

## An Update on High Grade Serous Ovarian Carcinoma - A Comprehensive Review

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### Abstract

Once function of these genes is lost it is associated with homologous recombination dysfunction (HRD).

Epithelial ovarian cancer (EOC) has evolved in the past few decades, that is now understood to be a collection of different histologic along with molecularly different carcinomas that might not originate from the earlier believed ovarian precursor. High Grade Serous Ovarian Cancer (HGSOC) is a special type of epithelial cancer where there is practically p53 mutations in all along with dysfunction of p53 genomic instability rather than mutations which drive them. The tumor has have an advanced stage at onset, probably derive from fallopian tube epithelium, starting with *in situ* carcinoma. It is the germline harmful mutations in BRCA1 and BRCA2 along with mutations in few prevalent DNA repair genes like PALB2 and RAD 51c and these might predict the susceptibility to various classes of treatment agents that include DNA damaging agents along with DNA repair inhibitors. HGSOC might be associated with wild type BRCA1 and BRCA2 with HRD phenotype associated with it. These might be detected by certain molecular biomarkers, that predict their sensitivity to poly adenosine-ribose (PARP) inhibitors. This has helped in creating novel treatment classes combination, which create a HRD-like cellular environments helping in getting therapeutic benefits. Further one can predict long term survival (LTS) using transcriptomic, epigenomic and proteomic platforms, which will define the conserved features that are associated with long term survival. More knowledge of getting factors contributing to LTS will help in understanding biology of OC, with the aim of improving survival of EOC patients.

**Keywords:** EOC; HRD; Germline BRCA Mutations; HGSOC; PARP Inhibitors; LTS

### Introduction

Epithelial Ovarian cancer (OC) shows the maximum cancer-related deaths with regard to gynaecological malignancies, with an estimated 204,000 cases and 125,000 deaths annually worldwide [1,2]. Of these > 75% don't get diagnosed till disease has reached advanced stage III and IV). Prognostic factors used currently don't allow reliable prediction of response to chemotherapy and survival for individual OC patients. Greater lethality, with poor rate of survival are due to absence of effective biomarkers for prognosis, hence need for finding reliable predictive biomarkers for prognosis along with developing novel therapeutic strategies for OC patients [2,3].

In the past two decades great progress has been done that has brought in changes in the field of Ovarian cancer (OC) in all aspects like diagnosis, treatment and research. OC has become plural from

singular in both our diagnosis and research. With these new classifications, drugs have come with greater chances of improving the quality and quantity of life for the women affected with cancer. This scientific progress has got answers which open directions to rethink screening along with prevention and target therapy more directly. This review aimed to update our knowledge on high grade serous cancer.

### Methods

We looked for the MeSH terms like ovarian cancer, fallopian tube cancer, peritoneal cancer, FIGO staging; predictors of chemosensitivity, biomarkers, most recommended chemotherapy in platinum sensitive and refractory cancers, various signatures of cell cycle alterations, besides both germline and somatic BRCA mutations, and other new biomarkers identified till 2018.

## Results

We found a total of 2463 articles pertaining to these of which 125 articles were used for this comprehensive review. Further cross references were sought from originally obtained articles. No meta-analysis was done.

### High grade serous ovarian cancer

The commonest histology found in OC is now agreed upon as being epithelial cancer, originating most commonly or more likely from the epithelium of the fimbria of fallopian tube. Previously this group of cancers was dumped together as high grade epithelial OC of serous or serous papillary type. An independent tumor of the fallopian tube was not recognized, partly as both the 2 organs lie so closely that to be able to distinguish origin was prevented once tumor had progressed. The new WHO histologic classification and grading system took the 2 tiered grading system of low and high grades in their revision done in 2014 [4]. High Grade Serous Ovarian tumors are recognized by their lack of architecture and sheets of malignant cells, that are often enlarged and dysmorphic nuclei and with further molecular characterization nearly 100% TP53 mutation frequency. This can be confirmed by immunohistochemistry showing overexpression of nuclear p53 staining or complete lack of such staining within the tumor, the latter getting lost in view of loss of function p53 mutations.

WHO Classification recognizes that the likely precursor lesion is serous tubal *in situ* carcinoma lesions [5,6], from where progression to invasive carcinoma might be found, although generally in small lesions. The outward facing exposure of the tubal (and ovarian) epithelium supports early shedding and implantation. The lack of an anatomic barrier between the pelvis and the abdomen, in addition to the permissive environment of the omentum, helps in local colocalization and further invasion. This is the possible reason why High Grade Serous Ovarian tumors present with advanced stage with abdominal involvement in > 70% of patients [7]. Main important cause of High Grade Serous Ovarian cancers is the dysregulation of p53 and associated effects on DNA repair genomic instability and the characteristics of high copy number viability [8]. These tumors also get characterized by expression of WT1, estrogen receptor  $\alpha$  and PAX8 [9-11]. High Grade Serous Cancers are now getting evaluated for subset analysis. Gene expression sets were found to differentiate High Grade Serous cancers into 4 distinct groups: proliferative, mesenchymal, immune, and differentiated [8,12]. These groups have yet to be applied either diagnostically or clinically. More studies will characterize genomic patterns and are ongoing. Most validated prognostic and predictive biomarkers within High Grade Serous cancers is germline deleterious mutation in either BRCA1 or

BRCA2 (gBRCA) [7,13] and with somewhat less support, somatic homozygous loss of function BRCA1 or BRCA2 [14]. A s true suppressor genes both copies must be disrupted or lost for the malignancy phenotype.

Protein that get encoded by BRCA1 or BRCA2 are critical for maintenance of the high fidelity double stranded DNA repair pathway, homologous recombination repair [7,15]. Loss of function of these genes requires loss of normal p53 regulation for cellular viability, which is consistent with the observation that p53 overexpression precedes actual tubal *in situ* carcinoma formation [6]. The Cancer Genome Atlas that analyzed biospecimens from cases of newly diagnosed high grade serous cancer, described 14% of HGSOC as having BRCA status [8]. Other 6% have somatic homozygous loss. Methylation of BRCA1 promoter has been described as associated with somatic homozygous loss. Methylation of the promoter of BRCA1 has been described as associated with loss of function; still there is controversy if this consistently yields a homologous recombination dysfunction [HRD] phenotype, as does gBRCA or somatic homozygous loss.

More lately studies have examined other proteins and genes within the homologous recombination pathway and established credibility for other genes wherein germline deleterious mutations have been seen. These were found in lower frequency, accounting for roughly 7% additional germline heritable mutations which accounted for OC [16-19]. Though inclusive of BRCA1 methylation, this accounts for roughly 1/3<sup>rd</sup> of all serous cancers. gBRCA, is prognostic of generally good outcomes of at least upto the 1<sup>st</sup> post diagnostic decade [20] and is predictive of platinum sensitivity and PARP inhibitor sensitivity. Studies are continuing for validating prognostic and predictive utility of germline mutations in the other genes associated with familial OC.

Biomarkers to identify cancers with HRD, those that are gBRCA-like have been developed [21,22] and one such biomarker has been approved as a companion diagnostic to the PARP inhibitor rucaparib [23].

Earlier transcription array studies also the identification of a subset of OC which overexpress cyclin E [8,12,24,27]. This has been further supported by genomic studies like the Cancer Genome Atlas [8]. It is predicted that the disruption of the G1/S transitions by CCN1 Amplification (20% as estimated by the Cancer Genome Atlas) by overexpressing the amplification of CCND1 or CCND2 (19%), or loss of the regulation of the G1/S checkpoint by loss of function Prb (10%) will account for nearly 1/3<sup>rd</sup> to 50% of cases. Disruption of normal G1/S Transitions also poor DNA repair, that also contributes to the classic genomic phenotype of OC [28-30].

Women in clinical trials have been HGSOC mainly represented in clinical trials done retrospectively. Hence most of the data in the literature in susceptibility to treatment, duration of response and OS are driven by the behavior of this most prevalent type of OC. Staging is used to categorize cancers regarding prognostic purposes, for guiding therapeutic decisions and as a classification method for data analysis. Recent 2014 International Federation of Gynaecology and Obstetrics (FIGO) staging system the primary system used worldwide, is a 4 tiered system with staging based on pathologic evaluation of surgical staging. It is thus biased by the completeness and department of surgery. However practically, most trials and therapeutic targets are based on disease being in early stage or organ confined (stage 1) or more than 70% of which are advanced disease at presentation. Not included in FIGO staging but importantly what was recognized decades earlier is the role of the extent of residual disease after primary or interval debulking surgery [7]. Residual disease affects prognosis and is not specific for OC and its utility.

The molecular make up of HGSOC might have the biggest implication of predicting patient's prognosis and treatment secondary to diagnosis of OC type. The aggressive genomic instability caused by various molecular mechanisms might selective directions. How this might affect initial treatment for HGSOC is currently the subject of many trials. The molecular makeup that has been used to define access to one class of new anticancer agents, that has been approved for use in OC patients. It has been seen that gBRCA associated OC's are much more susceptible to the class of PARP inhibitors, with platinum-sensitive gBRCA patients responding best (range 35 - 50% or more) and the lowest response rate (7 - 12%) in women with wild type BRCA1 and BRCA2 whose tumors are platinum resistant [23,32]. gBRCA status is thus a validated predictive biomarker for use of PARP inhibitors, which has led to a test that is used to define HRD, where biology argues susceptibility to these DNA-repair inhibitors [21-23].

Laboratory translational science has now expanded membership in the class of DNA repair inhibitor agents beyond the PARP inhibitors [15,42]. Disruption of homologous recombination can also come from inhibition of other important events in the complex homologous recombination pathway [30]. AIR and AIM kinases remain key to this form of DNA repair, and they have proved to have deleterious cancer associated germline mutations. Inhibitors of these kinases are now in clinical testing [15]. Other important element needed for proper DNA repair, is either cell cycle delay or sufficient time in the necessary cell cycle phase to

repair to proceed and complete. Block in G1/S or G2/M affects the type and extent of injury or repair as well as potentially the type of cell death [30,34,35]. Inhibitors of cell-cycle regulatory proteins are now found to be potential targeted agents for cancer treatment and might be included in the DNA repair inhibitor class. Example agents are, inhibitors of WEE kinase and CHEK kinase [36-40]. These kinases ultimately affect a G2/M cell cycle halt for allowing DNA repair to proceed. Dysregulation of this cell cycle checkpoint has been shown to propagate DNA damage, in view of inability of the ability to repair and have been shown to drive cells into apoptosis, autophagy, and mitotic catastrophe [41]. Initial clinical trials of agents which targeted these kinases have had mixed results. AZ1775, a WEE1 inhibitor has some single agent activity on gBRCA OC and limited single agent otherwise. Preclinical and early clinical data give a suggestion that it can synergize with chemotherapy or targeted agents to improve their activity markedly. A second generation CHEK1 inhibitor with some inhibition against CHEK2, that is a modulator of both G1/S and G2/M has been reported to have clinical activity in non-gBRCA recurrent high grade OC, and the study is getting further explored.

#### Developing clinical synthetic lethality

Clinical Synthetic Lethality might occur if a common underlying event or drug gain or loss of function phenotype which when combined with a drug targeted to a different pathway, collaborates to create antitumor effects [33,42]. E.g. targeting of PARP and its many downstream functions synergizes with existing loss of homologous repair function in tumors with homologous loss of function of BRCA1 or BRCA2 [15]. This more clinical benefit in these patients than is seen in patients with wild type and homologous recombination intact HSGOC [32]. This latter subgroup of women give a limited response. Investigations into creating clinical synthetic lethality to improve their outcomes in PARP inhibitors build on either contextual or chemical synthetic lethality. Chemical synthetic lethality occurs with the introduction of an additional agent (s) or modification of the microenvironment; contextual synthetic lethality leverages existing endogenous behaviors to greater benefit [33]. Targeted drug combination have added the opportunities to study the potential of clinical synthetic lethality. E.g. combination of cediranib, a pan-VEGRF1-3 inhibitor and the PARP inhibitor olaparib showed an unexpectedly high response rate and progression free survival in women with HGSOC [43,44]. Higher activity was seen in women without gBRCA in an unplanned post hoc subset analysis of the cediranib/olaparib study, 5 vs 16.5 months for single agent vs combination [43].

Angiogenesis inhibitors have been shown to cause hypoxia along with altering local blood flow [47]. Hypoxia has been shown to downregulate expression of critical DNA repair enzymes [48]. Hypoxia induction, combined with chemical disruption of DNA repair with a PARP inhibitor, is one example of clinical synthetic lethality.

Definitive studies are now ongoing to evaluate benefits of this combination in platinum sensitive (NCT02446600) and platinum resistant (NCT02502266) HGSOC.

With the understanding of the local tumour and stromal milieu of HGSOC new paths have got opened regarding therapeutic investigation. One fact has been known overtime that microvessel density and angiogenic perfusions is more common in advanced as well as aggressive OC's and appears to be most common in the high grade serous cancers [48-50]. Because of which antiangiogenic treatments are beneficial in newly diagnosed cancers [51,52], along with recurrent disease as single agents [45,53].

Local tumor microenvironment has immune infiltration. Presence of tumor infiltrating lymphocytes strongly has a prognostic value in the outcome of OC [53]. This is true for HGSOC [50,57]. Highly vascularized tumors might have different immune infiltration as compared to those non-vascularized and combination of the immune infiltration type and vascularity might affect the prognosis. Patients having high grade serous cancers that contain high regulatory T cell infiltration and high vascularity did better than patients with T cell infiltration without vascularity [50]. To understand what types of immune phenotypes are within that milieu is getting characterized to understand how to better use immunomodulating agents.

Further it has been seen that the very factors which drive angiogenesis are also important in attenuating the immune cell response [58]. VEGF causes the accumulation of myeloid-derived suppressor cells and regulatory T cells and inhibits the migration of T lymphocytes from the vasculature into the tumor. There has been a proposition that there exists a communication between hypoxia stress and immune suppression through the HIF  $\alpha$  and VEGF pathways via recruitment of regulatory T cells [60]. Utilizing this microenvironment interaction between the stromal and tumor vasculature and the peritumoral and intra tumoral immune response might help to identify reasons why current immune checkpoint inhibitors, stromal inhibitors or DNA repair inhibitors with immune checkpoint modulation help with both preclinical and clinical investigations ongoing.

If there is propagation of poorly or unrepaired DNA in cells that do not die following injury; mutations which though not harmful, might create or unmask neoantigens [61-63]. All such neoantigens might not play a role in immune stimulation. Apparently, there are common epitopes [61] or cancer-testis antigens like NESO1, which may activate T-cell mediated immunity more globally in HGSOC patients. For testing these queries, current research is incorporating measures of neoantigens and selective responsiveness for targeting cancer-testis antigens. Still what is not clear is whether these findings might turn out to be tumor type specific, microenvironment like organ) specific, or generalizable. Clinical approaches for testing these propositions are combination of immune checkpoint inhibitors with angiogenesis inhibitors have got started.

### Biomarkers and homologous recombination deficiency (HRD) phenotypes

Being able to measure homologous repair defects in a semiquantitative fashion to find and select patients for treatment with PARP inhibitors is in early stage phenotype analysis, although seems to be promising. Genomic instability can't be quantified with a single test; presence or absence of gBRCA mutations is not sufficient to give a more global assessment of this highly plastic genome in HGSOC. Currently 3 independent DNA-based measures (unweighted sum of scores > than 42) of genomic on the basis of loss of heterogeneity, telomeric allelic imbalance, and large scale transitions have been described, which characterize HRD [21,22]. Prospective validation of this in OC was done in the study presented at the 2016 congress of the European society of Medical Oncology. Further retrospectively biospecimens and data from women having triple negative breast cancers who received iniparib with cisplatin and gemcitabine was analyzed. Triple negative breast cancer tumors, including BRCA1/2 wild type tumors, were more likely to respond to platinum containing therapy if they showed HRD as measured by a weighted summed score of loss of heterozygosity, telomeric allelic imbalance, and large scale transition [64].

Rucaparib treatment was examined in a randomized prospective trial for women having platinum sensitive HGSOC, in ARIEL2. Overall response rate was reported as 70% [23]. In this trial Foundation Medicine companion diagnostic HRD test for BRCAness signature was tested, where 40% of patients with the signature and 8% without the signature showed a response to Rucaparib. Thus, this signature might be of use in finding patients that might benefit with PARP inhibitors.

The PARP inhibitor niraparib was studied in a randomized prospective trial of maintenance or placebo for women having high grade OC, in the ones who had completed platinum based therapy for recurrent disease. gBRCA patients getting niraparib vs placebo had significantly longer median progression free survival (PFS), 21 vs 5.5 months. The niraparib as compared to placebo outcome was 12.9 vs 3.8 months in the gBRCA wild type cohort with HRD as was measured using a composite HRD test. In the patients who had platinum sensitive, recurrent OC, median duration of progression free survival was significantly longer among those receiving niraparib than those getting placebo irrespective of the presence or absence of gBRCA mutations or HRA status. The presence of an HRD phenotype correlated with outcomes for the patients in each of the settings as referred to earlier. Thus, these steps to start with are very important in developing phenotypic biomarkers which can get used for finding the patients who have homologous DNA repair defects for treatment with PARP inhibitors and other inhibitors which take care of the DNA damage response which is an integral part of cell replication and genomic instability.

Further Xu, *et al.* conducted a study where they investigated the role of Cyclin G1 (CCNG1), a target gene of wild type tumor suppressor gene TP53 (p53wt) and CCNG1 in progression of HG-SOC and the possible regulatory mechanism between TP53 mutant (p53mt) and CCNG1 in the progression of HGSOC. High expression level of CCNG1 was found in 61.3% of HGSOC tissues and only 18.2% fimbriae of fallopian tubes. Also, overexpression of CCNG1 was significantly associated with a shorter overall survival ( $p < 0.0001$ ) and PFS ( $P < 0.0004$ ) in HGSOC patients. *In vitro* CCNG1 promoted both tumor cell motility by including epithelial mesenchymal transition (EMT) and resistance to cisplatin (CDDP). *In vivo* knock down expression of CCNG1 inhibited cancer metastasis. Furthermore, P53mt increased the expression of CCNG1 by regulating Notch 3 expression and a positive correlation between CCNG1 and Notch 3 protein expression was observed by immunohistochemistry (IHC) ( $r = 0.39$ ,  $p = 0.01528$ ). Thus they concluded that the activation of P53mt-Notch3-CCNG1 pathway was responsible for tumor progression to advanced disease with correlation with worse prognosis in patients with HGSOC. These data suggest a possible mechanism of disease and highlights and highlights CCNG1's potential role as a therapeutic target in HGSOC [65]. Further Akbarzadeh, *et al.* studied the MTT proliferation assays to evaluate effects of DAPT (N-[N-(3, 5-Difluorophenyl)-1]-S-Phenyl glycine t butyl ester) inhibitor on cell proliferation. For measurement of Hes-1 mRNA levels, quantitative reverse transcription polymerase chain reaction (QRT-PCR) was applied following 48h incubation with the inhibition. Additionally metalloproteinase (MMP'S) activ-

ity was assessed by zymography. They found Notch signaling resulted in a significant reduction in OVCAR3 cell proliferation. Additionally DAPT treatment in single cells significantly decreased Hes1 mRNA levels ( $p < 0.05$ ) as well as activity of MMP2 and 9 ( $p < 0.05$ ). Thus concluding that their results suggested that suppression of Notch via a reduction of the activity of metalloproteinase 2 and 9. Thus pharmacological targeting of the Notch signaling pathway could be a promising future treatment of ovarian cancer [66].

The epidermal growth factor receptor (EGFR) tyrosine kinase family consists of 4 members EGFR, ERBB2, ERBB3, ERBB4. These receptors get activated on the binding of a ligand to their extracellular domains, that trigger homodimerization or heterodimerization activation of various downstream cell signaling pathway and ultimately in tumor cell proliferation, decreased apoptosis along with tumor migration and invasion [67-69]. Over 3 last decades increased aberrant expression of the EGFR family members has been described in a big group of cancers of different kinds, and in some reports has also been associated with poor prognosis along with resistance to therapeutic options [68,70]. Further the EGFR family of tyrosine kinases has emerged as an important therapeutic target in malignancies, and till date various antibodies, recombinant proteins, peptide mimetics along with small molecules like cetuximab, panitumumab, trastuzumab, gefitinib, erlotinib and lapatinib have been produced to target EGFR family receptors as therapeutic targets for many types of solid tumors [67,70]. Function of various EGFR members add to ovarian tumorigenesis as per latest reports. Still the clinicopathological and prognostic values and expression patterns of EGFR family members in OC is controversial [71-73]. Also role of EGFR family members in OC and the underlying molecular mechanism responsible for its involvement in tumor development and progression are mostly not known.

Development of microarray and RNA sequencing technology has revolutionized both RNA and DNA research, that has become an important part of biology and biomedical research [74,75]. Thus Zhou, *et al.* reported distinct expression and prognostic value of EGFR family members in patients with OC by analyzing a series of databases including ONCOMINE Gene Expression profiling Interactive Analysis, Kaplan-Meier Plotter, cBio Portal. They found that in patients with OC mRNA expression level of ERBB 2/3/4 were significantly upregulated, while the transcriptional level of EGFR were downregulated. Aberrant EGFR expression and ERBB2/3/4 mRNA levels were associated with OC prognosis. Hence they concluded that EGFR and ERBB 3/4 are distinct prognostic biomarkers and might be potential targets for OC. Thus these results might help in better understanding the molecular underpinning of OC and may

be useful for developing tools for better and more accurate OC prognosis along with promoting development of EGFR targeted inhibitors for OC treatment [76].

Among the subtypes of ovarian cancer, high grade serous carcinoma is the most prevalent, of which FIGO Stage IIIc constitutes the majority. But due to genetic heterogeneity and lack of personalized treatment the prognosis of FIGO Stage IIIc patients varies even following optimal cytoreductive surgery along with combined platinum based chemotherapy [77].

In the past years prognostic biomarkers, were discovered in ovarian cancer. High expression of NQQ1 was reported to be up-regulated in serous ovarian carcinoma and predicts a poor prognosis [78], using immunohistochemical staining. Similarly MMSET expression is positively associated with aggressiveness and poor clinical outcome [79]. Increased expression of 3-phosphoinositide-dependent protein kinase 1 (PDK1) was also shown to be correlated with improved survival [80]. Additionally miRNAs associated with ovarian serous carcinoma were also marked [81]. In another study AXL was reported to be a therapeutic target of the aggressive OSE-derived SOC [82]. However because of heterogeneity of serous ovarian cancer [83,84], single molecular biomarker is usually not robust across datasets. Besides that, models integrating multiple genes were highlighted in the past years to evaluate prognosis in many cancer types [85-89]. Mammaprint was developed with 70 genes expression to predict the survival and guide the necessity of adjuvant therapy [90]. Another model, Oncotype DX, was also shown to have good performance for predicting prognosis and adjuvant therapy choice for various cancers [91]. Still multiple gene based prognostic model for high grade FIGO Stage IIIc serous ovarian cancer (HG3SOC) had not been reported till now.

Thus Liu., *et al.* screened the transcriptome of 401 primary FIGO Stage IIIc serous ovarian cancer samples, where seven genes based prognostic method was developed. The prognostic value of risk score of 4 different cohorts (TCGA-cohort, Poland cohort, Japan cohort and USA cohort) was validated. The relationship between risk score and other clinical indicators got analyzed. Tissue microenvironment difference among samples with different risk scores was investigated. They found that high risk group (n = 200, median survival months: 39.6, 95%CI: 35.9 - 46.3 months) had a significantly worse prognosis than low risk group (n = 20), median survival months: 52.6, 95%CI: 45.2 - 64.9 months). The risk score's performance was validated in Japan cohort (n = 90, Poland cohort (n = 48) and USA cohort (n = 84). The risk score is independent from age, primary tumor size, grade and treatment methods and

the performance of risk score is uniform in subgroups. Further the risk score predicted the response of HG3cSOC to platinum based regimen after surgery, and this finding was further validated in newly collected China cohort (n = 102). Gene set Enrichment Analysis and tumor infiltration analysis revealed that risk score reflected the immune infiltration and cell to cell interaction status, and the migration function of candidate genes were also verified. Thus they concluded that optimized seven genes based model is a valuable and robust model in predicting the survival of HG3cSOC, and served as a valuable marker for the response of platinum based chemotherapy [92].

Ovarian carcinoma is the most lethal type of cancers of female reproductive system with 5 year survival rate is relatively low, having the highest mortality rates. Platinum compounds have proved to be the most effective drugs for treatment of Ovarian carcinoma. Carboplatin has long been established as a first line drug for treatment of Ovarian carcinoma [93], but patients develop resistance to these Platinum compounds, which remains the biggest challenge regarding treatment of OC [94]. Currently no effective answer is there regarding this problem [95,96]. Hence there is importance of predicting response to carboplatin, that may allow development of methods of overcoming this resistance.

Inhibitor of apoptosis protein (IAP) family has been shown to stimulate tumor formation and metastasis [97,98]. X linked IAP (XIAP) is a member of the IAP family. XIAP not only exerts an anti-apoptotic function, but also inhibits autophagy via XIAP-Mdm2-p-53 signaling [99]. Additionally XIAP has been involved in regulating innate immune responses by mediating NOD signaling via interaction with RIP3 [100]. Further XIAP confers resistance to some chemotherapeutic drugs in different types of cancers that include OC [101-104]. For example phenoxodiol Piceatannol, and HtrA1 enhance cisplatin sensitivity to OC through degradation of XIAP [101-104]. But no studies have investigated the role of XIAP in conferring cisplatin sensitivity in OC. Thus Zhang., *et al.* examined expression of XIAP in OC by immunohistochemistry. Next they investigated role of XIAP in regulating carboplatin sensitivity in OC ES2 and 3AO cells through Cell Counting Kit-8 cell viability assay and fluorescein isothiocyanate-Annexin V propidium iodide apoptosis assay. Expression of apoptotic effectors got measured by Western blot. They found that the immunohistochemistry results showed that high expression levels inversely correlated with carboplatin response (p = 0.03) and progression free survival (p = 0.0068) in patients with OC. Knockdown of XIAP repressed the cell viabilities in the carboplatin treated cells and increased carboplatin-induced caspase activation. Thus they concluded

that their results showed that XIAP mediates carboplatin sensitivity of OC and that XIAP might be a novel target for the treatment of carboplatin-resistant OC [105].

OC is a family of many diseases, each having specific histology, risk factors, molecular characteristics and treatment [106]. Epithelial OC (EOC) constitutes 90% of cases of which, serous is the most common subtype [106]. Current standard treatment of EOC of all subtypes involves debulking surgery that is followed by combination chemotherapy with a platinum plus taxane based [107,108]. Once patients relapse following 1<sup>st</sup> line, treatment might be classified into 1 of 2 subgroups; those with platinum refractory disease/resistant disease and those with platinum sensitive disease [109]. Though many agents are available for platinum resistant or refractory disease which have also got paclitaxel, still no definitive 2<sup>nd</sup> line therapy for these patients exists [107,108].

Various phase II clinical studies of patients having platinum resistant or refractory disease have shown benefit of utilizing doxorubicin or combination therapy with other agents [110-112]. Liposomal doxorubicin has been approved by United States food and drug association (US FDA) and European medical agency for OC in women who failed platinum based chemotherapy [113,114]. The guidelines for treatment approve combining traditional chemotherapeutic agents with drugs that target growth factors/receptors might be more effective for treating platinum resistant or refractory recurrent OC than chemotherapy alone [107,108].

The platelet derived growth factors (PDGFs: PDGFR $\alpha$  and PDGFR  $\beta$ ) are transmembrane receptor tyrosine kinases which get activated by their cognate ligands [115]. Platelet derived growth factor (PDGF) AA binds PDGFR $\alpha$ , while PDGFAB and PDGF BB recognize both PDGFR $\alpha$  and PDGFR  $\beta$  [115]. Once circulating PDGF ligand gets bound, PDGFR $\alpha$  and PDGFR  $\beta$  subunits homodimerize or hetero dimerize, undergo autophosphorylation, and activate downstream signal transduction molecules including phosphoinositide-3 kinase, Ras, phospholipase C $\gamma$  and Src [116,117]. PDGF signaling plays an important role in mesenchymal biology, including mesenchymal stem cell differentiation, proliferation and angiogenesis. Abnormal PDGF/PDGFR signaling is involved in the development and maintenance of cancer, and has been implicated in modulating the tumor or stromal microenvironment thus facilitating metastasis in various malignancies [116,117]. The PDGF/PDGFR axis has proangiogenic activity and might contribute to resistance to anti-vascular endothelial factor therapy [118].

Expression of PDGFR $\alpha$  has been reported in OC, although the prevalence varies [119]. This might reflect the variety of methods

along with reagents used to measure PDGFR $\alpha$  and some reports giving a suggestion that some of the reagents used in earlier studies might have been nonspecific for PDGFR $\alpha$ . Matsuo, *et al.* studied the extent of PDGFR $\alpha$  protein expression in 176 human ovarian tumors, found that the expression of PDGFR $\alpha$  was significantly associated with serous histology (serous vs non-serous 77% vs 46% respectively; odds ratio, 4.0) and advanced stage (odds ratio, 1.7) [120]. Most common histology was high grade serous OC [120]. Among pts with high grade serous tumors, PDGFR $\alpha$  expressing tumors was associated with significantly poorer survival outcomes (median OS, 51 months) as compared to patients with PDGFR $\alpha$  non-expressing tumors (median OS 174 months;  $p = 0.014$ ). Additionally when controlled for age and stage, PDGFR $\alpha$  Expression remained a significant variable for OS [120].

When present, PDGFR $\alpha$  might be stimulated in an autocrine loop by ovarian tumors co-expressing PDGF AB [121]. This activation induced Akt and mitogen activated protein kinase (MAPK)-mediated proliferation of tumor cells [121]. In a clinical trial of patients who were platinum resistant or refractory, the PDGFR kinase inhibitor, imatinib, in combination with docetaxel showed an objective response rate (ORR) of 22% (5/23 patients) [122].

Olaratumab (LY3012207); formerly IMC-3G3 is a recombinant fully human immunoglobulin G subclass 1 (IgG1) monoclonal antibody which specifically binds to PDGFR $\alpha$ , blocking signaling of PDGF ligands [123]. The antibody inhibits PDGFR ligand-induced receptor autophosphorylation and phosphorylation of downstream signal transduction via Akt and MAPK [123]. Olaratumab has antitumor activity in *in vivo* tumor models thought to be driven by PDGF-PDGFR $\alpha$  autocrine loop [123]. In mouse models of pediatric osteosarcoma and malignant rhabdoid tumor, Olaratumab delayed tumor growth, and this activity was enhanced by chemotherapy (cisplatin or doxorubicin). Likewise Olaratumab alone and in combination with docetaxel significantly decreased tumor weight in *in vivo* models of OC as compared to control and docetaxel alone respectively. In a phase Ib/IIa study the combination of Olaratumab and doxorubicin significantly improved both progression free survival (PFS; 6.6 vs 4.1 months in phase II) and (OS; 26.5 vs 14.7 months in phase II) relative to doxorubicin alone in patients with advanced soft tissue sarcoma [29]. Thus Mc Guire, *et al.* randomized pts with platinum resistant or platinum refractory advanced OC 1:1 to receive liposomal doxorubicin (40 mg/m<sup>2</sup>, intravenous infusion) given every 4 weeks with or without Olaratumab (20 mg/kg intravenous infusion) every 2 weeks. Patients were stratified based on prior response to platinum therapy (refractory vs resistant). The primary endpoint was progression

free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate, duration of response and safety. They treated total of 123 patients (63 Olaratumab+liposomal doxorubicin, 61 liposomal doxorubicin). Median PFS was 42 months for Olaratumab+liposomal doxorubicin and 40 months for liposomal doxorubicin (stratified hazard ratio [HR] = 1043; 95% confidence interval (CI) 0.698 - 1.558; P = 0.837). Median OS was 16.6 months and 16.2 months in the Olaratumab+liposomal doxorubicin and liposomal doxorubicin arm, respectively (HR = 1098; 95%CI 0.71 - 1.71 in the platinum refractory subgroups, median PFS was 5.5 months (95% CI 1.6 - 9.2) and 3.7 months (95% CI 1.9 - 9.2) in the Olaratumab+liposomal doxorubicin (n = 15) and liposomal doxorubicin arms (n = 16) respectively (HR = 0.85; 95%CI 0.38 - 1.91). Overall 59.7% (Olaratumab+liposomal doxorubicin) and 65.6% (liposomal doxorubicin) of patients reported grade adverse events regardless of causality. The most common treatment emergent adverse effects (all grades) regardless of causality were fatigue related (61%), nausea (57%) and constipation (52%) with Olaratumab+liposomal doxorubicin and nausea (64%), fatigue related (62%) and mucositis (46%) with liposomal doxorubicin. Thus concluding that the addition of Olaratumab or liposomal doxorubicin did not result in significant prolongation of PFS or OS in platinum refractory OC [124]. Further Shao., *et al.* showed that pretreatment of chloroquine (CQ) as chemosensitizer markedly increased the anticancer effects in ovarian cancer, which efficiently improves the pH value of lysosomes in tumor cells reverse sequestration induced by lysosomes. They further encapsulated CQ to improve pharmacokinetic profiles and avoid systemic toxicities by using polymeric nanoparticles methoxy (polyethylene glycol-poly-lactic acid (MPEG-PLA). Thus this encapsulation of doxorubicin with CQ might significantly improve its anti-cancer effects [125].

## Conclusions

Thus it is clear that HGSOC involves a collection of tumors, not only of ovarian origin but those originating from the fallopian tube and primary peritoneum. Besides although 4 histology's described like serous, epithelial, endometrioid, mucinous and clear cell carcinoma, it is believed that endometrioid cancer represents a part of HGSOC's only. These HGSOC need p53 dysfunction to occur for the typical genomic instability to occur. Different degrees of DNA repair dysfunction have been found in various molecularly differentiated subsets of HGSOC which helps in deciding the therapeutic approaches. Identifying the endogenous DNA repair dysfunction that is caused by induction or accentuation of local hypoxia are some examples of clinical synthetic lethality which might further help in planning successful drug combinations. Besides these biomarkers

others line 7 gene signatures, XIAP, SIRT6 [126], Notch signaling constitute some of the biomarkers for predicting drug sensitivity. Further Hoppenot., *et al.* gave some criteria for factors which might predict long term survival of HGSOC [127], rather than the poor < 5 year median survival, by trying to find factors which contribute to rare 15% patients who survive over 10 years. These clubbed together will help in getting better 5 year survivals of these tumors with a poor prognosis.

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