ORIGINAL RESEARCH PAPER

Volume-7 | Issue-12 | December-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CA 125- A RELIABLE MARKER FOR RESPONSE EVALUATION IN OVARIAN CANCER?

Oncology

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ABSTRACT

Aim- Primary aim of our study is to establish and analyse the relationship between serum CA125 levels and response of epithelial ovarian cancer to treatment.

Patients and method- 46 patients of ovarian cancer of variable age group received treatment at our centre. Patients were then kept on follow-up and at each follow-up serum CA-125 was measured to observe the disease response. Later on level of serum CA-125 was then correlated with recurrence, residual or metastatic disease.

Results- Of 46 patients diagnosed with ovarian cancer serum CA-125 level was recorded in all the patients before treatment and on completion of first-line therapy at each follow-up. Serum CA 125 levels were found to be raised in all the patients before starting treatment. While during treatment and during post treatment follow-ups mean CA 125 level remained decreasing.

KEYWORDS

CA 125, epithelial ovarian cancer, metastatic disease.

INTRODUCTION

CA125 is expressed as a membrane-bound protein at the surface of cells that undergo metaplastic differentiation into a Mullerian-type epithelium or released in soluble form in bodily fluids [1]. CA125 concentration in bodily fluids parallels certain physical conditions. CA125 is still the most extensively studied biomarker for possible use in the early detection of ovarian carcinoma (OC), and it has proved valuable in both detection and disease monitoring [2]. There have been reports of elevated levels of soluble CA125 in a number of other malignant conditions such as breast cancer, mesothelioma, non-Hodgkin lymphoma (NHL), gastric cancer, leiomyoma and leiomyosarcoma of gastrointestinal origin [3]. CA125 levels have also been found elevated in benign conditions such as endometriosis, pregnancy, ovulatory cycles, liver diseases and congestive heart failure, as well as in infectious disease such as tuberculosis [4, 5].

Since its discovery, CA125 has become well established as a tumor marker for epithelial ovarian cancer (EOC), and has shown to have an important role in initial diagnosis, during therapy as a surrogate of clinical response and during follow-up. It is only raised in ~50% of stage I EOCs and in 75% to 90% of patients with advanced disease. False positive results have been noted in many medical disorders, both malignant and benign. CA125 has been proposed and widely adopted as a tool for the assessment of response during therapy. The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines are also commonly used in ovarian cancer to evaluate the effectiveness of the therapy given. Unfortunately, diagnostic imaging is not always able to accurately measure the multiple small peritoneal lesions typical of this disease or the so-called 'non-measurable lesions'; hence the choice of CA125 as a surrogate for monitoring the treatment of ovarian cancer.

METHODOLOGY

Patients of age group 30-60 years who had been histopathologically diagnosed with epithelial ovarian cancer were included in the study. Prior to start of treatment serum CA125 was evaluated for each patient. After each cycle of chemotherapy serum CA 125 was used as a marker for response evaluation. After completion of treatment serum CA 125 was measured at each follow-up. The number of CA125 tests performed during follow-up in each group was recorded. CT scan imaging was used to compare the response as indicated by serum CA 125. The number of patients who relapsed in each group was established, and the first indicator of relapse was recorded, namely: rising CA125 levels; development of new signs; or development of new symptoms.

The currently accepted criteria defined by Rustin et al. and the Gynecologic Cancer Inter-Group (GCIG) [6] defines three categories of response: 'complete response' as normalization of CA125 on two serial tests ≥1 month apart with no evidence of disease on imaging; 'partial response' as 50% decrease over two serial CA125 measurements ≥28 days apart; and 'progressive disease' as doubling of CA125 concentration from the patient's nadir. This procedure requires two pretreatment samples, the last within 1 week of starting therapy. The evaluation of response during treatment requires CA125 levels ≤50% of the basal value; this value has to be confirmed with another assay after 21 days.

RESULTS

Serum CA125 level was recorded in 46 patients diagnosed with ovarian cancer before starting chemotherapy and at each follow-up. Median age of patients was 43 years [Table1]. Thirty-two patients included in our study were postmenopausal while 14 patients were premenopausal [Table2]. Among 46 patients 22 patients were having serous cystadenocarcinoma while 14 patients were having mucinous histopathology, rest of the patients were having variable other histopathological variants of epithelial ovarian cancer [Table3]. Initial level of CA 125 was observed in all the patient found to be raised in all the patients and was above 35 U/ml. At the time of diagnosis all patients were having raised level of serum CA 125 (mean value of serum CA 125 = 547 U/ml). During treatment period mean CA 125 level remained decreasing while on further follow-ups the mean trend remained same [Graph1].

Table1. Age group wise distribution of patients

Age group (in years)	No. of patients
30-40	14
40-50	18
50-60	14

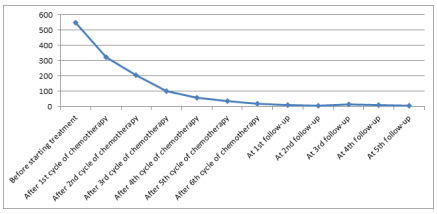
Table2. Menstrual status of patients

Menstrual status	No. of patients
Pre menopausal	32
Post menopausal	14

Table3. Histopathological distribution of patients

Histopathology	No. of patients
Serous cystadenocarcinoma	22
Mucinous	14
Endometroid	2
Brenner tumour	3
Undifferentiated	5

Graph1- Showing trend of mean CA 125 level of patients



DISCUSSION

Since the first publication on CA 125 (Bast et al. 1981) [7] other reports have confirmed the presence of this antigenic determinant in patients with epithelial ovarian cancer (Bast et al. 1983, 1984; Canney et al. 1984; Dodd et al. 1985; Heinonen et al. 1985; Crombach et al. 1985; Brioschi et al. 1985)[8-13]. CA 125 was proposed as a tumour marker to monitor the response to therapy in patients with ovarian cancer. Rising concentrations of the serum tumour marker CA 125 are seen weeks or months before clinical evidence of relapse of ovarian cancer in almost two-thirds of patients. A confirmed doubling of CA 125 from the upper limit of normal predicts relapse with a specificity of 98%.

Several small-scale retrospective studies have shown that either the rate of fall of CA125 levels following initial treatment or the absolute levels after one, two, or three courses of chemotherapy correlated with patient survival. In one of the first such studies, Canney et al. measured CA125 levels in patients with residual tumor following surgery and receiving chemotherapy. In three patients with apparently stable disease, the CA125 levels declined with a mean half-life of 22.6 days, whereas in 12 patients with a response to chemotherapy, the mean half-life was 9.2 days. In a later study, Vander Burg et al.[14] reported that patients with a CA125 half-life of 20 days or more had a 3.2 times progression rate and a significantly shorter time to progression than those with a half-life <20 days. Although different methods have been used to calculate the rate of CA125 decline (eg, time to normalize level, slope of the exponential regression curve, and half-life), in general, these early results have been confirmed.

The value of routine CA125 monitoring was examined in the OVO5/EORTC 55955 study of women who had achieved complete remission after first-line platinum-based chemotherapy [15]. This large randomized trial compared the earlier intervention of second-line treatment based on increased CA125 levels with delaying treatment until clinical evidence of relapse. The study demonstrated no overall survival benefit of early CA125-driven retreatment. Indeed, women assigned to delayed treatment started chemotherapy 4.8 months later than those assigned to early treatment, with no detriment to overall survival, whereas early treatment was detrimental to the quality of life. The counterintuitive results of the OVO5/EORTC 55955 study led to a variety of criticisms about the trial and its conclusions, which have been vigorously defended.

CONCLUSION

CA125 is the best available marker for epithelial ovarian cancer. As with most markers in clinical use, lack of sensitivity for stage I disease and lack of specificity limits its use for the early diagnosis of ovarian cancer. In postmenopausal women, however, measurement of CA125 may aid the differential diagnosis of benign and pelvic masses. Either absolute levels or its rate of decline during initial chemotherapy can provide independent prognostic information, but this is of little value for management of individual patients. Measurement of CA125 during initial chemotherapy can be useful in predicting response. Trends in levels suggesting failure should lead to the cessation of treatment. On the other hand, trends indicating response should result in the continuation of treatment. Although serial assay of CA125 in the follow-up of asymptomatic patients can lead to the early detection of recurrences, there is no evidence at present that the initiation of treatment based on rising CA125 levels results in either improved outcome or better quality of life. It is important to point out that CA125 levels are not elevated in 10–20% of patients with advanced ovarian cancer, in those patients, other markers or radiologic imaging techniques are necessary.

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