HE4: Another ‘Player’ in the Epithelial Tumor Marker Arena?

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While a prominent role for HE4 in these areas remains to be determined, this thorough review of HE4 demonstrates that the biomarker is complementary to, and occasionally more useful than, the widely used CA 125 in the management of gynecologic malignancies.

Three decades have elapsed since Robert Bast, working in the Gynecologic Research laboratory of Robert Knapp at Harvard, developed an antibody directed to an antigen in ovarian cancer cells, leading to the seminal publication on cancer antigen 125 (CA 125) for the monitoring of patients with ovarian cancer.[1] In the ensuing years, measuring serum CA 125 had a central role in the management of this and other gynecologic cancers of epithelial origin. Its usefulness and limitations were further defined, and many efforts to improve on its role in screening, diagnostic accuracy, and patient surveillance have been made. In addition, the eventual cloning of this MUC16 surface glycoprotein has allowed the development of, and phase III trials of, CA 125–based therapeutic vaccines.[2] Finally, we have now witnessed the successful emergence of another epithelial marker, HE4, with Bast’s group summarizing its salient features in this timely and definitive review.

What about early diagnosis, detection of recurrent disease, and future roles for HE4?

Will HE4 better distinguish benign from malignant conditions at presentation, and will it identify gynecologic cancers early?

CA 125 is often elevated in benign conditions or as a result of physiologic changes in premenopausal women; consequently, it has no established role in the early detection of gynecologic cancers. HE4 may be less frequently abnormal in benign gynecological conditions; therefore, HE4 combined with CA 125 may yield increased specificity in differentiating between benign and malignant conditions. On the other hand, HE4 may be elevated in the presence of conditions such as lung cancer, chronic kidney disease, and kidney fibrosis. Discrepant results have been reported in the sensitivity of HE4 compared with CA 125 for detection of benign ovarian tumors.[3,4] The high specificity required to use the combination of HE4 and CA 125 for screening general populations has not yet been met; others will likely comment in this area.

Is HE4 recommended in the clinical detection of recurrences?

A rising CA 125 level is the most common event pointing to recurrences after initial platinum and paclitaxel treatment for epithelial ovarian cancer. Therefore, in the United States, it is routinely used (at intervals that vary from 1 to 3 months) for monitoring patients after completion of their treatments; increasing levels often prompt confirmation by CT scans and lead to the initiation of second-line treatments, as well as—not infrequently—to cytoreductive procedures. While an increase in CA 125 levels in this setting approaches 100% specificity for recurrence,[5] the benefit of this finding prompting “early” treatment was addressed by Rustin et al in the Medical Research Council (MRC) OV05/European Organisation for Research and Treatment of Cancer (EORTC) 55955 trial. In this study, physicians (and patients) were randomly assigned either to an arm in which they were aware of changes in CA 125, leading to further documentation of disease (and consequently, to start of chemotherapy) or to an arm in which they were blinded to the CA 125 findings and relied on symptoms to identify recurrence (and to start their second-line treatment).[6] The authors of the HE4 review do not reference this trial but dismiss it as “flawed.” However, the OV05 trial provides us with the best information to date on this key question: Does initiating earlier treatment upon CA 125—identification of recurrence lead to better outcomes? This trial clearly showed that early treatment of relapse identified by elevations in CA 125, and starting treatment upon clinical recurrence, yielded similar outcomes. In fact, the only difference between the two groups was that patients blinded to CA 125 levels started treatment(s) nearly 5 months after the patients whose recurrences were identified “early” by CA 125 changes.[6]
Despite suggestions that early detection identifies patients who may benefit from cytoreductive surgery, the role of such interventions in the setting of disease recurrence has not been established. DESKTOP III and Gynecology Oncology Group (GOG) 213 are ongoing trials to assess their value. Even though the sensitivity of HE4 is higher than that of CA 125 for the detection of recurrent ovarian cancer,[7] this better detection is of uncertain clinical value. What is certain is that HE4 monitoring will result in additional costs, as well as heightened anxiety in some instances. We concur with Rustin’s emphasis on having patients understand the limitations of early detection of relapse in the absence of symptoms. In fact, delaying treatment for several weeks or months after marker identification of a recurrence should currently be viewed as likely not compromising outcome, and perhaps opening up opportunities for exploring personal options. Considered from this perspective, one might temper rather than encourage patients’ frequent wishes for excessive surveillance.

**What might be the future uses of HE4?**

Ovarian cancer subtypes have been shown to have distinct biomarker expression profiles. HE4 might be informative in monitoring ovarian cancer subtypes, such as mucinous histology, that are not associated with CA 125 elevations.[8] Also, in situations where CA 125 elevations may be associated with non–cancer-related peritoneal or pleural fluid accumulation, HE4 levels could shed additional light. Furthermore, HE4 overexpression may be associated with greater likelihood of tumor progression in endometrial cancer[9] and may potentially represent not only a biomarker, but also a new immunologic target. Undoubtedly, further research into HE4 will identify areas of additional clinical utility in the management of gynecologic cancers.

Our comments have expanded on areas that are a frequent focus of patients, their friends, and family: early identification of recurrences, and screening of well women. While a prominent role for HE4 in these areas remains to be determined, this thorough review of HE4 demonstrates that the biomarker is complementary to, and occasionally more useful than, the widely used CA 125 in the management of gynecologic malignancies.

**Financial Disclosure:** The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**

**REFERENCES**


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