Critical Reviews in Oncology/Hematology 102 (2016) 26–36

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Mucinous ovarian cancer: A therapeutic review

Wen Xu[a], Jack Rush[b], Kirsty Rickett[c], Jermaine I.G. Coward[a,b,d,*]

[a] Mater Health Services, Raymond Terrace, Brisbane, QLD 4101, Australia
[b] School of Medicine, University of Queensland, St Lucia, QLD 4072, Australia
[c] UQ/Mater McAuley Library, The University of Queensland Library, Brisbane 4101, Australia
[d] Princess Alexandra Hospital, Ipswich Road, Woolloongabba, QLD 4102, Australia

Contents

1. Introduction 26
2. Epidemiology 27
3. Histopathology 27
4. Molecular biology 28
5. Clinical management and pitfalls 29
6. Alternate chemotherapy algorithms 29
   6.1. Fluoropyrimidines 29
   6.2. Oxaliplatin 29
   6.3. 5FU/Leucovorin & oxaliplatin (FOLFOX) 30
   6.4. Gemcitabine & oxaliplatin 30
   6.5. Irinotecan 31
7. mEOC specific clinical trials 31
8. Targeted therapeutic approaches 31
   8.1. VEGF inhibition 31
   8.2. EGFR monoclonal antibodies 32
   8.3. Anti-HER2 therapy 32
   8.4. Targeting Src and PI3**K/Akt pathways** 32
9. Conclusions 33
   Conflict of interest 33
   References 33
   Biographies 36

ARTICLE INFO

Article history:
Received 30 November 2015
Received in revised form 1 March 2016
Accepted 9 March 2016

Keywords:
Mucinous ovarian cancer
Chemotherapy
Targeted therapy
Gastrointestinal cancers

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.

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

* Corresponding author at: Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, QLD 4102, Australia.
E-mail address: Jermaine.Coward@health.qld.gov.au (J.I.G. Coward).

http://dx.doi.org/10.1016/j.critrevonc.2016.03.015
1040-8428/

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 (International Collaborative Ovarian Neoplasm G, 2002; McGuire et al., 1996; Piccart et al., 2000; Muggia et al., 2000; Neijt et al., 2000). 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 (Alexandre et al., 2010; Hess et al., 2004; Naik et al., 2012; Zaino et al., 2011). Alarmingly, the current gold standard of HGSOC chemotherapeutic management is still counterintuitively adopted for mEOC; a relatively chemoresistant disease (Alexandre et al., 2010; Hess et al., 2004; Naik et al., 2012; Shimada et al., 2009). 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 (Hess et al., 2004; Naik et al., 2012; Kelemen and Köbel, 2011). 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 (McGuire et al., 2002). 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% (Zaino et al., 2011; Hart, 2005a; Seidman et al., 2003). Invasive mEOC most commonly presents in women between 39 and 50 years old (range 14–87) (Hart, 2005b). This middle-aged preponderance contrasts with the incidence of HGSOC which generally increases with age (Robbins et al., 2010). There also appears to be a clear aetiological discordance between HGSOC and mEOC. For example, HGSOC risk factors such as nuliparity, menarchal age, increased body mass index, oestrogen exposure, tubal sterilisation and lack of breastfeeding do not consistently correlate with mEOC prevalence (Gates et al., 2010). Similarly, smoking, which has no strong historical association with HGSOC, may be a significant risk factor for mEOC (Gates et al., 2010). 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 (Gates et al., 2010; Roett, 2016). A recent Danish population study observed an inverse relationship between statin use and mEOC incidence vs. a neutral relationship between statin use and HGSOC incidence (Baandrup et al., 2015). 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 (Risch et al., 2001).

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 (Hart, 2005b). Interestingly, stage I mEOC, where the management is primarily mandated by surgery alone, has a better prognosis than HGSOC (Hart, 2005b; Harrison et al., 2008). Moreover, retrospective evidence suggests that it is a reasonable option to offer women fertility sparing surgery for early stage mEOC (Lee et al., 2015). Conversely, advanced mEOC (≥stage III) typically has a significantly worse prognosis than HGSOC, with reported median survivals of 12–14 months vs. 37–42 months respectively (Zaino et al., 2011). 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 (Alexandre et al., 2010). 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 (Hess et al., 2004).

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 (Young and Hart, 1989; Lash and Hart, 1987), with metastases from the biliary tract, stomach, cervix, breast and uterus also described (Frumovitz et al., 2010; Lee, 2003). Pseudomyxoma peritonei, once considered a consequence of advanced mEOC, is now widely accepted as a result of metastatic appendiceal mucinous tumours (Prayson et al., 1994). 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 (Zaino et al., 2011; Hart, 2005a; Seidman et al., 2003), which accounts for the seemingly inferior outcomes synonymous with late stage mEOC. In a study by Zaino et al. (2011), 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 (Seidman et al., 2003; Maeda-Taniguchi et al., 2011). 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 (Seidman et al., 2003). Additionally, tumour size >10 cm is much more likely to be of primary origin. These two factors influenced Seidman et al. (Seidman et al., 2003) 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 (Yemelyanova et al., 2008; Khunamornpong et al., 2006).

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) (McCluggage, 2012). However, CK7 serves as a useful discriminator being diffusely positive in mEOC and predominantly negative in mucinous colorectal cancer (CRC) (McCluggage, 2012). Nevertheless, a revision of the mucinous cancer algorithm by Maeda-Taniguchi et al. (Maeda-Taniguchi et al., 2011) 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 demon-