Expert opinion; Inhibin B and Anti-Müllerian Hormone are sensitive and specific markers for the diagnosis and follow-up of patients with Adult-type Granulosa Cell Tumour

Adult-type granulosa cell tumour (AGCT) of the ovary is a unique subtype of ovarian cancer with distinct molecular and clinical characteristics [1,2]. AGCTs are usually diagnosed at an early stage with 80-90% presenting with stage I disease[3,4] and generally have an excellent prognosis, with 5-year survival of 97% [3,4]. However, AGCTs have a characteristically high propensity to recur after a prolonged period of time and even early stage patients carry a 30% risk of relapse. The median time to relapse is 7.0 years [3], but the tumour can recur even after decades. Tumour stage is the only consistent prognostic factor for disease relapse, and it is challenging to identify the patients at risk of recurrence among the predominantly early stage patients. Upon relapse, the prognosis significantly deteriorates with 50% of patients succumbing to the disease due to lack of efficient treatment alternatives.

AGCTs are hormonally active, producing e.g. estradiol, Inhibins and Anti-Müllerian Hormone, also known as Müllerian Inhibiting Substance [5]. Inhibin has been traditionally utilized as a marker for AGCT, and Inhibin B has been found to be superior to Inhibin A [6]. Other serum markers, such as Ca-125, or TATI are rarely elevated in AGCTs.

In a comprehensive analysis of 560 serial serum samples from 130 AGCT patients, serum AMH and Inhibin B were both sensitive (92% and 93%) and specific (82% and 83%) markers for AGCT [7]. Further, the levels of both markers positively correlated to tumour size ($p<0.05$). Only 6% of patients with AGCT presented with normal levels of both AMH and Inhibin B. AMH and inhibin B performed similarly in detecting AGCT; area under the curve (AUC) values were 0.92 (95% CI 0.88-0.95) for AMH, and 0.94 (95%CI 0.90-0.96) for inhibin B. However, in AUC comparison analyses, the combination of the markers was significantly superior to inhibin B alone ($p=0.03$).

In premenopausal AGCT patients who have undergone fertility-spearing surgery [8], Inhibin B levels can fluctuate significantly during follow-up. AMH levels, however, remain constant during the menstrual cycle, and combining AMH with Inhibin B in the surveillance of premenopausal patients will add accuracy to the detection of relapse. In postmenopausal patients, the levels of AMH and Inhibin B should be consistently below the detection limits.

AMH and Inhibin B levels can rise months to even years before detection of relapsed disease; lead-times have been reported 0.9-2.8 years for inhibin B, and 3.4 years for AMH [7,9]. Thus, patients presenting with rising AMH and/or Inhibin B levels should be closely monitored for disease progression.

In view of current literature and scientific evidence, we recommend the measurement of AMH and Inhibin B as serum markers for AGCT. Both markers should be measured at diagnosis, and either marker can be utilized during follow-up. Further, combining AMH and Inhibin B in AGCT patient follow-up significantly improves the detection of recurrent disease.

Sincerely

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