Biomarkers in epithelial ovarian cancer

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It is not always possible to have original ideas, whether it is enough to have them simply practicable.

José Saramago, La Caverna.

The use of biomarkers in cancer is useful for diagnosis and treatment, as well as for the monitoring of the evolution and the detection of risk of relapse. However, the majority of biomarkers are not unique for each type of tumor from there the importance of knowing what their applications are according to each neoplasm. In the case of epithelial ovarian cancer (EOC), CA125 has been the iconic marker of this pathology; however, it is necessary to refine its usefulness and indications.

The CA125 is a glycoprotein that is present in the mesothelial cells of the pleura, pericardium, peritoneum and Müllerian derivatives as the endocervical, endometrial and tubal cells. It is for this reason that this tumor marker is not associated exclusively to ovarian cancer, so it can raise in different oncological conditions, such as endometrial, breast, pancreas, lung and gastrointestinal tract cancer, as well as other benign conditions such as endometriosis, pregnancy, peritonitis, pelvic inflammatory disease, pancreatitis, uterine fibroids and abdominal surgery. The CA125 does
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not usually rise on all histological types of ovarian cancer, its rise is mainly observed in epithelial
tumors and only in 50% of cases at early stages\textsuperscript{1}, which limits its use as a test for early detection.

In January 2016 is published an update of the guidelines of the European Group on Tumour
Markers (EGTM) for tumor markers of the EOC\textsuperscript{2} in the International Journal of Gynecological
Cancer. After a review of the scientific evidence, this group made recommendations regarding the
use of the CA125, which include its use in screening, diagnosis, prognosis and follow-up.

According to the recommendations of this working group, the CA125 should not be used as a
single method for screening of CEO due to the low sensitivity in the early stages and in the
mucinous type, also having a low specificity, especially in patients at reproductive age. The
combination with other methods, as it was commented on this website in an article about the
UKCTOCS\textsuperscript{3} study, needs a longer term follow-up in order to establish a conclusion in this regard.
However, they consider that the combination with transvaginal ultrasound may be useful for
screening in women with mutations of BRCA1 and 2, where the frequency of the disease is higher.

EGTM recommends the use of a Risk of Malignancy Index (RMI 1 or RMI 2) for the differential
diagnosis of pelvic mass in post-menopausal women. The RMI is an index that combines the
findings of transvaginal ultrasound, as multilocular cyst, solid areas, presence of ascites, bilateral
lesion and presence of peritoneal metastases, the menopausal status and the value of CA125. It is
calculated by multiplying the value assigned to the ultrasound findings, by menopausal status and
the CA125 concentration, if the index is greater than 200 this correlates significantly with a risk
that the lesion may be malignant. It is estimated that the measurement of this biomarker, is not
enough to interpret a pelvic mass suspicious of malignancy, as ultrasound as a complementary
tool and establishing the presence or absence of ovarian function, making a morphological
characterization of the lesion, which allows putting in context the measurement of CA125 in the
differential diagnosis of a suspicious image.

In patients undergoing chemotherapy for CEO, the Group recommends the use of two
measurements to evaluate the response to treatment and is considered that a decrease greater
than 50% in CA125 measurement is associated with increased survival. The use of a single
measurement for prognosis is not suitable because it provides very limited information. Change of
the levels of CA125 in several determinations provides information on the behavior of the disease
in time.

Regarding the use of the CA125 to the monitoring of the disease, though the majority of scientific
societies does not advise the use of this marker, this group recommended it in the initial phase of
therapy and monitoring post-treatment, i.e., after the first two cycles of chemotherapy and after
completing drug treatment with the aim of detecting a possible relapse. A significant decline is
defined as a decline equal to or greater than 50% of the initial value, and supported by at least 28
days. Likewise, is defined as the CA125 increment: when the value never comes to normalize or
an increase above twice the pretreatment value. In patients whose value is normalized after the
treatment, it was considered as an elevation of the CA125 an increased more than 70 kU/L, i.e.
twice the upper limit of the normal range. On the basis of these parameters determines the possibility of relapse.

The Group also provides its recommendations regarding the use of other marker, the Human epididymis protein 4 (HE4), which is a glycoprotein that is overexpressed in EOC but not in benign conditions. The HE4 has also been identified in breast, lung and endometrial cancer so it is not specific to ovary. However, the condition that generates more false positive is renal failure. The main advantage of this marker is its usefulness in patients at reproductive age because the rate of false positives is less than with the single CA125. However, according to this working group, there is no consensus even with regard to the use of HE4 for screening, but its use as a prognostic marker could be recommended since pretreatment values relate to significantly worse prognosis of the disease. The use of Risk of Ovarian Malignancy Algorithm (ROMA), which combines CA125 with HE4, or HE4 alone, is recommended for the differential diagnosis of pelvic masses, particularly in premenopausal women. The Group makes no mention of the use of the OVA1, which is a test that combines different markers, which was discussed in another article in this blog, probably due to the fact that there is not still enough evidence to recommend its use.

The IOTA (International Ovarian Tumor Analysis) group enters in the algorithm Different Assessment of neoplasms in the Adnexa (ADNEXA) the value of CA125 to the differential diagnosis of pelvic masses, in combination with the ultrasound findings, the age of the patient and whether the patient is at a Cancer Center. EGTM considers it a useful tool for differential diagnosis of pelvic masses, particularly in pre-menopausal women, and to consider the reference to a center with a service specialized in Gynecology Oncology.

To date, as it can be seen this consensus and research discussed in previous articles, there is a no screening marker for EOC, alone or in combination with transvaginal ultrasound, which is sensitive and specific for this pathology, so it has to wait for the validation of the various algorithms that are being evaluated. It is consolidated the recommendation of the use of CA125 in combination with transvaginal ultrasound in patients with high risk for ovarian cancer, as carriers of mutations in the BRCA1 and 2 genes due to the high incidence of CEO in this group of women.

With regard to the differential diagnosis during the evaluation of an adnexal mass, the use of HE4 and CA125 in combination with transvaginal ultrasound is shaping up as the most appropriate tool, especially in patients at reproductive age, when it is more frequent the presence of non-malignant pelvic masses, many of them physiological.

The importance of a precise diagnosis of an adnexal mass is to offer the patient the best treatment. The overall survival of patients with EOC depends mainly on early diagnosis of pathology and is considerably greater if they are treated at cancer centers with experience.

For this reason, while the good news come with regard to the study on early disease diagnostic protocols, it is necessary to highlight that patients with a mass adnexal with suspicion of malignancy, because of the characteristic ultrasound and the elevation of the markers, should
initially be treated by a surgical team trained in the area of oncogynecology, to improve disease-free survival and ensure a better quality of life.

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