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Application of combined intraperitoneal and intravenous neoadjuvant chemotherapy in senile patients with advanced ovarian cancer and massive ascites

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Summary

Objective: The aim of this study was to explore the effects of neoadjuvant chemotherapy in senile patients with advanced ovarian cancer and ascites. *Materials and Methods:* One hundred eight senile patients with advanced ovarian cancer and ascites were randomly divided into two groups: experimental and control groups. Patients in the experimental group were treated with two courses of intraperitoneal combined with intravenous neoadjuvant chemotherapy, followed by cytoreductive surgery, and six courses of intravenous chemotherapy, while the patients in the control group only received cytoreductive surgery and six to eight courses of intravenous chemotherapy. *Results:* The operation duration, blood loss, ideal success rate of cytoreductive surgery, and prognosis of the two groups were then compared. Thirty-eight patients in the experimental group successfully received cytoreductive surgery, accounting for 74.14%, while only 23 patients in the control group received cytoreductive surgery successfully, accounting for 46%, showing significant difference between the two groups ($p = 0.0054$). The mean blood loss and operation duration in the experimental group were significantly less than those in the control group ($p < 0.001$). However, the median survival and the median progression-free survival showed no statistical difference between the two groups ($p > 0.05$). *Conclusions:* Neoadjuvant chemotherapy can obviously shorten the operation duration, reduce the intraoperative blood loss, and improve the ideal success rate of cytoreductive surgery, but does not obviously improve the prognosis.

Key words: Abdominal combined with venous neoadjuvant chemotherapy; Senile patients; Advanced ovarian cancer; Ascites.

Introduction

Ovarian cancer is a common gynecological malignant tumor. Among the patients, about 70% have been in advanced stage and more than 50% are over 65-years-old when they are first diagnosed [1, 2]. Due to their age and poor healthcare awareness, they seldom see the doctor until the occurrence of ascites. In addition, the elder always have more complications and their tissues are poorly flexible. Thus, bleeding occurs frequently during the operation, causing wide implantation metastasis of tumor cells in abdominal cavity, which is difficult to treat and has poor prognosis [3, 4], It has been reported that old age is an independent prognostic factor for the advanced ovarian cancer [5, 6]. Neoadjuvant chemotherapy can be used in the patients with advanced ovarian cancer and is tolerant to chemotherapy. It can cause the tumor to shrink and reduce the production of ascites, and thereby simplify a difficult surgery, while avoiding the occurrence of surgical complications [7]. Studies on the elderly patients with ovarian cancer have seldom been reported. It is believed that neoadjuvant chemotherapy in elderly patients can reduce the economical burden and slightly improve the overall survival, although it may reduce the quality of life [8-10]. In this study, intraperitoneal combined with intravenous neoadjuvant chemotherapy and surgery were applied to investigate its clinical values in senile patients with ovarian cancer and ascites, in order to explore a new treatment mode in these patients.

Materials and Methods

One hundred eight senile patients with advanced ovarian cancer and ascites were enrolled in this study. All patients were diagnosed as ovarian epithelial carcinoma by preoperative examinations, such as gynaecological examination, ultrasound examination, CT, and serum CA125 detection, and then confirmed pathologically by laparoscopic biopsy or laparotomy. The patients in the experimental group included 39 cases in Stage III and 19 cases in Stage IV, aged 67.6 ± 5.9 (range 60 to 75) years and weighed 62.5 ± 28.2 (range 51 to 63) kg, while the patients in the control group included 34 cases in Stage III and 16 cases in Stage IV, aged 65.5 ± 4.8 years and weighed 61.4 ± 13.2 kg. No statistical difference was found in the age, weight, clinical stage, and pathological type between the two groups. This study was conducted in accordance with the declaration of Helsinki and with the approval from the Ethics Committee of Hebei Medical University. Written informed consent was also obtained from all participants.

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Patients in the experimental group received neoadjuvant chemotherapy with 75 mg/m^2 cisplatin (d1p) and 75 mg/m^2 docetaxel for two cycles, for 21 days for each cycle. Then, the patients underwent cytoreductive surgery, including total hysterectomy, adnexectomy, greater omentectomy, appendectomy, pelvic and paraaortic lymph node resection, resection of the metastatic lesions (including the tumor tissues implanted in the bowel, mesenterium, peritoneum, diaphragm, and the surface of liver) and bowel resection (if bowel metastasis occurred). The ideal therapeutic effect was the longest diameter of the postoperative residual tumor lesion less than one cm. After that, the patients in the experimental group received an additional six cycles of cisplatin and docetaxel. The patients in the control group received cytoreductive surgery first, followed by six to eight cycles of treatment with cisplatin and docetaxel. No patient had any chemotherapy or surgery contraindications. Before the chemotherapy, patients were pretreated with anti-allergy, anti-nausea, and liver-protecting drugs. During chemotherapy, conventional hydration was performed on each patient for three days to protect renal function. Before the intravenous injection of docetaxel, patients were pretreated with antiallergic drugs to avoid allergies. During the infusion of docetaxel, the patients were monitored by ECG and kept in close observation for the allergic reaction of chemotherapy.

Adverse reactions of the patients were closely monitored after chemotherapy, such as bone marrow suppression, alopecia, gastrointestinal tract reaction, joint and muscle pain, rashes, etc. Regular check of blood tests, liver and kidney function, electrolyte and blood CA125 were performed before and after chemotherapy. The 24-hour urine output was also closely observed. Blood loss, operation duration and the ideal success rate of cytoreductive surgery of the both groups were observed.

After the treatment, the patients in both groups were followed-up every month in the first year and every three months from the second year. During the follow-up period, the clinical signs and symptoms were recorded, and the abdominal and pelvic cavity ultrasound examination were performed. If necessary, the chest, abdomen, and pelvic CT or MRI were also carried out. The serum CA125 levels were determined each time. Then the median overall survival and the one-, three-, and five-year survivals were calculated. The median progression-free survivals were also calculated.

All data were processed using SPSS v13.0 software. The comparisons of the measurement data were performed using *t*-test and the comparisons of the enumeration data were performed using Chi-square test. Survival analysis was carried out using Kaplan-Meier method. Cox regression was used to analyze the prognosis. The difference was considered statistically significant at $p < 0.05$.

Results

The general data, such as the age, weight, disease duration, clinical stage, pathological type. and histological grade showed no statistical difference between the two groups (Table 1).

In the experimental group, there were 43 patients that successfully received cytoreductive surgery, accounting for 74.14%, while there were only 23 patients in the control group that successfully received cytoreductive surgery, showing a significant difference between the two groups (74.14% *vs*. 46%; $\chi^2 = 7.7286$, $p = 0.0054$). The mean blood loss in the experimental group was 695 ± 48.6 ml, remarkably lower than that in the control group (956 ± 54.2 ml, $t = 26.3821$, $p < 0.001$). There were 19 patients in the experimental group that experienced blood loss of more than 800 ml, accounting for 32.76%, which was notably lower than that in the control group (92% (46/50); $\chi^2 = 41.4507$, $p = 0.0000$). The surgical time also showed a prominent difference between the two group (2.36 ± 0.32 hours *vs*. 3.63 ± 0.24 hours; $t = 23.5124$, $p < 0.001$). Two cases in the experimental group received bowel resection, while six in the control group (Table 2).

Table 1. — *Comparison of the general characteristics of the patients with epithelial ovarian cancer.*

Characteristics	Neoadjuvant chemotherapy (n=58)	Control (n=50)	*p* value
Mean age (year)	67.6 ± 5.9	65.5 ± 4.8	> 0.05
Body weight (kg)	62.5 ± 28.2	61.4 ± 13.2	> 0.05
Histological grade			
Serous	38	33	> 0.05
Mucinous	11	9	> 0.05
Endometrioid	6	5	> 0.05
Clear-cell	2	2	> 0.05
Undifferentiated	1	1	> 0.05
Tumor grading			
G1	26	22	> 0.05
G2	21	20	> 0.05
G3	11	8	> 0.05
FIGO staging			
III	39	34	> 0.05
IV	19	16	> 0.05

Table 2. — *The comparisons of the outcomes in the two groups.*

Variable	Neoadjuvant chemotherapy (n=58)	Control group (n=50)	Statistic value	*p*
Blood loss (ml)	695 ± 48.6	956 ± 54.2	$t = 26.3821$	< 0.001
Operative time (h)	2.36 ± 0.32	3.63 ± 0.24	$t = 23.5124$	< 0.001
Blood loss more than 800 ml (%)	19 (32.76)	46 (92.00)	$\chi^2 = 41.4507$	0.0000
Success rate of Cytoreductive surgery (%)	43 (74.14)	23 (46.00)	$\chi^2 = 7.7286$	0.0054

In the experimental group, there were still 24 cases with blood CA125 higher than or equal to 500 u/ml after two courses of neoadjuvant chemotherapy, among which 15 cases achieved satisfactory cytoreductive surgery (62.50% (15/24)). The five-year survival rate of this subgroup was 12.50% (3/24), remarkably lower than that in the patients with blood CA125 lower than 500 u/ml (32.35% (11/34); $\chi^2 = 4.1369$, $p = 0.0420$). Among the 34 patients with blood CA125 lower than 500 μ/ml, there were 28 cases that achieved satisfactory cytoreductive surgery, accounting for 82.35% (28/34), which was not statistically different from that in the patients with the blood CA125 higher than or equal to 500 u/ml (χ^2 =

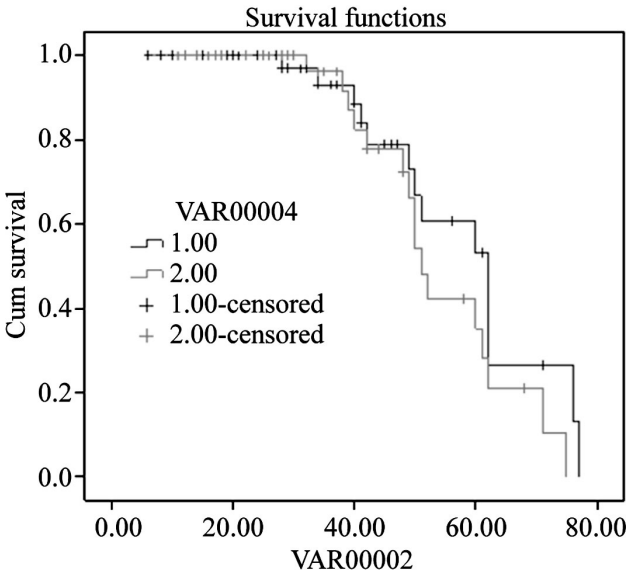

Figure 1. — The overall survival of the two groups. 1, the experimental group; 2, the control group.

2.8921, $p = 0.089$). In the control group, all of the 50 patients had a blood CA125 higher than or equal to 500 μ/ml, with a five-year survival rate of 18.0% (9/50). There were only 23 patients receiving successful cytoreductive surgery, accounting for 46%. The five-year survival rate showed no statistically significant difference between the experimental and control groups ($\chi^2 = 0.2902$, $p = 0.2902$).

Until August 2014, all the patients had a follow-up, with a median follow-up time of 47 (range from 6 to 77) months. The median survival, median progression-free survival, and mean survival time of the experimental group were 62 (range from 20 to 77) months, 26 (range from 15 to 39) months, and 58.427 (95% CI: 51.811-65.043) months, respectively. In the control group, the median survival, median progression-free survival, and mean survival time were 51 (range from 8 to 72) months, 22 (range from 12 to 26 and 54.607) months (95% CI: 48.919-60.296), respectively. The median survival, median progression-free survival and mean survival time showed no statistically significant difference between the two groups ($p > 0.05$, Figure 1). The one-, three-, and five-year survival rates in the experimental group were 94.83%, 58.62% and 24.14%, respectively. Single factor analysis showed that the clinical stage, histological grade, and residual tumor volume were important prognostic factors for the advanced ovarian cancer (all $p < 0.01$, Table 3). The multiple factors analysis showed that the tumor stage, histological grade, residual tumor size, and chemotherapy cycles were the independent factors affecting the prognosis of the patients with ovarian cancer (Table 4).

Table 4. — *Multivariate analysis for prognosis of epithelial ovarian cancer using COX model.*

Variable	β	Sx	Wald χ^2	*p*	RR
Tumor grading					
G1	0.3932	0.2021	8.6863	0.0292	1.341
G2	0.4630	0.2114	8.6953	0.0205	1.625
G3	0.5082	0.2103	10.8363	0.0027	1.738
FIGO Stage					
III	1.0342	0.1894	11.9684	0.0028	1.787
IV	1.2045	0.2165	23.9438	0.0017	2.812
Residual tumor					
≤ 1cm	1.1834	0.4932	15.6859	0.0029	1.793
> 1cm	1.1725	0.3802	20.2968	0.0001	2.753
Chemotherapy cycle	1.4208	0.3507	10.7064	0.0013	0.584

The side effects in the experimental group mainly included gastrointestinal reaction, alopecia, bone marrow suppression, and occasional allergies. The gastrointestinal reaction mainly included nausea, vomiting and loss of appetite. However intraperitoneal chemotherapy had less gastrointestinal reactions than venous chemotherapy. The bone marrow suppression mainly presented as the decrease of white blood cells and hemoglobin, especially the white blood cells. There was one case with degree-III bone marrow suppression but no case with degree IV in the experimental group, while there were two cases with degree-III bone marrow suppres-

Table 3. — *Univariate survival analysis for the prognosis of epithelial ovarian cancer using COX model.*

Variable	Cases		Survival rate (%)			χ^2	*p*
			One-year	Three-year	Five-year		
Histologic type	Serous	38	94.74 (36)	57.89 (22)	21.05 (8)	3.68	> 0.05
	Other	20	95.00 (19)	60.00 (12)	30.00 (6)		
FIGO Stage	III	39	97.44 (38)	82.05 (32)	35.90 (14)	14.21	< 0.01
	IV	19	89.47 (17)	10.53 (2)	0.00 (0)		
Tumor grading	G1	26	100.00 (26)	84.62 (22)	50.00 (13)	14.82	< 0.01
	G2	21	90.48 (19)	47.62 (10)	4.76 (1)		
	G3	12	83.33 (10)	16.67 (2)	0.00 (0)		
Residual size	≤ 1cm	38	100.00 (38)	55.26 (21)	34.21 (13)	9.75	< 0.01
	> 1cm	20	85.00 (17)	65.00 (13)	5.00 (1)		
Total		58	94.83 (55)	58.62 (34)	24.14 (14)		

Table 5. — *Comparison of the side effects of chemotherapy in the two groups.*

Side effects	Study group					Control group				
	0	I	II	III	IV	0	I	II	III	IV
Nausea, vomiting	18	30	10	0	0	12	25	12	1	0
Bone marrow suppression	9	32	16	1	0	6	21	20	2	1
Alopecia	2	34	16	6	0	3	21	19	7	0
Anaphylactic reaction	56	2	0	0	0	49	1	0	0	0

sion and one cases with degree IV in the control group, which recovered by treatment with subcutaneous injection of granulocyte colony stimulating factor (G-CSF). No patient died from chemotherapy (Table 5).

Discussion

Ovarian cancer ranks the sixth in female malignant tumors. In the United States, as many as 22 to 28 thousand women die of ovarian cancer each year [11, 12]. Senile patients with advanced ovarian cancer are difficult to treat because of their age, poor health, and many complications. Such patients have high difficulty and risk receiving an operation. Moreover, the prognosis is poor. Thus, how to improve the level of the treatment and prognosis for such patients is of great importance. Intraperitoneal chemotherapy began in the 1980's. Numerous studies have shown intraperitoneal chemotherapy to have a positive significance in reducing postoperative recurrence and metastasis, controlling ascites production, improving the quality of life, and prolonging the survival period. Intraperitoneal chemotherapy refers to the direct perfusion of chemotherapy drugs into peritoneal cavity, which can increase the local concentration of chemotherapy drugs in the tumor site and thereby enhancing its killing ability of the tumor cells. Studies have shown that intraperitoneal chemotherapy can increase the intraperitoneal concentration of cisplatin by ten- to 1000-fold at the blood level [13, 14]. Intraperitoneal administration can increase the effective utilization of cisplatin and reduce the side effects. It can reduce the concentration of cisplatin in the peripheral blood, which may slow down kidney excretion and reduce systemic side effects and renal toxicity. Intraperitoneal chemotherapy is especially suitable for ovarian cancer because of the broad implantation of cancer cells in the abdominopelvic cavity. A research by Elit *et al.* [15, 16] also showed that intraperitoneal venous chemotherapy is safe and effective and can improve the survival and quality of life of the patients with advanced ovarian cancer [17]. Vergote *et al.* [18] reported that more than 80% of the patients receiving neoadjuvant chemotherapy can achieve ideal cytoreductive surgery, while the patients receiving surgery directly can only achieve 41.6% of the ideal success rate. Thus, neoadjuvant chemotherapy is presumed to be able to create favorable conditions for surgery. Regardless of surgery or chemotherapy occurring first, the radical resection of lesions is the most important factor affecting prognosis.

Intraperitoneal chemotherapy has been popular due to its unique role. A meta-analysis showed that the intraperitoneal chemotherapy has more obvious advantages than intravenous chemotherapy. The risk ratio of disease-free survival to the overall survival was 0.79 [19]. Nevertheless, abdominal puncture may lead to some complications, such as puncture blockage, infection or damage to intestinal canal or blood vessels. Thus, intraperitoneal chemotherapy should be performed by highly skilled doctors and the whole course of the chemotherapy should be fully managed. The puncture site should be monitored closely in order to avoid serious complications [20, 21]. With regards to this, intraperitoneal chemotherapy has not been widely applied for gynecological tumor [22]. Intraperitoneal venous combined chemotherapy not only retains a high local concentration of chemotherapy drugs in abdominal cavity, but it also reduces the cisplatin-caused renal toxicity, bone marrow depression, and gastrointestinal reaction by decreasing the concentration of cisplatin in blood. Thus, it can improve the patients' adherence.

In conclusion, the present results showed that combined intraperitoneal with intravenous neoadjuvant chemotherapy could effectively control the production of ascites and reduce the difficulty of operation, in order to improve the success rate of ideal cytoreductive surgery. Blood loss during surgery was decreased and its duration was also significantly shortened. Although the five-year survival rate had not been improved, combined intraperitoneal and intravenous neoadjuvant chemotherapy may have great advantages in senile patients with advanced ovarian cancer and ascites. It could be a wise choice for the treatment of advance ovarian cancer. However, the effect of neoadjuvant chemotherapy on survival needs further supporting accumulative data.

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