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Mucinous Epithelial Ovarian Carcinoma

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Abstract

Mucinous tumours involving the ovary maybe benign, borderline, or malignant. Malignant tumours may be primary or metastatic. Differentiation between primary and metastatic involvement of the ovary is critical for patient optimal patient management. Even amongst skilled pathologists this distinction can be problematic, as can the distinction between borderline ovarian tumour of intestinal type and well differentiated invasive primary mucinous ovarian carcinoma. Primary invasive mucinous ovarian carcinoma and mucinous carcinoma metastatic to the ovary do have distinct patterns of macroscopic and microscopic involvement which will reveal the correct diagnosis in many cases. There are also well recognised patterns of immuno-histochemical staining that can further assist in this differentiation. As a result of the application of these histopathological techniques the incidence of primary invasive mucinous epithelial carcinoma has fallen over recent years from around 12%, to around 3%. However, even in recent multicentre clinical trials such as GOG 182, expert pathological review suggests that around 60% of tumours originally classified as primary invasive mucinous carcinomas were in fact metastatic tumours to the ovary. Review of outcome data for patients with mucinous carcinoma entered into multicentre trials suggests that this subtype of disease has a particularly poor prognosis in comparison with other subtypes of ovarian carcinoma. Historically patients with mucinous epithelial ovarian carcinoma have been treated in the same way as other subtypes of ovarian carcinoma. Whilst there is undoubtedly a response rate to platinum-based chemotherapy, retrospective reviews of individual centre experience suggests that this is substantially lower than for high-grade papillary serous carcinoma and in the order of only 30-40%. The mEOC trial was established to investigate the possibility that the combination of capecitabine and oxaliplatin

(chemotherapy drugs more commonly used in colorectal carcinoma) may be superior to conventional carboplatin and paclitaxel chemotherapy. In a 2 x 2 factorial design there was also a randomisation to bevacizumab. Unfortunately this trial closed early, 5 years after initiation having recruited just 50 of a proposed 322 patients. Mucinous epithelial ovarian carcinoma is now characterised as a type I tumour with an identifiable stepwise progression from a premalignant lesion, through non-invasive, to invasive malignancy. Molecular characterisation of mucinous epithelial ovarian carcinoma reveals it to be distinct from other subtypes of the disease with a KRAS mutation occurring in 40-50% of patients. Other gene abnormalities including Her2 amplification in around 19% also occur. This raises the possibility of the use of targeted molecular therapies which with molecular analysis of individual patient tumours could form the basis of a future clinical trial. It is however clear that if trials are to be conducted in this rare subtype of disease they will need to be truly international in nature and carefully designed, possibly using an adaptive stepwise approach and will require an appropriate level of funding with a realistic assessment of likely recruitment. Associated translational research will clearly be essential.

Introduction

Primary mucinous tumours of the ovary may be benign, borderline, or malignant. The ovary can however be involved by metastatic malignancy which is often of mucinous origin. It is important to accurately diagnose tumours which are metastatic to the ovary since treatment and outcomes may differ significantly from that of primary ovarian carcinoma. A patient with a localised mucinous primary will have a 90% 5-year survival [1], whereas a patient with a metastasis, for example, from a pancreatic cancer primary, may have a life expectancy of <6 months.

Involvement of the ovaries by metastatic disease

Metastasis to the ovaries may occur regardless of the location of the primary tumour [2]. The frequency with which the ovaries are involved in metastatic disease is difficult to assess from the literature because of differing methods of pathological examination and analysis. There is also a wide geographical variation in the incidence of the common gastric, breast and colonic carcinomas as well as changing incidences in many population groups over recent decades. Gastric carcinoma has become less common whereas breast and colorectal malignancy have become more common. Metastatic carcinoma was reported to account for approximately 40% of all ovarian malignancies in one series from Japan where gastric carcinoma is common, but for fewer than 3% in a series from Uganda where this form of cancer is relatively rare [3]. Approximately 4% of women with intestinal carcinoma may have ovarian metastasis at some time during the course of their disease [4-7]. In one detailed pathological study where 2mm ovarian slices were examined, this figure was as high as 10% [8]. In a study of secondary ovarian tumours [9] more than two-thirds of their cases of metastatic colonic carcinomas were initially interpreted as primary ovarian carcinoma.

Changing incidence of primary mucinous ovarian carcinoma

Primary mucinous epithelial ovarian carcinoma is a relatively rare subset of epithelial ovarian cancers. The historic literature suggests that the incidence of mucinous epithelial ovarian cancer is around 12% as exemplified by a recent population-based study (without pathology review) derived from the SEER database in which 11.9% of 40,571 women diagnosed with epithelial ovarian cancer between 1988 and 2007 were classified as having mucinous carcinoma [10]. More recent series conducted

with modern histopathologic techniques, improved specialisation within histopathology, and a better understanding of ovarian cancer biology suggest that the incidence of mucinous ovarian carcinoma is less common than previously thought. Two recent population-based studies which included central pathology review with modern diagnostic criteria suggest that the true incidence of invasive mucinous carcinoma is closer to 3% [11, 12].

Figure 1 illustrates the total number of epithelial ovarian cancers diagnosed at the Leeds Cancer Centre between the years 1990 and 2013. Over time there has been an increase in the total number of patients diagnosed with ovarian cancer due to planned centralisation of gynaecological cancer services. In keeping with the published literature, there has been a clear downward trend in the proportion of mucinous ovarian cancers over time.

Factors contributing to the fall in incidence of mucinous ovarian carcinoma include better recognition by pathologists of the clinical, gross and microscopic histological features that help distinguish between primary mucinous ovarian tumours and tumours which are metastatic to the ovary. It has also been determined that mucinous ovarian neoplasms associated with pseudomyxoma peritoneii do in fact arise from appendiceal primaries[13, 14].

Metastatic ovarian tumours tend to be bilateral, of relatively small size, they often have surface involvement of the ovary and have evidence of vascular invasion within the tumour. These features together with specific immunohistochemical staining patterns involving cytokeratin 7 and cytokeratin 20, CEA, Ca19.9, Ca125, oestrogen receptor, CDX2, DPC4/SMAD4, P16, PAX8, and Beta-catenin have been described

by a number of authors [15-19] and have recently been reviewed by Singh[20] and by Ip and Cheung[21].

Diagnosis has been further improved by advances in cross sectional imaging, and the development of diagnostic image guided biopsy together with pathological evaluation and multi-disciplinary discussion. Our group has demonstrated that this approach can identify disease metastatic to the ovary and prevent unnecessary surgery[22-25].

There remain areas of specific diagnostic difficulty for pathologists where there is the potential for significant intra-observer variability, an example is the spectrum of mucinous ovarian neoplasms of intestinal type; this is the most common subtype of mucinous ovarian neoplasm and exhibits a continuum of differentiation from benign through borderline to malignant. To properly differentiate between borderline mucinous tumour of intestinal type and well differentiated mucinous carcinoma of intestinal type extensive sampling and expert interpretation is required[26]. Differences between pathologists in the classification of such tumours may account for some of the differences in quoted incidence between centres.

When the incidence of mucinous carcinoma is investigated according to FIGO stage, the vast majority of mucinous carcinomas are found in patients with early stage disease (FIGO I & II) where they represent 8% of the total as compared to just 1% in patients with more advanced disease (FIGO III & IV) [11]. Similarly, unpublished figures from Leeds Cancer Centre illustrates that of the 211 mucinous epithelial ovarian cancers diagnosed between 1990 and 2013, 80.6% were FIGO stage I, 6.2% stage II, 10% stage III, and just 3.3% stage IV.

Conventional treatment and prognosis of mucinous epithelial ovarian carcinoma

Historically all patients diagnosed with epithelial ovarian cancer, irrespective of histological subtype have been treated in a uniform fashion with platinum based chemotherapy, and have been enrolled in multicentre clinical trials. For instance the ICON3 trial, which investigated the addition of paclitaxel to standard platinum based chemotherapy, recruited 148 patients with mucinous histology representing just 7% of the total trial population [27]. In ICON7, which investigated the addition of bevacizumab to standard carboplatin and paclitaxel chemotherapy; just 34 patients (2% of the trial population) were classified as having mucinous carcinoma [28].

With advances in pathology and molecular biology it has become increasingly clear that not all ovarian cancer subtypes behave in the same way. In an analysis of 7 phase 3 randomised GCIG trials Mackay demonstrated that for patients with FIGO stage III & IV disease the prognosis for the 3% of cancers classified as mucinous was substantially worse than for serous carcinomas with median OS of 14.6 months compared with 40.8 months [29]. Data from Mackay and from 6 smaller similar studies reaching same conclusions have also been summarised by Naik et al[30].

The difficulty of making a diagnosis of mucinous ovarian carcinoma, and the poor prognosis of advanced stage mucinous epithelial ovarian carcinoma is illustrated by a retrospective analysis of patients entered into the GOG 182 (ICON 5) trial [31]. Fifty-four of 3435 patients entered by GOG were classified as having mucinous ovarian carcinoma. Forty-four patients with sufficient material were reviewed independently by 3 pathologists according to 2 classification systems not involving immuno-histochemistry. Only 16-18% of the tumours were judged to be primary

mucinous epithelial ovarian carcinomas whereas between 57 and 63% were judged to be tumours metastatic to the ovary. There was no difference in overall survival between those tumours judged primary and those judged metastatic. However, survival of those with primary mucinous epithelial ovarian carcinoma was substantially worse than those with serous disease with respective median overall survivals of 14 months compared to 42 months ($p < 0.001$).

Data such as these, and data from other phase II trials illustrate the poor prognosis of advanced stage mucinous ovarian cancer but do not provide data as to the response rate of this subtype of ovarian carcinoma to standard platinum based chemotherapy. In an attempt to acquire such data Hess et al performed a retrospective analysis of 27 patients with stage III or IV mucinous ovarian cancer treated with platinum based chemotherapy at the Royal Marsden Hospital between 1992 and 2001. Two matched controls with non-mucinous carcinoma were identified for each patient. The response rate (to platinum-based therapy) of cases and controls was 26% and 65% respectively; median PFS and OS for cases and controls were 5.7 months vs 14.1 months and 12 months versus 16.7 months respectively [1]. Similar data from Pectasides et al and Pisano et al[32, 33] show response rates to platinum based chemotherapy of 38.5% and 42%, in 47, and 19 patients respectively.

Molecular characteristics of mucinous epithelial ovarian carcinoma

These data, together with emerging molecular data suggest that mucinous ovarian carcinoma is a rare but distinct clinical entity. Shih and Kurman[34, 35] have proposed that ovarian cancer be categorised into type I and type II based on molecular and clinicpathologic differences. Type I ovarian cancer which includes

mucinous ovarian cancer, low grade serous, endometrioid and clear cell carcinoma tend be lower grade malignancies and have an identifiable stepwise progression from a premalignant lesion through non-invasive, and culminating in invasive malignancy. Type II ovarian cancer is characterised by genetic instability, and a virtually ubiquitous p53 gene mutation without stepwise progression.

Each of the morphological subtypes of type I ovarian cancer have been shown to have a distinct pattern of gene mutation, which may be potentially targetable for therapeutic purposes by current or future targeted molecular therapies.

In the case of mucinous ovarian cancer the predominant mutation is in KRAS where a mutation is found in 40 to 50% of patients[36-38].

KRAS is a small molecule, mutation of which results in constitutive activation of the EGFR signalling pathway. EGFR targeted monoclonal antibody treatment such as cetuximab or panitumumab is effective for improving response rate and duration of response in the first-line treatment of metastatic colorectal carcinoma in patients where there is EGFR expression and where the tumour is KRAS wild type [39] and as a result is now licensed by the FDA and EMA for use in in this setting.

As yet, there is no clinical data to support the use of cetuximab in patients with mucinous ovarian carcinoma. Limited cell line data however have shown that cetuximab was able to inhibit the in vitro growth of 2 mucinous ovarian cancer cell lines without KRAS gene mutations and completely inhibit the in vivo growth of one of these cell lines. In another cell line with KRAS gene mutation at codon 12 there was no effect of cetuximab on in vivo growth, and only partial inhibition of in vivo growth[40]. Clinical studies will however be required to investigate this further.

Another tumour specific gene abnormality identified in mucinous ovarian cancer is HER2 gene amplification which is seen in 19% of invasive mucinous ovarian cancers and 6% of mucinous borderline ovarian carcinomas[41]. In the same series KRAS mutation was found in 44% of invasive mucinous carcinomas and 79% of mucinous borderline tumours, with KRAS mutation and HER2 amplification being close to mutually exclusive and seen in only 4 of 71 mucinous carcinomas where expression of both markers was known. Sixty-six percent of tumours expressed KRAS mutation or HER2 amplification and 33% expressed neither. Although not statistically significant in this small series, expression of either KRAS or HER2 appeared to provide a degree of protection against recurrence or death[41].

There is very limited clinical data with anti-HER-2 therapy in patients with mucinous ovarian carcinoma. McAlpine et al investigated HER-2 status in 33 mucinous epithelial ovarian carcinomas and 16 mucinous borderline ovarian tumours. Six of the mucinous epithelial ovarian carcinomas were HER2 positive (18%) and 3 (19%) of the mucinous borderline ovarian tumours. Three patients with prospectively determined HER2 positive recurrent mucinous epithelial ovarian carcinoma were anecdotally treated with trastuzumab and one showed a dramatic response to the combination of chemotherapy and trastuzumab [42].

Although KRAS gene mutations and HER2 amplification have reproducibly been described, they are not the only genetic abnormalities seen in mucinous ovarian carcinoma. Very recent data from the Australian Ovarian Cancer Study Group however suggests a greater degree of molecular diversity than has previously been reported, and in addition to the expected level of mutations in KRAS & BRAF, a high percentage of carcinomas also show p53 gene mutations[43].

In the last few years a number of commercial organisations have begun to offer comprehensive molecular analysis of tumours with the aim of guiding therapy and outcome. At ASCO 2015[44] data were presented from 304 apparent mucinous epithelial ovarian carcinomas submitted to Caris Life Sciences between 2009 and 2014 for a combination of tumour genome sequencing, protein expression, gene amplification and RNA fragment analysis. Alterations in MAP Kinase pathway were the most frequent (49% mutations in KRAS and 3.5% in BRAF). mTOR pathway alterations were less frequent (PIK3CA in 12%, and PTEN in 6%). cMET overexpression was seen in 33% of cases but no cMET gene amplification was seen. p53 mutation was seen in 37%; EGFR gene amplification by FISH was seen in 50% (57% overall had EGFR overexpression by immunohistochemistry). HER2 gene amplification (by FISH) was seen in 11%. PD-1 positivity was observed in tumour infiltrating lymphocytes in 43%, and PD-L1 was positive in 14%.

Prospective trials in invasive mucinous epithelial ovarian carcinoma (mEOC)

To date there have been no successful prospective phase II or III randomised clinical trials conducted specifically in mucinous ovarian carcinoma. The mEOC trial/GOG241[45] was initiated by the Gynecological Cancer InterGroup (GCIG), and set out to investigate the utility of chemotherapy agents more normally used in GI cancer. The rationale for the use of oxaliplatin and capecitabine has been previously reviewed [30]. Patients with newly diagnosed stage II to IV or recurrent chemotherapy naive stage I mucinous ovarian cancer were randomised to receive conventional ovarian cancer chemotherapy with carboplatin and paclitaxel or an alternative regimen of oxaliplatin and capecitabine. There was a second non-blinded randomistion to bevacizumab or to control. Regrettably the trial closed with a median follow-up of 23 months, 5 years after initiation having recruited just 50 of a proposed 322 patients. Preliminary data from mEOC was presented at ASCO 2015[46]. There was insufficent data to draw conclusions concerning the relative efficacy of the chemotherapy treatments or the efficacy from the addition of bevacizumab. Responses were seen in all arms of the trial (4 of 26 (15.4%) in the oxaliplatin / capecitabine arms of the trial and 6 of 24 (25%) in the carboplatin / paclitaxel arms of the trial). Central specialist histology review has so far been conducted in 36 patients and the results serve to further illustrate that the difficulties already described in correctly diagnosing mucinous epithelial ovarian cacinoma persist even in patients diagnosed recently in centres that are actively involved in clincal research. Seventeen patients were confirmed to have mucinous epithelial ovarian cancer and 19 were considered to have alternative diagnoses. Most of these were metastases to the overy from alternative primary sites although cases of primary

mucinous borderline tumour and primary ovarian cancer of other morphologies were also seen.

Discussion and conclusions

It remains clear that future trials in mucinous ovarian carcinoma will be challenging, they will have to be carefully designed probably using an adaptive approach so that inactive treatments can be identified and discarded early. Consideration should be given to real time pathology review to ensure consistency of diagnosis. Because of the rarity of the disease trials will need to be truly international and designed and funded realistically taking into account the likely slow accrual.

An alternative approach might be to design a trial suitable for the inclusion of all patients with mucinous tumours involving the ovary and utilising prospective molecular phenotyping of the tumour to determine treatment. Anglesio[41] proposed a treatment algoritm which could be adapted to form the basis of a clinical trial. Patients with advanced or recurrent mucinous carcinoma of the ovary would have HER2 testing of their tumour. Those that were HER2 positive would be treated with HER2 targeted therapy, whereas those who were HER2 negative and those who had failed HER2 directed therapy would have KRAS testing; those with KRAS wild type tumour would be eligible for EGFR directed therapy such as cetuximab, whereas those with KRAS gene mutation would be eligble for novel experimental therapies or alternatively conventional chemotherapy approaches utilising regimens directed against ovarian or colorectal carcinoma; the choice of chemotherapy regimen could potentially be guided by p53 mutation testing.

It is clear that whatever the trial design, prospective collection of samples and a robust translational research programme would be vital to underpin such a trial. It is

only through such collaborations that progress will be made against this rare subtype of ovarian cancer.

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