

# Can We Now Agree to Use the Same Definition to Measure Response According to CA-125?

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Oncologists use measurement of response as an indicator that the therapy they are administering is effective. This information can then be used to decide whether to continue, change, or stop therapy and may also be used as a surrogate end point in a clinical trial. The Response Evaluation Criteria in Solid Tumors (RECIST)<sup>1</sup> have been accepted as the standard methodology for measuring response. Many patients with ovarian cancer do not have measurable disease, so response cannot often be measured using RECIST criteria. Oncologists have therefore considered using the tumor marker CA-125 as an alternative method for monitoring the treatment of patients with ovarian carcinoma.

Serum levels of CA-125 are elevated in more than 90% of patients with advanced epithelial ovarian cancer.<sup>2,3</sup> Several different definitions of response based on CA-125 have been proposed, which has led to a variation in the response rate to a particular agent from 10% to 62% in the same group of patients, depending on which definition is used.<sup>4</sup> The Gynecologic Cancer Intergroup (GCIG) consists of representatives from the major gynecologic cancer trial groups around the world. After considerable debate—and after several versions—the GCIG has proposed a precise but simple definition for response according to CA-125, based on a 50% reduction in CA-125 levels that is confirmed and maintained for at least 28 days.<sup>5</sup> This definition, with examples demonstrating its implementation, is posted on the GCIG Web site (<http://ctep.info.nih.gov/resources/gcig/index.html>).

There are difficulties in validating a new response definition based on a tumor marker, as some patients are only assessable by scans and some are only assessable by the tumor marker. In some patients, scans might classify the response differently from the tumor marker. If a patient is classified as having stable disease by scans but as a responder according to the tumor marker, which is correct? The sim-

plest method used to validate definitions of response based on CA-125 has been to compare response rates according to CA-125 with response rates according to standard criteria and calculate the proportion of patients in whom the CA-125 prediction agrees or differs with the response determined by standard criteria.<sup>6</sup> The accuracy of the definition for response according to CA-125 has also been determined by examining how accurate the CA-125–defined response was in predicting the activity of drugs in phase II trials, compared with response rates obtained by standard criteria.<sup>7</sup>

It is most important to determine which response criterion is the more reliable method for predicting survival and clinical benefit. In this issue of the *Journal of Clinical Oncology*, Gronlund et al<sup>8</sup> validate the GCIG CA-125 response criteria by comparing the prognostic value of response by the CA-125 definition with response by the RECIST criteria. They retrospectively studied 131 patients who received either topotecan or paclitaxel plus carboplatin as second-line chemotherapy for ovarian cancer. To overcome the variability of response assessment by each criterion at different time points, they used the landmark method, which measures survival from the response evaluation after the fourth course of chemotherapy. They found that the CA-125 criteria were 2.6 times more accurate than RECIST at predicting survival. Although on univariate analysis both RECIST and CA-125 response were each significantly correlated with survival, in a Cox analysis, where both response classifications were included in the regression model, only the CA-125 response was significant.

One can question the choice of the landmark date and the limitation of the analysis to just 68 patients assessable by both RECIST and CA-125. In addition, the definition of the CA-125 response used by Gronlund et al differs slightly from that finally agreed on by the GCIG, which requires one pretreatment sample within 2 weeks before starting

treatment (not two) and requires that the response is maintained for at least 28 days (not 21 days). Despite these caveats, this study does support the GCIG CA-125 response definition.

The GCIG definition of CA-125 response is simple enough to be used in many circumstances, including in individual patient management, in standardizing care, and in performing retrospective analyses. In addition to CA-125 response, the GCIG has also proposed a definition of CA-125 progression.<sup>9</sup> Although this definition is recommended to help define first recurrence after initial therapy, it requires further validation in clinical trials of patients with relapsed disease. For patients who do not have elevated CA-125 levels or whose levels have neither responded nor progressed by the GCIG criteria, response and clinical benefit must be assessed by standard methods.

In clinical trials, the GCIG CA-125 response definition has great potential value. It should be used to support so-called go/no-go decisions for further development of drugs in phase II trials. Eligibility for trials in which response rate is an end point could be broadened to include either RECIST or CA-125 assessable patients, as many patients with peritoneal implants cannot be adequately assessed by conventional imaging techniques, but might well have elevated CA-125 levels. Trials could be designed with a 90% power to detect the minimal acceptable rate in either the standard RECIST or the CA-125 response, greatly saving patient resources.

It may not be possible to get fast-track regulatory approval based on CA-125 response alone because of the possibility that a novel agent could interfere with CA-125 synthesis or release. There have been reports of unreliable CA-125 measurements after paclitaxel therapy, but this has not been corroborated in other studies in which CA-125 half-life as a prognostic indicator or a precise definition for CA-125 response was used.<sup>10-12</sup> If a patient has received human antimouse antibody therapy, the assay may become unreliable, although there are ways to overcome this problem.<sup>13</sup> It is important to recognize other limitations of CA-125 when monitoring the course of disease. Levels can be altered dramatically by abdominal surgery or peritonitis. There is also the possibility of laboratory error and considerable variation in results among laboratories. Despite these

cautions, increased confidence in a CA-125 response definition should lead to a cheaper and, in some cases, more accurate method for monitoring ovarian carcinoma therapy than standard radiographic criteria.

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### **Author's Disclosures of Potential Conflicts of Interest**

The author indicated no potential conflicts of interest.

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