Biochemical Markers in Cancer of the Ovary: A Review

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The ideal tumour marker would be one which is detectable before obvious clinical involvement, follows the kinetics of tumour growth with reduction in serum concentration as the tumour mass is reduced by surgery or chemotherapy, and which reappears several months before clinical reappearance of the tumour. With the possible exception of beta HCG in trophoblastic tumours, there is no such biochemical marker, and one has to rely on a number of different parameters for the assessment of tumour growth.

A number of biochemical markers have been used to diagnose carcinoma of the ovary.

CA125 is an ovary associated antigen detectable by monoclonal antibodies, and for which sensitive immuno-assays have been developed.(1) The antigen is found in sera from patients with ovarian cancer, amniotic fluid, human milk, as well as supernatants from cancer clones in vitro. By specific immuno-histochemical labelling, it has been found in a number of tissues including benign, borderline and most malignant serious tumours of the ovary, as well as in some Mullerian and some mucinous tumours. It is also found in non-gynaecological tumours such as tumours of the lung, liver, stomach, gall bladder, pancreas, kidney and large bowel.

Normal serum levels are usually taken as below 35 U/mL. In carcinoma of the ovary, elevated levels (greater than 35 U/mL) are found in 80 - 85% of patients overall, and in more than 90% of patients with stage II to stage IV cancer.

Estimation of serum CA125 levels have been found to be of value. The prognosis is significantly better for those with pre- operative levels of CA125 less than 65 U/mL. Post-operatively, CA125 levels usually drop and it has been shown that the prognosis is worse in those patients where CA125 levels remains greater than 65 U/mL. It has been found useful also before undertaking a "second look" operation, because of the good correlation between serum CA125 levels and visible tumour (positive predicative value of 94.5%). (2-5). A rising level of CA125 is an ominous sign, and therefore our practice is to assess CA125 at regular intervals (every 1 -3 months). Elevated CA125 precedes clinical recurrence by up to 6 months.

Some of the problems associated with using CA125 levels in diagnosis of tumours of the ovary include the following:

It is elevated in 2% of normal healthy subjects, usually at low levels (less than 100 U/mL). It is elevated during menstruation and pregnancy, where high levels can be seen. It can also be elevated in endometriosis and in any conditions where there is irritation of the peritoneum. Other conditions where CA125 has been found elevated including endometrial cancer, salpingitis, uterine myoma, gastro-intestinal tract disorders, renal disease and renal failure, as well as in diabetics.

In spite of all these provisos, CA125 has been found useful and is a standard test in the workup and follow-up of patients with carcinoma of the ovary.

Figure 1 shows the typical pattern of serum levels variations in a patient with cancer of the ovary on treatment.

OTHER OVARIAN TUMOUR MARKERS

TISSUE POLYPEPTIDE ANTIGEN (TPA):

Elevated levels have been found in over 70% of patients with advanced cancer of the ovary, (the normal range being less than 85mU/ml).(4) It is positive also in up to 54% of non-ovarian tumours. However, the specificity and sensitivity are not as good as for CA125. In view of the fact that it bears no correlation with histological type, it could be useful in detecting those patients who are CA125 negative.

LIPID - ASSOCIATED SIALIC ACID (LASA-P)

This non-specific sialo glycoprotein on the cell surface of cancer cells is found elevated in the sera of most patients with ovarian cancer and normal in the majority of patients with benign ovarian neoplasms. It correlates fairly well with CA125 levels. It does not require immunoassay, and this could be advantageous in some laboratories (6).

CA 19-9

This antigen, a carbohydrate determinant related to the Lewis blood type (more specifically a ganglioside containing sialylated lacto - N Fucopentose), was first extracted from gastro- intestinal tumours. Immunoradio-metric assays are available, and serum levels less than 40 U/mL are considered abnormal. Elevated levels have been found in up to 93% of ovarian cancer and not in benign tumours of the ovary or healthy subjects (7,8). Mucinous (as well as serious) epithelial tumours of the ovary have a tendency to have high levels and therefore this test could prove useful for detection and follow-up of those ovarian cancers which are negative for CA125.

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CARCINOEMBRYONIC ANTIGEN (CEA)

Carcinoembrionic antigen was originally extracted from tumours of the colon (9) and immunofluorescent studies confirmed that it is present in abundant quantities in mucinous carcinomas of the colon. It is also present in mucinous adenocarcinoma of the ovary, endocervix, and to a lesser extent endometrium.

Sensitive immuno-assays have been developed to detect levels of CEA in the serum. CEA is elevated in only a small proportion of cancer patients and then only in advanced stages III and IV. Only 50% of ovarian cancer patients have elevated CEA at any time during serum measurements.

A number of studies (10,11) have shown that CEA estimation is of limited value. We found the sensitivity to be only 70%, and a positive predicative value of 46% at a cut-off level of 5ng/ml.
A high level of CEA is likely to be present when there is a large tumour mass. Prognosis is likely to be worse when levels of these markers are high (12), presumably because this implies a more wide spread or more bulky tumour. However, as it is a mucus-related antigen, it may detect those mucinous tumours not detectable by other markers.

ALPHA FETO PROTEIN AND BETA HCG

These markers are present only in a very small proportion of patients with ovarian tumours, and only in those with germ cell components. While extremely useful for the latter group, it is unlikely that they will be of any great relevance for the vast majority of ovarian cancer detection.

Other markers being investigated include NB/70k, HMFG2, DCA, MSA, B2 microglobulin, placental alkaline phosphatase etc. (13,14).

SCREENING FOR OVARIAN CARCINOMA IN A NORMAL POPULATION

Attempts have been made recently to assess the value of CA125 for screening normal (post menopausal) populations to determine the possible value of screening tests in the detection of cancer. Surveys are being carried out in our hospital and elsewhere (15,16) to evaluate use of CA125 with or without other modalities in the detection of carcinoma of the ovary.

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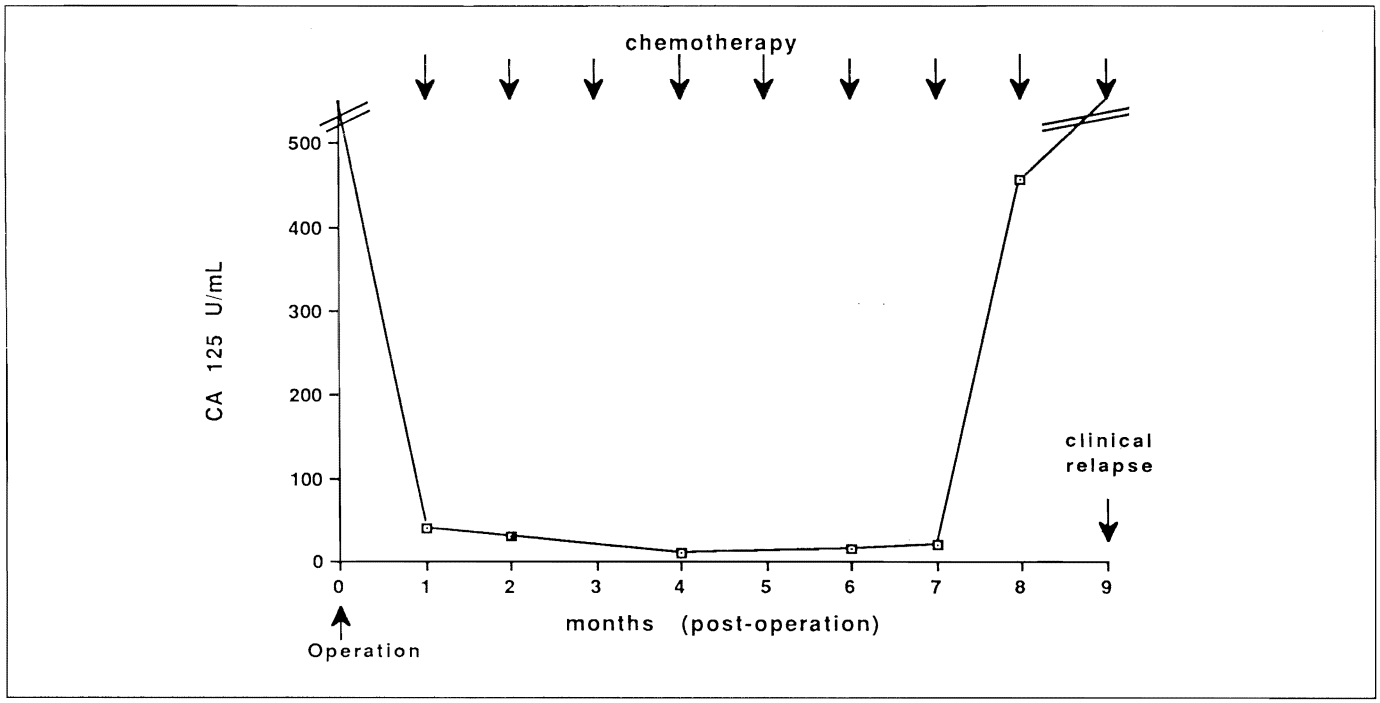

Fig. 1

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