Systematic Review

Role of human epididymis protein 4 (HE4) as predictor of response to platinum based chemotherapy: a systematic review of literature

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Summary

Objective: Although epithelial ovarian cancer (EOC) treatment has greatly improved over the last three decades, a fraction of patients (40-60%) with advanced-stage disease fail to completely respond to standard therapy, because of chemo-resistance to platinum. For this reason, new predictive and monitoring tools were studied to identify platinum resistant EOC patients, with the purpose of improving and personalizing the treatment. In this review, we aim to discuss the latest evidence reported in the literature about the use of Human Epididymis 4 (HE4) to predict platinum resistance among EOC patients. *Methods*: A comprehensive search of the literature was conducted using the terms "HE4 epithelial ovarian cancer" and "human epididymis protein 4 epithelial ovarian cancer" and they were combined with the terms "chemotherapy", "platinum" and "response". *Results*: The search identified twelve papers, from January 1952 to December 2019, in line with eligibility criteria for this systematic review, all of which demonstrated good performance of HE4 in predicting platinum sensitivity or resistance. *Conclusions*: All the available studies present limited and non-homogeneous data, therefore more studies are needed to validate and reinforce the role of HE4 in predicting the response to platinum based chemotherapy among ovarian cancer patients.

Key words: Ovarian cancer; HE4; Chemotherapy; Platinum; Markers.

Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death in gynecological cancers. Although the majority of patients achieve primary complete remission, only approximately 10%-15% of patients with advanced EOC reach extended, several-year-long disease free periods [1].

Such a high recurrence rate could be mainly attributed to either platinum resistance or incomplete primary cytoreduction [2].

Approximately 20% of patients receiving the treatment for the first time are resistant to platinum therapy and will therefore experience a lack of response to the treatment, experience disease progression during chemotherapy, or will present an early recurrence within 6 months of the chemotherapy ending [3, 4].

Based on the time from the end of therapy to relapse, documented according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, patients receiving platinum chemotherapy can be stratified into *platinum sensitive*, *intermediate* or *resistant*. This timeframe is referred to as the *platinum-free interval*. The *platinum-free interval* seems to be more accurate than the *progression free interval* which also includes the time to first-line surgery.

According to Gynecologic Cancer InterGroup (GCIG), timelines for platinum response classification have been defined as follows:

1) Platinum-sensitive: progression-free interval since last line of platinum of more than 12 months

2) Platinum-intermediate: progression-free interval since last line of platinum of 6-12 months and

3) Platinum-resistant: progression-free interval since last line of platinum of less than 6 months [5].

Platinum-sensitive EOC expresses a median survival of 2 years, ranging from 3 months to over 10 years. Platinum-resistant EOC, instead, has a median survival of 9-12 months and less than 15% of patients respond to subsequent chemotherapy [6].

According to these categories, the best second line chemotherapy treatments in case of resistance and prognosis have been defined for each group of patients.

For this reason, assessing platinum sensitivity before the initiation of chemotherapy would potentially have a role in reducing unnecessary toxicity and would have a strong prognostic value, in terms of saving time before switching to a second line treatment.

Table 1. — *PICO (Population Intervention Comparator Outcome) criteria.*

Parameter	Inclusion criteria
Population	Epithelial ovarian cancer underwent platinum chemotherapy
Intervention	Measuring HE4 serum levels before, during or/and after treatment
Comparator	No comparator
Outcome	Assessing the role of HE4 in detecting response to platinum therapy

The pursuit of biomarkers aimed at predicting platinum therapy response is therefore a major concern [7]. Interestingly, several case series have shown a potential role of Human Epididymis Protein 4 (HE4) marker. HE4 was first identified in the epithelium of the epididymis as a protease inhibitor involved in sperm maturation. It was also later found to be overexpressed in EOC but not in normal ovarian tissue [8, 9].

To date, all the available data from the published literature is still controversial, and some studies about HE4 are still ongoing.

The aim of the present work is to systematically review the evidence reported in the literature on the use of HE4 as a predictor of platinum chemotherapy response (Table 1).

Materials and Methods

We searched MEDLINE (PubMed), EMBASE, Cochrane Central Register of Controlled Trials, IBECS, BIOSIS, Web of Science, SCOPUS and Grey literature (Google Scholar; British Library). We used the terms "HE4 epithelial ovarian cancer" or "human epididymis protein 4 epithelial ovarian cancer" and they were combined with the terms "chemotherapy" or "platinum" or "response". The reference lists of all available primary studies were reviewed to identify additional relevant citations.

A collection of eligibility criteria was used to choose a selection of papers from the literature. Inclusion criteria for enrollment were as follows: all papers written in English, clinical trials conducted on humans *in vivo* or *in vitro* and original articles with available abstract. Reasons for exclusion were as follows: studies not available in English, studies concerning other kinds of tumours or surgical treatment, review articles and articles without abstract or not yet published.

Abstracts/titles identified from the search were screened by two investigators (M.B. and G.S.). After a primary examination, the retrieved studies were further evaluated. Disagreements about the inclusion or exclusion of studies were resolved by a third reviewer (F.P.).

Results

The search identified a total of 111 original papers from January 1952 to December 2019. Twenty-eight articles concerning the role of the HE4 marker in predicting chemo sensitivity were considered potentially relevant after initial evaluation. Among these, 16 full-text articles were excluded because they didn't actually investigate the role of HE4 in detecting platinum response. Twelve primary studies met the criteria for inclusion and were finally analysed, with a total of 802 patients (Figure 1).

We divided all the included studies into two different categories: "*in vivo* clinical studies" (Table 2) and "*in vitro* studies" (Table 3).

In vivo clinical studies

An early demonstration of HE4 as a promising candidate for future studies on the response to chemotherapy in EOC and demonstrating a higher predictive value than CA125 arose as a result of a study by Steffensen *et al.* [10] in 2012. Steffensen *et al.* analysed serum collected preoperatively and during first-line chemotherapy from 137 patients with newly diagnosed serous EOC. According to the validation set results, HE4 was able to predict platinum resistance with a 71.7% specificity, 64.5% sensitivity, 57.1% positive predictive value (PPV) and 77.6% negative predictive value (NPV) for preoperative levels. The analysis of the dynamic changes of several biomarkers' serum levels after therapy showed that after the second cycle, CA125 was reduced by 60% from baseline pre-chemotherapy level and HE4 was reduced to approximately 50%.

Interestingly, Hamed *et al.* [11], showed that prechemotherapy HE4 serum levels were significantly higher in patients with EOC (median 237.2 pmol/L) than in other gynecological conditions (66.1 pmol/L; $p = 0.001$). Additionally, after six cycles of standard chemotherapy treatment, consisting of carboplatinum plus paclitaxel as first-line, the normalization of HE4 blood levels from a main value of 237.2 (34.3-4090) pmol/L to 91.9 (45.4-180) pmol/L was able to predict the response to chemotherapy with a higher sensitivity (90% *vs.* 83.3%) and a higher specificity (95% *vs.* 85%) than CA125 (PPV 93.1% *vs.* 80.7%, NPV 92.7% *vs.* 87.2%).

In 2014, Angioli *et al.* [12] showed that patients who were non-responsive to treatment could already be identified after three cycles of chemotherapy. They found an 83% sensitivity and 87% specificity in predicting platinum therapy response at the third cycle of chemotherapy. The HE4 serum levels were determined in 76 patients at the first, third, and sixth cycles of chemotherapy, considering a threshold for HE4 normal values of less than 70 pmol/L. After six months of follow-up, 40 patients were classified as platinum-sensitive/intermediate and 36 as platinum resistant. At the third chemotherapy cycle, in platinum-resistant patients, HE4 levels were > 70 pmol/L in 36 of 36 cases (sensitivity 100 %, specificity 95 %). Conversely, in

Table 2. — *In vivo clinical studies.*

Date	References	Study design	N of Patients	HE4 evaluationcriteria	Spec	Sens	PPV	NPV	Others	Comments
2012 Nov	[10]	Prosp	137	Preoperative HE4 > 502 pmol/L can predict chemoresistance	HE 4 71.7%	HE4 64.5%	HE4 57.1%	HE4 77.6%		Dynamic analysis of HE4 values, that decrease already after 1-2 cycles of chemotherapy
				Preoperative HE4 > 502 plus CA125 > 216 UI/mL can predict chemoresistance	HE4 + CA125 79.2%	HE4 + CA125 54.8%	HE4 + CA125 60.7%	HE4 + CA125 76%		
2013 Jan	[11]	Retrosp	30	HE4 values < 91,9 pmol/L after 6 cycles of standard chemotherapy	HE4 90%	HE4 95%	HE4 93.1%	HE4 92.7%		Normalization of HE4 blood levels, from a main value of 237,2 (34,3-4090) pmol/L to 91,9
				can predict chemosensitivity	HE4 + CA125 96.7%	HE4 + CA125 80%	HE4 + CA125 97%	HE4 + CA125 80%		(45,4-180) pmol/L in 27 platinum sensitive patients after 6 cycles of chemotherapy can predict platinum sensitivity.
2014 Jan	[12]	Retrosp	76	HE4 reduction of almost 47 % at third chemotherapy cycle can predict chemosensitivity	83%	87%	86%	85%		At the third chemotherapy cycle: In platinum-resistant patients HE4 levels were > 70 pmol/L in 36 of 36 cases (sensitivity 100 %, specificity 95 %.)
										In platinum-sensitive/intermediate patients HE4 levels were < 70 pmol/L in 34 of 40 cases (sensitivity 100 %, specificity 95 %).
2014	[13]	Retrosp	56	Preoperative HE4 < 254.42 pmol/L (cut-off 218.43) can predict chemosensitivity	91.30%	86.60%	92.90%	84%	AUC 0, 949	Serum HE4 as marker of chemosensibility, showing a significant difference in the values of HE4 in patient group sensitive (254, 42 pmol/L)
				Preoperative HE4 > 566.22 pmol/L can predict chemoresistance						and resistant to chemotherapy (566,22 pmol/L), $p = 0, 045$

Table 2. — *Continued.*

Date References	Study design	N of Patients	HE4 evaluationcriteria	Spec	Sens	PPV	NPV	Others	Comments
2016 [14] April	Prosp	170	Preoperative HE4 >1000 pmol/L can predict chemoresistance	N.A.	N.A.	N.A.	N.A.	($p < 0.001$)	The cut-off of > 1000 pmol/L was defined dividing patients into tertiles
2016 [15] Sep	Retrosp	30	Preoperative HE4 < 115 pmol/L can predict chemosensitivity	HE4 92.9%	HE4 68.7%	HE4 72.2%	HE4 91.7%	DOR 28.6	HE4 showed a 92.9% sensitivity, a 68.7% specificity, a 72.2 % PPV and a 91.7% NPV in predicting platinum response. Combining CA125 + HE4, the same values were obtained.
			Preoperative HE4 < 115 pmol/L + CA125 < 35 can predict chemosensitivity	HE4 + CA125 92.9%	HE4 + CA125 68.7%	HE4 + CA125 72.2%	HE4 + CA125 91.7%		
2018 [16] March	Prosp	90	Preoperative HE4 < 239 pmol/L can predict chemosensitivity Preoperative HE4 > 455 pmol/L can predict chemoresistance	N.A.	N.A.	N.A.	N.A.	AUC 0.644 ($p = 0, 0351$) in detecting platinum sensitive patients. AUC 0.627 for patients after PDS and AUC 0.53 for patients treated with NACT.	The normalization of HE4 marker levels after the end of treatment and a reduction of HE4 concentrations by 50% before interval cytoreductive surgery are strong predictive factors

Table 3. — *In vitro studies.*

References	Patients	Results
[17]	89	HE4 overexpressing clones are less sensitive to cisplatin and paclitaxel treatment *in vitro* compared with controls.
[18]	-	The percentage of cells in the sub-G1 phase was decreased in the group treated with carboplatin combined with HE4, compared with the group treated with carboplatin alone ($p < 0.01$)
[19]	92	High expressions of Lewis y antigen, CD44, HE4, integrin $\alpha 5$ and $\beta 1$, and FIGO Stage III-IV, were independent risk factors for chemotherapeutic resistant reaction (all $p < 0.05$)
[20]	-	Survival was higher in HE4 knocked down cells group (92.2% *vs.* 81.9%, $p = 0.005$) than in HE4 overexpressing clones
[21]	-	HE4 mRNA was highly expressed in OVCAR-3 cells

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platinum-sensitive/intermediate patients, HE4 levels were < 70 pmol/L in 34 of 40 cases (sensitivity 100 %, specificity 95 %). A threshold for a mean reduction of almost 47 % in HE4 levels between the first and third chemotherapy cycles was shown to be significantly related to the platinum response reaching the 83% sensitivity, 87% specificity, 86% PPV and 85% NPV.

In the same year Chudecka-Glaz *et al.* [13] studied the role of HE4, CA125, YKL 40, Bcl-2 and Cathepsin L in predicting optimal debulking surgery and response to chemotherapy in 56 patients. HE4 was measured preoperatively, setting the cut-off at 218.43 pmol/L. A preoperative serum HE4 median level of 254.42 pmol/L has been considered a strong indicator of chemosensibility, with an 86.6% sensitivity, 91.3 % specificity, 92.9% PPV and 84% NPV ($p = 0,045$). Similarly, a preoperative serum HE4 median level of 566.22pmol/L has been considered a strong indicator of chemoresistance, again with an 86.6% sensitivity, 91.3 % specificity, 92.9% PPV and 84% NPV ($p = 0,045$).

Two years later, in 2016, Aarenstrup *et al.* [14] performed a prospective study by enrolling 170 patients affected by EOC and collecting serum samples (2 weeks before surgery) and tissue to determine HE4 levels. They gathered preoperative HE4 serum levels into tertiles-low (< 250 pmol/L), intermediate (250-1000 pmol/L), or high serum levels (> 1000 pmol/L) - and showed that preoperative HE4 serum levels > 1000 pmol/L (in the third tertile) was significantly correlated to chemo-resistance in univariate analysis ($p < 0.001$).

In the same year, in a retrospective study aimed at predicting the optimal cytoreduction and the predictive role of HE4, Pelissier *et al.* [15] (n = 117) measured HE4 and CA125 levels at the following stages: before starting chemotherapy, before Interval Debulking Surgery (IDS), at the third cycle of chemotherapy and at the relapse. They found that HE4 serum level < 115 pmol/L before chemotherapy and IDS showed a 92.9% sensitivity, 68.7% specificity, 72.2 % PPV and 91.7% NPV in predicting chemo-sensitivity, and the same accuracy was reached combining s-HE4 level < 115 pmol/L and CA125 serum levels < 35 UI/mL.

In March 2018 Chudecka-Glaz *et al.* [16] prospectively analyzed 90 EOC patients, measuring HE4 levels after surgical treatment, after the third course of adjuvant chemotherapy, before interval cytoreductive surgery and at the end of six courses of chemotherapy. The authors concluded that a preoperative HE4 median value of 239 pmol/L was predictive of platinum sensitivity, while a preoperative HE4 median value of 455 pmol/L was predictive of platinum resistance, AUC = 0.644 ($p = 0.035$).

In vitro studies

In parallel to clinical works, several *in vitro* studies were performed to assess potential molecular differences in EOC cells in respect to the overexpression of HE4 and related chemo-resistance.

In 2014 Moore *et al.* [17] developed stable cancer cell clones derived from ovarian epithelial adenocarcinoma and resistant to platinum based chemotherapeutics, to study the biological role of HE4 overexpression in EOC tumorigenesis and chemoresistance. In particular, the cell lines HE4 overexpressed SKOV-3 (HE4C1, HE4C7) or OVCAR-8 (HE4C5). They demonstrated that HE4C1 and HE4C7 tumour cell lines were less sensitive to cisplatin and paclitaxel treatment *in vitro* when compared with controls. Similarly, HE4 overexpressing OVCAR-8 HE4C5 clones showed increased resistance to cisplatin. In order to determine a potential role of HE4 in the response to standard therapeutics *in vivo*, mice were randomized to be xenografted with SKOV-3 HE4C1 or SKOV-3 and treated with cisplatin (10 mg/kg) for 14 days. Not only did cisplatin resistance arise in the mutated cell line recipients, but surprisingly, cisplatin seemed to induce enhanced tumour growth in the same group.

In 2015 Wang *et al.* [18] tested the HE4 capability to attenuate platinum-induced apoptosis by treating SKOV-3 cells with a combination of carboplatin and HE4 protein or with carboplatin alone. In particular, the viability of cells exposed to carboplatin (0-400 μg/mL) and the growth inhibitory effects of carboplatin on SKOV-3 cells were assessed. When compared with the group treated with carboplatin alone ($p < 0.01$), the results showed that the percentage of cells in the sub G1 phase was decreased in the group treated with carboplatin combined with HE4. Therefore, the authors concluded that HE4 protein attenuated carboplatin induced apoptosis.

In 2015 Zhu *et al.* [19] analyzed 92 patients, 36 resistant and 56 sensitive to platinum chemotherapy, with the aim of investigating the roles of Lewis y antigen and the markers associated with cell-adhesion-mediated drug resistance (CAM-DR). Results from a multivariate analysis demonstrated that high expressions of Lewis y antigen, CD44, HE4, integrin α5 and β1, and FIGO Stage III-IV, were independent risk factors for chemotherapeutic resistant reaction (all $p < 0.05$).

In 2016 Ribeiro *et al.* [20] studied the correlation between HE4 overexpression and inhibition of platinum inducted apoptosis. They examined SKOV3 and OVCAR8 EOC cells, establishing previously null vector and HE4 overexpressing stable cell lines. They found that HE4 overexpressing clones were more resistant to cisplatin and paclitaxel treatment for several reasons. Firstly, the authors studied the already mentioned mechanism of apoptosis. They showed that in HE4, overexpressing clones cisplatin, even in high doses, was not able to cleave poly-ADP ribose polymerase (PARP) or upregulate EGR1 (a MAPK-regulated gene involved in promoting apoptosis), as usually happens during platinum based chemotherapy. Then they knocked down HE4 in SKOV3 cells control group and measured survival in both HE4 overexpressing cells and in the control group, in response to cisplatin treatment. They proved that survival was higher in the HE4 knocked down cells group (92.2% *vs.* 81.9%, $p = 0.005$) than in HE4 overexpressing clones, and that knock down of HE4 partially reversed
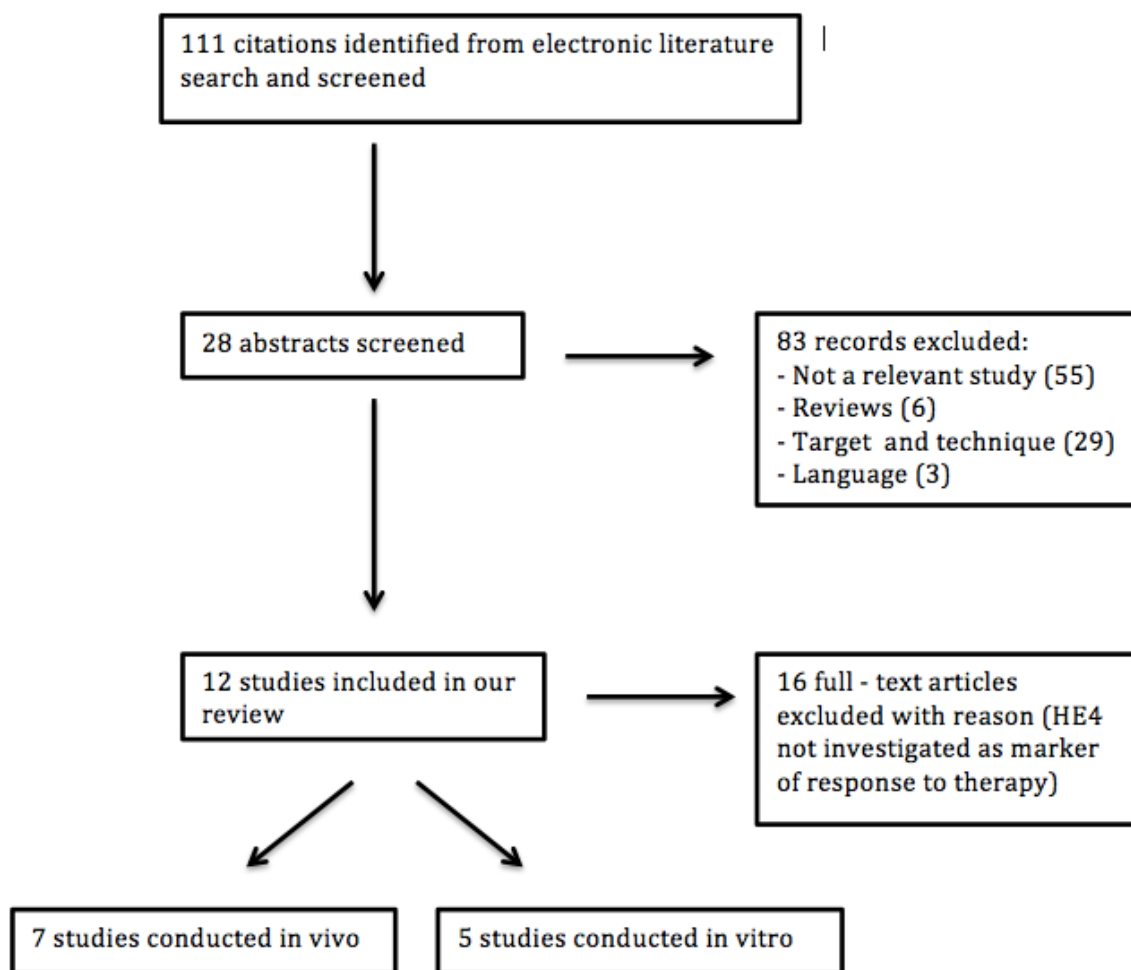
Figure 1. — PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

chemoresistance.

In the same year, Lee *et al.* [21] analyzed four EOC cell lines for expression level of HE4 mRNA by qRT-PCR; HE4 mRNA was found to be highly expressed in OVCAR-3 cells. A significantly higher proliferation in OVCAR-3 cells in comparison to the control group was seen. Consistently, HE4 overexpression decreased chemo-sensitivity and this could be related to enhanced EGF-induced activation of AKT and Erk.

Discussion

To date, EOC remains the main cause of death among gynecological tumours. Its treatment has greatly improved over the last three decades, with an increase in the five year survival from 38% to 46% [22]. This relates to the more consistent use of cytoreductive surgery and the standard use of platinum-based chemotherapy protocols, followed by anti-angiogenic monoclonal antibodies or Poly ADP Ribose Polymerase (PARP) inhibitors, as maintenance therapy [23, 24]. However, despite the aforementioned advances in therapeutic strategies, 40-60% of patients fail to completely respond to standard therapy, because of chemoresistance to platinum. This leads to a higher rate of tumours relapsing within less than 12 months of the treatment ending. The search for a tool to identify patients with platinum resistant EOC, with the purpose of improving and personalising the treatment is therefore a major concern worldwide. Currently, six cycles of chemotherapy are administered, and sensitivity assessed only after the last cycle. In the last years, however, increasing evidence suggests a potential role of novel serum biomarkers in predicting chemosensitivity. HE4 is a promising molecule in this context [25]. It is a relatively novel marker for ovarian carcinoma, which demonstrated good sensitivity and specificity in the diagnosis of EOC, overcoming the traditional role of Carbohydrate Antigen 125 (CA-125) [26, 27]. Interestingly, several papers focused on HE4 potential use, alone or in association with CA-125, in detecting EOC recurrence and found that it could have a better sensitivity than CA125 (91.3% *vs.* 52.2%, *p* value = 0.022) in predicting recurrent EOC [28]. Moreover, several authors analysed the role of HE4 as a prognostic factor. It was measured at the time of diagnosis and subsequently during treatments and follow-

up, and was compared to FIGO stage, residual tumour and other well-known prognostic factors, proving to have a significant prognostic value itself [29, 30]. On the other hand, the role of HE4 in predicting response to platinum therapies is still unclear.

Our review of the literature suggests that HE4 is an earlier indicator of chemo-sensitivity or chemo-resistance than CA125.

Different criteria were adopted to assess the HE4 predictive role, measuring its values at different time points, from the diagnosis to the end of treatment.

In particular, HE4 blood levels were assessed at different times:

Preoperatively.

At the end of the third cycle of chemotherapy.

At the end of the sixth cycle of chemotherapy.

Among all studies, five authors focused on preoperative HE4 value as a potential marker of response to platinum chemotherapy.

Although the results of different studies greatly differ from one another, all the studies agreed that a high preoperative HE4 value is a strong predictor of chemoresistance. Since platinum based chemotherapy remains the first treatment in EOC, this outcome could help us to identify potentially platinum resistant patients, to monitor their HE4 values at each cycle of chemotherapy and eventually switch to second line chemotherapy drugs in case of resistance.

However, these studies provide limited and non-homogeneous data. Therefore, more studies are needed to identify a single HE4 preoperative cut-off value, to assess patients' platinum response in advance.

Two studies reported that HE4 blood levels measured after the third cycle of chemotherapy could be used as a predictor of response to platinum based therapy.

The purpose of earlier detection (pre-operatively or at the third cycle of chemotherapy) of patients' response to treatment is that it may allow us to change the chemotherapic regimen before the end of six programmed cycles of treatment.

This would enable a reduction in unnecessary toxicity of platinum in chemo-resistant patients that often results in neutropenia and nephrotoxicity. It would also save time in finding and applying alternative chemotherapy treatments, which could possibly be more efficient and accurate, before EOC recurrence.

In only one study, by Hamed *et al*. HE4 value was assessed at the end of six courses of chemotherapy.

Detecting platinum resistant patients in advance, before tumour relapse, is important as it provides the opportunity to hypothetically select a high risk group of patients, who could then be closely monitored through a tight follow-up.

Moreover, several authors performed *in vitro* studies to demonstrate how HE4 overexpression could be related to platinum resistance. HE4 overexpressing clones were compared to normal epithelial EOC cells.

All the studies agreed that the inhibition of platinum induced apoptosis in HE4 overexpressing cells is the main biological mechanism responsible for chemo-resistance.

Conclusions

In conclusion, HE4 is a promising marker for detecting chemotherapy response in advance, but its performance should be tested in the follow-up of larger cohorts of OC patients in prospective, multicentric and randomised trials, in order to improve the surveillance strategies and treatment options. An additional limit is the use of different temporary criteria in measuring HE4 values, that results in different parameters and the inability to define a single cut-off. The challenge to predict platinum sensitivity and to anticipate other more efficient treatments, improving the OS and quality of life of patients affected by EOC, is still open. Another aspect to consider regards BRCA mutation and possible future target therapies, which would require an appropriate selection of patients.

More studies are needed to validate and reinforce the role of HE4 in predicting response to platinum based chemotherapy among ovarian cancer patients.

Authors' contributions

All authors discussed the results and contributed to the final manuscript.

Conflict of Interest

All the authors declare that they have no conflict of interest.

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