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RESEARCH ARTICLE

Impact of CTLA-4 Inhibitor Combined with Chemotherapy on Immunoglobulin Levels and General Condition in Breast Cancer Patients

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Abstract: This study conducted an evaluation of the CTLA-4 inhibitor ipilimumab plus standard chemotherapy on immunoglobulin levels, performance status, and Quality of Life (QoL) in patients with stage I-III Breast Cancer (BC) via a randomized controlled trial. 120 patients with stage I-III BC were randomly allocated to the experimental group (chemotherapy + ipilimumab) and the control group (chemotherapy), and the treatment cycle was 12 weeks. The results revealed that the combination treatment significantly increased the levels of serum IgG, IgA, and IgM (for example, IgG increased by 42.3%, $P < 0.01$), and the most significant improvement was found in the Luminal subtype. The experimental group had improved Karnofsky Performance Status (KPS) scores, increased body weight, and reduced patient-generated subjective global assessment (PG-SGA) scores, which indicated overall improvement in performance status; the QoL score exhibited a noticeable amelioration, with relief of symptoms (fatigue, pain, etc.) (vs. control group, $P < 0.01$). Correlation analysis concluded that IgG levels had a positive correlation with QoL ($r = 0.56$), and nutritional risk scores exhibited a negative correlation ($r = -0.64$). The incidence of immune-related adverse events (irAEs) was higher in the experimental group (63.3%), but most were grade 1-2 and controllable. In summary, the CTLA-4 inhibitor combined with chemotherapy can improve immune function and QoL in BC patients, with IgG potentially serving as a therapeutic monitoring indicator, especially for patients with the Luminal subtype who may benefit more significantly. In clinical applications, it is necessary to reasonably assess immune-related risks.

Keywords: CTLA-4 Inhibitor, Breast Cancer, Immunoglobulin, Quality of Life, Immune-Related Adverse Events

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Introduction

Breast Cancer (BC) is one of the most common malignant tumors in women worldwide. According to the WHO/IARC GLOBOCAN 2022 report, its incidence and mortality rates are ranked first among malignant tumors in women, seriously threatening women's health [1, 2]. With the updating of treatment concepts, BC treatment is gradually shifting from the traditional "tumor killing" approach to "immune modulation" [3].

Immune Checkpoint Inhibitors (ICI) have yielded noticeable therapeutic outcomes in various tumors by the means of relieving the suppression of T-cell activity resulted from tumors [4, 5]. However, the low immunogenicity of the immune

microenvironment in BC, especially in subtypes (hormone receptor-positive ones), has resulted in the limitation of using ICI alone [6]. The CTLA-4 inhibitor ipilimumab has offered the possibility for targeted combination treatment [7,8]. The systemic immune outcomes of these drugs in BC have lacked sufficient exploration [9]. Specifically, it hasn't reached a conclusion on whether CTLA-4 inhibition can effectively enhance the humoral immune response in BC patients and the relationship between this change and the overall condition of the patients.

Currently, the efficacy of immunotherapy for BC is mostly assessed through "tumor-centered" indicators such as tumor response rate and progression-free survival, with little attention paid to the dynamic changes in humoral immune components such as immunoglobulins (IgG, IgA, IgM). Changes in immunoglobulin levels may reflect the state of immune activation or related adverse effects [9, 10]. In addition, chemotherapy often results in physical and nutritional impairments in patients, and the impact of CTLA-4 inhibitors on the general condition of patients (such as weight) also needs to be clarified.

In summary, although the combination of CTLA-4 inhibitors and chemotherapy has been initially applied in BC, most existing studies have focused on tumor response and cellular immunity, while the systemic changes in humoral immunity and their relationship with patient function, nutrition and QoL have not been systematically explored. Therefore, this study hypothesizes that the combination treatment can significantly increase immunoglobulin levels and improve the performance status and QoL of patients. It innovatively evaluates the impact of the combination treatment on humoral immunity levels and analyzes the internal links between immunoglobulin changes and performance status, nutritional status and QoL, providing new evidence for the individualized monitoring of BC immunotherapy in the form of "immune-organism integration".

The introduction section of this study first elaborated on the background, necessity, and innovation of the study. The current progress and deficiencies were then sorted out through a review of relevant studies. The design and implementation process of the treatment plan were subsequently detailed. The evaluation methods and results analysis were the focus, including the general condition of patients, immunoglobulin levels, QoL, safety, and differences in responses among different molecular subtypes. Finally, the study conclusions were summarized and future directions were anticipated.

Related Studies

With the in-depth application of immunotherapy, CTLA-4 inhibitors, as the first generation of ICI, have shown potential in various solid tumors [11]. A meta-analysis covering 7,056 patients demonstrated that the combination of PD-1 and CTLA-4 significantly prolonged progression-free survival and overall survival compared with monotherapy [12], but it also increased high-grade immune-related Adverse Events (irAEs), indicating the need to balance efficacy and toxicity [13]. In the field of BC, the application of immune phenotyping, Tumor-Infiltrating Lymphocytes (TILs) assessment, and combination treatment strategies in recent years has gradually drawn attention to the potential of CTLA-4 inhibitors. Studies have attempted to combine CTLA-4 antibodies with PD-1/PD-L1 inhibitors or chemotherapy in metastatic and neoadjuvant treatments and observed enhanced immunogenicity and clinical benefits for some patients. For example, in a multicenter phase II clinical trial in 2023, the anti-PD-L1/CTLA-4 bispecific antibody KN046 combined with paclitaxel achieved an objective response rate of 44.0% and a median progression-free survival of 7.33 months in patients with metastatic triple-negative BC, showing good efficacy and tolerability [14]. However, most studies have small sample sizes and short follow-up periods, and the clinical evidence is still limited. On the other hand, studies on the impact of CTLA-4 pathway intervention on patients' immune status have mostly focused on the cellular immune level, such as T cell subsets and cytokine profiles, with relatively limited systematic research on humoral immunity. Animal experiments suggest that the CTLA-4 signal can affect B cell immunoglobulin secretion and isotype switching, involving the regulation of pathways such as NF-κB and STAT6 [15] in addition, it has been found that CTLA-4 is also expressed in B cells and can affect immunoglobulin production by regulating T-B cell interactions [16]. Meanwhile, methodological advances, such as [17] using a classification model based on transfer learning to predict the clinical outcomes of BC, [18] exploring the molecular activity and metabolic regulation of plant extracts, and Nuruzzaman [19] optimizing cancer imaging assessment and tissue segmentation with the ResECA-U-Net model, provide references for future prediction of the efficacy of CTLA-4 inhibitors based on multimodal data (clinical, imaging, and immunological indicators) and offer possibilities for the design of personalized immunotherapy strategies incorporating humoral immune indicators. Therefore, there is an urgent need to conduct clinical studies at the population level to systematically evaluate the impact of the combination of CTLA-4 inhibitors and chemotherapy on immunoglobulins (IgG, IgA, IgM) and humoral immune function in BC patients, so as to more comprehensively reveal the systemic effects of immunotherapy and provide a basis for efficacy prediction and adverse reaction management.

Materials and Methods

Study Design

The study was a prospective, randomized, single-blind, controlled clinical trial. The study protocol was reviewed and approved by the Ethics Committee of Zhejiang University-University of Edinburgh Institute (approval number: ER2421). The trial was conducted in strict accordance with the *Declaration of Helsinki* and the Good Clinical Practice (GCP). Written informed consent was obtained from all participants before enrollment. The overall plan and implementation process of the study are illustrated in Figure 1.

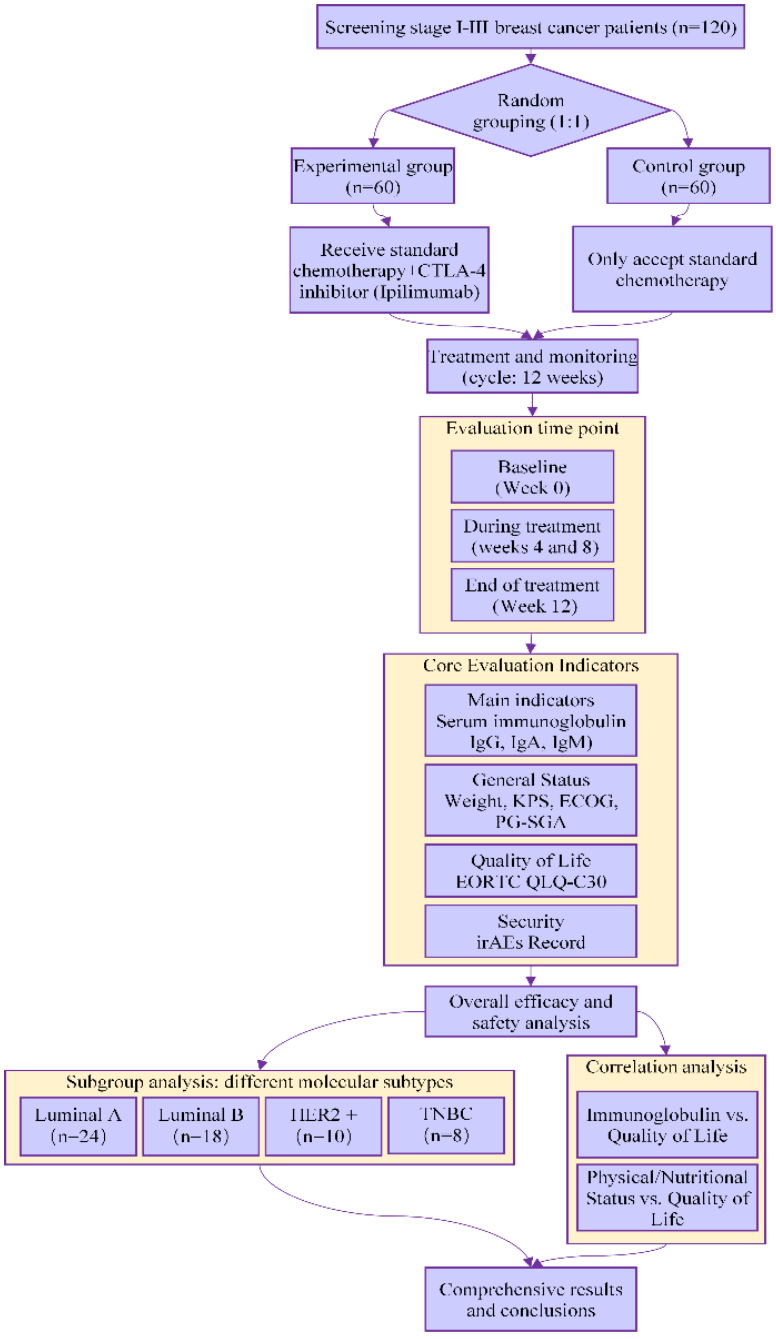

Fig. 1: Flowchart of study methods

Study Subjects and Data Collection

Study subjects: A total of 120 BC patients who met the inclusion criteria were included in this study, and all patients signed the informed consent form. The inclusion criteria included: pathologically confirmed BC, clinical stage I-III, Karnofsky Performance Status (KPS) score ≥60, and age between 18 and 75 years. The exclusion criteria included a history of prior immunotherapy, autoimmune diseases, and severe dysfunction of heart, liver, and kidney. Patients were randomly assigned to two groups at a 1:1 ratio using a random number sequence generated by computer. Allocation concealment was implemented by using sequentially numbered, opaque, sealed envelopes, which were only opened after the enrolled patients had completed all baseline assessments to reveal the group assignment. Due to the nature of the intervention (whether or not to administer an additional intravenous drug), researchers involved in treatment administration and outcome assessment (such as laboratory technicians, data analysts) were aware of the group assignment. However, to minimize assessment bias as much as possible, patients were blinded in this study (single-blind). Patients were informed that they would receive standard chemotherapy, with or without an investigational drug aimed at modulating immune function, but they were not told the specific name and nature of the additional drug. The experimental group (n = 60) adopted standard chemotherapy plus CTLA-4 inhibitor ipilimumab, and the control group (n = 60) only adopted standard chemotherapy. The treatment lasted for 12 weeks, with a 6-month follow-up.

Sample size estimation: The G*Power 3.1 software was applied. Referring to the data from the preliminary pilot study, the effect size was determined at 0.5, the significance level (α) at 0.05, and the statistical power (1-β) at 0.8. It was calculated that at least 54 patients were needed per group. Taking into account an anticipated dropout rate of about 10%, it was finally determined to include 60 patients per group, with a total of 120 patients, to ensure that the study results had sufficient statistical inference power.

Data collection: General clinical data (baseline characteristics): Basic demographic data: age (years)\BMI (kg/m²)\marital status (single/married/divorced/widowed)\education level (primary school and below/secondary school/university/graduate and above)\smoking history (yes/no), drinking history (yes/no)\menstrual status (premenopausal/postmenopausal); Disease-related data: BC molecular subtypes (Luminal A/Luminal B/HER2 positive/triple-negative BC, TNBC), clinical stage (TNM stage: stage I-IV), pathological type (invasive ductal carcinoma/invasive lobular carcinoma/other), ER, PR, HER2, Ki-67 expression status (positive/negative and specific proportion), history of previous surgery (yes/no), type of surgery (breast-conserving/modified radical/total mastectomy), whether received radiotherapy/endocrine therapy/targeted therapy.

Peripheral venous blood (4 mL) was collected at baseline (week 0), during treatment (week 4 and week 8), and at the end of treatment (week 12) to measure serum immunoglobulin levels. The KPS score, Eastern Cooperative Oncology Group (ECOG) performance status score, and Patient-Generated Subjective Global Assessment (PG-SGA) nutritional score were collected at the same time points. The EORTC QLQ-C30 score was recorded before and after treatment. IrAEs were also recorded in real-time during the study period.

Treatment Protocol Design and Implementation

A comprehensive treatment protocol was designed in this study, aiming to perform a systematical evaluation of the effects of the CTLA-4 inhibitor on the performance status and immunoglobulin levels of BC patients. Referring to patient preference and clinical eligibility, participants were assigned to undergoing either the standard chemotherapy regimen or the same standard chemotherapy plus a CTLA-4 inhibitor. The entire treatment protocol was tailored strictly in accordance with the latest clinical guidelines and individual distinctions of patients to ensure the scientific nature, safety, and individualization of the treatment. To reduce bias, the study was designed as single-blind: patients were unaware of their group assignment (experimental or control group), but researchers and the clinical care team could not be blinded as they needed to manage irAEs. All assessment indicators were collected and analyzed by an independent evaluation team who were unaware of the group assignment to minimize assessment bias.

Standard Chemotherapy Regimen

In accordance with the BC Diagnosis and Treatment Guidelines of the Chinese Anti-Cancer Association (2024 edition) [20], this study adopted a combined chemotherapy regimen containing the doxorubicin (Bayer) and paclitaxel (Shanghai Pharmaceuticals Holding Co., Ltd.). Doxorubicin was administered via intravenous infusion at a dose of 60 mg/m², with a 21-day cycle, and each 21-day period constituted one treatment course; paclitaxel was also administered intravenously at a dose of 175 mg/m², with the same frequency as doxorubicin. Some patients, based on tumor stage and performance status, chose

to replace paclitaxel with docetaxel (Roche) at a dose of 75 mg/m², with the same dosing frequency. Patients received 3 to 6 courses of chemotherapy, with the number of courses dynamically adjusted by the attending physician according to the patient's tumor response and tolerance. During chemotherapy, patients also received supportive care, including the use of granisetron (Novartis) for preventive anti-nausea and vomiting therapy, and the use of recombinant human granulocyte colony-stimulating factor (G-CSF, Sanofi) to prevent or treat chemotherapy-induced neutropenia based on white blood cell count. Blood transfusion therapy was administered as needed to ensure patient safety and Quality of Life (QoL).

CTLA-4 Inhibitor Administration

For the immunotherapy component, the CTLA-4 inhibitor ipilimumab (Merck & Co., Inc.) approved by the National Medical Products Administration was selected. The drug was administered via intravenous infusion, with an initial dose of 3 mg/kg, given every 3 weeks for a total of 4 courses. The attending physician could individually adjust the dose or dosing frequency based on the patient's clinical response and immune tolerance. The CTLA-4 inhibitor treatment was usually carried out concurrently with standard chemotherapy and could be extended if necessary. During the treatment process, the liver and kidney function, blood cell count, and immune-related indicators of patients were regularly monitored using a multi-parameter vital signs monitor (Medtronic, USA) and an automatic biochemical analyzer (Mindray, Beijing). irAEs (rash, diarrhea, etc.) were monitored. If there were moderate-to-severe adverse reactions, glucocorticoids, for example, prednisone (Eli Lilly and Company), were promptly adopted to implement immune-suppressing therapy. In severe cases, suspending the use of the CTLA-4 inhibitor ensured patient safety.

Combination Treatment Management

This study established a systematic management process. Before treatment started, all patients received comprehensive clinical assessments: medical history, physical examination, chest and abdominal CT scans (dual-energy CT device, Siemens Healthcare), bone scans, and immune function tests. Immunoglobulins IgG, IgA, and IgM were detected, and T-cell subset was analyzed (flow cytometer, Beckman Coulter). During treatment, regular vital signs were monitored, laboratory tests were carried out, and particular attention should be paid to the dynamic changes in immunoglobulins. An automatic immunoassay analyzer (Roche) was applied. When irAEs occurred, it was necessary to take intervention measures (glucocorticoid therapy and drug suspension or plan adjustment). Moreover, it should implement a systematic patient education program: introducing the treatment plan, identifying and responding to adverse reactions, and guiding healthy living). The program was executed by a professional nursing team, and its objective was to ameliorate patient treatment compliance and QoL. The combination intervention plan obtained the approval from the hospital's ethics committee for guaranteeing the scientific nature, ethical compliance, and protection of patient rights.

Evaluation Indicators and Detection Methods

Performance Status Assessment

Body weight, KPS score, ECOG score, and PG-SGA nutritional score were used to comprehensively reflect the patients' daily function, living ability, and nutritional status. The KPS score was used to assess the patients' daily function and performance status, with a range from 0 (death) to 100 (no symptoms, completely normal), and a higher score indicating better health status [22]. The ECOG score was used to assess the patients' performance status, with a range from 0 to 5, and a higher score indicating worse performance status [22]. The PG-SGA score [23] was used to assess the patients' nutritional status, which includes the patient-reported part (Part A), the clinical assessment part (Part B), and the disease and metabolic requirements parts (Parts C and D). The total score was obtained by summing the scores of all parts of the PG-SGA score. A higher score indicates worse nutritional status, with a score ≥9 indicating severe malnutrition.

Immunoglobulin Detection

Serum IgG, IgA, and IgM were detected by Enzyme-Linked Immunosorbent Assay (ELISA), the kits were from Shanghai Meilian Technology Co., Ltd., and an automatic microplate reader (Mindray, Beijing) was adopted. The detection strictly complied with the quality control procedures, which could ensure the accuracy and reliability of the data.

QoL Assessment

The internationally recognized EORTC QLQ-C30 questionnaire was adopted for assessing the QoL of cancer patients. It comprises 30 items involving five functional dimensions (physical function, role function, cognitive function, emotional function, and social function), three symptom dimensions (fatigue, nausea and vomiting, pain), six single-item measurement items,

and one overall QoL scale. The raw data of each item were converted into a score (0 to 100), and a higher score means superior QoL.

Safety Assessment

During treatment and follow-up, standardized monitoring of adverse events was sustained, particularly focusing on irAEs and detailed recording their types and severity. The clinical safety monitoring team periodically reviewed all adverse event information and compared the incidence and grading distribution of adverse events among the subjects via statistical analysis.

Statistical Analysis Methods

Statistical analysis was performed using SPSS 26.0 statistical software (IBM Corp., Armonk, NY, USA). Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm SD$). An independent samples t-test was employed for intergroup comparisons, while a repeated-measures ANOVA was applied to analyze intragroup data with multiple measurements. Count data were presented as frequencies and percentages, and intergroup comparisons were made using χ^2 test or Fisher's exact probability method. The correlation between variables was analyzed using Pearson correlation coefficient. All tests were two-sided, with a significance level set at $P < 0.05$.

Study Results

Comparison of General Clinical Data of Subjects

A total of 120 BC patients were included, with 60 in the experimental group and 60 in the control group. There were no statistically significant differences between the two groups in terms of age (52.8 ± 8.3 years vs 53.4 ± 7.9 years), BMI (23.7 ± 3.2 kg/m² vs 23.1 ± 3.4 kg/m²), marital status, education level, smoking and drinking history, menopausal status, BC molecular subtypes, TNM clinical stage, pathological type, hormone receptor (ER, PR) status, HER2, Ki-67 expression status, history of previous treatment, and whether they had received targeted therapy/radiotherapy/endocrine therapy ($P > 0.05$), indicating good baseline comparability (Table 1).

Table 1: Comparison of baseline clinical data of patients

Item	Experimental group (n = 60)	Control group (n = 60)	Statistic	*P*
Age (years)	52.8 ± 8.3	53.4 ± 7.9	$t = 0.402$	0.688
BMI (kg/m²)	23.7 ± 3.2	23.1 ± 3.4	$t = 0.992$	0.323
Marital status			$\chi^2 = 0.211$	0.976
Unmarried	5 (8.3%)	4 (6.7%)		
Married	48 (80.0%)	50 (83.3%)		
Divorced	4 (6.7%)	3 (5.0%)		
Widowed	3 (5.0%)	3 (5.0%)		
Educational level			$\chi^2 = 0.348$	0.951
Primary school or below	7 (11.7%)	9 (15.0%)		
Secondary school	20 (33.3%)	18 (30.0%)		
University	25 (41.7%)	24 (40.0%)		
Postgraduate or above	8 (13.3%)	9 (15.0%)		
Smoking history	4 (6.7%)	3 (5.0%)	FET	0.500
Alcohol consumption history	6 (10.0%)	5 (8.3%)	FET	0.500
Menstrual status			$\chi^2 = 0.034$	0.854
Premenopausal	27 (45.0%)	28 (46.7%)		
Postmenopausal	33 (55.0%)	32 (53.3%)		
Molecular subtype			$\chi^2 = 0.373$	0.946
Luminal A	24 (40.0%)	22 (36.7%)		

Luminal B	18 (30.0%)	20 (33.3%)		
HER2 positive	10 (16.7%)	11 (18.3%)		
TNBC	8 (13.3%)	7 (11.7%)		
Clinical stage			$\chi^2 = 0.036$	0.850
Stage Ⅱ	26 (43.3%)	27 (45.0%)		
Stage Ⅲ	34 (56.7%)	33 (55.0%)		
Histological type			$\chi^2 = 0.208$	0.901
Invasive ductal carcinoma	50 (83.3%)	51 (85.0%)		
Invasive lobular carcinoma	6 (10.0%)	5 (8.3%)		
Others	4 (6.7%)	4 (6.7%)		
ER positive	47 (78.3%)	45 (75.0%)	$\chi^2 = 0.194$	0.660
PR positive	41 (68.3%)	43 (71.7%)	$\chi^2 = 0.164$	0.685
Ki-67 >14%	36 (60.0%)	38 (63.3%)	$\chi^2 = 0.149$	0.700
Previous surgical history	48 (80.0%)	49 (81.7%)	$\chi^2 = 0.053$	0.818
Type of surgery			$\chi^2 = 0.086$	0.958
Breast-conserving surgery	20 (33.3%)	21 (35.0%)		
Modified radical mastectomy	25 (41.7%)	24 (40.0%)		
Total mastectomy	15 (25.0%)	15 (25.0%)		
Previous treatment history				
Radiotherapy	12 (20.0%)	13 (21.7%)	$\chi^2 = 0.053$	0.818
Endocrine therapy	35 (58.3%)	33 (55.0%)	$\chi^2 = 0.144$	0.704
Targeted therapy	29 (48.3%)	28 (46.7%)	$\chi^2 = 0.034$	0.854

Simulation Experiment on Immune Improvement in BC Patients Based on ICI Combined With Standard Chemotherapy

To evaluate the immunomodulatory effects of ICI combined with chemotherapy on patients with BC, the levels of serum immunoglobulins (IgG, IgA, IgM) in patients receiving combined intervention and those receiving chemotherapy alone were dynamically monitored during the treatment period (at weeks 0, 4, 8, and 12). The patients' performance status (KPS, ECOG score), nutritional status (PG-SGA score), and changes in body weight were also comprehensively analyzed. The baseline characteristics of the participants were balanced and comparable ($P > 0.05$).

After 12 weeks of treatment, the serum levels of IgG, IgA, and IgM in the experimental group were significantly higher (vs. baseline, $P < 0.01$; vs. the controls). Among them, the increase in IgG was the most significant ($\Delta IgG \approx +23.4\%$, $P < 0.001$). Participants receiving combined intervention showed a trend of immune reconstitution from week 8 (Fig. 2).

Regarding changes in performance status and nutritional indicators, the KPS of the experimental group was significantly higher at the end of treatment (85.3 ± 6.2 vs. 78.7 ± 7.4 in the controls, $P < 0.01$), and the ECOG score decreased more significantly from baseline ($P < 0.05$). In terms of nutrition, the PG-SGA score of the experimental group decreased more markedly, with a lower incidence of severe malnutrition (PG-SGA ≥ 9) compared to the controls ($P < 0.01$). The experimental group experienced an average weight gain of 1.6 ± 1.2 kg, while the controls had an average weight loss of 0.8 ± 1.0 kg ($P < 0.01$). The trends in changes of performance status and nutritional indicators are illustrated in Fig. 3.

Analysis of EORTC QLQ-C30 Scores of Subjects

The EORTC QLQ-C30 scale was employed. Following treatment, the experimental group exhibited significant improvements in the scores of physical function, emotional function, and social function dimensions, with all dimension scores exceeding those of the controls (all $P < 0.01$). Regarding the symptom dimensions, the experimental group experienced significant reductions in fatigue, pain, and nausea/vomiting scores compared to baseline, indicating a marked decrease in symptom burden compared to chemotherapy alone and a more pronounced improvement in QoL (Fig. 4).

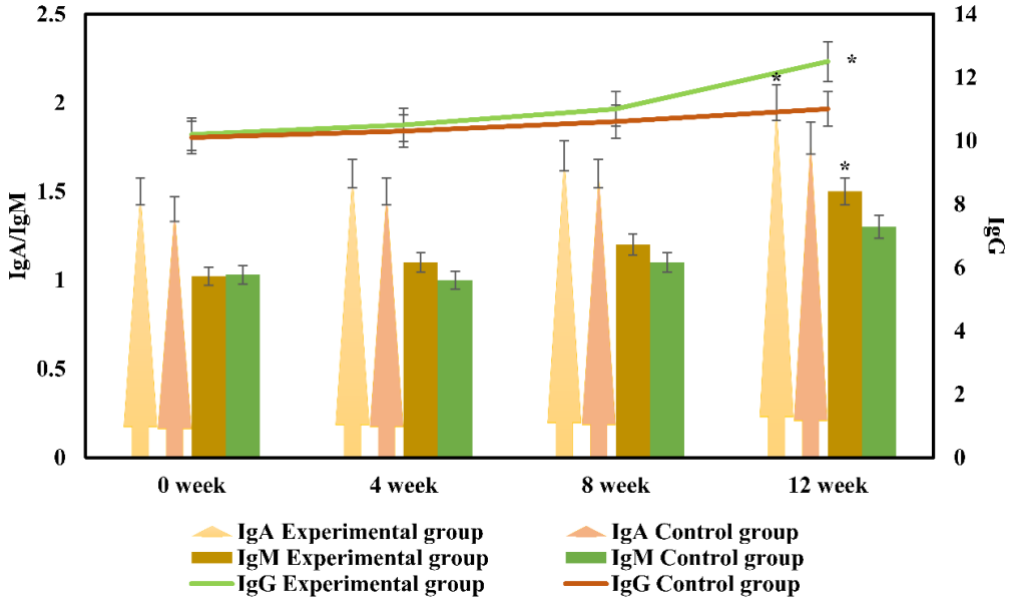

Fig. 2: Trends in serum IgG, IgA, and IgM levels of subjects at different time points ("*": *P* < 0.05 as against the control group)

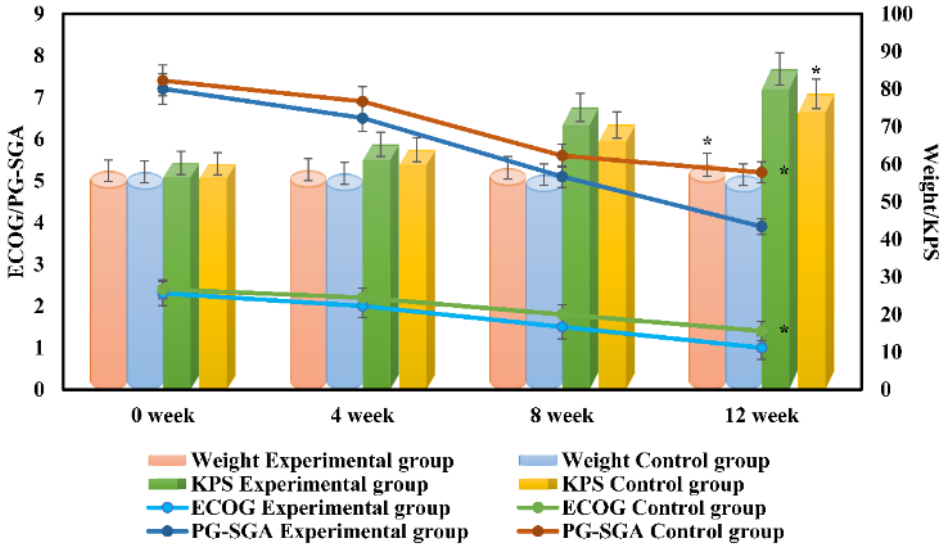

Fig. 3: Effects of different treatment modalities on KPS score, ECOG score, PG-SGA score, and body weight changes ("*": *P* < 0.05 as against the control group)

Correlation Analysis Between Performance Status, Immunoglobulin Levels, and Qlq-C30 Scores

Partial correlation analysis (controlling for confounding factors such as age, baseline immune status, and previous treatment history) revealed that at the end of treatment, patients' serum immunoglobulin levels were significantly positively correlated with QoL (QLQ-C30 total score): IgG (r = 0.52, P < 0.001), IgA (0.45, < 0.001), and IgM (0.38, < 0.01).

KPS score (r = 0.59) and changes in body weight (0.48) were positively correlated with the QLQ-C30 total score; whereas ECOG score (-0.55) and PG-SGA nutritional score (-0.62) were negatively correlated with the QLQ-C30 total score (P < 0.001).

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Correlation heatmap analysis further showed that immunoglobulin indicators (especially IgG) clustered with positive physical indicators such as KPS and body weight and were positively correlated with the QLQ-C30; ECOG and PG-SGA clustered into another category and were negatively correlated with the QLQ-C30 (Fig. 5).

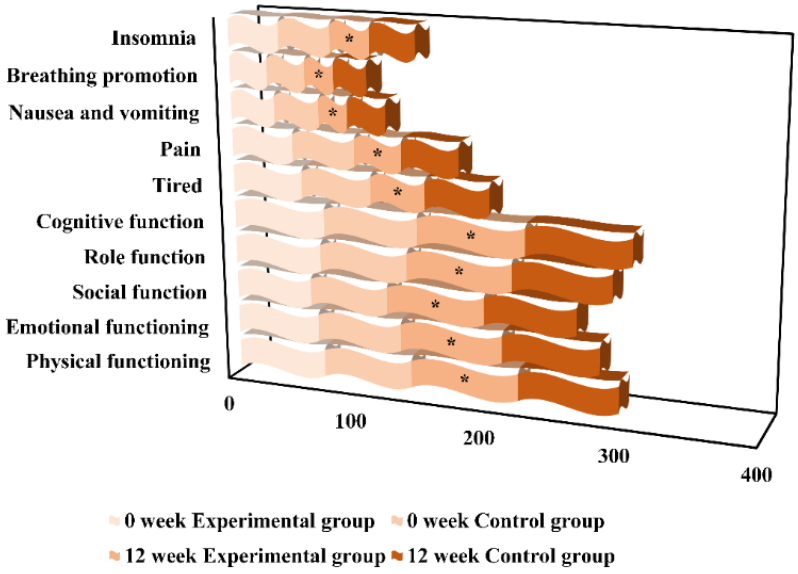

Fig. 4: Changes in function and symptom dimensions of the EORTC QLQ-C30 questionnaire of subjects ("*": *P* < 0.05 as against the control group)

Fig. 5: Pearson correlation heatmap of QLQ-C30 scores with IgG, IgA, IgM, KPS score, ECOG score, PG-SGA score, and body weight

Safety and Adverse Reaction Analysis

During the entire treatment and follow-up period, a total of 52 irAEs were recorded, with 38 cases (63.3%) occurring in the experimental group and 14 cases (23.3%) in the controls (P < 0.01). The incidence of rash (26.7% vs. 8.3%), fatigue (21.7% vs. 6.7%), gastrointestinal reactions (20.0% vs. 5.0%) (all P < 0.01), and elevated transaminases (16.7% vs. 3.3%, P < 0.05) were significantly higher in the experimental group relative to the controls. The majority of irAEs were mild to moderate (CTCAE v5.0 grade 1-2), and the proportion of grade 1-2 irAEs in the experimental group (58.3% vs. 21.7% in the controls)

was significantly higher (P < 0.01). The overall incidence of serious adverse events (≥grade 3) was low, at 5.0% and 1.7%, respectively. Although the incidence of ≥grade 3 irAEs was numerically higher in the experimental group, the inter-group difference was not statistically significant (P = 0.37) (Fig. 6).

Changes in Performance Status and Immunoglobulin Levels in Different bc Subtypes

To further explore the effects of the combination immunotherapy regimen (chemotherapy + ipilimumab) on BC patients with different molecular subtypes, a subgroup analysis was conducted for the experimental group (n = 60) in this study. The subgroups included Luminal A type (n = 24), Luminal B type (n = 18), HER2-overexpressing type (n = 10), and TNBC (n = 8). The body weight, KPS score, ECOG score, PG-SGA nutritional score, and serum immunoglobulin (IgG, IgA, IgM) levels of each group were assessed at weeks 0, 4, 8, and 12 during the treatment cycle. The distinctions in performance status and immune function improvement among patients with different subtypes in response to the combined immunotherapy regimen were explored. It should be noted that in this subgroup analysis, the sample sizes of the HER2-overexpressing and TNBC subgroups were small (especially the TNBC group, n = 8), limiting the statistical power. Therefore, the following results mainly reflected the dynamic changes within each group, and the comparison of differences between groups was an exploratory finding.

Changes in Performance Status in Different BC Subtypes

The performance status indicators of patients with different BC molecular subtypes all improved during the combined treatment cycle, but the degree of improvement showed subtype-specific distinctions (Fig. 7).

Regarding changes in body weight: Individuals with the Luminal subtype showed a continuous trend of weight gain. By week 12, the average weight increase in the individuals with Luminal A and Luminal B was approximately 2.0 kg and 1.8 kg, respectively (P < 0.05). In contrast, the weight changes in the individuals with HER2 overexpression and TNBC were smaller. The individuals with TNBC maintained stable body weight without significant increase.

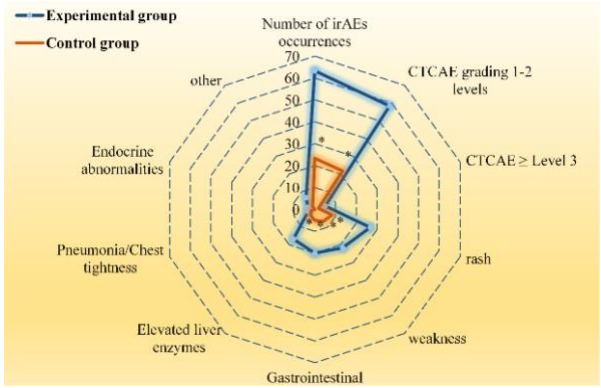

Fig. 6: Incidence and grading distribution of irAEs in subjects ("*": P < 0.05 as against the control group)

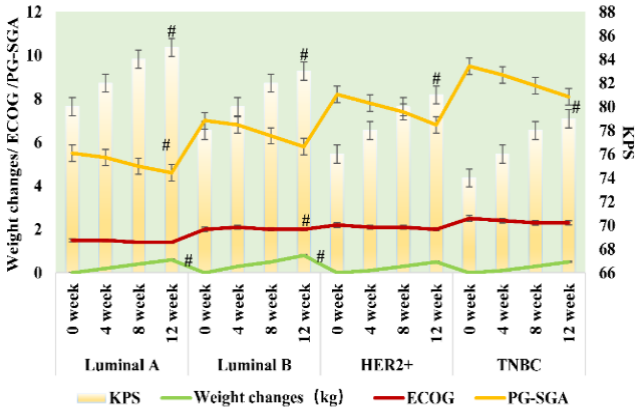

Fig. 7: Changes in performance status in subjects with different BC subtypes ("#": P < 0.05 as against 0 week)

Functional status assessment: The KPS of all subtypes of patients improved significantly with treatment ($P < 0.01$), with the most significant improvement observed in the Luminal A population (increasing from a baseline of 78.5 ± 5.2 to 87.6 ± 4.8 at week 12). The change pattern of ECOG score had the same trend, and the largest decrease occurred in the Luminal B population (average decrease of 1.2, $P < 0.01$), meaning that individuals with the Luminal subtype gained more pronounced physical functional improvements following the combined treatment. The degree of improvement in the individuals with TNBC was relatively limited ($P < 0.05$).

Nutritional status assessment: The SGA nutritional scores of all subtypes of patients decreased, indicating an improvement in nutritional status. The improvement in nutrition was most significant in the Luminal A population, with the proportion of individuals with severe malnutrition (PG-SGA ≥ 9) decreasing from 22% to 12%. The degree of nutritional improvement in individuals with TNBC was relatively limited.

Changes in Immunoglobulin Levels in Different BC Subtypes

The dynamic changes in immunoglobulins exhibited distinct subtype-specific patterns (Fig. 8), providing a new perspective for understanding the differential responses of different subtypes to ICI. Analysis of the IgG response showed that at weeks 8 and 12, in the Luminal A and Luminal B population, IgG levels were significantly higher (vs. baseline, $P < 0.01$; vs. the HER2 overexpression and TNBC population). The dynamics of IgA revealed unique subtype-specific differences. IgA levels increased in all subtypes of patients, but the increase was most significant in the Luminal B population (an average increase of 15.4%) ($P < 0.01$), while changes in the HER2 overexpression and TNBC population were not significant ($P > 0.01$), suggesting specific immune responses in different BC subtypes. The pattern of IgM changes showed that, except for individuals with TNBC, IgM levels in the other three subtypes peaked at week 8 and then remained stable.

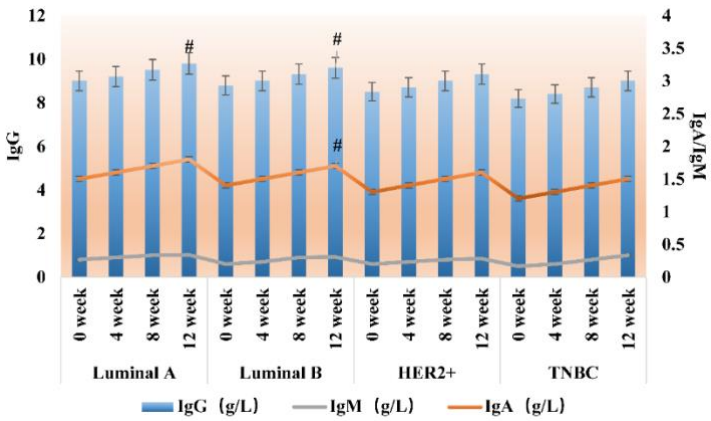

Fig. 8: Changes in immunoglobulin levels in subjects with different BC subtypes ("#": *P* < 0.05 as against 0 week)

Discussion

This study, through a prospective randomized controlled design, systematically evaluated for the first time the comprehensive impact of CTLA-4 inhibitor ipilimumab combined with standard chemotherapy on the humoral immunity, performance status, and quality of life of breast cancer patients. The main findings include that combined treatment can significantly enhance serum immunoglobulin levels (especially IgG), simultaneously improve patients' KPS scores, nutritional status, and QoL, and that these improvements vary among different molecular subtypes. The following will integrate existing literature to comprehensively interpret the deeper meaning, potential mechanisms, and clinical significance of the results of this study.

Firstly, this study found that the CTLA-4 inhibitor combined with chemotherapy can significantly promote the reconstruction of humoral immunity in BC patients, manifested by the comprehensive increase in serum IgG, IgA, and IgM levels. This finding has great innovative significance, previous studies on ICI have concentrated on cellular immune responses (T cell activation, TILs, etc.), and less attention was paid to the impact on systemic humoral immunity. The most noticeable elevation observed in IgG levels suggested that CTLA-4 blockade may enhance B cell activation, class switching, and antibody secretion through regulating T cell function, especially enhancing the activity of follicular helper T cells [15,16]. The trend of immune suppression

and decreased immunoglobulin levels often is resulted from chemotherapy alone [24], but the combined regimen presents a unique immune-protective and enhancing effect. It indicates that CTLA-4 inhibitors may partially reverse chemotherapy-related immune suppression and help restore immune homeostasis. The improvement in KPS and ECOG scores in this study is similar to the trend of functional status improvement that has been reported by [14] Li et al. (2024) in the Phase II trial of KN046 plus chemotherapy for metastatic TNBC; the degree of improvement in this study is greater and covers more BC subtypes because of the broader systemic immune regulatory effects of CTLA-4 inhibitors.

Secondly, the combined treatment significantly enhanced immunoglobulin levels, and yielded synchronous improvements in patients' performance status and QoL. Correlation analysis demonstrated a noticeable positive correlation between IgG levels and the total QoL score, the nutritional risk score showing a noticeable negative correlation. It means an intrinsic link between the enhancement of humoral immune function, the improvement of nutritional status, and the subjective increase in QoL, generating a synergistic pathway of "immune function recovery-physiological status improvement-QoL enhancement" [25]. This finding breaks through the traditional "tumor shrinkage" paradigm, and converts to pointing towards a systemic "immune-organism integration" effect [6]. It also differs from studies that focus on objective efficacy endpoints [26]. There are some studies demonstrating the effects of immunotherapy on patient-reported outcomes [27-29] but this study links specific humoral immune indicators with multidimensional QoL scales. It offers a potential immunological explanation for such improvements.

The heterogeneity of treatment responses was revealed via subgroup analyses. Patients with Luminal A and Luminal B subtypes presented noticeable elevated levels of immunoglobulins (especially IgG) and ameliorated physical status relative to TNBC patients). The complex interplay between the tumor microenvironment of different subtypes and the systemic immune and metabolic status possibly results in the difference. Luminal subtype has lower immunogenicity, but its hormone receptor signaling may exert specific regulation on the immune system. In this study, there was a more pronounced increase in body weight in patients with this subtype, which aligns with the trend of weight changes after chemotherapy reported in the literature [30] and may also reflect metabolic improvement yielded by immune activation. TNBC has a more strongly immunosuppressive microenvironment, manifested as enrichment of regulatory T cells, elevated levels of immunosuppressive cytokines [31, 32] and obesity-associated chronic inflammatory states [33]. This microenvironment may limit the initial intensity of immune responses, which yields delayed and unstable humoral immune reconstitution. Mechanistically, CTLA-4 inhibitors mainly enhance T-B cell interactions, indirectly driving B cell activation and antibody secretion [15,16]. The role of B cells in tumor immunity is complex, as they can exert antitumor effects and also participate in immune regulation [34, 35]. Differences in B cell activation gene expression profiles and immunoglobulin subclass distribution among different subtypes [36] may partly explain the observed heterogeneity of IgG and IgA responses. In addition, the dynamic changes of IgM suggest the initiation of a new antibody response, with its fluctuation pattern reflecting the early process of B cell activation and class switching [37], and the larger fluctuations in the TNBC group may reveal the instability of its immune status and the ongoing tug-of-war between immune activation and suppression [3]. Therefore, the observations in this study not only provide clinical evidence for the differential responses of different molecular subtypes to CTLA-4 inhibitor combined with chemotherapy, but also provide preliminary basis and directions for in-depth exploration of future individualized immune combination strategies based on subtype characteristics and integrating systemic immune and metabolic status.

In terms of safety, as expected, the incidence of irAEs in the combination therapy group was significantly higher than that in the chemotherapy-alone group. However, the vast majority of these events were grade 1–2 and manageable, with a low incidence of severe adverse events. This safety profile is consistent with reports in the literature that CTLA-4 inhibitor combination therapy increases the risk of irAEs [13, 38]. It is worth noting that the observed incidence of irAEs was higher than the range of fatal irAE incidence reported in breast cancer immunotherapy literature (0.3%–1.3%) [39] which may be related to the prospective and systematic monitoring and recording of all-grade events in this study. Despite the risk of adverse reactions associated with immune activation, the results of this study indicate that the overall safety of combination therapy is controllable through standardized monitoring and management.

However, this study also has several limitations. First, the sample size was relatively small, and the follow-up period was short, especially with a limited number of cases in the TNBC subgroup, which restricted the statistical power and generalizability of the subgroup analysis conclusions. Second, this was a single-center study, and the results need to be validated by multicenter, large-sample studies. Third, although a correlation between changes in immunoglobulins and improvements in QoL was revealed, the exact causal relationship and molecular mechanisms between them still need to be elucidated through more in-depth basic research.

Conclusion

This study has been confirmed through a prospective randomized controlled trial that the combination of the CTLA-4 inhibitor and chemotherapy shows significant clinical value in improving humoral immune function, overall condition, and QoL, providing new theoretical and practical basis for the optimization of comprehensive BC treatment. For the first time, this study systematically reveals the positive regulatory effects of the combination of the CTLA-4 inhibitor and chemotherapy on the humoral immunity of BC in a clinical trial and proposes a mechanism model of "immune function recovery-physical improvement-reduced nutritional risk". They work together to promote the improvement of QoL, expanding the new paradigm of treatment evaluation of immune-organism integration. Despite the limited sample size and follow-up time, the small size of the TNBC subgroup, and the single-center design of the study, the results still provide a basis for subsequent multicenter validation. In the future, its long-term survival benefits should be assessed in larger samples with longer follow-up duration, and the efficacy prediction model should be constructed in combination with multimodal data to achieve more precise personalized immunotherapy.

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Author's Contributions

Lie Yang and Rundong Qin: Designed the experiment, collated the data, and prepared the paper.

Jiahuan Liu and Dongmei Ma: Performed the experiment, analyzed the data, and wrote the paper.

Lingyu Li and Bin Yang: Participated in the experiment, collated the paper and revised the manuscript.

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