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Measurement Tool of Chemotherapy Sensitivity in Advanced Ovarian Cancer

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SUMMARY

The modeled Ca125 ELIMination rate constant K (KELIM) can be used as a measure of chemotherapy sensitivity in women with newly diagnosed advanced epithelial ovarian cancer who are being treated with neoadjuvant chemotherapy. This marker may aid in decision-making regarding surgical resection and alternate systemic treatments in this cohort.

See related article by You et al., p. 4625

In this issue of *Clinical Cancer Research*, You and colleagues present results of an ancillary study of the phase II CHIVA trial investigating the change in Ca125 level as predictor of chemosensitivity in women with advanced ovarian cancer (1). The authors studied patients with stage IIIC and IV epithelial ovarian cancer enrolled in the CHIVA trial who were undergoing neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS; ref. 2). In the phase II, double-blind CHIVA trial, 188 patients were randomized to carboplatin, paclitaxel, and the receptor tyrosine kinase inhibitor, nintedanib in the experimental arm, or to carboplatin, paclitaxel, and placebo in the control arm (2). In this work, You and colleagues examined the predictive value of the modeled Ca125 kinetic parameter (KELIM) and whether it is a marker of clinical outcomes including surgical resectability, platinum sensitivity, and survival in this cohort. In this study, Ca125 was collected at diagnosis, prior to cycle 2, prior to cycle 3, and prior to IDS. The KELIM was calculated with the Ca125 longitudinal kinetics during the first 100 NACT days. A of minimum of three Ca125 values were required for this analysis and 134 of 188 patients (71%) met this inclusion criteria.

You and colleagues identified an association between the tumor chemotherapy response rate and the KELIM measurement. The authors noted that a higher KELIM value represents a faster Ca125 elimination rate and hence, higher chemotherapy sensitivity. The predictive value of KELIM was assessed for completeness of IDS, platinum-free interval (PFI), subsequent platinum-resistant relapse, progression-free survival (PFS), and overall survival (OS). Chemosensitivity is an important predictor of survival in ovarian malignancies. To date, a commonly used indicator of platinum sensitivity is the PFI, which measures the time lapse between the last platinum treatment and the date of recurrence. This measure is helpful in selecting second-line therapies in recurrent ovarian carcinoma. It is, however, a retrospective measure and is therefore not applicable in the first-line setting. Identifying predictive markers of chemosensitivity at diagnosis or during the initial treatment phase may allow oncologists to tailor systemic and surgical treatments in the first-line setting. Our group has examined the significance of Ca125 in women with advanced high-grade serous ovarian carcinoma being treated with primary cytoreductive surgery (3). Ca125 expression is believed to correlate with tumor burden, therefore, a decline in Ca125 often indicates reduction in residual disease. Our results indicated baseline Ca125 level at diagnosis to be an independent predictor of OS and inversely associated with OS (3). Furthermore, our data show that a 7-fold or greater postoperative decline in Ca125 is associated with improved survival in patients after primary cytoreductive surgery. In their article, You and colleagues investigated the value of KELIM in the neoadjuvant setting in patients undergoing IDS.

To assess surgical completeness, the authors utilized the peritoneal carcinomatosis index (PCI) as judged by the surgeon at the conclusion of IDS with the following criteria: complete resection with no residual disease (CC0); incomplete resection with residues less than 2.5 mm (CC1); incomplete resection with residues from 2.5 mm to 2.5 cm (CC2); and incomplete resection with residues more than 2.5 cm (CC3; ref. 4). To ensure surgical accuracy, only ovarian cancer expert centers were included in the CHIVA trial. In addition, diagnostic laparoscopy was performed at diagnosis and prior to IDS by the same surgeon to document the surgical findings. In this cohort, 48% of patients achieved complete IDS with CC0 resection and 52% had incomplete resection with CC1, CC2, or CC3 resections. The authors found that the median standard (std) KELIM was significantly higher (1.04) in patients with complete resection as opposed to incomplete resection (0.54).

Preoperative prediction of cytoreductive outcomes in patients with peritoneal dissemination is challenging. Gynecologic oncologists often rely on surrogate indicators including genomic fingerprinting, tumor markers, and imaging assessment. These assessment tools have inherent limitations and lack precision and accuracy. Hence, some groups have introduced diagnostic laparoscopy into the treatment algorithm of patients with advanced ovarian malignancies as a measure of disease volume and disease distribution. Patients with favorable scores on laparoscopic assessment, which are predictive of tumor resectability, undergo cytoreductive surgery. Those with unfavorable scores are not taken for attempted cytoreduction, thus avoiding futile laparotomy. Nonetheless, diagnostic laparoscopy has not been widely adopted. Some of its limitations include the increased cost associated with the procedure, the added surgical resource, possible complications associated with the general anesthetic, and the delay to definitive treatment. Therefore, nonresource intensive, accurate markers of surgical resectability are critically needed in advanced ovarian cancer.

Interestingly, patients with favorable KELIM had improved PFS and OS, as compared with patients with unfavorable KELIM, regardless of

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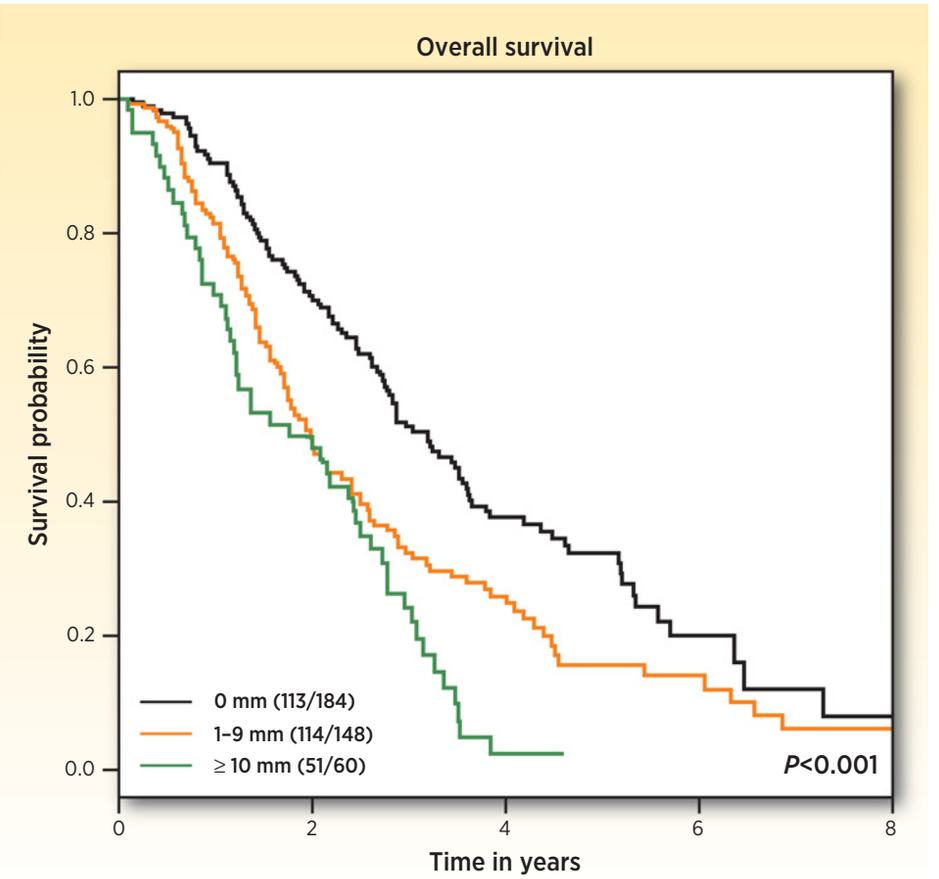

Figure 1.
OS by extent of residual disease at the time of IDS in patients with stage IIIC and IV epithelial ovarian cancer treated with NACT. Adapted by permission from BMJ Publishing Group Limited (5).

the completeness of IDS. This suggests that in patients with substantial platinum sensitivity, platinum-based therapy may have a larger impact on survival than the degree of surgical resection at IDS. Alternatively, in patients with unfavorable KELIM, surgery played a more crucial role. In patients with KELIM scores less than 0.54, achieving complete CC0 resection during IDS was associated with improved survival as compared with patients with similar KELIM who had incomplete surgical resection at IDS. This finding suggests that tumors that are less sensitive to chemotherapy appear more reliant on the degree of surgical resection where complete resection harbors significant survival advantage. This knowledge might be of great importance to the gynecologic oncology surgeons as the KELIM value may aid in preoperative and intraoperative decision-making. In patients with poor KELIM, who are reliant on surgical completeness, prolonged surgery, multivisceral resection, and increased surgical morbidity might be acceptable in favor of improved survival. However, the role of IDS and the added benefit harbored by complete cytoreduction in women with favorable KELIM deserves further studying.

Notably, the authors utilized the PCI score to report on residual disease in their article. This score is often used in peritoneal malignancies and commonly utilized in patients undergoing hyperthermic intraperitoneal chemotherapy procedures (4). In gynecologic oncology, surgical studies often classify the degree of residual disease according to the degree of cytoreduction with complete cytoreduction as 0 mm residual disease, optimal cytoreduction as 1–9 mm residual disease, and suboptimal cytoreduction as ≥10 mm residual disease (**Fig. 1**; ref. 5). It would be imperative to correlate the std KELIM values described by You and colleagues with these commonly reported cytoreduction classifications so that the KELIM values can have wider surgical applicability. Furthermore, epithelial ovarian tumors are heterogenous and harbor multiple clones with variable chemotherapy sensitivities and cytoreduction may play an important role in surgically eliminating resistant clones. The authors envision that platinum resistance may be identified at an earlier time in the patient journey using the KELIM measurement, therefore allowing for introduction of alternate systemic treatments, which may improve survival outcomes. This hypothesis would be important to test.

In summary, the KELIM measurement as described by You and colleagues is a reproducible tool that can be used to assess chemotherapy sensitivity in patients with newly diagnosed advanced ovarian cancer following NACT. The KELIM value is a helpful measurement that allows the clinicians to measure the degree of chemosensitivity prior to IDS. This can aid in surgical decision-making regarding the role and extent of IDS as well as alternate systemic therapies. This knowledge may allow for individualized treatment plans for women with advanced epithelial ovarian cancer based on their KELIM scores.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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