

ORIGINAL ARTICLE

Usefulness of human epididymis protein 4 in predicting optimal cytoreductive therapy in patients with advanced ovarian cancer

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Summary

Purpose: Human Epididymis Protein 4 (HE4) is a novel promising serum biomarker of high sensitivity and specificity for ovarian cancer (OC). We investigated the usefulness of HE4 in predicting the outcome of surgery of advanced OC.

Methods: Fifty patients with OC (FIGO stage III and IV) entered the study. Serum concentrations of HE4 and CA125 were evaluated preoperatively. All patients had been operated between January 2014 - January 2016.

Results: Preoperatively, the mean concentration of HE4 was 628pmol/L. Optimal cytoreduction was achieved in 44% of the patients, accompanied with decline of the mean values to HE4 478pmol/L, while in patients with suboptimal cytoreduction these values were 756pmol/L ($p<0.001$). Optimal cytoreduction was achieved in 52.9% of the patients with ascites $\leq 1,000$ ml and in 48% of those with ascites $>1,000$ ml ($p=0.023$). These patients had preoperative values of HE4 405 and 713pmol/L, respectively ($p=0.001$).

Optimal debulking was achieved in those patients with positive lymph nodes and ascites >1000 ml, whose preoperative values of HE4 and CA125 were <413 pmol/L and <500 U/mL, respectively. Our results indicated that the significant predictor of optimal cytoreduction was the value of $HE4 \leq 413$ pmol/L. In patients whose preoperative values HE4 were ≥ 413 pmol/L the optimal cytoreduction was less probable (odds ratio 4.921, $p=0.021$).

Conclusion: Preoperative concentrations of HE4 can be of predictive value for the achievement of optimal debulking of OC. Additional research in larger populations is necessary to prove the ability of preoperative values of HE4 in helping answer the question of whether or not optimal cytoreduction would be achieved.

Key words: human epididymis protein 4, optimal cytoreduction, ovarian cancer

Introduction

OC is the most lethal gynecologic malignancy in most countries [1] including Serbia [2]. Since most OCs are diagnosed in advanced stages (III and IV), standard therapy is maximal surgical debulking followed by chemotherapy, which improves overall survival [3,4].

Since OC is detected in advanced stages and has poor prognosis, many attempts to define effective tumor markers for early diagnosis have been carried out thus far. Currently, carbohydrate

antigen 125 (CA125) is the so-called "golden standard" for detecting OC, disease recurrence, and monitoring therapeutic response. However, the sensitivity and specificity of this tumor marker is low, since it is not expressed in a significant proportion of OCs. Moreover, it can be elevated in various benign lesions [5].

It seems that HE4 is the most promising tumor marker that shows a better diagnostic performance concerning the sensitivity and specificity

compared with CA125 [6]. HE4 is also found to be superior to CA125 as diagnostic marker of OC among patients with suspected gynecological disease, because it can differentiate among various ovarian masses [7,8], since it outperforms CA125 in identifying OC. Moreover, it may be useful as prognostic marker, since it was found that the risk for OC is significantly increased in patients with HE4 positive results [9]. Therefore, this marker is suggested to be an aid in the diagnosis and prognosis of OC [10,11].

In this study we investigated whether the

preoperative HE4 serum concentrations can predict the outcome of cytoreductive surgery in advanced OC.

Methods

Patients

Fifty patients aged between 25-81years (mean 52), with primary OC (FIGO III and IV stage) entered this prospective study. Patients with borderline tumors, those who had recurrent disease or ovarian metastases from other primary tumors, and those who previously had re-

Table 1. Median serum HE4 levels and clinical characteristics of patients (N=50)

Characteristics	N	%	Serum HE4* (pmol/L)	p value
FIGO stage				
III	43	86	628 (37-8.19)	0.81
IV	7	14	657 (42 -2.19)	
Grade				
1	3	6	318 (92-715)	0.621
2	8	16	591 (61- 5.89)	
3	39	78	668 (28-5.97)	
Histopathology				
Serous	34	68	681 (42-3.03)	0.73
Non-serous	16	32	632 (37-6.72)	
Lymph node status				
Lymphadenectomy not done	18	36	739 (31-7.18)	0.427
Negative	11	22	427 (69-2.01)	
Positive	21	42	656 (34-2.98)	
Residual disease (mm)				
No gross visible	11	22	341 (67-2.10)	0.341
1-10	14	28	584 (198-2.02)	
11-20	2	4	891 (641-890)	
>20	23	46	832(48-6.78)	
Optimal or suboptimal cytoreduction				
Optimal	22	44	478 (68-1.39)	0.011
Suboptimal	28	56	756(48-6.11)	
Ascites (mL)				
≤ 1,000	26	52	405(21-3.11)	0.023
> 1,000	24	48	713(65-7.74)	
Location of residual tumor in suboptimal cytoreduction (N=18)				
Pelvis	12	66.6	717 (39-2.76)	0.415
Omentum	7	38.8	815(164-7.74)	
Upper abdomen	2	11.1	1,178(477-2.82)	
Retroperitoneal node	1	5.5	766 (598-1.12)	
Other	1	5.5	851 (654-1.23)	

*median (range); HE4: human epididymis protein 4; FIGO: International Federation of Gynecology and Obstetrics

ceived neoadjuvant chemotherapy were excluded from the study. During a 2-year period (January 2014-January 2016), all patients had been operated at the University Gynecological Clinic "Narodni Front", Belgrade, Serbia. The tumor bulk, volume of ascites, lymph nodes status, optimal or suboptimal cytoreduction, and residual tumors, were determined intraoperatively. Residual disease was classified as no visible, and gross residues 1-10, 11-20 and ≥ 20 cm. Cytoreductive outcome was identified as optimal or suboptimal (threshold ≤ 1 cm).

Measurement of HE4 and CEA125

These two tumor markers were determined preoperatively. Serum samples for CA125 and HE4 analysis were obtained by venous puncture and centrifuged at 3000 g for 10 min. Serum concentrations of CA125 and HE4 were determined sera using chemiluminiscent microparticle immunoassay (CMIA) test (Abott, USA), and expressed as U/mL. The cut-off point for HE4 was 413pmol/L.

Statistics

Data were processed using SPSS version 20 statistical software. For statistical analysis, the chi-square test, Wilcoxon rank sum test, Mann-Whitney U test, Kruskal-Wallis analysis and Cox univariate logistic regression analysis (Backward-Wald method) were used, and p values < 0.05 were considered as statistically significant.

Results

All 50 patients had FIGO stage III (86%) or IV (14%) OC. Most tumors (78%) had histopathological grade III. Almost all patients (98%) underwent hysterectomy, 50 (100%) patients omentectomy, and in 10% resection of the gut was performed. Ascites was present in all patients. Optimal or suboptimal cytoreduction was achieved in 44% and 56% of the cases, respectively. In suboptimal cytoreduction, residual tumor was found in the pelvis in 12 out of 18 cases, in the omentum in 7 cases, and rarely in the upper abdomen, retroperitoneal nodes, or other places. In 69% of the cases lymphadenectomy was done, and nodal disease was positive in 42% of the patients (Table 1).

Mean preoperative values of HE4 in FIGO stages III and IV disease were 628 and 657pmol/L, respectively, the difference being not significant. The only significant differences were found between subgroups with optimal and suboptimal cytoreduction ($p=0.011$), and between subgroups with ≤ 1000 ml and > 1000 ml of ascites ($p=0.023$) (Table 1).

The relationship between tumor characteristics and the outcome of cytoreductive surgery in OC patients is shown in Table 2. Optimal debulking was achieved in patients with positive lymph nodes and ascites > 1000 ml, whose preoperative values of HE4 and CA125 were < 413 pmol/L and < 500 U/mL, respectively.

For analysis of preoperative clinical characteristics (age, volume of ascites, preoperative values of HE4 and CA125) influencing surgical cytoreduction, binary logistic regression was used. Significant predictor of optimal cytoreduction was HE4 concentration ≤ 413 pmol/L, while patients with HE4 values ≥ 413 pmol/L had lower chances for optimal debulking (Table 3).

Discussion

Our results, although found in a relatively small number of patients, indicated that optimal cytoreduction can be expected in patients whose preoperative values of HE4 and CA125 were < 413 pmol/L, and < 500 U/mL, respectively. Patients with higher preoperative concentrations of these two markers will probably undergo suboptimal cytoreduction.

Little is known about the preoperative CA125 value for predicting optimal cytoreduction. If CA125 preoperative concentrations are ≥ 500 U/ml, it is less probable that the residual tumor would be less than 1cm [12].

On the other hand, HE4 measurements seem to be superior to CA125 [13] not only in terms of diagnosis of OC [9,14], but also as predictors of whether optimal cytoreductive surgery could be undertaken [15-17].

In predicting the outcome of cytoreductive surgery, HE4 was found superior to CA125, when the serum concentrations of these two markers were measured preoperatively in the same group of patients [18,19]. In our study, 22 out of 28 patients with preoperative HE4 concentrations above 413pmol/L underwent suboptimal cytoreduction; at the same time, in 7 out of 9 patients whose preoperative concentrations were below 413pmol/L, the preoperative values of CA125 were > 500 U/ml. This indicates that preoperative values of these two biomarkers might improve the prediction for suboptimal cytoreduction. Moreover, binary logistic regression for HE4 values is the most important indicator for optimal cytoreduction.

It should be noted that preoperative HE4 values > 413 pmol/L does not mean that optimal cytoreduction is impossible. In our study, the pro-

Table 2. Relationship between clinical characteristics and cytoreductive outcomes

Characteristics	Optimal debulking*		Suboptimal debulking**		p value
	N	%	N	%	
FIGO stage					
III	20	44.4	25	55.6	0.421
IV	2	40	3	60	
Grade					
1	2	66.7	1	33.3	0.718
2	4	36.3	7	63.6	
3	17	47.2	19	52.7	
Histopathology					
Serous	15	62.5	9	37.5	0.062
Non-serous	10	38.4	16	61.6	
Preoperative HE4 (pmol/L)					
< 413	14	70	6	30	<0.001
≥ 413	8	26.6	22	73.3	
Preoperative CA125 (U/mL)					
< 500	11	61.1	7	38.9	0.021
≥ 500	12	37.5	20	62.5	
Lymph node status					
Lymphadenectomy not done	3	16.6	15	83.3	0.012
Negative	6	66.7	3	33.3	
Positive	14	60.8	9	39.2	
Ascites (mL)					
≤ 1,000	13	59.1	9	40.9	0.019
> 1,000	9	32.1	19	67.9	

*Optimal was identified using the threshold of ≤ 1cm residual disease; ** Suboptimal was with residual disease >1cm. FIGO: International Federation of Gynecology and Obstetrics, HE4: human epididymis protein 4

Table 3. Binary logistic regression analysis of factors influencing primary surgical cytoreduction outcomes

Variables	B	S.E.	Wald	Df	Sig.	Exp(B)	95%CI
Age	0.038	0.024	2.714	1	0.081	1.011	0.079-1.098
Preoperative HE4	1.521	0.318	8.751	1	0.021	4.921	1.311-12.814
Preoperative CA125	1.022	0.419	3.411	1	0.072	2.72	0.818-7.614
Constant	-2.812	1.417	3.598	1	0.071	0.049	

B: coefficient of regression, S.E.: standard error, df: degree of freedom, Sig.: significance, Exp(B): odds ratio, CI: confidence interval

portion of optimal cytoreduction in patients with HE4 concentrations more than 413pmol/L vs below 413pmol/L was 30%:70%, indicating that patients with lower HE4 values have better chance for maximal cytoreduction. According to the results of another study [20], patients with high preoperative HE4 concentrations are candidates for neoadjuvant chemotherapy followed by surgery [21].

In conclusion, all clinical parameters (age, imaging diagnostics, complications of the disease, and tumor markers) must be integrated in order to

preoperatively assess the chances for optimal cytoreduction in OC patients. Preoperative HE4 measurements may predict the success of optimal cytoreduction. In order to estimate the true value of HE4 as predictive factor for achieving optimal cytoreduction, additional research with larger OC populations is warranted.

Conflict of interests

The authors declare no conflict of interests.

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