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ORIGINAL ARTICLE

Utility of CA 125 in Determining the Response to Neoadjuvant Chemotherapy

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Abstract

Background CA-125 is the tumor marker for surface epithelial carcinoma of ovary, and it is used to determine the response to chemotherapy, relapse, and disease progression. Neoadjuvant chemotherapy followed by interval debulking surgery is an acceptable treatment for patients with advanced disease. Most patients will require 2–4 cycles of neoadjuvant chemotherapy. However, some patients receive more than 4 cycles of neoadjuvant chemotherapy in many centers, and the most common reason for this is extensive disease at the beginning of neoadjuvant chemotherapy.

Purpose To determine if a normal CA-125 level following neoadjuvant chemotherapy is an indicator of satisfactory reduction in the extent of the disease and should CA-125 levels be considered in deciding the number of cycles of neoadjuvant chemotherapy.

Methods The histopathology report of all patients who underwent successful interval cytoreduction between 01-09-2020 and 31-08-2021 was analyzed to determine if the preoperative CA-125 level following neoadjuvant chemotherapy is reflective of the extent of disease resolution.

Results There was no correlation between the pre-neoadjuvant chemotherapy CA-125 level, pre-operative CA-125 level, and the histopathology report. Some patients with a very high pre-neoadjuvant chemotherapy and pre-operative CA-125 level had no extra-ovarian involvement. Conversely, some patients with a low pre-neoadjuvant chemotherapy and a pre-operative CA-125 level had significant extra-ovarian involvement.

Conclusion After how many cycles of neoadjuvant chemotherapy should surgery be performed must be decided by clinical examination and imagining. The purpose of neoadjuvant chemotherapy is to increase the rate of achieving complete cytoreduction in patients with extensive disease and poor performance status. Administering more than 3–4 cycles can be counterproductive.

Keywords Neoadjuvant chemotherapy · CA 125 · Primary Debulking · Interval Debulking

Introduction

CA-125 is a glycoprotein and is a commonly used tumor marker for surface epithelial carcinoma of the ovary [1]. It is used to determine the response to chemotherapy, relapse, and disease progression, even though it is far from being an ideal tumor marker [1]. It is raised in a number of benign and malignant gynecological conditions like leiomyoma of the uterus, endometriosis, pelvic inflammatory disease, benign ovarian tumors, carcinoma endometrium, germ cell and sex cord ovarian malignancies, etc. [2, 3]. It is also raised in some non-gynecological conditions such as liver disease, postoperatively following any laparotomy, intestinal perforation, pancreatitis, GI malignancies, carcinoma lung, etc. [2, 3]. It is also raised in normal pregnancy and menstruation, which are physiological conditions [2, 3]. But a CA-125 level of more than 100 IU/ml in a patient with an adnexal mass is suggestive of carcinoma ovary, and if it is more than 1000 IU/ml, it is virtually confirmatory of surface epithelial carcinoma of the ovary,

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though levels above 1000 IU/ml have been rarely reported in benign conditions [4–6].

CA-125 levels are raised in germ cell and sex cord ovarian tumors, though not to the extent of other tumor markers specific for the malignancy, like alpha-fetoprotein for yolk sac tumor. Even among surface epithelial malignancies, mucinous cystadenocarcinoma does not show a raised CA-125 level as much as papillary serous cystadenocarcinoma [7, 8]. In fact, CA-125 level can be well within normal limits in a case of surface epithelial carcinoma if the capsule of the tumor is intact, and if there is no extra-ovarian spread or peritoneal inflammation [7, 8]. Practicing gynecological oncologists do come across situations where patients having moderately raised CA-125 levels have extensive extra-ovarian disease on laparotomy, which has not been picked up on imaging. And conversely, patients with CA-125 levels more than 1000 IU/ml can have an easily resectable disease.

A surgical staging with primary debulking followed by adjuvant chemotherapy is the preferred treatment for surface epithelial carcinoma of the ovary. A surgical staging involves a thorough inspection of the entire abdomen, collecting free fluid or saline lavage for cytology from pouch of Douglas, paracolic spaces, subhepatic space, and subdiaphragmatic spaces, generous sampling of all adhesions and suspicious areas, and random peritoneal biopsies. Primary debulking surgery involves removal of both ovaries, uterus, fallopian tubes, pelvic and para-aortic lymphadenectomy, and total omentectomy. The surgery can also involve resection of one or more segments of the bowel, appendicectomy, splenectomy, cholecystectomy, pelvic or total peritonectomy, and even resection of the diaphragmatic deposits with repair, if these organs are involved [9–11]. Fertility sparing surgery and withholding of adjuvant chemotherapy can be offered if there is a unilateral tumor with an intact capsule with no extra-ovarian spread, and if the histology is low grade and well differentiated on frozen section [12].

However, if the disease is widespread making the possibility complete cytoreduction unlikely, and/ or the performance status of the patient is poor with high likelihood of severe postoperative morbidity, mortality, and high treatment costs, neoadjuvant chemotherapy followed by interval debulking surgery can be offered [13–15]. The gynecological oncologist must assess the patient prior to assigning the patient as a candidate for neoadjuvant chemotherapy. The patient must be reassessed again after 2 cycles of neoadjuvant chemotherapy to determine whether there has been sufficient reduction in the extent of the disease to permit interval debulking surgery. Most patients will require 2–4 cycles of neoadjuvant chemotherapy [14–16]. However, some patients receive more than 4 cycles of neoadjuvant chemotherapy in many centers, and the most common reason for this is extensive disease at the beginning of neoadjuvant chemotherapy [16]. CA-125 levels usually fall drastically, very often to normal levels following neoadjuvant chemotherapy.

Purpose

To determine whether a normal CA-125 level following neoadjuvant chemotherapy is an indicator of satisfactory reduction in the extent of the disease and should CA-125 levels be considered in deciding the number of cycles of neoadjuvant chemotherapy.

Methods

This study was carried out in the department of gynecologic oncology between 01-09-2020 and 31-08-2021. Our institution is the largest and presently among the few fully dedicated cancer hospitals in the state of Bihar, India. The histopathology report of all patients who underwent successful interval cytoreduction after neoadjuvant chemotherapy for surface epithelial carcinoma of ovary was analyzed to determine whether the pre-operative CA-125 level following neoadjuvant chemotherapy is reflective of the extent of disease resolution.

In our institution, we perform total abdominal hysterectomy with bilateral salpingo-oophorectomy, total omentectomy, and pelvic peritonectomy during interval debulking surgery. In addition, we remove the enlarged pelvic and para-aortic nodes if seen, or mentioned in pre-operative imaging, and if required, also perform total peritonectomy, cholecystectomy, splenectomy, radical omentectomy, resection of mesenteric and diaphragmatic deposits, and resection of the involved segments of bowel.

Results

A total of 42 patients underwent successful interval cytoreduction after receiving neoadjuvant chemotherapy for carcinoma ovary during the above period. All patients received paclitaxel and carboplatin. All patients received more than 4 cycles of neoadjuvant chemotherapy, and most patients received 6 cycles. The CA-125 level prior to neoadjuvant chemotherapy and the level prior to surgery is shown in Table 1. The histopathology report of each patient is also mentioned in Table 1.

As can be seen, there is no correlation between the pre-neoadjuvant chemotherapy CA-125 level, pre-operative CA-125 level, and the histopathology report. Some patients who had a very high CA-125 level prior to neoadjuvant

Table 1 Patients who underwent successful interval debulking surgery between 01–09-2020 and 31–08-2021

S. no	Patient's Age	Pre-NACT CA-125 (IU/ml)	Post-NACT CA-125 (IU/ml)	Histopathology
1	46	617	14.3	Ovaries show residual tumor cells, pelvic peritoneum, and omentum involved
2	56	1845	11.9	Ovary shows residual tumor cells, rest not involved
3	25	774	10.3	Ovary unremarkable, uterine surface-involved diffuse deposits
4	51	762	42.4	Ovaries—papillary serous cystadenocarcinoma, omentum, and peritoneum involved
5	52	235.4	7.3	Right ovary shows residual tumor with chemotherapy-induced changes, left ovary unremarkable, uterine surface, and omentum involved
6	65	261	37.6	Ovaries show papillary serous cystadenocarcinoma, lymph nodes, and omentum involved
7	31	142	36.1	Ovaries show papillary serous cystadenocarcinoma with chemotherapy-induced changes, rectum, and omentum involved
8	59	6445	4.4	Right ovary shows minimal residual adenocarcinoma, left ovary unremarkable, omentum involved
9	43	1930	437	Ovaries show residual tumor with chemotherapy-induced changes; rest uninvolved
10	41	2359	91.5	Right ovary shows residual tumor, rest uninvolved
11	36	996	43.7	Ovaries show residual tumor, rest uninvolved
12	41	> 1000	70.6	Left ovary shows serous cystadenocarcinoma, right ovary unremarkable; omentum, peritoneum, and appendix involved
13	62	3591	8.2	Ovaries show only necrotic tissue; rest uninvolved
14	56	12,090	9.4	Ovaries show serous cystadenocarcinoma; rest uninvolved
15	53	8860	16.6	Ovaries unremarkable; rest uninvolved
16	45	346.2	10.7	Ovaries show necrotic tissue; rest uninvolved
17	61	4845	196.5	Right ovary shows serous cystadenocarcinoma; rest uninvolved
18	36	3845	46.2	Right ovary shows poorly differentiated carcinoma, left ovary unremarkable; omentum; and lymph nodes involved
19	51	317	4.4	Right ovary shows residual tumor with chemotherapy-induced changes; left ovary unremarkable; omentum involved
20	57	3945	49	Both ovaries show residual tumor with chemotherapy-induced changes; omentum involved
21	46	2130	8.2	Left ovary shows residual tumor, right ovary is unremarkable; rest uninvolved
22	41	4695	7.7	Ovaries unremarkable; rest uninvolved
23	34	299	26	Ovaries show papillary serous adenocarcinoma; rest uninvolved
24	72	1330	35.3	Ovaries unremarkable; rest involved
25	65	778.5	11.5	Right ovary shows serous cystadenocarcinoma, left ovary shows benign cyst; rest uninvolved
26	46	> 6000	> 1000	Ovaries show papillary serous cystadenocarcinoma; both fallopian tubes, omentum, and pelvic peritoneum involved
27	60	631.4	4.1	Ovaries unremarkable; rest uninvolved
28	60	1000	6.8	Ovaries unremarkable; rest uninvolved
29	45	260	126	Left ovary shows papillary serous cystadenocarcinoma, right ovary unremarkable; rest uninvolved
30	60	8860	16.6	Left ovary shows endometrioid adenocarcinoma, right ovary unremarkable; rest uninvolved
31	41	2359	14.7	Ovaries show residual tumor; rest uninvolved
32	51	354	5	Ovaries show serous cystadenoma; peritoneum involved
33	45	1642	Was missed	Ovaries show papillary serous cystadenocarcinoma; pouch of Douglas deposits positive for malignancy, omentum, and peritoneum involved
34	46	1001.6	208	Right ovary shows serous cystadenocarcinoma, left ovary unremarkable; lymph nodes involved, capsular involvement present
35	42	1715	39.4	Left ovary shows papillary serous cystadenocarcinoma, right ovary unremarkable; omentum, peritoneum, and lymph nodes involved, lymph nodes show capsular involvement

Table 1 (continued)

S. no	Patient's Age	Pre-NACT CA-125 (IU/ml)	Post-NACT CA-125 (IU/ml)	Histopathology
36	67	3887	10	Ovaries unremarkable; rest uninvolved
37	66	4121	58.6	Ovaries show papillary serous cystadenocarcinoma; uterus, omentum, and peritoneum involved
38	26	310	15.9	Left ovary shows papillary serous cystadenocarcinoma, right ovary unremarkable; rest uninvolved
39	41	874	14	Ovaries show serous cystadenocarcinoma; omentum; and peritoneum involved
40	56	687	10.8	Ovaries unremarkable; rest uninvolved
41	41	732	8.9	Ovaries minimal residual tumor; rest uninvolved
42	46	6800	25.6	Right ovary papillary adenocarcinoma; omentum involved

The surgery being performed in our institution is TAH + BSO + total omentectomy + removal of enlarged retroperitoneal nodes + pelvic peritonectomy. In addition, in those patients who have visible involvement of other organs, total peritonectomy, radical omentectomy, splenectomy, cholecystectomy, resection of involved segment(s) of bowel with anastomosis and creation of a stoma are performed accordingly. Patient 7 underwent resection of distal sigmoid with LAR

chemotherapy have no extra-ovarian involvement on histology. Some patients with an elevated CA-125 level pre-operatively also have no extra-ovarian involvement on histology. Conversely, some patients with a pre-neoadjuvant chemotherapy CA-125 level in the range 300–600 IU/ml and a low pre-operative CA-125 level (below 10 IU/ml) have significant extra-ovarian involvement.

Discussion

The decision to send the patient for neoadjuvant chemotherapy should be taken by the operating gynecological oncologist since it is the operating surgeon who can best decide the possibility of achieving complete cytoreduction. The presence of ascites, pleural effusion, or a large omental cake by itself is not a contraindication for upfront surgery, i.e., staging with primary debulking surgery. Interval debulking surgery performed following neoadjuvant chemotherapy can be very similar to a primary debulking surgery, in the sense that both surgeries might involve widespread resection and removal of the same organs. The patient has to be examined after 2 cycles of neoadjuvant chemotherapy to assess the response, and if the disease appears resectable, the patient should be posted for interval debulking surgery. This is not an institutional protocol or a guideline proposed by any authority. But it does make a difference if the operating gynecological oncologist assesses the response of the tumor to neoadjuvant chemotherapy after 2 cycles, and every cycle thereafter, rather than leaving the decision entirely to the medical oncologist. We believe that most patients should receive 2–4 cycles of neoadjuvant chemotherapy. A very high pretreatment CA 125 level has a poor prognosis compared to a normal pretreatment CA 125 level [7]. And a normal CA 125 level following neoadjuvant chemotherapy indicates a good prognosis as compared to a high CA 125 level following neoadjuvant chemotherapy [17]. But it does not mean that the tumor no longer harbors malignant cells. The histopathology of tissues following neoadjuvant chemotherapy can be altered making the interpretation subjective. It needs to be studied if the histopathological changes induced by neoadjuvant chemotherapy can be of prognostic significance [18, 19]. And therefore, giving more cycles of neoadjuvant chemotherapy in order to lower CA 125 level, or to sterilize the tumor of malignant cells, or to reduce the size of the tumor and the extent of the disease to the lowest level possible in a responding patient is not advisable. Neoadjuvant chemotherapy can only improve the rate of complete cytoreduction and not the overall survival [17].

If the response to neoadjuvant chemotherapy is unsatisfactory, it could be due to the tumor being platinum refractory, or it developing chemoresistance [20]. It is unlikely that further cycles of neoadjuvant chemotherapy will help, and the patient should be offered surgery [16, 20]. Further chemotherapy will induce platinum resistance and make the surgical dissection more difficult on account of postchemotherapeutic changes. Among the four clinical scenarios—primary debulking surgery with no residual disease, interval debulking surgery with no residual disease, primary debulking surgery with residual disease, interval debulking disease with residual disease, the prognosis is the best in the first, and the worst in the fourth

case scenario [14, 21]. In fact, interval debulking surgery after neoadjuvant chemotherapy with no residual disease for stage IIIC and IV disease is not inferior to primary debulking surgery with no residual disease [22]. The surgical goal should be complete resection of all macroscopic disease. And the main purpose of neoadjuvant chemotherapy should be to help achieve complete cytoreduction in advanced carcinoma ovary [22].

Chemoresistance carries poor prognosis. Every tumor has a variable proportion of chemosensitive and chemoresistant cells. When a patient undergoes primary debulking surgery, there is a reduction of both chemosensitive and chemoresistant cells. On the other hand, if a patient undergoes chemical debulking in the form of neoadjuvant chemotherapy, there is reduction of only chemosensitive cells, and what remains behind is largely composed of chemoresistant cells. The poorly vascularized hypoxic areas in the center of a large tumor are where chemotherapeutic agents do not reach significant concentrations, and hence are chemoresistant. Therefore, the residual tumor following interval debulking surgery after neoadjuvant chemotherapy will have a greater the proportion of chemoresistant cells. Patients with chemoresistant disease who have residual disease after interval debulking surgery carry the worst prognosis [14, 21].

In our institute, we receive many patients who have already received neoadjuvant chemotherapy outside, sometimes as many as six cycles. The reason for giving more than four cycles of neoadjuvant chemotherapy are—extensive disease despite neoadjuvant chemotherapy, patient's reluctance to get operated, presence of comorbid factors which might delay surgery, etc. Given the very low socioeconomic status of our patients, there is very often a long delay of more than 6 weeks between the end of neoadjuvant chemotherapy and reporting to us. We believe that the purpose of neoadjuvant chemotherapy is to increase the rate of achieving complete cytoreduction in patients with extensive disease and poor performance status and not merely to reduce the tumor load. Therefore, administering more than 3–4 cycles can be counterproductive.

Conclusion

CA-125 is a tumor marker for surface epithelial carcinoma of the ovary. It is elevated in normal pregnancy, menstruation, certain benign and malignant gynecological, and non-gynecological conditions. But very high levels of CA-125 are confirmatory of carcinoma ovary, though not reflective of the tumor load, stage, or the surgical resectability. But nevertheless, determining the CA-125 is useful is the pre-operative diagnosis of ovarian carcinoma. A declining CA-125 level during neoadjuvant chemotherapy shows a responsive disease, and a rising CA-125 level following treatment is indicative of disease recurrence. However, the fall in CA-125 levels during neoadjuvant chemotherapy is not related to surgical resectability. And the number of cycles of neoadjuvant chemotherapy required, should not be determined in response to the extent of decline of CA-125 level. The decision of when to perform an interval debulking surgery following neoadjuvant chemotherapy should be taken by clinical examination and imaging. An unresponsive/poorly responding tumor is unlikely to respond to further neoadjuvant chemotherapy. In addition, excessive neoadjuvant chemotherapy can make surgical dissection difficult by inducing postchemotherapeutic reaction. It also has an adverse effect on postoperative wound healing by adversely affecting neovascularization. And lastly, the systemic toxicity of excessive chemotherapy and increase in treatment costs cannot be overemphasized.

Declarations

Conflict of interest Both the authors declare that they have no conflict of interest.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

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