MUCINOUS OVARIAN CANCER: A THERAPEUTIC REVIEW

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Highlights

- Mucinous epithelial ovarian cancer (mEOC) is a rare chemo-resistant subtype of ovarian cancer with distinct epidemiology, pathology and natural history.
- mEOC can often masquerade as metastatic mucinous tumours from the gastrointestinal (GI) tract.
- Molecularly, in contrast to high-grade serous ovarian cancer (HGSOC), mEOC are far less defined by p53 mutations and instead commonly harbour KRAS and HER 2 mutations.
- The current gold standard of 1st line platinum/taxane doublet chemotherapy, is more tailored towards HGSOC and generally ineffective for mEOC.
- This review summarises the limited evidence for using GI style chemotherapeutic agents in treating mEOC and explores novel therapeutic possibilities such as targeting HER2, VEGF and Src.

Abstract

Mucinous ovarian cancer represents approximately 3% of epithelial ovarian cancers (EOC). Despite this seemingly low prevalence, it remains a diagnostic and therapeutic conundrum that has resulted in numerous attempts to adopt novel strategies in managing this disease. Anecdotally, there has been a prevailing notion that established gold standard systemic regimens should be substituted for those utilised in cancers such as gastrointestinal (GI) malignancies; tumours that share more biological similarities than other EOC subtypes. This review summarises the plethora of small studies which have adopted this philosophy and influenced the design of the multinational GOG142 study, which was ultimately terminated due to poor accrual. To date, there is a paucity of evidence to support delivering ‘GI style’ chemotherapy for mucinous ovarian cancer over and above carboplatin-paclitaxel doublet therapy. Hence there is an urge to develop studies focused on targeted therapeutic agents driven by refined mutational analysis and conducted within the context of harmonised international collaborations.
Keywords: mucinous ovarian cancer, chemotherapy, targeted therapy, gastrointestinal cancers

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1. Introduction

Epithelial ovarian cancer (EOC) remains the most lethal gynaecological malignancy in developed nations. Amongst the various histotypes, mucinous epithelial ovarian cancers (mEOC) represent approximately 3% of EOC presentations and are generally classified as Type I (i.e. low grade) tumours. Alongside all other EOC subtypes, the cornerstone of therapeutic management for this disease traditionally involves surgical debulking (either primary or interval) in conjunction with platinum/taxane doublet chemotherapy delivered with either neoadjuvant or adjuvant intent [1-5]. However, mEOC embodies a disease entity with a distinct natural history, molecular biology, chemo-sensitivity and prognosis in comparison with the predominant high-grade serous (HGSOC) subtype [6-9]. Alarmingly, the current gold standard of HGSOC chemotherapeutic management is still counterintuitively adopted for mEOC; a relatively chemoresistant disease [6-8, 10]. Hence, within the burgeoning era of personalised medicine, there is an urge to pursue a more refined approach in systemically managing mEOC. This may well involve learning lessons from treatment algorithms utilised in other malignancies, which share significant histopathological and molecular characteristics with this unique subtype [7, 8, 11]. The review herein presents numerous studies utilising such approaches in addition to outlining the key molecular drivers of mEOC which hold some promise in stratifying patients who would gain significant survival advantages with novel therapies.

2. Epidemiology

In comparison to HGSOC (70% EOCs), mEOC is a relatively rarer subtype which comprises 7-14% of all primary epithelial ovarian cancers in historical cohorts [12]. However, given the
notorious difficulties in distinguishing true primary mEOC from metastatic mucinous carcinomas from the gastrointestinal (GI) tract, the actual prevalence of mEOC may be closer to 3% [9, 13, 14]. Invasive mEOC most commonly presents in women between 39 and 50 years old (range 14-87) [15]. This middle-aged preponderance contrasts with the incidence of HGSOC which generally increases with age [16]. There also appears to be a clear aetiological discordance between HGSOC and mEOC. For example, HGSOC risk factors such as nulliparity, menarchal age, increased body mass index, oestrogen exposure, tubal sterilisation and lack of breastfeeding do not consistently correlate with mEOC prevalence [17]. Similarly, smoking, which has no strong historical association with HGSOC, may be a significant risk factor for mEOC [17]. Whilst most ovarian cancers are diagnosed without family history, a positive history of mucinous cancer has been shown to dramatically increase the risk ratio of further cancers, particularly in comparison to EOC [17, 18]. A recent Danish population study observed an inverse relationship between statin use and mEOC incidence versus a neutral relationship between statin use and HGSOC incidence [19]. Furthermore, BRCA1 and BRCA2 oncogenes which increase lifetime risk of breast and other epithelial ovarian cancers (in particular HGSOC), has a negligible influence on mEOC risk [20].

Despite sharing a common müllerian cell origin, the understanding of mEOC has evolved to the point where it must be considered a separate disease entity. In contrast to HGSOC, the vast majority (80%) of mEOC are diagnosed at an early stage [15]. Interestingly, stage I mEOC, where the management is primarily mandated by surgery alone, has a better prognosis than HGSOC [15, 21]. Moreover, retrospective evidence suggests that it is a reasonable option to offer women fertility sparing surgery for early stage mEOC [22]. Conversely, advanced mEOC (≥stage III) typically has a significantly worse prognosis than HGSOC, with reported median survivals of 12-14 months versus 37-42 months respectively.
This is exemplified by the fact that in comparison to HGSOC, mEOC is more likely to present with particular adverse prognostic features such as parenchymal liver metastases. However, paradoxically, advanced mEOC is also more likely to feature classically favourable prognostic feature such as limited peritoneal carcinomatosis, and higher likelihood of optimally debulked disease [6]. Nevertheless, from a therapeutic perspective, advanced mEOC is less chemoresponsive and subsequently has a worse progression free (PFS) and overall survival (OS) than other EOC subtypes [7].

3. Histopathology

Differentiating primary ovarian mucinous tumour from metastatic mucinous tumour of gastrointestinal or other gynaecological origin is challenging. GI tract malignancies, particularly the large intestine, appendix, and pancreas are frequently identified in the ovary [23, 24], with metastases from the biliary tract, stomach, cervix, breast and uterus also described [25, 26]. Pseudomyxoma peritonei, once considered a consequence of advanced mEOC, is now widely accepted as a result of metastatic appendiceal mucinous tumours [27]. Furthermore, it is well documented that metastatic mucinous tumours from other organs can frequently masquerade as advanced primary mEOC. As metastatic cancers of GI origin generally have a worse prognosis than ovarian cancers, it is certainly possible that a proportion of patients labelled as late stage mEOC may have been misdiagnosed [9, 13, 14], which accounts for the seemingly inferior outcomes synonymous with late stage mEOC. In a study by Zaino et al. [9], 61% (27/44) of patients initially described as having a primary mEOC were eventually reclassified to be likely metastatic rather than primary mucinous ovarian tumours. Interestingly the median survival did not appear to differ significantly between the primary or metastatic cohorts. Additional studies have also described this pattern of reclassification after exhaustive review [14, 28]. Significantly, certain pathological
differences are apparent between mucinous metastases and primary mEOC (Table 1). Key diagnostic clues include bilaterality; a phenomenon apparent in >90% of metastatic tumours and a relatively rare presentation in primary cancers [14]. Additionally, tumour size > 10cm is much more likely to be of primary origin. These two factors influenced Seidman et al. [14] to devise an algorithm that correctly identified 90% of tumours as either primary tumours or metastases; a concept which has also been validated in subsequent studies [29, 30].

In the instance of diffusely metastatic disease, distinguishing between primary mEOC and metastatic mucinous tumours from other primaries can be particularly complex. Within this sphere, immunohistochemistry (IHC) is an invaluable pathological tool (Table 2). Primary mEOC commonly shares positive IHC patterns for CK20, CEA, CA 19.9 and CDX2 with metastatic colorectal cancer (CRC)[32]. However, CK7 serves as a useful discriminator being diffusely positive in mEOC and predominantly negative in mucinous colorectal cancer (CRC)[32]. Nevertheless, a revision of the mucinous cancer algorithm by Maeda-Taniguchi et al. [28] has also found that combining serum biomarkers CA125 and CA19-9 further improved the positive predictive values of tumour classification. Other markers not commonly analysed that are frequently demonstrated in mucinous CRC include a-methyl acyl-CoA racemase, meprin a, guanylyl cyclase C, MUC2, dipeptidase 1 and -catenin; however these are currently of limited diagnostic use due to considerable overlap with other tumour types [32]. Moreover, a retrospective study of 500 ovarian cancer cases by Kobel et al.[33] found consistent differences in the expression of 20 out of 21 biomarkers when comparing various subtypes of EOC. This consolidates the notion of the deep heterogeneous nature of this disease and the necessity for each sub-type to be handled as separate disease entities, with unique prognostic and therapeutic paradigms [33].

Intriguingly, the level of histological complexity also extends to hormone receptor expression. Historically, mEOC tumours were deemed less likely to express oestrogen and
progesterone receptors (ER, PR) than HGSOC, but a recent paper challenges this notion, finding higher rates of ER and PR expression in mEOC (88% & 84%) vs. HGSOC (66% & 64%). However, there is a paucity of prospective evidence on the differential efficacy of endocrine therapy for mEOC vs. HGSOC [34].

4. Molecular biology

Distinct differences in gene expression distinguish mEOC from other epithelial ovarian cancer subtypes. In general, mEOC appears to share many molecular biological characteristics with primary GI tumours (Table 3). In contrast to HGSOC, mEOC typically demonstrates overexpression of the K-RAS oncogene. Moreover, KRAS mutations are prevalent in 43-46% of mEOC, 30% mucinous CRC and 28% non-mucinous CRC (35-37). With respect to P53 mutations which represent the hallmark of HGSOC (approx. 96%)[35], this is only limited to < 30% of mEOC cases [36]. However, a recent Australian study using whole genome sequencing of 24 tumours reported a surprisingly high rate of TP53 mutations (52%), again highlighting the heterogeneity of entities that are classified as mEOC [37]. BRAF mutations, a well-established adverse prognostic marker in CRC, appears to be rare in mEOC, accounting for none of the mEOC samples assessed by Gemigani et al. [38]. This contrasts to BRAF mutations evident in 20% of mucinous CRC and 8% of non-mucinous CRC. APC mutations also vary significantly between these cancer types, from 9% in mEOC to 88% in non-mucinous CRC [11, 39, 40]. Furthermore, recent research has reviewed HER2 amplification in mEOC. Whilst relatively uncommon in EOC, HER2 overexpression rates up to 35% in mEOC have been documented [41-46] [47].

With the advent of genome wide association studies (GWAS), there have been recent advances specific to mEOC within this realm. Kelemen et al. [57] evaluated 1644 patients with mEOC vs. 21693 controls and identified 3 new single nucleotide polymorphism (SNP) which were associated with mEOC risk at independent genomic loci. This consortium also
used expression quantitative trait locus (eQTL) analysis to identify associations between candidate SNP variants and gene expression in both HGSOC and CRC tumours from the Cancer Genome Atlas. One of the susceptibility genes for mEOC, HOXD9, is an established high grade HGSOC susceptibility gene, indicating a possible shared role for this gene in oncogenesis of both distinct types of EOC. Another SNP identified was associated with mEOC risk and PAX8 expression in colorectal cancers but not HGSOC [57].

5. Clinical management and pitfalls

The current standard of care for all EOC, regardless of histology, is defined by surgical debulking in early stage (Ia – Ib) disease; and adjuvant platinum/taxane doublet chemotherapy in addition to surgical debulking in more advanced disease (Ic-IIIc)[1-5]. However, whilst representing an efficacious strategy for the majority of ovarian cancers comprised mainly of HGSOCs, this does not directly translate to rarer subtypes such as mEOC.

As a reflection of its low prevalence, the landmark randomized control trials which established platinum/taxane as the ‘gold standard’ standard of care in the first-line management of EOC only comprised a small number of mEOC subjects (Table 4). Significantly, there has not been a sub-group analysis on the differential efficacy of treatment on patients with mEOC in these studies. Moreover, if such data was available, any conclusions would be limited by a lack of statistical power. As previously mentioned, mEOC is more likely to diagnosed at an earlier stage and lower grade compared with HGSOC [6, 7, 12]. Stage I mEOC has an excellent prognosis with 5 year survival of 90% with surgery
alone, which is comparable if not superior to HGSOC [6, 8, 58]. Conversely, in the advanced
disease setting, a number of studies have consistently demonstrated markedly inferior
outcomes for mEOC compared with HGSOC, when treated with platinum-based
chemotherapy both in the first-line, as well as the recurrent setting (table 5).

In comparison with HGSOC, the poor prognosis of advanced mEOC is manifested by its’
inherent aggressive biology (i.e. proclivity in visceral dissemination) and inferior response
rates to platinum chemotherapy. Overall, the data would seem to support that relative
chemoresistance is the major reason for inferior outcomes in advanced mEOC. In both in
vitro and in vivo preclinical models, mEOC cell lines demonstrate intrinsic platinum
resistance [65]. As outlined in Table 5, a multitude of retrospective studies have
demonstrated the markedly inferior response rates to platinum-based chemotherapy for
mEOC compared with HGSOC [6, 7, 10, 63, 64].

6. Alternate chemotherapy algorithms

Due to the numerous pathological and molecular commonalities shared by mEOC and GI
tumours, it has long been hypothesised that adopting standard GI treatment algorithms maybe
more effective for mEOC than the current standard of care involving platinum-taxane based
therapy.

6.1 Fluoropyrimidines

The thymidylate synthase inhibitor 5-fluorouracil (5FU) has long been the cornerstone of
systemic therapy for CRC. A number of early phase II studies in the 1990s [66-71] evaluated
the role of 5FU with leucovorin as second line settings and beyond in advanced EOC with modest response rates ranging between 0 to 23%. The 5FU regimens selected differed widely between studies and hence variable efficacy is reported. Furthermore, these were predominantly small studies which did not specify the histological subtypes of EOC treated. A more recent retrospective study [72] of 53 heavily pre-treated patients (>3 lines of previous therapy), treated with 5FU (600mg/m$^2$ weekly for 6/8 weeks) and leucovorin found a response rate by Rustin Criteria (CA 125 decline >50%) [73] of 25%. However, under 2% (1/53) had mucinous histology, with the remainder being serous or endometrioid.

As an oral analogue of 5FU, capecitabine has equivalent efficacy to 5FU in a number of GI cancers [74-77]. Capecitabine was evaluated in a phase I/II study of 14 platinum refractory ovarian cancer patients, showing a 25% response rate (1 CR, 2 PR) [78]. However, subsequently a larger multi-centre Italian phase II study (MITO 6), [79] evaluated capecitabine at 1250mg/m$^2$ q2-3weekly in 32 platinum refractory advanced EOC patients and found a disappointing response rate of 3.1%, with a median PFS of 68 days. However, there were no mEOC patients in this cohort.

6.2 Oxaliplatin

Oxaliplatin is a synthetic platinum agent with relative non cross-resistance in vitro with cisplatin or carboplatin [80]. In combination with 5FU/leucovorin, it represents the preferential first-line regimen in the management of CRC in both adjuvant [81] and metastatic [82] settings. With respect to EOC, phase II studies with single agent oxaliplatin have reported an overall response rate (ORR) of 5.6-17% and 42-46% with single agent oxaliplatin in platinum resistant and platinum sensitive disease respectively [83, 84]. However there is still no clear data as to the specific efficacy of oxaliplatin monotherapy for mEOC patients.

6.3 5FU/Leucovorin & Oxaliplatin (FOLFOX)
Four studies have demonstrated reasonable efficacy with an acceptable toxicity profile of FOLFOX (5FU/leucovorin + oxaliplatin) in platinum resistant, heavily pre-treated EOC [85-88] (Table 6). Again, these studies were all in the second-line or beyond setting and included only a handful of mEOC patients, so it is difficult to draw conclusions. However there is *in vitro* and *in vivo* data to suggest that this could prove an effective regime in mEOC. Sato et al. found synergistic efficacy of 5FU with oxaliplatin in 4 of 5 mEOC cell lines, which were resistant to cisplatin and paclitaxel. Furthermore, the combination of oxaliplatin and 5FU significantly prolonged survival in a mEOC murine xenograft model [89].

### 6.4 Gemcitabine & Oxaliplatin

Several studies have also demonstrated the efficacy of oxaliplatin combined with gemcitabine (GEMOX) in the 2nd line setting for platinum resistant ovarian cancer. Vici et al. [90] reported an ORR of 37% in 41 heavily pre-treated platinum resistant EOC patients, of which 7% (3/41) were mEOC. Yuan et al. [91] also noted an ORR of 35% (bolus gemcitabine) to 43.2% (infusional gemcitabine) with GEMOX in pre-treated ovarian cancer. 16 of the 64 patients in this cohort had mucinous histology, but it is unclear whether there was any differential efficacy in response to GEMOX with mEOC in comparison to other histologies.

### 6.5 Irinotecan

The topoisomerase I inhibitor, irinotecan, also has a well-established role in the systemic management of metastatic colorectal cancer [92] both as a single agent [93] and in combination with 5FU/leucovorin (FOLFIRI) [94-96]. After initially demonstrating *in vitro* efficacy of irinotecan against mEOC cells lines [65], Shimizu et al. conducted a phase II study using irinotecan and mitomycin C in 25 patients with platinum resistant EOC of either clear cell or mucinous histology [97]. This study reported a 52% ORR with 80% (4/5) of mEOC patients demonstrating an objective response. Furthermore, the median OS was of
33.7 months versus 6.1 months for responders and non-responders respectively. Additionally, a small phase II study with irinotecan (50mg/m$^2$) in combination with docetaxel (35mg/m$^2$) day 1 an 8, q21 days was evaluated as 2$^{nd}$ line therapy in 62 patients with platinum refractory EOC; and as first-line treatment in 15 patients with either mEOC or clear cell ovarian cancer [98]. The ORR was 53% in the 15 patients with either clear cell or mucinous histology, with 4 out of the 15 patients (27%) having mEOC.

7. mEOC specific clinical trials

In the GOG241 trial [99], the GCIG Intergroup made an ambitious but ultimately unsuccessful attempt to conduct an mEOC specific trial to definitively answer the question of whether CRC style chemotherapy would compare favourably to the traditional platinum/taxane doublet approach. In light of the triumph witnessed in metastatic CRC, the trial also sought to clarify the efficacy of inhibiting angiogenesis with bevacizumab in the mEOC setting. GOG241 commenced recruitment in December 2009, with a planned target of 330 patients with advanced or recurrent mEOC in the first-line setting. The trial had originally planned a 2x2 factorial design with an aim of recruiting 83 patients per arm on a 1:1:1:1 basis for treatment with either carboplatin-paclitaxel +/-bevacizumab or oxaliplatin-capecitabine +/- bevacizumab. However, in early 2013, the trial had to be ceased prematurely due to poor accrual (only 50 patients recruited). The median PFS for the oxaliplatin/capecitabine arms was 10.1mths vs 15.4 mths for the carboplatin/paclitaxel arms (HR 1.08; 95% CI 0.53-2.19; p=0.83). The median PFS in arms with bevacizumab was 17.4mths vs 8.8mths in arms without bevacizumab (HR 0.88; 95% CI 0.43-1.79; P=0.72) (Table 7). Although this latter observation suggests a trend in superior PFS for bevacizumab, the limited number of participants precludes any meaningful conclusions being deduced from
this trial. Interestingly, on specialist pathology review 17/36 patients were actually considered to have not primary mEOC [99].

Another mEOC specific study follows on from the success of the oral combination fluoropyrimidine S1 in patients with various GI malignancies [100-103]; whereby a Japanese group has initiated a phase II trial of S1 plus oxaliplatin for mEOC [104].

8. Targeted therapeutic approaches

8.1 VEGF inhibition

The monoclonal VEGF-A antibody, bevacizumab, has been shown to modestly improve OS in addition to chemotherapy in metastatic CRC in several meta-analyses [105-108], and is currently established within the standard armamentarium in first line management of this disease. The role for the bevacizumab in EOC is also evolving with two large phase III trials confirming improve PFS in addition to adjuvant chemotherapy following primary debulking surgery [109, 110] and in both the recurrent platinum sensitive [111] and resistant settings [112]. Significantly, recent subgroup analyses demonstrate that adjuvant bevacizumab confers an OS advantage for high-risk patients with suboptimally debulked disease [109, 110]. As with all aforementioned studies, the phase III bevacizumab EOC trials all included only a handful of mEOC patients. Consequently, a subgroup analysis has not been conducted to verify any specific efficacy associated with bevacizumab in mEOC patients.

Nevertheless, there have been case reports documenting the anecdotal efficacy of bevacizumab monotherapy in mucinous ovarian cancer of low malignant potential [113] and in pseudomyxoma peritonei [114]. Bevacizumab is also effective and safe in combination with oxaliplatin and docetaxel in the first-line setting, as demonstrated by an ORR of 58.6%
in a phase II trial of 132 EOC patients [115]. However, only 3 mEOC patients were represented in this cohort.

### 8.2 EGFR monoclonal antibodies

Cetuximab has been evaluated in phase II studies as both monotherapy [116], and in combination with platinum-based chemotherapy [117, 118] in EOC with disappointing results. However, these studies were limited by inclusion of all histological subtypes and a lack of assessment KRAS status; an established negative predictive biomarker for anti-EGFR monoclonal antibody therapy in the treatment of metastatic CRC. KRAS mutations are prevalent in 43-46% of mEOC [41, 48, 49] and the efficacy of anti-EGFR monoclonal antibody therapy may be restricted to KRAS wild type cases [119]. In a preclinical study, Sato et al. reported that cetuximab was only able to exert anti-proliferative activity in mEOC cell lines which did not harbour KRAS mutations [120]; an observation recapitulated with an in vivo murine model [120]. In a single arm, phase II study, Steffensen et al. evaluated the efficacy of panitumumab in combination with pegylated liposomal doxorubicin in 43 platinum resistant EOC patients who were KRAS wild type. A modest efficacy was demonstrated with an ORR of 18.6%, PFS 2.7 months alongside significant skin toxicity. Again, it is unclear if any of these patients had mucinous histology [121]. Nevertheless, given the biological plausibility and encouraging early data, future studies involving the prospective use of cetuximab in KRAS wild type mEOC patients certainly merit consideration.

### 8.3 Anti-HER2 therapy

Anti-HER2 targeted therapy has been a major success story in the management of HER2 amplified breast cancer [122-124]. Trastuzumab (HER2 monoclonal antibody) also has
proven efficacy in the management of HER2 positive gastric and gastro-oesophageal junction cancer as evidenced by the TOGA trial where its’ combination with chemotherapy improved response rates from 34.5% to 47.3% and resulted in an OS benefit of 2.7 months (HR 0.74)[125]. However, HER2 overexpression is significantly less likely in mucinous gastric cancers compared with gastric cancers in general[126]. Combinatorial anti-HER 2 therapies with trastuzumab and lapatinib (HER 2 tyrosine kinase inhibitor) has also shown early promise in the small proportion of heavily pre-treated colorectal cancer patients with HER2 amplification in the HERACLES trial, with a response rate of 33.3% [127].

In comparison with breast cancer, HER2 expression is relatively rare in EOC (11.4%) and targeted therapy with trastuzumab has subsequently garnered an ORR of 7% [128]. Conversely, the HER2 expression in mEOC is significantly higher with a reported frequency of 18-35% [41-46, 52] and a preponderance in Asian as opposed to Caucasian populations [42, 46]. Preliminary data suggests that HER2 is not a prognostic marker in mEOC [42, 129], but there is growing interest in its role as a predictive biomarker for anti-HER2 targeted treatment. In a study of 189 mEOC patients, Anglesio et al. reported HER2 amplification in 18.8% (29/154) of patients and was almost mutually exclusive of KRAS mutations [41]. Furthermore, Kommoss et al. [130] proposed subdivision of mEOC into 3 major molecular subtypes based on: (1) HER2 over amplification, (2) KRAS mutations and (3) those with neither KRAS nor HER2 abnormalities. Such reclassification may forge new horizons in influencing treatment decisions and novel targeted therapy development in this subtype.

As expected, there is a paucity of specific studies focusing on targeted HER2 therapy in mEOC. McAlpine et al. reported the anecdotal efficacy of trastuzumab in combination with chemotherapy in 2 out of 3 patients with mEOC who had HER 2 amplification [47]. A phase II combinatorial study with lapatinib and topotecan failed to demonstrate meaningful benefit in platinum pre-treated EOC [131]. Notably, none of these patients had tumours
overexpressing HER2 which would certainly support the negative results. Although there is a solitary case report of progressive mEOC treated successfully with dual HER2 inhibition with trastuzumab and lapatinib [132], larger studies involving anti-HER 2 targeted therapy specific for HER2 amplified mEOC patients are certainly warranted.

8.4 Targeting Src and PI3K/Akt pathways

Another potential avenue for future research in mEOC therapy includes targeting Src kinase. Src kinase is a non-receptor tyrosine kinase which is a convergence point for numerous oncogenic pathways [133] and has been implicated in mechanisms of oxaliplatin resistance in colorectal cancer[134]. In preclinical mEOC models, encouraging results have been achieved by targeting Src signaling with dasatinib [135] and KX-01; a novel Src inhibitor and anti-tubule agent, in synergy with oxaliplatin [136].

The PI3K/AKT/MTOR pathway may also serve as a putative target in mEOC. Using a dual PI3K and mTOR inhibitor, Kudoh et al. were able to successfully suppress tumour growth in mEOC cell lines and xenografted murine models [137].

9. Conclusions

Future strategies for the treatment of mEOC hinge on improved molecular understanding of this subtype. Ultimately, there is a dire need for more sophisticated therapies, which improve upon the efficacy witnessed with the current crude paradigm consisting of platinum/taxane doublets. Clearly, whilst there is good biological rationale with the trial of ‘GI style’ chemotherapy in mEOC, adopting this philosophy should be viewed with an element of caution. Unfortunately, although the investigators of the GOG241 study should be applauded for their attempts to investigate this concept; it demonstrates the immense difficulty in conducting a multicentre cooperative group study in a rare subtype. Furthermore, a direct
translation of this approach maybe hindered by the fact that mEOC has more pathological and molecular characteristics in common with mucinous colorectal cancers [11], as opposed to the more common non-mucinous counterparts which are generally more sensitive to the aforementioned chemotherapy regimes commonly used in CRC [138, 139]. While ‘GI style’ systemic chemotherapy may initially appear an intuitive notion, there is a paucity of evidence to substitute this for platinum/taxane doublet therapy in mEOC. Hence, from a practical perspective, until randomised trials confirm superior efficacy with this approach, current gold-standard EOC treatment algorithms should be adopted for mEOC patients. Nevertheless, it is clear that in order to facilitate advances in this setting, future mEOC studies should focus on combinatorial trials incorporating novel targeted therapies alongside either standard and/or alternative chemotherapy regimes described herein. Encouragingly, both preliminary pre-clinical and clinical reports with anti-HER2 [47, 129] and PI3k/Src inhibitors [135-137] in mEOC certainly pave foundations for the development of such clinical trials. However, in view of the challenges associated with accrual of sufficient numbers of patients to generate statistical validity in such a rare tumour stream, novel approaches to trial design within international collaborations will be of increasing importance.

10. CONFLICT OF INTEREST STATEMENT.

None to declare

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Author Biographies

**Jermaine I.G. Coward** is a consultant medical oncologist at the Princess Alexandra Hospital, Brisbane. He was appointed as a UK Medical Research Council Clinical Fellow at Barts Cancer Institute, Queen Mary, University of London and conducted basic research into the role of IL-6 in ovarian cancer. This included the first translational clinical trial of anti-IL-6 antibody therapy in patients with platinum resistant ovarian cancer and this work culminated in his PhD award in 2010. After completing specialist oncology training at the Royal Marsden Hospital, London, he was appointed as a Senior Research Fellow and Leader of the Inflammation & Cancer Therapeutics Group (2012-2015) at Mater Research housed at the Translational Research Institute, Brisbane, Australia. He is currently the co-lead of the Princess Alexandra Hospital Medical Oncology Phase I unit and the primary remit of his research revolves around efficient translation of novel bench-side discoveries into combinatorial clinical trials.

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Table 1. *Similarities between primary mEOC and metastatic mucinous cancers to the ovary*

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<th>Primary mEOC</th>
<th>Metastatic mucinous cancer to the ovary</th>
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<tr>
<td><strong>Histological type</strong></td>
<td>Intestinal/Müllerian [15], generally heterogeneous cancer tissue [15]</td>
<td>Usually homogenous in tissue [15]</td>
</tr>
<tr>
<td><strong>Bilateral presentation</strong></td>
<td>Uncommon ~5% [14, 15, 26]</td>
<td>Common ~90% [14, 15, 26]</td>
</tr>
<tr>
<td><strong>Mean age of presentation</strong></td>
<td>36-50 yrs [31]</td>
<td>49-60 yrs [14, 28, 30]</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>&gt;10cm [15]</td>
<td>&lt;10cm [15, 28]</td>
</tr>
<tr>
<td><strong>Distinct Features</strong></td>
<td>Complex papillary pattern, smooth external surface, benign/borderline areas within the tumour, microscopic cystic glands, necrotic luminal debris [15, 25, 26]</td>
<td>Nodular growth pattern, ovarian hilar involvement, single cell invasion, signet-ring cells (gastric), vascular invasion, surface mucin, pseudomyxoma peritonei [15, 25-27]</td>
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Table 2. *IHC expression markers and molecular biology mutations seen in mEOC, HGSOC*

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<tr>
<td>CK7</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CK20</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CEA</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CA 19.9</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CDX2</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CA125</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>ER</td>
<td>-/+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>DPC4</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>P16</td>
<td>-</td>
<td>-</td>
<td>-/+</td>
</tr>
<tr>
<td>PAX8</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>WT1</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

*and mucinous CRC.*
Table 3. Molecular mutation profiles in mEOC, HGSOC and mucinous CRC

<table>
<thead>
<tr>
<th>Molecular mutations</th>
<th>mEOC</th>
<th>HGSOC</th>
<th>Mucinous CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>P53</td>
<td>26%-55% [36, 37]</td>
<td>96% [35]</td>
<td>31-41% [51]</td>
</tr>
<tr>
<td>BRAF</td>
<td>0-9% [38, 50]</td>
<td>0% [50]</td>
<td>15-27% [51]</td>
</tr>
<tr>
<td>HER2</td>
<td>18-35% [41-46, 52]</td>
<td>-</td>
<td>&lt;1% [53]</td>
</tr>
<tr>
<td>APC</td>
<td>9% [40]</td>
<td>-</td>
<td>24% [54]</td>
</tr>
<tr>
<td>MSI-H</td>
<td>22%[55]</td>
<td>13.8% [55]</td>
<td>25-36% [54, 56]</td>
</tr>
</tbody>
</table>
Table 4. Proportion of mEOC in landmark first-line platinum-taxane trials in EOC

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Regimens</th>
<th>Total no. of patients</th>
<th>No. (%) mEOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 111 McGuire et al.[2]</td>
<td>cisplatin + cyclophosphamide vs cisplatin + paclitaxel</td>
<td>386</td>
<td>14 (3.6%)</td>
</tr>
<tr>
<td>GOG 132 Muggia et al. [4]</td>
<td>cisplatin vs paclitaxel vs cisplatin + paclitaxel</td>
<td>648</td>
<td>16 (2.5%)</td>
</tr>
<tr>
<td>Neijt et al. [5]</td>
<td>cisplatin + paclitaxel vs carboplatin + paclitaxel</td>
<td>208</td>
<td>11 (5.3%)</td>
</tr>
<tr>
<td>ICON 3 [1]</td>
<td>carboplatin + paclitaxel vs carboplatin or CAP (cyclophosphamide/doxorubicin/ cisplatin)</td>
<td>2074</td>
<td>148 (7.1%) (1/3 mEOC pts stage I, II)</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Type</td>
<td>No. of Patients</td>
<td>RR</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------------</td>
<td>----------------</td>
<td>------</td>
</tr>
<tr>
<td>Hess et al. [7]</td>
<td>Retrospective 1st line Stage III/IV</td>
<td>27 mEOC</td>
<td>26.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54 other histology (68% HGSOC)</td>
<td>64.9%</td>
</tr>
<tr>
<td>Pectasides et al. [59] 2005</td>
<td>Retrospective 1st line Stage III/IV</td>
<td>47 mEOC</td>
<td>38.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>94 HGSOC</td>
<td>70%</td>
</tr>
<tr>
<td>Tian et al. [60] 2009</td>
<td>Retrospective analysis of 7 GOG Trials 1st line Stage III/IV</td>
<td>73 mEOC</td>
<td>7 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3292 Other Histo (majority HGSOC)</td>
<td>16.7 mo</td>
</tr>
<tr>
<td>Mackay et al. [61] 2010</td>
<td>Retrospective meta-analysis of 7 trials Stage III/IV</td>
<td>264 mEOC,</td>
<td>14.6 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8440 Other Histo (majority HGSOC)</td>
<td>40.8 mo</td>
</tr>
<tr>
<td>Alexandre et al. [6] 2010</td>
<td>Retrospective meta-analysis of 4 trials 1st line Stage IIB/IV</td>
<td>54 mEOC, 60%</td>
<td>11.4 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>786 HGSOC</td>
<td>81%</td>
</tr>
<tr>
<td>Bamias et al. [62] 2010</td>
<td>Retrospective 1st line Stage III/IV</td>
<td>24 mEOC</td>
<td>15.4 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>367 HGSOC</td>
<td>47.7 mo</td>
</tr>
<tr>
<td>Zaino et al. [9] 2011</td>
<td>Prospective 1st line Stage III/IV</td>
<td>54 mEOC</td>
<td>14 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3381 Other Histo (majority HGSOC)</td>
<td>42 mo</td>
</tr>
<tr>
<td>Karabuk et al. [63] 2013</td>
<td>Retrospective 1st line Stage III/IV</td>
<td>50 mEOC</td>
<td>57.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>88 HGSOC</td>
<td>70.8%</td>
</tr>
<tr>
<td>Pignata et al. [64] 2008</td>
<td>Retrospective Platinum sensitive recurrent disease</td>
<td>20 mEOC</td>
<td>36.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>388 Other Histo</td>
<td>62.6%</td>
</tr>
</tbody>
</table>
Table 6. Efficacy of 5FU/leucovorin & oxaliplatin (FOLFOX) in EOC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Cohort</th>
<th>No. of Patients: mEOC vs HGSOC</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sundar et al. [88] 2004</td>
<td>Prospective Phase II</td>
<td>No. of mEOC not specified</td>
<td>RR – 30% by WHO Criteria</td>
</tr>
<tr>
<td></td>
<td>27 patients</td>
<td>5 (19%) other histology</td>
<td>RR 56% by Rustin Criteria</td>
</tr>
<tr>
<td></td>
<td>30% Platinum sensitive</td>
<td>(not serous or endometrioid)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 median line of prior therapy</td>
<td>18 (67%) HGSOC</td>
<td></td>
</tr>
<tr>
<td>Pectasides et al. [86] 2004</td>
<td>Prospective Phase II</td>
<td>2 (5%) mEOC</td>
<td>RR – 29% by WHO Criteria</td>
</tr>
<tr>
<td></td>
<td>38 patients</td>
<td>25 (66%) HGSOC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All Platinum resistant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 Median line of prior therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosa et al. [87]</td>
<td>Retrospective review</td>
<td>1 (7%) mEOC</td>
<td>RR- 28.6% by RECIST criteria</td>
</tr>
<tr>
<td></td>
<td>14 patients</td>
<td>8 (57%) HGSOC</td>
<td>RR 42.9% by Rustin Criteria</td>
</tr>
<tr>
<td></td>
<td>Heavily pre-treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 median lines of prior therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al. [85] 2013</td>
<td>Retrospective Review</td>
<td>2 (7%) mEOC</td>
<td>RR – 22.2% by RECIST Criteria in 9 patients with measurable disease</td>
</tr>
<tr>
<td></td>
<td>28 patients: 9 measurable disease – assessed by RECIST</td>
<td>21 (75%) HGSOC</td>
<td>RR - 26.3% by Rustin Criteria in 19 patients with non-measurable disease</td>
</tr>
<tr>
<td></td>
<td>19 non-measurable disease – assessed by Rustin criteria</td>
<td></td>
<td>All responses were in HGSOC or endometrioid EOC</td>
</tr>
<tr>
<td></td>
<td>Heavily pre-treated</td>
<td></td>
<td>Both mEOC patients progressed</td>
</tr>
<tr>
<td>Arm</td>
<td>Treatment</td>
<td>No. recruited</td>
<td>Response rates/evaluable pts</td>
</tr>
<tr>
<td>-----</td>
<td>------------------------------------------</td>
<td>---------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>A</td>
<td>Carboplatin + Paclitaxel</td>
<td>13</td>
<td>2/7 (28.6%)</td>
</tr>
<tr>
<td>B</td>
<td>Oxaliplatin + Capecitabine</td>
<td>13</td>
<td>2/10 (20%)</td>
</tr>
<tr>
<td>C</td>
<td>Carboplatin + Paclitaxel + Bevacizumab</td>
<td>11</td>
<td>4/7 (57.1%)</td>
</tr>
<tr>
<td>D</td>
<td>Oxaliplatin + Capecitabine + Bevacizumab</td>
<td>13</td>
<td>2/7 (28.6%)</td>
</tr>
</tbody>
</table>