The importance of serum insulin-like growth factor-I level determination in the follow-up of patients with epithelial ovarian cancer

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Summary

Purpose of investigation: The aim of our study was to assess whether serum levels of serum insulin-like growth factor-I (IGF-I) could be used for the follow-up of the patients with epithelial ovarian cancer and to identify whether it was superior to serum CA 125.

Methods: Our study group consisted of 28 patients diagnosed with epithelial ovarian cancer who had initial high serum CA 125 levels and have received chemotherapy following the operation. Preoperatively and before each chemotherapy administration, serum CA 125 and IGF-I levels were measured.

Results: The mean value of preoperative serum CA 125 was 364.0 ± 152.9 U/ml. Serum CA 125 levels decreased with chemotherapy (Spearman rs= - 0.641, p=0.000). The mean preoperative serum IGF-I concentration was 58.04 ± 52.7 ng/ml, and it showed a slight increase with chemotherapy. (Spearman rs=0.318, p=0.001). We observed that there was a weak-moderate negative correlation between the two markers, and when chemotherapy was administered serum CA125 levels which were initially high started to decrease while serum IGF-I levels showed a mild increase (Spearman rs= - 0.350, p=0.000).

Conclusion: The measurement of serum IGF-I does not provide any additional benefit in monitoring the response of the disease to chemotherapy.

Key words: Epithelial ovarian cancer; IGF-I; CA 125.

Introduction

Insulin-like growth factors (IGFs) are low molecular weight polypeptides similar to proinsulin, and their synthesis is growth-hormone dependent. They play very important roles in maintaining the continuity of cellular growth, and in the replication and differentiation of the cells [1]. There are two types in humans - IGF-I and II. Both molecules have molecular weights of about 7,000 Daltons. Human IGF-I is a single chain basic peptide with 70 amino acids and IGF-II is a slightly acidic peptide with 67 amino acids. The human IGF-I gene is located on chromosome 12, whereas the IGF-II gene is found on chromosome 11. IGF-I mediates much of the growth-promoting actions of the pituitary growth hormone while IGF-II regulates fetal growth [2]. IGFs show their effects by binding to specific receptors that are located on the surface of target cells. The transport of IGFs takes place after being bound to specific proteins (IGFBP). There are six types of transport proteins [3,4]. Although, IGFs are secreted from various cell types, they are predominantly synthesized in the granulosa and theca cells of the ovaries and in the liver under the stimulus of the growth hormone [5].

IGFs show their effects on normal cellular proliferation via endocrine, paracrine and autocrine pathways [6]. In tumor tissues of different origin one or both IGF genes can be expressed and the secreted IGFs can have mitogenic effects at the cellular level while controlling tumor growth at the same time [7-10]. Although IGF-I is primarily synthesized from the granulosa cells of the ovaries, Yee et al showed the expression of mRNA for IGF-I in cell lines of ovarian cancers of epithelial origin such as OVCAR-3 OVCAR-7 and PEO4 [11]. Resnicoff et al. demonstrated that the addition of IGF-I to the environment increases the growth rate of adenocarcinoma cell lines in the culture plate such as OVCAR-3 and CAOV-3, which originate from human ovarium epithelium and they stated that IGF-I and its specific receptor mediate the autocrine proliferation of human ovarian carcinoma cell lines [12].

The aim of our study is to demonstrate whether measurement of IGF-1 can be used as a marker for the follow-up of patients with ovarian carcinoma of epithelial origin.

Materials and Methods

The patients, who were admitted to our department for surgery between November 1997 and August 1999 with the initial diagnosis of an adnexal mass, had their serum CA125 levels determined (at Fikret Biyal Laboratory of Cerrahpasa Medical School). Preoperatively 10 ml of venous blood was obtained from these patients, and serum was separated after centrifugation for five minutes at a speed of 5,000 rpm. Serum samples were than stored at –70°C until their IGF-I levels were measured. From the patient group that were diagnosed with epithelial ovarian cancer after histopathological examination, the ones with high initial serum CA 125 levels and who were candidates for chemotherapy after the surgery were selected. This group consi-

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Table 1. — *The results of Tukey's HSD post-hoc multiple comparison analysis for CA 125 levels*

Serum CA 125	Preop.	Before 1st chemotherapy	Before 2nd chemotherapy	Before 3rd chemotherapy	Before 4th chemotherapy	Before 5th chemotherapy
Preop.		0.041	0.008	0.000	0.000	0.000
Before 1st chemotherapy	0.041		0.975	0.093	0.000	0.000
Before 2nd chemotherapy	0.008	0.975		0.576	0.023	0.011
Before 3rd chemotherapy	0.000	0.093	0.576		0.555	0.389
Before 4th chemotherapy	0.000	0.000	0.023	0.555		1.000
Before 5th chemotherapy	0.000	0.000	0.011	0.389	1.000	

sted of 28 patients and formed our study group. Patients with non-epithelial tumors such as germ cell, sex-cord stromal ovarian tumors and cases with double primers were not included in the study group. Patients then received chemotherapy with 135 mg/m2/24hr or 175 mg/m2/3hr Paclitaxel and Carboplatin AUC 6 (Area Under Curve). All the patients in the study group had their serum CA 125 levels measured before each chemotherapy regime was administered. Venous blood samples were obtained, and serums were then separated and stored at –70°C until the time of IGF-I measurement. After six doses of standard chemotherapy, second-look laparotomy was recommended for suitable patients.

After the chemotherapy administration of the last patient in the study group had ended, the study was closed and IGF-I levels were determined from the serum samples that were stored at -70°C. 'Active IGF-I with extraction' kit from Diagnostic Systems Laboratories (DSL) which utilized the IRMA technique (coated tube immunoradiometric assay) was used for measuring IGF-I levels. This measurement was performed in the Endocrinology Laboratory of the Department of Obstetrics and Gynecology, Cerrahpasa Medical School. Mean values and reference ranges for the Active IGF-I kit given by DSL: Females, age group 30-40, mean: 214 ± 88 (range 100-494 ng/ml); age group 40-50, mean: 180 ± 48 (range 101-303); age group 50-70, mean: 153 ± 49 ng/ml (range 78-258) were accepted as standards. Serum CA 125 levels were determined in the Fikret Biyal Laboratory of Cerrahpasa Medical School. A CA 125 II kit that utilized the RIA technique for serum CA 125 measurement was used (Centocor®). Cut-off value for CA125 was accepted as 35 U/ml.

All the data obtained from the patients were evaluated by using 7.0 SPSS for windows. The Student's t-test, one-way variance analysis and Spearman's correlation analysis were used for statistical evaluation; p value of < 0.05 was accepted for statistical significance.

Results

The mean age of the 28 patients who were included in the study was 57 ± 9.97 years (range 38-76). When the cases were classified according to their stages: two cases (7.1%) were stage IC, two cases (7.1%) were stage IIC, 19 cases (67.9%) were stage IIIC and five cases (17.9%) were stage IV.

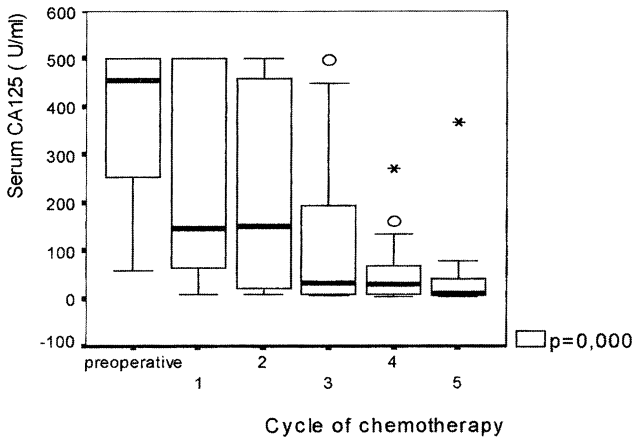

Figure 1. — *Mean serum CA 125 measurements before each chemotherapy administration.*

Before the operation the mean serum CA 125 level of the patients was 364.0 ± 152.9 U/ml. Mean serum CA 125 level before the first chemotherapy was 239.4±203.3 U/ml, before the second chemotherapy it was 203.6± 209.3, before the third chemotherapy it was 125.6±168.8 U/ml, before the fourth chemotherapy the CA 125 level was 49.4±65.5 U/ml and before the fifth chemotherapy it was 36.5 ±78.8 U/ml (Figure 1).

In order to evaluate whether there was a difference between the mean serum CA 125 levels before each chemotherapy, one-way variance analysis was performed and a statistically significant difference was found (F=15.515, p=0.000). In order to investigate in which groups this difference existed, Tukey's HSD post-hoc multiple comparison analysis was initiated. The results of this analysis are presented in Table 1.

A correlation analysis was performed in order to see how serum CA 125 levels changed in time with the administration of chemotherapy. Serum CA125 levels decreased with chemotherapy administration and there was a statistically significant negative correlation of moderate degree (Spearman rs=–0.641, p=0.000) (Figure 2).

Table 2. — *The results of Tukey's HSD post-hoc multiple comparison analysis for IGF-I levels*

Serum CA 125	Preop.	Before 1st chemotherapy	Before 2nd chemotherapy	Before 3rd chemotherapy	Before 4th chemotherapy	Before 5th chemotherapy
Preop.		0.966	0.413	0.361	0.311	0.192
Before 1st chemotherapy	0.966		0.908	0.884	0.814	0.720
Before 2nd chemotherapy	0.413	0.908		1.000	1.000	0.999
Before 3rd chemotherapy	0.361	0.884	1.000		1.000	1.000
Before 4th chemotherapy	0.311	0.814	1.000	1.000		1.000
Before 5th chemotherapy	0.192	0.720	0.999	1.000	1.000	

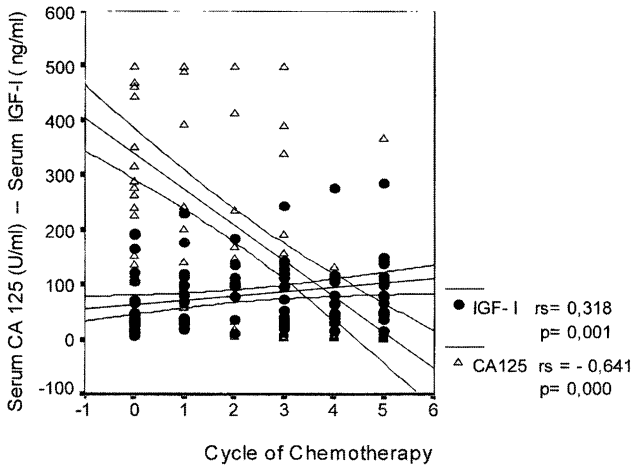

Figure 2. — *Distribution of serum IGF-I and CA 125 levels during the administration of chemotherapy.*

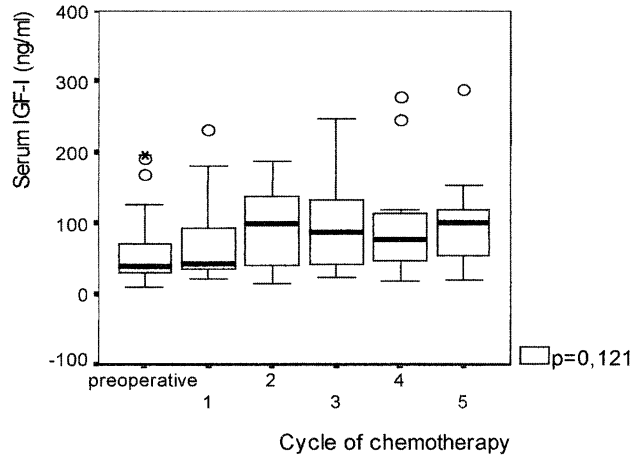

Figure 3. — *Mean serum IGF-I measurements before each chemotherapy administration.*

The mean preoperative serum IGF-1 level of the patients was 58.04±52.7ng/ml. Mean IGF-1 before the first chemotherapy was 72.5±57.5 ng/ml, before the second chemotherapy it was 93.3±57.19 ng/ml, before the third chemotherapy 94.2±65.09 ng/ml, before the fourth chemotherapy 99.09±76.5 ng/ml and before the fifth chemotherapy 100.6±60.18 ng/ml (Figure 3)

One-way variance analysis was performed in order to compare mean serum IGF-I values before each chemotherapy administration . Means of serum IGF-I values were not different from each other (F=1.789, p=0.121). The results of Tukey's HSD post-hoc multiple comparison analysis for comparing mean serum IGF-I levels before each chemotherapy are presented in Table 2.

A correlation analysis was conducted to demonstrate how serum IGF-levels changed during the administration of chemotherapy. Serum IGF-I values showed a slight increase after chemotherapy and there was a weak-moderate positive correlation (Spearman rs = 0.318, p=0.000) (Figure 2).

In a total of 28 patients, the relationship between the serum CA 125 and IGF-I levels measured before each chemotherapy administration was investigated by correlation analysis. There was a weak-moderate negative relationship between serum CA 125 and serum IGF-1 levels. With the administration of chemotherapy, serum CA 125 levels that were high in the beginning started to decrease whereas serum IGF levels increased (Spearman rs= –0.350, p=0.000) (Figure 4).

Discussion

One of the most convenient methods in the follow-up of the patients with ovarian cancer and evaluation of the response to the treatment is to monitor the levels of the serum tumor markers that are elevated at the beginning. The decrease that is seen in the serum tumor markers with the treatment administered is an indicator for a good prognosis of the disease. Until now, in patients with the diagnosis of ovarian cancer, many studies have been carried out with several tumor markers in an attempt to monitor the follow-up of the disease. After Bast *et al.* identified IgG-I OC 125, a monoclonal antibody against epithelial ovarian tumor tissue, cancer antigen CA 125 has been defined and shown to increase in about 80% of all the ovarian carcinomas of epithelial origin [13, 14].

Within the tumor markers that are used for epithelial ovarian carcinoma cases, CA 125 is the one that generally demonstrates abnormal levels and that is why CA 125 is the most commonly used marker for monitoring and evaluating the response to the treatment [15-17]. In our study all the patients had high levels of serum CA125 before the operation which significantly decreased in most of the patients after administering chemotherapy.

One might think that using multiple markers instead of only one could be more helpful in the follow-up of the disease [18,19]. However, Bast *et al.* showed that in patients with epithelial ovarian carcinoma, monitoring CA 125, CA 19-9 and CEA together was not superior to monitoring CA 125 by itself [14]. Gadducci et al. demonstrated that upon comparison with other tumor markers

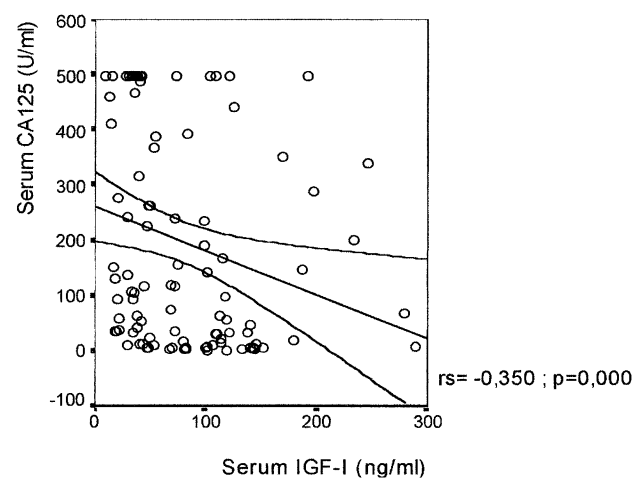

Figure 4. — *Correlation analysis of serum IGF-I versus serum CA 125 levels.*

such as CA19-9, 15-3, CA 50 and 72-4, serum CA 125 proved to be more successful in monitoring the disease, and concluded that other markers could only be of value for the patients who had normal preoperative serum CA 125 levels [20]. In the studies that have been conducted so far, a marker that could replace CA 125 has not yet been identified for the follow-up of epithelial ovarian carcinoma patients. Yet, Xu et al. found that plasma lysophosphatidic acid was increased in nearly all the patients (47/48) with ovarian carcinoma [21]. We certainly need further studies on this topic.

In recent years, several growth factors secreted from tumor tissue have attracted significant attention [22,23], and it has been speculated that endocrine, paracrine and autocrine growth factors might play a role in the development of malignant tumors with unlimited capacity for proliferation [24,25]. IGF-I, one of such growth factors, was shown to stimulate both in vivo and in vitro cellular proliferation and mitosis [6, 26-28].

IGF-I levels have also been measured in various benign tissues. IGF-I may play a role in the development and growth of myomas as well [29]. IGF-I and IGF-I receptor levels were found to be high in infertility cases[30]. IGF-I receptor was shown on the membranes of normal ovarian stromal cells in females with hyperinsulinism and androgen excess, and insulin could exert its effect by binding to IGF-I receptors [31], and insulin might cause hyperandrogenism via binding to IGF-I receptors [32].

Papa *et al.* showed that the number of insulin receptors in breast cancer tissue was six times higher when compared with normal breast tissue[33]. Stewart et al. showed that addition of IGF-I increased the proliferative effect of estradiol on breast cancer cells [34]. Talavera et al. investigated the presence of IGF-I receptor in both normal and neoplastic endometrial tissues and showed that the receptors that can bind IGF-I and II were present in both. However, the number of IGF-I receptors was significantly high in neoplastic endometrium and it was stated that IGF-I with its mitogenic effect could play an important role in the growth of neoplastic tissue [35]. Nagamani et al. showed that in endometrial cancer tissue, the mean concentration of insulin receptors was not different than that of normal endometrium. However, the concentration of IGF-I receptors was significantly higher than that of normal endometrium [36].

In studies performed with ovarian cancer cells, the cancer cells were found to secrete many autocrine growth factors and tumor cells contained their related receptors [37,38]. In an attempt to see whether IGF-I, IGFBP and receptors were present, Yee *et al* conducted a study in primary and metastatic ovarian cancer tissues of epithelial origin and in ovarian cell cultures. In all the cases (100%), they found IGF-I receptor mRNA [11]. Beck *et al.* searched for insulin and IGF-I receptors in normal ovarian tissue and in primary, recurrent and metastatic ovarian cancers. All types of ovarian tissue were positive for insulin receptors, however, IGF-I receptors were only found in 77% of primary ovarian cancers, 100% of metastatic tumors, 75% of recurrent tumors, 92% of normal ovarian tissues and only 83.7% of all the tissues under investigation. These findings are in contrast to the results by Yee et al. However, determining mRNA for encoding IGF-I receptors does not mean that production of IGF-I receptors will be realized up to 100% [26].

Karasik *et al.*, in an effort to evaluate the in vivo effects of IGF-I in epithelial ovarian cancers, measured IGF-1 and IGFBP levels in ovarian cyst fluids of benign and malignant nature. They found that IGF-I levels were significantly higher in the cancer group when compared to the control group. However, in the same study, IGF-I levels were not measured in the serum [39]. Shah *et al.* showed that mean preoperative serum EGF (epidermal growth factor) levels were similar in both epithelial ovarian cancer patients and in controls. However, in ovarian cancer patients the preoperative serum IGF-I level was 7.38±1.77 ng/ml, which was lower than that of the control group (33.3± 8.32ng/ml) and the difference between the two groups was statistically significant. When they made an evaluation as to the stage of the disease, they found that preoperative mean IGF levels decreased as the stage of the disease increased [40]. In a previous study we conducted, in patients with advanced stage epithelial ovarian cancer, serum IGF-I levels were lower than that of simple ovarian cyst cases and normal controls [41]. On the other hand, Beck *et al.* based on the results of their unpublished study, claimed that serum IGF-I levels of ovarian carcinoma patients were within normal limits [26].

Before the operation, at a stage where the disease burden and cancer cell load is high, theoretically the level of serum IGF-I, which influences cellular multiplication, should be high as well. However, the results of the two clinical studies mentioned above are not in accordance with this expectation. In our recent study we showed that in the preoperative period with the highest load for cancer cells, serum IGF-I levels did not differ significantly from the levels obtained following chemotherapy, and had even increased slightly. IGF-I also shows an antiapoptotic effect [42]. In ovarian carcinoma patients of high grade and late stage, it is very well known that the level of apoptosis is high [43,44]. Although it could be hypothesized that IGF-I levels would decrease as the rate of apoptosis increased, we need further studies to investigate this relationship.

Conclusion

Our study is the first clinical study in the literature to evaluate serum IGF-I and CA 125 levels simultaneously in patients with epithelial ovarian cancer. Serum CA 125 levels which were high before the operation generally showed a significant decrease following chemotherapy. During administration of chemotherapy serum IGF-I levels showed a slight increase with time. However, this increase was not as significant as the decrease in CA 125. In conclusion, since serum CA125 is a very valuable marker for the follow-up of these patients, IGF-I would not bring any additional benefit.

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