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ORIGINAL ARTICLE

Capecitabine metronomic chemotherapy combined with autologous CIK cell immunotherapy in the treatment of recurrent and metastatic triple-negative breast cancer

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Summary

Purpose: *The purpose of this study was to investigate the efficacy and safety of maintenance therapy of capecitabine metronomic chemotherapy combined with autologous cytokine-induced killer (CIK) cell immunotherapy in patients with recurrent metastatic triple-negative breast cancer (mTNBC).*

Methods: *The clinical data of 110 patients with recurrent mTNBC were retrospectively analyzed. Among, 55 were treated with maintenance therapy of capecitabine metronomic chemotherapy combined with autologous CIK cell immunotherapy (DC-CIK group), while the rest 55 were treated with simple metronomic chemotherapy (control group).*

Results: *The ORR of patients in DC-CIK group and control group was 29.1% and 16.4%, and the DCR was 74.5% and 63.6%, respectively. After treatment, the proportions of $CD3^+$ T lymphocytes, $CD4^+$ T lymphocytes and NK cells as well as the CD4/CD8 cell ratio were notably higher in DC-CIK group than those in control group, while the proportion of $CD8^+$ T lymphocytes was notably lower in DC-CIK group than that in control group. Compared with those before treatment, the scores of quality of life evaluated using the FACT-B-V4.0 scale were remarkably improved in both groups after treatment. The score of emotional status and total score were distinctly higher in DC-CIK group than those in control group. Moreover, the follow-up results together with log-rank test revealed that the PFS in DC-CIK group was notably superior to that in control group.*

Conclusions: *The maintenance therapy of capecitabine metronomic chemotherapy combined with DC-CIK cell immunotherapy is effective in the treatment of recurrent mTNBC, with tolerable adverse reactions. It can improve the patients' immune function, improve their quality of life, and prolong their PFS.*

Key words: *capecitabine, metronomic chemotherapy, immunotherapy, breast cancer, recurrent and metastatic*

Introduction

Triple negative breast cancer (TNBC) is a type of breast cancer with loss of expressions of estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2, which accounts for 15-20% of all pathological types of breast cancer [1]. It is characterized by a younger onset age, poor pathological grade, high invasiveness, and high rates of recurrence, metastasis and mortality. Therefore, it is necessary to conduct combined chemotherapy for TNBC patients who are in good physical conditions, so as to control the tumor. However, for patients whose disease is controlled after combined chemotherapy, once the drug is withdrawn, the disease will deteriorate easily and rapidly, so maintenance therapy is very important [2,3]. Metronomic chemotherapy is a treatment method featured by relatively low toxicity, low dosage, continuously high-frequency administration and no obvious intermission, which prolongs the survival time of patients through anti-tumor

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angiogenesis, immune regulation and induction of tumor cell dormancy [4,5]. Since metronomic chemotherapy possesses such characteristics as good tolerance and no cumulative toxicity, it can be used as one of the methods of maintenance therapy for recurrent metastatic TNBC (mTNBC) to a certain extent [6].

Cytokine-induced killer (CIK) cells, a category of novel and high-efficient competent cells, have the tumor-killing activity of T lymphocytes and the major histocompatibility complex (MHC) non-restricted tumoricidal effect of natural killer (NK) cells. Meanwhile, they can ameliorate the immune function in the body and improve the quality of life, becoming one of the vital means of adoptive immunotherapy for malignant tumors [7,8]. This study aims to explore the efficacy and safety of the maintenance therapy of capecitabine metronomic chemotherapy combined with dendritic cell-CIK (DC-CIK) cell immunotherapy for patients with recurrent mTNBC, hoping to provide a basis for the selection of treatment protocols for such patients.

Methods

General data

The clinical data of 110 patients with recurrent mTNBC who were treated in our hospital from January 2016 to December 2018 were collected. The inclusion criteria involved: (1) patients with an age ≥18 years old, (2) those who were definitely diagnosed with infiltrating ductal carcinoma at clinicopathological stage IV by histopathological diagnosis and immunohistochemical examination, (3) those with measurable or assessable lesions, (4) those with an ECOG score of 0-2 points, and (5) those with life expectancy ≥3 months. The exclusion criteria were as follows: (1) patients with severe dysfunction of parenchymatous organs such as liver and kidney, (2) those with drug allergy, (3) those with severe infection, (4) those who were pregnant or breastfeeding, (5) those with mental disorders, or (6) those with life expectancy <3 months. According to the different treatment regimens received, the patients were assigned into DC-CIK group (n=55, receiving maintenance therapy of capecitabine metronomic chemotherapy + autologous CIK cell immunotherapy) and control group (n=55, undergoing simple metronomic chemotherapy). The age of the 110 patients ranged 26-72 years old, with an average of (53.3±9.6) years old. No statistically significant differences were observed in the general clinical baseline data such as age, pathological type, metastasis site and number of metastatic lesions between the two groups (p>0.05), which were comparable (Table 1). All patients enrolled were informed of and signed the informed consent in accordance with the *Declaration of Helsinki*. This study was approved by the Ethics Committee of Shaanxi Provincial People's Hospital.

Treatment methods

In DC-CIK group, cells were isolated and sent to laboratory for DC-CIK cell culture. Metronomic chemo-

Table 1. Baseline demographic and clinical characteristics of the studied patients

Indicators	*DC-CIK group (n=55)* *n (%)*	*Control group (n=55)* *n (%)*	*p*
Age (years old)	54.31±9.79	52.83±9.51	0.423
BMI (kg/m^2)	22.6±2.3	22.9±2.7	0.532
Menstrual status			0.431
Menopause	37 (67.3)	32 (58.2)	
Premenopause	18 (32.7)	23 (41.8)	
Metastasis site			0.640
Bone	5 (9.1)	4 (7.3)	
Lung	26 (47.3)	23 (41.8)	
Liver	24 (43.6)	28 (50.9)	
Number of metastasis sites			0.367
1	21 (38.2)	26 (47.3)	
≥2	34 (61.8)	29 (52.7)	
Previous treatment			0.446
First-line	29 (52.7)	25 (45.5)	
Second-line	26 (47.3)	30 (54.5)	
ECOG			0.623
0	15 (27.3)	18 (32.7)	
1	27 (49.1)	25 (45.5)	
2	13 (23.6)	12 (21.8)	

Notes: DC-CIK: Dendritic cell- cytokine induced killer cells; BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group.

therapy was performed from d 3: capecitabine at 500 mg bid on d 1-14 and cyclophosphamide at 50 mg qd on d 8-21. Metronomic chemotherapy was suspended at 48 h before back transfusion of DC-CIK cells. Then, DC-CIK cells were infused 2-3 times a cycle every other day, and metronomic chemotherapy was restored at 48 h after back transfusion. One cycle included 21 consecutive days. The treatment continued until intolerable adverse reactions occurred or the disease progressed, and DC-CIK cells were reinfused continuously for 1 year at most. Patients in control group received simple metronomic chemotherapy: continuous oral administration of capecitabine at 500 mg bid on d 1-14 and cyclophosphamide at 50 mg qd on d 8-21. One cycle included 21 consecutive days. The treatment continued until intolerable adverse reactions occurred or the disease progressed.

Observation indexes

The short-term efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), which was categorized as complete remission (CR), partial remission (PR), progressive disease (PD) and stable disease (SD). The objective response rate (ORR) was calculated according to the formula below: ORR = (CR cases +PR cases)/total cases × 100%. The disease control rate (DCR) was calculated as follows: DCR = (CR cases + PR cases + SD cases)/total cases × 100%.

Routine laboratory examinations including routine blood, urinary and stool test, liver and kidney function test, blood coagulation function test, electrocardiogram and cardiac ultrasound were performed in both groups along with the chemotherapy cycle. Adverse reactions involving vitality, physical strength, appetite and sleep, as well as the presence of fever, nausea, vomiting, rash, drowsiness, fatigue and pain were observed during and after CIK cell reinfusion. According to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0, the adverse reactions were graded as I-IV.

T lymphocyte subsets in peripheral blood were detected by flow cytometry. Peripheral blood samples were collected before and after CIK cell culture, before CIK treatment and at 1 month after the 3rd CIK treatment (3rd cycle) to detect the changes in the expressions of T lymphocyte subsets *in vivo*.

Follow-up was performed at 1, 2, 3, 6, 9 and 12 months after treatment, and every 3-6 months thereafter. The tumor progression in the patients was recorded up to May 2020. Progression-free survival (PFS) was defined as the time from the start of treatment to the occurrence of PD for the first time or death of any cause.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was utilized for statistical analyses. The measurement data were expressed as mean ± standard deviation, and *t*-test was performed for intergroup comparison. The enumeration data was expressed as rate (%), and x^2 test was conducted for intergroup comparison. Log-rank test was performed for comparison of PFS between the two groups. $P<0.05$ suggested that the difference was statistically significant.

Results

Comparison of short-term clinical efficacy between the two groups

Patients in DC-CIK group received 4-20 cycles of treatment, with an average of 14.9 cycles. There were 3 cases (5.5%) of CR, 13 cases (23.6%) of PR, 25 cases (45.5%) of SD, and 16 cases (29.1%) of PD, with an ORR of 29.1% (16/55) and a DCR of 74.5% (41/55). Patients in control group received 4-18 cycles of treatment, with an average of 12.2 cycles. There were 0 cases of CR, 9 cases (16.4%) of PR, 26 cases (47.3%) of SD, and 20 cases (36.4%) of PD, with an ORR of 16.4% (16/55) and a DCR of 63.6% (35/55). There were no statistically significant differences in the ORR and DCR between the two groups (p=0.111, p=0.216) (Table 2).

Comparisons of T lymphocyte subsets in peripheral blood between the two groups before and after treatment

Before treatment, there were no statistically significant differences in the proportions of cluster of differentiation 3 $(CD3)^+$ T lymphocytes, $CD4^+$ T lymphocytes, $CD8^+$ T lymphocytes and NK cells, and the CD4/CD8 cell ratio between DC-CIK group and control group (p>0.05). After treatment, the

Table 2. Clinical effective rates of the two studied groups

	DC-CIK group (n=55) *n (%)*	*Control group (n=55)* *n (%)*	*p*
CR	3 (5.5)	0 (0)	
PR	13 (23.6)	9 (16.4)	
SD	25 (45.5)	26 (47.3)	
PD	14 (25.5)	20 (36.4)	
ORR	16 (29.1)	9 (16.4)	0.111
DCR	41 (74.5)	35 (63.6)	0.216

CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Objective response rate; DCR: Disease control rate.

proportions of $CD3^+$ T lymphocytes, $CD4^+$ T lymphocytes and NK cells and the CD4/CD8 cell ratio rose markedly, while the proportion of $CD8^+$ T lymphocytes declined evidently in both groups in comparison with those before treatment, with statistically significant differences ($p<0.05$). After treatment, the proportions of $CD3^+$ T lymphocytes, $CD4^+$ T lymphocytes and NK cells, as well as the CD4/CD8 cell ratio, in DC-CIK group were notably higher than those in control group ($p<0.05$), while the proportion of $CD8^+$ T lymphocytes was obviously lower in DC-CIK group than that in control group ($p=0.007$) (Table 3).

Comparisons of adverse reactions between the two groups

The patients tolerated the treatment well, and the major adverse reactions included fatigue, gastrointestinal reactions, liver function damage, hand-foot syndrome and bone marrow depression, mostly in grade I-II. The gastrointestinal reactions were relieved after administration of granisetron hydrochloride, and leukopenia could be recovered by leukocyte-increasing therapy with G-CSF. The grade III-IV adverse reactions included bone marrow depression, gastrointestinal reactions and hand-foot syndrome. In DC-CIK group and control group, there were 0 cases and 2 cases (3.6%) of grade III-IV anemia, 1 case (1.8%) and 4 cases (7.3%) of grade III-IV leukopenia, 2 cases (3.6%) and 1 case (1.8%) of grade III-IV thrombocytopenia, 2 cases (3.6%) and 4 cases (7.3%) of grade III-IV gastrointestinal reactions, and 2 cases (3.6%) and 2 cases (3.6%) of grade III-IV hand-foot syndrome, respectively. The incidence rates of leukopenia and gastrointestinal reactions in DC-

Table 3. Comparison of pretreatment and posttreatment cellular immune function indicators between the two groups of patients

	DC-CIK group (n=55)	*Control group (n=55)*	*p*
CD3+ T cell (%)			
Pretreatment	62.65±11.90	64.33±12.43	0.439
Posttreatment	80.51±13.76	68.58±12.74	0.001
CD4+ T cell (%)			
Pretreatment	32.13±6.09	33.53±7.31	0.278
Posttreatment	38.49±8.48	34.83±9.05	0.031
CD8+ T cell (%)			
Pretreatment	34.97±10.19	33.68±11.37	0.532
Posttreatment	26.63±7.66	30.32±6.41	0.007
CD4/CD8 ratio			
Pretreatment	0.91±0.19	0.97±0.23	0.139
Posttreatment	1.28±0.24	1.07±0.26	0.001
NK cell (%)			
Pretreatment	5.22±1.88	4.79±1.70	0.211
Posttreatment	11.10±3.04	6.17±3.48	0.001

DC-CIK: Dendritic cell-cytokine induced killer; NK: Natural killer.

Table 4. Comparison of adverse reactions and complications between the two groups of patients

Indicators	*DC-CIK group (n=55)*		*Control group (n=55)*		*p*
	Grade I-II *n (%)*	*Grade III-IV* *n (%)*	*Grade I-II* *n (%)*	*Grade III-IV* *n (%)*	
Leukopenia	21 (38.2)	1 (1.8)	27 (49.1)	4 (7.3)	0.045
Anemia	16 (29.1)	0 (0)	20 (36.4)	2 (3.6)	0.229
Thrombocytopenia	21 (38.2)	2 (3.6)	25 (45.5)	1 (1.8)	0.565
Gastrointestinal reactions	30 (54.5)	2 (3.6)	37 (67.3)	4 (7.3)	0.039
Liver function damage	19 (34.5)	0 (0)	23 (41.8)	0 (0)	0.432
Fatigue	22 (40.0)	0 (0)	24 (43.6)	0 (0)	0.599
Hand-foot syndrome	18 (32.7)	2 (3.6)	15 (27.3)	2 (3.6)	0.545

DC-CIK: dendritic cell-cytokine induced killer.

Table 5. Comparison of FACT-B-V4.0 scores between the two groups of patients

Indicators	*DC-CIK group (n=55)*	*Control group (n=55)*	*p*
Pretreatment			
Physiological status	17.12±3.98	16.65±3.81	0.528
Social / family status	17.73±4.68	17.07±4.53	0.454
Emotional status	16.78±4.84	16.24±4.36	0.540
Functional status	17.84±3.90	18.34±4.16	0.417
Additional concerns	19.33±5.11	20.03±5.09	0.473
Total score	88.80±14.75	88.33±16.39	0.675
Posttreatment			
Physiological status	23.23±4.57	21.96±4.74	0.156
Social / family status	24.39±4.49	22.81±4.89	0.080
Emotional status	21.60±4.58	18.54±4.52	0.007
Functional status	22.23±4.13	20.80±4.71	0.093
Additional concerns	25.61±4.89	24.31±5.22	0.181
Total score	117.06±18.94	108.42±20.83	0.025

DC-CIK: dendritic cell-cytokine induced killer.

CIK group were significantly lower than those in control group (p=0.045, p=0.039), but there were no statistically significant differences in the other adverse reactions (p>0.05). There was no nephrotoxicity or chemotherapy-related death in all cases (Table 4).

Evaluation of quality of life of patients in both groups before and after treatment

The quality-of-life scores evaluated using the Functional Assessment of Cancer Therapy-Breast (FACT-B)-V4.0 scale were compared between the two groups. In contrast with those before treatment, the scores of the quality of life in the FACT-B-V4.0 scale were markedly improved in both groups after treatment, displaying statistically significant differences (p<0.05). There were no statistically significant differences in the scores of physiological status, social/family status, emotional status, functional status and additional concerns between the two groups after treatment (p>0.05), while the emotional status score and total score were distinctly higher in DC-CIK group than those in control group (p=0.007, p=0.025) (Table 5).

Follow-up results of tumor progression in patients

As of May 2020, all the patients were followed up for 6-25 months. In DC-CIK group and control group, the median PFS (mPFS) of patients was 9.7 months and 6.9 months, and the 1-year PFS rate was 18.2% (10/55) and 9.1% (5/55), respectively. The results of log-rank test manifested that the PFS in DC-CIK group was notably superior to that in control group, displaying a statistically significant difference (p=0.035).

Discussion

Due to the lack of effective drugs for endocrine therapy and targeted therapy, TNBC often metastasize to the lung, bone, liver and brain. Chemotherapy is the conventional treatment choice currently. The treatment strategy is to keep maintenance therapy after reaching CR, PR or SD by combined chemotherapy, so as to alleviate the symptoms of, prolong the disease progression time, improve patients' quality of life, and extend their survival time as much as possible [9,10]. The ideal drugs for maintenance chemotherapy should be effective when used alone, with a relatively low toxicity, and convenient for long-term use [11,12]. Capecitabine is a kind of fluorouracil preparation that can be taken orally for a long time. The effective rate of monotherapy with capecitabine in the treatment of advanced breast cancer is up to 20-40%, with high safety and high quality of life of patients. At present, it has been widely applied in the maintenance treatment of advanced breast cancer [13,14]. In a retrospective analysis on 55 patients with advanced TNBC in 2014, after undergoing TX regimen of combined chemotherapy, 32 patients continued to receive capecitabine monotherapy, while the rest 23 patients received no further treatment. The results revealed that the mPFS was 10.1 months and 6.7 months (p=0.032), respectively. All patients tolerated the treatment well, and exhibited no grade IV hematological toxicity and gastrointestinal reactions caused by chemotherapy [15]. A study involving 87 patients with advanced breast cancer in 2013 manifested that after combined chemotherapy, the mTTP of capecitabine monotherapy group (n=50) was 9.43

months, which is significantly longer than that (4.5 months) in non-maintenance group (n=37) (p=0.004), suggesting that capecitabine monotherapy following combined chemotherapy can significantly prolong the survival time of patients, and there is no significant difference in safety between the two groups [16]. Cyclophosphamide is a kind of commonly used alkylating antineoplastic drug. In this study, capecitabine was combined with cyclophosphamide. Considering the toxic and side effects of cyclophosphamide, metronomic chemotherapy was adopted in this study, and cyclophosphamide was orally administered at small doses and in short intervals, which not only avoided the occurrence of adverse reactions such as bone marrow depression and gastrointestinal reactions, but also ensured the anti-tumor effect of cyclophosphamide. Meanwhile, it also has the advantages of metronomic chemotherapy such as anti-tumor angiogenesis, immune regulation and influence of stem cell production [17-19]. A foreign study found that the PFS of oral cyclophosphamide in low dosage combined with methotrexate metronomic chemotherapy in the first-line treatment of advanced breast cancer is up to 21 months [20]. Capecitabine and cyclophosphamide have different mechanisms of action, and there is no cross-resistance between them. Combined use of the two drugs can enhance the killing effect on tumor cells, and the toxic and side effects will not superimpose on each other.

The immune function of patients with tumors is suppressed in varying degrees during chemotherapy, so it is difficult to mobilize the immune response of the body. Immunotherapy not only kills tumor cells, but also regulates the immune function of the body. Its adverse reactions are mild, so it is suitable for patients receiving multiple cycles of chemotherapy continuously. CIK has the specific killing activity of T cells and the non-MHC restriction of NK cells, so it is regarded as the first choice for anti-tumor adoptive immunotherapy [21]. Due to the existence of tumor heterogeneity, standard chemotherapy can kill the majority of cancer cells in the body. However, the residual cancer cells are the root cause of recurrence, which are most likely to be multidrug-resistant. Studies have demonstrated that CIK is very sensitive to multidrug-resistant tumor cells, and adjuvant CIK therapy can effectively improve the PFS and the quality of life of patients with lymphoma, hepatocellular carcinoma, gastric cancer and lung cancer [22,23]. In this study, the proportions of $CD3^+$, $CD4^+$ and NK cells and the CD4/CD8 cell ratio in DC-CIK group rose markedly after treatment in contrast with those before treatment, indicating that immunotherapy kills the tumor cells and activates and repairs the body's immune function at the same time, thus enhancing its anti-tumor ability. In terms of the quality of life, the emotional well-being score and total score of patients in DC-CIK group were significantly higher than those in control group (p=0.007, p=0.025), indicating that the combination with DC-CIK cell immunotherapy can significantly improve the quality of life of patients with mTNBC.

In this study, the maintenance therapy of capecitabine and cyclophosphamide metronomic chemotherapy was combined with DC-CIK cell immunotherapy in treating patients with recurrent mTNBC. The results revealed that there were statistically significant differences in the ORR (29.1% *vs.* 16.4%) and the DCR (74.5% *vs.* 63.6%) of patients between DC-CIK group and control group (p=0.111, p=0.216). The results of follow-up manifested that DC-CIK cell immunotherapy combined with capecitabine could improve the PFS of patients, and the mPFS was prolonged by 2.8 months. In terms of the adverse reactions, the patients showed good tolerance. The incidence rates of leukopenia and gastrointestinal reactions in DC-CIK group were evidently lower than those in control group (p=0.045, p=0.039), but no statistically significant differences were observed in the incidence rates of other adverse reactions (p>0.05).

There were some limitations in this study. For example, the sample size was limited, the follow-up time was short, the follow-up content was not comprehensive enough, and the long-term survival of the patients was not further analyzed. In the future, prospective clinical studies with rigorous design, high credibility and large sample sizes are needed to support the conclusions in this study.

Conclusions

The maintenance therapy of capecitabine metronomic chemotherapy combined with DC-CIK cell immunotherapy is effective in the treatment of recurrent mTNBC, with tolerable adverse reactions. It can improve the patients' immune function, improve their quality of life, and prolong their PFS.

Conflict of interests

The authors declare no conflict of interests.

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