

THE IMPORTANCE OF THE IMMUNOLOGICAL MARKERS IN OVARY CARCINOMA

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Abstract: *The biological markers are substances produced by tumour, observable in periphery blood, urine, tumour tissue, identifiable through radio – immunology laboratory methods. The most usually biomarkers of ovary neoplasm with prognostic importance and predictive for diagnosis and treatment are the CA125.*

Keywords: *carcinoma of the ovary, biological markers*

Rezumat: *Cancerul ovarian reprezintă a șasea localizare neoplazică ca frecvență la femei, pe plan mondial și principala cauză de mortalitate prin cancerule ginecologice. Markerii biologici sunt substanțe produse de tumoră evidențiable în sângele periferic, urină, țesut tumoral, identificabile prin mijloace de laborator radio-imunologice. Cei mai uzuali biomarkeri din cancerul ovarian cu rol prognostic și predictiv pentru diagnostic și tratament sunt CA125.*

Cuvinte cheie: *cancer ovarian, markeri tumoralii*

INTRODUCTION

Ovary carcinoma represents the sixth neoplasia localization in women, at world level, and it is the most important cause of death when talking about gynecological cancers.(2)

Global mortality in 1990 was 4.2/100.000 citizens, and in the EU 9.2/100.000 citizens (1) from the 3.8 million of new cases of cancers; most of women cancers were discovered in breasts and in the genital system.

The American Cancer Society shows that mortality is increasing continuously, although survival has also increased from 36 % in 1970 to 50 % in 1990.

Tumour markers of the ovary carcinoma are used in screening, positive diagnosis, controlling the prognosis, watching the response to the treatment and the relapses.

The most used marker is CA 125. CA 125 (CANCER ANTIGEN 125) is produced by a variety of cells, but most of all, by the cancerous cells of the ovary. It is the most important serum marker (gold standard) when talking about ovary carcinoma, used especially in the treatment management of the ovary carcinoma. CA 125 may have high values when talking about other types of neoplasia or benign affections. 35U/l is also considered a normal value.

Other immunological markers which could be of

great importance in treating ovary carcinoma are: ACE (carcino-embryonic antigen) which registers high levels in 30-50 % of the epithelial ovary tumours, in advanced phases of the illness; CA 19-9 antigen, which has high values in 17-30 % of the cancer mucin; LASA antigen (lipid-associated sialic acid) which registers a low sensitiveness of 52.1 % and a specificity of 87.8 %.

Other tumour markers are OVXI antigen, M-CSF, CASA, CA 54-61, and CA 72-4 antigens, with a lower importance, but still studied.

The mutation of the c-myc, H-ras, erb B-2 oncogenes gives also a negative course of the disease. It is considered that the tumour transformation of the ovary epithelium represents the consequence of the continuous gathering of genetic anomalies, as a result of the inactivation of the suppressor tumour genes and of the exaggeration or overexposure of the oncogenes.

The most known suppressor tumour genes involved in the ovary tumour genesis are: p53 and BRCA1 and BRCA2 genes.

OBJECTIVES AND METHOD

The present paper encircles itself between the papers which describe the ovary carcinoma and it aims at accomplishing a preliminary prospective analysis over a 80 homogenous group of patients with ovarian cancer, in order to build up a clinical-therapeutically characterization and to identify theoretical possibilities of using the immunological markers when diagnosing this type of carcinoma, the relapses of the illness, using them as prognosis and monitoring treatment factors.

Through this analysis, we evaluated a series of clinical and para-clinical aspects, gathered from the patients with ovary carcinoma (the extension degree of the tumour, the stage of the illness, the moment of the local recurrence and the appearance of the metastasis), in order to show some possible connections between these ones and the value of the immunological markers.

Study inclusion criteria: TNM stages; histopathological confirmation: information regarding the extension degree of the tumour and ganglionic infection; patients with specific oncologic treatment; the value of the immunological markers at the beginning and during the treatment; objective documentation regarding the metastasis and the local recurrence. Observed markers:

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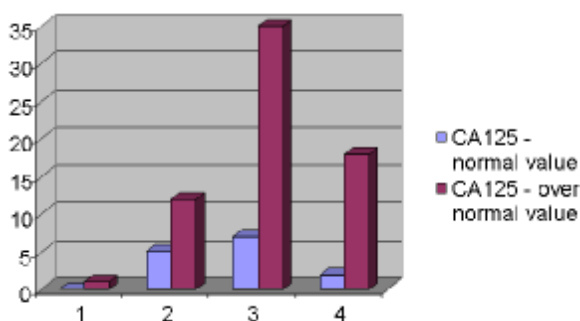
CA 125

RESULTS AND DISCUSSION

During the present study, we analyzed a group of 80 patients, aged between 36-79 years old (average age – 57 years old).

53 patients (66.2 %) registered an evolution of the illness (metastasis or relapses); from this total of 53, 40 patients registered metastasis (osseous, of the lungs, hepatic) and 13 patients registered local recurrence. From the total amount of 80 patients, 68 patients (85 %) registered in the moment of diagnosis, values of the CA 125 over the normal limit and regarding the other 12, the value of CA 125 was below normal limits.

Picture no. 1. Correlation between CA 125 in the moment of diagnosis and in the stages of the illness P=0.036*likelihood ratio



In the moment of diagnosis, an over normal CA 125 value was registered in the case of 66 patients (80 %) and a normal value in the case of 14 patients (20 %); the idea is that the CA 125 value registered in the moment of diagnosis is important for that particular diagnosis, no matter of the stage of the illness. When talking about the advanced stages of the illness, we see that in the moment of diagnosis, an over normal CA 125 value was registered in the case of a large number of patients: in the 3rd stage, 35 patients (43 %), in the 4th stage - 18 patients (21 %); compared to the initial stages, when CA 15-3 registered only one value over normal – 1 patient (1.25 %) in the first stage – and 12 patients (15 %) in the 2nd stage, which proves to be statistically of great importance. This result confirms the result of those studies which show that in advanced stages of the illness, the CA 125 value is high in 80-90 % cases, and in initial stages, in only 50 % cases. It also reflects the dimensions of the tumours, the postsurgical level having a raised predictive value.

High value of the CA 125 marker represents an indicator in the diagnosis of ovary carcinoma.

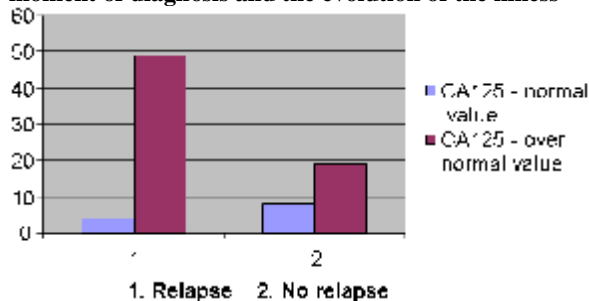
From the 68 patients (85 %) with high value of the CA 125 in the moment of diagnosis, 49 (61.25 %) registered an evolution of the illness (metastasis or relapses), and the rest of 15 patients (18.7 %) registered no evolution (metastasis or relapses). And out of 12 patients (15 %) with normal CA 125 value in the moment of diagnosis, 4 patients (5 %) registered an evolution of the illness (metastasis or relapses) and 8 patients (33.75 %) registered no evolution (Table no. 2, Picture no. 2)

During the treatment, 37 patients (46.25 %) had normal CA 125 values: 4 patients (5 %) registered an evolution of the illness (metastasis or relapse), and the rest of 33 (41.25 %) did not register an evolution of the illness.

Table no. 1. Correlation between CA 125 in the moment of diagnosis and the evolution of the illness (metastasis or relapses) P<0.05

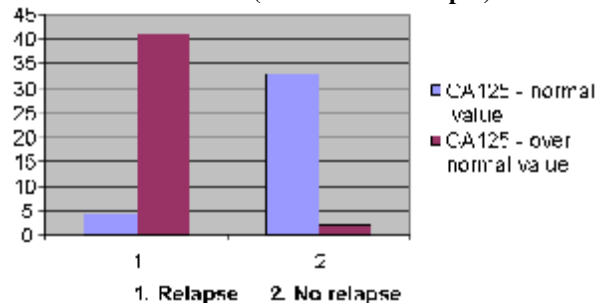
CA 125 in the moment of diagnosis	Evolution	No evolution	Total
Normal value	4 (5 %)	8 (10 %)	12 (15 %)
Over normal value	49 (61.3 %)	19 (23.7 %)	68 (85 %)
Total	53 (66.3 %)	27 (33.7 %)	80 (100 %)

Picture no. 2. Correlation between CA 125 in the moment of diagnosis and the evolution of the illness



Out of the total of 80 patients in this study, 43 had normal CA 125 value; from these, 41 patients (51.25 %) registered an evolution of the illness (metastasis or relapse) and only 2 patients (2.50 %) registered no evolution of the illness. (Diagram 3 P<0.05).

Picture no. 3. Correlation between CA 125 and the evolution of the illness (metastasis or relapse)



CA 125 identified, both in the moment of diagnosis and during treatment, may indicate an evolution of the illness, either relapse or metastasis, or both of them.

Monitoring the treatment of the patients, we notice that out of the 37 patients (46.25 %) with normal

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CA 125 value, the majority, meaning 33 patients (41.25 %) had no evolution of the illness (metastasis or relapse) and only 4 patients (5 %) registered an evolution of the illness; when talking about those patients who registered an over the normal value for CA 125, the majority of 41 patients (51.25 %) registered an evolution of the disease (metastasis or relapse) and only 2 patients (2.50 %) registered no evolution of the illness, a result which is statistically significant.

The value for CA 125 is proved to be an indicator for the negative prognosis of the illness, giving the opportunity to be detected three or four months before the moment of illness' failure.

The use of CA 125 plays an important role in monitoring the treatment, relapse and prognosis.

The 80 patients in the study group followed surgical intervention and auxiliary cytostatic therapy. After the surgical intervention, the ovary neoplasm diagnosis was histologically confirmed: 53 patients (66 %) were submitted to a complete operation and 27 patients (34 %) were incompletely operated.

The serial determination of CA 125 brings forward useful information regarding the treatment of ovary carcinoma (surgical treatment and auxiliary chemotherapy). Well-known studies (e.g. Rustin's papers) defined precise criteria of judging the response of the illness or its progression, according to CA 125 variations. They showed that a 25 % growth in three successive tests represented a progression. A value over 100 u/l for CA 125, which did not get lower after three stages of treatment, with at least 50 %, was a progress, too. We may also add that a growth of CA 125 value, equal with the double of the superior normal value, indicates an evolution of the illness, as Rustin shows. If after chemotherapy, low levels of CA 125 are detected, it means that the tumour responds to treatment. The increase of the values for CA 125, during or after treatment, may indicate a lack of response to treatment or a semi-response (residual illness).

The present paper shows that a great number of patients registered, after the radical surgical therapy, followed by auxiliary chemotherapy, normal values of the tumour marker at the end of the therapy – 43.75 %, and only 18.75 % of the patients managed to register these values after sub-optimum surgery followed by auxiliary chemotherapy. Monitoring the treatment (surgical intervention and 1st line chemotherapy), out of the 80 patients included in this study, 16 patients (20 %) registered high values for CA 125, 54 patients (67 %) registered normal values, and in the case of 10 patients, the CA 125 value could not be identified (Picture no. 4).

We can see that regarding the patients who were under radical surgery, a larger number registered normal values of the tumour marker after therapy, than those who were under sub-optimum surgery: 43.75 % compared to 18.75 %.

The value for CA 125 may be a therapeutic indicator of the therapy efficiency.

From the studied group, 53 patients (66 %)

registered an evolution of the illness (metastasis or relapse). From those 2 patients who were diagnosed in the 1st and 2nd stages, both registered high values for CA 125, and from the other 53 patients diagnosed in the 3rd and 4th stages of the illness, 2 registered normal values for CA 125, while the rest of 49 patients registered over normal values for CA 125 (Table no. 2, Picture no. 5).

Picture no. 4. Correlation between CA125 values and therapy P=0.05

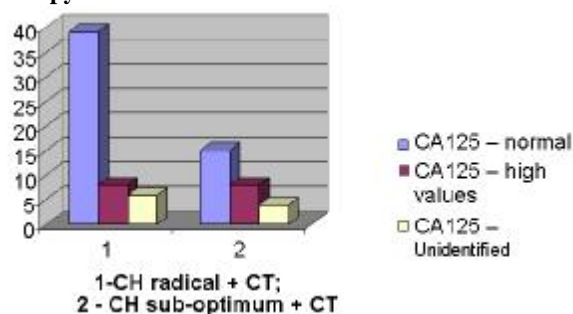
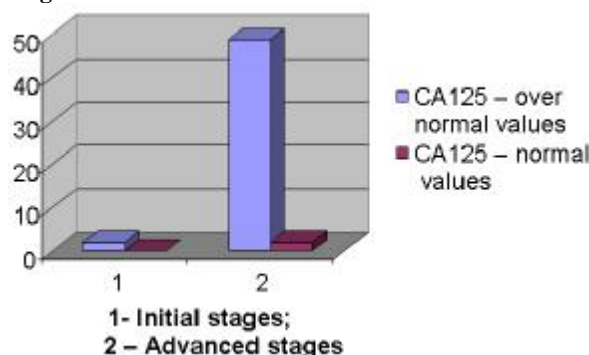


Table no. 2. Correlation between CA 125 value, the stage of the illness and the moment of illness' evolution

Patients who registered failure - stage	High CA125	Normal CA125	Total
I + II (initial)	2 (3.77 %)	0	2 (3.77 %)
III + IV (advanced)	49 (96.25 %)	2 (3.77 %)	51 (96.22 %)
Total	51 (96.22 %)	2 (3.77 %)	53 (100 %)

Picture no. 5. Correlation between CA 125 value, the stage of the illness and the moment of illness' evolution



Correlation between the advanced stage of the illness and the high value for CA 125 marker represents an indicator for a negative prognosis in the illness evolution, showing the failure of the therapeutic process, either through metastasis or relapse.

We can see that Ca 125 identified, both in the moment of diagnosis and during the treatment may indicate an evolution, either through relapse or metastasis, or both. Therefore, monitoring the therapy of the patients through monitoring the CA 125 values, it was shown that from the total of 37 patients (46.25 %) with normal values for CA 125, the majority, meaning 33 patients (41.25 %)

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did not register any relapse in their illness, and only 4 patients (5 %) registered a relapse; while in the case of the 43 patients (53.75 %) with over normal value for CA 125, the majority, meaning 41 patients (51.25 %), registered a relapse of the illness, and only 2 patients (2.50 %) did not register any relapse, results which are statistically significant.

CA 125 value is proved to be a good indicator of negative prognosis of the illness.

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CONCLUSIONS

1. High values for **CA 125** correspond to advanced stages of the ovary neoplasia.
2. **CA 125** is useful especially in monitoring the treatment (low values of the marker represent an effective treatment, detecting some high values or the continuous growth of the markers values during or after the therapy means the patient faces an unfavourable evolution of the illness or the lack of response to the treatment, which requires changing the treatment).
3. **CA125** may be also used as a prognosis marker in ovary neoplasia.

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