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Measurement of HE4 six months after first-line treatment as optimal time in identifying patients at high risk of progression advanced ovarian cancer

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ABSTRACT

Objectives: The objective of the study was to assess the usefulness of determining HE4 and CA125 in ovarian cancer patients, to indicate which of the measurements may be optimal in the prognosis, depending on the treatment scheme.

Material and methods: The concentrations of CA125 and HE4 were performed in 70 patients with advanced ovarian cancer during I-line therapy and after treatment. The subjects were divided based on the treatment scheme: group I - primary surgery and adjuvant chemotherapy, II- neoadjuvant therapy, and surgery.

Results: Multivariate analysis showed that HE4 levels six months after treatment was significantly higher in patients with disease progression. ROC analysis in the group of patients treated with neoadjuvant therapy showed that the cut-off values indicating relapse for HE4 and CA125 after six months of follow up, were > 90.4 pmol/L, > 25.6 IU/mL, respectively. In the group of patients not treated with neoadjuvant therapy, the cut-off points differentiating patients with progression were: HE4 > 79.1 pmol/L, CA125 > 30.7 IU/mL. We demonstrated significantly higher HE4 and CA125 at both 6- and 12-months follow-up in patients treated with neoadjuvant therapy. In both groups of patients, the cut-off points were lower than those proposed by the manufacturer of the kits.

Conclusions: Measurement of HE4 six months after treatment may be useful in identifying patients at high risk of progression, especially when CA125 levels may be non-specifically elevated. The cut-off values indicating relapse for HE4 and CA125 after six months of follow up may be lower than the normal range.

Key words: CA125; human epididymis 4; ovarian cancer; treatment monitoring; progression

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INTRODUCTION

Ovarian cancer is the second most frequent gynaecological neoplasm [1]. The results of ovarian cancer treatment are unsatisfactory, as most patients are diagnosed with clinically advanced cancer. However, the treatment outcomes depend not only on the severity of the disease, but also on a number of biological and molecular features of the tumour. Much also depends on the experience and skills of the treatment team, and the efficiency of the health care system in each country. Over the last 30 years, significant progress has been made in the treatment outcomes of this cancer and the 5-year survival rate has improved by approximately 15% [2]. Although up to 80% of patients with advanced ovarian cancer achieve remission after the treatment, 65% are diagnosed with recurrence in the first two years [3]. Overall, 75% of patients in stage III and IV, according to the FIGO classification, die of the cancer [4]. Surgical radicalism is one of the most important prognostic factors [5]. Compared to the group when infiltrative changes were left in patients after complete resection (*i.e.*, R0), the 5-year survival results are about 64% higher [6]. Other prognostic factors include family predisposition related mainly to mu-

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tations in the BRCA 1 and 2 genes, and Lynch syndrome, as well as infertility, childlessness, endometriosis, obesity, menopausal age and the use of talcum powder in cosmetics [7]. A mutation in the BRCA 1 gene increases the *in vivo* risk of ovarian cancer by 40–60%, and in BRCA 2 by 11–27% [8, 9]. The factors reducing the risk of this cancer are mainly oral contraceptives and having many children.

The most common and aggressive type of cancer is high grade serous ovarian cancer, which accounts for almost 70% of cases [10]. Almost 20% of cases of this type of cancer have a confirmed family predisposition related to mutations in the BRCA 1 or 2 genes [8]. The second type of serous ovarian cancer is low grade with a completely different clinical course and prognosis. This type is characterized by mutations in the following genes: *BRAF* and *KRAS* [11, 12]. It usually expresses both oestrogen and progesterone receptors, therefore hormone therapy may be effective. Other histopathological types include clear cell, mucous or endometrioid carcinoma.

The cytostatic treatment and maintenance therapy with the use of targeted procedures significantly changed the fate of patients. Still, surgery appears to be a very important stage of treatment. It is debated whether primary cytoreductive surgery or interval surgery after neoadjuvant treatment has an advantage in advanced cases. Disputes on this topic have not ended so far, therefore the results of clinical trials are still pending. The AGO-OVAR study clearly indicates the benefit of primary surgery [6]. However, the assessment of genetic and molecular factors by Riester et al. [13] showed that in certain constellations of molecular factors, radical cytoreduction may not be possible. Thus, starting with systemic treatment may be the most optimal manner.

Proper supervision of patients who have undergone treatment for ovarian cancer is extremely important. In addition to the clinical examination, the results of imaging examinations and monitoring of the value of CA125 and HE4 are also important. The results of these examinations can be used to predict the recurrence and thus allow for timely treatment. HE4 is a new test used in the monitoring of treatment results and follow-up after the therapy. The application of CA125 and HE4 is a very useful tool for the surveillance of patients with ovarian cancer, both during treatment and in post-treatment monitoring. This management is widely recommended by all Societies of Oncological Gynecology and Clinical Oncology.

Objectives

The aim of the study was to assess the usefulness of determining HE4 and CA125 during therapy and flow up of ovarian cancer patients, to indicate which of the time point may be optimal in the prognosis of the disease and determination cut-off points for the tumour markers differentiating patients with progression depending on the treatment scheme.

MATERIAL AND METHODS

We retrospectively analysed data from ovarian cancer patients' disease who were treated at the Gynecological Oncology Department, National Institute of Oncology in Warsaw, in 2017–2019. The study group consisted of 70 patients with epithelial ovarian cancer (EOC) stage FIGO III–IV, aged 40–84 years; median 61 years. In 37 patients (group I), primary surgical treatment was followed by standard systemic treatment, and in 33 patients (group II) neoadjuvant chemotherapy (NACT) was introduced prior to the surgery. All patients received the same cytostatic treatment — Carboplatin AUC 5 and Paclitaxel 175 mg/m^2 every three weeks. A total of six cycles in follow up treatment. For neoadjuvant chemotherapy group, 3/4 cycles before and three cycles after deferred cytoreduction surgery. FIGO stage IV patients additionally received Bevacizumab at a dose of 7.5 mg for 18 cycles. The markers were determined in the blood serum during treatment monitoring at the following time points:

- before treatment (collection 0),
- after surgery/NACT,
- after 3/4 CHTH/NACT courses,
- after 6 CHTH courses (the end of treatment),
- 6 months after the end of treatment,
- 12 months after the end of the first line of treatment.

A total of about 350 blood serum samples were collected for the study. The follow-up time was about 2.5 years. The clinical and pathological characteristics of the study group are presented in Table 1.

Tumor markers were determined in serum samples, stored in low-temperature freezers (–80°C). CA125 and HE4 determinations were performed in a total of 350 serum samples selected during treatment monitoring of 70 patients. CA125 and HE4 concentrations were determined by COBAS e601 system. The cut-off points for CA125 and HE4 were set according to the recommendations of the kit manufacturer. All methods were carried out in accordance with relevant guidelines and regulations.

Statistical calculations used the Statistica PL. 6.0 software for Windows. The Wilcoxon test and the Mann-Whitney U test were used to analyse the differences in variables within and between groups. The impact of clinico-pathological features and biochemical factors on DFS and OS was estimated in the univariate analyses according to the Kaplan-Meier method. Log-rank tests were used for comparisons and the Cox proportional hazards regression model was applied in the multivariate analyses. The diagnostic power of determined parameters was analysed using the MedCalc program. The analysis of the receiver operat-

Table 1. Clinicopathological characteristics of patients with EOC

Characteristics	*Group I n = 37		**Group II n = 33	
Age/years/range	40 - 76		30 - 80	
Median age	61		61	
	n	%	n	%
Menopausal status				
< 50/premenopausal	8/37	22	2/33	6
≥ 50/postmenopausa	29/37	78	31/33	94
Stage/FIGO				
3A-3B	34/37	92	20/33	61
4-4B	3/37	8	13/33	39
Histological Grade/G				
G3	34/37	92	29/33	88
Gx	3/37	8	4/33	12
Clinical status (6 months after treatment)				
Progression/P	10/35	29	14/29	48
Remission/R	20/35	57	14/29	48
Stabilization/SD	5/35	14	1/29	4

*patients primary surgical treatment; **neoadjuvant therapy

ing characteristic (ROC) was applied to determine our own cut-off points for the tested parameters depending on the clinical condition.

We performed a single center, retrospective, observational study according to the ethical standards of the Declaration of Helsinki. The samples were taken after informed consent form all the study participants.

Written informed consent was obtained from all patients before the treatment.

RESULTS

In our study, the concentrations of tumor markers were measured during monitoring and after treatment of patients. The subjects were divided based on the treatment regimen used in the first: group I - primary surgery and adjuvant CHTH, group II- NACT, and surgery.

The comparison of the levels of tumor markers in patients with EOC, depending on the treatment scheme

In both study groups, median concentrations of HE4 and CA125 before treatment were significantly above the cut-off points, but in patients qualified for NAT (group II) the values were several times higher, and for HE4 the differences were significant (p = 0.0004) (Fig. 1).

The comparison of the levels of markers in patients during monitoring with the treatment schedule showed that HE4 concentrations (p = 0.003) were significantly higher in

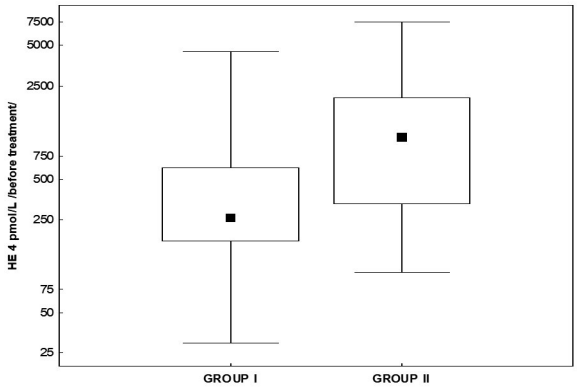

Figure 1. Distribution of HE4 concentrations and medians in patients before treatment, according to the treatment used

patients after NAT than in those after surgery, but no such differences were found for CA125 (Tab. 2).

In both groups of patients, a significant decrease in median markers was observed as a result of the treatment. It was demonstrated that in patients initially treated surgically (group I), the median concentrations of HE4 and CA125 decreased after the surgery by 67% and 66%, respectively, compared to the level before the treatment. In Group II, however, after using NACT, the decrease was much greater and amounted to HE4 by 84% and CA125 by 94%. In Group I, a similar decrease in medians of both markers, HE4 72% and CA125 96%, was observed only after the administration of six courses of adjuvant chemotherapy. In the first group, significantly lower concentrations of both markers, HE4 (p = 0.001) and CA125 (p = 0.003), were noted after surgery, compared to the concentrations before treatment, and significantly lower values of CA125 were reported in the sixth vs third course of CHTH. However, no such a relationship was found for HE4. Similarly, in group II: the concentrations of HE4 (p = 0.002) and CA125 (p = 0.0001) were significantly lower after NACT, compared to the concentrations before treatment. Such a relationship was also found when comparing the values of both markers after the first step of treatment (NACT) and the sixth CHTH course: HE4 (p = 0.009), CA125 (p = 0.021).

The comparison of the levels of markers measured 6 and 12 months after the first line of treatment showed significantly higher values of HE4 (p = 0.003; p = 0.005) and CA125 (p = 0.002; p = 0.003) in patients treated in the first step with NAT, compared with the concentrations observed in surgically treated patients (Tab. 2).

The concentrations of CA 125 and HE4, depending on the clinical status after treatment

In the next step of the study, the concentrations of tumor markers were analysed depending on the clinical condition, which was determined 6 and 12 months after the first line

Table 2. Median levels of CA 125 and HE4 in patients with EOC during follow-up, depending on the treatment scheme

Time points serum collection	Marker	Group I * n = 37	Group II** n = 33	P
		median	median	
Before treatment	CA 125 IU/mL	460.0	947.6	0.12
	HE4 pmol/L	256.5	1027	**0.0004**
After surgery/NACT	CA 125 IU/mL	156.3	61.5	0.32
	HE4 pmol/L	85.1	168.5	**0.003**
After 3/4 CHTH courses	CA 125 IU/mL	16.7	24.2	0.15
	HE4 pmol/L	85.3	110.9	0.051
After 6 CHTH courses	CA 125 IU/mL	16.4	34.9	0.057
	HE4 pmol/L	71.5	83.0	0.048
6 months after treatment	CA 125 IU/mL	10.4	79.4	**0.002**
	HE4 pmol/L	78.2	140.8	**0.003**
12 months after treatment	CA 125 IU/mL	15.8	75.9	**0.002**
	HE4 pmol/L	75.3	110.2	**0.005**

* patients primary surgical treatment; ** neoadjuvant therapy followed surgery

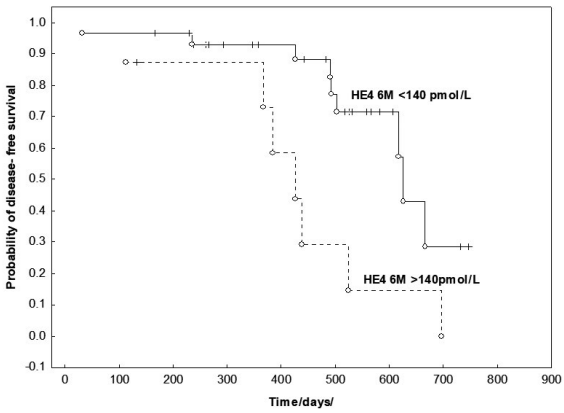

Figure 2. Probability of disease free survival to HE4 concentrations in patients 6 months after completion of first-line treatment

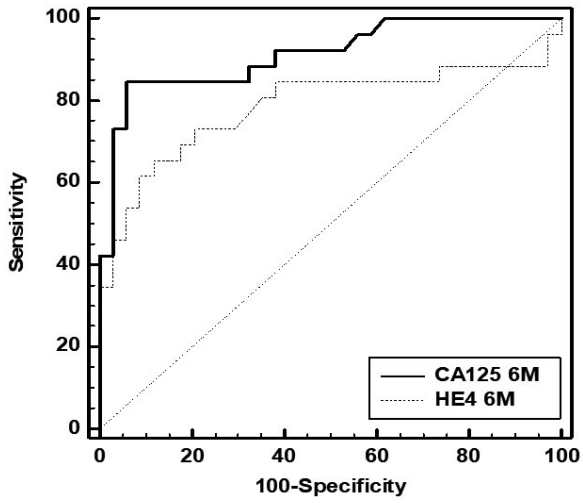

Figure 3. Receiving operation curve for HE4 and CA 125 concentrations determined 6 months after first-line treatment

of treatment. After six months of the follow-up, remission was observed in 62% and progression in 37% of the subjects; after 12 months, the percentage of patients with remission was lower (52%) and with progression higher (49%). As for the treatment method, remission was confirmed in a significantly higher percentage of patients treated surgically, both after 6 (72%) and 12 months (67%), compared to patients treated with NACT (53% and 33%). Five patients died during the follow-up, all of them were treated with neoadjuvant therapy (Group II). The comparison of the concentrations of both markers determined during post-treatment monitoring, both after 6 (CA125 and HE4 p = 0.0001) and 12 months (CA125 p = 0.0001; HE4 p = 0.003) showed significantly higher concentrations in patients with progression.

The univariate analysis demonstrated that only HE4 levels (p = 0.010) 6 months after the treatment (regardless of the regimen) were significantly higher in patients in whom at the end of the follow-up (about 2.5 years), progression was found and confirmed in the Cox multivariate analysis (HR = 2.74, p = 0.026) (Fig. 2).

The assessment of the diagnostic sensitivity of the tests and the analysis of ROC curves (progression vs remission) showed a greater AUC for CA125 at 6 (AUC = 0.913) and 12 (AUC = 0.844) months of the follow-up than for HE4 (AUC = 0.785; AUC = 0.739). These differences were statistically significant (p = 0.032) (Fig. 3).

Serum levels of CA 125 and HE4 in differentiating patients with progression

At the final step of the work, considering the method of treatment, cut-off points were determined for the markers

differentiating patients with progression. The ROC analysis conducted for the group of patients treated in the first surgically showed the cut-off point for HE4 concentrations measured after six months indicating a recurrence (> 79.1 pmol/L) (with sensitivity = 80% and specificity = 72.7%), and CA125 > 30.7 IU/mL (sensitivity = 80% and specificity = 100%). In the group of patients treated with NAT, the cut-off points for markers differentiating patients with progression were HE4 > 90.4 pmol/mL (sensitivity = 100%, specificity = 76.9%) and CA125 > 25.6 IU/mL (sensitivity = 100%, specificity = 86.7%). In both groups of patients, the cut-off points were lower than those proposed by the manufacturer of the kits.

DISCUSSION

Although tumor markers have a recognized position in laboratory oncological diagnostics (especially in oncological gynecology), they are still the subject of research and clinical evaluation in terms of usefulness in patients with malignancies. Determinations of serum markers in the clinical practice shows that they can provide important information regarding, among others, the assessment of sensitivity to the treatment, or the prognosis of disease [14–16].

A recently published meta-analysis proved that the sensitivity of HE4 is 0.86 (95% CI: 0.79–0.91) and specificity is 0.90 (95% CI: 0.49–0.99). The positive predictive value was 8.33 and the negative predictive value was 0.15 [17]. Studies emphasize that the monitoring of patients after treatment with HE4 may be more sensitive than with CA125 [18–20]. The value of CA125 determinations in treatment effect monitoring and post-treatment surveillance has been known and used for years. An increase in this marker, even by several months, may precede the clinical features of cancer progression [21].

In the literature, there is little research on the determination of serum markers in the treatment of patients. The subjects were divided based on the treatment regimen used in the first: group I — primary surgery and adjuvant CHTH, group II — NACT, and surgery. As a result of the treatment, in both groups of patients, a significant decrease was observed in the median concentration of markers, but the decrease was much greater after the use of NACT.

The analysis of the dynamics of changes in the concentrations of the markers during treatment monitoring revealed significant differences in the medians of both markers: in group I, significantly lower values of both markers after surgery only CA125 after the sixth course of adjuvant CHTH. Such relationships were not found for HE4 concentrations. It was similar in group II, significantly lower concentrations of CA125 and HE4 after NACT and then after the sixth course of adjuvant therapy. Chudecka et al. [18] demonstrated significantly lower HE4 values after the neoadjuvant therapy.

The analysis of the concentrations of tumor markers in the groups, I vs II, showed that patients who received NACT in the first step of treatment (group II) had significantly higher values of both HE4 and CA125. The analyses confirm the fact that after the surgical removal of the tumor, the concentrations of both markers are much lower, and their decrease is much greater than in patients after NACT. Therefore, we have shown that the surgical treatment used in the first stage has a greater impact on the reduction of CA125 and HE4 levels compared to neoadjuvant therapy, which may have a prognostic value. Other researchers found that a decrease or even normalization of HE4 levels during the first-line therapy of ovarian cancer may have a beneficial effect on PFS and OS [18].

In the next step of our research, the concentrations of neoplastic markers were analysed depending on the clinical condition assessed at the end of the follow-up. Remission (CR) after 6 and 12 months of the follow-up was confirmed in a much higher percentage of patients treated surgically than in those after NACT.

EOC is, in a way, a chronic disease characterized by relapses and, finally, resistance to treatment [16, 22]. Hence, it is very important to determine the importance of the markers in assessing the response to treatment. Although the literature contains many studies on CA125 and HE4 in ovarian cancer, only a few concern the evaluation of the clinical usefulness of markers in treatment monitoring, and thus focus on the analysis of their concentrations not only before treatment, but also during therapy and follow-up. Therefore, the most important issue of our work was to indicate the marker and determine the time of blood collection during treatment monitoring as important in the prognosis of the disease. We showed that, regardless of the regimen, the elevated HE4 levels six months after treatment, are a prognostic factor for EOC recurrence, but we did not observe such relationships for CA125. Other authors have demonstrated that HE4 levels after cytoreductive surgery are an independent prognostic factor for PFS in both low and high-stage patients during the first-line treatment of EOC [18, 20]. Analysing the concentrations of these markers, Ying et al. [23] found that HE4 was a better predictor of cancer recurrence than CA125 in patients initially operated on in the FIGO III/IV stage. Other researchers have shown a relationship between changes in the concentrations of both markers determined during monitoring and the prognosis of the recurrence of ovarian cancer in operated patients [16, 20].

There are works in which the authors attempt to set their own cut-off points for marker concentrations, differentiating patients in terms of predictive or prognostic value. The cut-off points are very different, and to a large extent depend on the clinical advancement of the study group,

and are most often determined before treatment [22, 23]. In our study, it was important to identify our own cut-off points for HE4 and CA125 (taken 6 months after treatment), which indicated progression, depending on the first-line treatment regimen. The very high sensitivity and specificity of both markers should be emphasized with these cut-off values in the assessment of the clinical status. In both study groups, the cut-off points indicating a relapse of the process were lower than the manufacturer's recommended reagent kits. Thus, it was confirmed that an increase in the concentration of markers during treatment monitoring (especially 6 months after treatment), even below the so-called norm, is most often associated with disease progression, which should be confirmed by imaging examinations.

CONCLUSIONS

In summary, significant changes in the concentrations of both markers during treatment, irrespective of the regimen, correlate with the clinical state, indicate their usefulness in monitoring the response to treatment, with the primary surgery having a greater impact on the decrease of the concentration of the markers. Measurement of HE4 six months after treatment may be useful in identifying patients at high risk of progression, especially when CA125 levels may be significantly nonspecifically elevated (e.g., recurrent ascites). Our own cut-off points for HE4 and CA125 concentrations determined 6 months after treatment may be helpful in differentiating patients with progression, without visible changes in imaging examinations.

Conflict of interest

All authors declare no conflicts of interests related to this article.

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