Tumour markers in ovarian cancer

While histology remains the gold standard in confirming the presence of ovarian malignancy, tumour markers have evolved to become part of the routine presurgical investigations, enhancing the clinician's ability to suspect that ovarian carcinoma is the likely diagnosis. Such markers also have a role in predicting response to adjuvant therapy and indeed in disease recurrence. Most notable is serum CA125, which was first recognized in the 1980s. Although some rare ovarian tumours do have other specific serum markers, this review will concentrate on CA125 as it has the most prominent role within the present clinical setting.

SCREENING FOR OVARIAN CANCER

The ability to detect ovarian malignancy when confined to the ovary would have a significant impact on overall survival rates. For ovarian cancer, approximately 75% of women present when disease has spread beyond the ovaries. The 5-year survival for this group is about 35% compared with 85% for early stage disease.

Results from non-randomized studies have shown the possibility of using CA125 as a screening tool (Rosenthal and Jacobs, 1998). It is thought that serial CA125 levels alone or in conjunction with pelvic ultrasound may form a reliable method for population screening in ovarian cancer. To this end, a multicentre randomized study (called UKCTOCS) has now commenced in postmenopausal women in order to determine whether screening is effective in reducing mortality from ovarian cancer. The results will be awaited with great interest but will take some years to compile.

TUMOUR MARKERS IN DIAGNOSTIC SETTING

Even now, many women with ovarian cancer are first referred to specialists other than a gynaecologist. In part, this is the result of the symptoms of advanced ovarian cancer, which are similar to other conditions, such as colonic carcinoma. In this setting, a markedly elevated CA125 (particularly with a normal carcinoembryonic antigen; CEA) can help the family doctor in directing referral appropriately.

Ensuring that patients with ovarian cancer are managed by a gynaecological oncologist is recognized to improve survival (Junor et al, 1999), and here again CA125, in conjunction with ultrasound scan findings and the patient's age, can be used to develop the risk of malignancy index (RMI). Hence when a non-oncological gynaecologist sees a woman with an ovarian mass, CA125 is of value in the clinical decision regarding the necessity for further referral to a tertiary centre.

However, many non-epithelial ovarian tumours and some epithelial tumours (e.g. mucinous carcinomas) may not express CA125. Also, CA125 can be elevated in other conditions, such as pregnancy, menstruation, endometriosis, pelvic infection, abdominal tuberculosis and in benign ovarian tumours. Therefore, CA125 forms part of a series of investigations which guide the clinician, but alone it cannot be deemed diagnostic.

PREDICTOR OF SURGICAL RESECTION

In ovarian carcinoma, the approach of debulking disease forms part of present management. In this setting, debulking means reducing the tumour burden, even in the knowledge that disease will be left in situ and that adjuvant therapy will be required. However, the evidence for a survival advantage with debulking disease is only in the context of interval surgery, whereby an operation is performed after three cycles of therapy in patients with chemosensitive disease (van der Burg et al, 1995). If one can identify patients likely to have suboptimal primary surgery, then, logically, chemotherapy should be commenced and debulking retained for a time when surgical intervention is evidence base.

Chi et al (2000) have shown that preoperative CA125 levels can predict the probability of achieving optimum debulking (<1 cm residual disease) at primary surgery in advanced ovarian cancer. Therefore, CA125 levels may be of use to select patients for the appropriate timing of surgery, although determination of this appropriate timing requires completion of a clinical trial.

PREDICTOR OF CHEMOTHERAPEUTIC RESPONSE

Platinum, alone or in combination with taxol, forms the main chemotherapeutic regimen used in ovarian carcinoma. In patients with residual disease, response is evaluated according to the alteration in tumour size by clinical and radiological means. It may take three or more cycles of therapy to detect tumour size changes. However, should the CA125 level fall to 50% of pre-therapy levels after two cycles of chemotherapy, the probability is that the patient will respond to continued treatment (Rustin et al, 1996).

The converse is also true in that with unaltered levels response remains unlikely. In the latter setting, CA125 has impacted on care, in facilitating the oncologist's decision to either change the cytotoxic agents or, in some cases, prevent unnecessary treatment.

TUMOUR MARKERS IN PATIENT FOLLOW-UP

The follow-up of patients who have completed primary treatment for ovarian malignancy is presently hospital based for 5 years. In those with elevated preoperative CA125 levels, the tumour marker is measured at each visit. A rising CA125, in particular a doubling of values, is indicative of tumour relapse (Meyer and Rustin, 2000). This rise may precede a detectable tumour or symptoms by as long as 3 months to 2 years.

This poses a certain dilemma as an elevated CA125 level may indicate recurrent disease in an asymptomatic patient. Should intervention in the form of surgery or chemotherapy be commenced immediately or only when disease is detectable? Could treatment be more effective with lower tumour volume? The answers remain unknown at present, but an ongoing prospective Medical Research Council study is endeavouring to address this very issue.

OTHER TUMOUR MARKERS

Both β-human chorionic gonadotrophin (β-hCG) and α-fetoprotein are associated with the rarer germ cell tumours (Kehoe, 2001). These normally occur in women under the age of 40 years and are a recommended test in this age group when ovarian cancer is suspected. As with measuring CA125, debates exist as to their true value and impact on outcome in the follow-up of patients. Granulosa cell tumours can produce increased serum oestrogen and also inhibin, which may also occur in other ovarian tumours. Both may be used in monitoring patients.

The one exception, whereby therapy is dictated by abnormal tumour marker levels, is in the very rare case of choriocarcinoma of the ovary. β-hCG levels are excellent markers for this disease, and as with choriocarcinoma in general, rising levels would indicated the need for chemotherapy even without evidence of detectable disease.

CONCLUSIONS

Tumours markers have impacted on the management of ovarian carcinomas. They have a role in indicating the potential that an ovarian mass may be malignant, in facilitating the correct referral of patients and in monitoring therapeutic efficacy and follow-up. Of particular importance is the role of CA125 as part of a population screening programme and indeed whether marker-based therapy in the relapse setting will prove advantageous. However, CA125 may rise as a result of other causes, and in the future a combination of markers may be used to enhance the predictive accuracy of these tests. HM

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KEY POINTS

- Raised CA125 levels are suggestive but not diagnostic of ovarian cancer.
- CA125 levels are raised in 80–85% of epithelial ovarian carcinomas.
- In women with a pelvic mass, CA125 levels, ultrasound scan findings and age can be used to predict the potential risk of malignancy.
- Although yet to be proven, CA125 may play an important role in screening for ovarian cancers.
- Changes in CA125 levels are valuable in monitoring both disease treatment and recurrence.
- Serum β-human chorionic gondaotrophin, α-fetoprotein and inhibin are markers for rarer non-epithelial ovarian tumours.