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Management of Platinum Resistant – Refractory Ovarian Cancer: A Short Review

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Abstract Ovarian cancer accounts for 3% of cancer deaths among women and is the most lethal gynecological malignancy. The five year survival for all stages collectively is 45.6% and relapsed ovarian cancer is incurable. Platinum resistance is a major prognostic determinant but the molecular pathways involved in resistance mechanism are unknown. Resistance prediction methods are only evolving. The goal of therapy is preservation of performance status and quality of life. Sequential single agent chemotherapy offers the best benefit however no preferred sequence is recommended. Incorporating targeted therapy with conventional chemotherapy presents attractive additional therapeutic options with bevacizumab and olaparib licensed for clinical use. Survival with current management is dismal and enrollment in a clinical trial offers the best scope for platinum resistant ovarian cancer patients.

Keywords: *ovarian cancer, platinum resistance, cisplatin refractory, management*

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1. Introduction

Ovarian cancer accounts for 3% of cancer deaths among women and is the most lethal gynecological malignancy [1]. Ovarian cancer includes a heterogeneous group of neoplasms originating from epithelial, germ cell or stromal components. Most are epithelial in derivation and present formidable therapeutic challenges. The life time risk of epithelial ovarian cancer varies from 1.3% for sporadic cases to up to 40% for women with familial predisposition [2]. The median age of presentation is 60 years but women with familial predisposition present a decade earlier. Nulliparity and strong familial history are associated with exaggerated risk while higher parity, oral contraceptive use and breast feeding are coupled with a low risk status [2]. The five year survival for all stages is 45.6% with the five year relative survival being 92% for localized, 73% regional and 28% for distant disease. Incidence and mortality trends between 1975- 2012 depict a gradual decline of 1% per year for incidence and 2% per year for disease specific mortality [3]. It is postulated that this mortality decline may be attributed to the adoption of comprehensive surgical staging and the addition of paclitaxel to traditional chemotherapy regimes.

2. Management of Ovarian Cancers

Contemporary management of epithelial ovarian cancer involves a combination of debulking surgery and chemotherapy. Comprehensive surgical staging for early disease and primary or interval debulking surgery for loco regionally advanced disease is considered standard of care. The role of secondary cytoreduction for recurrent disease is still evolving while second look laparotomy is not recommended outside the scope of a clinical trial. Ovarian cancer is a chemosensitive disease and response to therapy is an important prognostic determinant irrespective of IV/IP route of administration. GOG-111,OV-10 firmly established the cisplatin/Taxol doublet as the most effective, compared to traditional chemotherapy regimes [4]. GOG-158 and a AGO phase III studies proved the non inferiority of carboplatin / taxol combination with the attractive benefit of a favorable toxicity profile [5]. Consequently carboplatin/paclitaxel remains the preferred combination with docetaxel substituted for paclitaxel in patients with pre existing neuropathy. Dose dense regimes, weekly paclitaxel regimes and intra peritoneal chemotherapy have shown a modest improved survival benefit to intravenous three weekly carbotlatin/Taxol chemotherapy. Despite apparent clinical response to chemotherapy in 80% of the patients, most relapse within a variable period and are incurable. A small proportion of patients progress whilst on therapy or relapse within a short time and their outcome is exceptionally dismal.

3. Defining Recurrent Disease

Recurrent ovarian cancer includes a heterogenous group with variable prognosis and unpredictable treatment response. Traditional definitions of platinum resistance as disease relapsing within 6 months and sensitive disease as recurring beyond 6 months after chemotherapy were based on three small retrospective studies in the pre CA-125 era. Platinum refractoriness was defined as progression while on platinum based therapy [6,7]. These definitions by the Gynecologic oncology group (GOG) are now considered

inadequate to identify subsets of patients within recurrent ovarian cancers as platinum sensitivity continues to be the major prognostic determinant even in relapsed ovarian cancers. Platinum sensitivity is best viewed as a continuous variable with response waning with early relapse. Consequently Platinum free interval (PFI) predicts the likelihood of response at relapse and has been used to define the relapsing ovarian cancers rather than the terms platinum sensitivity or resistance [8]. The fourth ovarian cancer consensus conference of gynecologic cancer intergroup (GCIG) in 2010 adopted PFI as the defining criteria for enrollment in clinical trials of recurrent ovarian cancers. PFI is defined from the last date of platinum dose to documentation of disease progression. Accordingly a PFI of less than six months is considered resistant or refractory disease, while more than 6 month of PFI is defining of a platinum sensitive relapse [8,9]. This GCIG definition permits CT/PET imaging to evaluate rising CA-125 levels during surveillance to detect recurrent disease, however some argue such practice results in a lead time bias rather than a precise indicator of PFI [9]. Despite limitations PFI continues to define recurrent ovarian cancer.

4. Mechanisms of Platinum Resistance

The mechanisms of platinum resistance in ovarian cancers are unknown. One model postulates platinum sensitivity as a inverse function of chemoresistant tumor stem cell population, while the tumor dormancy mechanism hypothesizes that chemotherapy induces adverse microenvironment alterations (hypoxia, nutrient stress etc) that drive a proportion of tumor cells into dormancy only to relapse later [10]. An extracellular matrix dependant resistance model has been proposed based on the observation that ovarian cancer tumor cells are resistant to platinum if grown on collagen VI than on collagen III [11]. Studies have focused around cisplatin resistance predominantly, though paclitaxel resistance is also well documented. Reduced intra cellular uptake of cisplatin is due to altered transport protein expression with reduced expression of the influx copper transporter -1 (CTR1) and over expression of efflux proteins ATP7A, ATP7B and MRP related proteins [12]. MRP-2 expression may predict sensitivity to platinum agents. Intracellular inactivation of cisplatin by Thiol conjugation mediated by GSH transferase is an important resistance mechanism noted in ovarian cancer. Cisplatin cytotoxicity is mediated by the formation of DNA adducts, intra and inter strand cross links. The nucleotide excision repair, mismatch repair and homologous recombination DNA repair pathways are involved at various levels in the restoration of cisplatin induced cellular damage [12]. Ovarian cancer cells exhibit mutations in theses repair pathways contributing to cisplatin sensitivity of ovarian cancer cells however over expression of ERCC-1(nucleotide excision pathway) and restorating mutations in mismatch repair pathways has been demonstrated in ovarian cell culture lines exposed to cisplatin and hence this mechanism may explain clinical resistance [12]. BCL-xL overexpression has been linked to resistance to platin, paclitaxel, topotecan and gemicitabine. Whole genome sequencing of platinum resistant, refractory and sensitive types of ovarian tumor has shown inactivating gene breakages of RB -1, NF-1,RAD51 B and PTEN genes in high grade serous cancers. CCNE1 amplification is the commonest in resistant – refractory cancers [12].

5. Predicting Chemoresistance

The use of biomarkers for predicting response to therapy is an attractive concept as it permits individualized treatment. This strategy has been successful in other cancers, however the target biomarkers and the detection technology continue to be elementary in ovarian cancers. The approaches include functional assays, identification of resistance gene markers and micro RNA analysis. Functional assays test the in vitro sensitivity of harvested ovarian cancer cells against a panel of chemotherapeutic agents. The extreme drug resistance assay (EDR) was developed in 1990, however in view of conflicting clinical evidences the American society for clinical oncology (ASCO)in its technological update 2011 recommended against the use of functional assays outside the context of a clinical trial [13]. The chemoFx (Precision therapeutics INC, Pittsburg, USA) assay has been recently reported to predict resistance to carboplatin /taxol therapy [14]. Micro RNAs -21,484,642,217 have been reported to predict resistance based on expression patterns. Multi gene assays like 277 gene signature have yielded promising results, however both these technologies suffer from poor reproducibility and hence remain unvalidated for clinical uses. A systematic review of resistance prediction technologies used pubmed to identify 42 studies, however modeling techniques were heterogeneous and very few genes were identifiable by more than two studies,hence the authors concluded that a clinically applicable gene signature test remain elusive [42].

6. Treatment

Seventy five percent of ovarian cancer patients develop recurrent or progressive disease within five years. Eight percent relapse within 6 months and another twenty percent in the first year [15]. Relapsing ovarian cancer is incurable and subsequent therapy challenging due to declining performance status, cumulative chemotoxicity and the absence of effective second line therapeutic agents. An strategy that preserves quality of life with minimum toxicity is preferable. Chemotherapy, hormonal agents and targeted therapy have been tested in trials. With limited phase III trial data the use of sequential single agent chemotherapy has been advocated and best achieves the treatment goals, however no preferred sequence is recommended. Prior therapy, residual toxicity and organ function should guide the selection of non cross reacting second line agents. The importance of stable disease as a measure of therapy benefit and quality of life factors as appropriate study endpoints in clinical trials involving resistant ovarian cancers has been emphasized by GCIG [8,9].

6.1. Chemotherapy

Liposomal doxorubicin, weekly paclitaxel, docetaxel, topotecan, gemicitabine and etoposide are the

recommended agents (NCCN version 2.2015 OV-D). The response rates to these drugs varies from 10 - 35 % in phase II studies and the responding period is typically short (less than 8 months) [6]. Liposomal doxorubicin is an accepted first line therapy with modest survival benefit however in contemporary practice its utility as primary therapy has been relegated by paclitaxel. In platinum resistant disease liposomal doxorubicin and polyethylene glycol coated (PEG) formulation has been studied as a single agent or as a doublet with topotecan, paclitaxel, gemicitabine, oxaliplatin,, vinorelbine and carboplatin. The response varies from 0- 37 % with a median time to response of 8 weeks. The dose and scheduling are heterogenous and vary from 20- 40 mg /m² in 3 or 4 weekly cycles [16,17]. The hand foot syndrome was the most dose limiting toxicity and cardiomypathy as confirmed by cardiac biopsies are significantly less up to a cumulative dose of 440-840 mgs/m² [18]. The lack of severe neutropenia and high rates of stable disease make liposomal doxorubicin an attractive option in recurrent ovarian cancers.

Topotecan has been approved following exhaustive testing as a second line therapy. It has demonstrated a response of 12- 33% and 13 % in phase II and III studies respectively. The FDA recommended dose of 1.5 mgs/m² /day for 5 days results in 80 % grade 4 neutropenia and 25% severe thrombocytopenia and this could prevent utility in heavily pretreated patients. These limitations may be negated by reducing the starting dose to 1-1.25 mgs/m²/day and altering to a 3 day schedule or 24 hour infusion [19,20,21].

Gemicitabine has been evaluated as monotherapy and as a doublet. Twelve monotherapy studies with 411 patients has demonstrated a partial response in 14- 22 % and stable disease of 30 % translating into a clinical benefit of 50%. The responses remained durable for 4- 6 months. Doublet studies have combined gemicitabine with topotecan and liposomal doxorubicin, a response of 13-40 % and a median survival of 13- 21 months has been obtained in phase II studies, as expected grade 3-4 myelosuppression toxicity predominated [22]. A dose of 800 – 1250 mgs/m² as a 30 minute infusion on days 1,8 and 15 of a 28 day cycle often results in dose limiting neutropenia which is fortunately non cumulative and management by dose reductions or delays is recommended [22,23].

Paclitaxel in a dose of 135- 175 mgs/m² (3hr and 24 Hr infusion) 3 weekly or 80 mgs/m² weekly schedule has been tested, yielding a average response rate of 21%. Both grade 4 neutropenia and grade 3 neuropathy resulting in treatment withdrawals and morbidity including fatalities has been reported. The weekly regime retains antitumor activity and additionally minimizes myelotoxicity. Trials testing docetaxel report an objective response of 20-35 % at a dose of 100mg/m² as 1 hr infusion on a 3-4 week schedule. Major toxicities are neutropenia and the capillary leak syndrome both cumulative with subsequent cycles. Efficacy of Docetaxel in paclitaxel pretreated patients remains uninvestigated though a benefit has been reported in preliminary studies. A phase II study testing the docetaxel vinorelbine doublet reported a overall response of 24 % and 35 % for stable disease. Grade 4 Myelotoxicity was noted in 50 % and despite a protocol adherence of 60 % only a median survival of 10 months was observable [24,25,26,27].

Low dose oral etoposide at a dose of 50 mgs/m² has the advantage of outpatient care but the predominant myelosuppression requires careful weekly follow up and the modest response of 25 % makes this option less preferable [28]. The other oral formulation, altretamine has a response of only 10 % but the high gastrointestinal toxicity precludes its use [29]. Single agent ifosfamide and cyclophosphamide have shown a response rate of 10- 15 % but these agents typically have significant renal, CNS or bladder toxicities [8]. Vinorelbine in a dose of 25 – 30 mgs/ m² on a 3 weekly schedule offers a salvage response rate of 15 -20 % but was ineffective in alleviating symptom related physical dysfunction [30,31]. Following anecdotal reports of response to pemetrexed a systematic review of single institution case series confirm anti neoplastic activity in heavily pretreated ovarian cancer patients but its efficacy is unproven in a formal clinical trial [32].

A systematic review of major chemotherapy trials conducted till 2010 included 2298 platinum resistant ovarian cancer patients. The study identified gemcitabine as the best effective drug with a response rate of 27% when used in combination with liposomal doxorubicin. The review confirmed higher antitumor activity to combination therapy (21 vs 10 %) compared to monotherapy [43].

6.2. Hormonal Therapy

Hormonal therapy represents potentially effective treatment strategy in resistant -refractive ovarian cancers. High possibility of achieving of stable disease at favorable or absent toxicity in an elderly, heavily pretreated patient group is an attractive concept worthy of further evaluation. Antiestrogens, aromatase inhibitors and gonodotropin releasing hormone analogs have been evaluated in trials. The correlation between hormone receptor positivity and response is inconsistent. Tamoxifen 20 mgs/day demonstrated a disease control rate of 55 % and Intra muscular fulvesterant dosed at 500mgs on day 1, 250 mgs on days 15 and 29 and every 28 days thereafter revealed a control rate of 50 % with median time to progression of 2 months [33,34]. Studies involving letrozole 2.5 mgs/ day or anastrazole 1mg/day show identical benefit of 42 % for disease control [35,36]. A AGO phase III study comparing Leuproreline 3.75 mgs subcutaneously every 4 weeks to treosulfan 7gms/m² was stopped at interim analysis due to lack of efficacy, though on long term follow up the overall survival did not differ between the two arms [37]. It is important to note the chemotherapy arm did not evaluate contemporary chemotherapy.

6.3. Targeted Therapy

Bevacizumab, the humanized monoclonal antibody against the angiogenic vascular endothelial growth factor (VEGF) is the most extensively evaluated targeted therapy. The ICON-7 and GOG-218 established bevacizumab as frontline therapy in high risk platinum sensitive ovarian cancer. A phase II trial evaluating bevacizumab monotherapy in platinum resistant or refractory ovarian cancer demonstrated a response of 16 % and 27 % progression free survival at 6 months. An alarming 11%

bowel perforation rate prompted early closure of this trial with data suggesting patients with bowel involvement on imaging, intestinal obstruction and more than three prior regimes at high risk of perforation [38]. Food and drug administration (FDA) approved bevacizumab at a dose of 10 mgs/kg every 2 weeks or 15 mgs/ks 3 weekly in combination with topotecan (days 1,8,15 every 4 weeks), liposomal doxorubicin (4 weekly) and paclitaxel (days 1,8,15, 22 every 4 weeks) based on the AURELIA trail. This trial excluded patients with above high risk features and induced a significant benefit of 6.8 months median progression free survival benefit (PFS), with exploratory analysis a maximum benefit to weekly paclitaxel emerged. High blood pressure, neuropathy and neutropenia were the common toxicities with only reporting 1.7 % gastrointestinal perforations and 2 % fistulae [39].

Olaparib is the only other NCCN and FDA recommended targeted therapy in BRCA mutant relapsed ovarian cancers. Its effectiveness is related to the concept of synthetic lethality where by its non lethal PARP inhibition coupled with a pre existing BRCA1/2 mutation confers extreme tumor cytotoxicity. Following initial dose determining and tolerability studies, a prospective multicenter phase II trial evaluated olaparib 400 mgs twice daily in combination with mono chemotherapy in 178 BRCA 1/ 2 mutant patients with resistant ovarian cancers. This trial demonstrated a clinical response in 61 % (including stable disease), a median progression free survival of 7 months and overall survival of 18 months. Serious adverse effects were observed in 30% with fatigue, anemia and vomiting predominately reported [40,41].

A myriad of investigational agents are under study and include trabectedin,pertuzumab,cediranib, halichondrin B and geftinib, however none has demonstrated satisfactory benefit. Sunitinib is under evaluation for the non P53 mutant intrinsically chemoresistant low grade serous and clear cell histological types. Table 1 shows a selected list or open phase II/III clinical trials involving various therapeutic approaches in platinum resistant ovarian cancer.

Table 1. Selected open phase II/III trials in platinum resistant ovarian cancer

Trial No	Protocol	Type
NCT02580058	Avelumab with or with out Pegylated Liposomal doxorubicin	Phase III
NCT 02421588 (COPAIL)	Lurbinectedin Vs PLD or topotecan	Phase III
NCT 02502266	Cediranib & olaparib Vs Chemotherapy	Phase II/III
NCT 02354586	Niraparib (single arm)	Phase II
NCT 02608684	Pembrolizumab with cisplatin & gemicitabine	Phase II
NCT 02272790	AZD1775 with or without combination chemotherapy	Phase II
EORTC 55092	Pazopanib in combination with carboplatin/taxol	Phase II

7. Conclusion

Platinum resistant ovarian cancer is an invariably fatal disease. The mechanisms of chemoresistance are unclear and resistance prediction methods are still evolving. The management strategy revolves around preservation of performance status and well being with current approach involving sequential single agent chemotherapy offering the best benefit. Targeted therapy offers an attractive alternative with two drugs currently approved for use, however robust research is underway and is likely to change the scenario in future. GCIG has recognized this sub group of relapsed ovarian cancer as biologically unique and faced with formidable treatment challenges posed, has revisited the definition and has set recommendation for the conduct of future clinical trails. The best scope for this patient group is an enrollment in an appropriate clinical trial.

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Competing Interests

The authors declare no competing interests.

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