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Multiple Potential Markers of Chemosensitivity of Ovarian Cancer, among Which KELIM of CA125 Is Low Cost and Efficient

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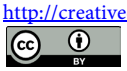

Abstract

Aim: Ovarian cancer (OC) is a malignant cancer with the highest death rate among various kinds of gynecological tumors. The treatment pattern of HGSCs is mainly primary debulking surgery (PDS), followed by platinum-based adjuvant chemotherapy, which has been the preferred treatment plan in recent years. Treatment decision-making remains a problem that needs to be addressed. We write this article to summarize the relevant indicators reported and find better decision-making tools. Methods: We have extensively read and understood the literature in the research field involved. We searched for keywords in Pubmed: ovarian cancer; KELIM; chemosensitivity. Later we summarized and organized the current research status in the last two decades. Results: There are many predictors of chemotherapy sensitivity, including pathological chemotherapy response score (CRS), the level of tumor-infiltrating lymphocytes (TILs), BRCA mutations in germ lines or somatic cells, tumor homologous recombination deficiency (HRD), KELIM of CA125 and so on. Many clinical trials have testified that this marker of chemosensitivity all have their own advantages and disadvantages. KELIM of CA125 is low-cost and efficient, which is worth promoting and applying in clinical practice. Conclusions: Many studies have validated the predictive and guiding value of the KELIM of Ca125 in the diagnosis and therapy of ovarian cancer. Nowadays, KELIM of Ca125 is rarely known by clinical doctors and lacks clinical application. We advise that KELIM of CA125 is a potential prognostic factor of ovarian cancer. As a clinical doctor in the process of treating ovarian cancer, we can combine the patient's situation with KELIM, to develop personalized treatment plans. Not only can it reduce the occurrence of complications, but it can also lower medical costs.

Keywords

Epithelial Cancer of the Ovary, Chemotherapy in GYN Cancers

1. Introduction

Ovarian cancer (OC) is a malignant cancer with the highest death rate among various kinds of gynecological tumors. In the early phase of the disease, most high-level ovarian cancer patients are already in the advanced stage (III-IV stage) at the initial diagnosis due to the lack of characteristic manifestations in the early phase of the disease, which also indicates a poor prognosis for patients. At present, the standard therapeutic plan for advanced ovarian cancer is a combination of surgical treatment and chemotherapy. Despite progress in diagnosis and treatment during this period, ovarian cancer is still one of the important sources of incidence and mortality rates on a global scale. The five-year relative survival rate of OC is 30% - 50%. High-grade serous ovarian cancer (HGSOC) is the most common histological subtype of epithelial ovarian cancer, accounting for 60% - 80% of all cases [1]. The treatment pattern of HGSCs is mainly primary debulking surgery (PDS), followed by platinum-based adjuvant chemotherapy, which has been the preferred treatment plan in recent years [2]. However, the treatment plan of neoadjuvant chemotherapy has also been increasingly valued. Vergote *et al*. found that neoadjuvant chemotherapy followed by interval debulking surgery (IDS) was not inferior to PDS followed by chemotherapy as a treatment plan for patients with bulky stage IIIC or IV ovarian carcinoma [3]. Fagotti *et al*. concluded that PDS and neoadjuvant chemotherapy followed by IDS have the same efficacy when used at their maximal possibilities, but there are more postoperative complications after PDS [4]. Similarly, Kehoe *et al*. agreed that in women with stage III or IV ovarian cancer, survival with primary chemotherapy is non-inferior to primary surgery [5]. Therefore, the primary sensitivity of patients to chemotherapy has also been emphasized, and personalized treatment options based on the different situations of patients may achieve better efficacy, better quality of life, and longer overall survival.

Many scholars have proposed some predictive indicators related to primary chemotherapy sensitivity, which provide some reference for guiding clinical treatment. These include the pathological chemotherapy response score, tumor-infiltrating lymphocytes (TILs), and tumor homologous recombination deficiency. They each have advantages and disadvantages, and currently, there are still no ideal and clear chemical sensitivity and prognosis prediction indicators to guide treatment. In 2013, YOU, Benoit *et al*. designed a mathematical model and introduced the modeled CA-125 elimination rate constant K (KELIM), which can be used as an early marker of primary chemotherapy sensitivity during neoadjuvant chemotherapy or adjuvant chemotherapy. This article aims to introduce KELIM, promote its clinical application, and apply it to guide treatment.

2. The Potential Marker of Chemosensitivity

If it is highly possible to achieve complete reduction surgery without residual diseases to the naked eye, tumor cell reduction surgery can be recommended. Cytoreductive surgery can be used as PDS or as IDS after neoadjuvant chemotherapy, depending on the assessment of the possibility of initial complete resection [6].

It is necessary to integrate the primary sensitivity of tumors to the therapeutic schedule when making decisions. Primary chemotherapy sensitivity requires objective and measurable markers to be evaluated, which can be obtained during the early stage of chemotherapy. There are already some potential primary chemosensitivity indicators for tumors.

Predictors of Chemotherapy Sensitivity

The pathological chemotherapy response score (CRS) has been widely used to evaluate the chemotherapy response of HGSOC by conducting histopathological examination of specimens. CRS was proposed and developed by Bohm *et al*. by evaluating the tumor structure and tumor microenvironment (TME) at the omental lesion after chemotherapy, which had a significant correlation with mixed results of progression-free survival (PFS) and overall survival (OS) [7]. First, Bohm *et al*. proposed a six-tier scoring system by assessing the residual tumor environment in both omental and adnexal sections. Notably, CRS has a statistically significant connection with PFS and OS when applied to the omentum. However, it is not related to prognosis when applying CRS to the adnexal. Later, a three-tier system that was simpler to use was proposed by the author: 1) CRS1: minimum tumor response; 2) CRS 2: moderate tumor response, residual tumor lesions are easy to identify; 3) CRS 3: complete or nearly complete remission, with no residual tumor cells or the smallest dispersed tumor lesions, with a maximum size of up to 2 millimeters. The three-tier scoring system showed significant differences in prognosis between the CRS 1/2 group and the CRS 3 group. In Böhm's article, when evaluating the adnexal and omental CRS in a single patient, unlike some other cancers, the chemotherapy response was evaluated at the primary tumor site. The authors testified that the omentum is the most relevant disease site for prognosis in the pathological evaluation of OC chemotherapy response. However, Santoro *et al*. proved significant differences in PFS between CRS1, CRS2, and CRS3 patients based on the evaluation of adnexal CRS for the first time [8]. Similarly, Lawson *et al*. observed that the three-tier CRS system and a modified two-tier CRS (CRS1/2versus CRS3) system in the adnexal were related to PFS but not to OS [9]. Furthermore, a systematic review and meta-analysis was conducted on 691 ovarian HGSC patients in six studies, demonstrating the predictive effect on the prognosis of adnexal CRS [10]. At present, the CRS is always used to predict disease progression and prognosis. Lawson *et al*. pointed out that the [9] adnexal CRS score has great significance in predicting platinum-resistant relapse. Due to the different con-

clusions drawn from various studies, there are still many limitations in its application to clinical neoadjuvant chemotherapy patients. At the same time, assessing the CRS score requires obtaining tumor tissue through IDS, which limits the possibility of adjusting preoperative treatment plan management. Recently, studies have validated that the expression of AQP1 is closely related to worse omental reactions (CRS1-2) to chemotherapy, indicating that AQP1 may also be a predictive indicator for resistance to platinum-based chemotherapy in OC [11].

Some studies have shown that the level of tumor-infiltrating lymphocytes (TILs) is an effective factor for predicting prognosis and survival. As a result, solid tumors are classified into three categories: 1) T-cell-inflamed tumors (also called "hot" tumors), in which deposits (islets) of tumor cells and the intervening and surrounding stroma are infiltrated by T cells; 2) T cells exclude tumors, in which infiltration of T cells can be seen in the stroma and is absent from deposits of tumor cells; 3) Noninflamed tumors, also called "cold" tumors, mean the absence of T cells both in deposits and stroma [12]. The Ovarian Tumor Tissue Analysis consortium verified that HGSOC is the most common type, with a large number of CD8+ T cells infiltrating all types of ovarian cancers. Moreover, CD8+ tumor-infiltrating lymphocytes (TILs) infiltrating epithelial cells can be a favorable independent prognostic indicator, whether cytoreduction is completely reduced or not and whether germline BRCA1 is mutated or not [13]. A study also concluded from 540 patients who a high level of intraepithelial infiltration of CD8 (+) TILs (except for CD3 (+) TILs) was an independent favorable prognostic factor for disease-free survival of tumors. Furthermore, the presence of CD8(+) T cells in the epithelium is also significantly associated with the absence of BRCA1 [14]. Another retrospective study involving 122 patients showed that infiltration of low cytotoxic T lymphocytes (CTLs) was an independent factor of platinum resistance in multivariate analysis (OR, 3.77; 95% CI, 1.08 - 13.12; $P = 0.037$). EOCs resistant to platinum exhibit a poor immune response. One of the mechanisms of platinum resistance in EOCs may be the immune escape system. Its characteristic is the early progression of the disease after first-line treatment (negative vs. positive: 97.7% vs. 9.0%; $P < 0.001$) [15]. Further research is needed to test and verify the prognostic significance of TILs in OCs for the benefits of platinum-based chemotherapy and maintenance therapy. The application of this method in disease diagnosis and treatment will be limited by obtaining tumor specimens, which must be obtained from biopsy or surgical specimens.

Studies have shown that BRCA mutations in germ lines or somatic cell cells are associated with higher efficacy and better prognosis of platinum-based chemotherapy for tumors and better response to PARP inhibitors [16] [17] [18]. A systematic review and meta-analysis confirmed that BRCA1 and BRCA2 mutations are related to better prognosis, including OS and PFS. Part of the reason may be that their disease has high chemical sensitivity [19]. Among 225 ovarian cancer patients receiving neoadjuvant chemotherapy, 34% (and 46%) of BRCA

mutant cancer patients observed a complete clinical response (and pathological response), while 4% (and 25%) of BRCA wild-type ovarian cancer patients did so. The data confirm the high sensitivity of OC to platinum agents driven by BRCA [20]. Although these results indicated that BRCA mutations have a strong predictive effect on the benefits of platinum-based chemotherapy, it has not yet been truly resolved to use BRCA mutation as a decision-making tool for first-line chemotherapy and/or surgical treatment. Moreover, a retrospective study showed that compared to patients without BRCA mutations, secondary debulking surgery did not increase survival in patients with BRCA mutations among platinum-sensitive recurrent patients [21]. The GOG-0213 Phase III trial analyzed the data from 485 patients with diseases that can be resected to no residual lesion. Patients were divided into two groups, undergoing secondary surgical cytoreduction followed by platinum-based chemotherapy or platinum-based chemotherapy alone. In those patients, no benefits of secondary debulking surgery were found, especially in those who were very sensitive to platinum-based chemotherapy, whose characteristic was a platinum-free interval >12 months [22].

In addition, tumor homologous recombination deficiency (HRD) has been proven to be closely related to the benefit of PARPis in ovarian cancer, but DNA sequencing has some limitations in evaluating HRD status. In fact, approximately 50% of HRD-positive ovarian cancer patients carry known HR gene mutations, while the remaining patients exhibit epigenetic silencing or inactivation of HR-related genes, as well as variants of uncertain significance (VUS) [23]. Recent studies have shown that the methylation level of the BRCA1 promoter in high-grade OC patients is associated with HRD status and clinical behavior. OC patients with high levels of BRCA1 methylation are inclined to have a high genomic instability score (GIS), making them an ideal candidate for PARPi maintenance treatment. Further prediction of BRCA1 hypermethylation may be associated with other tumor types predicting HRD status [24]. Takamatsu *et al*. identified gene expression differences between tumors with and without HRD genomic scars and named these genes the "HRDness signature". They reached the conclusion that patients with HRD signature gene expression tend to have a better prognosis, while those with BRCA1 methylation always have a worse prognosis [25]. Within HRD-associated genes, researchers still seek new biomarkers that can accurately guide treatment and predict prognosis. Another study used an immunofluorescence assay (IF) to assess the ability of tumor cells to form RAD51 lesions when there is DNA damage. Although OC exhibits high levels of DNA damage, 54% cannot form RAD51 lesions. RAD51-low OC patients are inclined to have a better response to neoadjuvant platinum. The RAD51 assay also distinguished a group of RAD51-high BRCAmut tumors with unexpectedly low platinum sensitivity [26].

It is well known that it may be difficult to measure lesion size through imaging examinations in many ovarian cancers. Therefore, response evaluation criteria in solid tumors (RECIST) are often not used to evaluate tumor response.

Scholars have turned to other indicators to assess the response of OCs to treatment. The most commonly used tumor marker is CA125. Scholars have conducted in-depth studies on the decline curve of CA125 concentration in ovarian cancer patients during chemotherapy and surgical treatment. In 2004, the Gynecological Cancer Intergroup (GCIG) defined the CA-125 reaction as a 50% decrease in CA-125 levels that lasted for at least 28 days [27]. Lee *et al*. analyzed data from 886 patients in the CALYPSO phase III trial and found that early decline (defined as a rate of at least 50% decrease in CA125 per month) was associated with improved PFS, but early response (complete or partial responses) was not. In this study, compared with carboplatin paclitaxel (CP), carboplatin pegylated liposomal doxorubicin (CPLD) was associated with improved PFS (HR = 0.82, 95% CI = 0.69 - 0.96, P = 0.01). However, fewer patients with CPLD experience early decline or early response compared to CP patients [28]. Therefore, the presence of early decline does not indicate more clinical benefits from subsequent chemotherapy. Similarly, Coleman *et al*. have shown that a large number of RECIST-defined tumor response patients experience an increase in the concentration of CA125 in the first two cycles of PLD [29]. Later, You, *et al*. advised that the strategy used in pharmacokinetic studies can be implemented in the analysis of serum ovarian cancer marker kinetics. They proposed semimechanistic models to dynamically investigate CA-125 kinetics during the chemotherapy process [30]. A total of 976 patients were from CALYPSO [31]. The study used a population kinetic semimechanistic model to characterize CA-125 kinetics (**Figure 1**).

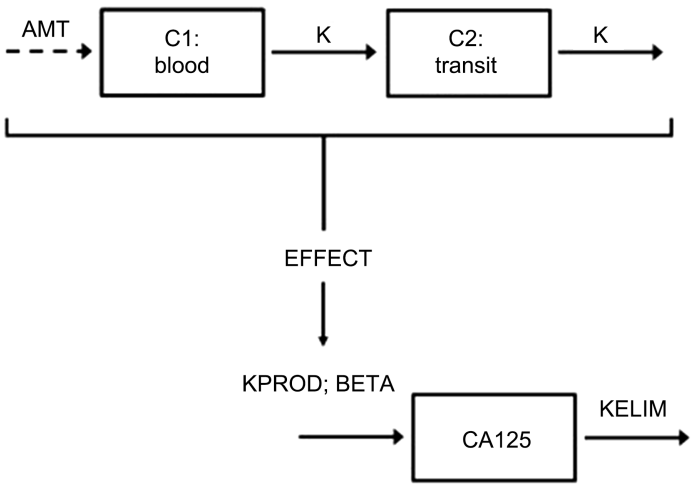

Figure 1. Description of the semi-mechanistic model. AMT: Unknown CA-125 dose amount; K: treatment kinetics; KPROD: CA-125 tumor production rate; BETA: tumor growth rate; KELIM: CA-125 elimination rate; EFFECT: production inhibition; C1: central compartment receiving chemotherapy dosing; and C2: transit compartment to describe the treatment lag-time effect where K is the treatment kinetic rate constant (days−1); KPROD is the CA-125 tumor production rate (IU days−1); BETA is the tumor growth rate (days−1); A50 is the concentration producing 50% of the maximum effect (IU); and KELIM is the CA-125 elimination rate (days−1).

They discovered that KELIM is a kinetic parameter related to tumor marker elimination, which can be interpreted as CA-125 clearance and can produce a strong independent predictive value of prognosis and chemosensitivity. The higher the KELIM, the faster the clearance rate of CA-125 for the same chemotherapy regimen and the better the chemotherapy effect. This is a large-scale study modeling CA-125 kinetics in ovarian cancer patients during treatment for the first time (Table 1).

3. The Potential Role of KELIM

For the modeled CA-125 elimination rate constant K (KELIM), many studies have validated the predictive and guiding value of the KELIM of Ca125 in the diagnosis and therapy of ovarian cancer.

Table 1. Potential utility for disease management in first-line setting.

Some types of potential indicators of the tumor primary chemosensitivity	Relation with the progression-free survival (PFS)	Relation with the progression-free survival (PFS)	Relation with the progression-free survival (PFS)	the disadvantages of the application to the management of ovarian cancers
Pathology examination Chemotherapy response score (CRS) on surgery specimen	In the adnexal and omentum,CRS3 related to better PFS compared to CRS1/2		Evaluating the tumor structure and tumor microenvironment	The demand for tumor tissue after chemotherapy limits the possibility of adjusting disease management plan before surgery
The level of tumor-infiltrating lymphocytes (TILs)	A high CD8(+)/FoxP3(+) ratio and high levels of CD8 (+) TILs related to better disease-free survival	Higher levels of intraepithelial TILs related to better OS	Suitable for most of solid tumors	The demand for tumor tissue limits the possibility of adjusting disease management plan before surgery
BRCA1 or BRCA 2 mutations	Patients with BRCA mutations related to higher PFS	Patients with BRCA mutations related to higher OS	Higher benefit from PARP inhibitors	Higher benefit from PARP inhibitors
Homologous recombination deficient (HRD) status	HRD-positive Patients related to higher PFS		HRD-positive Patients related to higher PFS	Difficulties for building a validated panel with HR-related genes due to many unknown genes.
Modeled CA-125 kinetic parameter, KELIM	Difficulties for building a validated panel with HR-related genes due to many unknown genes.	Difficulties for building a validated panel with HR-related genes due to many unknown genes.	Low cost, high availability.	Abnormal CA-125 >35 IU/L at baseline

1) The Prognostic Value of Predicting Survival

In 2013, the dynamic characteristics of individual CA-125 kinetics in 895 patients in the phase III trial CALYPSO were modeled. Authors drew the conclusion that: KELIM was one of the independent prognostic factors of progression-free survival (PFS), and this modeled kinetic parameter may contain the prognostic information linked to cancer size [30]. In 2019, Olivier, *et al*. analyzed data from large-scale Phase III trials including ICON7 (validation set: CP ± bevacizumab; n = 1388), AGO OVAR 9 [learning set: carboplatin-paclitaxel (CP) ± gemcitabine; n = 1288] and AGO OVAR 7 (validation set: CP ± topotecan; n = 192). They confirmed that the predictive value of KELIM for progression-free survival and overall survival is higher than the GCIG criterion [32]. In the randomized phase II trial CHIVA (carboplatin-paclitaxel regimen ± nintedanib, n = 188) in 2020, the CA-125 concentrations were prospectively measured. You, *et al*. concluded that KELIM was an independent and major predictor of the risk of subsequent platinum-resistant relapse (PtRR), PFS and OS [33]. Furthermore, You, *et al*. also proposed that KELIM is an independent prognostic factor of the possibility of complete remission > 5 years after first-line treatment [34]. Alao, Van, *et al*. analyzed the data from 1582 patients treated with NACT with >2 CA-125 concentration measurements. KELIM during NACT has prognostic value not only for the possibility of complete resection but also for PFS, OS and progression-free survivorship [35]. Studies have verified that the CA-125 KELIM values were not affected by the addition of a third drug (chemotherapy or antiangiogenic drugs) to the carboplatin-paclitaxel chemotherapy regimen or the administration frequency (weekly versus every 3 weeks) of chemotherapy drugs [36]. Regardless of the therapeutic regime received, KELIM always has prognostic value for overall survival.

2) Potential to Predict the Possibility of Complete Interval Debulking Surgery

There are some comparative randomized trials of neoadjuvant chemotherapy and primary debulking surgery for advanced ovarian cancer. Some trials have concluded that neoadjuvant chemotherapy results in noninferior OS and PFS when compared with primary debulking surgery [3] [5]. On the other hand, compared with PDS, a survival noninferiority of NACT was not confirmed in some clinical trials [37]. 4 Undoubtedly, patients with stage III or IV ovarian cancers who cannot tolerate primary debulking surgery or cannot undergo complete primary debulking surgery because of the high cancer burden can choose to receive neoadjuvant platinum-based chemotherapy [38]. NACT followed by IDS is associated with reduced morbidity and mortality, combined with a trend of improving quality of life. A major independent predictor of prolonged survival is complete cytoreduction without microscopic residues (CC0 surgery) [39] [40]. Therefore, not only chemotherapy sensitivity but also complete surgical resection plays an important role in first-line treatment.

You *et al*. analyzed the data of patients participating in the randomized phase II trial CHIVA (NCT01583322), and they concluded that the only significant

parameter about the possibility of complete IDS was std KELIM. The authors used a multivariate logistic regression model to assess the possibility of complete IDS (**Figure 2**) [33]. Similarly, Van *et al*. and You *et al*. verify the same conclusion [41] [42]. In 2020, the analysis of the CHIVA trial verified that in the multivariate logistic regression model, complete IDS (no vs. yes, OR = 0.30; 95% CI, 0.11 - 0.76) and std KELIM (continuous covariate, OR = 0.13; 95%, 0.03 - 0.49) were both significant. Based on the std KELIM value and IDS completeness, the model was used to develop a platinum-resistant recurrence score that can provide the possibility of subsequent platinum-resistant relapse. The platinum-resistant recurrence score can be used for decision-making about IDS when it is uncertain whether to undergo surgery. When patients have unfavorable std KELIM, the role of a complete IDS is decisive. However, patients with favorable std KELIM always have a better prognosis, and invasive operations require careful consideration, especially in situations where operability is uncertain.

3) Potential Value for Decision-Making about the First-Line Treatment and Maintenance Treatment Plan

You, *et al*. analyzed the data from ICON 8. Patients were divided into three subgroups: a) a group of patients with favorable KELIM who underwent complete surgery and had the best PFS and OS; b) a group of patients with favorable KELIM undergoing incomplete surgery or undergoing complete surgery and with unfavorable KELIM who had intermediate PFS and OS; and c) a group of patients undergoing incomplete surgery and with unfavorable KELIM who had the worst prognosis. The last group of patients obtained a great benefit from weekly dose-dense chemotherapy [36]. Later, Colomban *et al*. reached a conclusion that fractionated dose-dense chemotherapy might be beneficial for patients belonging to the poor prognostic group characterized by lower tumor chemosensitivity assessed with the online calculator CA-125-Biomarker Kinetics and incomplete debulking surgery [43].

Previous studies have suggested that stage III-IV ovarian cancer patients obtain benefits in progression-free survival when bevacizumab is added to standard first-line chemotherapy [44] [45]. However, in the final survival analysis report of GOG-0218, no evidence showed that bevacizumab can provide benefits in OS [46]. Oza *et al*. found that bevacizumab addition can benefit the OS of high-risk patients, including patients with stage IV and those with unoperated or suboptimally debulked (>1 cm) stage III cancers [47]. Later, Olivier *et al*. demonstrated that only approximately 53% of high-risk patients with poor chemosensitivity (std KELIM < 1.0) reaped survival benefits from the expensive addition of bevacizumab. However, those patients are still unable to achieve survival rates similar to those of high-risk disease patients with favorable KELIM [48]. That is, primary chemosensitivity may play a more essential role in predicting survival. Currently, there are still no clear indicators to guide the use of bevacizumab, and KELIM can provide some guidance.

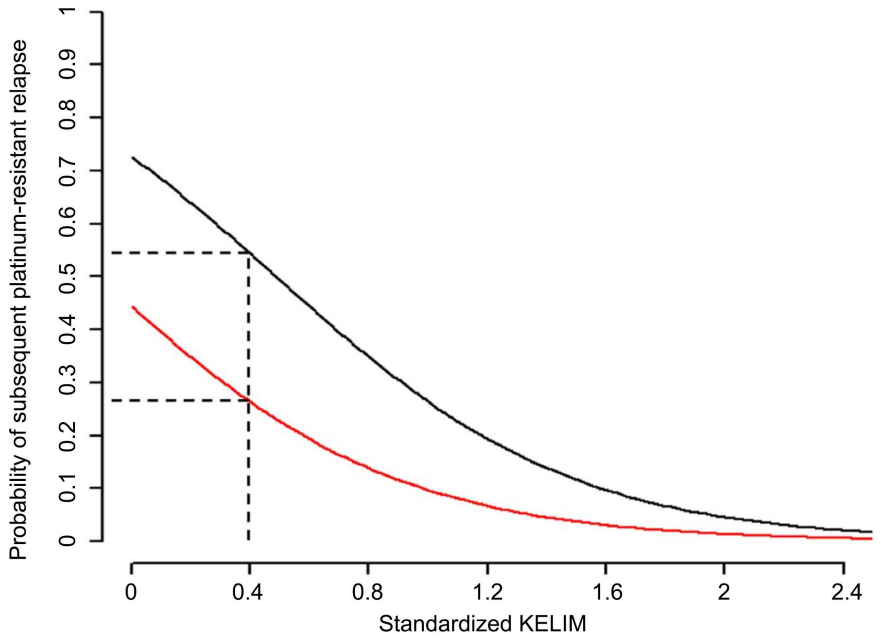

Figure 2. Platinum-resistant recurrence score. Probability of subsequent platinum-resistant recurrence according to standardized (std) KELIM. Red curve: prob-ability line for patients operated with complete IDS; Black curve: probability line for patients operated with incomplete IDS. Dashed black line: illustration for a patient with std KELIM¼ 0.4; the risk of platinum-resistant relapse probability of 26% if IDS was complete, or 54% if IDS was incomplete.

Maintenance PARP inhibitor therapy after first-line chemotherapy response is now the standard of treatment in advanced HGSOC. Hannaway. *et al*. analyzed data and concluded that patients with KELIM scores ≥ 1 had a trend toward greater PFS from niraparib vs. those with KELIM < 1, with a median PFS of 15 months vs. 8.3 months, respectively (p = 0.06) [49]. You, *et al*. innovatively analyzed interactions between veliparib benefits and KELIM according to HR status. In patients with BRCA mutation and BRCA wild-type HRD cancers, the increasing KELIM value is related to the higher efficiency of veliparib. In other words, there is a higher efficacy of veliparib in patients with platinum-sensitive diseases. Conversely, in patients with HRP cancers, a decreasing KELIM value sometimes seemed to be associated with a higher benefit from veliparib, which may be a result of a chemosensitizing effect of veliparib [41]. Colomban. *et al*. assessed using the Ca-125 KELIM™ adjusted to rucaparib (called KELIM-PARP), which may help identify the patients who will benefit from rucaparib [50].

4) An Online Calculator of KELIM

An online calculator to easily calculate std KELIM is available during neoadjuvant (https://www.biomarker-kinetics.org/CA-125-neo, accessed on 26 June 2023) or adjuvant chemotherapy (at https://www.biomarker-kinetics.org/CA-125, accessed on 26 June 2023). To calculate the std KELIM, clinicians need to collect the dates of chemotherapy cycles and the CA-125 values and dates during the first 100 days after the start of chemotherapy.

4. Discussion

Although international guidelines have pointed out the significant prognostic and therapeutic role of complete debulking surgery in first-line treatment, tumor primary chemosensitivity has not yet been elevated to the same important position, which also has a great impact on prognosis and decision-making regarding systemic treatment schedules.

The predictive values of KELIM regarding overall survival and the potential utility for disease management in first-line decision-making have been verified. Compared with other indicators of tumor primary chemosensitivity, KELIM has the advantages of low cost and low complexity of methodology. Additionally, to calculate KELIM, tumor tissue is not necessary. Clinicians can adjust the medical-surgical management before debulking surgery. However, the baseline CA-125 level needs to exceed 35 IU/L. If the baseline CA-125 level is <35 IU/L, KELIM may not be an ideal monitoring indicator.

We need to promote the application of the KELIM to clinical practice to provide more references for making treatment plans. Furthermore, KELIM can also be a potential indicator of patients who have extremely poor survival due to poor chemotherapy sensitivity. These patients are the best candidates for innovative strategies such as immunotherapy aimed at reversing chemoresistance. Future clinical trials will be carried out.

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Disclosure

We have no relationships with manufacturers of medication.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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