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Research Article
Efficacy and Prognosis Analysis of PD-1 Inhibitor Combined with GP Regimen in the Treatment of Patients with Advanced Triple-Negative Breast Cancer

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Abstract

Background and Objective: Advanced Triple-Negative Breast Cancer (TNBC) exhibits suboptimal sensitivity to endocrine therapies, coupled with availability of limited targeted agents, posing considerable challenges to clinical management. To explore the efficacy and prognosis of Programmed Cell Death Protein-1 (PD-1) inhibitor combined with the GP regimen in the treatment of patients with advanced TNBC. **Materials and Methods:** A retrospective analysis was conducted on the clinical data of 87 advanced TNBC patients who underwent treatment in hospital from September 2020 to August 2022. The patients were divided into two groups based on different treatment regimens, including a control group (n = 45, treated with the GP regimen) and a study group (n = 42, received combination therapy of camrelizumab and the GP regimen). The clinical efficacy, tumor markers (CEA, CA125 and CA15-3), immune function (levels of $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$), angiogenic factors (MMP-9, VEGF and TGF-β1), quality of life (WHOQOL-BREF scale scores), adverse reactions and survival outcomes (PFS, OS) were compared between the two groups. **Results:** The study group exhibited significantly higher overall efficacy compared to the control group ($p<0.05$). After treatment, the levels of CEA, CA125 and CA15-3 markedly decreased in both groups, with the study group demonstrating even lower levels ($p<0.05$). After treatment, $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ levels significantly increased in both groups, while $CD8^+$ levels notably decreased, with the study group showing more pronounced improvements ($p<0.05$). After treatment, the levels of MMP-9, VEGF and TGF-β1 significantly decreased in both groups, with the study group exhibiting even lower levels ($p<0.05$). After treatment, scores on various dimensions of the WHOQOL-BREF scale notably increased in both groups, with the study group demonstrating higher scores ($p<0.05$). The incidence of adverse reactions did not exhibit significant differences between the two groups ($p>0.05$). The study group displayed superior PFS and OS compared to the control group ($p<0.05$). **Conclusion:** The combination of PD-1 inhibitor and GP regimen demonstrated precise therapeutic efficacy in the treatment of advanced TNBC, which facilitated the restoration of patients' immune function, reduced tumor marker levels, suppressed tumor angiogenesis, promoted enhancement in quality of life, improved short-term prognosis and exhibited favorable safety profile.

Key words: Triple-negative breast cancer, PD-1 inhibitor, GP regimen, tumor marker, prognosis

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Triple-Negative Breast Cancer (TNBC) is a common type of infiltrating ductal carcinoma in clinical practice, characterized by negative pathological findings for the hormone receptors progesterone receptor (PR), estrogen receptor (ER) and Human Epidermal Growth Factor Receptor 2 (Her-2)[1]. According to statistics, TNBC accounts for about 15% of all breast cancers, which not only possesses invasiveness and metastasis, but also has a high risk of recurrence, leading to generally unfavorable prognoses[2]. Although TNBC exhibits high sensitivity to chemotherapy, many patients are diagnosed at an advanced stage, rendering them resistant to taxanes or anthracyclines and even with the implementation of the GP regimen, the therapeutic efficacy and prognosis for some patients remain unsatisfactory[3]. Concurrently, advanced TNBC exhibits suboptimal sensitivity to endocrine therapies, coupled with a limited array of available targeted agents, thus posing considerable challenges to clinical management[4].

In recent years, with the continuous advancement of immunotherapy techniques, agents such as camrelizumab, representing Programmed Cell Death Protein-1 (PD-1) inhibitors, have progressively been applied in the clinical treatment of a variety of malignant tumors, yielding notable efficacy[5]. This class of medications can effectively inhibit the binding of PD-1 and PD-L1, preventing the occurrence of immune evasion phenomena in tumor cells, thereby promoting the cytotoxic effect of T cells on tumor cells and exerting an anti-tumor effect, demonstrating promising prospects for application[6,7]. However, currently, there is limited clinical report regarding the treatment of advanced TNBC using PD-1 inhibitors in combination with GP regimen. In this study, a combination of PD-1 inhibitor and the GP regimen was applied in the treatment of advanced TNBC to investigate its impact on patients' efficacy and prognosis, with the aim of providing insights for the formulation of therapeutic strategies for this condition.

MATERIALS AND METHODS

Clinical data: The clinical data of 87 advanced TNBC patients who underwent treatment in Affiliated Hospital of Jiangnan University from September 2020 to August 2022 were retrospectively analyzed. Patients aged 36-67 years, with a mean age of (47.82±9.10) years. Their Body Mass Index (BMI) ranged 19-30 kg/m^2, with a mean BMI of (22.85±3.02) kg/m^2.

Pathological classification: There were 60 cases of invasive ductal carcinoma, 23 cases of invasive lobular carcinoma and 4 cases of medullary carcinoma. The TNM staging revealed 50 cases in stage III and 37 cases in stage IV. The patients were divided into a control group (n = 45) and a study group (n = 42) based on different treatment regimens.

Eligibility criteria

Inclusion criteria: Patients who conformed to the diagnostic criteria of TNBC[8] and were histologically confirmed as advanced TNBC through pathological biopsy; presence of $\geq$1 tumor target lesion; expected survival time of $\geq$3 months; patients with the history of taxane or anthracycline chemotherapy, with the occurrence of metastasis or recurrence; patients with normal liver and kidney function; patients with normal results on blood routine examination; patients with no history of radiotherapy or chemotherapy within the past month, patients with complete clinical data.

Exclusion criteria: Concurrent other types of malignant tumors; presence of mental or cognitive disorders, lack of adequate understanding or language communication ability; allergic reactions to relevant drugs; inability to tolerate chemotherapy; concurrent infectious diseases and concurrent autoimmune diseases.

Therapeutic method: The control group was treated with GP regimen. On day 1 and day 8, 1.0 g/m^2 of gemcitabine injection (Suzhou Erye Pharmaceutical Co. Ltd., No. H20193069) was administered intravenously at a constant rate after dilution with 100 mL of saline solution, with an infusion time controlled within 30 min, with 3 weeks as one cycle and four consecutive cycles of intravenous infusion; 1000 mL of saline solution was used to hydrate 75 mg/m^2 of cisplatin injection (Guangdong Lingnan Pharmaceutical Co. Ltd., No. H20183341), which was then divided into three daily infusions over 3 days, with 3 weeks as one cycle and four consecutive cycles of intravenous infusion. The study group was additionally treated with camrelizumab based on GP regimen. Each administration consisted of an intravenous infusion of 0.2 g of camrelizumab for injection (Suzhou Suncadia Biopharmaceuticals Co. Ltd., No. S20190027), administered once every 3 weeks, with 3 weeks as one cycle and four consecutive cycles of intravenous infusion.

Observation indicators

Clinical efficacy: After treatment, efficacy assessment was conducted according to the "Response Evaluation Criteria in Solid Tumors"[9]. Complete response (CR) is defined as the complete disappearance of target lesions with all pathological

lymph nodes <1 cm in diameter. Partial response (PR) is defined as a decrease of ≥70% in the maximum diameter of target lesions. Progressive disease (PD) is defined as an increase of ≥20% in the maximum diameter of target lesions or the appearance of new lesions. Stable disease (SD) is defined as being between PR and PD. The overall clinical efficacy is the sum of the CR rate and PR rate.

Tumor markers: About 4 mL of fasting venous blood samples were collected in the early morning from both groups before treatment and at the end of the treatment, respectively. The samples were centrifuged at a speed of 3000 r/min with a radius of 6 cm for 10 min using a high-speed centrifuge to separate the serum. The levels of Carcinoembryonic Antigen (CEA), Cancer Antigen 125 (CA 125) and Cancer Antigen 153 (CA15-3) were measured using the ELISA method. The reagent kits were purchased from Uping Biotechnology Co. Ltd.

Immune function: Before treatment and at the end of treatment, 3 mL of fasting venous blood samples were collected in the early morning from both groups. After centrifugation to obtain serum, automated flow cytometry was utilized to assess the serum levels of $CD3^+$, $CD4^+$ and $CD8^+$ in both groups, followed by calculation of the $CD4^+/CD8^+$ ratio.

Angiogenic factors: The 3 mL of fasting venous blood samples were collected in the early morning from both groups before treatment and at the end of the treatment, respectively. The samples were centrifuged at a speed of 3000 r/min with a radius of 6 cm for 10 min using a high-speed centrifuge to separate the serum. The levels of Matrix Metalloproteinase-9 (MMP-9), Vascular Endothelial Growth Factor (VEGF) and Transforming Growth Factor β1 (TGF-β1) were measured using the ELISA method. The reagent kits were purchased from Uping Biotechnology Co. Ltd.

Quality of life: Before and after treatment, the World Health Organization Quality of Life Scale (WHOQOL-BREF)[10] was utilized to evaluate the quality of life in both groups, including four dimensions: Physical health, psychological health, social relationships and environmental health, with higher scores indicating better quality of life.

Adverse reactions: The adverse reactions occurring during the treatment period including nausea and vomiting, anemia, proteinuria and decreased white blood cell count were recorded in both groups.

Survival status: After the completion of treatment, a 12-month follow-up was conducted for both groups to compare progression-free survival (PFS) and overall survival (OS) between the two groups.

Statistical analysis: The SPSS version 23.0 software was used for data processing. The Shapiro-Wilk test was utilized to assess the normality of the data distribution. Measurement data conforming to normal distribution were represented as Mean±Standard Deviation ($\bar{\chi}\pm S$) and analyzed using the t-test. Counting data were expressed as percentage (%) and subjected to the χ^2 test. A significance level of $p<0.05$ was considered indicative of statistical significance.

Ethical consideration: This research was reported to the Ethics Committee of Affiliated Hospital of Jiangnan University and conducted with the approval. All procedures in this research were conducted in accordance with the Helsinki Declaration. Due to the retrospective nature of the research, informed consent was waived by the Ethics Committee of Affiliated Hospital of Jiangnan University.

RESULTS

Clinical data: The clinical data from two groups (including age, BMI, pathological classification and TNM staging) did not exhibit significant differences ($p>0.05$). The data from both groups were comparable, as shown in Table 1.

Clinical efficacy: The clinical overall efficacy of the study group was 57.14%, higher than that of the control group at 33.33%, exhibiting significant difference ($p<0.05$). This indicates superior therapeutic effectiveness in the study group compared to the control group (Table 2).

Tumor markers: There was no significant difference in the levels of tumor markers (CEA, CA125 and CA15-3) between the two groups before treatment ($p>0.05$). After treatment, the levels of CEA, CA 125 and CA15-3 markedly decreased in both groups, with the study group demonstrating even lower levels ($p<0.05$) (Fig. 1(a-c)).

Immune function: The immune function indicators ($CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$) of the two groups showed no significant difference ($p>0.05$) before treatment. After treatment, $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ levels significantly increased in both groups, with the study group showing even higher levels, while $CD8^+$ levels notably decreased, with the study group demonstrating even lower levels, showing significant difference ($p<0.05$) (Fig. 2(a-d)).

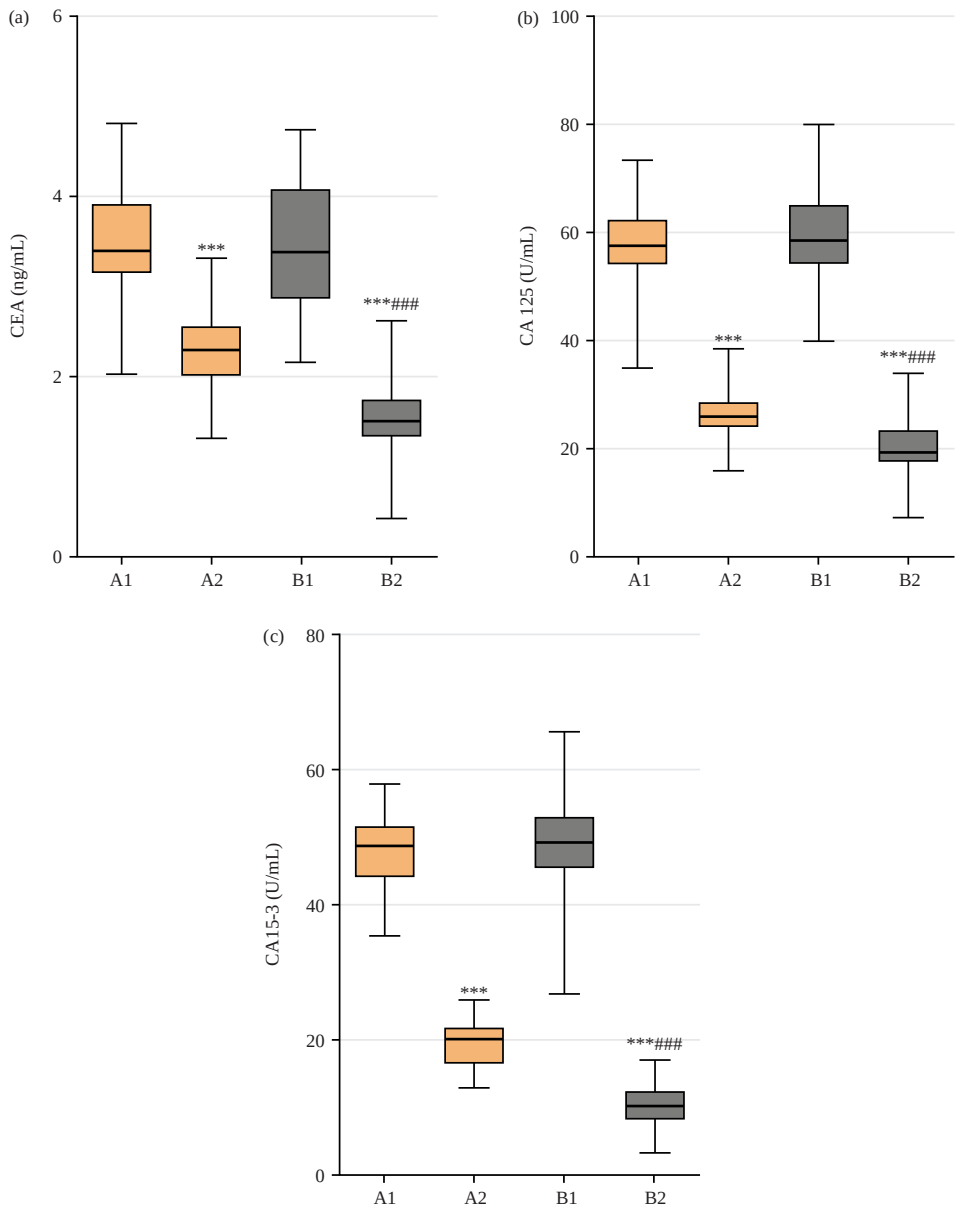

Fig. 1(a-c): Comparison of tumor marker levels between the two groups, (a) Levels of CEA, (b) CA 125 and (c) CA15-3 markedly decreased in both groups after treatment, with the study group demonstrating even lower levels
Compared with before treatment, ***p<0.001; Compared with the control group, ###p<0.001, A1/A2: Control group and B1/B2: Study group

Table 1: Comparison of clinical data between the two groups n/($\bar{\chi}\pm$S)

Group	Number of cases	Age (years)	BMI (kg/m^2)	Pathological classification (invasive ductal carcinoma/ invasive lobular carcinoma/medullary carcinoma)	TNM staging (III stage/IV stage)
Control group	45	47.55±8.77	22.81±2.87	33/10/2	26/19
Study group	42	47.89±9.65	22.94±3.07	27/13/2	24/18

Table 2: Comparison of clinical efficacy between the two groups n (%)

Group	Number of cases	CR	PR	SD	PD	Overall efficacy
Control group	45	2 (4.44)	13 (28.89)	12 (26.67)	18 (40.00)	15 (33.33)
Study group	42	3 (7.14)	21 (50.00)	10 (23.81)	14 (33.33)	24 (57.14)*
χ^2						4.979
p-value						0.026

CR: Complete response, PR: Partial response, SD: Stable disease and PD: Progressive disease

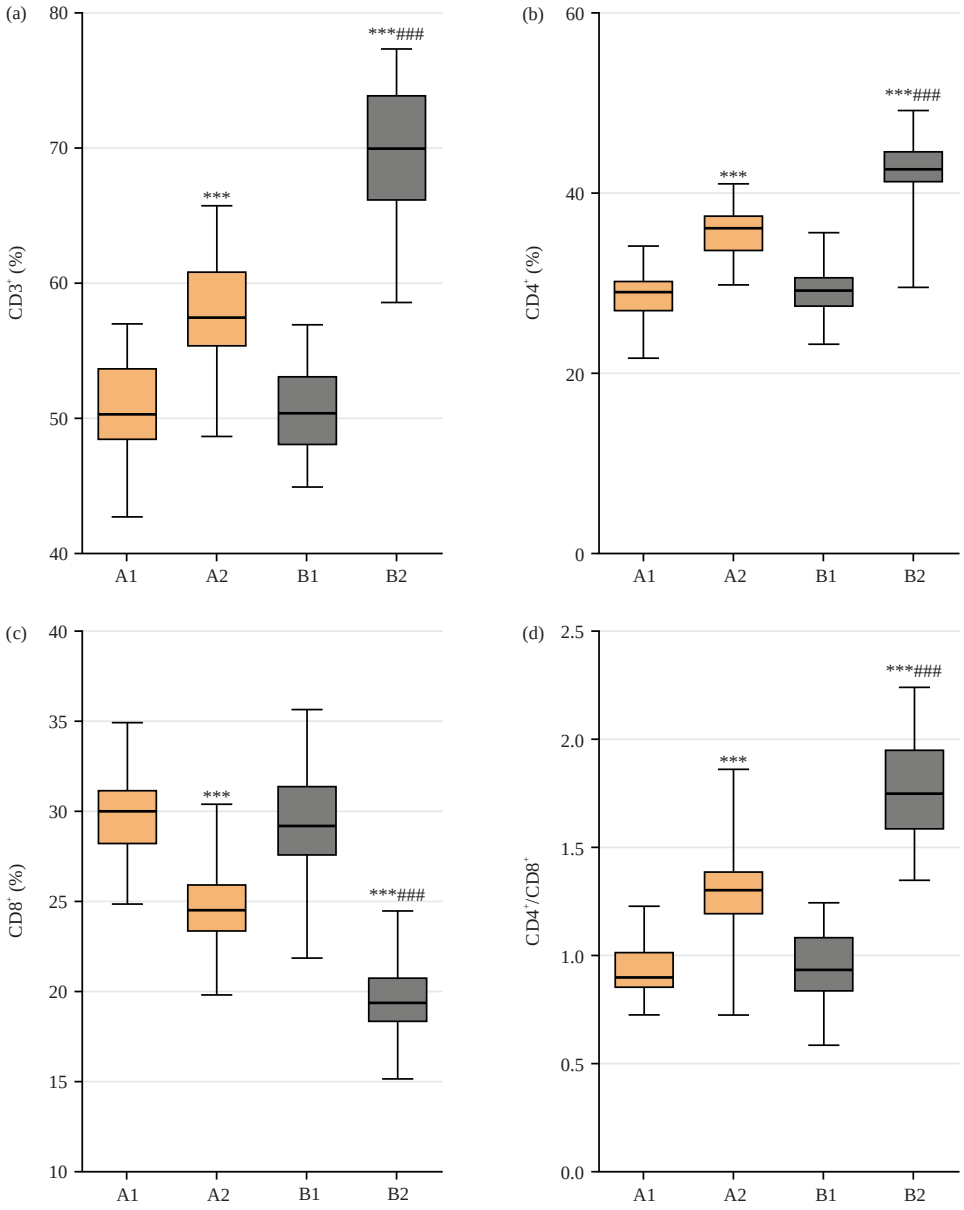

Fig. 2(a-d): Comparison of immune indicator levels between the two groups, it shows that after treatment, (a) $CD3^+$, (b) $CD4^+$ and (d) $CD4^+/CD8^+$ levels significantly increased in both groups, with the study group showing even higher levels, while (c) $CD8^+$ levels notably decreased, with the study group demonstrating even lower levels, showing significant difference

Compared with before treatment, ***p<0.001; Compared with the control group, ###p<0.001, A1/A2: Control group and B1/B2: Study group

Angiogenic factors: Before treatment, there was no significant difference in angiogenic factors (MMP-9, VEGF and TGF-β1) between the two groups (p>0.05). After treatment, the levels of MMP-9, VEGF and TGF-β1 significantly decreased in both groups, with the study group exhibiting even lower levels, showing significant difference (p<0.05) (Fig. 3(a-c)).

Quality of life: There was no significant difference in WHOQOL-BREF scale scores between the two groups before treatment (p>0.05). After treatment, scores on various dimensions of the WHOQOL-BREF scale notably increased in both groups, with the study group demonstrating higher scores, showing significant difference (p<0.05) (Table 3).

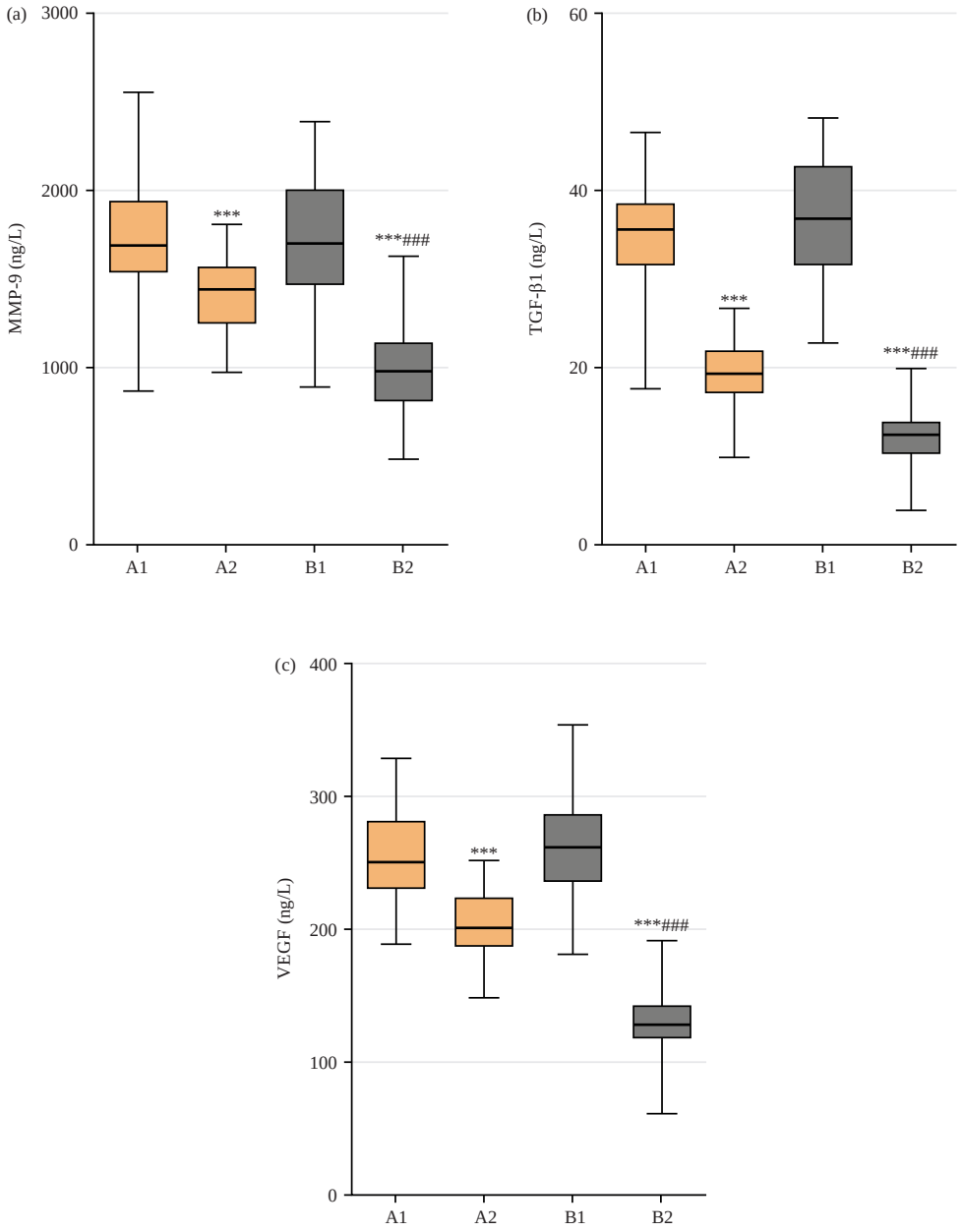

Fig. 3(a-c): Comparison of angiogenic factor levels between the two groups, it shows that after treatment, the levels of (a) MMP-9, (b) TGF-β1 and (c) VEGF significantly decreased in both groups, with the study group exhibiting even lower levels

Compared with before treatment, ***p<0.001; Compared with the control group, ###p<0.001, A1/A2: Control group and B1/B2: Study group

Table 3: Comparison of quality of life scores between the two groups ($\bar{\chi}\pm S$, scores)

		Physical health		Psychological health		Social relationships		Environmental health	
Group	Number of cases	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	45	48.12±1.73	60.55±5.08$^{\Delta\Delta\Delta}$	50.20±2.77	63.00±4.03$^{\Delta\Delta\Delta}$	59.67±2.12	72.75±5.30$^{\Delta\Delta\Delta}$	60.12±2.13	73.10±4.22$^{\Delta\Delta\Delta}$
Study group	42	48.04±1.60	72.76±4.65$^{\Delta\Delta\Delta***}$	50.05±2.53	74.30±4.47$^{\Delta\Delta\Delta***}$	59.40±2.35	84.35±5.54$^{\Delta\Delta\Delta***}$	60.02±2.09	82.98±5.31$^{\Delta\Delta\Delta***}$

$^{\Delta\Delta\Delta}$p<0.001: Compared with before treatment and ***p<0.001: Compared with the control group

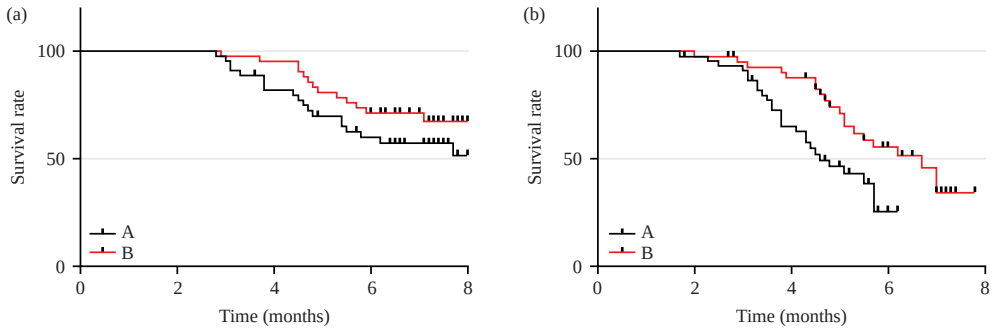

Fig. 4(a-b): Comparison of short-term prognosis between the two groups, it shows that the study group demonstrated significantly longer, (a) PFS and (b) OS compared to the control group

Table 4: Comparison of adverse reactions between the two groups n (%)

Group	Number of cases	Nausea and vomiting	Anemia	Proteinuria	Decreased white blood cell count
Control group	45	24 (53.33)	28 (62.22)	9 (20.00)	12 (26.67)
Study group	42	23 (54.76)	28 (66.67)	7 (16.67)	12 (28.57)

Table 5: Comparison of survival status between the two groups ($\bar{\chi}\pm S$, months)

Group	Number of cases	OS	PFS
Control group	45	5.86±1.74	4.25±1.28
Study group	42	6.55±1.37*	5.32±1.43*

OS: Overall survival, PFS: Progression-free survival and *p<0.05: Compared with the control group

Adverse reactions: The incidence of adverse reactions (nausea and vomiting, anemia, proteinuria and decreased white blood cell count) did not exhibit significant differences between the two groups (p>0.05) (Table 4).

Short-term prognosis: The study group demonstrated significantly longer PFS and OS compared to the control group (p<0.05), indicating a superior short-term prognosis in the study group (Table 5, Fig. 4(a-b)).

DISCUSSION

The findings of this study showed that the combination of PD-1 inhibitor with GP regimen could effectively treat advanced TNBC, fostering the restoration of patients' immune function, reducing tumor marker levels, inhibiting tumor angiogenesis, promoting an enhancement in quality of life, improving short-term prognosis and exhibiting favorable safety profiles. Breast cancer is a malignancy commonly found in the female population, of which TNBC is more aggressive and has a generally poor prognosis, with a 5-year survival rate of only approximately 11% in patients with advanced TNBC[11]. Clinical observations reveal that TNBC exhibits limited sensitivity to conventional endocrine and targeted therapies; while it displays sensitivity to chemotherapy, its clinical benefits remain restricted for patients with advanced TNBC[12]. Taxanes and anthracyclines are commonly utilized chemotherapeutic agents in recent clinical practice for the treatment of advanced TNBC, imparting a certain degree of prognosis improvement for patients. However, for those with advanced TNBC exhibiting resistance to such chemotherapeutic agents, platinum-based regimens like GP have garnered widespread acknowledgment in clinical management[13,14]. The cisplatin in the GP regimen interacts with the DNA bases in tumor cells, altering template function, inhibiting tumor cell DNA replication, thus preventing cellular division and proliferation[15]. Gemcitabine, functioning as a nucleoside chemotherapy agent with antimetabolic effects, can inhibit DNA synthesis by binding to deoxyribonucleosides in tumor cells, thereby exterminating tumor cells[16]. However, long-term clinical experience reveals that utilizing the GP regimen alone for the treatment of advanced TNBC still fails to achieve satisfactory outcomes, necessitating the exploration of more efficacious combination therapies to further enhance therapeutic efficacy.

The PD-1 is a prevalent immunological checkpoint protein in clinical settings, exhibiting widespread expression in T and B cells, capable of inducing programmed death of antigen-specific T cells and participating in the cellular immune processes of the body[17]. Currently, relevant research has confirmed that some TNBC tumor cells contain a large amount of PD-L1, i.e., the ligand of PD-1 and the activated PD-1/PD-L1

system inhibits the synthesis of the relevant cytokines, prompting the apoptosis of cytotoxic T-cells within the tumor cells, thus affecting the body's ability to recognize the tumor cells, leading to immune escape and ultimately resulting in a significant decline in the body's anti-tumor immune response[18]. Camrelizumab is a PD-1 inhibitor commonly utilized in the clinical treatment of solid tumors such as breast cancer[19]. The findings of this study showed that the overall efficacy of the study group was higher that of the control group and after treatment, the study group exhibited lower CEA, CA 125 and CA15-3 levels, superior immunological function indicators and higher WHOQOL-BREF scale scores compared with the control group; the incidence of adverse reactions in both groups was equivalent. These results suggested that treatment with PD-1 inhibitor in addition to the GP regimen for advanced TNBC patients could further enhance therapeutic efficacy, suppress tumor marker expression, ameliorate patient immune function, improve quality of life and demonstrate favorable safety profiles. The reason may be due to the fact that the GP regimen can eradicate tumor cells by inhibiting DNA replication and synthesis but cannot achieve complete elimination[20]. Camrelizumab, by inhibiting the effective binding of PD-1 and PD-L1, promotes the restoration of T-cell immune function, thus exerting potent cytotoxic effects on tumor cells[21]. Concurrently, TNBC contains a large amount of PD-L1, which largely increases its role as a target for clinical immunotherapy, thereby further enhancing the anti-tumor effect[22].

Research has indicated that the persistent proliferation, infiltration and metastasis of malignant tumor cells are crucial factors exacerbating their malignancy and neovascularization, cellular growth, differentiation and extracellular matrix degradation constitute prerequisites for the occurrence of proliferation, infiltration and metastasis phenomena[23,24]. The VEGF is a pivotal regulator in neovascularization, which not only fosters vascular regeneration in tumor cells to accelerate disease progression in patients, but also exerts an activating effect on various protein kinase pathways to enhance MMP-9 activity, further facilitating tumor cell proliferation, infiltration and metastasis[25]. The MMP-9, functioning as an extracellular matrix proteolytic enzyme, facilitates not only the degradation of extracellular matrix and collagen in the basement membrane, thereby enabling tumor cells to further breach the basement membrane and consequently promoting infiltration and metastasis, but also accelerates the formation of tumor neoangiogenesis, enhancing tumor cell resilience to the external environment. The TGF-β1, serving as a growth factor with the capacity to regulate cellular growth and differentiation, can inhibit the proliferation of immune effector cells while promoting the proliferation, infiltration and metastasis of tumor cells. The results of this study showed that the levels of VEGF, MMP-9 and TGF-β1 in the study group were lower than those in the control group after treatment, indicating that the addition of PD-1 inhibitor therapy on the basis of GP regimen for patients with advanced TNBC could inhibit the generation of tumor neovascularization in patients by further regulating the levels of the above angiogenic factors, thereby accelerating the process of apoptosis. Furthermore, the findings of this study indicated that both the PFS and OS of the study group were longer than those of the control group, which further illustrated the efficacy of PD-1 inhibitor in conjunction with the GP regimen for the treatment of advanced TNBC patients, thus enhancing short-term prognosis.

CONCLUSION

The combination of PD-1 inhibitor and GP regimen demonstrated precise therapeutic efficacy in the treatment of advanced TNBC, which facilitated the restoration of patients' immune function, reduced tumor marker levels, suppressed tumor angiogenesis, promoted enhancement in quality of life, improved short-term prognosis and exhibited favorable safety profile. However, this study is a retrospective analysis, characterized by limitations such as a small number of cases and a single source, which may lead to bias in the results. Furthermore, the long-term prognosis of PD-1 inhibitors combined with GP regimens in patients with advanced TNBC was not evaluated, which is a direction for future research.

SIGNIFICANCE STATEMENT

Triple-Negative Breast Cancer (TNBC) is invasive and metastatic, with a high risk of recurrence and an unfavorable prognosis. Although TNBC exhibits high sensitivity to chemotherapy, patients at advanced stages are often resistant to taxanes or anthracyclines, exhibiting poor therapeutic efficacy and prognosis. This study aimed to explore the efficacy and prognosis of Programmed Cell Death Protein-1 (PD-1) inhibitor combined with the GP regimen in the treatment of patients with TNBC. The findings indicate that PD-1 inhibitors combined with GP regimens for advanced TNBC can promote quality of life and improve short-term prognosis with a favorable safety profile, providing insights for the formulation of therapeutic strategies for this condition.

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