Am J Transl Res 2024;16(5):1945-1952
www.ajtr.org /ISSN:1943-8141/AJTR0156538

Original Article

Clinical effectiveness and safety of gemcitabine plus capecitabine in the treatment of advanced triple-negative breast cancer

Ya Wang, Yulan Zhu

Nanjing Medical University, Nanjing 213003, Jiangsu, China

Received March 12, 2024; Accepted May 8, 2024; Epub May 15, 2024; Published May 30, 2024

Abstract: Purpose: To determine the clinical effectiveness and safety of Gemcitabine (GEM) plus Capecitabine (CAP) for advanced triple-negative breast cancer (aTNBC). Methods: Eighty aTNBC patients treated in Affiliated Hospital of Nanjing Medical University between June 2020 and June 2022 were retrospectively included and divided into an observation group (Obs; 42 cases treated with GEM + CAP) and a control group (Con; 38 cases treated with docetaxel + CAP) according to different chemotherapy regimens. The clinical effectiveness and the serum levels of tumor markers and inflammatory factors pre- and post-treatment were detected for comparative analyses. In addition, the two groups were compared in terms of side effects, 1-year survival, and quality of life after 1 month of treatment. Cox regression was performed to identify the independent risk factors affecting patient prognosis. Results: Higher clinical effectiveness was observed in the Obs group compared to the Con ($P < 0.05$). The pre-treatment TPS, CA153, TNF-α, and IL-6 levels were comparable between groups (all $P > 0.05$); however, better post-treatment TPS, CA153, and inflammatory factors were observed in the Obs group compared to the Con (all $P < 0.05$). The Obs group also showed markedly lower drug-induced toxicities than the Con group, with higher 1-year survival and better quality-of-life after 1 month of treatment (all $P < 0.05$). According to multivariate analysis, clinical stage and lymph node metastasis were independent risk factors for poor prognosis, and GEM + CAP chemotherapy was a protective prognostic factor. Conclusions: GEM + CAP is effective in treating aTNBC and provides clinical benefit for patients, with fewer side effects and good patient tolerance.

Keywords: Gemcitabine, capecitabine, triple-negative breast cancer, effectiveness, safety

Introduction

Breast cancer (BC) is a prevalent malignancy and the most common non-skin tumor among women. Among its various subtypes, triple-negative breast cancer (TNBC) is noteworthy due to its high prevalence. Recurrence or metastasis of TNBC is usually correlated with a poor prognosis, significantly affecting patients' physical and mental well-being and potentially leading to mortality in severe cases [1, 2].

Currently, various drugs are available for treating TNBC, with anthracyclines, platinum-based agents, and taxanes being the first-line chemotherapy regimens. Platinum-based dual-drug regimens, with documented superiority over non-platinum-based combinations, are particularly recommended as the initial therapy for advanced TNBC (aTNBC) patients [3, 4]. Nevertheless, the lack of standardized clinical criteria for selecting induction chemotherapy regimens for TNBC and the development of robust drug resistance in some patients pose challenges, leading to a high risk of disease progression and compromising treatment outcome [5]. Consequently, current research endeavors are concentrated on overcoming these challenges and identifying more effective chemotherapy agents to improve the prognosis of aTNBC patients.

Gemcitabine (GEM) and capecitabine (CAP) represent novel chemotherapy approaches for aTNBC. However, there is a paucity of clinical research in this area, and the therapeutic efficacy of this dual-drug chemotherapy remains controversial [6]. GEM, a nucleotide analogue, exerts its anti-tumor effects by inhibiting DNA

https://doi.org/10.62347/QOWN3646

synthesis and is frequently used as second-line treatment for advanced BC due to its high therapeutic efficacy [7]. CAP, on the other hand, is an oral anticancer agent with selective activity against tumor cells [8]. Despite their own merits, there is limited discussion on the role of these two drugs in aTNBC patients. Therefore, this study aims to investigate the clinical efficacy and safety of GEM + CAP in the treatment of aTNBC, aiming to provide additional clinical data to guide treatment selection for aTNBC patients.

Materials and methods

Clinical data

This study retrospectively included 80 female patients with aTNBC who were treated in the Affiliated Hospital of Nanjing Medical University between June 2020 and June 2022. They were grouped based on different chemotherapy schemes, with 42 cases treated with GEM + CAP being assigned to the observation group (Obs) and 38 cases receiving docetaxel (DTX) + CAP to the control group (Con). Inclusion criteria: (1) Those pathologically diagnosed as aTNBC; (2) Completely preserved case data; (3) An expected survival > 1 month. Exclusion criteria: (1) Estimated survival < 1 month; (2) Concomitant blood system diseases; (3) Contraindications to chemotherapy; (4) Severe liver and kidney dysfunction; (5) Expressive language disorders or mental illness. Ethics committee approval was obtained from Affiliated Hospital of Nanjing Medical University and the tenets of the Declaration of Helsinki were followed throughout the research.

Chemotherapy regimen

GEM + CAP scheme in Obs group: GEM was injected intravenously on the 1st and 8th day of chemotherapy (Beijing Xiehe Pharmaceutical Co., Ltd., National Drug Approval Number H20103522), with a dosage of 100 mg/m^2 within 30 minutes; and 1 g of CAP (Jiangsu Hengrui Pharmaceutical Co., Ltd., National Drug Approval Number H20133365) was given orally from day 1 to day 14, twice a day. With 21 days as a chemotherapy course, patients who responded to the above treatment received three courses.

DTX + CAP scheme in Pa Con group: 75 mg/(m^2·d) of DTX (Sanofi, Batch Number: H20030513) was administered intravenously once on the first day; and on days 1-14, 1 g of CAP was given orally twice a day. The patients received three 21-day courses of treatment. Drug withdrawal was generally not considered unless the presence of progressive disease (PD) or intolerable drug-induced toxicities.

Endpoints

(1) Therapeutic effectiveness was evaluated and compared. The Response Evaluation Criteria in Solid Tumors formulated by the World Health Organization (WHO) [9] were adopted for response assessment in this study. Based on the patient's physical examination and post-treatment imaging data, the therapeutic effect was judged as complete response (CR; tumor disappearance), partial response (PR; tumor reduction ≥ 50%), stable disease (SD; tumor growth < 25% or shrinkage < 50% for more than 4 weeks), or progressive disease (PD; tumor enlargement > 25%). Clinical overall response rate (RR) = CR + PR. (2) Electrochemiluminescence immunoassay was performed to measure serum tumor markers, including tissue polypeptide-specific antigen (TPS) and carbohydrate antigen 153 (CA153), before and after treatment. (3) Enzyme-linked immunosorbent assays (ELISAs) were carried out to quantify serum levels of inflammation-related factors tumor necrosis factor (TNF-α) and interleukin-6 (IL-6) (Abcam, ab181421, ab178013) before and 4 weeks after treatment in the two groups. (4) The drug-induced toxicities during treatment were recorded and compared, including liver and kidney dysfunction, leukopenia, gastrointestinal reactions, and thrombocytopenia. (5) The 1-year survival rate was evaluated and compared. (6) Patients' quality of life was assessed 1 month after treatment with the Quality-of-Life Questionnaire Core 30 (QLQ-C30) [10] from physical, role, emotional, cognitive, and social functions. The score is proportional to the quality of life. (7) Cox regression was carried out to analyze independent risk factors affecting patient 1-year survival.

Statistical methods

SPSS18.0 (Beijing NT times Technology Co., Ltd.) and GraphPad Prism 6 were employed for

Table 1. General data [n (%)]

Factors	Observation group (n=42)	Control group (n=38)	χ^2	P
Age (years)			0.001	0.982
≤ 62	20 (47.62)	18 (47.37)		
> 62	22 (52.38)	20 (52.63)		
BMI (kg/m^2)			0.802	0.371
≤ 23	23 (54.76)	17 (44.74)		
> 23	19 (45.24)	21 (55.26)		
Smoking history			0.051	0.822
Yes	12 (28.57)	10 (26.32)		
No	30 (71.43)	28 (73.68)		
Clinical staging			0.028	0.867
III	28 (66.67)	26 (68.42)		
IV	14 (33.33)	12 (31.58)		
Lesion type			0.055	0.814
Multiple lesions	21 (50.00)	18 (47.37)		
Single lesion	21 (50.00)	20 (52.63)		
Tumor diameter			0.045	0.832
≤ 5 cm	20 (47.62)	19 (50.00)		
> 5 cm	22 (52.38)	19 (50.00)		

Table 2. Comparison of curative effects [n (%)]

Curative effect	Observation group (n=42)	Control group (n=38)	χ^2	P
Complete response	0	0	-	-
Partial response	30 (71.43)	20 (52.63)	-	-
Stable disease	8 (19.05)	4 (10.53)	-	-
Progressive disease	4 (9.52)	14 (36.84)	-	-
Overall response rate	38 (90.48)	24 (63.16)	8.538	0.004

the analysis and image rendering of the experimental data, respectively. Chi-square tests and independent samples t tests were used for the comparison of categorical and continuous variables between two groups, respectively. For intra-group comparison before and after treatment, paired t-test was applied. Patient survival was analyzed by the log-rank test and visualized by the Kaplan-Meier plot. A significant difference was denoted by $P < 0.05$.

Results

Comparison of general data

The two groups were comparable, with no marked differences identified in sex, age, smoking history, orother baseline data (all $P > 0.05$; **Table 1**).

Comparison of therapeutic effectiveness

The number of patients with CR, PD, SD, and PD was 0, 30, 8, and 4 in the Obs group and 0, 20, 4, and 14 in the Con, respectively. The overall RR was calculated to be 90.48% in the Obs group, which was significantly higher than 63.16% in the Con group ($P < 0.05$; **Table 2**).

Comparison of pre- and post-treatment TPS and CA153

TPS and CA153 did not differ statistically between groups at baseline (all $P > 0.05$). An obvious reduction was observed in TPS and CA153 levels in both groups after treatment, with significantly lower levels in the Obs group compared to the Con group (all $P < 0.05$; **Figure 1**).

Comparison of pre- and post-treatment inflammatory factors

The two groups were comparable in pre-treatment serum TNF-α and IL-6 levels ($P > 0.05$). Serum TNF-α and IL-6 decreased significantly in both groups after treatment ($P < 0.05$), with significantly lower levels in the Obs group compared to the Con group (all $P < 0.05$; **Figure 2**).

Comparison of drug-induced toxicities during treatment

The numbers of patients in the observation group who developed abnormal liver and kidney function, leukopenia, gastrointestinal reactions, and thrombocytopenia were 2, 2, 1, and 1 respectively, with a total incidence rate of 14.29%. The numbers of patients in the control group who experienced abnormal liver and kidney function, leukopenia, gastrointestinal reactions, and thrombocytopenia were 3, 5, 4, and 3 respectively, and the incidence of toxic and side effects was 39.47%. The total incidence

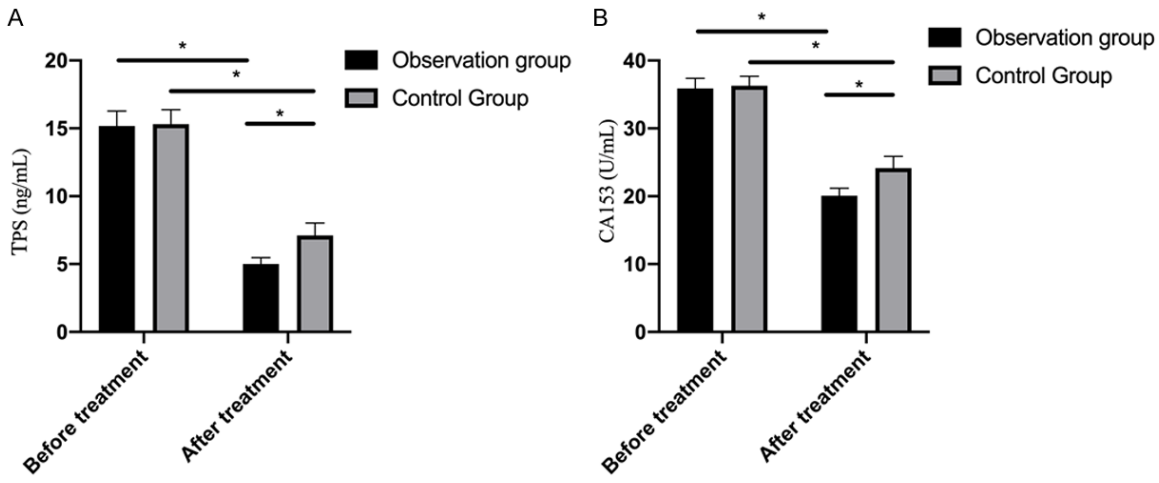

Figure 1. Comparison of pre- and post-treatment TPS and CA153; A: Comparison of tissue polypeptide-specific antigen (TPS); B: Comparison of carbohydrate antigen 153 (CA153). *P < 0.05.

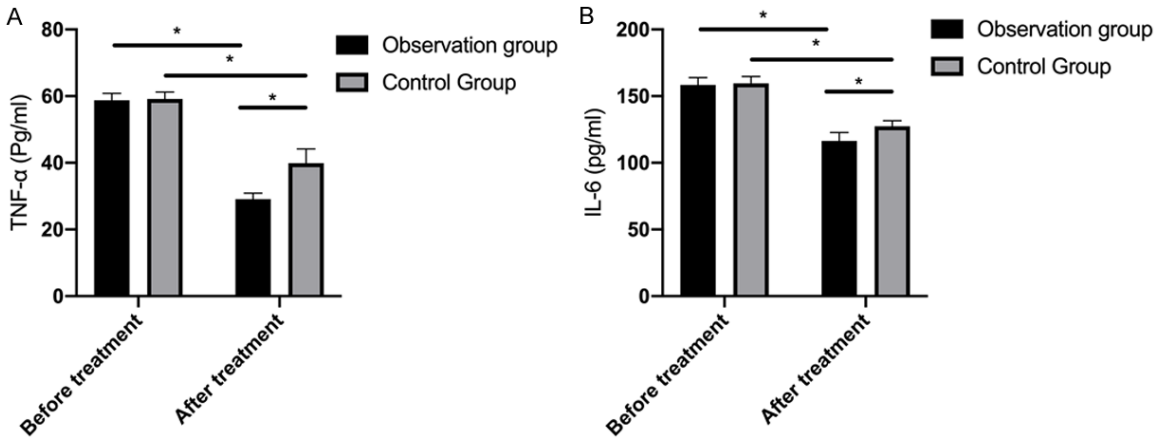

Figure 2. Comparison of pre- and post-treatment inflammatory factors; A: Comparison of tumor necrosis factor (TNF-α); B: Comparison of interleukin-6 (IL-6). *P < 0.05.

rate in the Obs group was significantly lower than that of the Con group (P < 0.05; **Table 3**).

Comparison of quality of life after 1 month of treatment

Compared to the Con group, the scores of physical, role, emotional, cognitive, and social dimensions of quality of life in the Obs group showed significantly more improvement after treatment (all P < 0.05; **Table 4**).

Comparison of 1-year survival rate

With no patients lost to follow-up, 13 cases in the Obs group died one year after surgery, with a one-year survival rate of 69.05%; while 20 patients in the Con died, with a one-year survival rate of 47.37%. The one-year survival rate was statistically higher in the Obs group versus the Con group (P < 0.05; **Figure 3**).

Analysis of risk factors affecting patient prognosis

To analyze risk factors affecting patient 1-year survival, we performed analysis using univariable and multivariable Cox proportional hazards models. According to multivariate analysis, clinical stage and lymph node metastasis were independent risk factors for poor prognosis, and GEM + CAP chemotherapy was a prognostic protective factor (**Tables 5**, **6**, all P < 0.05).

Table 3. Comparison of incidence of drug-induced toxicities [n (%)]

Drug-induced toxicity	Observation group (n=42)	Control group (n=38)	χ^2	P
Liver and kidney dysfunction	2 (4.76)	3 (7.89)	-	-
Leukopenia	2 (4.76)	5 (13.16)	-	-
Gastrointestinal reactions	1 (2.38)	4 (10.53)	-	-
Thrombocytopenia	1 (2.38)	3 (7.89)	-	-
Total incidence	6 (14.29)	15 (39.47)	6.538	0.012

Table 4. Comparison of quality of life

Factor	Observation group (n=42)	Control group (n=38)	t	P
Physical function	71.16±1.95	61.41±4.26	13.37	< 0.001
Role function	72.17±2.09	62.03±4.3	13.61	< 0.001
Emotional function	74.21±1.95	62.69±4.32	15.62	< 0.001
Cognitive function	71.35±1.88	62.21±3.78	13.89	< 0.001
Social function	72.98±2.02	58.49±5.44	16.09	< 0.001

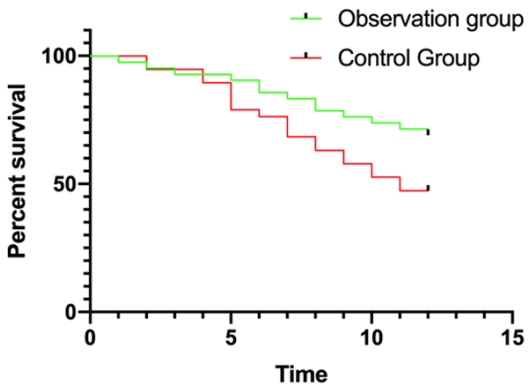

Figure 3. Comparison of 1-year survival rate.

Discussion

Breast cancer (BC), a prevalent malignancy among women, has been rising in China in recent years [11]. Despite advancements in BC treatment, approximately 40% of patients experience metastasis or recurrence within 3-5 years postoperatively, with some diagnosed with distant metastasis at presentation [12]. Chemotherapy remains a common approach for advanced BC, with platinum-containing combination regimens recommended as the first-line therapy [13]. However, due to the aggressive nature, poor differentiation, and development of platinum resistance in aTNBC patients, there is a lack of standardized treatment regimens. Consequently, the pursuit of effective chemotherapy strategies holds significant clinical importance.

This study investigated the effectiveness and safety of GEM + CAP in aTNBC patients. Initially, we observed higher clinical effectiveness in the Obs group compared to the Con group. GEM, an antimetabolite antineoplastic agent, offers broad antitumor activity and minimal adverse reactions, making it a first-line antineoplastic drug [14]. Numerous clinical studies have demonstrated the high effectiveness of GEM in treating advanced BC. It acts on the DNA synthesis and disrupts nuclear replication, to exert a therapeutic effect. This efficacy extends to advanced metastatic BC patients, even those who develop resistance to taxanes and anthracyclines [15]. In recent years, there have been many studies on the combination of GEM and cisplatin. As mentioned earlier, GEM + cisplatin was employed in the treatment of nasopharyngeal carcinoma, achieving an overall effective rate of 42.7% and a 1-year survival rate of 67.0% [16]. Additionally, CAP, as previously discussed, was an oral anticancer medication known for its selective activity against tumor cells [17]. GEM and CAP, with different anti-tumor mechanisms and targets, exhibit no overlap of adverse drug reactions. Their combined use can give full play to their different anti-tumor mechanisms, thus improving treatment efficiency, consistent with our observations.

CA153 is a soluble fragment of mucin-1 (MUC-1), which can be used as an index for postoperative condition monitoring, curative response assessment, and prognosis evaluation in BC patients [18]. TPS, a carcinoembryonic antigen, can reflect the proliferative activity of malignancies [19]. In this study, the Obs group showed significantly reduced post-treatment serum levels of CA153 and TPS compared to the Con group, suggesting that GEM + CAP therapy can effectively lower serum tumor marker levels. The superior efficacy of CAP + GEM over CAP + DTX in TNBC treatment can be attributed pri-

Table 5. Univariate analysis of factors affecting the prognosis of patients

Factor	Univariate HR (95% CI) 95% CI		P
Age	0.48	0.33-0.81	0.322
≤ 62 (n=38)			
> 62 (n=42)			
Body mass index	0.87	0.51-1.47	0.851
≤ 23 kg/m^2 (n=40)			
> 23 kg/m^2 (n=40)			
Smoking history	0.81	0.61-1.31	0.409
Yes (n=22)			
No (n=58)			
Lymph node metastasis	2.54	1.16-5.19	0.013
Yes (n=44)			
No (n=36)			
Clinical stage	2.18	1.04-4.91	0.024
III (n=54)			
IV (n=26)			
Treatment programs	0.51	0.41-0.97	0.013
Gemcitabine combined with capecitabine treatment (n=42)			
Docetaxel combined with capecitabine (n=38)			

Table 6. Multivariate analysis of factors affecting prognosis

Factor	β	S.E.	Wald	HR (95% CI)	P
Lymph node metastasis	1.021	0.156	24.669	2.65 (1.15-9.05)	0.003
Clinical stage	0.827	0.423	6.014	2.41 (1.24-8.77)	0.011
Treatment programs	0.113	0.270	10.169	0.49 (0.022-0.95)	0.018

marily to the potent antitumor activity and affinity of GEM, a pyrimidine antitumor drug. GEM intervenes in the DNA synthesis phase, inhibiting the transition from G1 to S phase and inducing cancer cell death [20, 21]. CAP, with high selectivity for tumor tissues, can interfere with protein synthesis and kill tumors [22]. Previous studies have shown that based on the significant efficacy of GEM, its combination with other chemotherapy drugs may be an alternative or even the first-line chemotherapy for patients with metastatic TNBC [23]. In addition, a more significant reduction in inflammation-related factors and a higher one-year survival rate were found in the Obs group versus the Con group, suggesting better efficacy of GEM + CAP than CAP + DTX for aTNBC. For tumor patients, chemotherapy toxicity must be considered, as well as efficacy [24]. In this study, we identified a lower incidence of drug-induced toxicity in the Obs group versus the Con group, suggesting that GEM + CAP contributes to no added drug-induced toxicities and is safe for the treatment of aTNBC. Furthermore, the quality-of-life investigation revealed higher quality of life scores in the Obs group after 1 month of treatment compared to control patients, which we hypothesize, is attributed to the better curative effect in the Obs group and the fewer toxicities.

Taken together, GEM plus CAP is effective in the treatment of aTNBC, which is well tolerated by patients with minor side effects and multiple benefits, warranting clinical popularization. However, this study has certain shortcomings. First, the overall survival data is relatively immature due to the limited follow-up time (1 year), so longer follow-up is needed for validation. Second, given the small sample size, it is necessary to further expand the sample size in the future to solidify the results of this study.

Disclosure of conflict of interest

None.

Address correspondence to: Yulan Zhu, Nanjing Medical University, Nanjing 213003, Jiangsu, China. Tel: +86-025-86869077; E-mail: zhuyulan2023-123@163.com

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