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Original Research

The effects of chemotherapy with anthracyclines vs capecitabine on tumour size, survival rate and estradiol levels in patients with locally advanced breast cancer

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Summary

Objectives: To investigate the therapeutic effect of anthracycline chemotherapy in advanced breast cancer and its impact on Estradiol and tumor size. *Methods:* A total of 136 breast cancer patients in our hospital were divided into NH group (anthracycline chemotherapy) and CG group (non-anthracycline chemotherapy). The clinical effects on patients in both groups were observed. The levels of estrone (E1), estradiol (E2) and follicle stimulating hormone (FSH) before and after treatment were measured. The tumor size, adverse reactions and 2-year survival rate of NH group and CG group were evaluated after 1-3 courses of treatment. *Results:* There was no significant difference in the serum E1, E2 and FSH levels before treatment between the NH group and the CG group ($p > 0.05$). After treatment, the levels of E1 and E2 in the NH group and the CG group were lower than those before treatment, and the FSH levels were higher than those before treatment ($p < 0.05$). Compared with the NH group, whilst the FSH levels were lower, the E1 and E2 levels in the CG group were significantly higher. There was no significant difference in the tumor size between the NH group and the CG group before treatment ($p > 0.05$). Compared with those of before treatment, the FSH levels in the NH group and the CG group after treatment were higher ($p < 0.05$). The tumor volume gradually decreased over the course of treatment, and the tumor size during treatment in the NH group was smaller than that of the CG group ($p < 0.05$). There was no significant difference between the two groups ($p > 0.05$). The 2-year survival rate of NG group and CG group was 82.3% and 71.3%, respectively with the NH group being significantly higher than that of the CG group. *Conclusions:* The effects of anthracycline on advanced breast cancer was better, showing lowered levels of serum E2, and decreased tumor volumes.

Key words: Breast cancer; Anthracyclines; E2; Clinical efficacy.

Introduction

As one of the common tumors in women, breast cancer accounts for a high mortality rate in women with cancer globally. Research advancement throughout the years has made significant progress in the treatment of breast cancer. Breast-conserving surgery, which can improve the quality of life of patients for 5 to 10 years, is currently regarded as a quick and effective treatment approach, although there are risks of metastasis and recurrence after radical mastectomy [1-2]. The 5-year and 10-year survival rates of breast cancer patients can effectively be improved through early diagnosis and comprehensive treatment. However, about 20% of breast cancer patients develop recurrence and metastasis, making clinical treatment challenging [3]. Currently, anthracyclines such as doxorubicin (adriamycin), epirubicin and pirarubicin are commonly used clinically due to their significant chemotherapy effect in treating tumors. They are especially effective in breast cancer treatment, showing high mortality, high tolerance and low recurrence rates [4]. In this study, epirubicin which is one of the derivatives of anthracycline with a lower incidence of cardiotoxicity and good leakage effect is selected Upon cell entry, epirubicin controls cancer progression by inhibiting nucleic acid generation and cell mitosis [5-6]. The growth and development of human breast tissues is regulated by endocrine and a number of participating hormones, such as E1, E2, FSH, etc [7]. Estrogen, which is one of the important endocrine indicators of women, plays an important role in the diagnosis of breast cancer [8]. In this study, the effects of anthracycline chemotherapy in advanced breast cancer treatment on E2 and the tumor size were investigated.

Objects and Methods

Subjects and groups

A total of 136 breast cancer patients (2 males) aging from 21 to 74 years admitted in our hospital between March 2014 to July 2016 were included in the study. The patients were divided into NH group (anthracycline chemotherapy) and CG group (conventional drugs), 78 each according to the admission order. The average age of patients in NH group and CG group was 45.23 ± 3.03 years old and 45.31 ± 2.87 years old, respectively. There was no statistical difference in the clinical data between the NH group and CG group ($p > 0.05$), as shown in Table 1.

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Table 1. — *Clinical data.*

Group	n	Average age / year	BMI	Cancer measurement		Marital status	
				Left	Right	Married	Unmarried
Group Nh	68	45.23 ± 3.03	26.23 ± 3.45	28	32	50	8
Group Cg	68	45.31 ± 2.87	26.19 ± 3.71	27	31	49	9
$X^{2/t}$		0.158	0.065		0.069		
p		0.874	0.948		0.702		

Inclusion and exclusion criteria

The patients have the following inclusion criteria: (1) at stage III or stage IV breast cancer, with primary tumor invading the chest wall, and single or multiple distant metastasis, (2) age between 21-75 years old, (3) have complete admission and screening data, and (4) with good physical condition during the experiment. Patients with the following conditions were excluded: (1) exhibit functional abnormalities of other organs, (2) have multiple types of tumor simultaneously, (3) pregnant or lactating, (4) and have poor communication ability.

Therapeutic method

The patients in the two groups were given nutritional support, dexamethasone and inhibitor of 5-HT3 receptor before chemotherapy to prevent adverse reactions. In NH group, patients were given epirubicin and docetaxel intravenously, each at a dose of 75 mg/m^2 for one day, once a course of treatment; in CG group, capecitabine was administered at a dose of 2 g/m^2, with no more than 4 g/m^2 per day, for two consecutive weeks, once a course of treatment. A course of treatment comprises 21 days, and a total of 3 courses were given in NH group and CG group.

Observation targets

The following parameters were observed in both NH and CG group: the clinical effects; E1, E2 and FSH; the tumor size after 1-3 courses of treatment; adverse reactions; 2-year follow-up of survival rates.

Detection methods

In determining the E1, E2 and ESH levels, 5ml of venous blood after fasting was collected from patients before and after treatment. The plasma was separated by centrifugation, and the changes of E1, E2 and ESH levels were measured by ELISA. In tumor size measurement, Siemens acusons2000 ABVS system was used with 14l5bv high-frequency linear array probe at a frequency of 11mhz to scan and record the lateral, central and medial breast, before sending to ABVS workstation for image reconstruction using three-dimensional method by including the coronal and sagittal planes, and finally calculating the volume of the focus using selected largest sections.

Curative effect evaluations

The curative effects based on the evaluation standards of short-term effects of solid tumor were listed as follow: (1) Complete relief: disappearance of pain on the affected side, absence of beneficial fluid from the nipples, and absence of lesions; (2) Partial remission: shrinkage in more than 30% of lesions; (3) Disease stability: shrinkage in tumor diameter and volume without achieving partial remission; (4) Disease progression: disease progression with an increased volume size in more than 20% of the lesions or the generation of new lesions.

Statistical analysis

The changes of E1, E2, ESH levels, the survival rates and tumor volumes before and after treatment were statistically analyzed by GraphpadPrism 8. Chi square test was used for n (%) with $(\bar{X}+S)$.as the variable. LSD t or bonferonni test was used for comparison between the two groups. Repeated measurement analysis of variance and log rank test were used for comparison between the two groups at different time points, with $p < 0.05$ as the level of significance.

Results

Efficacy evaluation criteria of NH group and CG group.

The NH group and CG group showed a total efficacy rate of 64.7% and 23.5% respectively, with the CG group being significantly lower than that of the NH group ($p < 0.05$), as shown in Table 2.

Level changes of serum E1, E2 and FSH

The serum E1, E2 and FSH levels before treatment showed no significant difference between the NH group and the CG group ($p > 0.05$). After treatment, whilst the E1 and E2 levels in both groups were lower than those before treatment, the FSH values were higher ($p < 0.05$). Compared with the NH group, the serum E1 and E2 levels in the CG group were significantly higher, while the FSH levels were lower, as shown in Table 3.

Tumor size after 1-3 courses of treatment

There was no significant difference in tumor size between the NH group and CG group ($p > 0.05$). Compared with that of before treatment, the tumor volume of each group decreased gradually over treatment time. The tumor size of each course of treatment in the NH group was smaller than that of in the CG group ($p < 0.05$), as shown in Table 4.

Adverse reactions

Adverse reactions were observed in the two groups. In the NH group, there were 12 cases of nausea and vomiting,

Table 2. — *Clinical efficacy of NH group and CG group.*

Group	n	Complete remission	Partial remission	Disease stabilization	Total efficacy rate
Group Nh	68	9 (13.2%)	35 (51.4%)	2 (33.8%)	44 (64.7%)
Group Cg	68	4 (5.8%)	12 (17.6)	39 (57.3%)	16 (23.5%)
X^2					15.562
p					0.002

Table 3. — *Level changes of serum E1, E2 and FSH in NH and CG groups.*

Group	n	E1 (pg/mL)		E2 (pg/mL)		FSH (mIU/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Group Nh	68	68.19 ± 5.2	35.46 ± 3.35#	82.65 ± 5.61	53.91 ± 4.72#	50.23 ± 5.09	74.56 ± 7.15#
Group Cg	68	68.23 ± 5.12	50.34 ± 4.62#	82.71 ± 5.48	63.03 ± 6.28#	50.36 ± 4.78	65.23 ± 6.22#
t		0.038	18.44	0.054	8.209	0.131	6.961
p		0.969	< 0.001	0.956	< 0.001	0.895	< 0.001

 # denotes the comparison with the same group before treatment ($p < 0.05$)

Table 4. — *Tumor size after 1-3 courses of treatment in NH group and CG group.*

Group	n	Before treatment	First course of treatment	Second course of treatment	f	*p*
Group Nh	68	47.25 ± 13.14	36.23 ± 10.21*	19.75 ± 12.03*#	77.63	< 0.001
Group Cg	68	47.30 ± 12.36	41.15 ± 10.36*	35.26 ± 11.58*#	7.894	< 0.001
t		0.019	2.392	6.568		
p		0.984	0.018	< 0.001		

** denotes the comparison with the pretreatment $p < 0.05$, # denotes the comparison with the first course $p < 0.05$, * denotes the comparison with the second course $p < 0.05$.*

12 cases of alopecia, 14 cases of leucopenia, 11 cases of central granulocytopenia and 13 cases of peripheral neurotoxicity. Meanwhile, in the CG group, there were 17 cases of nausea and vomiting, 17 cases of leucopenia, 15 cases of alopecia, 18 cases of central granulocytopenia and 15 cases of peripheral neurotoxicity. There was no significant difference in the adverse reactions between the two groups ($p > 0.05$), as shown in Table 5.

Two-year survival rate

The 2-year survival rate of NH group and CG group was 82.3%, and 71.3%, respectively. The 2-year survival rate of NH group was significantly higher than that of CG group, as shown in Figure 1.

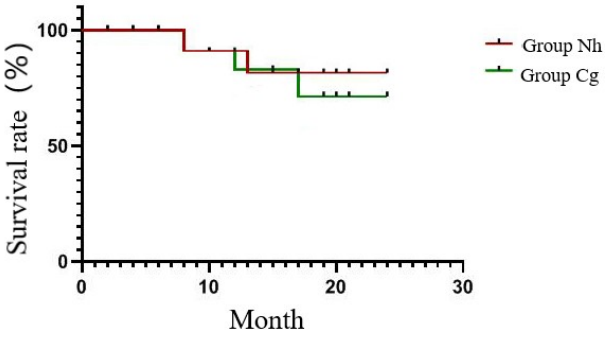

Figure 1. — The 2-year survival rate of NH group and CG group.

Conclusions

With over 200,000 of women diagnosed annually worldwide, breast cancer has shown a high mortality rate over the years. The causative factors of breast cancer are complex and vary widely. Currently, there are very limited surgical and therapeutic interventions available for treating breast cancer effectively. In addition, chemotherapy drugs presently available on the market have toxicity issues that may cause a number of side effects, and many patients develop drug resistance after long-term use [9-10]. Similar to the occurrence of other tumors, breast cancer tumorigenesis is a long-term and multi-step process that involves complex genetic and epigenetic abnormal changes [11]. Although many studies over the past few decades have explored the pathogenesis of breast cancer, the detailed molecular mechanism of the occurrence and development of breast cancer is still poorly understood to date. The post-surgery clinical effect of patients is poor with unsatisfactory long-term prognosis [12].

In this study, we found 9, 35, 23 and 8 patients with complete remission, partial remission, disease control, and dis-

Table 5. — *Adverse reactions of NH group and CG group.*

Group	n	Nausea and vomiting	Alopecia	Leukopenia	Central granulo-cytopenia	Peripheral neurotoxi-city
Group Nh	68	12	12	14	11	13
Group Cg	68	17	15	17	18	15
X^2		0.711	0.278	0.237	1.395	0.118
p		0.399	0.598	0.626	0.237	0.731

ease progression, respectively in the NH group; and only 4, 12, 39 and 13 patients with complete remission, partial remission, disease stable and disease progression, respectively in the CG group. The total effective rate of the NH group was higher than that of the CG group. Compared with those of the NH group, the serum E1 and E2 levels of the CG group were significantly higher, whilst the serum FSH levels of the NH group were significantly higher than those of the CG group. It has been reported that a number of hormones such as E1, E2 and FSH. in females can promote the proliferation and invasion of cancer cells, and that their mechanism of actions may be related to the activation of proteins, enzymes or oncogenes involved in nucleic acid synthesis which promotes tumorigenesis [13-14]. While conventional macromolecular chemotherapy drugs are difficult to be absorbed, chemotherapy drugs at low concentrations have little effect on cancer cells. Epirubicin, an anthracycline drug which can be absorbed at a higher concentration can kill tumor cells before they invade into other organs, hence lowering the possibility of recurrence and metastasis [15-16]. Consistent with the results in this paper, some studies have confirmed that epirubicin exhibit an outstanding ability to be absorbed into cancer cells by close binding with DNA, which causes reduction of DNA replication tenderness, decreased DNA dependent polymerase activity, the obstruction of RNA transcription, and ultimately the inhibition of tumor growth from the inside out [17]. Qin Xingxing found that doxorubicin combined with cisplatin has a good therapeutic effect on cervical cancer patients, by effectively increasing the expression of FHIT and Bax protein in HeLa cells, reducing the expression of Ki-67 protein, improving the survival rate of patients, and lowering the incidence of adverse reactions, making it a safe and effective treatment method [18]. Consistently, Zhong Jinyi found that doxorubicin enhanced the ability of three negative breast cancer cells to form spheres by activating stat3-oct-4 signal pathway, increased the expression of CD133 and CD44, the dry markers of 4T1 cells, and induced the generation of dry breast cancer cells [19].

In this study, we only found 14 cases of neutropenia cases in the NH group, while most neutropenia cases were found it the CG group. The number of adverse reactions in the CG group was significantly higher than that of the NH group. The survival rate of the patients in the NH group was significantly higher than that in the CG group. The post-treatment tumor volume of each group decreased gradually over the course of treatment, and the tumor reduction degree of the CG group was lower than that of the NH group. According to the literature, although the effects of different drugs vary greatly, chemotherapy can inhibit tumor neovascularization and kill tumor cells by apoptosis. After periodic treatment, tumor volume can be decreased significantly. Although the clinical effect of single use or combined use is considerably good, the incidence of cardiotoxicity of epirubicin is significantly lower than that of adriamycin [20]. Xu Zidu found that adriamycin combined with thalidomide is effective in the treatment of HCC, which can effectively regulate cytokines, reduce the level of tumor markers and improve the survival rate, and hence has good clinical application value [21]. In agreement with this, Wei Zhaozhao, *et al.* found that the combination of liposomal adriamycin and oxaliplatin in treating recurrent epithelial ovarian cancer is effective to a certain extend with less adverse reactions and good tolerance, which ultimately improves the treatment compliance and survival time of patients [22]. Additionally, doxorubicin combined with other drugs has a significant effect in the treatment of breast cancer. Compared with conventional chemotherapy drugs, doxorubicin has lower adverse reactions with less prognosis, which is worth to be used widely in clinical practice [23].

In summary, anthracycline is effective in the treatment of advanced breast cancer by lowering the level of serum E2 and the tumor volume.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Shan Xi Bethune Hospital (approval number: 2017L03415).

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Conflict of Interest

The authors declare no conflict of interest.

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