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Original Article

Short- and long-term efficacy of olaparib combined with chemotherapy in advanced triple-negative breast cancer

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Abstract: Objective: To evaluate the short- and long-term efficacy of olaparib combined with chemotherapy as adjuvant therapy in patients with advanced triple-negative breast cancer (TNBC). Methods: This retrospective cohort study included 274 patients with advanced TNBC, divided into an observation group (olaparib + chemotherapy, n = 116) and a control group (chemotherapy alone, n = 158). Primary outcome measures included Objective Response Rate (ORR), Disease Control Rate (DCR), immune function indicators (CD3+, CD4+/CD8+ ratio, Natural Killer T cells), cytokine levels (Interferon-gamma, Interleukin-2, Interleukin-6), tumor markers [Carcinoembryonic Antigen, Carbohydrate Antigen 153, Human Epididymis Protein 4], Karnofsky Performance Status (KPS), Progression-Free Survival (PFS), Overall Survival (OS), and adverse event incidence. Results: The observation group showed significantly higher ORR and DCR (both $P < 0.05$) than the control group. Immune function and cytokine levels improved significantly in the observation group (both $P < 0.05$). In contrast, IL-6 levels increased significantly in the control group ($P < 0.05$). Tumor marker levels were lower in the observation group (all $P < 0.001$). KPS scores were significantly higher in the observation group at 1, 3, and 6 months post-treatment (all $P < 0.05$). The observation group exhibited prolonged PFS and OS (both $P < 0.05$). Conclusions: Olaparib combined with chemotherapy enhances short- and long-term efficacy, improves immune function, and prolongs survival in advanced TNBC without increasing treatment-related toxicity, supporting its clinical utility.

Keywords: Olaparib, chemotherapy, advanced triple-negative breast cancer, short-term efficacy, long-term efficacy

Introduction

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer with a poor prognosis. The loss of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2) makes endocrine and targeted therapies ineffective. Despite treatment, patients face a 30-40% risk of recurrence, and the five-year survival rate after metastasis is less than 20% [1, 2]. While neoadjuvant chemotherapy has improved pathological complete response rates in some early-stage patients, the median survival for advanced cases remains limited to 12-18 months. Traditional chemotherapy is also associated with toxic side effects, including bone marrow suppression and gastrointestinal reactions, which affect treatment tolerance [3, 4].

In recent years, poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors have provided new treatment options for TNBC. PARP inhibitors target DNA damage repair mechanisms and induce a “synthetic lethal” effect in tumor cells carrying BRCA1/2 mutations [5, 6]. Olaparib, a highly selective PARP inhibitor, is approved for the treatment of BRCA-mutated HER2-negative metastatic breast cancer, including TNBC [7, 8]. Clinical studies have shown that olaparib monotherapy significantly prolongs progression-free survival (PFS) in BRCA-mutated breast cancer patients with a favorable safety profile [9, 10]. However, the combination of olaparib with chemotherapy in advanced TNBC, particularly its synergistic effect and long-term efficacy with standard chemotherapy (e.g., taxanes or platinums), requires further exploration. Current research on olapa-

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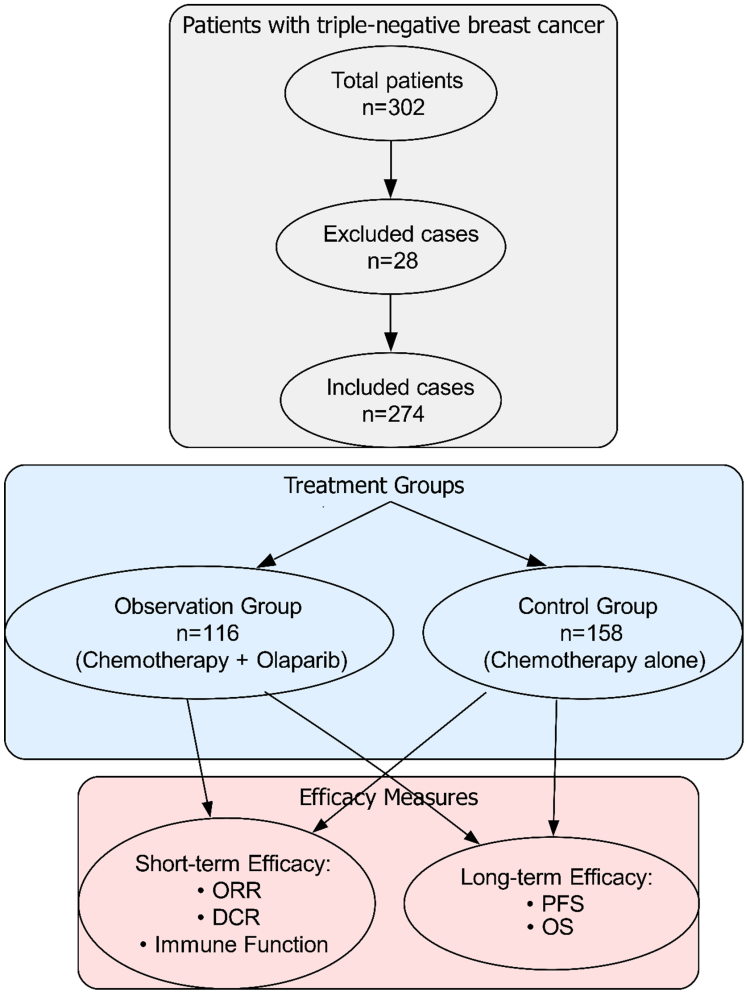

Figure 1. Study flow chart. Note: ORR, Objective Response Rate; DCR, Disease Control Rate; PFS, Progression-Free Survival; OS, Overall Survival.

rib combined with chemotherapy in advanced TNBC is limited, mostly focusing on BRCA-mutated populations. Given the high heterogeneity of TNBC and the potential benefits for some BRCA-wild-type patients (e.g., those with homologous recombination repair [HRR] defects), expanding the study population to evaluate the broader applicability of this combination is clinically important [11]. Moreover, existing studies mainly assess short-term efficacy (e.g., objective response rate [ORR], PFS), while long-term outcomes such as overall survival (OS), quality of life, and long-term safety remain underexplored.

This study aims to evaluate both the short and long-term efficacy of olaparib combined with chemotherapy in patients with advanced TNBC, including ORR, PFS, OS, and treatment-related adverse reactions. The findings are expected to provide comprehensive evidence for clinical practice and identify the patient population that may benefit from this combination regimen.

Materials and methods

Clinical data

This retrospective cohort study reviewed the medical records of 274 patients with TNBC who were admitted to Shanxi Province Cancer Hospital between March 2020 and March 2022. Based on their treatment regimens, patients were divided into two groups: an observation group (116 cases, olaparib combined with chemotherapy) and a control group (158 cases, chemotherapy alone) (**Figure 1**). The study was approved by the Ethics Committee of Shanxi Province Cancer Hospital. All procedures followed the Declaration of Helsinki (2013 revision).

Inclusion criteria

Patients met the following criteria: (1) TNBC diagnosis confirmed by immunohistochemistry, imaging, and pathological examination according to the 2011 Guidelines for Diagnosis and Treatment of Breast Cancer [12]; (2) clinical stage III-IV based on the 2010 American Joint Committee on CanceTNM staging; (3) at least one course of first-line standard chemotherapy (e.g., anthracycline- or taxane-containing regimens); (4) age 18-75 years; (5) Eastern Cooperative Oncology Groupperformance status score ≤ 2; (6) predicted survival time ≥ 3 months; (7) complete clinical data, including treatment completion and outcome evaluation.

Exclusion criteria

Exclusion criteria included: (1) patients with other malignancies or non-TNBC breast cancer subtypes; (2) severe heart, liver, or renal insuf-

ficiency; (3) poor treatment compliance; (4) history of active infection, autoimmune disease, or immunosuppressive therapy; (5) prior treatment with PARP inhibitors (e.g., olaparib, niraparib); (6) receipt of other anti-tumor therapies (such as immune checkpoint inhibitors or targeted drugs) during the study period.

Methods

Patients in the control group received standard chemotherapy based on taxanes (e.g., paclitaxel or docetaxel), with the dose adjusted according to the patient's body surface area. If there were no contraindications, anthracyclines (e.g., epirubicin 75-100 mg/m^2) or platinums (e.g., carboplatin) could be added. Chemotherapy was administered every 3 weeks for a total of 6 to 8 cycles. To prevent allergic reactions, dexamethasone (Pfizer Inc., USA, Specification: 0.75 mg/tablet, Batch No.: 20230115) and diphenhydramine (Johnson & Johnson, USA, Specification: 25 mg/tablet, Batch No.: 20230320) were given. After chemotherapy, recombinant human granulocyte colony-stimulating factor (G-CSF, Chugai Pharmaceutical Co., Ltd., Japan, Specification: 300 μg/injection, Batch No.: 20230210) was used based on the degree of bone marrow suppression.

Patients in the observation group were treated with olaparib (AstraZeneca, UK, Specification: 150 mg/capsule, Batch No.: 20230405) in addition to the chemotherapy regimen. Olaparib (300 mg, bid) was administered orally until disease progression or intolerable toxicity occurred. During treatment, blood routine tests, liver and kidney function tests, and electrocardiograms using electrocardiograph (Mindray Medical International Limited, China, Model: BeneHeart R3, Device No.: EC-20230510) were monitored. The drug dose was adjusted, or treatment was halted if grade III-IV adverse reactions occurred.

Observation indicators

Short-term efficacy: Short-term efficacy was evaluated according to the solid tumor evaluation criteria, categorizing responses as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The ORR was calculated as CR + PR, and the Disease control rate (DCR) was calculated as CR + PR + SD. Short-term efficacy was assessed 4-6 months after chemotherapy completion.

Immune function: Peripheral blood samples (2 mL) were collected before and after treatment (post-chemotherapy). Peripheral blood mononuclear cells were isolated using lymphocyte separation medium (Tianjin HaoYang Biological Manufacture Co., Ltd., China, Specification: 200 mL/bottle, Batch No.: 20230125), washed with PBS, and treated with saline. Fluorescently labeled monoclonal antibodies (BD Biosciences, USA: FITC-labeled CD3, Catalog No.: 555332; PE-labeled CD4, Catalog No.: 555346; Allophycocyanin-labeled CD8, Catalog No.: 555369; PerCP-Cy5.5-labeled CD56/16, Catalog No.: 556758, Batch No.: 20230218) were added and incubated for 30 minutes in the dark. Red blood cells were lysed, and flow cytometry was performed using flow cytometer (Beckman Coulter, USA, Model: CytoFLEX S, Device No.: FC-20230308). The proportions of CD3+ T cells, the CD4+/CD8+ T cell ratio, and the proportions of CD3+CD56+ or CD3+CD16+, Natural Killer T (NKT) cells were analyzed using FlowJo software (Tree Star Inc., USA, Version: 10.8.1). Isotype controls were used to exclude non-specific staining.

Cytokines: Expression levels of IFN-γ, IL-2, and IL-6 in peripheral blood were measured by ELISA before and after treatment using ELISA kits (R&D Systems, USA: IFN-γ Catalog No.: DIF50; IL-2 Catalog No.: D2050; IL-6 Catalog No.: D6050, Batch No.: 20230322).

Quality of life: The Karnofsky Performance Scale (KPS) was used to evaluate patients' quality of life before treatment and 1 month, 3 months, and 6 months after chemotherapy completion.

Tumor markers: Fasting venous blood (5 mL each time) was collected before and after treatment, and serum was separated by centrifugation using centrifuge (Eppendorf AG, Germany, Model: 5810R, Device No.: CF-20230415). The levels of tumor markers, including carcinoembryonic antigen (CEA), carbohydrate antigen 153 (CA153), and human epididymis protein 4 (HE4), were measured using an automatic biochemical analyzer (Roche Diagnostics, Switzerland, Model: cobas c702, Device No.: BA-20230220).

Adverse reactions: Toxicity related to chemotherapy and immunotherapy was graded (0-IV) according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0) and recorded. Additionally, side effects such as fever or rash following autologous DC-CIK cell infusion in the observation group were noted.

Follow-up

This retrospective analysis used data from medical records, with a minimum follow-up period of 3 years after treatment initiation for all patients. The final follow-up was on March 1, 2025. PFS and OS were calculated based on documented clinical events: PFS: The interval from treatment initiation to the first recorded disease progression or death (whichever occurred first). OS: The interval from treatment initiation to death from any cause. Patients without recorded events were censored at their last confirmed follow-up visit within the 3-year window.

Statistical analysis

Statistical analyses were conducted using SPSS v29.0 (IBM Corp., Armonk, NY, USA). Normality of the data was assessed using the Shapiro-Wilk test or Kolmogorov-Smirnov test. For metric variables, if the data were normally distributed, parametric tests were applied: one-way analysis of variance (ANOVA) was used for comparisons among three or more groups, and subsequent pairwise comparisons were performed using the LSD-t test (Least Significant Difference t-test); the Student's t-test was used for comparisons between two groups. If the data were non-normally distributed, non-parametric tests were adopted: the Kruskal-Wallis H test was used for comparisons among three or more groups, with pairwise comparisons conducted using the Bonferroni correction; the Mann-Whitney U test was used for comparisons between two groups. Categorical variables were expressed as frequencies (n) and percentages (%) and compared using χ^2 tests. Data are presented as mean ± SD unless specified otherwise. Statistical significance was set at $P < 0.05$.

Results

Comparison of clinical data

The comparison of clinical data between the groupsrevealed no significant differences in most variables. Age, duration, height, weight, BMI, prevalence of comorbidities (hypertension, diabetes, coronary heart disease, hyperlipidemia), smoking and drinking history, previous surgery, education level, low-income status, menopausal status, tumor location, Karnofsky Performance Status (KPS), and TNM staging were similar between the two groups (all $P > 0.05$), as shown in **Table 1**.

Comparison of short-term efficacy

For the short - term efficacy, the number of cases with CR was 4 (3.4%) and 2 (1.3%) in the observation and control groups, respectively. For PR, it was 24 (20.7%) and 16 (10.1%) respectively; for SD, 15 (12.9%) and 17 (10.8%) respectively; and for PD, 73 (62.9%) and 123 (77.8%) respectively. The ORR was significantly higher in the observation group (24.1%) compared to the control group (11.4%) ($\chi^2 = 7.689$, $P = 0.006$). The DCR was also higher in the observation group (37.1%) compared to the control group (22.2%) ($\chi^2 = 7.423$, $P = 0.006$), as shown in **Table 2**.

Comparison of immune function

Before treatment, there were no significant differences in CD3+, CD4+, CD8+, CD4+/CD8+, and NKT cell levels between the two groups. After treatment, the levels of CD3+, CD4+, CD8+, CD4+/CD8+ ratio, and NKT cells in the observation group were significantly higher than those in the control group, with statistically significant differences (all $P < 0.05$), as shown in **Table 3**.

Changes in cytokine levels before and after treatment in the two groups

For IFN-γ levels (**Figure 2A**), the observation group showed a significant increase post-treatment ($P < 0.001$ vs. baseline). The control group did not show a significant change in IFN-γ levels. A highly significant difference was observed between the observation and control groups post-treatment ($P < 0.001$).

Regarding IL-2 levels (**Figure 2B**), the observation group exhibited a marked increase post-treatment ($P < 0.001$ vs. baseline), while the control group showed no significant change. A highly significant difference was observed between the post-treatment observation and control groups ($P < 0.001$).

Table 1. Comparison of clinical data between the two groups

Clinical data	Observation group (n = 116)	Control group (n = 158)	t/x^2	P
Age (years, $\bar{x}\pm s$)	52.32 ± 9.04	51.03 ± 11.21	1.020	0.309
Duration (months, $\bar{x}\pm s$)	6.49 ± 2.16	7.02 ± 2.35	1.908	0.062
Height (cm, $\bar{x}\pm s$)	163.51 ± 8.20	161.8 ± 9.10	1.452	0.148
Weight (kg, $\bar{x}\pm s$)	62.41 ± 10.50	60.70 ± 11.31	1.234	0.219
Body Mass Index (BMI, $\bar{x}\pm s$)	23.41 ± 3.21	22.90 ± 3.51	1.187	0.236
Hypertension [n (%)]	28 (24.1%)	39 (24.7%)	0.023	0.880
Diabetes [n (%)]	17 (14.7%)	22 (13.9%)	0.065	0.798
Coronary heart disease	9 (7.8%)	12 (7.6%)	0.003	0.954
Hyperlipidemia [n (%)]	15 (12.9%)	20 (12.7%)	0.002	0.963
Smoking history [n (%)]	21 (18.1%)	30 (19.0%)	0.051	0.821
Drinking history [n (%)]	14 (12.1%)	22 (13.9%)	0.304	0.581
Previous surgery [n (%)]	32 (27.6%)	47 (29.7%)	0.218	0.641
Education level [n (%)]				
Primary school	25 (21.6%)	38 (24.1%)	1.054	0.590
Junior high school	48 (41.4%)	65 (41.1%)		
High school and above	43 (37.1%)	55 (34.8%)		
Low-income status	31 (26.7%)	45 (28.5%)	0.156	0.693
Menopausal status [n (%)]				
Yes	42 (36.2%)	64 (40.5%)	0.521	0.470
No	74 (63.8%)	94 (59.5%)		
Tumor location [n (%)]				
Lung	45 (38.8%)	62 (39.2%)	0.010	0.920
Breast	32 (27.6%)	41 (25.9%)	0.143	0.705
Colorectal	23 (19.8%)	30 (19.0%)	0.043	0.836
Others	16 (13.8%)	25 (15.8%)	---	---
Karnofsky Performance Status (KPS, $\bar{x}\pm s$)	78.51 ± 10.21	76.82 ± 11.51	1.289	0.198
TNM staging [n (%)]				
Stage III	78 (67.2%)	102 (64.6%)	0.214	0.644
Stage IV	38 (32.8%)	56 (35.4%)		

Note: KPS, Karnofsky Performance Scale; TNM, Tumor Node Metastasis.

Table 2. Comparison of short-term efficacy between the two groups [n (%)]

Variables	Observation group (n = 116)	Control group (n = 158)	x^2	P
CR	4 (3.4%)	2 (1.3%)	-	-
PR	24 (20.7%)	16 (10.1%)	-	-
SD	15 (12.9%)	17 (10.8%)	-	-
PD	73 (62.9%)	123 (77.8%)	-	-
ORR	28 (24.1%)	18 (11.4%)	7.689	0.006
DCR	43 (37.1%)	35 (22.2%)	7.423	0.006

Note: CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; DCR, Disease Control Rate; ORR, Objective Response Rate.

For IL-6 levels (**Figure 2C**), the control group showed a significant increase post-treatment ($P < 0.001$ vs. baseline), while the observation group did not show a significant change. No significant difference was found between pre-treatment levels in the observation and control groups. However, post-treatment IL-6 levels were significantly higher in the control group compared to the observation group ($P < 0.001$), as shown in **Figure 2**.

Comparison of quality of life

Before treatment, the KPS scores were comparable between the two groups. One month

Table 3. Comparison of immune function between the two groups ($\bar{x} \pm s$)

Variables	Time points	Observation group (n = 116)	Control group (n = 158)	t	P
CD3+	Before treatment	66.18 ± 7.15	66.76 ± 8.35	0.612	0.549
	After treatment	72.29 ± 5.61	50.81 ± 6.91	-27.497	< 0.01
CD4+	Before treatment	25.39 ± 4.02	25.11 ± 4.91	-0.507	0.613
	After treatment	29.23 ± 3.29	22.08 ± 3.07	-18.457	< 0.01
CD8+	Before treatment	30.45 ± 4.55	30.88 ± 4.28	0.795	0.427
	After treatment	35.21 ± 3.34	31.39 ± 3.37	-9.331	< 0.01
CD4+/CD8+	Before treatment	1.61 ± 0.16	1.54 ± 0.26	1.398	0.163
	After treatment	1.68 ± 0.11	1.41 ± 0.16	-15.876	< 0.01
NTK	Before treatment	5.68 ± 0.89	5.63 ± 0.98	-0.451	0.653
	After treatment	7.84 ± 1.17	5.01 ± 0.74	-24.448	< 0.01

Note: CD3+, Cluster of Differentiation 3; CD4+, Cluster of Differentiation 4; CD8+, Cluster of Differentiation 8; NKT, Natural Killer T Cells.

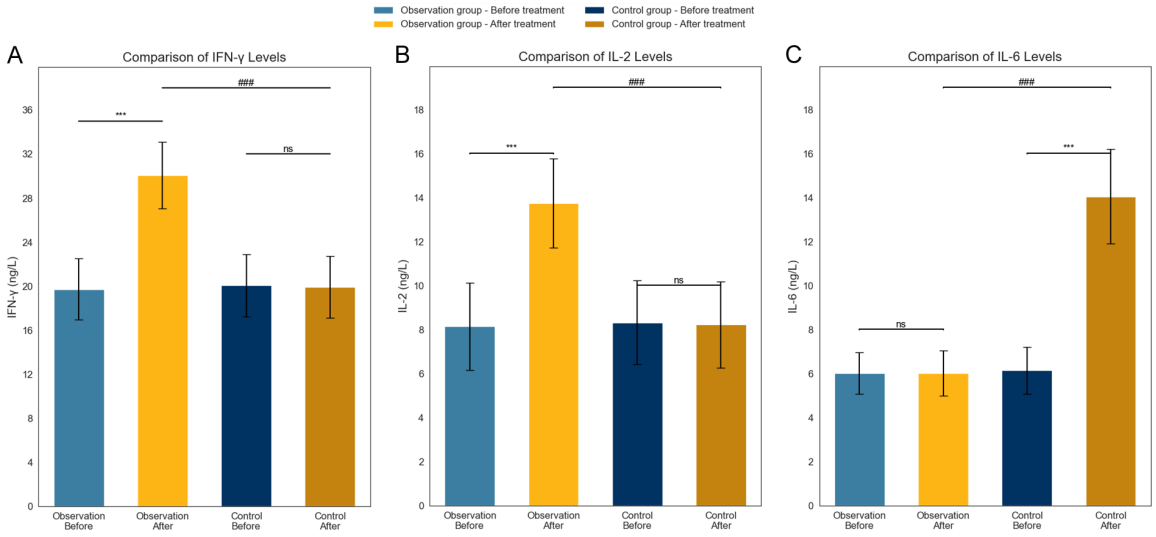

Figure 2. Changes in cytokine levels in the two groups. A. Comparison of IFN-γ Levels Between Observation and Control Groups (Before vs After Treatment); B. Comparison of IL-2 Levels Between Observation and Control Groups (Before vs After Treatment); C. Comparison of IL-6 Levels Between Observation and Control Groups (Before vs After Treatment). ***P < 0.001, ###P < 0.001, ns. Note: IFN-γ, Interferon-Gamma; IL-2, Interleukin-2; IL-6, Interleukin-6.

post-treatment, the KPS score in the observation group increased significantly and showed a steeper upward trend compared to the control group. At three months post-treatment, the KPS score in the observation group remained relatively high, whereas the control group showed some improvement but to a lesser extent. Six months post-treatment, the KPS score in the observation group slightly decreased but remained higher than in the control group, with both groups maintaining relatively stable scores compared to their respective post-treatment levels, as shown in **Figure 3**.

Changes in tumor marker levels before and after treatment in the two groups

The observation group showed significant reductions in tumor markers compared to the control group. For CEA, the post-treatment decrease in the observation group was statistically significant (t = 12.345, P < 0.001), while the control group showed no significant change (t = 0.287, P = 0.775). Post-treatment CEA levels in the observation group were significantly lower than those in the control group (t = 14.231, P < 0.001). For CA153, the observation group exhibited a marked decline post-

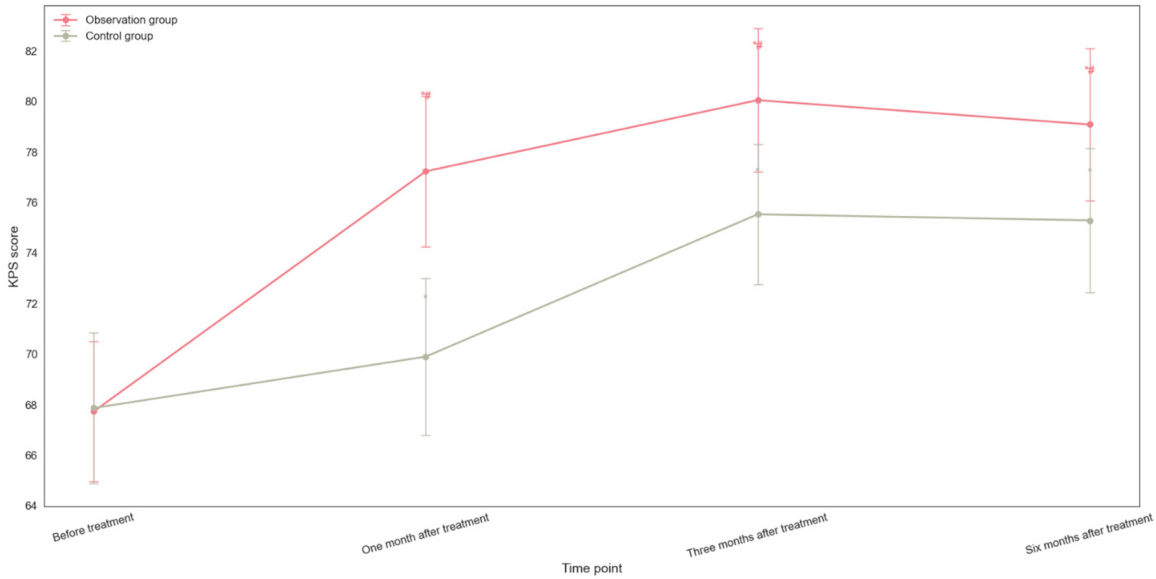

Figure 3. Comparison of quality of life. Note: *P < 0.05, #P < 0.05. KPS, Karnofsky Performance Scale.

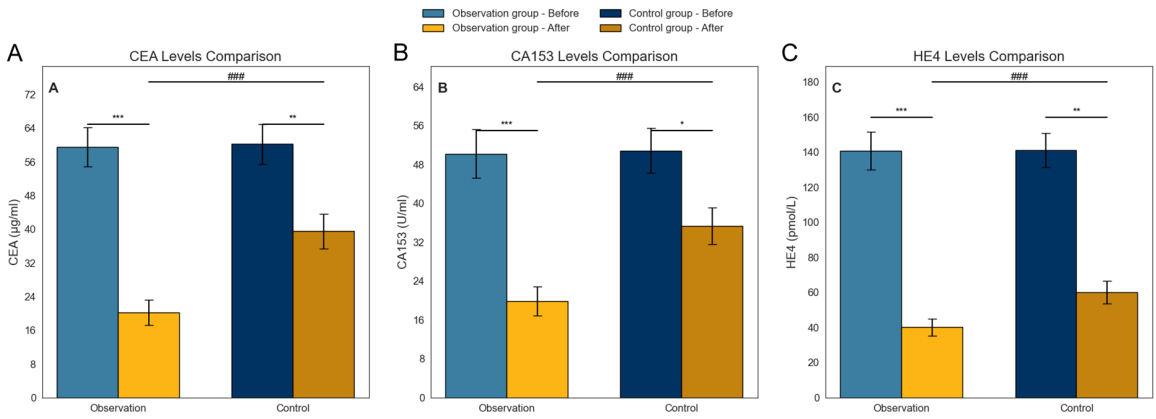

Figure 4. Comparison of tumor markers. A. CEA Levels in Observation and Control Groups (Before vs After); B. CA153 Levels in Observation and Control Groups (Before vs After); C. HE4 Levels in Observation and Control Groups (Before vs After). *P < 0.05, **P < 0.01, ***P < 0.001, ###P < 0.001. Note: CA153, Carbohydrate Antigen 153; CEA, Carcinoembryonic Antigen; HE4, Human Epididymis Protein 4.

treatment (t = 9.876, P < 0.001), while the control group showed no significant change (t = 0.562, P = 0.575). Post-treatment CA153 levels in the observation group were significantly lower than those in the control group (t = 16.543, P < 0.001). Regarding HE4, the observation group showed a statistically significant decrease post-treatment (t = 8.921, P < 0.001), while the control group showed minimal change (t = 0.483, P = 0.629). Post-treatment HE4 levels in the observation group were significantly lower than those in the control group (t = 13.872, P < 0.001), as shown in **Figure 4**.

Moderate to severe adverse reactions

More than 70% of patients in both groups experienced alopecia. The incidence of grade II or higher leukopenia was 46.55% (27/58) in the observation group and 25.32% (20/79) in the control group, with recovery observed after treatment with G-CSF. No water or sodium retention or allergic reactions occurred in either group. Most gastrointestinal reactions were less than grade III. No intolerable adverse reactions were observed in either group, and there were no significant differences in adverse

Table 4. Comparison of the incidence of moderate and severe adverse reactions between the two groups [n (%)]

Adverse reactions	Observation group (n = 116)						Control group (n = 158)						x^2	P
Toxic effects	0	I	II	III	IV	Incidence rate	0	I	II	III	IV	Incidence rate		
Hair loss	12	18	19	9	0	39.7%	13	21	17	7	0	28.5%	3.064	0.080
Leukopenia	8	22	19	8	1	43.1%	16	22	18	2	0	26.6%	5.690	0.017
Thrombocytopenia	43	11	4	0	0	12.9%	45	8	5	0	0	8.2%	1.364	0.243
Nausea, vomiting	38	14	6	0	0	17.2%	40	14	4	0	0	11.4%	1.635	0.201
Liver function impairment	51	6	1	0	0	6.0%	52	5	1	0	0	3.8%	0.634	0.426
Renal impairment	58	0	0	0	0	0.00%	54	3	1	0	0	2.5%	2.692	0.101
Neurotoxicity	53	4	1	0	0	4.3%	51	4	3	0	0	4.4%	0.018	0.893
Fever	58	0	0	0	0	0.00%	52	4	2	0	0	3.8%	4.556	0.033

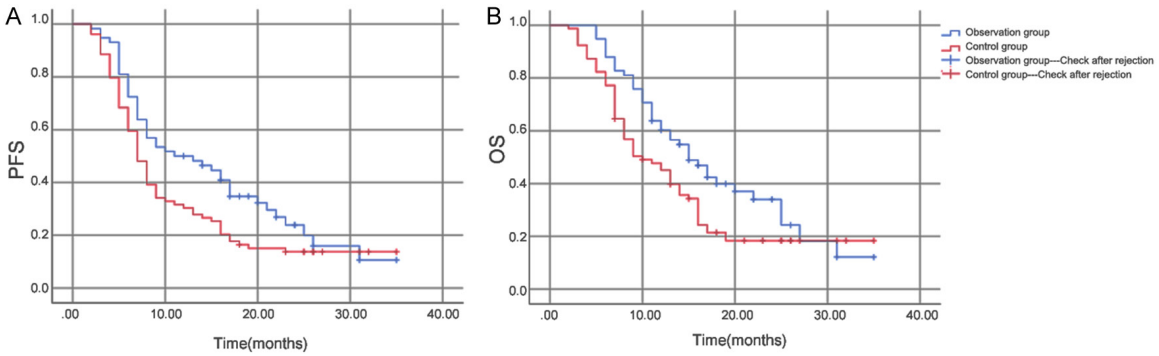

Figure 5. Survival prognosis analysis. A. Kaplan-Meier plot shows PFS over months for observation (blue) and control (red) groups. Initially, both have high PFS (near 1.0). Over time, PFS drops for both, but observation group maintains higher PFS longer. Control group's PFS stabilizes at a lower level earlier; observation group shows a more gradual PFS decline over 40 months. B. Kaplan-Meier plot illustrates OS over months for observation (blue) and control (red) groups. At baseline, OS probabilities are near 1.0 for both. With time, OS decreases. Control group's OS drops faster, reaching a lower stable level sooner. Observation group has a relatively slower OS decline, keeping higher survival probability longer over 40 months. Notes: PFS, Progression-Free Survival; OS, Overall Survival.

reactions between the two groups (P > 0.05), as shown in **Table 4**.

Prognostic analysis

For PFS, the observation group had a longer survival without progression compared to the control group over time. In terms of OS, the observation group also demonstrated better survival compared to the control group. The survival curves showed clear differences, with the observation group maintaining a more favorable survival probability in both PFS and OS analyses, as shown in **Figure 5**.

Prognostic single factor and cox regression analysis

In the univariate analysis, significant prognostic factors included age (HR = 2.393, 95% CI 1.251-3.325, P < 0.01), TNM staging (HR = 2.736, 95% CI 1.712-4.161, P < 0.01), and olaparib treatment (HR = 2.593, 95% CI 1.457-4.174, P < 0.01). These factors were significantly associated with survival outcomes, with higher hazard ratios for advanced TNM stages and older age. Notably, olaparib treatment remained independently significant in the multivariate analysis (HR = 2.421, 95% CI 1.496-3.953, P = 0.007), confirming its robust prognostic value after adjusting for confounding variables. Other factors, such as BMI (HR = 0.834, 95% CI 0.525-1.513, P = 0.612), menopausal status (HR = 0.984, 95% CI 0.701-1.422, P = 0.424), tumor diameter (HR = 1.516, 95% CI 0.925-1.955, P = 0.163), lymph node metastasis (HR = 1.170, 95% CI 1.032-1.941, P = 0.271), and histological grade (HR = 1.385, 95% CI 1.063-2.091, P = 0.197), did not reach

Table 5. Univariate analysis of prognostic factors affecting overall 3 years survival of patients

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	2.393 (1.251-3.325)	< 0.01	1.942 (1.316-3.841)	0.020
BMI (< 23 kg/m^2/≥ 23 kg/m^2)	0.834 (0.525-1.513)	0.612		
Menopause (Yes/No)	0.984 (0.701-1.422)	0.424		
TNM staging (I/II/III)	2.736 (1.712-4.161)	< 0.01	2.194 (1.629-4.582)	0.012
Tumor diameter (< 5 cm/≥ 5 cm)	1.516 (0.925-1.955)	0.163		
Lymph node metastasis (Yes/No)	1.170 (1.032-1.941)	0.271		
Histological grade (grade 1/grade 2/grade 3)	1.385 (1.063-2.091)	0.197		
Olaparib treatment (Yes/No)	2.593 (1.457-4.174)	< 0.01	2.421 (1.496-3.953)	0.007

statistical significance in the univariate analysis and were excluded from the multivariate model. However, TNM staging remained significant in the multivariate analysis (HR = 2.194, 95% CI 1.629-4.582, P = 0.012), though its hazard ratio decreased slightly compared to the univariate result, suggesting partial confounding by other variables. Age also remained significant in the multivariate analysis (HR = 1.942, 95% CI 1.316-3.841, P = 0.020), with a reduced hazard ratio compared to the univariate analysis, as shown in **Table 5**.

Discussion

The integration of PARP inhibitors, such as olaparib, into the treatment regimen for TNBC represents a significant advancement in oncology [13]. The mechanism of action of PARP inhibitors stems from their ability to exploit DNA repair deficiencies in tumor cells, particularly those with mutations in BRCA1/2 genes. By inhibiting PARP enzyme activity, these drugs disrupt the base excision repair pathway, leading to the accumulation of DNA single-strand breaks, which collapse into double-strand breaks during DNA replication [14]. In BRCA1/2-mutated cells, which already lack functional homologous recombination (HR) repair, this synthetic lethality leads to catastrophic genomic instability and tumor cell death [15]. However, the clinical efficacy of PARP inhibitors extends beyond BRCA mutations, as demonstrated by this study, in which olaparib combined with chemotherapy showed improved outcomes in advanced TNBC patients regardless of BRCA status. This observation is consistent with emerging evidence suggesting that PARP inhibitors may exert anti-tumor effects through multiple mechanisms, including modulation of the tumor microenvironment and immune system. Our findings indicate that the benefits of olaparib in advanced TNBC extend beyond BRCA-mutated cases, supporting new evidence that PARP inhibitors combat tumors through diverse mechanisms - such as modifying the immune landscape [16].

This study suggests that olaparib could enhance anti-TNBC immunity [17]. Significant increases in CD3+ cells, CD4+/CD8+ ratios, and NKT cells were observed after adding olaparib, indicating a potential boost in the body's immune defenses. These immune shifts were accompanied by higher levels of IFN-γ and IL-2, which are key for T-cell-mediated tumor destruction, while IL-6 - an inflammatory cytokine linked to tumor growth and immune evasion - remained stable. Maintaining low IL-6 levels points to a healthier tumor microenvironment [18], aligning with preclinical studies where PARP inhibitors influenced immune cell trafficking and cytokine signals in tumors [19]. PARP inhibitors may activate interferon genes in cancer cells, potentially making tumors more recognizable to T-cells. Suppressing IL-6 could also reduce widespread inflammation, which may protect tumors [20]. Combining olaparib with chemotherapy likely works by targeting DNA repair from different angles. Standard chemotherapy agents, such as platinum-based drugs or taxanes, damage DNA through cross-linking or microtubule disruption [21]. Adding a PARP inhibitor intensifies the effect, overwhelming the cancer cell's repair mechanisms and inducing fatal genetic chaos. This dual approach is reflected in our data, showing improved tumor shrinkage ORR and DCR with the combination. Additionally, prolonged PFS and OS indicate the long-term benefits of this

strategy. While the precise mechanisms are still under investigation, it appears that impairing DNA repair through multiple pathways amplifies the tumor-killing effect [22].

The immune changes observed in this study raise intriguing questions. The increase in IFN-γ and IL-2 suggests that olaparib may shift the immune response toward a Th1 phenotype, which is crucial for activating cell-based tumor killers like CTLs and NK cells [23]. By stabilizing IL-6 levels (as opposed to the rise seen with chemotherapy alone), olaparib may help counteract the tumor's immunosuppressive microenvironment. Since IL-6 supports Tregs and Myeloid-Derived Suppressor Cells (MDSCs, immune response inhibitors), blocking its effects could free up immune effector cells such as T cells and NK cells, potentially explaining the improved outcomes observed in the observation group [24].

The reductions in tumor markers (CEA, CA153, HE4) further support olaparib's therapeutic potential [25]. The sharper declines in these markers in the combination group align with better response rates and PFS. While tumor markers are not perfect predictors of survival, they generally reflect treatment efficacy [26]. The significant reduction in CEA and CA153 suggests that olaparib may inhibit tumor growth and metastasis beyond its effects on DNA repair - possibly by triggering cell death or halting cell cycle progression. Lowering HE4 levels, which are associated with breast and ovarian cancers, may indicate disruption of tumor blood supply or metastatic pathways [27, 28].

Safety is a critical consideration, and the addition of olaparib did not significantly increase side effects. This is particularly important for advanced TNBC patients, who often require multiple treatments. The manageable safety profile of olaparib makes it a viable option for frailer patients [29, 30], though long-term risks, such as blood count reductions, should still be monitored [31, 32]. Additionally, patients in the olaparib group reported improved quality of life, as evidenced by higher KPS scores. This suggests that the combination therapy not only extends survival but also helps maintain daily functional capacity. This aspect of quality of life is crucial. Beyond survival rates, how patients feel on a day-to-day basis is paramount. The better KPS scores observed in the olaparib group indicate that this combination therapy helps patients function more effectively and feel reasonably well, even in the face of advanced cancer. Achieving the right balance between effective treatment and maintaining patient quality of life is essential in advanced cancer care. We suspect that the improved well-being may be directly related to olaparib's tumor-shrinking effects and potential reduction in inflammation. However, further research is needed to fully understand how immune changes and cytokine shifts (such as the increases in IFN-γ and IL-2) translate into real-world quality-of-life improvements for patients receiving PARP inhibitors.

Our study has some limitations. As a retrospective analysis, patient selection was not entirely controlled at the outset, leaving room for potential bias. Although we captured significant effects with 274 patients, smaller immune changes may have been overlooked. Additionally, the absence of subgroup analyses based on BRCA status presents a gap, as we cannot yet determine whether the benefits differ across these subgroups. The follow-up duration was also too short to capture all long-term immune responses or delayed side effects. To provide more robust conclusions, larger, prospective trials with extended follow-up periods are needed.

In summary, the combination of olaparib and chemotherapy represents a meaningful step forward in treating advanced TNBC. The evidence strongly supports its use, showing improved immune activity, better tumor responses, and extended survival. These findings reinforce the clinical application of PARP inhibitors in treating this aggressive cancer. What stands out is the insight into how olaparib works, particularly its effects on the immune system. This raises new questions about how inhibiting DNA repair might interact with immune responses. Further studies will solidify these findings and refine treatment strategies. However, it is clear that olaparib provides a promising approach to targeting cancer more effectively without significantly increasing patient burden. As cancer immunotherapy continues to evolve, it will be important to observe how PARP inhibitors reshape the tumor microenvironment and enhance immune surveillance. By disrupting DNA repair and modulating immune responses,

drugs like olaparib have the potential to revolutionize treatment for TNBC and other cancers with defective DNA repair mechanisms.

Disclosure of conflict of interest

None.

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References

[1] Li Y, Zhang H, Merkher Y, Chen L, Liu N, Leonov S and Chen Y. Recent advances in therapeutic strategies for triple-negative breast cancer. J Hematol Oncol 2022; 15: 121.

[2] Yin L, Duan JJ, Bian XW and Yu SC. Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Res 2020; 22: 61.

[3] Yang F, Xiao Y, Ding JH, Jin X, Ma D, Li DQ, Shi JX, Huang W, Wang YP, Jiang YZ and Shao ZM. Ferroptosis heterogeneity in triple-negative breast cancer reveals an innovative immunotherapy combination strategy. Cell Metab 2023; 35: 84-100, e108.

[4] Shiao SL, Gouin KH 3rd, Ing N, Ho A, Basho R, Shah A, Mebane RH, Zitser D, Martinez A, Mevises NY, Ben-Cheikh B, Henson R, Mita M, McAndrew P, Karlan S, Giuliano A, Chung A, Amersi F, Dang C, Richardson H, Shon W, Dadmanesh F, Burnison M, Mirhadi A, Zumsteg ZS, Choi R, Davis M, Lee J, Rollins D, Martin C, Khameneh NH, McArthur H and Knott SRV. Single-cell and spatial profiling identify three response trajectories to pembrolizumab and radiation therapy in triple negative breast cancer. Cancer Cell 2024; 42: 70-84, e78.

[5] Bianchini G, De Angelis C, Licata L and Gianni L. Treatment landscape of triple-negative breast cancer - expanded options, evolving needs. Nat Rev Clin Oncol 2022; 19: 91-113.

[6] Sukumar J, Gast K, Quiroga D, Lustberg M and Williams N. Triple-negative breast cancer: promising prognostic biomarkers currently in development. Expert Rev Anticancer Ther 2021; 21: 135-148.

[7] Karim AM, Eun Kwon J, Ali T, Jang J, Ullah I, Lee YG, Park DW, Park J, Jeang JW and Kang SC. Triple-negative breast cancer: epidemiology, molecular mechanisms, and modern vaccine-based treatment strategies. Biochem Pharmacol 2023; 212: 115545.

[8] van den Ende NS, Nguyen AH, Jager A, Kok M, Debets R and van Deurzen CHM. Triple-negative breast cancer and predictive markers of response to neoadjuvant chemotherapy: a systematic review. Int J Mol Sci 2023; 24: 2969.

[9] Zou Y, Xie J, Zheng S, Liu W, Tang Y, Tian W, Deng X, Wu L, Zhang Y, Wong CW, Tan D, Liu Q and Xie X. Leveraging diverse cell-death patterns to predict the prognosis and drug sensitivity of triple-negative breast cancer patients after surgery. Int J Surg 2022; 107: 106936.

[10] Asleh K, Riaz N and Nielsen TO. Heterogeneity of triple negative breast cancer: current advances in subtyping and treatment implications. J Exp Clin Cancer Res 2022; 41: 265.

[11] Kudelova E, Smolar M, Holubekova V, Hornakova A, Dvorska D, Lucansky V, Koklesova L, Kudela E and Kubatka P. Genetic heterogeneity, tumor microenvironment and immunotherapy in triple-negative breast cancer. Int J Mol Sci 2022; 23: 14937.

[12] MacDonald I, Nixon NA and Khan OF. Triple-negative breast cancer: a review of current curative intent therapies. Curr Oncol 2022; 29: 4768-4778.

[13] Kumar H, Gupta NV, Jain R, Madhunapantula SV, Babu CS, Kesharwani SS, Dey S and Jain V. A review of biological targets and therapeutic approaches in the management of triple-negative breast cancer. J Adv Res 2023; 54: 271-292.

[14] Zhou L and Yu CW. Epigenetic modulations in triple-negative breast cancer: therapeutic implications for tumor microenvironment. Pharmacol Res 2024; 204: 107205.

[15] Rizzo A, Cusmai A, Acquafredda S, Giovannelli F, Rinaldi L, Misino A and Palmiotti G. KEYNOTE-522, IMpassion031 and GeparNUEVO: changing the paradigm of neoadjuvant immune checkpoint inhibitors in early triple-negative breast cancer. Future Oncol 2022; 18: 2301-2309.

[16] Liu S, Li J, Gu L, Wu K and Xing H. Nanoparticles for chemoimmunotherapy against triple-negative breast cancer. Int J Nanomedicine 2022; 17: 5209-5227.

[17] Mehraj U, Mushtaq U, Mir MA, Saleem A, Macha MA, Lone MN, Hamid A, Zargar MA, Ahmad SM and Wani NA. Chemokines in triple-negative breast cancer heterogeneity: New challenges for clinical implications. Semin Cancer Biol 2022; 86: 769-783.

[18] Bando Y, Kobayashi T, Miyakami Y, Sumida S, Kakimoto T, Saijo Y and Uehara H. Triple-negative breast cancer and basal-like subtype: pathology and targeted therapy. J Med Invest 2021; 68: 213-219.

[19] Zhao N, Kabotyanski EB, Saltzman AB, Malovannaya A, Yuan X, Reineke LC, Lieu N, Gao Y, Pedroza DA, Calderon SJ, Smith AJ, Hamor C, Safari K, Savage S, Zhang B, Zhou J, Solis LM, Hilsenbeck SG, Fan C, Perou CM and Rosen JM. Targeting EIF4A triggers an interferon response to synergize with chemotherapy and suppress triple-negative breast cancer. bioRxiv 2023; 2023.09.28.559973.

[20] Craven KE, Gokmen-Polar Y and Badve SS. CIBERSORT analysis of TCGA and METABRIC identifies subgroups with better outcomes in triple negative breast cancer. Sci Rep 2021; 11: 4691.

[21] Choi E, Mun GI, Lee J, Lee H, Cho J and Lee YS. BRCA1 deficiency in triple-negative breast cancer: protein stability as a basis for therapy. Biomed Pharmacother 2023; 158: 114090.

[22] Tran J, Thaper A, Lopetegui-Lia N and Ali A. Locoregional recurrence in triple negative breast cancer: past, present, and future. Expert Rev Anticancer Ther 2023; 23: 1085-1093.

[23] Inayatullah M, Mahesh A, Turnbull AK, Dixon JM, Natrajan R and Tiwari VK. Basal-epithelial subpopulations underlie and predict chemotherapy resistance in triple-negative breast cancer. EMBO Mol Med 2024; 16: 823-853.

[24] Farshbafnadi M, Pastaki Khoshbin A and Rezaei N. Immune checkpoint inhibitors for triple-negative breast cancer: from immunological mechanisms to clinical evidence. Int Immunopharmacol 2021; 98: 107876.

[25] Liu CC, Chen L, Cai YW, Chen YF, Liu YM, Zhou YJ, Shao ZM and Yu KD. Targeting EMSY-mediated methionine metabolism is a potential therapeutic strategy for triple-negative breast cancer. Cell Rep Med 2024; 5: 101396.

[26] Lee YM, Oh MH, Go JH, Han K and Choi SY. Molecular subtypes of triple-negative breast cancer: understanding of subtype categories and clinical implication. Genes Genomics 2020; 42: 1381-1387.

[27] Mazzeo R, Sears J, Palmero L, Bolzonello S, Davis AA, Gerratana L and Puglisi F. Liquid biopsy in triple-negative breast cancer: unlocking the potential of precision oncology. ESMO Open 2024; 9: 103700.

[28] Shoukat I and Mueller CR. Searching for DNA methylation in patients triple-negative breast cancer: a liquid biopsy approach. Expert Rev Mol Diagn 2023; 23: 41-51.

[29] Guha L, Bhat IA, Bashir A, Rahman JU and Pottoo FH. Nanotechnological approaches for the treatment of triple-negative breast cancer: a comprehensive review. Curr Drug Metab 2022; 23: 781-799.

[30] Haiderali A, Huang M, Pan W, Akers KG, Maciel D and Frederickson AM. Pembrolizumab plus chemotherapy for first-line treatment of advanced triple-negative breast cancer. Future Oncol 2024; 20: 1587-1600.

[31] Zhou Y, Che Y, Fu Z, Zhang H and Wu H. Triple-negative breast cancer analysis based on metabolic gene classification and immunotherapy. Front Public Health 2022; 10: 902378.

[32] Li Y, Kong X, Wang Z and Xuan L. Recent advances of transcriptomics and proteomics in triple-negative breast cancer prognosis assessment. J Cell Mol Med 2022; 26: 1351-1362.