The Role of HE4 in Ovarian Cancer Follow-up: A Review

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The authors declare no conflicts of interest.

Abstract

Objective: The aim of this review was to analyze the state of the art about HE4 and follow-up in patients treated for ovarian cancer.

Methods: A literature search was conducted in the MEDLINE database using the key words "HE4" and "ovarian cancer" and "recurrence" or "relapse" or "follow up."

Results: Seven of 28 clinical studies were selected. Four studies were prospective, and all of them were based on a small number of patients (8–73 women). A failure of HE4 levels to normalize at completion of standard therapy may indicate a poor prognosis, thus suggesting the need of a closer follow-up. Moreover, HE4 showed better sensibility and specificity in the diagnosis of ovarian cancer recurrence with respect to CA-125, being also an earlier indicator of the relapse with a lead time of 5 to 8 months. HE4 showed a better performance in this setting if performed in association with other markers (CA-125, CA-72.4). HE4 seems to be an independent predictive factor for the surgical outcome at secondary cytoreductive surgery and to maintain its prognostic role even after the recurrence.

Conclusions: These preliminary data start to suggest a superiority of HE4 over CA-125 in the detection of ovarian cancer recurrence. Moreover, the prognostic role of HE4 could help clinicians to personalize the follow-up program, whereas its predictive role could be useful to plan the treatment of the relapse. The role of HE4 in ovarian cancer follow-up deserves to be further investigated in prospective randomized multicentric studies.

Ovarian cancer (OC) is the second most common gynecologic cancer and the leading cause of death from gynecologic malignancy among women in industrialized countries.1 The global incidence in both developed and developing countries can be estimated as 165,000 new cases per year.2 A heavy difference in prognosis exists between the early-stage disease (International Federation of Gynecology and Obstetrics [FIGO] I-II) and the advanced stages (FIGO III-IV).3 Unfortunately, at present, we do not have an effective screening strategy for this malignancy; most (>80%) of the cases are diagnosed as advanced-stage disease, and this explains the high mortality rate.4

These aggressive features of the OC encouraged in recent years a big effort in order to find new

strategies for early diagnosis of OC. These studies focused mainly on new markers and diagnostic algorithms.5

Among new markers, HE4 is one of the most promising.6 It is a protein initially identified in the epithelium of the distal epididymis and may be involved in sperm maturation; it is also called WFDC2 because of its molecular structure, containing 2 whey acid protein domains and a 4-disulfide-bond core with 8 cysteine residues. Further studies demonstrated the presence of HE4 in the female genitourinary tract, the respiratory tract, the renal epithelium, and the salivary ducts, whereas it is absent in the gastrointestinal tract, liver, pancreas, spleen, lymph nodes, mammary gland, and nervous system. Despite its wide distribution, it is overexpressed only in pathological tissue, and it has demonstrated good sensibility and specificity in detecting OC, overcoming the traditional role of CA-125.7

Despite an aggressive upfront treatment strategy (surgery plus chemotherapy), leading to clinical remission in more than 80% of patients, the relapse-free survival varies from 95.8% (for early FIGO stages) to 33.6% (for advanced stages) at 2 years.6

At present, periodical evaluation of CA-125 combined with physical examination is the recommended strategy for OC follow-up, typically every 3 to 4 months in the first 1 to 2 years after primary treatment and then every 6 months until the fifth year.8–10 Five years' overall survival rate, however, is 49.7% (ranging from 83%–89% in stage I OC to 18% in stage IV).11 New markers should be tested in the follow-up of patients with OC to improve the surveillance program performance: the challenge is to try to anticipate the diagnosis of OC recurrence and to translate this early diagnosis of relapse in a survival improvement.

The aim of this review was to examine the state of art about HE4 and follow-up of OC through a complete literature search.

MATERIALS AND METHODS

A literature search was conducted in the MEDLINE database using the key words "HE4" and "ovarian cancer" and "recurrence" or "HE4" and "ovarian cancer" and "relapse" or "HE4" and "ovarian cancer" and "follow up." Then, a ClinicalTrials.gov search for "ovarian cancer follow-up and HE4" was carried out.

RESULTS

Twenty-eight articles were found from 2005 to 2014. Among these articles, 7 clinical studies were selected (Table 1),1,3,4,6,12–14 excluding the reviews and the articles showing poor consistency with our topic. The ClinicalTrials.gov search revealed a French trial titled "Determination of the prognostic and predictive value of the new marker HE4 in metastatic OC monitoring"; this trial is still recruiting, and no data have been published yet.

The first study to analyze the role of HE4 in OC follow-up was published by Havrilesky et al 4 in 2008: they analyzed the utility of a combination of multiple markers in differential diagnosis of benign and neoplastic pelvic masses at the first diagnosis, and then the application of a subset of these markers in the follow-up. Monitoring 27 patients with recurrent OC, they found 100% sensitivity for HE4, MMP7, and glycodelin combination, and 96% sensitivity using CA-125 alone. At least one of the markers from the panel showed increased levels 6 to 69 weeks before CA-125 rise and before clinical signs of relapse in 52% of the patients. In 41% of women with recurrent OC, CA-125 rose simultaneously to the biomarker panel, and in 4% in advance of it.

Anastasi et al 6 included 8 patients in a follow-up study based on the availability of serum samples at diagnosis of OC and every 4 months after surgery; among them, 20 months after debulking surgery, 5 women showed a rise in the levels of the tumor markers (HE4 and CA-125). In these patients, the rise of HE4 always preceded the rise of CA-125 by 5 to 8 months and coincided with

the recurrence of the disease, as confirmed by instrumental examination or by the death of 3 patients.

In 2012, Schummer et al 12 compared the effectiveness of CA-125, HE4, mesothelin, and MMP7 in OC follow-up. The study involved 23 patients: 20 women developed a relapse of OC with a median progression-free-interval of 18 months (range, 9–48 months). Among them, 3 showed a rise of CA-125 alone, 1 was detected first by CA-125, 5 were revealed only by HE4, 2 were detected first by HE4 and then by CA-125 rise, 6 were simultaneously diagnosed by HE4 and CA-125; in 3 cases of recurrence, there was no markers' elevation. HE4 displayed advantages over CA-125 in predicting recurrence, confirming a better lead time than for CA-125 and proving to be useful in cases without CA-125 elevation too. Authors suggest that HE4 may be more sensitive than imaging in confirming elevated CA-125 levels, with several advantages such as being a cheaper examination and lacking of ionizing radiations. HE4 could be used alongside CA-125 to identify patients with persistent disease not detected by physical examination or computed tomography (CT) imaging after primary treatment, in order to identify a high-risk group who could potentially benefit from additional treatment or more intensive monitoring.

Granato et al 1 investigated in 2012 the role of CA-125, HE4, and CA-72.4 at the diagnosis of OC in 39 patients and throughout the follow-up in 20 of them (6–48 months of follow-up). A statistically significant difference was observed between the elevation of HE4 and CA72.4 over that observed for CA-125 at the diagnosis of disease recurrence. Authors concluded that the combination of HE4 and CA-72.4 performs better than CA-125 alone and better than other markers' combination and reveals a positivity in more than 75% of the patients at OC relapse.

Plotti et al 3 published the first prospective controlled study in the literature evaluating the sensitivity and specificity of HE4 and CA-125 in detecting recurrent OC. They recruited 34 patients with suspicious recurrent OC and 34 women with benign adnexal pathology. CA-125 (normal value is considered <35 U/mL) sensitivity and specificity in detecting recurrent OC were 35% and 59%, respectively. HE4 sensitivity and specificity (with cutoff 70 pmol/L) were 73% and 100%, respectively.

Combining CA-125 and HE4 at cutoff of 70 pmol/L, the sensitivity to detect recurrent OC is 76% with a specificity of 100%. The authors conclude that the combination of CA-125 and HE4 at cutoff of 70 pmol/L improves the overall sensitivity and specificity of CA-125 alone, suggesting a useful application of HE4 in strategies for surveillance of OC recurrence. They also underline the importance of further studies to determine the correlation between HE4 and the amount of recurrent disease volume.

Manganaro 13 retrospectively enrolled 21 patients with FIGO stage III/IV epithelial OC who underwent surgery and adjuvant chemotherapy. From each patient, 3 serum samples were collected at time interval I (1–3 months from surgery), II (4–6 months from surgery), III (7–10 months from surgery). On these samples, HE4 and CA-125 were determined by enzyme immunoassay and immunoradiometric assay. At the same time, contrast-enhanced CT was also performed at 6-month intervals. During the follow-up study, 9 patients had recurrent disease, and 12 had stable disease. In patients with relapsed OC, increased values of HE4 were observed in 22%, 78%, and 89% of the samples, respectively, within the time intervals I, II, III. Positivity for CA-125 was revealed later (at time interval III) and only in 44% of patients. In contrast, for patients with stable disease, only CA-125 showed high values. These data lead authors to conclude that HE4 could be useful as an early biomarker for recurrence of OC. Moreover, data provided by contrast-enhanced CT showed significant correlation with biochemical results, suggesting the usefulness of their combined employment.

Braicu et al 14 prospectively enrolled 73 patients with OC first recurrence: they showed that HE4 is an independent predictive factor for maximal tumor reduction in terms of macroscopic tumor

clearance (at an HE4 cutoff value of 250 pMk, a sensitivity of 52% and a specificity of 93.8% were reached in predicting total macroscopic tumor clearance, P = 0.001; 95% confidence interval [CI], 0.601–0.861). No significant association between HE4 expression and response to platinum-based chemotherapy could be detected instead. Moreover, plasma HE4 concentration was an independent prognostic factor for overall survival after the relapse (P < 0.001; hazard ratio, 18.77; 95% CI, 4.68–75.25).

DISCUSSION

Despite the high recurrence rate of OC, surveillance strategies are not standardized yet. This leads to a variety of follow-up strategies, sharing CA-125 periodic evaluation.

Recent advances in biomarkers research brought HE4 and other new markers to clinicians' attention. After being tested for differential diagnosis between benign and malignant adnexal masses at first diagnosis, alone or in combination (eg, ROMA, Risk of Ovarian Malignancy Algorithm, combining CA-125 and HE4 values 15), they will be probably tested as screening instruments. Moreover, FDA has recently approved the use of HE4 in OC follow-up together with CA-125, even if few studies are available to date about its use in this setting 1,3,4,6,12–14 (Table 1). Only 1 prospective controlled study has been published,3 and all of these studies analyzed a small number of women (8–73).

Among the most interesting points from these articles, there is a possible prognostic role of HE4. A failure of HE4 levels to normalize at completion of primary therapy may indicate a poor prognosis,12 thus suggesting the need of a closer follow-up in these women. Even after the relapse, HE4 seems to maintain its prognostic role.14 HE4 was shown then as an earlier indicator of recurrence of OC with respect to CA-125, with a lead time of 5 to 8 months.6 Moreover, the sensibility and specificity of HE4, alone or in association with other markers (CA-125, CA-72.4), seem to be higher in the diagnosis of the OC relapse with respect to CA-125 alone, as shown by Plotti et al.3 Larger prospective, controlled, and randomized studies are needed to confirm these preliminary data.

The other side of the question is whether the patient is advantaged by an earlier detection of the recurrent disease, in terms of overall survival, disease-free survival, and quality of life.

Early detection and treatment of cancer in general or its recurrence are usually associated with better outcomes for patient, this being the rationale behind screening programs and follow-up strategies.

In OC follow-up, periodical CA-125 evaluation can detect recurrence of cancer about 5 months before clinical signs or symptoms.16 At the same time, we have to remind that treatments of relapsing OC are rarely curative and have heavy adverse effects, and elevation of CA-125 is often cause of anxiety in patients undergoing follow-up.

The main study that tried to clarify the role of CA-125 in OC follow-up was EORTC (European Organisation for Research and Treatment of Cancer) 55955 trial,16 a randomized study comparing early versus delayed treatment in women with relapsed OC. Five hundred twenty-nine women were assigned to treatment, on the basis of increased levels of CA-125: 265 to early treatment and 264 to delayed treatment. Patients in the early treatment group were treated within 28 days from the detection of an increased CA-125 value. Patients in the delayed treatment group were treated only at clinical or symptomatic relapse. Women assigned to early treatment started chemotherapy 4.8 months earlier than those allocated to the delayed treatment. With a median follow-up of 56.9 months, there was no evidence of a difference in overall survival between the 2 groups. In particular, the results provided no evidence of an improved overall survival or a better quality of life in the early treatment group. The authors' explanation for these findings was that the lead time between CA-125 rise and the clinical recurrence could be too short for chemotherapy to give a beneficial effect. In this setting, HE4 employment could be a valid strategy to anticipate the

diagnosis of the relapse as much as to get a beneficial effect from second-line chemotherapy. Moreover, earlier detection of the relapse could potentially lead to more patients being diagnosed with completely resectable recurrent disease and thus potentially to a longer survival. However, the efficacy in terms of survival of early surgical treatment of OC relapse has yet to be demonstrated. In a retrospective study on 74 patients who underwent secondary cytoreductive surgery for recurrent OC, Fleming et al 17 found that patients who achieved an optimal secondary cytoreduction were those who underwent surgical treatment of the relapse after a shorter interval time from CA-125 elevation, in comparison to patients achieving suboptimal secondary cytoreduction (5.3 vs 16.4 weeks; hazard ratio, 1.03; 95% CI, 1.01–1.06; P = 0.04). In other words, each week delay after CA-125 elevation correlated with a 3% increased chance of suboptimal resection at secondary cytoreductive surgery. Interestingly, whereas in EORTC 55955 trial CA-125 elevation was defined as elevation to twice the upper limit of standard CA-125 value (>=75 U/mL), Fleming et al 17 defined CA-125 elevation as twice the nadir value, based on the study by Santillan et al,18 which demonstrated that CA-125 elevations, even within the reference range, could predict disease recurrence with an even better lead time. However, published randomized controlled trials demonstrating a survival advantage with secondary cytoreductive surgery are still lacking (the DESKTOP 3 study is still ongoing).

Rustin and colleagues'16 trial was criticized by Morris and Monk 19 because the interpretation of its results did not consider the problem of platinum sensitivity: platinum-free interval was imbalanced because some patients started an early treatment, and others were delayed. Furthermore, contemporary therapies such as bevacizumab and pegylated liposomal doxorubicin plus carboplatin were not available to most of the trial participants.

A recent Cochrane Review 20 analyzed the effectiveness and safety of optimal secondary cytoreduction for women with platinum-sensitive recurrent epithelial OC, in 9 nonrandomized studies. Meta-analyses and single-study analyses showed a statistically significant prognostic difference between women treated with complete secondary cytoreduction and those with residual disease. Despite the absence of adequate randomized controlled trials, the authors conclude that in women with platinum-sensitive recurrent OC, the ability to achieve a complete secondary cytoreduction seems to be associated with significant improvement in overall survival. However, it is not clear whether this is solely due to surgical effect or due to tumor biology. In the absence of high-level evidence, the authors underline that the risks of major surgery have to be carefully balanced against potential benefits on a case-by-case basis.

In summary, in the first published articles, HE4 has demonstrated a potential role in terms of diagnostic accuracy and lead time in the follow-up of OC. However, the utility of an early diagnosis of the OC relapse is still an open question, because at present evidence of survival advantages from earlier chemotherapeutic treatment is still lacking, and evidence of survival advantage from earlier secondary cytoreduction is still weak. Moreover, elevation of markers in the follow-up often has detrimental effects on patients' quality of life, because of the charge of anxiety that it brings. An answer to our questions may come from ongoing studies on surgical management of recurrent OC, from future studies analyzing quality of life of OC patients during their follow-up and from future randomized trials about HE4 and follow-up.

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