

Is CA125 useful in monitoring patients with platinum-resistant ovarian cancer?

Patients with recurrent ovarian cancer are offered chemotherapy (CT) with the aim of improving survival and palliating symptoms. Due to the toxicity of therapy and expense particularly of biological therapy, treatment should only be continued if it is known to be effective. This requires regular monitoring during therapy to determine whether the cancer is responding or progressing. Providing patients are tolerating the therapy, it would normally be continued for a specified number of cycles or until it was shown to be ineffective. RECIST criteria, which rely upon serial measurements of tumour size by radiological imaging, are routinely used in clinical trials to define whether a tumour is responding if there is a decrease of $\geq 30\%$ in unidimensional measurements, or progressing if $\geq 20\%$ increase in unidimensional measurements, or development of new lesions [1]. There is great interest in determining whether CA125 is as reliable as RECIST in monitoring ovarian cancer as ovarian cancer can be difficult to accurately image and a blood test can be repeated more frequently than scans [2].

The Gynecological Cancer Intergroup (GCIG) agreed criteria based on serial changes in CA125 levels that could be used in clinical trials to define progression-free survival (PFS) after treatment of first line or recurrent disease, and to define response to treatment of recurrent disease [3]. The GCIG stated that there were no data to validate whether CA125 should be used to define response or progression in patients on maintenance or consolidation therapy. Lindemann et al. [4] have now retrospectively analysed the GCIG definition for progression in the Aurelia trial. This trial compared CT alone versus chemotherapy plus bevacizumab (BEV-CT) in patients with platinum-resistant ovarian cancer (PROC). To validate the use of CA125, the GCIG have previously analysed an end point such as response or PFS, and determined whether a similar trial result would have been found if PFS had been measured using either RECIST or CA125. In the original Aurelia publication, the objective response rate (ORR) according to RECIST alone in 287 patients was 11.8% versus 27.3% for CT and BEV-CT, respectively ($P = 0.001$) and according to GCIG CA125 criteria alone in 297 patients was 11.6% with CT versus 31.8% with BEV-CT ($P < 0.001$), indicating a consistent ORR response irrespective of the assessment method used [5].

The primary objective of the study by Lindemann et al. was to assess concordance between a modification of the GCIG CA 125 criteria and RECIST-defined progressive disease (PD), but not to validate the use of the GCIG CA125 criteria. This was not possible as they could not compare PFS according to RECIST with PFS according to CA125 criteria between the CT and BEV-CT arms in the Aurelia trial, as CA 125 results were not collected

after RECIST-defined PD and 40% of patients in the CT arm received bevacizumab on progression. There were 218 patients with RECIST-defined PD and sufficient CA125 values out of 361 patients entered into Aurelia. Only 94 (42%) patients had concordant RECIST and CA125 PFS status, with a further 56 (26%) patients having rising CA125 levels which were not classified as PD by GCIG criteria. Patients without RECIST PD were excluded from formal analysis, but interestingly, 37 of 52 (71%) of those excluded patients who progressed had a CA125 confirmed progression.

RECIST requires a 20% increase in unidimensional diameter while GCIG require a 50% increase in CA125 values to classify a patient's tumour as progressing. One would therefore expect some patients with $< 20\%$ increase in unidimensional diameter to have a $> 50\%$ decrease in CA125, and some patients to have $> 20\%$ increase in unidimensional diameter but $< 50\%$ decrease in CA 125 levels. The timing of a declared PD by the two surrogate criteria is also likely to be different. Previous studies during follow-up after first-line CT showed that CA125 predicted PD some months before RECIST [6]. This was not shown in Aurelia probably because patients with PROC have a far shorter PFS, with most progressing according to RECIST while still on therapy when some cancer clones producing CA125 might still be responding.

There were 42 patients (19%) who had falling CA125 levels at the time of RECIST PD. It is not recorded whether any of these had a fall in CA 125 sufficient to be classified as responding according to GCIG criteria. Again one would expect some patients to have fluctuating or even falling levels at the time of RECIST-defined PD as the latter is an arbitrary surrogate measure. Furthermore, we and others have noted that CA125 levels can fall in some terminally ill patients, which would include many with progressive platinum-resistant disease. As Bowtell's group have observed several molecular events associated with acquired resistance of high-grade serous ovarian cancer, it would be no surprise if CA125 expression was also reduced in some patients under the selective pressure of CT [7].

There is increasing concern that therapy should not necessarily be stopped based purely on progression according to RECIST as particularly with biological therapies, the rate of tumour growth could still be slower on that therapy than if it was stopped [8]. Lindemann et al. correctly state that a major role of therapy in platinum-resistant disease is palliation of symptoms. The randomised trial data showing no benefit from earlier reintroduction of CT just because of rising CA125 levels should persuade oncologists to delay CT for recurrent ovarian cancer until they develop symptoms [6]. Most oncologists would use the palliation of those symptoms as a good guide to the effectiveness of the therapy. Better objective measurement of symptom control is also leading to an increasing interest in patient-reported outcomes (PROs) as an end point in clinical trials involving these patients [9]. The use

of PROs in the Aurelia trial showed that the use of bevacizumab significantly improved abdominal symptoms [10].

So how should the paper of Lindemann et al. effect the way we use CA125 in patients with PROC? In clinical trials, it remains reasonable to continue using a CA125 level \geq twice the upper limit of normal within 2 weeks as eligibility criteria and to use GCIG CA125 criteria as part of the multimodal response assessments, particularly if including patients without RECIST-evaluable disease. It seems reasonable to continue therapy if there is a response according to GCIG CA125 criteria. Future validation is required before GCIG CA125 criteria are used to define PD. A change of therapy particularly in patients with PROC should not be based just on rising CA125 levels. Most patients will continue to have CA125 measured before each cycle of CT, but clinicians need to be cautious in interpreting the result, as they should be with RECIST-defined PD. For example, a very small new lesion with stable or improved disease elsewhere should not immediately make us stop therapy, simply alert us to the possibility of impending PD. Over-riding importance must continue to be placed on changes in patients' symptoms, performance status, and the clinical need for treatment.

G. J. S. Rustin* & M. R. Hall

Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, Middlesex HA62RN, UK
(*E-mail: grustin@nhs.net)

disclosure

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Prognostic pathways in early-stage ovarian cancer: can gene expression transcend histological subtype?

Ovarian cancer, like many other solid malignancies, presents a paradox. Things change, and yet they stay the same: our understanding of fundamental disease biology has improved dramatically [1], yet most patients still present with advanced disease, and overall survival still remains poor [2].

One critical change has been the realisation that ovarian cancer is a series of separate diseases, driven by distinct mutational processes [1]. The most common histological subtype, high-grade serous carcinoma, is marked by universal mutation in *TP53* [3], chromosomal instability [4] and rapid dissemination around the peritoneal cavity, with many cases arising in the secretory cells of the distal fallopian tube rather than the ovary itself [5]. In contrast, clear cell and low-grade endometrioid carcinomas are *TP53* wild-type but often contain mutations in *ARID1A*, a component of the SWI/SNF chromatin re-modelling complex [6], and *PIK3CA* [7]. Many mucinous ovarian cancers, with frequent *KRAS* mutations, represent metastases from gastrointestinal tumours [8, 9], while low-grade serous carcinomas, arising on the background of borderline/low malignant potential tumours, harbour mutations in *KRAS* and *BRAF* [10]. Improved immunohistochemical

analyses now allow for more accurate classification of tumours [11], and pathological re-examination of archival specimens frequently leads to re-classification [12]. Critically, patterns of expression are consistent within anyone ovarian cancer subtype, and do not alter with stage [13].

Gene expression studies have also been revealing. Early array data indicated that the individual subtypes of ovarian cancer had very distinct patterns of gene expression [14, 15] that correlated with different putative tissues of origin [16]. More recently, large consortium studies have indicated that, within cohorts of predominantly high-grade serous tumours, there are distinct expression subgroups, with markedly different prognoses [4, 17]. Exactly how these gene expression subgroups link to specific mutation patterns, however, remains unclear.

Only around 20% of patients are diagnosed with stage I disease (confined to the ovary with or without cyst rupture and/or positive cytology in peritoneal washings). Outcome for these patients is generally good, with 80% still alive 5 years following diagnosis [18]. Two large randomised trials, ICON1 and ACTION, indicated that there is a significant improvement in overall survival when platinum-based chemotherapy is given following initial surgery [19, 20]. This improvement remained after long-term follow-up, although debate remains as to whether patients with low-grade stage IA/B disease [21] and