Chemotherapy Resistance in Advanced Ovarian Cancer Patients

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ABSTRACT: Ovarian cancer is the seventh most common gynaecologic malignancy seen in women. Majority of the patients with ovarian cancer are diagnosed at the advanced stage making prognosis poor. The standard management of advanced ovarian cancer includes tumour debulking surgery followed by chemotherapy. Various types of chemotherapeutic regimens have been used to treat advanced ovarian cancer, but the most promising and the currently used standard first-line treatment is carboplatin and paclitaxel. Despite improved clinical response and survival to this combination of chemotherapy, numerous patients either undergo relapse or succumb to the disease as a result of chemotherapy resistance. To understand this phenomenon at a cellular level, various macromolecules such as DNA, messenger RNA and proteins have been developed as biomarkers for chemotherapy response. This review comprehensively summarizes the problem that pertains to chemotherapy resistance in advanced ovarian cancer and provides a good overview of the various biomarkers that have been developed in this field.

KEYWORDS: Chemo-therapy, advanced ovarian cancer, biomarkers, proteomics

Introduction

Malignant transformation of the ovarian surface epithelium causes epithelial ovarian cancer.[1] Ovarian cancer is 1 of the seventh most common cancer affecting women worldwide and accounting for 295 414 new cases and 184 799 deaths annually.[2] The lifetime risk of developing ovarian cancer in a woman is 1 in 75, with her chance of mortality due to the disease being 1 in 100.[3] It occurs in peri-menopausal and post-menopausal women, with 80% to 90% of cases occurring after the age of 40 with the peak incidence of occurring at age of 60.[4] Other risk factors for cancer include family history, *BRCA1* and *BRCA2* mutations, Lynch II syndrome, infertility, nulliparity, early menarche and late menopause.[5] The familial cases account for only 10% to 15% of the patients while most cases are sporadic.[6,7] Studies have consistently reported the use of oral contraceptives as being inversely associated with the risk of ovarian cancer, with a protective effect increasing with longer duration of use.[8,9]

Ovarian cancer is staged according to the FIGO system (*Fédération Internationale de Gynécologie et d'Obstétrique*) that considers the extent of tissue involvement, lymph node status and the magnitude of metastasis.[10] Accordingly, stage I and stage II cancers limited to the pelvic cavity are called early stage cancer and the stage III and stage IV cancers that spread beyond the pelvic cavity are called advanced stage cancer.[11] Early detection of ovarian cancer provides an opportunity for successful treatment; however, the disease is rarely diagnosed at an early stage due to lack of symptoms during the early stage. Only one-fourth of the patients present with the disease localized to the ovaries when the 5-year survival rate is 92%, while in contrast more than 75% patients present with the advanced stage disease, with a 5-year survival ranging from 15% to 25%.[12,13] As most patients are diagnosed with advanced stage of the disease, it leads to a high fatality-to-case ratio among all gynaecologic malignancies.[5]

The standard treatment for advanced ovarian cancer is primary cytoreductive surgery followed by platinum-based chemotherapy.[14] The cytoreductive surgery is done to accurately establish a diagnosis, to remove poorly perfused tissue that may harbour the disease and to decrease the tumour bulk to enhance adjuvant chemotherapy.[15,16] The amount of residual disease after surgery is inversely related to overall survival (OS); patients with optimum cytoreduction (defined as <1 cm residual disease) having a more superior outcome compared with those with sub-optimal cytoreduction (>1 cm residual disease).[17] The chemotherapeutic strategy for treating advanced ovarian cancer comprises different chemotherapeutic drugs, and different combinations that have been tried to improve clinical response (CR) and OS and decrease toxicity.[18] The chemotherapeutic regimens used to treat advanced ovarian cancer are comprehensively summarized in Table 1 and the important and most pertinent aspects of various combinations have been discussed below.

Melphalan as a Single Agent and Its Combinations

During the 1950s, the main therapeutic strategy for treating advanced ovarian cancer was cytoreductive surgery and radiotherapy. An improvement in the treatment was achieved with the use of alkylating agents like melphalan which causes cytotoxicity against tumour cells by alkylating DNA at N7 position

Table 1. First-line chemotherapeutic regimens in advanced ovarian cancer.

CHEMOTHERAPY COMBINATIONS	CLINICAL RESPONSE	MEDIAN PFS (IN MONTHS)	OVERALL SURVIVAL (IN MONTHS)	REFERENCE
Melphalan	20.0%	7.7	12.3	19,20
Melphalan hexamethylmelamine	28.0%	6.0	13.5	19
Cyclophosphamide doxorubicin	32.0%	9.5	14.2	19
Cyclophosphamide doxorubicin	26.0%	7.7	15.7	21
Carboplatin Etoposide	43.0%	8.5	19.5	22
Carboplatin Hexamethylmelamine Etoposide	92.0%	–	–	23
Cisplatin Cyclophosphamide	60.0%	17.9	24.4	24
Cisplatin Cyclophosphamide	60.0%	13.0	24.0	24
Cisplatin Cyclophosphamide	16.0%	19.0	35.0	25
Cisplatin Cyclophosphamide Doxorubicin	51.0%	13.1	19.7	21
Cisplatin Paclitaxel	73.0%	18.0	38.0	24
Cisplatin Paclitaxel	81.4%	19.1	44.1	26
Cisplatin Ifosfamide	69.0%	14.0	25.0	27
Cisplatin Ifosfamide	67.5%	–	–	28
Paclitaxel	55.0%	6.1	–	29
Carboplatin Cyclophosphamide	14.0%	26.0	37.0	25
Carboplatin Ifosfamide	67.0%		24.9	30
Carboplatin Paclitaxel Hexamethylmelamine	76.0%	–	–	31
Cisplatin Docetaxel	69.0%	–	–	32
Cisplatin Docetaxel	58.0%	14.4	43.0	33
Cisplatin thio-TEPA	80.0%	12.0	18.0	34
Cisplatin Paclitaxel Topotecan	60.0%	–	–	35
Carboplatin Paclitaxil Epirubicin	86.0%	18.7	–	36
Carboplatin Paclitaxil Epirubicin	90.0%	–	65.0	37
Carboplatin Paclitaxel Etoposide Cyclophosphamide with G-CSF	92.0%	4.0	–	38
Cisplatin Paclitaxel Ifosfamide	85.0%	22.2	52.8	39
Cisplatin Paclitaxel Ifosfamide	85.0%	–	51.0	37
Carboplatin Paclitaxel Gemcitabine	94.0%	16.0	28.0	40
Carboplatin Paclitaxel Gemcitabine	97.5%	19.5	31.2	41
Cisplatin Gemcitabine	70.7%	10.4	23.4	42
Cisplatin Gemcitabine	64.9%	13.4	24.0	43
Cisplatin Irinotecan	76.0%	–	30.9	44
Carboplatin Paclitaxel Epidoxorubicin	86.0%	19.5	36.0	45
Carboplatin Docetaxel	73.0%	18.0	24.4	46
Carboplatin Docetaxel	78.8%	12.0	35.3	47
Carboplatin Paclitaxel Topotecan	77.0%	10.6	22.2	48

Table 1. (Continued)

CHEMOTHERAPY COMBINATIONS	CLINICAL RESPONSE	MEDIAN PFS (IN MONTHS)	OVERALL SURVIVAL (IN MONTHS)	REFERENCE
Carboplatin Paclitaxel Amifostine	38.0%	22.0	–	49
Carboplatin Paclitaxel Etoposide	75.0%	12.0	24.0	50
Carboplatin Gemcitabine	83.3%	11.6	29.2	51
Carboplatin Paclitaxel Gemcitabine Oxaliplatin	85.0%	14.5	31.5	52
Carboplatin Paclitaxel Epirubicin	60.1%	18.4	45.8	53
Carboplatin Paclitaxel Epirubicin	65.7%	16.4	42.4	54
Carboplatin Paclitaxel Bevacizumab	80.0%	–	–	55
Carboplatin Paclitaxel Bevacizumab	48.0%	16.9	29.9	56
Carboplatin Topotecan	71.0%	–	47.0	57
Cisplatin Paclitaxel Doxorubicin	64.0%	18.1	44.3	58
Carboplatin Doxorubicin	57.0%	19.0	61.6	59
Carboplatin Paclitaxel lonafarnib	–	11.5	20.6	60
Oxaliplatin Docetaxel Bevacizumab	58.6%	16.3	47.3	61
Carboplatin Paclitaxel Sorafenib	69.0%	15.4	–	62

Abbreviations: G-CSF, granulocyte colony stimulating factor; PFS, progression-free survival.

of guanine and induces DNA inter-strand cross-linkages, leading to inhibition of replication and transcription.[63] The use of single-agent melphalan benefitted the patients with advanced ovarian cancer.[64] However, the CR was 20%, median progression-free survival (median PFS) was 7.7 months and median OS was 12.3 months, along with toxicity manifestations such as myelosuppression with neutropenia.[19,20] The combination of melphalan and hexamethylmelamine produced a CR of 28%, median PFS of 6 months and median OS of 13.5 months as compared with the combination of adriamycin and cyclophosphamide, which produced a slightly improved CR of 32%, median PFS of 9.5 months and median OS of 14.2 months; however, it produced significant hematologic and gastrointestinal toxicity.[19] The use of melphalan is limited as it causes severe myelosuppression.[65]

Cyclophosphamide as a Single Agent and Its Combinations

Previous studies have demonstrated the efficacy of other alkylating agents like cyclophosphamide and anthracycline doxorubicin. The *GOG* (*Gynecologic Oncology Group*) trial comparing cyclophosphamide, melphalan and doxorubicin demonstrated an improvement in response rate; however, there was no OS advantage.[19] Clinical trials studying the effect of this combination have shown a CR of 26% and median OS of 15.7 months with side effects such as nausea, vomiting and leukocyte toxicity.[21]

Cisplatin as a Single Agent and Its Combinations

The inclusion of cisplatin in the chemotherapeutic regimen for advanced ovarian cancer proved to be a major landmark. Cisplatin binds to nuclear DNA leading to interference with transcription and/or DNA replication and eventually cell death induced by cell repair machinery.[66] A Cochrane review and meta-analysis confirmed a modest 2- and 5-year survival advantage in women with advanced stage epithelial ovarian cancer who were given platinum-based combination chemotherapy compared with those given combination therapy lacking platinum.[67] The use of cisplatin in combination with thio-TEPA produced an improved CR; however, OS was not good.[34] The combination of cisplatin, cyclophosphamide and doxorubicin showed an increased CR of 51% and median OS of 19.7 months.[21] Chemotherapy combinations containing an alkylating agent and a platinum coordination complex produced a high response rate in women with advanced ovarian cancer. Cisplatin-based combination chemotherapy showed improved CR and progression-free interval (PFS) as compared with alkylating agents alone or combinations without cisplatin.[24] The CR in the cisplatin-cyclophosphamide group was 60% and median OS was of 24.4 months.[24] As long-term disease control in patients with advanced ovarian cancer was not significant, new drug combinations were investigated. The efficacy of cisplatin-ifosfamide combination showed improved CR and OS.[27,28] Cisplatin-docetaxel combination produced an improved CR of 69%; however, increasing the docetaxel dose
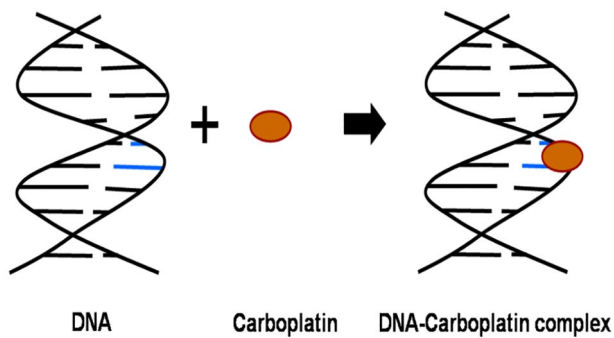
Figure 1. Mechanism of action of cisplatin. Double stranded DNA is shown in black; Cisplatin is shown as a brown oval; and purine bases are shown as blue coloured lines.

caused significant hematologic toxicity to the patient.[32,33] Cisplatin with gemcitabine, a nucleoside antimetabolite, is an active agent in ovarian cancer and produced significantly increased CR.[42,43] A similar study reported a 71% CR; however, 63% of patients developed high-grade neutropenia and 28% developed high-grade thrombocytopenia.[68] The combination of cisplatin with irinotecan, an inhibitor of DNA topoisomerase I, showed improved activity in chemotherapy-naive patients with advanced ovarian cancer; however, neutropenia was the dose-limiting adverse effect.[44,69]

Carboplatin as a Single Agent and Its Combinations

Carboplatin which has good efficacy and less toxicity than cisplatin was introduced in the 1980s as first-line chemotherapeutic agent.[66,70] Carboplatin crosses the cell membrane where it is hydrolysed to 1,1-cyclobutanedicarboxylate and therefore gains a positive charge.[71,72] The positively charged intermediate interacts with nucleophilic molecules such as DNA or RNA by covalent bond formation with the N7 site of purine bases leading to formation of platinum adducts (Figure 1).[73,74] Carboplatin is less toxic than cisplatin as the former forms an intermediate 1,1-cyclobutanedicarboxylate which is a poorer leaving group as compared with chloride, which leads to low reactivity rate and there is therefore less adduct formation.[75] The clearance of cisplatin occurs majorly by host tissues; however, for carboplatin, it occurs by renal function, therefore targeted area-under-the-curve (AUC) dosing based on estimated renal clearance improved safety and tolerability of carboplatin.[76] Carboplatin and etoposide, which showed significant synergistic activity in animal models of ovarian cancer, had a relatively low CR of only 43% along with increased toxicity rate.[22] Combination of carboplatin, hexamethylmelamine and etoposide produced a very high CR of 92%; however, the study was on a very small sample size.[23] Carboplatin and cyclophosphamide combination proved to be effective in optimally debulked advanced ovarian cancer patients; however, the combination did not significantly prevent tumour progression in a majority of patients.[25] A combination of carboplatin and ifosfamide too has showed improved CR.[30] Carboplatin

and docetaxel produced an improved CR of 73%; however, it has substantial myelotoxicity.[46] Gemcitabine, a nucleoside analogue, and carboplatin also showed significant CR.[51] Carboplatin and topotecan, which is a specific topoisomerase I inhibitor that causes single-stranded breaks in DNA during replication, showed a CR of 71%.[57]

Paclitaxel as a Single Agent and Its Combinations

In the 1990s, paclitaxel was found to be the most effective agent in patients with relapsed platinum-refractory disease.[77] It acts by binding to intracellular β-tubulin, which leads to microtubule stabilization, *G2–M* arrest and apoptosis, via both p53-dependent and p53-independent pathways.[78] Earlier the most commonly used combination was cyclophosphamide and cisplatin; however, the OS was not sufficient. At this stage, paclitaxel was included in first-line chemotherapy for patients with sub-optimally debulked advanced ovarian cancer which led to increase in the duration of the PFS and OS.[24] Paclitaxel used alone emerged as an effective and safe drug for first-line treatment of advanced ovarian cancer.[29] Paclitaxel-cisplatin produces an overall higher CR although it has low tolerability than the conventional combination of carboplatin-paclitaxel.[24,26] A GOG study along with other randomized studies concluded that the inclusion of paclitaxel with a platinum analogue produced significant improvement in response and survival.[24,79] At this stage, combination of paclitaxel, cisplatin and ifosfamide was investigated which produced a CR of 85%.[39] Paclitaxel, cisplatin and doxorubicin combination produced a CR of 64%, a marginal improvement in PFS; however, there was improved survival benefit when compared with the standard carboplatin-paclitaxel combination.[58] It may be noted here that combinations of paclitaxel and carboplatin along with a third agent have also been tested across various clinical trials (Table 1). However, these combinations have had their own limitations like no improvement in CR as compared with carboplatin and paclitaxel, increased haematological toxicities, neutropenia, alopecia and thrombocytopenia.[53,80,81]

Carboplatin and Paclitaxel as a Combination

Carboplatin and paclitaxel have been a standard chemotherapy combination used and the related clinical studies summarizing its efficacy are provided in Table 2. It is seen that the combination therapy of carboplatin-paclitaxel achieves a CR ranging from 50% to 81% and median PFS range of 13.6 to 19.3 months. Numerous trials have established that a combination of paclitaxel and carboplatin is well tolerated in advanced ovarian cancer.[90] A few earlier randomized trials too demonstrated that the combination of cisplatin and paclitaxel was superior to cisplatin and cyclophosphamide in advanced ovarian cancer.[91] Also, trials have showed that carboplatin and paclitaxel was a less toxic and highly effective combination regimen.[92] A study conducted by *GOG* in patients with optimally debulked advanced ovarian cancer revealed that the median PFS and

OS were 19.4 and 48.7 months, respectively, for the cisplatin-paclitaxel as compared with 20.7 and 57.4 months, respectively, for carboplatin-paclitaxel. In addition, gastrointestinal, renal, metabolic toxicity and leukopenia were significantly more in cisplatin-paclitaxel group as compared with carboplatin-paclitaxel.[92] Another clinical trial compared carboplatin-paclitaxel and carboplatin, paclitaxel and cisplatin combination. The median PFS and OS were not statistically different, although carboplatin-paclitaxel combination was associated with better tolerability and quality of life (median PFS: 17.2 vs 19.1 months; median OS: 43.3 vs 44.1 months). The mean global quality-of-life scores at the end of treatment were statistically significantly better with the use of carboplatin-paclitaxel (65.25 vs 51.97).[26] In the HeCOG (Hellenic Cooperative Oncology Group) study comparing carboplatin-paclitaxel and cisplatin, paclitaxel and doxorubicin, the latter showed a slight increase in PFS; however, there was no additional survival benefit (CR: 69% vs 64%; median PFS: 13.25 vs 18.13 months; median OS: 37.97 vs 44.33 months).[58] Previous trials comparing cisplatin and paclitaxel against carboplatin and paclitaxel, 1 using different paclitaxel schedules on the 2 arms suggested that carboplatin and paclitaxel had more favourable toxicity profile and convenience of a shorter schedule.[93,94] Other studies have demonstrated that quality of life was better during treatment with carboplatin and paclitaxel as compared with cisplatin and paclitaxel.[95,96] Such landmark studies established the combination of carboplatin-paclitaxel as the standard of care in advanced ovarian cancer.

Chemotherapy Resistance in Advanced Ovarian Cancer

First-line chemotherapy with carboplatin and paclitaxel achieves an improved CR; however, recurrence occurs in 25% of patients with early stage disease and more than 80% of patients with advanced disease.[97] A majority of advanced ovarian cancer patients experience disease relapse within 2 years of the initial treatment of combination chemotherapy.[98] The heterogeneity of tumour cells leads to molecular variations in signalling pathways including oncogene activation, tumour suppressor inactivation and various pro-survival genetic mutations.[99] Therefore, chemo-resistance to standard chemotherapy regimen has emerged as a major challenge.[100] Whereas the current therapeutic regimens are fixed linear protocols, cancer biology is a highly dynamic system. Adapting a therapeutic strategy using systems biology approach based on temporal and spatial variations in tumour is a futuristic goal in oncology.[101] Other studies including poly (ADP-ribose) polymerase inhibitors and anti-angiogenic agents have shown that trial design with restricted eligibility criteria rather than testing chemotherapeutic agents in unselected populations can lead to improved clinical outcomes in the targeted populations.[102–104] Drug resistance is 1 of the most important factors for failure of chemotherapy in advanced ovarian cancer. Chemotherapy

Table 2. First-line chemotherapeutic treatment with carboplatin-paclitaxel in advanced ovarian cancer.

CLINICAL RESPONSE	MEDIAN PFS (IN MONTHS)	OVERALL SURVIVAL (IN MONTHS)	REFERENCE
57.0%	–	–	82
75.0%	–	–	83
70.0%	–	–	83
57.0%	–	–	25
74.0%	–	–	84
81.0%	–	20.0	85
50.0%	–	–	86
67.7%,	17.2	43.3	26
60.0%	17.9	41.0	53
69.0%	18.1	38.0	58
77.5%	19.3	51.5	87
59%	16.8	53.2	88
80.0%	16.0	40.2	54
56.2%	18·3	–	89
74.0%	16.3	–	62

Abbreviation: PFS, progression-free survival.

resistance is of 2 types: (a) intrinsic chemo-resistance, where the cancer cells are inherently resistant to drug treatment, and (b) acquired chemo-resistance, which can be acquired during the course of treatment.[105] Intrinsic chemo-resistance is caused due to cancer cells possessing several biological modifications including inhibited drugs uptake, increased drug efflux, increased detoxification of chemotherapeutic drugs, inhibition of apoptosis and so on.[106] While acquired chemo-resistance can arise due to genetic and epigenetic alternations that assist the cancer cells to adapt to chemotherapy induced effects such as stress, DNA damage and apoptosis.[106] Therefore, chemo-resistance, which is a multifactorial phenomenon, is being investigated with the view to decipher chemo-resistance mechanisms and develop drugs to overcome it.[107,108] However, the major problem is that identification of patients pre-disposed to chemo-resistance is challenging as there are no available tests to guide clinicians to make an informed decision to alter treatment course before chemotherapy.

Biomarkers and Chemotherapy Resistance in Advanced Ovarian Cancer

Despite initial responsiveness to combination chemotherapy of carboplatin and paclitaxel, the occurrence of chemo-resistant tumours is a major hurdle and therefore demands elucidation of its pathogenesis. The delineation of molecular signatures from

these tissues has paved the way for biomarker discovery. Biomarkers are biological macromolecules that can be objectively measured and evaluated and indicate the functioning of biological processes and pharmacologic response in the human body.[109] Biomarker discovery has made many strides in the field of medicine and health.[110–112] Over the past decade, clinical proteomics has helped in biomarker discovery in the field of advanced ovarian cancer.[113,114] An understanding of biomarkers in chemotherapy resistance in advanced ovarian cancer will have the following benefits: (a) to elucidate the molecular mechanisms at a cellular level that dictate drug resistance, (b) design new therapeutic strategies to overcome drug resistance, (c) plan the best chemotherapeutic strategy and improve patient management, (d) help to improve patient compliance and reduce financial expenditure and (e) predict the sensitivity of tumour to chemotherapeutic regimen allowing chemotherapy administration to the patient who would benefit and prevent the toxic effects of chemotherapy to non-responder patients.

Various biomarkers and their mechanism of action that help to understand chemotherapy resistance are summarized in Table 3. Even though chemo-resistance has plagued the CR and survival in advanced ovarian cancer since the beginning of chemotherapy administration, the research investigating predictive biomarkers began much later. It can be observed that much of the research in chemo-resistance biomarker discovery has focussed on transcriptomics and proteomics with very few genomic studies investigating the same.

The field of genomics encompasses the systematic study of the genome of an organism. In advanced ovarian cancer, genomics has been primarily used to reveal chromosomal abnormalities or mutations such as insertions and deletions or abnormal chromosomal numbers in a process.[125,128,155,156] Other studies have focused on the study of single nucleotide polymorphisms (SNPs) in deciphering individual response to the chemotherapeutic drugs.[157,158] In the past, very few studies have explored the frontier of genomics in the field of biomarker discovery for chemo-resistance in advanced ovarian cancer. The major limitation of genomics approach is that the investigation of mutation and SNPs does not correlate with the level of proteins. For instance, in a previous study 12 genes were identified using DNA microarray technology; however only *HSP-10* could be validated using immunohistochemistry.[159]

Transcriptomics is the study of the complete set of mRNA (messenger RNA) transcripts produced by a tissue or an organism under specific conditions at a particular point in time. Messenger RNA detection and estimation have been widely used in the study of chemo-resistance in advanced ovarian cancer (Table 3). However, many studies have suffered from a major limitation of inaccurate correlation between gene expression and protein expression. Correlation between mRNA and protein level is insufficient to predict protein expression levels from quantitative mRNA data.[159] For some genes with similar mRNA levels, the protein levels may vary by more than 20-fold and conversely, for proteins with similar levels, corresponding

mRNA levels may vary by as much as 30-folds.[160] Such discrepancy can be explained by taking into account post-translational events such as alternative splicing, translational regulation and differences in protein *in vivo* half-lives.[161,162]

Proteomics is the study of the set of all expressed proteins in a cell, tissue or organism at a specific time under specific conditions. It can be used to characterize the flow of information in biological pathways and their networks to establish functional relevance of proteins. The proteome of a biological entity represents the dynamic relationship between the genes, environment and pathological states. Proteins are the macromolecules that are majorly affected in diseases and participate in the subsequent disease response. It is evident that proteins have the advantage to be used as biomarkers in various clinical states and to assess associated therapeutic response due to the following advantages: (a) genome is largely similar in individuals of the same species, whereas protein expression is specific to a cell type under specific conditions; (b) effect of environment is reflected in proteome more easily than genome which remains stable; (c) protein expression level is result of transcriptional activation, transcript degradation and translation efficiency and (d) proteins are the key downstream effectors and affecters in various cellular functions. Therefore, a majority of the studies have used proteomics to study the phenomenon of chemo-resistance in advanced ovarian cancer.

Post-translational modifications are important determinants of protein functionality and are an important mechanism to increase the diversity of proteome along with regulatory interactions with the various cellular functions.[163] Several studies have investigated the role of post-translational modifications as potential biomarkers in cancer.[164] Some post-translational modifications also play a role in chemo-response mechanisms in ovarian cancer and is summarized in Table 4. These modifications have an effect on cytoskeletal integrity, protein folding, metabolic function and apoptotic activity of tumour cells that in turn determines the response of ovarian cancer cells to the chemotherapeutic drug.

Biomarkers and Their Biological Functions

The identified genes, mRNA or proteins are involved in various biological functions such as cell cycle and checkpoint proteins, protein folding, chaperones, DNA repair proteins, cytoskeletal proteins, metabolic enzymes, transcriptional activators, drug-efflux pumps, and cellular redox protein and regulators of the apoptotic pathway as can be seen in Table 3.

The different mechanisms that cause chemo-resistance are explained. (a) Apoptosis is 1 of the main mechanisms employed by the cells to evade drug-induced cytotoxicity and subsequently manifest as chemo-resistance. PI3K/AKT and ERK1/2 pathway are at the centre stage of mediating anti-apoptotic activity in chemo-resistance. Various proteins interact with this pathway to prevent cell death such as increased expression of insulin-like growth factor I receptor

Table 3. Biomarkers for chemo-resistance to first-line chemotherapy in advanced ovarian cancer.

CHEMOTHERAPY	MACROMOLECULE	BIOMARKER	SOURCE	CELLULAR MECHANISM	CLINICAL PHENOTYPE	CHEMO-RESISTANCE	REFERENCES
Platinum-based drug/ Alkylating agent	Protein	Lung resistance protein (*LRP*) ↑	Tissue	Increases drug efflux	Non-responder	Intrinsic	115
Doxorubicin, cisplatin and paclitaxel	*mRNA*	Human epidermal growth factor receptor 2 (*HER-2*) ↑	Cell line	Increases drug efflux and increases drug metabolism	Responder	N/A	116,117
Paclitaxel	RNA	Inactive X chromosome-specific Transcripts (*XIST*) ↓	Cell line and tissue	Reactivates resistance-specific genes on inactive X chromosome in the absence of *XIST* RNA.	Non-responder	Acquired	118
Cisplatin	Protein	Cycloxegenase-2 (*COX-2*) ↑	Tissue	Increases proliferation and inhibits apoptosis	Non-responder	Intrinsic	119
Cisplatin	Protein	P-glycoprotein (*Pgp*) ↑	Tissue	Increases drug efflux	Non-responder	Intrinsic	119
Cisplatin	*mRNA*	Trophinin (*TRO*) ↑	Cell line	Homophilic adhesion molecule involved in blastocyst implantation	Responder	N/A	120
Carboplatin and cyclophosphamide	Protein	Excision repair cross-complementation group 1 (*ERCC-1*) ↑	Tissue	Increases DNA repair	Non-responder	Intrinsic	121
Platinum-based drug and paclitaxel	Protein	Vascular endothelial growth factor (*VEGF*) ↑	Ascites	Increases tumour angiogenesis	Non-responder	Intrinsic	122
Platinum-based drug and paclitaxel	Protein	Tumour necrosis factor alpha (*TNF*α) ↑	Ascites	Increases inflammation	Non-responder	Intrinsic	122
Paclitaxel	Protein	Endoplasmic reticulum resident oxidoreductase 57 (ERp57) ↑	Cell line	Increases protein folding under stress and inhibits apoptosis	Non-responder	Acquired	123
Platinum-based drug and cyclophosphamide or paclitaxel	*mRNA*	Mesothelin (*MSLN*) ↑	Tissue	Alters the time spent by cytotoxic drugs in the peritoneal cavity or changes the tumour microenvironment of ovarian cancer patients; therefore inhibiting the effects of cytotoxic drugs	Non-responder	Intrinsic	124
Cisplatin	*DNA*	Insulin-like growth factor I receptor (*IGF1R*) ↑	Cell line	Inhibits apoptosis	Non-responder	Acquired	125–127
Cisplatin	*DNA*	Phosphatidylinositol-3-OH kinase (*PIK*) ↑	Cell line	Inhibits apoptosis	Non-responder	Acquired	125–127
Platinum-based-drug	*DNA*	Cyclin E (*CCNE1*) ↑	Tissue	Increases cell proliferation	Non-responder	Intrinsic	128

(Continued)

Table 3. (Continued)

CHEMOTHERAPY	MACROMOLECULE	BIOMARKER	SOURCE	CELLULAR MECHANISM	CLINICAL PHENOTYPE	CHEMO-RESISTANCE	REFERENCES
Paclitaxel	Protein	Heterogeneous nuclear riboprotein A2 (hnRNPA2) ↓	Cell line	Increased cell stability	Non-responder	Acquired	129,130
Paclitaxel	Protein	Rho GDP dissociation inhibitor (GDI 2) ↓	Cell line	Increases invasion	Non-responder	Acquired	129,131
Cisplatin	Protein	Pyruvate kinase-M2 (PKM2) ↓	Cell line	Increases drug inactivation	Non-responder	Acquired	132,133
Cisplatin	Protein	Heat shock protein D1 (HSP-D1) ↑	Cell line	Inhibits apoptosis	Non-responder	Acquired	132,134
Cisplatin	Protein	Hypoxia up-regulated protein 1 precursor (HYOU1) ↑	Cell line	Inhibits apoptosis	Non-responder	Acquired	132,135
Cisplatin	Protein	Isoform 1 of collagen XII alpha-1 chain (COL12A1) ↓	Cell line	Increases tumour angiogenesis and invasion	Non-responder	Acquired	132,136,137
Cisplatin	Protein	Calnexin (CNX) ↑	Cell line	Inhibits apoptosis	Non-responder	Acquired	132,138
Cisplatin	Protein	High mobility group protein B1 (HMGB1) ↑	Cell line	Reduces DNA damage	Non-responder	Acquired	132,139
Cisplatin	Protein	Lung resistance protein (LRP) ↑	Cell line	Increases drug efflux	Non-responder	Acquired	104,121
Cisplatin	Protein	Nestin (NES)↑	Tissue	Increases tumour angiogenesis	Non-responder	Intrinsic	130,131
Cisplatin	Protein	Activated leukocyte cell adhesion molecule (ALCAM)↑	Cell line	Increased interaction with pro-growth NFκB pathway	Non-responder	Acquired	132
Cisplatin	Protein	A-kinase anchoring protein 12 (AKAP12) ↑	Cell line	Inhibits apoptosis	Non-responder	Acquired	132
Carboplatin	Protein	Steroid receptor coactivator 3 (SRC-3) ↑	Tissue	Increases cell survival	Non-responder	Intrinsic	114,133
Cisplatin	Protein	Pro-alpha1(XI) chain (COL11A1) ↑	Cell line	Increases invasion	Non-responder	Acquired	134,135
Paclitaxel	mRNA	Chitinase 3-like 1 (CHI3L1) ↑	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	136
Platinum-based drug and paclitaxel	mRNA	Insulin-like growth factor 2 mRNA-binding protein (IGF2BP) ↑	Tissue	Increases tumour proliferation	Non-responder	Intrinsic	137

Table 3. (Continued)

CHEMOTHERAPY	MACROMOLECULE	BIOMARKER	SOURCE	CELLULAR MECHANISM	CLINICAL PHENOTYPE	CHEMO-RESISTANCE	REFERENCES
Platinum-based and paclitaxel	mRNA	Lin-28 Homolog B (Lin28B) ↑	Tissue	Acts as oncogene by blocking let-7 miRNA biogenesis and subsequent depression of let-7 miRNA target genes	Non-responder	Intrinsic	139
Platinum-based drug	Protein	Leptin (LEP) ↑	Ascites	Inhibits apoptosis	Non-responder	Intrinsic	138,139
Cisplatin paclitaxel	Protein	Midkine (MK) ↑	Tissue	Increases cytotoxicity	Responder	N/A	140
Paclitaxel	Protein	Musashi-2 (MSI2) ↑	Cell line	Increases drug efflux	Non-responder	Acquired	141
Platinum-based	Protein	RAN Binding Protein 1 (RANBP1) ↓	Tissue	Increases tumour proliferation, decreases drug binding to DNA and inhibits apoptosis	Non-responder	Intrinsic	142
Platinum-based drug	Protein	Actinin Alpha 4 (ACTN4) ↑	Tissue	Increases invasion	Non-responder	Intrinsic	142
Platinum-based drug	Protein	Keratin 19 (KRT19) ↑	Tissue	Increases invasion	Non-responder	Intrinsic	142,143
Platinum-based drug	Protein	Lactate dehydrogenase A-like 6A (LDHAL6A) ↑	Tissue	Increases anaerobic metabolism	Non-responder	Intrinsic	142,144
Platinum-based drug	Protein	Thiopurine S-methyltransferase (TPMT) ↓	Tissue	Decreases metabolism of drug	Responder	N/A	142,145
Platinum-based and paclitaxel	Protein	Mesothelium vascular cell adhesion molecule-1 (VCAM-1) ↑	Serum	Increases invasion	Non-responder	Acquired	146,147
Platinum-based drug	Protein	Epithelial cell adhesion molecule (EpCam) ↑	Tissue	Inhibits apoptosis	Non-responder	Acquired	148
Platinum-based drug	mRNA and protein	Forkhead box M1 (FOXM1) ↑	Tissue	Increases cell-cycle progression, response to DNA damage	Non-responder	Intrinsic	149,150
Carboplatin	mRNA and protein	Keratin 5 (KRT5) ↑	Cell line, tissue and ascites	Increases cytoskeletal stability	Non-responder	Acquired	151
Cisplatin	mRNA	Colony-stimulating-factor-1 receptor (CSF-1R) ↑	Cell line	Inhibits apoptosis	Non-responder	Acquired	152
Cisplatin	mRNA	3-Oxoacid CoA transferase 1 (OXCT1) ↓	Cell line	Inhibits apoptosis	Non-responder	Acquired	153,154

Table 4. Effect of post-translational modifications on chemo-response carboplatin and paclitaxel in ovarian cancer.

PROTEIN	POST-TRANSLATIONAL MODIFICATION	EFFECT OF POST-TRANSLATIONAL MODIFICATION ON CELLULAR FUNCTION	PHENOTYPE	REFERENCES
Tubulin	De-tyrosination	Microtubule stabilization that is essential for apoptosis	Chemo-sensitive	[165,166]
p53	Phosphorylation	Leads to apoptosis	Chemo-sensitive	[167,168]
Tumour rejection antigen	Glycosylation	Tumour proliferation, anti-apoptotic activity, metastasis	Chemo-resistance	[169,170]
Triose phosphate Isomerase	Glycosylation	Facilitates glycolysis that helps to keep up with the increased energy demand in rapidly growing tumour	Chemo-resistance	[170,171]
Palmitoyl-protein thioesterase 1 precursor	Glycosylation	Anti-apoptotic activity	Chemo-resistance	[170,172]
ER-associated DNAJ	Glycosylation	Protein folding, transport, translational initiation and gene expression	Chemo-resistance	[170,173–175]
Fas-associated death domain-like interleukin-1b-converting enzyme (FLICE)-like inhibitory protein	Ubiquitination	Suppressor of apoptosis	Chemo-resistance	[176,177]
Peptidyl-prolyl cis-trans isomerase A	N-terminal acetylation	Conformational maintenance of oncogenes, cell proliferation, anti-apoptotic activity	Chemo-resistance	

(IGF1R), phosphatidylinositol-3-OH kinase (PIK), A-kinase anchoring protein 12 (AKAP12), chitinase 3-like 1 (CHI3L1), leptin (LEP), epithelial cell adhesion molecule (EpCam) and colony-stimulating-factor-1 receptor (CSF1R) that causes evasion of apoptosis as a downstream effect of PI3K/AKT and ERK1/2 pathway activation.[125,126,127,143,147] Other proteins like cyclooxygenase-2 are known to increase production of prostaglandin E2 which is involved in resistance to apoptosis.[119] Proteins like endoplasmic reticulum resident oxidoreductase 57 (ERp57) show class III β-tubulin (TUBB3) mediated anti-apoptotic activity.[123] (b) Drug efflux from the cells plays an important role in the response of tumour cells to chemotherapy. Some of the interesting mechanisms include HER2 mediated increase in activity of drug-efflux pumps including the adenosine triphosphate (ATP)–binding cassette, sub-family B, member 1 (ABCB1) and ABCC3.[14] Other mechanisms include increased activity of drug-transporters like lung resistance protein and ATP-driven P-glycoprotein (Pgp).[115,119,132] (c) Cell adhesion and tumour invasion pose a challenge to the efficacy of chemotherapeutic drugs. For example, down-regulation of isoform 1 of collagen XII alpha-1 chain (COL12A1) causes extracellular matrix remoulding and tumour migration.[132] Other cytoskeletal modulations include actinin alpha-4 (ACTN4) up-regulation that enhances cell motility by bundling the actin cytoskeleton causing metastasis.[153] Other proteins like mesothelium vascular cell adhesion molecule-1 (VCAM1) is up-regulated in non-responders and is known to mediate tumour invasion by the epithelial and mesenchymal transition. (d) Drug metabolism is common in chemo-resistant tumour cells as an important pathway to eliminate active drug molecules and evade cytotoxic effect. Human epidermal growth factor *receptor*-2 (HER2) up-regulation increases expression of drug metabolism proteins including glutathione S-transferase P1 (GSTP1) and cytochrome P450 3A4 (CYP3A4).[117] In contrast, down-regulation of thiopurine S-methyltransferase reduces the metabolism of thiopurine chemotherapeutic agents, such as 6-mercaptopurine. (e) Increase in pathways involved in tumour angiogenesis contributes to increased vascularity and nutrient supply to cells under stress condition induced by chemotherapy. For instance, up-regulation of vascular endothelial growth factor and nestin provide the tumour with a replenished microenvironment to enhance survival.[122,141] (f) Increased cell proliferation and survival pathways are an important marker for chemotherapy resistance. An interesting observation is the up-regulation of HER2 mediated activation of pro-survival proteins such as survivin, p21 and p53.[117]

Research has been done to understand these aspects using an array of human tissue samples. Some of the sources include ascitic fluid, serum, ovarian cancer cell lines and ovarian cancer tissue samples. A comprehensive review by Kaur and group revealed that pharmacological studies using cell lines suffer from some major drawbacks[191]: (a) Cell lines get genetically altered, and this sometimes alters their phenotype, native functions and their response to stimuli; (b) genotypic and phenotypic variation may occur due to serial passage of cell lines over

Table 5. Biomarkers in chemo-resistance to carboplatin and paclitaxel in advanced ovarian cancer.

CHEMOTHERAPY	MACROMOLECULE	BIOMARKER	SOURCE	CELLULAR MECHANISM	CLINICAL PHENOTYPE	CHEMO-RESISTANCE	REFERENCE
Carboplatin and paclitaxel	Protein	Heat shock protein 10 (*HSP-10*) ↓	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	159
Carboplatin and paclitaxel	Protein	Matrix metalloproteinase 1 (*MMP-1*) ↑	Tissue	Promotes tumour invasion	Non-responder	Intrinsic	159,178
Carboplatin and paclitaxel	DNA	Ecotropic virus integration site 1 protein homolog (*EVI1*) ↑	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	156,179
Carboplatin and paclitaxel	DNA	SH3 domain-containing kinase-binding protein 1 (*CIN85*) ↓	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	156,180
Carboplatin and paclitaxel	DNA	Endophilin A1 (SH3GL2) ↓	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	156,181
Carboplatin and paclitaxel	Protein	Ki-67 ↑	Tissue	Marker for increased cell proliferation	Responder	N/A	182
Carboplatin and paclitaxel	Protein	Adenosine triphosphate–binding cassette sub-family C member 2 (*ABCC2*) ↓		Increases apoptosis	Responder	N/A	182,183
Carboplatin and paclitaxel	mRNA	Insulin-like growth factor-1 (*IGF1*) ↑	Tissue	Enhances ovarian cancer cell proliferation through PI3K/Akt/mTOR signalling	Non-responder	Intrinsic	184,185
Carboplatin and paclitaxel	mRNA	Telomerase reverse transcriptase (*TERT*) ↑	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	186,187
Carboplatin and paclitaxel	mRNA	E2F transcription factor 1 (*E2F*) ↑	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	186,188
Carboplatin and paclitaxel	mRNA	Cyclin-dependent kinase inhibitor 1A (CDKN1A) ↓	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	186,189
Carboplatin and paclitaxel	mRNA	FBJ murine osteosarcoma viral oncogene homolog (*FOS*) ↑		Inhibits apoptosis	Non-responder	Intrinsic	186,190
Carboplatin and paclitaxel	mRNA	Tumor necrosis factor (TNF) receptor superfamily, member 10A (*TNFRSF10A*) ↓	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	186
Carboplatin and paclitaxel	mRNA	TNF receptor superfamily, member 10C (*TNFRSF10C*) ↓	Tissue	Decreased activity as p53-regulated DNA damage-inducible gene	Non-responder	Intrinsic	186
Carboplatin and paclitaxel	mRNA	TNF receptor superfamily, member 10D (*TNFRSF10D*) ↑	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	186
Carboplatin and paclitaxel	mRNA	TNF receptor-associated factor 1 (*TRAF-1*) ↓	Tissue	Increases apoptosis	Non-responder	Intrinsic	186,191

(Continued)

Table 5. (Continued)

CHEMOTHERAPY	MACROMOLECULE	BIOMARKER	SOURCE	CELLULAR MECHANISM	CLINICAL PHENOTYPE	CHEMO-RESISTANCE	REFERENCE
Carboplatin and paclitaxel	*mRNA*	Goosecoid homeobox (*GSC*) ↑	Tissue	Increases metastasis	Non-responder	Intrinsic	186,192
Carboplatin and paclitaxel	*mRNA*	Snail homolog 1 (*SNAI 1*) ↑	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	186,193
Carboplatin and paclitaxel	Protein	Class III β-tubulin (*TUBB3*) ↑	Cell line	Cytoskeletal modulation and overcomes stress conditions	Non-responder	Acquired	194
Carboplatin and paclitaxel	Protein	Lewis y ↑	Tissue	Increases cell adhesion and invasion	Non-responder	Intrinsic	195,196
Carboplatin and paclitaxel	Protein	CD44 ↑	Tissue	Increases cell adhesion and invasion, increases drug efflux	Non-responder	Intrinsic	195–197
Carboplatin and paclitaxel	Protein	CD147 ↑	Tissue	Interacts with drug resistance proteins	Non-responder	Intrinsic	195,198
Carboplatin and paclitaxel	Protein	Human epididymis protein 4 (*HE4*) ↑	Tissue	Increases tumour cell proliferation	Non-responder	Intrinsic	195,199
Carboplatin and paclitaxel	Protein	Integrin α5β1 ↑	Tissue	Increases cell adhesion and invasion	Non-responder	Intrinsic	195,200
Carboplatin and paclitaxel	Protein	Integrin αvβ3 ↑	Tissue	Increases cell adhesion and invasion	Non-responder	Intrinsic	195,201
Carboplatin and paclitaxel	Protein	CD44 ↑	Tissue	Increases cell adhesion and invasion, increases drug efflux	Non-responder	Intrinsic	196,197,202
Carboplatin and paclitaxel	Protein	IL-8 ↑	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	202,203
Carboplatin and paclitaxel	Protein	α-Enolase (*ENO1*) ↑	Tissue	Cytoskeleton modulation and inhibition of apoptosis	Non-responder	Intrinsic	114,204–206
Carboplatin and paclitaxel	Protein	Enoyl CoA hydratase (*ECH*) ↑	Tissue	Decreases apoptosis	Non-responder	Intrinsic	114,207
Carboplatin and paclitaxel	Protein	Prohibitin (*PHB*) ↑	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	114,208

Table 5. (Continued)

CHEMOTHERAPY	MACROMOLECULE	BIOMARKER	SOURCE	CELLULAR MECHANISM	CLINICAL PHENOTYPE	CHEMO-RESISTANCE	REFERENCE
Carboplatin and paclitaxel	Protein	Peroxiredoxin-4 (*PRDX4*) ↑	Tissue	Overcomes stress condition and inhibits apoptosis	Non-responder	Intrinsic	114,209,210
Carboplatin and paclitaxel	Protein	Fibrin β ↑	Tissue	Increases tumour angiogenesis and inhibits apoptosis	Non-responder	Intrinsic	114,211–213
Carboplatin and paclitaxel	Protein	Fibrin γ ↑	Tissue	Increases tumour angiogenesis and inhibits apoptosis	Non-responder	Intrinsic	114,211–213
Carboplatin and paclitaxel	Protein	Heat shock protein-27 (*HSP27*) ↑	Tissue	Increases apoptosis and reduces drug efflux	Responder	Intrinsic	114,214,215
Carboplatin and paclitaxel	Protein	Actin (*ACT*) ↑	Tissue	Increases apoptosis	Responder	Intrinsic	114,216,217
Carboplatin and paclitaxel	Protein	Heterogeneous ribonucleoprotein particle (*hnRNP*) ↑	Tissue	Increases apoptosis	Responder	Intrinsic	114,218,219
Carboplatin and paclitaxel	Protein	Aldose reductase (*ALDR*) ↑	Tissue	Increases apoptosis	Responder	Intrinsic	114,220,221
Carboplatin and paclitaxel	Protein	α-enolase (*ENO1*) ↑	Tissue	Cytoskeleton modulation and inhibition of apoptosis	Non-responder	Intrinsic	204–206,222
Carboplatin and paclitaxel	Protein	Elongation factor Tu mitochondrial (*TUFM*) ↑	Tissue	Regulation of autophagy and innate immunity	Non-responder	Intrinsic	222
Carboplatin and paclitaxel	Protein	Glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) ↑	Tissue	Increases glycolysis enhancing cell survival	Non-responder	Intrinsic	222,223
Carboplatin and paclitaxel	Protein	Stress-70 protein mitochondrial (*GRP75*) ↑	Tissue	Inhibits apoptosis	Non-responder	Intrinsic	222,224
Carboplatin and paclitaxel	Protein	Annexin A 1 (*ANXA1*) ↑	Tissue	Overcomes stress and inhibits apoptosis	Non-responder	Intrinsic	222

an extended period of time and (c) unsuspected heterogeneity may occur due to genetic drift. Therefore, cell lines do not provide the actual reflection of molecular events as compared with tissue-based experiments. Also, most of the ovarian cancer cell line studies have been done for individual drugs such as cisplatin and paclitaxel, which may not correspond with the actual use of drug combinations in patients. It is of interest to note that the standard protocol for advanced ovarian cancer is a debulking surgery followed by chemotherapy. The procurement of the ovarian cancer tissue offers a window of opportunity for discovering biomarkers for innate resistance.

Studies have looked into the role of biomarkers to evaluate patient response to carboplatin and paclitaxel. This has been summarized in Table 5. Some of the important observations are as follows: (a) Genomic and transcriptomic studies that have been done to understand chemo-resistance to carboplatin and paclitaxel in ovarian cancer do not correspond to protein expression; (b) the chemotherapy response results from cell-cycle pathways that include apoptosis, drug-efflux mechanisms, regulation of innate immunity and cell survival; (c) observed chemoresponse outcomes were mostly intrinsic by nature, indicating pre-mediated cellular mechanisms that determine clinical phenotypes and (d) metabolic proteins, chaperones, transporters, transcription regulators and cytoskeletal proteins are up-regulated in ovarian cancer tissues of patients who had chemo-resistance. Although proteomics was used to study the problem of chemo-resistance in advanced ovarian cancer, substantial progress was not made due to the absence of whole cell proteome comparison between chemo-resistant and chemo-sensitive patient tissue samples. To address this, our group has sought to delineate distinct protein signatures that could red flag an innate chemotherapy resistance in advanced ovarian cancer. In this endeavour, we employed fluorescence-based differential in-gel expression coupled with mass spectrometric analysis to identify differentially expressed proteins in the advanced ovarian cancer tissue of patients resistant and sensitive to carboplatin and paclitaxel combinations.[114] Aldehyde reductase, hnRNP, cyclophilin A, heat shock protein-27 and actin that were expressed in the chemo-sensitive state are proteins intricately involved in apoptosis, and prohibitin, enoyl-coA hydratase, peroxiredoxin, fibrin-β and fibrin-γ that were expressed in the chemo-resistant state are proteins that dictate cell survival.[225,226] This clearly establishes the importance and relevance of biomarker discovery for chemoresponse in ovarian cancer. This is a positive step that can pave the way for better patient management and compliance.

Conclusions

Clinical research for chemotherapy combinations in advanced ovarian cancer has progressed over the years with a view to achieve better CR and tolerability. Currently, carboplatin and paclitaxel combination is widely used to treat advanced ovarian cancer globally. Even though there has been significant improvement in the CR and OS, a large proportion of the patients relapse due to chemo-resistance. A lot of progress has been made in the fields of genomics, transcriptomics and proteomics to understand the molecular processes that determine and dictate chemotherapy response. Clinical proteomics holds a lot of promise for biomarker discovery that can pave the way for development of diagnostics that can help monitor chemotherapeutics in patients with advanced ovarian cancer.

Author Contributions

Concept was concieved by GH; Drafted by RP, RH and GH; Proof read by LK, RH and GH.

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