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Original Article

Clinical observation of intraoperative local chemotherapy with lobaplatin in breast cancer modified radical mastectomy

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Abstract: Background: To evaluate the clinical efficacy of intraoperative local chemotherapy with Lobaplatin in patients underwent breast cancer modified radical mastectomy. Patients and methods: 50 cases of primary breast cancer patients intended to receive modified radical mastectomy were included and randomly divided into two groups. In observation group, operative wound was washed and steeped by physiological saline containing 50 mg Lobaplatin for 15 min. After sucking out the washing fluid, another 50 mg Lobaplatin was multi-point sprayed in tumor bed, axillary lymph node dissection area, and any other potential area of residual cancer cells before flap suture. Control group only received a treatment of same amount of physiological saline. Then, drug safety, short-term effects and long-term results were tracked and compared. Results: Several postoperative adverse effects including myelosuppression (number of leukocytes and platelets), hepatic and renal functions (serum creatinine and alanine aminotransferase), local pain as well as gastrointestinal reactions (nausea and vomiting) and primary healing time showed no significant difference between two groups ($P>0.05$). Positive rate of exfoliative tumor cytology in observation group was remarkably lower than control group ($\chi^2=5.1$, $P<0.05$). The 3-year overall survival rates seemed no different between two groups (88.9% *vs.* 87.5%, $P>0.05$), whereas the 3-year disease free survival in observation group was higher than that in control group (90.0% *vs.* 79.1%, $P<0.05$). Conclusion: Intraoperative Lobaplatin chemotherapy in patients undergoing breast cancer modified radical mastectomy is safe and effective and could improve 3-year disease free survival. It is worthy of further clinical promotion.

Keywords: Breast cancer, lobaplatin, intraoperative chemotherapy, disease free survival

Introduction

Breast cancer (BCa) is the most common malignancy and the second leading cause of cancer death in females worldwide [1]. Classical modified radical mastectomy coupled with postoperative adjuvant chemotherapy and/or radiotherapy is considered to be an effective and standard treatment for BCa. However, a large percentage of patients ultimately have locoregional recurrence and die with progressive disease [2]. This presents challenge in terms of achieving satisfied tumor control. The possibility of cancer cell seeding during surgery has been well reviewed as a significant factor in the occurrence of local relapse or distant metastasis [3]. Ma *et al.* performed a cytological examination of surgical field washing in 104 patients undergoing surgery for BCa. Thirty-six patients had positive or suspicious cytology in at least one of the samples, offering a theoretical basis for killing or removing of the exfoliative cancer cells in surgical field [4]. In addition, several studies in which circulating tumor cells could be found in disease-free BCa patients for more than seven years and even up to 20 years after successful treatment indicated that dormant micrometastases may shed tumor cells into

blood, further providing support for the above notion [5, 6].

The optimal cytoreduction still remains an open and critical question for the BCa oncologists. To date, many attempts have been adopted to eliminate tumor cell spread during surgery by changing gloves and surgical instruments after successful lumpectomy and by irrigating the operative wound with physiological saline. During the last 10 years, cytoreductive surgery in combination with intraoperative chemotherapy was proposed as the "up-front treatment" for ovarian cancer [7]. Although several published trials failed to reach a worldwide consensus [8, 9], the use of such locoregional approach has been shown to improve prognosis of peritoneal carcinomatosis from colorectal and appendix cancer and is recently recommended in patients with gastric cancer [10, 11]. It is our hypothesis that if intraoperative chemotherapy is employed in BCa surgery, the high rate of local recurrence would be greatly decreased. Therefore, we have carried out a pilot study to better clarify the role of this treatment modality. The objective of our work was to assess the benefit from modified radical mastectomy with or without intraoperative Lobaplatin chemotherapy in BCa patients.

Patients and methods

Patient selection

General inclusion criteria were pathologically confirmed primary BCa, age between 18 and 75 years, Eastern Cooperative Group Performance Status ≤2, life expectancy of at least 5 years, adequate cardiac, hepatic, renal and bone marrow functions, no serious medical condition like diabetes mellitus, and no hypersensitivity to Lobaplatin. Patients were excluded if they were previously treated with oral chemotherapy or endocrine agents, or had evidence of distant metastasis. The study was approved by the Ethical Committee of Jiangsu Cancer Hospital. All the patients signed an informed consent including explicit consent about the modified radical mastectomy and experimental nature of the intraoperative chemotherapy procedure before being enrolled. From August 2011 to November 2014, a total of 50 were collected. Cases in observation group received modified radical mastectomy plus intraoperative chemotherapy with Lobaplatin, and controls were represented by patients with similar clinical-pathologic characteristics who only underwent surgery in the same study period.

Treatment modality

Standard modified radical mastectomy was performed according to the pathological results obtained from core needle biopsy. In observation group, operative wound was washed and steeped by 100 mL physiological saline containing 50 mg Lobaplatin for 15 min. After sucking out the washing fluid, another 50 mg Lobaplatin was prepared, diluted in 10 mL physiological saline, and multi-point sprayed in tumor bed, axillary lymph node dissection area, and any other potential area of residual cancer cells before flap suture. Then, drainage tubes were carefully placed, and vacuum suction was connected to clean the rest washing fluid under skin flap. Control group only received a treatment of same amount of physiological saline without Lobaplatin.

Clinical evaluation

Postoperative details including gastrointestinal symptoms (nausea and vomiting), myelosuppression (number of leukocytes and platelets), hepatic and renal functions (serum creatinine and alanine aminotransferase), local pain, the amount of drainage fluid, and primary healing time were monitored and documented. Several agents were given to relieve the corresponding symptoms when needed.

Patient's drainage fluids after operation 72 h were centrifuged at 4000 r/min for 5 min, and the precipitates were examined under the microscope using HE staining [4]. Any biological sample containing one or more tumor cells was referred to as positive for exfoliative tumor cells.

All patients received standardized postoperative chemotherapy and/or radiotherapy according to the extent of disease and regular follow-up including physical examination, tumor marker analysis, and imaging detection. Follow-up was conducted until March 2015 or until death, data were collected based on medical records or telephone consultation. Overall survival was defined as the time elapsed between intraoperative chemotherapy and the date of death or

Table 1. Comparison of leukocytes (WBC), platelets (PLT), serum creatinine (Cr), alanine aminotransferase (ALT), amount of drainage fluid and primary healing time between two groups (mean ± standard deviation)

Group	N	WBC ($\times 10^9$)	PLT ($\times 10^9$)	Cr (μmol/L)	ALT (U/L)	Drainage fluid (ml)	Primary healing time (d)
Observation	28	7.5±1.0	236.1±51.8	77.6±10.1	32.6±5.6	538.3±62.0	17.4±2.6
Control	22	7.2±1.2	226.6±34.2	76.3±8.9	30.6±7.1	469.8±69.7	16.8±2.5
t value		0.7	0.6	0.4	0.9	2.9	0.7
p value		>0.05	>0.05	>0.05	>0.05	<0.05	>0.05

Table 2. Comparison of local pain, nausea, vomiting and positive rate of exfoliative tumor cytology between two groups (N%)

Group	N	Local pain	Nausea	Vomiting	Exfoliative tumor cytology
Observation	28	8 (28.6%)	6 (21.4%)	3 (10.7%)	2 (7.1%)
Control	22	6 (27.3%)	5 (22.7%)	1 (4.5%)	7 (31.8%)
χ^2 value		0.01	0.01	0.6	5.1
p value		>0.05	>0.05	>0.05	<0.05

last follow-up. Disease free survival was defined as the time elapsed between intraoperative chemotherapy and the date of first recurrence or metastasis.

Statistical analysis

All statistical calculations were performed using the SPSS 16.0 package. Postoperative details between the observation group and control group were compared using the *t* test or χ^2 test, as appropriate. Kaplan-Meyer method and log-rank test were used to identify difference in survival. *p* Values less than 0.05 were accepted as statistically significant.

Results

Between August 2011 and November 2014, a total of 28 patients with primary BCa undergoing modified radical mastectomy plus intraoperative chemotherapy with Lobaplatin (observation group) have been selected. They have been matched as closely as possible for inclusion criteria with 22 patients experiencing similar surgical operation, treated without Lobaplatin (control group). There were no statistically significant differences in clinical characteristics between two groups (not shown).

Drug safety and short-term effects

Details of myelosuppression (number of leukocytes and platelets) and hepatic and renal functions (serum creatinine and alanine aminotransferase) were compared. No differences were found between the observation group and control group ($P>0.05$). The amount of drainage fluid was significantly higher in observation group at 538.3±62.0 mL compared to 469.8±69.7 mL in control group ($t=2.9$; $P<0.05$). Primary healing time was 17.4±2.6 d for the cases and 16.8±2.5 d for the controls ($P>0.05$; **Table 1**). In addition, the incidence of local pain and gastrointestinal reactions including nausea and vomiting displayed no difference between two groups ($P>0.05$; **Table 2**).

Exfoliative tumor cytology and long-term results

In observation group, 2/28 patients (7.1%) showed positive for exfoliative tumor cytology compared to 7/22 patients (31.8%) in control group ($\chi^2=5.1$, $P<0.05$; **Table 2**). All patients had been followed up. The median follow-up time was 22.3 months for observation group and 25.2 for control group. During this period, 7 recurrences were documented. In particular, 5 (22.7%) controls recurred, while 2 out of 28 (7.1%) in observation group experienced recurrence. Among 3 deaths, 2 (9.1%) belonged to controls and 1 (3.6%) to the observation group. No relevant difference in the 3-year overall survival rate was found concerning the patients undergoing intraoperative chemotherapy with Lobaplatin *versus* those without agents (88.9% *vs.* 87.5% respectively for observation and control group, $P>0.05$; **Figure 1**). However, the observation group survived better than controls, with a 3-year disease free survival of 90.0% *vs.* 79.1%, respectively ($P<0.05$; **Figure 2**).

Discussion

BCa is the most common cancer and the second leading cause of cancer death among

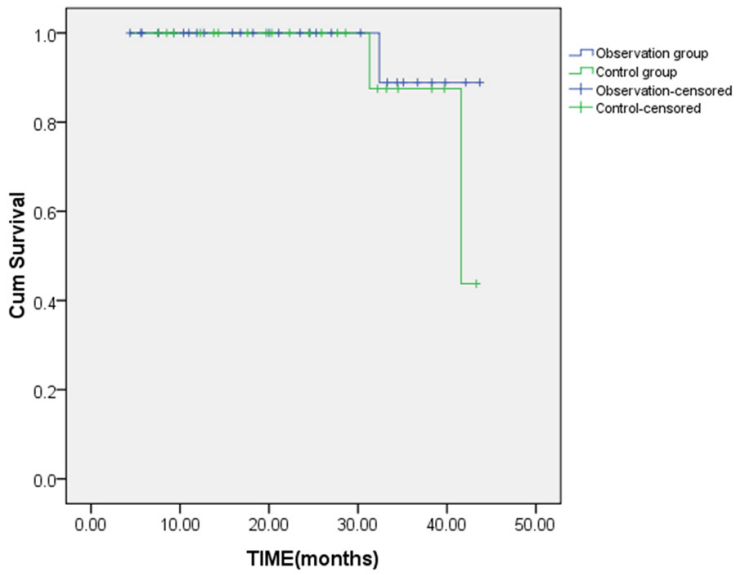

Figure 1. The 3-year overall survival of two groups. No relevant difference in the 3-year overall survival rate was found concerning the patients undergoing intraoperative chemotherapy with Lobaplatin vs. those without agents (88.9% vs. 87.5% respectively for observation and control group, P>0.05).

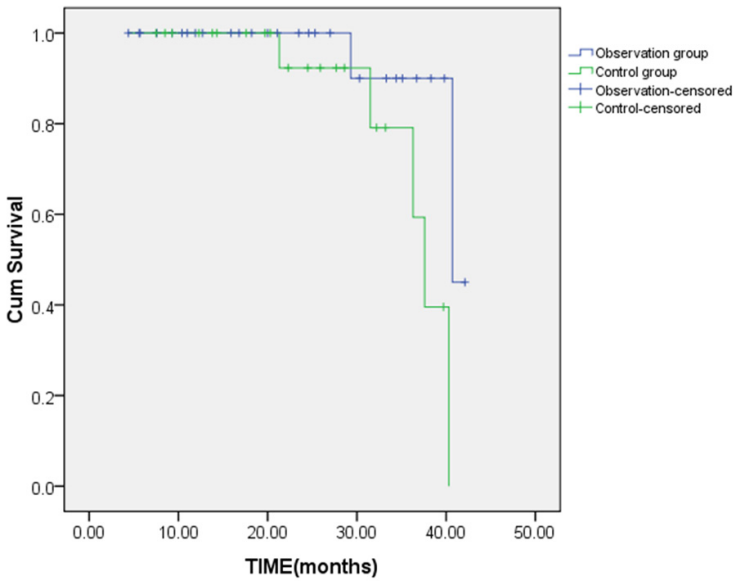

Figure 2. The 3-year disease free survival of two groups. The 3-year disease free survival in observation group was higher than that in control group (90.0% vs. 79.1%, P<0.05).

women after lung cancer. Approximately 20% of BCa patients will have locoregional recurrence and even die with progressive disease [2]. Although the pathophysiology of local relapse or distant metastasis remains unclear, the finding of tumor cell seeding has been proposed as an important factor [3]. Hansen *et al*. reported that tumor cells were isolated from intraoperative salvaged and washed blood in 57 of 61 patients. These cells displayed proliferation capacity, invasiveness as well as tumorigenicity [12]. It has also been demonstrated that circulating tumor cells could be detected in surgeries performed for many malignancies including BCa [13, 14]. Obviously, there is an absolute need for optimal cytoreduction in addition to surgical resection.

It is common practice to change gloves and surgical instruments and to irrigate the wound after tumor removal. The eradication of exfoliative cancer cells may also be possible by using intraoperative chemotherapy. For example, intraoperative gemcitabine irrigation increased rates of long-term disease control in human squamous cell carcinoma-contaminated surgical wounds by a xenograft model. Gemcitabine irrigation did not affect wound healing and was free of local complications [15]. In clinical practice, patients with pancreatic cancer undergoing potentially curative resection in combination with intraoperative use of gemcitabine showed a survival benefit [16]. This approach has recently been tried in some other malignant tumors with success by using different chemotherapeutic agents [17, 18]. However, intraoperative Lobaplatin chemotherapy during BCa surgery has not been reported. We compared postoperative data between a group of BCa cases treated with modified radical mastectomy plus intraoperative Lobaplatin chemotherapy and a similar group of women not experiencing intraoperative chemotherapy, thus describing such a treatment modality in BCa for the first time. Lobaplatin was chosen because it has been

proved to be very effective in adjuvant treatment of BCa and is currently unclear in local control [19]. The major toxicity of this regimen is due to Lobaplatin-induced nausea, vomiting and visceral dysfunction, resulting in acute hepatic and renal failure. Our work showed that intraoperative local chemotherapy with Lobaplatin in patients having modified radical mastectomy is well tolerated and does not produce severe toxicity. No one developed grade III myelosuppression or hepatic and renal damage, and none of them required any specific treatment. This might attributed to the low plasma concentration of Lobaplatin when it was local used. Remarkably, the amount of drainage fluid was significantly higher in observation group compared to control group. We hypothesized that cytoclasis, cell liquefaction and humoral immunity induced by exogenous Lobaplatin may be responsible for the increased drainage fluid. It has been reported that cytotoxic drugs could affect the synthesis and maturation of collagen and intraoperative chemotherapy may lead to anastomotic leakage in gastrointestinal cancer patients, resulting in delayed healing [20]. Information of wound recovery after intraoperative chemotherapy is scarce for BCa. Although we had not compared the indwelling time of drainage tube and duration of hospital stay between two groups, our data showed that there was no significant difference in primary healing time. Besides, no hyperpyrexia, purulent drainage, and flap necrosis were observed. Thus, intraoperative Lobaplatin chemotherapy during modified radical mastectomy is quite safe.

The notion of cancer cell seeding has been demonstrated as an important factor for local relapse or distant metastasis. In our study, positive rate of exfoliative tumor cytology in observation group was lower than control group, suggesting that intraoperative treatment could decrease the exfoliative cancer cells. The 3-year overall survival rates seemed no different between two groups, whereas the 3-year disease free survival in observation group was higher. It appears that intraoperative Lobaplatin chemotherapy may have a favorable effect in reducing recurrence and metastasis. As a matter of fact, Lobaplatin was multi-point sprayed in tumor bed, axillary lymph node dissection area, and any other potential area of residual cancer cells. On one hand, cancer cells were long exposed to high concentration of agents because of local chemotherapy and low drug clearance of chest wall, resulting in improved tumoricidal activity and decreased local recurrence; on the other hand, Lobaplatin could be absorbed by capillary microcirculation and then enter blood via axillary vessels and lymphatic system, which is similar with the metastasis pathway of BCa. So theoretically, intraoperative Lobaplatin chemotherapy could not only eliminate the exfoliative cancer cells but also eradicate the dormant micrometastases in axillary lymph system. It is noteworthy that 100% of tumor free is hard to achieve even intraoperative chemotherapy is immediately performed. Residual cancer cells may still be transferred to liver via sheath of rectus abdominis muscle and hepatic falciform ligament. We will continue to follow up and look forward to the subgroup analysis (unpublished data) and 5 years of survival data.

As far as therapy-related morbidity and mortality are concerned, it was out of the aim of this work. However, recent progresses in perioperative care, safer administering of chemotherapy and improvements in surgical skill has made such aggressive approach. Limitations of our work reside in the short follow-up time and in the low number of patients, but the close matching between two groups should theoretically assure the quality of data.

In conclusion, this case-control pilot study showing a statistically significant benefit of modified radical mastectomy plus intraoperative Lobaplatin chemotherapy compared to no-intraoperative chemotherapy just disclose the possible clinical promotion of such treatment modality in BCa patients.

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Disclosure of conflict of interest

None.

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