

## The Ca125 Concentration in Intraperitoneal Fluid as A Prognostic Factor in Ovarian Cancer Patients with Refractory Malignant Ascites

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### ABSTRACT

**AIM:** Chemotherapy refractory malignant ascites in ovarian cancer patients is still a serious problem which leads to significant deterioration in the quality of life by causing distressing symptoms such as pain, nausea, vomiting, anorexia, dyspnea. In this group of patients overall survival is short. Efficacy and tolerability of current available treatments is limited. The serum Ca125 concentration has been well documented as a useful marker for evaluating intravenous chemotherapy response in epithelial ovarian cancer patients. The main goal of this study was estimation of Ca125 concentration decline rate in the intraperitoneal fluid as a prognostic factor for intraperitoneal chemotherapy response and patients survival.

**METHOD:** Patients included in this analysis had malignant ascites in the ovarian cancer course with no regression after any available

intravenous chemotherapy. An intraperitoneal chemotherapy was cisplatin based. Ca125 concentration was measured twice in intraperitoneal fluid: before intraperitoneal chemotherapy infusion and 24 hours after.

**RESULTS:** Patients with Ca125 intraperitoneal concentration decrease more than 3 times lived longer than patients with lower Ca125 concentration reduction (78.5 vs 33,1 months),  $p = 0.06$ . The results of this study have many limitations, mostly due to the group of pts being small. That is why the results should be taken into consideration with caution.

**CONCLUSIONS:** Intraperitoneal fluid Ca125 concentration decrease rate after intraperitoneal chemotherapy seems to be a prognostic factor for overall survival in ovarian cancer patients with refractory malignant ascites.

**Key words:** Ca125; Ovarian cancer; Intraperitoneal chemotherapy; Prognostic factor; Intraperitoneal Ca125 concentration

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### INTRODUCTION

Among gynecologic cancers, ovarian cancer (OC) is the most common cause of mortality<sup>[1]</sup>. In Poland in 2011 almost 3600 women developed ovarian cancer and more than 2500 died. An incidence of mortality is independent of age of the patient at the onset in Polish population [<http://onkologia.org.pl>]<sup>[2]</sup>. The most distinctive features of OC are lack of characteristic symptoms at the beginning of the

disease. OC frequently spreads to the peritoneum which in turn causes ascites. That makes advanced tumor stage IIIC and IV according to FIGO classification at the time of diagnosis in 70% of pts.

Surgery with a total abdominal hysterectomy, bilateral salpingoophorectomy, omentectomy, pelvic and paraaortic lymph node dissection with maximal tumor debulking is a standard and basic management for OC. Platinum derivatives and taxane based chemotherapy is the next stage in the OC patients treatment. In advanced OC patients tumor recurrence rate is high. Refractory malignant ascites is still a difficult problem which leads to significant deterioration in the quality of life by causing distressing symptoms such as pain, nausea, vomiting, anorexia, dyspnea. In this group of pts overall survival is short and efficacy and tolerability of current treatments is limited<sup>[3,4]</sup>. An effective treatment for malignant ascites is still a big challenge not only for oncologists but also for palliative care physicians.

The ability of Ca125 concentration monitoring for OC therapy for the first time was described by Bast<sup>[5]</sup>. Ca125 is not pathognomonic for OC. It's non-specific marker of any peritoneal irritation. It is also found with endometrial and fallopian tumors or any malignant tissue of mesothelial origin like cancer of stomach, colon, pancreas, liver, lung and breast<sup>[6]</sup>. The serum Ca125 antigen concentration has been well documented as a useful marker for evaluating chemotherapy response in epithelial OC patients treated with intravenous chemotherapy. It is also extremely useful in the early detection of recurrence during the follow up period. The half time of ca125 is between 6 and 14 days<sup>[7]</sup>.

It was shown that Ca125 concentration in the peritoneal fluid is almost an order of magnitude higher than Ca125 serum concentration and correlates with serum levels<sup>[6]</sup>. However there are limited data regarding Ca125 assessment in peritoneal fluid as a prognostic marker during intraperitoneal chemotherapy. Authors did not find any data on Ca125 levels measured in intraperitoneal fluid during intraperitoneal chemotherapy. Authors also did not find any data on Ca125 concentration in intraperitoneal fluid monitoring.

The current study presents preliminary results of evaluating changes in Ca125 concentration in peritoneal fluid during intraperitoneal cisplatin based chemotherapy. The main goal of this study was estimation of decline Ca125 concentration in intraperitoneal fluid rate as a prognostic factor for intraperitoneal chemotherapy response and patients survival.

## MATERIAL AND METHOD

The study was approved by the Ethics Committee at Maria Skłodowska-Curie Memorial Cancer Center and Institute in Gliwice Poland (COI). Informed consent was obtained from all individual participants recruited to the study. This analysis included 17 consecutive ovarian cancer patients treated due to malignant ascites who failed on previous chemotherapy regimens. All of the women were diagnosed, treated and followed up in Clinical and Experimental Chemotherapy Department in COI by the same medical team. All laboratory tests were done within the same laboratory in COI, where a Ca125 serum concentration reference interval is less than 35 IU/mL. The analysis of patients' medical records was performed according to the national law regulation. The data including the age at onset, disease stage, surgical procedures, histology and chemotherapy treatment details and survival were gathered from hospital records. All of the patients underwent surgery, 10 of them had optimal or suboptimal surgery according to ovarian cancer operation protocol. The remaining pts had palliative

surgery due to cancer stage extent. The most common surgical procedures in these cases were tumor biopsies for histopathological examination. All pts had microscopic confirmation of epithelial OC. The most prevalent microscopic type was adenocarcinoma serosum papillare (77%) and adenocarcinoma endometrioides (12%). At the time of diagnosis most patients had OC in IIIC stage according to FIGO classification (76%). All patients received paclitaxel and carboplatin based intravenous chemotherapy in post-surgery setting. Patients characteristics are presented in Table 1.

The choice of consecutive chemotherapy type depended on patients general condition, type of response to the previous chemotherapy regimen and the drugs availability in the country or the financing possibilities by the health insurance.

### Study design

All the patients included in this analysis in the course of the disease attained chemotherapy refractory malignant ascites. Intraperitoneal chemotherapy (IPCT) administration was given as the treatment of last choice for malignant ascites in intravenous chemotherapy refractory ovarian cancer. Median chemotherapy regimens before IPCT was 2 (range 1-6). In all pts an IPCT was cisplatin based one. Cisplatin was given after the peritoneal cavity decompression. The cisplatin dose was 80 mg/m<sup>2</sup> in 1000 mL saline solution in one hour intraperitoneal infusion using cannula. Before chemotherapy administration a typical for cisplatin therapy antiemetic premedication was used. Cytostatic solution in the peritoneal cavity was left for 24 hours, after which the liquid was removed. Ca125 concentration was measured twice in intraperitoneal fluid: before IPCT infusion (IPCT) and 24 hours after. Then cannula was removed. After IPCT all pts with clinical response continued intravenous cisplatin based chemotherapy. Clinical effectiveness was evaluated using RECIST criteria including Ca125 testing every 12 weeks.

### Statistical analysis

Statistical analysis was performed using STATISTICA 8 PROGRAM. The impact of variables such as patients age, previous treatment lines, type of surgical treatment on the increase of CA125 concentration in peritoneal fluid were analyzed by chi-squared test with Yates' correction. Differences were considered as significant if the *p* value was ≤ 0.05. Survival evaluation was performed using the Kaplan Meier estimate with log rank test.

**Table 1** Patients characteristics.

Age	Median 58 years (range 41-67)
<b>Microscopic type</b>	
Adenocarcinoma papillare	77%
Adenocarcinoma endometrioides	12%
Other	11%
<b>Primary stage according to FIGO</b>	
II	12%
IIIC	76%
IV	12%
<b>Previous chemotherapy lines (including paclitaxel, platine derivatives, gemcitabine, topotecan, doxorubicin, endoxan)</b>	
I	41%
II	18%
III	12%
V	18%
VI	11%
Ca125 intraperitoneal fluid concentration before intraperitoneal chemotherapy	Median 15319.40 range 538.9-192482.8
Ca125 intraperitoneal fluid concentration after intraperitoneal chemotherapy	Median 1832.50 range 145.1-28831.0

## RESULTS

This analysis included 17 consecutive ovarian cancer patients treated due to malignant ascites who failed on previous chemotherapy regimens. Median age at diagnosis was 58 years (range 41-67). Before OC diagnosis 88% of pts was in postmenopausal period.

During the observation 12 patients (71%) died. Median overall survival time (OS) was 37,4 months. OS on 2 and 5 years was 65%, 34% respectively. The median time from OC diagnosis to malignant ascites development and starting the palliative IPCT was 18 months (range 3-143). Median survival time after palliative intraperitoneal cisplatin chemotherapy administration was 8 months (range 2-30). One patient did not continue CT due to the lack of ITCT response. She died 2 months later.

The most frequently reported toxicity were nausea and vomiting, and weakness. Toxicity was never the reason of IPCT discontinuation.

This paper was focused on Ca125 level measurement. That is why authors did not analyze other treatment details.

Median serum Ca125 level measured before the first chemotherapy administration (in postoperative setting) was 645.7 IU/mL (range 6.4-5006). IPCT administration was given as the treatment of last choice for malignant ascites in intravenous chemotherapy refractory ovarian cancer. At the time of design of the protocol and during the study in Poland there was no access to other types of intraperitoneal treatment. IPCT is also unpopular for logistic reasons. Median serum Ca125 concentration before IPCT infusion was 1921.30 (range 18.3-30430.0). Median Ca125 concentration in intraperitoneal fluid before chemotherapy infusion was 15319.40 (range 538.9-192482.8). In our group of patients Ca125 concentration in intraperitoneal fluid was higher than in the serum. This had no influence on OS,  $p = 0.54$ .

All patients experienced a decrease of intraperitoneal CA125 concentration after IPCT administration. Median CA125 concentration in intraperitoneal fluid after chemotherapy infusion was 1832.50 (range 145.1-28831.0). Median decline of Ca125 concentration was 11525.0 (range 28.7-163651.8). Patients with Ca125 intraperitoneal concentration decrease more than 3 times lived insignificantly longer than pts with lower Ca126 concentration reduction (78.5 vs 33.1 months),  $p = 0.07$ . Decrease of the Ca125 intraperitoneal concentration was not dependent on the number of previous chemotherapy regimen, surgery type or age,  $p = 0.6, 0.09, 0.34$ , respectively.

## DISCUSSION

Ca125 is well known as marker of peritoneal irritation<sup>[8,9]</sup>. Ca125 marker concentration is elevated in most advanced epithelial OC patients<sup>[7]</sup>. Ca125 has been used in diagnosis and, more important, in monitoring intravenous chemotherapy response and in follow up<sup>[5,10]</sup>. Many studies indicate that serum Ca125 level nadir after chemotherapy completion may be a strong prognostic factor for progression free survival time as well as for OS<sup>[11,12,13]</sup>. It has been showed that women with nadir serum Ca125 lower than 10 U/mL live longer than women with higher nadir<sup>[14]</sup>. Ca125 regression after two cycles of neoadjuvant chemotherapy appears to be an important prognostic factor for probability of radical surgery and OS for OC patients<sup>[15]</sup>.

Although the wide intraperitoneal therapy use there are limited data of Ca125 concentration level monitoring its efficacy. Authors did not find any data on Ca125 concentration in peritoneal fluid monitoring. There are only a few reports addressed to Ca125 measurement during IPCT but all of them are related to the Ca125 concentration in the

serum, not in intraperitoneal fluid. In one of them authors did not find significant difference in serum Ca125 regression among patients receiving IPCT and intravenous CT<sup>[16]</sup>. In the other one the authors found difference in anticancer drugs as well as Ca125 concentration in intraperitoneal fluid and plasma<sup>[7]</sup>.

At the time of chemotherapy refractory ascites diagnosis 88% of pts had Ca125 serum level elevated. At the same time in all patients Ca125 concentration in peritoneal fluid was up normal range. Median Ca125 concentration in intraperitoneal fluid before intraperitoneal chemotherapy was 8 times higher than median serum Ca125 concentration at the same time.

Randomized controlled studies are few with small series and aimed at use of diuretics, octreotide, intraperitoneal therapy and targeted therapy with antiangiogenics drugs. The pharmacokinetic rationale for IPCT was described almost 30 years ago<sup>[17]</sup>. When malignant ovarian cancer cells are dispersed into the peritoneal cavity and case the peritoneum irritation resulting in ascites as a direct effect of cancer. High concentration of chemotherapy drugs in intraperitoneal cavity with direct cells exposure to the drug may lead to better tumor response than after intravenous CT administration<sup>[3]</sup>.

## CONCLUSIONS

IPCT is an effective, safe and relatively cheap method of treatment with no burden substantially staff. In our group of pts the Ca125 concentration in intraperitoneal fluid was higher than Ca125 concentration in serum. Decrease rate of intraperitoneal fluid Ca125 concentration after intraperitoneal chemotherapy seems to be a prognostic factor for overall survival in ovarian cancer patients with refractory malignant ascites.

The findings of the present study must be considered in terms of a small number of patients. However, the results of the present study suggest that the reduction rate of Ca125 level in intraperitoneal fluid may distinguish a group of patients who will benefit from this treatment.

The results of this study have many limitations, mostly due to the group of pts being small. That is why the results should be taken considered with caution.

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