Time to reevaluate clinical trials for mucinous ovarian cancer

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Abstract

Invasive mucinous epithelial ovarian cancer (mEOC) accounts for approximately 10% of all epithelial ovarian cancers. There is evidence to suggest that the mucinous tumours are biologically distinct from the serous sub-type and are likely to evolve via an adenoma-carcinoma pathway. Recent studies looking at the genetic profile of benign, borderline and invasive mucinous ovarian tumours demonstrate a link between borderline and invasive tumours. Exploratory analysis of the genes that are differentially expressed provides some information on the potential genetic events involved in progression from the benign to the malignant phenotype.

There is a paucity of clinically reliable information to allow true evidenced-based decision making for the mucinous sub-type. There appears to be a real difference in outcome for patients with advanced mucinous ovarian cancer and a relative resistance to platinum-based chemotherapy is well recognised. Separate trials need to be performed, ideally incorporating translational research to further elucidate the mechanisms underlying drug resistance, molecular characteristics and potential targets for future therapy.

Introduction

Invasive mucinous carcinoma of the ovary accounts for approximately 10% of epithelial ovarian cancers (EOC) [1]. The biology of mucinous epithelial ovarian cancer (mEOC) appears to differ from serous epithelial ovarian cancer (sEOC), however, the principles of management are identical. The International Federation of Gynaecology and Obstetrics (FIGO) stage is the most important prognostic variable. Patients with FIGO stage I mucinous tumours have a favourable prognosis which is similar to the more common pathological types [2], however, the outcome of patients presenting with advanced disease is generally poor and inferior to matched patients with non-mucinous pathology [3,4].

For all patients with FIGO stage I invasive EOC, approximately one-quarter will have mucinous pathology [2]. The 5-year disease free survival for these patients was 90.8% in one study which included 410 patients with FIGO stage I mEOC. Compared to other histological types the hazard ratio for recurrence was 0.37 (95% CI, 0.25–0.53) and mucinous pathology was not a significant prognostic factor on multivariate analysis [2].

In contrast, for patients with invasive EOC presenting with FIGO stage II–IV tumours, less than 10% will have mucinous pathology [5]. Randomised clinical trials of first and second-line chemotherapy for advanced EOC usually include <5% with this histological subtype. The results may not, therefore, necessarily reflect the outcome to treatment for mEOC. Sub-group analysis for mucinous pathology is rarely performed and small patient numbers limit the reliability of such an analysis. Case-control studies have highlighted that response rates to standard platinum-based chemotherapy and survival are inferior compared to sEOC [3,4]. In the absence of alternate data to direct evidence-based management, patients with advanced mEOC receive adjuvant platinum-taxane based chemotherapy following surgical debulking.

Refining the management of mEOC will require prospective clinical trials that enroll adequate patient numbers and reflect the clinical, histological and molecular differences in this sub-type rather than simply including these patients in general trials of EOC.

Molecular studies

Mucinous EOC may develop through an adenoma-carcinoma sequence originating from cystadenomas and mucinous borderline tumours. Histological examination of borderline and invasive mucinous tumour has shown both areas of normal epithelium and sites of transitional epithelium in the adjacent tissue [6]. Increasing frequency of mutations in the k-ras oncogene in benign, borderline and malignant mucinous

tumours has been demonstrated [7], and similar k-ras mutations in adjacent benign and borderline areas of grade 1 mucinous adenocarcinomas have been seen [8]. Mutations in k-ras are likely to represent an early genetic event in the development of mEOC. These observations support the theory that invasive mucinous ovarian cancer may develop from their benign counterpart.

Gene expression profiling has the ability to screen a wide range of genes that may be involved in the pathogenesis of various tumours. By analysing a large number of candidate genes, comparison between normal tissue and different tumour types from benign or malignant tumour specimens is thereby possible. This methodology has been applied to benign, borderline and malignant mucinous and serous ovarian tumours.

Firstly, there appears to be a relationship between mucinous borderline tumours and adenocarcinomas that is distinct from cystadenomas and normal ovarian surface epithelium. By examining the gene profiles for these tumours, unsupervised hierarchical clustering and binary tree analysis found mucinous borderline tumours had a misclassification rate of approximately 40% to grade 1 and 2 mucinous adenocarcinomas. Cystadenomas were rarely misclassified as mucinous borderline or invasive tumours. However, a number of co-regulated genes are suggested to explain the low rate (8.8%) of misclassification. These data demonstrated a link among the various mucinous tumours, which was separate from normal ovarian tissue and serous ovarian tumours [9].

Examination of genes that were differentially expressed in normal ovarian tissue compared to mucinous tumours, or genes that potentially involved in malignant progression, found some interesting correlations. There was up-regulation of genes known to be involved in multi-drug resistance, cell cycle regulation, cellular proliferation and transformation in both borderline and invasive mucinous tumours, while genes involved in cytoskeleton modulation and motility appeared to be up-regulated mainly in the invasive mucinous tumours. The finding of over-expression of genes involved in multi-drug resistance (ABCC3 and ABCC6) is in accordance with the clinical observation of low response rates to standard chemotherapy for ovarian cancer seen in patients with mucinous pathology [9].

Clinical studies

Phase III trials first and second-line chemotherapy for advanced EOC typically include few patients with mEOC. If we review the pivotal trials that have determined standard first-line chemotherapy for advanced ovarian cancer, the percentage of patients with mucinous pathology is 3.5% (14 patients) and 4.5% (30 patients) for cisplatin and cyclophosphamide versus cisplatin and paclitaxel in the Gynaecologic Oncology Group (GOG) 111 and European-Canadian intergroup trials respectively [10,11]; 2.5% (16 patients) and for cisplatin versus paclitaxel versus cisplatin and paclitaxel in the GOG 132 trial [12]; 2.5% (19 patients) and not specified for cisplatin and paclitaxel versus carboplatin and paclitaxel in the GOG158 and Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Oncology Cancer Study Group – OVAR3 trials [13,14]; and 7% (140 patients) for carboplatin versus carboplatin and paclitaxel in the International Collaborative Ovarian Neoplasm 3 (ICON 3) trial [5]. The results of these trials, which largely reflect the outcome of patients with serous pathology, have been applied to all histological types in the absence of alternate data. However, simply extrapolating these results to patients with mEOC may not be appropriate.

The small number of patients with mEOC in these trials is not sufficient to perform a separate analysis specific for mEOC. The only trial sited above that performed a separate analysis for mEOC was the ICON 3 study. Their analysis was limited in that they did not report outcome for response rate, progression-free survival (PFS) or overall survival (OS) for patients with mEOC compared to the other pathological types. The sub-group analysis reported compared the results for mEOC based on treatment received, carboplatin or carboplatin and paclitaxel. There was no difference in PFS or OS in this comparison. Therefore, based on this study, we can not conclude whether patients with mEOC have an inferior outcome compared with sEOC to standard first-line platinum-based chemotherapy, only that the outcome based on treatment was not significantly different between the two treatment arms [5].

Several groups have sought to review the outcome of patients with mEOC who receive platinum-based chemotherapy. Two of these studies compared results for matched patients with mEOC and non-mucinous pathology, while the third was a retrospective study of patients with mEOC receiving first, second or third-line chemotherapy. The overall response rate was 26–42% to first-line platinum-based chemotherapy confirming platinum-resistance for most mucinous ovarian tumours [3,4,15].

The Hellenic Cooperative Oncology Group (HeCOG) conducted a case-control study comparing first-line

platinum-based chemotherapy for advanced ovarian cancer with mucinous and serous pathology. Forty seven patients had mucinous pathology compared with 94 with serous pathology. The majority (83%) received platinum-combination chemotherapy, and the remainder single agent cisplatin or carboplatin. The response rate was 38.5% (95% CI, 23.4–55.4%) versus 70% (95% CI 58.5–80.3%) for mEOC and sEOC respectively ($P = 0.001$). Only 18% with mEOC had complete remission compared to 47% with sEOC ($P = 0.002$). They did not find a significant difference in time to progression (TTP) 11.8 months (95% CI, 7.2–16.4 months) versus 20.0 months (95% CI 15.7–24.2 months) or OS 33.2 months (95% CI 23.3–43.1 months) versus 38.0 months (95% CI, 26.8–49.2 months) for mEOC and sEOC respectively, although there was a trend to a worse survival for patients with mEOC ($P = 0.46$) [3].

The Royal Marsden Hospital conducted a case-control study comparing the outcome of first-line platinum-based chemotherapy for advanced ovarian cancer for mucinous and non-mucinous pathology. Twenty seven patients with mucinous pathology were compared with 54 matched controls which reflected the frequency of the non-mucinous pathological types, the majority (68%) had serous pathology. Treatment consisted of platinum-combination in 67% and single agent carboplatin in the remaining 33%. The response rate was 26.3% (95% CI, 9.2–51.2%) versus 64.9% (95% CI, 47.5–79.8%), for mucinous pathology and controls respectively ($P = 0.01$). Sixty three percent of patients with mucinous pathology were platinum refractory with disease progression while receiving chemotherapy. The median PFS was 5.7 months (95% CI, 1.9–9.6 months) versus 14.1 months (95% CI, 12.0–16.2 months; $P < 0.001$) and OS was 12.0 months (95% CI, 8.0–15.6 months) versus 36.7 months (95% CI, 25.2–48.2 months; $P < 0.001$) for mucinous pathology and controls, respectively [4].

The third retrospective study reviewed the response to first and subsequent chemotherapy for patients with mEOC. Twenty one patients (19 patients had evaluable disease, 12 with measurable disease and seven assessed with second-look laparotomy) were included in their analysis. The majority (85%) received carboplatin and paclitaxel, with the remainder treated with a cisplatin based non-taxane containing therapy. For patients with evaluable disease, eight (42%) patients responded to first-line platinum-based chemotherapy. Sixty percent of all patients were platinum refractory with disease progression during first-line chemotherapy. Second or third-line chemotherapy with topotecan or liposomal doxorubicin did not produce any responses [15].

Conclusions

At present, chemotherapy for ovarian cancer is similar for all histological subtypes. The subgroup of patients with mEOC is under represented in large clinical trials and there are real differences in the response rate and outcomes for patients with this histological subtype who have advanced disease. It is unlikely that advances for this tumour type will be gained from enrolling small numbers into generic ovarian cancer trials. Rather, trials that are specifically designed for mucinous ovarian cancer are required. Ideally these trials should incorporate a translational element to further elucidate the molecular characteristics, mechanisms underlying drug resistance, predictive factors for response and potential targets for future therapy.

Conflict of interest statement

None declared.

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