflibercept (VEGF trap): Aflibercept is a heterodimeric molecule and it has a lower molecular weight than bevacizumab. Specifically it have domains of vascular endothelial growth factor 1 (VEGFR1) and VEGFR2 with immunoglobulin G Fc, and possesses a higher affinity for VEGF isoforms (VEGF-A, VEGF-B), and placental growth factor (Aravantinos and Pectasides, 2014). Coleman et al. treated 46 patients in this setting with a combination of aflibercept (6 mg/kg iv) and docetaxel (75 mg/m2 iv) and found 54% objective response rate (ORR), and ten patients with median Progression free survival (PFS) and Overall survival (OS) of 6.2 months and 24.3 months, respectively (Coleman *et al*., 2011). In another one randomized trial in 55 patients with EOC, reported that aflibercept considerably extended time to ascitic drainage and there was no effect on OS (Gotlieb *et al*., 2012).

Nintedanib: Nintedanib (BIBF 1120) was the angiokinase inhibitor which obstructs tumor angiogenesis at many levels by targeting VEGF, fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF). A placebo-controlled Phase II study investigated with nintedanib (250 mg twice daily) in 83 recurrent EOC patients found some PFS advantages (Ledermann *et al*., 2011). One Phase III study comparing nintedanib combined with either carboplatin/paclitaxel or placebo confirmed considerably protracted PFS (Du Bois *et al*., 2013).

Treatment of Stages I and II EOC: Most ovarian cancer treatment recommendations are reliant on the stage of the disease and extent of surgical debulking. Approximately 25% of women with ovarian cancer have stage I and stage II disease. Even among this good-prognosis group, the failure rate is high enough to warrant adjuvant chemotherapy in most patients. Two parallel randomized trials compared a platinum-containing adjuvant chemotherapy regimen with after surgery with over 4 years of median report on over 900 cases and found the risk ratio for recurrence-free survival is 0.64 (95%) confidence interval in favor of adjuvant chemotherapy, and the OS is 0.67 (95%). Studies from last 3 decades has shown that patients with stage IA or IB disease found that 91% of 5-year disease-free survival (DFS) rate and 94% of 5-year Overall Survival rate with surgery alone. However, chemotherapy improves PFS for patients with stage IA or IB and stage IC, or stage II disease (Young *et al*., 1990).

Treatment of Advanced Stage (Stages III and IV) EOC: Most of the women with ovarian cancer present with advanced stages of (stage III or IV disease). As prognosis of stage III or IV disease are correlates with the extent of remaining disease after primary debulking surgery. Although, continually those with the slightest tumour burden after surgery has the best prognosis with the diameter of the smallest residual lesion increases (Bristow *et al*., 2002). A randomized comparative trial of primary debulking surgery then platinum-based chemotherapy with neoadjuvant platinum-based chemotherapy in stage IIIC

or IV EOC (Vergote *et al*., 2010). From this trial found that the median OS of the two groups (30 and 29 months) respectively.

Genetic Alterations in Ovarian cancer and existing therapies: Mostly genetic mutations associate with ovarian neoplasm are not inherited but instead happen during a woman's life. A study, from 316 HGS-OvCa samples the exome capture and sequencing on DNA isolated and from matched normal samples for each individual. From Two different algorithms nine genes identified for which the number of non-synonymous or splice site mutations. Consistent with published results (Ahmed *et al*., 2010), TP53 mutation identified in 303 of 316 samples, and the germ line mutations of BRCA1 and BRCA2 identified in 9% and 8% of cases, respectively, and showed somatic mutations in a further 3% of cases. The BRCA1and BRCA2 gene, located on chromosome (17q, and 13q) respectively. Its function is repair of double strand DNA (Venkitaraman, 2002). Any deleterious mutations interfere with their function, which appear to act as tumor suppressor genes. Inheritance of a deleterious mutation in BRCA genes is 27% to 44% associated with lifetime risk of ovarian cancer compared with 1.4% in the general population. Once the BRCA1 or BRCA2 are mutated and homologous recombination (HR) is compromised, the repair mechanism is greatly reduced, and less reliable repair pathways such as non-homologous end joining (NHEJ) will be used, leading to increased genomic volatility. *BRCA* mutated ovarian cancer patients may be more sensitive to platinum based chemotherapy (Cass *et al*., 2003; Tan *et al*., 2008). Another PARP protein is also involved in DNA repair and thus *BRCA* mutated cells are greatly responsive to PARP inhibition. Mutations in members of the HR pathway such as ATM and CHK2 are common in cancers with deficient BRCA (Sullivan *et al*., 2002; Tommiska *et al*., 2008; Roy *et al*., 2012). However, cells with several mutations in the HR pathway will have a noticeable sensitivity towards PARP inhibitors. Several PARP inhibitors are currently used in the clinic for patients with BRCA mutations or methylation. Although six other recurrently mutated genes are RB1, NF1, FAT3, CSMD3, GABRA6 and CDK12. There are nine CDK12 mutated identified, five of the nine non-sense, suggesting potential loss of function and the four missense mutations (Arg882Leu, Tyr901Cys, Lys975Glu and Leu996Phe) were clustered in its protein kinase domain. GABRA6 and FAT3 both are less significantly mutated but did not seem to be expressed in HGS-OvCa or fallopian tube tissue. The inherited (germline) mutation represents the Knudsen's 2-hit model of carcinogenesis. It is hypothesized that when mutations obstruct with the DNA repair mechanism of the normal gene, as a result in the increase of chromosomal abnormalities and a tendency to produce malignancy. When the second allele of the gene develops a defect, the state is set for the progress of cancer (Brody LC, Biesecker, 1998).

CONCLUSION

Treatment of recurrent ovarian cancer is challenging. So find a cure or manage the disease is much more important. The high complete response rate seen after maximal surgical debulking surgery and platinum combination chemotherapy. The CA-125 glycoprotein antigen is the mainly considered tumor marker for epithelial ovarian tumors, which report for 85–90% of ovarian cancers. Different miRNAs may represent potentially targets for detection, diagnosis, and therapy of ovarian cancer. Currently several studies focused on establishing miRNA as novel molecular biomarkers for ovarian cancer. Recurrent ovarian cancer is challenging, and despite the many advances in therapeutic options for this disease, many controversies remain. Research findings continue to resolve many of these issues, including data from trials evaluating the role of secondary cytoreduction, maintenance therapy, and the prognostic significance of CA 125. Finding the optimal treatment paradigms for ovarian cancer patients will remain the goal for improving outcomes. To achieve this daunting task needs to be discovered.

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