ORIGINAL RESEARCH

Clinical Study of Deep Hyperthermia Combined with Computational Medicine of Platinum Chemotherapy in the Treatment of Ovarian Cancer

Xiaoming Du, MD; Jie Zheng, BD; Lu Zhao, MD

ABSTRACT

Objective • Deep hyperthermia combined with platinum-based chemotherapy (DHCT) might lead to the development of better therapeutic strategy for patients with malignant tumor. This study aimed to analyze the computational medical differences in ovarian cancer patients treated with DHCT compared with platinum-based chemotherapy alone.

Methods • 78 patients with advanced ovarian cancer admitted from November 2017 to November 2021 were randomly selected as subjects. Overall survival analysis and CA125 clinical efficiency evaluation were performed to explore the effect of DHCT on cis-platinum therapy. All patients were informed and consented, and approved by the hospital committee. The data were systematically analyzed by chi-squared test to analyze clinical effect and safety observation, and the Kaplan-Meier method and log-rank test were used for survival analysis.

Results • Survival analysis showed that DHCT was strongly associated with improved overall survival (OS) in the platinum treatment of ovarian cancer patients (Hazard Ratio = 1.57, 95% CI: 0.93–2.44, P = .017). For ovarian cancer patients receiving lobaplatin treatment, DHCT could also elevate their survival (Hazard Ratio = 1.52, 95% CI :1.02–2.25, P = .013). The study also showed a statistically significant difference in clinical outcomes between the two groups (P < .001), and the opposite is true for adverse reactions.

Conclusion • Our results suggest that DHCT is expected to be combined with platinum chemotherapy, which is helpful for the molecular classification of ovarian cancer patients. More studies are needed to further verified the clinical significance. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Ovarian cancer is a common malignant gynecological tumor with a relatively high fatality rate, coupled with the lack of early diagnosis and effective screening methods.[1] Ovarian cancer ranks the first in the mortality rate of female tumors in China and the world.[2] It showed that 225 000 new cases of ovarian cancer occur in women worldwide and 52 000 in China each year. The incidence has increased by 30% in the past decade.[3] Patients with advanced ovarian cancer can appear abdominal distention, abdominal pain, abdominal mass, abdominal fluid, vaginal drainage and other symptoms,[4,5] and some patients can show wasting, anemia, and other cachexia phenomenon.[6] Patients with advanced ovarian cancer are often accompanied by a large peritoneal effusion, metastasis, and adhesion, which worsens the patient's condition and increases the difficulty of treatment.[7,8] Therefore, it is of great importance to improve the treatment options.

Current therapy recommendations depend on several prognostic factors, including the patient's age at presentation, performance status, and stage at presentation. For patients with stage I disease, resection is the first option with the need for adjuvant therapy. Postoperative combination chemotherapy with paclitaxel and cis-platinum has become the standard first-line treatment for ovarian cancer.[9,10] Most patients achieve remission, but 70% to 80% of patients progress again after the initial response.[11] Unable to operate poor curative effect, often for palliative reduction disease.[12] Therefore, further research is needed to improve the treatment of advanced ovarian cancer. There is growing research on the use of local tumor heating to enhance the effectiveness of

conventional treatments in advanced ovarian cancer.[13-15] Data reported in the New England Journal in 2018 showed that deep hyperthermia combined with chemotherapy (DHCT) significantly reduced ovarian cancer recurrence and prolonged survival.[16] However, it did not focus on a specific type of chemotherapy with microwave hyperthermia protocol for clinical relevance analysis, and further clinical data are needed to determine whether hyperthermia is appropriate for clinical use.[17] The effect of whole-body hyperthermia (WBH) combined with platinum-containing chemotherapy in the treatment of recurrent ovarian cancer was examined in a previous study. The increasing growing interest in using local tumor heating (hyperthermia) as well as the lack of specific protocols for hyperthermia combined with different chemotherapy agents implying the need to enhance conventional treatments. It showed that patients of 4.8% had a complete remission, 33.3% had a partial remission, stable disease was noted in 47.6%, and 14.3% did not respond and had progressive disease.[18] Median time to progression was 6.5 months, and median survival time, 16.5 months.[18] Deep hyperthermia also deserves further clinical verification.

This retrospective study focused on the differences in ovarian cancer patients treated with hyperthermia combined with cis-platinum-based chemotherapy compared with cis-platinum-based chemotherapy alone, which will show the clinical significance of hyperthermia on the treatment of advanced ovarian cancer patient and will brings light for the future of these patients. Our study utilizes a retrospective approach to investigate these differences.

MATERIALS AND METHODS

General Information

In this study, 78 patients with ovarian cancer admitted to the Wanbei Coal-Electricity Group General Hospital from November 2017 to November 2021 were randomly selected as subjects. All patients were informed and consented, and approved by the hospital committee.

The inclusion and exclusion criteria

The inclusion criteria were conducted as follows: (1) Patients diagnosed with ovarian cancer Wanbei Coal-Electricity Group General Hospital; Blood test: CA-125 levels are elevated. Imaging: transvaginal ultrasound, MRI or CT scan may be selected; (2) Agree to participate in this study. (3) Aged 18-60. The exclusion criteria: (1) With systematic diseases, including cardiovascular diseases, cerebrovascular disease, and bleeding prone disease. (2) Patients did not follow up as suggested.

Treatment methods

All patients were admitted to the hospital after regular primary tumor resection in surgical treatment or puncture biopsy treatment. The treatment was divided into deep hyperthermia combined with a chemotherapy group (38 cases) and a single chemotherapy group (40 cases). Deep tissue hyperthermia dilates blood vessels around the tumor, causing oxygen-carrying red blood cells to spread into the tumor. When the patient is later exposed to radiation treatment, the radiation reacts with the high oxygen levels in the tumor, potentially destroying the tumor cells.

Microwave are absorbed and converted into heat after irradiating cancer tissue, and when the cancer area is heated to 41.5 ~43, it can inhibit the synthesis of RNA and DNA of cancer cells, resulting in the death of cancer cells. In the deep hyperthermia combined with the chemotherapy group, 18 patients with ascites were treated with abdominal puncture and drainage followed by intraperitoneal infusion chemotherapy. After intravenous chemotherapy, the remaining 20 patients received 30-45 minutes of deep hyperthermia. The intravenous chemotherapy regimen was conventional two-drug chemotherapy regimen (TP, GP, IP and EP) for ovarian cancer, repeated every 3 weeks. Intravenous chemotherapy drugs should be applied one day before infusion chemotherapy. For patients undergoing abdominal infusion chemotherapy, abdominal puncture and drainage catheterization were conducted under the guidance of color ultrasound. Tumor cells were found in liquid-based cytology of ascites, and then intraperitoneal infusion chemotherapy (cisplatin 60mg, Day1/3 or loplatin 50mg, Day1) was performed. At the same time, 5mg dexamethasone was intraperitoneal perfusion to alleviate the reaction, and deep hyperthermia was performed 1h after intraperitoneal infusion of chemotherapy drugs. Deep hyperthermia machine for microwave tumor hyperthermia instrument (Jiangsu Novan Medical Equipment Co., LTD., N-9001, 0-400W, National instrument note 20193091535).

Operation steps are as follow:

1. Before starting the machine, check all kinds of connecting cables first, ensure the connection is reliable and correct, turn on the power switch, and put it in grade I. The power indicator on the front panel of the host is on.
2. Turn on the computer's power switch, the computer starts, and enter the Windows desktop. Double-click the "microwave treatment" button on the desktop to enter the treatment program.
3. The operator checked the patient's information, removed the metal items carried by the patient, checked whether any joints of the radiator were loose, took the patient's supine position, and fixed the conduction temperature line according to the irradiation site set by the doctor.
4. The operator opens the program's main screen and click "Start treatment" to enter the treatment control program.
5. Observe the patients for adverse reactions and local skin conditions every 10-15 minutes. Record the treatment information and log out of the computer operating system after the treatment time expires.

Evaluation of clinical outcomes

The primary endpoint was overall survival (OS), defined as the time from the first dose of chemotherapy to investigator-assessed disease progression or death from any cause.

Figure 1. Rationale and techniques of cytoreductive surgery and peritoneal chemo hyperthermia.

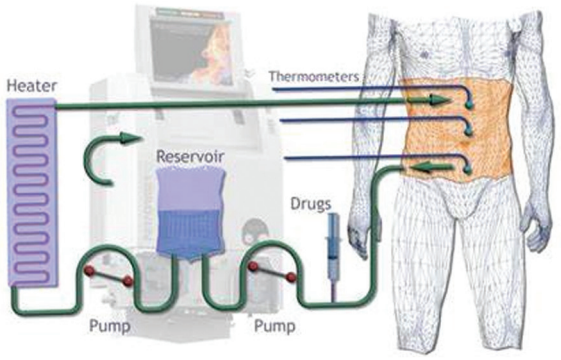


Table 1. Characteristics of the Study Population

Characteristic	Platinum chemotherapy group	Deep hyperthermia + platinum chemotherapy group	*P* value
Patients, no.	40	38	
Age, mean (year)	58.32±9.65	60.53±10.82	.16
Pathological types			
serous cystadenocarcinoma	20%	18%	.11
mucinous cystadenocarcinoma	14%	11%	
clear cell carcinoma	4	5	
undifferentiated carcinomas	2	4	
Clinical stage			
Stage II patients	10	4	.12
Stage III patients	18	23	
Stage IV patients	12	11	

Note: Deep hyperthermia combined with cis-platinum chemotherapy (DHCT), Chi-squared test was used to analyze clinicopathological characteristics, and $P < .05$ was considered to be statistically significant.

Secondary endpoints were the proportion of patients achieving an objective response (according to RECIST and Gynecological Cancer InterGroup [GCIG] CA-125 criteria [19, 20]). According to the evaluation criteria of tumor efficacy, the outcome of all patients were divided into (1) Complete response (CR, complete disappearance of all target lesions except nodular disease. All target nodules must be reduced to normal size with the short axis < 10 mm), (2) Partially relieved (PR, the sum of diameters of all measurable target lesions ≥ 30% below baseline. Target nodule combined with short diameter, the sum of all the other target lesion and use the longest diameter) (3) Stable disease (SD, reduce the degree of target lesions is not up to PR, increase the degree of also did not reach the PD level, somewhere in between, the diameter can be the sum of the minimum value as a reference) is considered to be has a good curative effect. (4) Disease progression (PD, based on the minimum sum of the diameter of all target lesions measured during the whole experimental study, and the diameter and relative increase is at least 20%. If the baseline measurement value is the minimum, the baseline value is used as the reference. In addition, an absolute increase of at least 5 mm in diameter and the appearance of one or more new lesions must be considered as disease progression.

Duration of response is based on WHO efficacy evaluation criteria for unmeasurable lesions of malignant tumors. Complete absorption or significant reduction of ascites (> 50%) for more than 4 weeks is effective, obvious ascites reduction for less than 50% reduction or less than 25% increase and maintained for at least 4 weeks is ineffective for an increase in abdominal fluid of more than 25%. The proportion of patients achieving an objective response was defined as the proportion with the best response of complete or partial response. All RECIST and CA-125 responses were confirmed by a second assessment after at least 4 weeks. Duration of confirmed response (complete or partial response) was calculated from the initial date a response was detected to the first date of progressive disease.

Statistical methods

Statistical analyses and chart preparation were performed using GraphPad Prism software 8.0 (GraphPad Software, Inc., San Diego, CA, USA). Student's *t*-test was used for comparison between two groups. Spearman's correlation analysis was used to analyze the relationship among clinicopathological characteristics, and the Kaplan-Meier method and log-rank test were used for survival analysis. $P < .05$ was considered to be statistically significant.

RESULTS

General characteristics of the study population

As shown in Table 1, all patients were divided into two groups, the platinum chemotherapy group (n = 40) and the deep hyperthermia combined with the DHCT group (n = 38). The platinum chemotherapy group with an average of 58.32±9.32 years old. Pathological types: 20 serous cystadenocarcinoma, 14 mucinous cystadenocarcinoma, 4 clear cell carcinoma and 2 undifferentiated carcinomas. Clinical stages: 10 stage II patients, 18 stage III patients, 12 stage IV patients; Deep hyperthermia combined with platinum chemotherapy group, with an average age of 60.53±10.82. Pathological types: 18 serious cystadenocarcinoma, 11 mucinous cystadenocarcinoma, 5 clear cell carcinoma and 4 undifferentiated carcinomas. Clinical stage: 4 stage II patients, 23 stage III patients, 11 stage IV patients. There was no statistical significance in gender, age, pathological type and clinical stage between the two groups ($P > .05$), but there was certain comparability.

Overall survival analysis of DHCT

Survival analysis showed that compared with deep hyperthermia combined with platinum chemotherapy (DHCT) was strongly associated with improved overall survival (OS) in ovarian cancer patients (Hazard Ratio = 1.57, 95% CI: 0.93–2.44, $P = .017$) (Figure 2A). Especially for ovarian cancer patients of seroperitoneum, DHCT could also elevate their OS values (Hazard Ratio = 1.52, 95% CI: 1.02–2.25, $P = .013$) (Figure 2B).

Clinical efficiency evaluation of DHCT

To determine the outcome of solid tumor treatment: complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD) were used.This study showed that 17 patients were evaluated as PD (42.5%), and 3 CR (7.5%) patients, 5 PR (12.5%) patients, 15 SD (37.5%)

Figure 2. (**A**) The overall-survival analysis of chemotherapy and deep hyperthermia combined with chemotherapy in response to ovarian cancer development. (Hazard Ratio = 1.57, 95% CI: 0.93–2.44, $P = 0.017$). (**B**) The overall-survival analysis of patients with peritoneal effusion drainage followed by intraperitoneal infusion chemotherapy combined with hyperthermia in response to ovarian cancer development. (Hazard Ratio = 1.52, 95% CI: 1.02–2.25, $P = 0.013$)

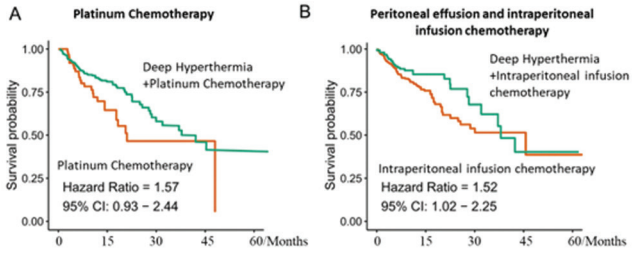
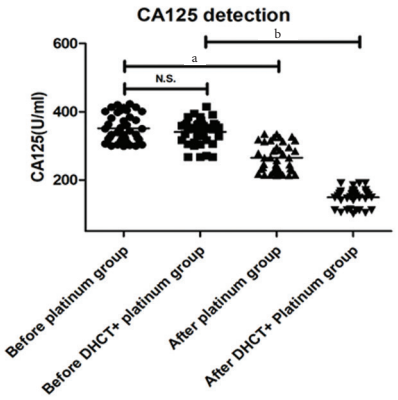


Table 2. Clinical Efficiency Evaluation

Characteristic	Cis-platinum chemotherapy group	DHCT+ Cis-platinum chemotherapy group	*P* value
Patients, no.	40	38	
Complete Remission	3	5	< .001
Partial Remission	5	11	
Stable Disease	15	10	
Progressive Disease	17	12	

Figure 3. Comparison of CA125 concentrations decrease between platinum chemotherapy group (n = 40) and DHCT plus group (n = 38).



[a]$P < .05$
[b]$P < .001$

Table 3. Adverse Reaction Evaluation

Characteristic	Grading	Platinum chemotherapy group	DHCT group	*P* value
Bone marrow suppression	0	1	0	.088
	I-II	0	2	
	III-IV	1	1	
Digestive tract reaction	0	2	3	.123
	I-II	0	2	
	III-IV	0	1	
Intestinal obstruction	0	0	1	.231
	I-II	1	0	
	III-IV	0	0	
Liver function injury	0	0	0	.343
	I-II	1	1	
	III-IV	0	1	
Kidney function injury	0	1	1	.208
	I-II	0	1	
	III-IV	0	0	

patients were respectively confirmed after platinum chemotherapy alone. In contrast, 12 patients were evaluated as PD (31.6%), and 5 CR (13.2%) patients, 11 PR (28.9%) patients, 10 SD (26.3%) patients were respectively defined under the treatment of DHCT plus platinum chemotherapy. After analysis, we found that hyperthermic intraperitoneal chemotherapy (DHCT) could significantly decrease the ratio of PD and SD patients when treated with cis-platinum chemotherapy ($P < .001$) (Table 2). Besides we have also determined the concentrations of ovarian cancer biomarker carbohydrate antigen 125(CA125) for the above two groups of patients. It manifested that the levels of patients treated with DHCT plus platinum chemotherapy were decreased much lower than these of cis-platinum chemotherapy alone ($P < .001$), but their initial CA125 levels were not significantly different (Figure 3).

Adverse reaction of DHCT

The other side of consideration of this combination treatment is the adverse reaction. We thus recorded and compared all adverse reactions to the whole process of treatments for the above two groups of patients. Bone marrow suppression ($P = 0088$), digestive tract reaction ($P = .123$), intestinal obstruction ($P = .231$), liver function injury ($P = .343$), and kidney function injury ($P = .208$) all demonstrated no significant statistical difference between cis-platinum chemotherapy alone group and DHCT plus cis-platinum chemotherapy group (Table3).

DISCUSSION

Ovarian cancer rates have fallen in recent years, with increased use of oral contraceptive pills. The treatment of patients with advanced ovarian cancer mainly includes operation, radiotherapy, and chemotherapy, in which most patients can achieve clinical relief.[21-24] However, 60% to 70% of advanced ovarian cancer patients are confronted with metastasis, which is the main form of recurrence. The treatment option included poly ADP-ribose polymerase (PARP) inhibitors, immunotherapy, and heated intraperitoneal chemotherapy. DHCT may positively impact the prognosis of these patients, which can improve the patient's PFS and operating systems.[25-27] It was reported that 78 cases were retrospectively analyzed for the treatment of chemotherapy in ovarian cancer. Its mean survival value is 22.4 months. Cascales et al. reported a case-control study of 87 cases stage III/IV ovarian cancer, including 52 patients with DHCT group and 60 patients with platinum treatment plus 35 mg/m^2 paclitaxel and 42°C hot perfusion chemotherapy.[28-29] Multivariate analyses showed that the effect of DHCT is an independent prognostic factor.[30-32]

For patients who are not suitable for surgery or patients for whom surgery is not expected to be completely satisfactory, NACT (Neoadjuvant Chemotherapy) with reasonable application of DHCT can improve the quality of surgery, improve the rate of complete surgical resection, and reduce the incidence of surgical complications and the risk of early

mortality. In 2017, Medina Franco et al.[33] reported that a group of stage III/IV ovarian cancer patients who received NACT + IDS (Interval Debulking Surgery) were more likely to achieve satisfactory debulking surgical outcomes. Their complete tumor resection rate was as high as 64.5%, whereas the complete resection rate of PDS (Primary Debulking Surgery) in another group was only 35.5%. The incidence of infections, deep vein thrombosis, pneumonia, pulmonary embolism, and other complications was 8.7%, 5.1%, 2.7%, and 0 respectively in patients who received NACT + IDS, which was lower than that in patients who received PDS (12.7%, 8.9%, 2.7%, and 1.7% respectively). Ba et al.[34] evaluated the treatment outcomes of 53 patients with ovarian cancer complicated by malignant ascites. 34 patients underwent DHCT immediately after platinum (platinum + DHCT group) and 19 patients then underwent platinum (deep hyperthermia + platinum group). It was found to have 100% resolution of ascites, with 30 patients achieving satisfactory tumor cytoreduction in the platinum + DHCT group and 17 patients achieving satisfactory tumor cytoreduction in the DHCT + platinum group, and a median survival of 39 and 38 months in the platinum + DHCT group and DHCT + platinum group respectively. Ryu et al.[35] retrospectively analyzed 117 stage I-III ovarian cancer patients, 57 of whom received two cycles of both cytoreductive surgery and intraperitoneal hyperthermic perfusion chemotherapy and 60 of whom received both cytoreductive surgery and conventional chemotherapy, and 5-year survival rates were 63.4% and 52.8%, respectively ($P < .05$), arguing that intraperitoneal hyperthermic perfusion chemotherapy is an independent prognostic factor for ovarian cancer, which independent of surgical stage effect, size of residual lesion at secondary surgery and patient age.

For patients with recurrent ovarian cancer, DHCT also can improve PFS and OS. The results of an Italian study in 2012 comparing treatment with SCS (Spinal Cord Stimulation) + DHCT (n = 37) and SCS without DHCT (n = 37) in platinum sensitive patients with recurrent ovarian cancer, found that there was no phenomenon of delayed adjuvant chemotherapy in the DHCT group, and that within 2 years all patients in the control group had relapsed, whereas in the DHCT group only two-thirds of the patients had relapsed, and 53% of patients had a longer period of clinical remission after relapse than initially. In 2015, the group published their 5- and 7-year survival rates. Their findings were consistent with a 2012 report that, more than 52% of patients in the SCS + DHCT group had a longer period of clinical remission than initially, with a median PFS interval of 27 months (range 5-104 months) and 5- and 7-year median PFS of 52.8% and 44.7% respectively.[36] Spiliotis et al.[37] reported a double-blind prospective phase III study of 120 patients with stage II/IV epithelial ovarian cancer who had failed primary surgery plus chemotherapy, and received platinum combined with deep hyperthermia in 60 patients and platinum plus systemic chemotherapy in 60 patients. Median OS was 26.7, 13.4 months ($P < .01$), and 3-year survival was 75.0%, 18.0% ($P < .01$) respectively. In the DHCT treatment group, the median OS was 26.8, 26.6 months in platinum sensitive and insensitive patients respectively ($P > .01$).

This retrospective study has shown that for ovarian cancer patients of intraperitoneal perfusion treatment, DHCT could also elevate their survival. Thes data suggested that DHCT might be an potential treatment method for overian patients. Collectively, hyperthermic intervention could efficaciously improve the treatment of platinum chemotherapy. However, this study also owned its limitation, as insufficient number of patients were included and we need more DHCT prospective randomized studies to be conducted on initial treatment, retreatment and preoperative treatment of advanced ovarian cancer. Second, there was no underlying mechanism of this study. We look forward to more multi-center large-scale clinical data to guide clinical practice in the near future. In future, more experiments are still need to compare the well-tolerated and safe of DHCT, thus bring light for ovarian patients.

CONCLUSION

For ovarian cancer patients of platinum treatment, deep hyperthermia combined with computational medicine of platinum chemotherapy could be effective on recurrent and refractory ovarian cancer with low side effects, especially in those who have platinum-sensitive tumors.

DATA AVAILABILITY

The data used to support this study is available from the corresponding author upon request.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

FUNDING

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