Comparative evaluation of standard criteria and CA-125 in ovarian cancers treated with platinum or paclitaxel

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Summary

Purpose: To assess CA-125 in defining tumor response in patients treated with paclitaxel.

Patients and Methods: We analyzed 150 women treated for epithelial ovarian carcinoma with platinum or paclitaxel. We compared the patients treated with two agents, using a precise definition of CA-125 response, determined by 50% and 75% reductions, like other authors have published.

Results: CA-125 criteria gave response rates very similar to the standard response rates, both for patients treated with platinum (75% vs 63%) and also for those treated with paclitaxel (40% vs 39%). Rates of false-positive prediction of response by CA-125 were also similar for patients treated with these two agents.

Conclusion: Precise 50% or 75% CA-125 response criteria are as sensitive as standard criteria for assessing activity of therapy for the ovarian cancers treated with platinum or paclitaxel. We propose that they may be useful in defining response in lieu of or in addition to standard response criteria in clinical trials involving epithelial ovarian cancer.

Key words: Paclitaxel; Platinum; CA-125; Ovarian cancer.

Introduction

Progression-free survival is an important end-point in cancer clinical trials [1]. The currently used definitions for progression depend on clinical signs, scans or X-rays. These are defined by the World Health Organization (WHO) as "standard criteria" [2]. According to this standard criteria, response was classified as: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not measurable or not assessable. A number of studies have suggested that serum CA-125 levels may be an important prognostic factor for survival, defining response or progression in patients with ovarian carcinoma [3, 4]. Thus it was suggested that serum CA-125 can substitute for conventional measures in defining tumor response [5-17]. According to these CA-125 criteria, more patients would become assessable for response and would not require sequential computed tomography (CT) or ultrasound scans. However in some studies [18-20] there has been evidence that women with advanced epithelial ovarian cancer, who respond according to standard criteria, do not correlate with those who respond according to CA-125 criteria. Moreover, while patients who respond according to standard criteria have a better progression-free survival than nonresponders, those who respond as determined by CA-125 criteria do not. This is particularly true when the role of CA-125 is analyzed in patients undergoing second-line treatment with paclitaxel. A possible, but not proven, explanation for this is increased shedding of CA-125 antigen induced by paclitaxel. However the small number of patients analyzed in these studies and insufficiently stringent definitions of response according to CA-125 criteria, would explain that [18-20]. According to a previous study, we studied patients with epithelial ovarian cancer treated with paclitaxel and compared them with those treated with platinum, using a precise definition of CA-125 response, determined by 50% and 75% reductions, like other authors have published [21].

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Patients and Methods

We analyzed 150 patients treated with adjuvant chemotherapy after optimal surgery for epithelial carcinoma of the ovary at the Department of Obstretics and Gynaecology of the Second University of Naples between 1992 and 2002. Ninety-six patients were treated first-line with platinum, while the remainder were treated with paclitaxel (22 in first-line therapy and 32 in second-line). Platinum and paclitaxel were used as single agents. To be eligible, patients had to have CA-125 measurements performed on at least three serum samples, with at least one sample having a level more than or equal to 40 U/ml at the start of therapy. The maximum period during which a response might occur is the first six months after the start of the treatment. Response, as determined by CA-125 criteria, was classified as: "response" or "no response". In particular, response to the treatment occurred if after two samples there was a 50% decrease, confirmed by a fourth sample (50% response), or a serial decrease over three sample of greater than 75% (75% response) [9]. The final sample had to be at least 28 days after the previous sample. An upper limit of normal for CA-125 of 30 U/ml and a lower limit of accuracy of 15 U/ml were used. Moreover, for inclusion in the analysis, patients were required to have at least one bidimensionally measurable lesion as evidenced by computed tomography (CT), magnetic resonance imaging (MRI), ultrasound or physical examination. The standard response criteria were determined according to WHO criteria [3]. The difference between the observed and expected

number of responses was calculated using standard methodology. The X_2 test was used for statistical analysis.

Results

Table 1 shows that CA-125 criteria give response rates very similar to the standard response rates, both for patients treated with platinum and those treated with paclitaxel. A greater proportion of patients treated with platinum are assessable by CA-125 criteria (89%; 82 of 96 patients) than by standard criteria (68%; 66 of 96 patients). Indeed, a similar number of patients treated with paclitaxel are assessable by CA-125 criteria (87%; 47 of 54 patients) than by standard criteria (89%; 48 of 54 patients). This reflects the requisite for assessable disease, according to WHO criteria, for admission into second-line paclitaxel trials, as was accepted in the years considered in this work. Tables 2, 3 and 4 list false-positive CA-125 assessment rates of 4% and 5% for patients treated with platinum and paclitaxel, respectively. A false-positive result reflects clinical disease progression even if there is a decreasing level of CA-125, which is suggestive of response. Therefore if CA-125 alone is used as a response criteria, 4% to 5% of patients would be managed as responders but would in fact have clinical progressive disease. In summary false-positive rates for platinum and paclitaxel are similar and low using CA-125 as response criteria. The single false-positive patient treated with platinum had a clear clinical progression on physical examination, even if there was a reduction of serum CA-125 concentration, like the false-positive one treated with paclitaxel. The same tables also list false-negative CA-125 assessment rates of about 20% both for patients treated with platinum and paclitaxel, respectively. A false-negative result represents a failure of CA-125 to identify a clinical response. Thus, if CA-125 was used as the only criteria to stop treatment based on failure to respond, about 20 in 100 patients may be undertreated by virtue of a missed response.

Table 1. — *Comparison of standard and CA-125 responses in patients treated with platinum or paclitaxel.*

	Platinum		Paclitaxel	
	No.	%	No.	%
Standard response	42/66	63	19/48	39
CA-125 response	62/82	75	19/47	40

Table 2. — *Comparison of standard and CA-125 responses for patients treated with platinum.*

	Standard response					
	CR+PR		SD		PD	
	No.	%	No.	%	No.	%
CA-125 response	32	48	1	1.5	1	1.5
CA-125 no response	8	12	1	1.5	23	34

Table 3. — *Comparison of standard and CA-125 responses for patients treated with placitaxel.*

	Standard response					
	CR+PR		SD		PD	
	No.	%	No.	%	No.	%
CA-125 response	22	46	1	2	1	2
CA-125 no response	4	8.5	1	2	18	38

Table 4. — *Sensitivity, specificity and positive predictive value of CA-125 as a measure of response.*

	Platinum %	Paclitaxel %
Sensitivity	80	85
Specificity	96	95
Positive predictive value	97	96

Discussion

A variety of serum tumor markers have been developed and used in ovarian cancer. These markers of monoclonal antibodies could detect three different classes of cell surface antigen. In fact, while CA-125, CA-30, CA-602 are antibodies raised against the core protein of the proteoglycan molecule, CA-19-9, CA50, KMO-1 and CA-72-4, STN and CA-546 are antibodies against a different portion of the glycosaminoglycan chain from the core protein [22]. The CA-125 antigen is a glycoprotein with a high molecular weight that is expressed by most epithelial cancers. Since the initial reports of CA-125, publications have assessed the use of this marker in the management of ovarian cancer. In fact serum CA-125 concentrations have an established role in the differential diagnosis of ovarian cancer, monitoring of disease status during treatment and tumor follow-up [23]. If CA-125 criteria were shown to be as accurate as conventional measures, more patients would become assessable for response and would not require serial CT scans. In both clinical trials and everyday practice, CA-125 criteria are more widely applicable than standard criteria. It is clear from this study that response rates according to CA-125 are similar to standard response rates not only for patients treated with platinum, but also for patients treated with paclitaxel. This suggests that for evaluation of clinical trials both methods of response estimation seem satisfactory. Doubt has been cast on the role of CA-125 in the evaluation of patients undergoing second-line treatment with taxanes. Eisenhauer *et al.* [19] studied 391 patients treated with paclitaxel as a second-line agent. Using a definition of CA-125 response as serial decreases in CA-125 levels, they found that although 49% of patients demonstrated a CA-125 response, only one-third of these patients responded according to standard criteria. Pearl *et al.* [20], studying the rate of CA-125 decrease by regression analysis in 66 patients, observed an improved progression-free survival for responders according to standard criteria, but not if determined by CA-125 regression curves. Davelaar *et al.* [18] demonstrated significantly improved progression-free survival of patients treated with paclitaxel, who responded according to CA-125 criteria compared with nonresponders. They also demon-

strated similar improvements in progression-free survival using both CA-125 and standard criteria to evaluate response. Bridgewater *et al.* [21] proposed that precise 50% or 75% CA-125 response criteria are as sensitive as standard response criteria for assessing the activity of therapy for patients with ovarian cancer treated with platinum or paclitaxel. According to this study, our impression is that, although not all authors found a statistically significant correlation between CA-125 defined response and efficacy, the use of precise definitions appeared to improve this correlation. We have shown that the false-positive rate is low, while the false-negative rate is high. This suggests that in the context of a CA-125 response, CA-125 assessment with physical examination is sufficient, as suggested by Gore *et al.* [24]. Instead the high false-negative rate suggests that approximately one in five patients without CA-125 response are objective responders, and such patients may be undertreated if CA-125 was used as the only criteria to stop treatment. Thus, for CA-125 non responders CT scans may still be of value in management. In conclusion, our study is only one report and must be enlarged enrolling more patients in the analyses.

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