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Clinical efficacy and safety of docetaxel in combination with cisplatin on the platin-sensitive recurrent ovarian cancer in comparison of whole abdominal radiotherapy

F.L. Zhang*

Department of Pharmacy, the Second Affiliated Hospital of Dalian Medical University，Dalian, Liaoning116023, China

► ***Original article***

Corresponding author:
Dr. Fengling Zhang,
E-mail:
correspond.Zhang@yahoo.com

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ABSTRACT

***Background*:** To investigate the clinical efficacy and safety of docetaxel in combination with cisplatin in comparison of standard methods of in treatment of platin-sensitive ovarian cancer regimens and in addition to radiotherapy for whole abdomen radiotherapy in platin-sensitive recurrent ovarian cancer and the effect on the levels of VEGF and MMP-2. ***Materials and Methods*:** We recruited a total of 160 platin-sensitive recurrent ovarian cancer patients between April 2017 and April 2020 who were treated in this hospital, and assessed them based on the treatment chemotherapy and radiotherapy regimens to control, the docetaxel+cisplatin, and Whole abdomen radiotherapy groups. Patients in the control group received the co-medication of paclitaxel and carboplatin, while those in the docetaxel+cisplatin group received the docetaxel in combination with cisplatin. Following treatment, we compared the clinical efficacy, levels of vascular endothelial growth factor (VEGF) and MMP-2 and safety of these three methods between two groups. ***Results*:** the total effectiveness rate of the docetaxel+cisplatin group was 69.09%, significantly higher than 16.36% in the control group and 24% in WAR group (P<0.05). Besides, it was found that treatment in the docetaxel+cisplatin group decreased the levels of VEGF and MMP-2 in serum of patients more evidently than those in the control and whole abdomen radiotherapy groups (P<0.05). ***Conclusion*:** docetaxel in combination with cisplatin performs well, with significant decreases in the levels of VEGF and MMP-2 and reliable safety; while there was a high rate of adverse reactions in patients undergoing whole abdomen radiotherapy.

INTRODUCTION

Ovarian cancer is the most common disease in the reproductive system [1]. In recent years, the overall mortality rate and prevalence of malignant ovarian cancer keep increasing, ranking third, only secondary to the carcinoma of uterine cervix and body [2]. According to the available data, ovarian cancer is very susceptible to the metastasis that may diffuse to the key organs, including uterine and omentum majus, or even resulting in the life-threatening outcome. Ovarian cancer patients, with less significant clinical symptoms, may have progressed into the advanced stage at the time of diagnosis, with less significant efficacy [3, 4]. While there were advancements in chemotherapy, most patients experience abdominal or pelvic recurrence of cancer and poor prognosis afterwards [5]. Docetaxel is belonging to the taxane plant alkaloid groups that have become the first line of treatment for breast cancer in the two decades since their introduction to the world pharmaceutical market. Docetaxel inhibit cell cycle and division in tumors. Microtubules that are highly dynamic cellular polymers and play a key role in the mitosis process, are one of the most important targets in the treatment of cancer [6]. Clinical evidence suggests acceptable efficacy of docetaxel in the treatment of benign tumors, early-stage cancer, and even advanced and metastatic cancers. However, Docetaxel have blood and non-blood side effects that can be problematic for the patient or even lead to discontinuation of the drug. In recent years, much research has been done on the combined use of docetaxel with other chemotherapeutic agents such as doxorubicin, cisplatin and 5-fluorouracil in various cancers [7]. Cohen *et al.* evaluated its effect in a multi-drug regimen for ovarian cancer and showed that it may help those who have resisted different lines of conventional cytotoxic therapy [8]. Removal of malignant tissue and chemoradiotherapy is the most important treatment for various cancers, including ovarian cancer. Cisplatin is one of the most common anticancer drugs that can be used alone or in combination with other chemotherapy drugs to treat ovarian cancer [9]. However, despite the initial efficacy of this drug, its long-term use causes drug

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resistance to the point that the emergence of Platinum-resistance in ovarian cancer is still considered as a major barrier to chemotherapy [10].

So, deciding to choose the right chemotherapy regimen for recurrent ovarian cancer is difficult, and the toxicity and efficiency of each regimen must be considered before selecting it. However, the choice of type of taxane alkaloids due to its toxicity is still debated. Various studies have examined the toxicity of these drugs in different treatment regimens of ovarian cancers. In a study of patients with ovarian cancer, the toxicity of docetaxel and carboplatin was shown to be Neutropenia [11].

Although radiation therapy is rarely thought to be used for the initial treatment of ovarian cancer, despite advances in surgery and chemotherapy, some patients have recurrences and abdominal involvement, in which case the use of All-abdominal radiation therapy responds to better treatment [12]. Also, the role of radiation therapy in the effectiveness of chemotherapy drugs in these patients to increase survival is significant [13], it can be noted that radiotherapy, despite invasion and removal of cancer cells also damages normal cells [13].

So, one of the main objectives in patients who are experiencing cancer recurrence but still are Platin-sensitive, is timely treatment of the disease to prevent Platin-resistance. To this aim, there is a need for determining the best chemotherapy regimens and also using radiation for the treatment. But side effects of invasive treatment methods may disturb treatment. Based on these issues, our study aimed to compare treatment outcomes of docetaxel in combination with cisplatin and whole abdominal radiotherapy for the recurrent ovarian cancer. Treatment side effects and biological assessment of the patient condition was also needed for this aim. So, two biological factors of the vascular endothelial growth factor (VEGF) and MMP-2 were selected for study. VEGF for leading to the development of ovarian cancer by encouraging angiogenesis as well as increasing vascular permeability and being highly corelated with ovarian cancer invasion and metastasis [14]. MMP-2 for being a predictor of the Patients' Response to platinum-taxane chemotherapy [15].

MATERIAL AND METHODS

General material

Between April 2017 and April 2020, we selected a total of 110 patients with platin-sensitive recurrent ovarian cancer (i.e. recurrence occurred at the time longer than 6 months after the withdrawal of platin for the first time) in this hospital. Inclusion criteria: Patients with diagnosis of ovarian cancer according to the pathological test and imaging examination; Patients at FIGO III or IV. Exclusion criteria: Patients in lactate or pregnancy; Patients complicated with the primary organic dysfunction. Patients were randomized into three groups, the docetaxel+cisplatin group and the control group, with 55 patients in each group of control (paclitaxel+carboplatin) and docetaxel+cisplatin and 50 patients in whole abdomen radiotherapy (WAR) group as adjuvant of paclitaxel+carboplatin. All patients agreed to participate in this study, and the protocol of this study had been approved by the Ethical Committee of the hospital.

Methods

Patients in the control group underwent the treatment by co-medication of paclitaxel+carboplatin in following doses: Paclitaxel injection (SFDA Approval No.: H20090175, Hospira Australia Pty Ltd) at dose of 135 mg/m2 via intravenous infusion for 3 h; carboplatin injection (SFDA Approval No.: H20090175, Hospira Australia Pty Ltd) at dose of 135 mg/m2 via intravenous infusion for 3 h. Simultaneously, patients received the treatment for diuresis. Treatment would be carried out for 6 cycles (1 cycle = 3 weeks).

Patients in whole abdomen radiotherapy received paclitaxel+carboplatin (as like as controls) and adjuvant radiotherapy. The abdominal radiotherapy was applied from the diaphragm domes to the pelvic floor through open A-P fields. Linear 12—18 MV photon-energy accelerators were used. The dosage for each fraction was 1.0 Gy, 20 fractions 5 days a week. No insulation has been added. Another 20.4 Gy (1.7 Gy per fraction, 5 days a week, 12 fractions) was administered via lower abdominopelvic A-P fields as a boost dosage ((TomoTherapy) [16].

Patients in the docetaxel+cisplatin group underwent the treatment by co-medication of docetaxel and cisplatin in following doses: Docetaxel injection (SFDA Approval No.: J20130008, Sanofi-Aventis) at dose of 70 mg/m^2 via intravenous infusion for 1 h; cisplatin injection (SFDA Approval No.: H20090175, Hospira Australia Pty Ltd) at dose of 30 mg/m^2 via intravenous infusion. Simultaneously, patients received the treatment for diuresis. Treatment would be carried out for 6 cycles (1 cycle = 3 weeks).

Following one month of treatment, we detected the CA125 levels in serum isolated from 3 to 5 mL peripheral venous blood by use of the chemiluminescence kit (Abbott, USA), and CA125 <35 U/mL was deemed normal.

Follow ups

Evaluation of clinical efficacy

One month after the treatment and based on the clinical visitation of patients by physician, according to the Response Evaluation Criteria In Solid Tumors (RECIST), patients with no lesions and a decrease of CA125 level in serum over 75% were considered as complete remission (CR), those with a decrease in diameter of lesion ≥30% and a decrease of CA125

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level in serum between 50% and 75% as partial remission (PR), those with an increase in diameter of lesion ≤20%, or increase < 30%, and a decrease in the level of CA125 in serum < 50% as stable disease (SD), while those with new lesions or an increase of diameter > 20%, and no change in the level of CA125 in serum as the progression disease [17]. The total effectiveness rate = the rate of CR + the rate of PR [17].

Criteria for evaluation of safety

We compared the incidence rates of the adverse reactions between three groups, including the thrombocytopenia, neutropenia, alopecia, nausea and vomiting.

VEGF and MMP-2

Following treatment, we also detect the levels of VEGF and MMP-2 in serum to find out the changes when comparing to the levels before treatment in three groups. 5 ml Venous blood samples were taken before and after the treatment in our follow ups at One month of treatment. Until centrifugation, the blood samples were permitted to coagulate. Serum was extracted, aliquotted, and preserved until assayed at −80 °C. Blood levels of MMP-2 was determined based on the manufacturer's instructions utilizing enzyme-linked immunosorbent assay (ELISA) kits (R & D Systems kit made in USA) after being diluted 10-fold. Until centrifugation, the blood samples were permitted to coagulate. Sera was removed, aliquotted, and preserved until assayed at −80 °C. Blood levels of MMP-2 was determined based on the manufacturer's instructions utilizing enzyme-linked immunosorbent assay (ELISA) kits.

Measurement of VEGF in serum was performed by ELISA method (R & D Systems kit made in USA, catalog number DVE00). Standard serum and vitreous solutions were added to the respective microplates and incubated at room temperature for two hours. After washing three times with a special solution, 200 cc of conjugate was added and incubated again at room temperature and washed and added three times. The substrate was incubated at 200 cc, then 50 cc solution was added and the plate was read at a wavelength of 650-570.

Statistical analysis

Data were analyzed by using the SPSS 20.0 software. Measurement data were presented by mean ± standard deviation, and compared by the t test. Enumeration data were presented by rate (%), and compared by the chi-square test. $P/0.05$ suggested that the difference had statistical significance.

RESULTS

In the docetaxel+cisplatin group, patients aged between 35 and 71 years old, with an average of (54.2±3.2) years; the average diameter of tumor was (3.1±0.2) cm. In the WAR group, patients aged between 37 and 69 years old, with an average of (59.7±1.8) years; the average diameter of tumor was (3.2±0.4) cm. In the control group, patients aged between 38 and 67 years old, with an average of (55.3±3.4) years; the average diameter of tumor was (3.2±0.2) cm. Comparison of the baseline data between three groups showed no statistical significance between age and BMI (P>0.05), suggesting the comparability of data.

Table 1. Demographic characteristics of patients.

Group	Control group(n=55)	WAR (n=50)	Docetaxel+cisplatin (n=55)	P
Age, year, mean ± SD	55.3±3.4	59.7±1.8	54.2±3.2	0.574
BMI, kg/m^2	22.4±2.7	23.5±3.1	21.4±4.6	0.981

Comparison of the clinical efficacy of patients between study groups

After treatment, the total effectiveness rates of patients in the docetaxel+cisplatin group, WAR group, and the control group were 69.09%, 24 and 16.36%, and the difference had statistical significance (P<0.05; table 2). After treatment, the incidence rates of the adverse reactions were 18.18% and 16.36% in the docetaxel+cisplatin group and control group, while adding radiotherapy increased the rate of adverse reactions extremely in WAR group (P<0.05; table 2).

Table 2. Comparison of the clinical efficacy and adverse effects after treatment.

	Group	Control group (n=55)	WAR (n=50)	Docetaxel +cisplatin group (n=55)	P
clinical efficacy	CR (n)	0	0	0	0.00033
	PR (n)	9	12	38	
	SD (n)	15	18	14	
	PD (n)	9	7	3	
	Total effectiveness rate [n (%)]	9 (16.36)	12 (24)	38(69.09)	
Adverse effects	Thrombocytopenia (n)	2	7	4	0.029
	Neutropenia (n)	4	5	2	
	Alopecia (n)	2	8	2	
	Nausea and Vomiting (n)	1	11	2	

Comparison of the levels of VEGF and MMP-2 in serum between study groups

Prior to the treatment, comparison of the levels of VEGF and MMP-2 in serum of patients between all study groups, showed no significant differences (P>0.05). While in all groups of study VEGF and MMP-2 levels decreased, the decrease in the docetaxel+cisplatin group was more evident than that in the control and radiotherapy group (P<0.05; table 3).

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Table 3. Comparison of the levels of VEGF and MMP-2 in serum between study groups (Mean ± standard deviation).

Group		docetaxel+cisplatin (n=55)	WAR (n=50)	Control group (n=55)	*t1*	*P1*	*t2*	*P2*
VEGF (pg/mL)	Before treatment	700.88±42.53	689.93±37.11	700.53±41.77	0.1904	0.8494	0.035	0.972
	After treatment	165.97±22.80	178.12±38.11	177.20±23.91	0.02	0.9841	2.067	0.043
MMP-2 (mg/mL)	Before treatment	599.75±42.52	593.91±40.17	598.54±41.75	0.07	0.9365	0.124	0.902
	After treatment	241.88±23.85	239.71±38.05	248.87±25.16	0.204	0.838	2.277	0.026

t1, p1: docetaxel+cisplatin vs. control; t2, p2: WAR vs. control.

DISCUSSION

For cell cycle, cisplatin and carboplatin are non-specific drugs [18]. Carboplatin can aid to the intrastrand and interstrand cross-linking in DNA and inhibition of unwinding of DNA by targeting the 6th oxygen and 7th nitrogen in guanine of DNA, thereby exerting the cytotoxicity [19]. Cisplatin, as one of the metal complexes, can promote the generation of cisplatin-DNA complex by targeting DNA, thus inhibiting the replication of DNA [20]; in addition, cisplatin shows potent anti-cancer effect by binding to the cytoplasmic or nucleic proteins [21]. As a common anti-microtube drug, paclitaxel can facilitate the polymerization of microtubulin and inhibit the depolymerization to maintain the stability of microtubulin and inhibit the mitosis [22]. Docetaxel is also one of the common anti-cancer drugs that target the microtubulin [23].

VEGF, a factor in close association with the proliferation and mitosis of tumor cells, can enhance the effusion of plasma fibrinogen and increase the permeability of microvessel to form the fiber network during the angiogenesis, thereby promoting the migration of a variety of cells, including tumor cells [24, 25]. MMP-2 is able to enhance the angiogenesis that requires the MMP-2 to degrade the extracellular matrix and vascular basal membrane. Besides, evidence has shown that a high level of MMP -2 may indicate the possibility of tumor metastasis [26, 27].

As indicated by the results of this study, we found that following treatment, the total effectiveness rate of the docetaxel+cisplatin group was 69.09%, significantly higher than 16.36% in the control group (P<0.05), suggesting that docetaxel in combination with cisplatin shows more potent efficacy in treatment of the cisplatin-sensitive recurrent ovarian cancer [28]. Docetaxel in combination with cisplatin shows similar safety to that of the paclitaxel in combination with carboplatin. But WAR group showing very higher rate of adverse reactions. Serious adverse reactions have given rise to serious questions about this care process in previous studies [29].

While Arians *et al.* study showed that following intensive surgery and carboplatin/paclitaxel chemotherapy, dose modulated WAR is correlated with a reasonable low likelihood of toxicity [30]. There may be differences due to type of chemotherapy regimens in various studies.

Besides, we found that treatment in the docetaxel + cisplatin group decreased the levels of VEGF and MMP-2 in serum of patients more evidently than those in the control and WAR group (P < 0.05), revealing the promising efficacy of docetaxel in combination with cisplatin on the patients with cisplatin-sensitive recurrent ovarian cancer patients, with significant decreases in the levels of VEGF and MMP-2 in serum [31].

In conclusion, docetaxel in combination with cisplatin performs well in treatment of the cisplatin-sensitive recurrent ovarian cancer patients, with reliable safety, and significant decreases in the levels of VEGF and MMP-2 in serum. Thus, it is worthy of being promoted in clinical practice.

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Authors' Contributions: (F.Zh) designed experiments, carried out experiment, analyzed experimental results, analyzed sequencing data and developed analysis tool, assisted with Illumina sequencing and wrote the manuscript.

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