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RESEARCH ARTICLE

Prospective study of cyclophosphamide, thiotepa, carboplatin combined with adoptive DC-CIK followed by metronomic cyclophosphamide therapy as salvage treatment for triple negative metastatic breast cancers patients (aged <45)

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Abstract
Background The recent immunotherapy treatment on triple-negative breast cancer (TNBC) leads to the breakthrough assignation. In this study, we have tried the new combinations of specific chemo with DC-CIKs immunotherapy to treat those patients.
Patients and methods Twenty-three metastatic anthracyclines and taxanes pretreated TNBC younger (mean 41.5 years) patients were initially mobilized with cyclophosphamide (3 g/m^2) for the preparation of CD34$^+$ peripheral blood mononuclear cells as the resources for generating DC/CIKs and marrow function supports. All cases were subsequently experienced 2 cycles of chemotherapy with cyclophosphamide 3 g/m^2, thiotepa 150 mg/m^2, and carboplatin AUC = 6, Q4w. The patients then received 3 infusions of DC-CIKs at the chemo intervals and followed by maintenance therapy with oral cyclophosphamide 50 mg daily. The endpoints were progression-free survival and overall survival.
Results The partial response rate was 13.0 %, stable and progressive disease rates were 56.5 and 30.4 %, respectively. The median PFS was 13.5 months (95 % confidence interval (CI) 10.1–16.9 months) and OS was 15.2 months (95 % CI 12.5–18.1 months). The most common serious adverse events were neutropenia (100.0 %) and anemia (69.7 %) but without treatment-related mortality.
Conclusion These data suggested that such combination therapy model be effective and safe for younger metastatic TNBC exposure to previous anthracyclines and taxanes based adjuvant chemotherapy.

Keywords Triple negative breast cancer · Immunotherapy · Thiotepa · Younger

Introduction

There were increasingly demands for releasing treatment strategies for the triple-negative breast cancer (TNBC) featured by lacking of estrogen receptor (ER) and progesterone receptor (PR) expression as well as human epidermal growth factor receptor-2(HER2) amplification [1, 2]. A few of sporadic clinical study has explored the efficacy by the different combination of epirubicin, cisplatin and fluorouracil and followed by paclitaxel with oral low dosage of cyclophosphamide could achieve 56 % PCR [3]. Lehmann et al. has identified 6 TNBC subtypes displaying unique gene expression and ontologies, including two basel-like (BL1 and BL2), one immunomodulatory (IM), one mesenchymal (M), one mesenchymal stem-like (MSL), and one luminal androgen receptor (LAR) subtypes [4]. These tremendous findings elucidated the different subtypes existing in TNBC, which led to the complexity of treatment, thus the relapse and recurrent rate were retained higher and shorten life span [5]. While in the metastatic

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setting, the prolonged progression-free survival (PFS) by palliative chemotherapy was limited and in the most cases the median PFS was usually less than 6 months for the patients with TNBC who had received first-line single agent or combined chemotherapy [6–8]. The recent breakthrough treatment was the landmark by the implementation of PD-1 and PD-L1 immunotherapy [9]. Those data indicated that the immunotherapy has become promising advantage in improving such patients. The identification of TNBC subtype characterized by elevated expression of immune genes suggested that some patients might benefit from immune-based therapies [10]. Therefore chemotherapy combined with immunotherapy may provide an alternative option for the treatment of patients with metastatic TNBC. The present study was registered on Clinical Trials with number NCT01232062, for the treatment of metastatic TNBC with cyclophosphamide, thiotepa, carboplatin and adoptive immunotherapy followed by low-dose (50 mg) of cyclophosphamide maintenance therapy. To our knowledge, this is the first report using effective combination of chemotherapy and immunotherapy followed by low-dose oral cyclophosphamide maintenance therapy in Chinese younger patients with metastatic TNBC.

Patients and methods

Patients

The enrolled patients should meet the following inclusion criteria: all cases were previously treated with anthracyclines and taxanes and in progressive conditions without previous chemotherapy or immunotherapy for any recurrence or metastatic lesion. All women aged 30–45 years (mean 41.5 years) with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0–2, adequate renal and hepatic functions, no active infection and no central nervous system metastasis, with anticipated survival >12 weeks. All enrolled subjects had qualified bone marrow functions. The study protocol was approved by the Institutional Review Board of Beijing Cancer Hospital, and informed consent was obtained from all patients (in Table 1).

Table 1 Characteristics of patients and tumors

Characteristic	Category	N (%) ($N = 23$)
Age (years)	Median	41.5
	Range	30–45
Menopausal status	Pre-	15 (65.2 %)
	Post (chemo-induced)	8 (34.7 %)
Stage at diagnosis	I	4 (17.4 %)
	II	7 (30.4 %)
	III	10 (43.4 %)
	IV	2 (8.7 %)
Neoadjuvant chemotherapy	Yes	8 (34.8 %)
	No	15 (65.2 %)
Surgery	Mastectomy	20 (87.0 %)
	Breast-conserving	3 (13.0 %)
Adjuvant chemotherapy	Yes	20 (87.0 %)
	No	3 (13.0 %)
Adjuvant radiotherapy	Yes	12 (52.2 %)
	No	11 (47.8 %)
DFS (months)	Median	24.3
	Range	3.5–112.7
Site of metastatic disease	Lymph node	11 (47.8 %)
	Liver	6 (26.1 %)
	Bone	10 (43.5 %)
	Lung	8 (34.8 %)
	Brain	2 (8.7 %)

Pathological review

All patients' specimens were reviewed by dependent pathologists. Triple-negative tumors were defined as those negative for ER and PR expression by IHC, and negative for HER2 status. HER2 was scored using a four-tier IHC scale from 0 to 3+. HER2 IHC grades 0, 1+ were defined as a negative result for HER2, and the lack of amplification of HER2 was confirmed by fluorescence in situ hybridization (FISH) if HER2 was rated as grade 2+ by IHC [11, 12].

Treatment protocol

Mobilization of $CD34^+$ PBMCs was performed with cyclophosphamide (3 g/m^2) as initial chemotherapy to cause the myelosuppression. The peripheral white blood cell count was decreased to the average of 2.0×10^9/L (at median duration of post mobilization of 4.5 days). The subcutaneous injection of granulocyte-colony stimulating factor (G-CSF) (5 μg/kg/day) was used to recover the blood cell until the level of mononuclear cells (MNCs) reached 1.5×10^9/L. Apheresis was performed until $\geq 2.0 \times 10^6$ $CD34^+$ cells per kilogram were collected, in preparation both for the generation of DC/CIK and post-chemotherapy support. Patients were treated with the regimen as follows: cyclophosphamide 3 g/m^2 (1 h infusion) plus mesna (100 % of total dose of cyclophosphamide) for 2 consecutive days on days 0 and 1, thiotepa 150 mg/m^2 on day 0, and carboplatin target area under the curve(AUC) = 6 on days 0 and 1. $CD34^+$ progenitor cells

were re-infused on day 3 and G-CSF was administered at 5 μg/kg/day from day 4 until polymorphonuclear (PMN) cells reached above 1.5×10^9/L. Irradiated-platelet transfusion was performed to maintain the platelet count above 20×10^9/L and irradiated leukocyte-free red blood cells were transfused if the hemoglobin level fell below 70 g/L. Cyclophosphamide plus thiotepa and carboplatin chemotherapy was administered for two cycles at 4 weeks intervals. All patients received maintenance therapy with oral cyclophosphamide 50 mg per day after chemotherapy and immunotherapy [13–16].

Evaluation

Response to therapy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [17]. Progression-free survival (PFS) was defined as the time from the first day of cyclophosphamide initial chemotherapy to the date of progressive disease (PD) or cancer-specific death. Patients clearly documented without PD on the date of death were censored for PD on that date. The overall survival (OS) after mobilization chemotherapy was calculated as the time from the first day of mobilization chemotherapy to the date of death from any cause or to the last follow-up. Patients alive at the most recent follow-up were censored for survival on the date of that follow-up. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 [18].

Statistical analysis

All analyses were performed using the statistical software package SPSS 13.0. Descriptive statistics were used to summarize safety and efficacy outcomes. The median follow-up was calculated using the reverse Kaplan–Meier method. OS and PFS analyses were calculated using the Kaplan–Meier product-limit estimator.

Results

Patient characteristics

Twenty-three eligible patients were enrolled in the study. The median patient age was 41.5 years (range 30–45 years), and the median time from initial diagnosis to metastasis was 24.3 months (range 3.5–112.7 months). The median follow-up of the surviving patients at the time of the analysis was 11.2 months (2.1–19.1 months). Six patients had died, giving a death rate of 26.1 %.

Efficacy

Responses to cyclophosphamide plus thiotepa and carboplatin chemotherapy are shown in Table 2. Among the 23 assessable patients, 3 had PR, 7 had PD (30.4 %), and 13 patients had SD. The objective response rate (ORR) was 13.0 %. The disease control rate (DCR) was 69.6 %, including SD (56.5 %). The median PFS was 13.5 months (95 % confidence interval (CI) 10.1–16.9 months) (Fig. 1). The median OS was 15.2 months (95 % CI 12.5–18.1 months) (Fig. 2) for all patients.

Treatment-related adverse events

Myelosuppression was the major toxicity, and nonhematologic toxicity was usually mild (Table 3). The median duration with a neutrophil count less than 0.5×10^9/L was 6 days (range 2–12 days) and the median time with a platelet count less than 20×10^9/L was 4.5 days (range 0–12 days). No treatment-related deaths occurred. No dose modification or treatment delay was necessitated.

Discussion

TNBC is biologically aggressive and associated with a poor prognosis and a significantly shorter survival featured by recurrence and metastasis compared with non-triple negative breast cancer. The molecular substudy of CALGB 9342 demonstrated that patients with TNBC had a shorter median survival with metastatic disease than non-TNBC patients (8.6 versus 12.8 months; $p = 0.009$) [19]. It has been suggested that they seem to respond to chemotherapy better than other types of breast cancer, but prognosis remains very poor, if treated by conventional chemotherapy [20, 21]. There were some trials to deploy the clinical responses through different chemotherapeutic regimens in the settings of the neoadjuvant, adjuvant, metastatic in pursuing of obtaining reliable responses. For the instance, one trial dealt with the single cisplatin sensitivity could result in 10 of 12 pathological complete response (pCR) in TNBC carrying BRCA 1 mutation [22]. Another study has also shown that single cisplatin in TNBC could achieve 21 % pCR among 28 case in the setting of neoadjuvant [23]. Moreover, some investigators have attempted to add the new pathway inhibitors such as PARP, mTOR/EGFR, VEGF, NOTCH, HIF-1 and others, in combination with the chemotherapy. When considering the efficacy and clinical benefit by incorporation PARP inhibitor with gemcitabine and carboplatin, iniparib in phases I and II, results have shown that for those of 123 metastatic TNBC previously treated with up to two lines of chemotherapy, median PFS

Table 2 Efficacy of cyclophosphamide plus thiotepa and carboplatin chemotherapy

	DCR			PD	ORR	DCR
	RR		SD			
	CR	PR				
Response	0/23 (0 %)	3/23 (13.0 %)	13/23 (56.5 %)	7/23 (30.4 %)	3/23 (13.0 %)	16/23 (69.6 %)

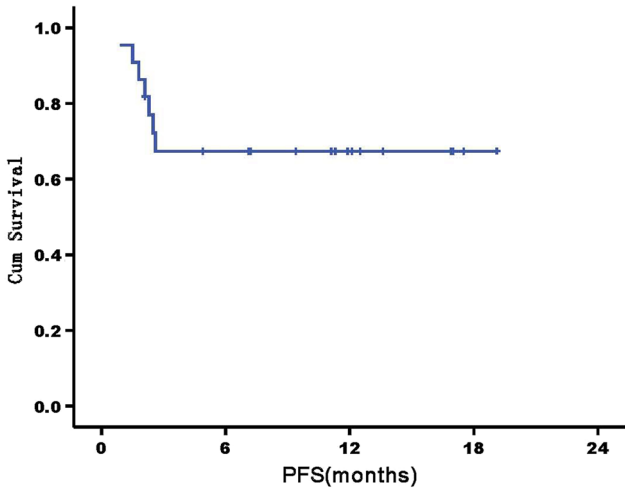

Fig. 1 The progression-free survival among the 23 TNBC patients. The median PFS was generated by 13.5 months

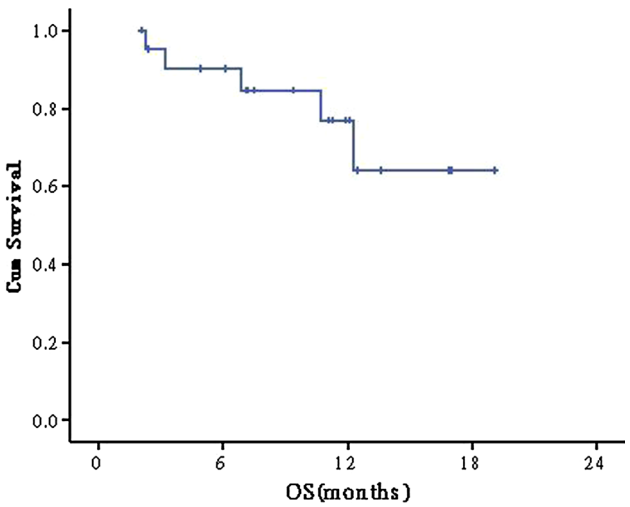

Fig. 2 The overall survival among the 23 TNBC patients. The median OS was generated by 15.2 months

was increased from 3.6 to 5.9 months ($p = 0.01$), and the OS was reached from 7.7 to 12.3 months ($p = 0.01$) [24]. However, bevacizumab combined with paclitaxel could prolong the median PFS of TNBC patients to 10.2 months. In terms of BRCA1 gene status, some investigators have compared the use of olaparib in 18 BRCA1 and 9 BRCA2 deficiency breast cancer patients pretreated with a median of three lines of chemotherapy, there was a dose-dependent response rate of 5.7 months (400 mg dosage) versus 3.8 (100 mg dosage) months in PFS harboring [25].

Until recently the novel immunotherapy regimen anti-PD-L1 (Keytruda) in the treatment of TNBC while expression PD-L1, the total clinical response rate was 18.5 % ($n = 5/27$), in which CR was 3.7 % ($n = 1/27$), PR was 14.8 % ($n = 4/27$), SD was 25.9 % ($n = 7/27$), PD was 44.4 % ($n = 12/27$), the median progressive free duration was 18 weeks [26]. Gibson et al. has reported another similar product MPDL3280A was administrated among 54 TNBC, 21 of 54 were assessed, the subject response rate was 24 % (CR 2, PR3), the PFS could reach more than 24 weeks [9].

Based on those milestone studies in the past years, we have been encouraged to continue our pre-established chemotherapy plus cancer immunotherapy perspectives which the OS could reach 33.1 months among metastatic breast cancer whatever hormone status appearances [27]. For this further study it was surprisingly known that the clinical outcome was even longer median PFS of 13.5 months compared with other chemotherapy-based treatment for the patients with metastatic TNBC. This study suggested that optimized chemotherapy combined with immunotherapy might provide better clinical benefit for metastatic TNBC patients. The previous study from Rodenhuis et al. has updated and re-analyzed results of a prospective randomized trial that compared five courses of FEC (fluorouracil, epirubicin and cyclophosphamide) with four courses of the same regimen followed by a single shot of high-dose chemotherapy (HDC) with cyclophosphamide (6 g/m^2), thiotepa (480 mg/m^2) and carboplatin (1600 mg/m^2) in high-risk breast cancer, showing that HER2-negative tumors benefited from HDC, while HER2-positive tumors did not [28]. However, authors concluded that a subgroup of breast cancer existed 'that is specifically sensitive to high-doses of alkylating agents, mainly characterized by the absence of HER2 amplification'. A retrospective analysis of the WSG AM 01 randomized trial has tried to identify patient subgroups with maximum benefit from HDC. Most of these patients could be attributed by *K*-means clustering to basal-like type and an undefined proliferative group characterized mainly by the

Table 3 Treatment-related adverse events

Grade	0 ($N = 23$)	I ($N = 23$)	II ($N = 23$)	III ($N = 23$)	IV ($N = 23$)	III + IV (%)
ANC count	0	0	0	1	22	100
Hemoglobin	0	1	6	15	1	69.7
Platelets	0	0	0	1	22	100
Nausea and vomiting	0	10	11	2	0	8.7
Diarrhea	21	1	1	0	0	0
Mucositis	17	5	1	0	0	0
Liver dysfunction	11	9	3	0	0	0
Cardiac	22	1	0	0	0	0
Renal	23	0	0	0	0	0
Other	22	1	0	0	0	0

absence of specifying markers [29]. Although retrospective analyses, both studies showed the efficacy of HDC chemotherapy based on cyclophosphamide and thiotepa in TNBC. Recent clinical long-term survival data showed that HDC, including cyclophosphamide, thiotepa, and carboplatin combined with peripheral stem cell rescue, may prolong PFS and OS in patients with high-risk, locally advanced/inflammatory and oligo-metastatic ($\leq$3 sites) breast cancer [30]. The median follow-up of 84 months (6–136 months) in patients with locally advanced cancer showed 5-year PFS and OS rates of 53 % (95 % CI 41–63 %) and 71 % (95 % CI 60–80 %), respectively. In patients with metastatic cancer and a median follow-up of 40 months (24–62 months), the 3-year PFS and OS were 49 % (95 % CI 19–73 %) and 73 % (95 % CI 38–91 %), respectively [31].

Our latest clinical data has demonstrated that selections of appropriate regimen of high-dose chemotherapy combined with adoptive cellular therapy with dendritic and cytokine-induced killer cells could improve both progression-free and overall survival in patients with metastatic breast cancer. The predominant subgroup benefited from this treatment was from premenopausal TNBC [27]. Our clinical data also showed that low-dose oral cyclophosphamide could achieve the comparable clinical response as combination chemotherapy under the conditions of progression and/or chemotherapy refractory and non-tolerance [14]. More recently, key roles of cellular immunity and tumor infiltration cytokines in tumor recurrence regulation had been revealed. Accumulating evidence suggested that, among the ER negative breast cancer, basal TNBC may be most regulated by intratumoral T cells and thus most responsive to immunotherapies [10, 32]. Therefore, we further explore such combination of specific chemotherapy regimens plus immunotherapy and oral cyclophosphamide maintenance in the treatment of those young TNBC patients previously treated with taxanes and anthracyclines. Our results had proven that thiotepa could effectively eliminate chemo-resistant cancer stem cells [33, 34]. On the other hand, low-dose (50 mg) oral cyclophosphamide is an attractive option for maintenance therapy because of its easy administration and low toxicity. The underlying mechanisms probably involve anti-angiogenesis, rather than the classical anti-proliferative effect like standard maximally tolerated dose-based regimens [35]. Although the feasibility of this therapeutic model for the metastatic breast cancer patients younger than 45 years, who had experienced anthracyclines and taxanes adjuvant therapy, warrants further study probably together with simultaneous genetic profiling, our data presented here suggests that it may serve as a novel strategy to effectively overcome the drug resistance and improve clinical response and benefit. Furthermore, the positive data we got from this single-arm study with limited enrolled number encourages us to further set up a randomized controlled clinical trial. We may conclude that it was the first trial to provide the useful strategy for such difficult condition of TNBC breast cancer patients and will result in the future randomized trials within defined biological chemo-sensitive subtypes.

Conclusion

These data suggested that cyclophosphamide, thiotepa and carboplatin as first-line regimen combined with DC-CIK immunotherapy and followed by oral low dosage cyclophosphamide as maintenance therapy was effective and safe for younger metastatic TNBC exposure to previously anthracyclines and taxanes based adjuvant chemotherapy.

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Compliance with ethical standards

Conflict of interest There is no any interest conflict of all authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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