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ORIGINAL RESEARCH

Thymosin α1 Combined with PD-1/PD-L1 Inhibitor Plus Chemotherapy in Platinum-Resistant Recurrent Ovarian Cancer : A Retrospective Analysis

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Background: Platinum-resistant recurrent ovarian cancer remains a major therapeutic challenge. Immune checkpoint inhibitors (ICIs) combined with chemotherapy are widely used, but clinical benefits remain limited. Thymosin α1 (Tα1), an immunomodulatory peptide, may synergize with ICIs to enhance anti-tumor immunity.

Methods: This retrospective study included 386 patients with PROC, with 193 patients receiving Tα1 combined with PD-1/PD-L1 inhibitors and chemotherapy (experimental group), and 193 patients receiving PD-1/PD-L1 inhibitors and chemotherapy alone (control group). Baseline clinical characteristics, clinical efficacy, immune parameters, progression-free survival (PFS), and adverse events were compared between the two groups. Kaplan–Meier survival analysis and multivariate Cox proportional hazards regression were used to assess PFS and associated prognostic factors. Continuous and categorical variables were compared using *t*-test and χ^2-test, respectively. Statistical significance was defined as $p < 0.05$.

Results: Baseline characteristics were comparable between the two groups. The experimental group showed significantly higher objective response rate (43% vs 30.2%; $p = 0.008$) and disease control rate (87% vs 69.8%; $p = 0.000$). The median PFS was significantly longer in the experimental group (3.0 vs 1.1 months; HR = 3.22, 95% CI: 2.59–4.01; $p = 0.000$). Post-treatment, patients in the experimental group demonstrated significantly elevated levels of IgA, IgG, IgM, $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ ratio, and NK cells compared to the control group (all $p < 0.01$), while CD8 levels remained similar. The incidence of adverse events was lower in the experimental group (50.8% vs 65.8%; $\chi^2 = 8.35$, $p = 0.004$), primarily due to a reduced rate of myelosuppression.

Conclusion: The addition of Tα1 to PD-1/PD-L1 inhibitor-based chemotherapy may enhance treatment efficacy, improve immune response, and reduce immunosuppression-related toxicity in patients with platinum-resistant recurrent ovarian cancer.

Keywords: thymosin α1, PD1/PD-L1 inhibitors, immunotherapy, T lymphocyte subsets, platinum-resistant ovarian cancer

Introduction

Ovarian cancer remains one of the deadliest gynecologic malignancies, with epithelial ovarian carcinoma accounting for the majority of cases.[1] Although platinum-based chemotherapy initially shows effectiveness, many patients relapse and develop platinum-resistant recurrent ovarian cancer (PROC), which is associated with poor prognosis and limited treatment options.[2,3]

Immune checkpoint inhibitors (ICIs), especially PD-1/PD-L1 blockers, have shown potential in treating PROC when combined with chemotherapy, achieving disease control rates of around 65–70%.[4,5] However, progression-free survival (PFS) remains short, often less than three months, partly due to chemotherapy-induced immunosuppression limiting immune activation.[6] Therefore, novel adjunct therapies are urgently needed to enhance and sustain antitumor immunity. Thymosin α1 (Tα1), a well-characterized immunomodulatory peptide, represents a promising candidate for strengthening the efficacy of ICI-based regimens in PROC.

Tα1 is an endogenous thymic peptide with well-established immunomodulatory functions, including the promotion of T-cell maturation, activation of cytotoxic $CD8^+$ T lymphocytes, and enhancement of natural killer (NK) cell cytotoxicity.[7] Additionally, Tα1 modulates the tumor microenvironment by attenuating immunosuppressive cell populations, such as

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regulatory T cells and myeloid-derived suppressor cells, thereby facilitating antitumor immune responses.[8] Importantly, several clinical studies in solid tumors, such as non-small cell lung cancer and hepatocellular carcinoma, has demonstrated that Tα1 can potentiate the efficacy of ICIs, resulting in improved response rates and prolonged survival.[9,10] Beyond its immunostimulatory capacity, Tα1 has been shown to alleviate chemotherapy-induced immunosuppression and reduce hematologic toxicities, such as neutropenia and leukopenia, thereby improving both immune reconstitution and treatment tolerance.[11,12] Recent preclinical and clinical evidence further indicates that Tα1 may enhance the efficacy of ICIs when combined with chemotherapy by promoting dendritic cell maturation, enhancing antigen presentation, and creating a more favorable immune microenvironment for antitumor responses.[13,14] This dual role—enhancing immune responsiveness while mitigating treatment-related toxicity—suggests that the combination of Tα1, ICIs, and chemotherapy could achieve superior and more durable clinical benefits than conventional regimens.

Although no large-scale clinical studies have yet evaluated Tα1 in gynecologic malignancies, emerging evidence from other solid tumors supports its capacity to enhance immune reconstitution and therapeutic efficacy, reinforcing its potential as an adjuvant to ICI-based chemotherapy in ovarian cancer.[15] Considering the limited PFS and substantial adverse events associated with ICI-based chemotherapy in PROC, combining Tα1 with ICIs and chemotherapy may offer a synergistic therapeutic strategy that enhances antitumor immunity while improving treatment tolerance.

To address this gap, we conducted a retrospective study to evaluate the efficacy and safety of adding Tα1 to PD-1/PD-L1 inhibitors plus chemotherapy in patients with PROC. We aimed to assess not only clinical outcomes but also changes in immune function and the incidence of treatment-related adverse events. This study may provide evidence for a promising immunochemotherapy combination that improves both efficacy and tolerability in this challenging patient population.

Materials and Methods

Study Design and Patients

This was a multi-center, retrospective, observational cohort study. Patients diagnosed with platinum-resistant recurrent ovarian serous carcinoma between January 2023 and December 2024 were included from Neijiang Maternal and Child Health Hospital and The Second People's Hospital of Neijiang. Patients were divided into two groups: Experimental group received T α1 + PD-1/PD-L1 inhibitor + chemotherapy; Control group received PD-1/PD-L1 inhibitor + chemotherapy. Patients were included if they had at least one measurable lesion per RECIST v1.1,[16] an ECOG performance status of 0–1, and complete immune marker data (IgA, IgG, IgM, $CD3^+$, $CD4^+$, $CD8^+$ T cells, NK cell) before and after treatment. This study has been approved by the Academic Ethics Committee of the Second People's Hospital of Neijiang (No. 2024RP-806-05).

Treatment Schedule

Tα1 was administered via subcutaneous injection at a dose of 1.6 mg, three times per week. PD-1/PD-L1 inhibitors, such as Tislelizumab or Sintilimab, were given intravenously at 200 mg every three weeks. Second-line single-agent chemotherapy was administered in accordance with NCCN guidelines, with agents including topotecan, docetaxel, gemcitabine, and liposomal doxorubicin.[17] Treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal. Patients were followed up every 4 weeks with clinical assessments and imaging studies, and the follow-up period continued until disease progression, unacceptable toxicity, or patient withdrawal.

Endpoints and Assessments

The primary endpoints were objective response rate (ORR), disease control rate (DCR), and PFS. Secondary endpoints included safety, assessed using the Common Terminology Criteria for Adverse Events version 5.0. Immunological endpoints comprised serum IgA, IgG, IgM levels and lymphocyte subsets ($CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ ratio). Peripheral blood samples were collected within one week before treatment and at 4–6 weeks after initiation. Lymphocyte profiling was performed by flow cytometry. Serum immunoglobulin levels were quantified using an immunoturbidimetric assay (Beckman Coulter AU5800 Analyzer, USA). Lymphocyte subsets were analyzed by flow cytometry (BD FACSCanto II, USA) using fluorochrome- conjugated monoclonal antibodies following the manufacturer's instructions.

Statistical Analysis

All statistical analyses were conducted using SPSS version 26.0. Continuous variables were presented as mean ± standard deviation. Normality of continuous variables was assessed using the Shapiro–Wilk test. Parametric data were compared using Student's *t*-test, while non-parametric data were analyzed using the Mann–Whitney *U*-test. Categorical variables were compared using the chi-square or Fisher's exact test. For immune parameters, multiple comparisons were corrected using the Bonferroni method to reduce the risk of type I error. Confidence intervals for proportions (ORR and DCR) were calculated using the Wilson score method with continuity correction (95% CI). Survival outcomes were estimated using the Kaplan–Meier method and compared with the Log rank test. Median PFS (with 95% confidence intervals) is reported throughout the manuscript. Changes in immunological markers before and after treatment were assessed both within and between groups. A two-sided p-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 386 patients were included, with 193 patients in both the experimental and control groups. Baseline clinical and demographic characteristics were well balanced between the two groups, with no significant differences in age, performance status, disease stage, or prior treatments. Patient characteristics are summarized in Table 1.

Clinical Efficacy

The ORR in the experimental group was 43.0% (95% CI, 36.0–50.0%), while the DCR was 87.0% (95% CI, 82.3–91.7%). In comparison, the control group exhibited an ORR of 30.1% (95% CI, 23.6–36.6%) and a DCR of 69.9% (95% CI, 63.5–76.5%). These differences between the two groups were statistically significant ($p < 0.05$) (Table 2), indicating that the addition of Tα1 to PD-1/PD-L1 inhibitors in combination with chemotherapy significantly enhances the efficacy of treatment for patients with recurrent platinum-resistant ovarian cancer.

Table 1 Comparison of Baseline Clinical and Demographic Characteristics Between Groups

Characteristics	Experimental Group (n=193)	Control Group (n=193)	χ^2or *t* value	*p* value
Age(year)	50.1 ± 8.8	49.9 ± 9.2	$t = 0.22$	0.83
Staging			$\chi^2 = 0.09$	0.76
FIGO III	102(52.8%)	98(50.8%)	$\chi^2 = 0.21$	0.65
FIGO IV	91(47.2%)	95(49.2%)	$\chi^2 = 0.17$	0.68
ECOG				
0	96 (49.7%)	91 (47.2%)	$\chi^2 = 0.37$	0.54
1	97 (50.3%)	102 (52.8%)	$\chi^2 = 0.26$	0.61
First-line chemotherapy				
TP	90(46.6%)	94(48.7%)		
TC	103(53.4%)	99(51.3%)	$\chi^2 = 0.166$	0.68
Ascites				
Yes	72(37.3%)	86(44.6%)	$\chi^2 = 2.14$	0.14
No	121(62.7%)	107(55.4%)	$\chi^2 = 1.57$	0.21
BRCA mutation status				
BRCA1/2 mutation	42(21.8%)	37(19.2%)	$\chi^2 = 0.47$	0.49
BRCA1/2 wild-type	64(33.2%)	75(38.9%)	$\chi^2 = 1.54$	0.22
Undetermined genetic status	87(45.0%)	81(41.9%)	$\chi^2 = 0.56$	0.45
Chemotherapy agents				
Liposomal doxorubicin	74(38.3%)	80(41.5%)	$\chi^2 = 0.57$	0.45
Docetaxel	44(22.8%)	52(26.9%)	$\chi^2 = 0.86$	0.35
Gemcitabine	37(19.2%)	41(21.2%)	$\chi^2 = 0.27$	0.60
Toptecan	38(19.7%)	20(10.4%)	$\chi^2 = 6.19$	0.01

Abbreviations: TP, Paclitaxel + Cisplatin; TC, Paclitaxel + Carboplatin.

Table 2 Comparison of Treatment Efficacy and Survival Between Experimental and Control Groups

Group	N	CR (n)	PR (n)	SD (n)	PD (n)	ORR,% (95% CI)	DCR,% (95% CI)	Median PFS (months,95% CI)	3-month PFS rate (%)	6-month PFS rate (%)
Experimental	193	18	65	85	25	43.0(36.0–50.0)	87.0(82.3–91.7)	3.0(2.67–3.33)	49.2	2.1
Control	193	11	47	77	58	30.1(23.6–36.6)	69.9(63.5–76.5)	1.1(0.95–1.25)	11.9	0
χ^2 value						6.90	18.24	HR=3.22	66.27	1.96
p value						0.009	<0.001	<0.001	<0.001	0.162

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; CI, confidence intervals; PFS, progression-free survival.

Among patients who achieved disease control, 168 were in the experimental group and 135 in the control group. The 3-month PFS rates were 49.2% vs 11.9%, and the 6-month PFS rates were 2.1% vs 0% (all $p < 0.001$), respectively. The median PFS was 3 months (95% CI, 2.67–3.33) in the experimental group and 1.1 months (95% CI, 0.95–1.25) in the control group. This difference was statistically significant (HR = 3.22, 95% CI: 2.59–4.01, $p < 0.001$), indicating a substantial PFS benefit with the addition of Tα1 (Figure 1 and Table 2).

Changes in Immune Parameters

At baseline, there were no statistically significant differences in the levels of IgA, IgG, IgM, CD3, CD4, CD8, CD4/CD8 ratio, or NK cell counts between patients in the experimental group receiving Tα1 and those in the control group ($p > 0.05$). Following treatment, the experimental group exhibited significantly higher levels of IgA, IgG, IgM, CD3, CD4, CD4/CD8 ratio, and NK cells compared to the control group ($p < 0.01$), while CD8 levels remained comparable between groups (Table 3). After Bonferroni correction for multiple comparisons, the statistical significance of the observed differences remained unchanged. These findings indicate that Tα1 significantly enhances immune function in ovarian cancer patients undergoing immunochemotherapy.

Adverse Events

The primary adverse events observed in both groups included leukopenia, nausea, vomiting, and fever. A total of 98 patients in the experimental group and 127 patients in the control group experienced adverse events, with the difference reaching statistical significance ($\chi^2 = 8.35$, $p < 0.05$). This difference was mainly attributable to a higher incidence of

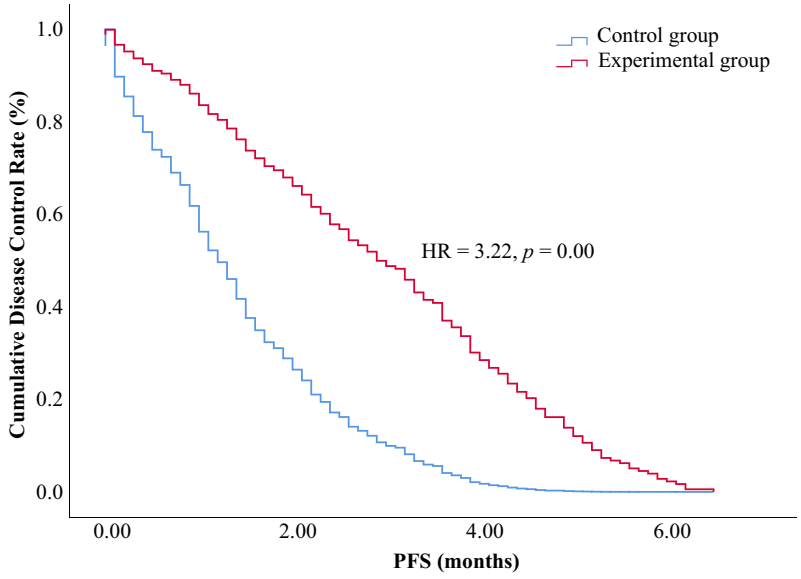

Figure 1 Kaplan-Meier curve for PFS in the experimental and control group.

Table 3 Pre- and Post-Treatment Comparison of Serum IgA, IgG, and IgM Levels in Two Groups of Patients with Ovarian Cancer (Mean ± SD)

Parameters	Pre-Treatment				Post-Treatment			
	Experimental	Control	U	*p*	Experimental	Control	U	*p*
N	193	193	-	-	193	193	-	-
IgA (g/L)	2.08±0.17	2.10±0.18	1.11	0.27	2.52±0.21	2.12±0.19	20.04	<0.001
IgG (g/L)	9.49±0.45	9.50±0.45	0.25	0.81	10.02±0.46	9.60±0.41	9.48	<0.001
IgM (g/L)	1.03±0.54	1.02±0.52	0.03	0.98	1.37±0.76	1.075±0.60	4.25	<0.001
$CD3^+$ (%)	56.12±4.87	56.97±5.40	1.62	0.11	61.59±5.37	55.51±4.70	7.74	<0.001
$CD4^+$ (%)	29.61±5.10	30.25±5.01	1.25	0.21	50.59±5.62	32.79±5.30	27.55	<0.001
$CD8^+$ (%)	23.82±4.75	24.38±4.67	1.16	0.25	24.95±4.52	24.59±4.33	0.81	0.42
$CD4^+/CD8^+$	1.30±0.38	1.28±0.34	0.58	0.56	4.20±0.90	1.13±0.31	45.06	<0.001
NK cell (%)	12.27±4.36	11.86±4.01	0.96	0.34	14.81±4.59	12.73±3.91	4.78	<0.001

Notes: Data are presented as mean ± SD. P-values were calculated using the Mann–Whitney *U*-test. Bonferroni correction was applied for multiple comparisons.

Table 4 Comparison of Treatment-Related Adverse Events Between the Experimental and Control Groups

AEs	Experimental (n, %)	Control (n, %)	χ^2	*p*
Leukopenia	54 (27.98%)	94 (48.78%)	17.67	0.00
Neutropenia	36 (18.65%)	73 (37.64%)	17.51	0.00
Thrombocytopenia	33 (17.10%)	29 (15.00%)	0.34	0.56
Anemia	56 (29.02%)	63 (32.5%)	0.45	0.50
Nausea	47 (24.35%)	53 (27.50%)	0.39	0.53
Vomiting	29 (15.03%)	34 (17.50%)	0.46	0.50
Diarrhea	31 (16.06%)	29 (15.00%)	0.13	0.72
Anorexia	45 (23.32%)	39 (20.45%)	0.75	0.39
Fever	16 (8.29%)	28 (14.29%)	4.08	0.04
Rash	26 (13.47%)	24 (12.5%)	0.11	0.74
Liver enzyme elevation	19 (9.84%)	21 (11.11%)	0.11	0.74
Fatigue	59 (30.57%)	74 (38.10%)	3.43	0.06
Total	98 (50.78%)	127 (65.80%)	8.35	0.00

bone marrow suppression, such as leukopenia and neutropenia, in the control group (Table 4). These results suggested that the addition of Tα1 may help mitigate the risk of immunosuppression associated with immune checkpoint inhibitor-based chemotherapy in patients with ovarian cancer.

Discussion

This retrospective analysis demonstrated that the addition of thymosin α1 to PD-1/PD-L1 inhibitors combined with chemotherapy significantly improved clinical outcomes in patients with PROC. Specifically, the Tα1-treated group exhibited a notably higher ORR (43.0% vs 30.1%) and DCR (87.0% vs 69.9%) compared to the control group. Moreover, PFS was substantially prolonged (3 months vs 1.1 months), with a hazard ratio indicating more than a threefold reduction in the risk of disease progression. These results suggest that Tα1 may enhance the efficacy of immune checkpoint inhibitors (ICIs) and chemotherapy by modulating antitumor immunity and improving treatment tolerance.

The present results are consistent with prior studies in other solid tumors, where Tα1 has demonstrated a range of immunostimulatory and therapeutic benefits. In non-small cell lung cancer, Tα1 was shown to augment T-cell activation and attenuate chemotherapy-induced lymphopenia, thereby improving the therapeutic efficacy of ICIs.[14,18] Similarly, in hepatocellular carcinoma, Tα1 reduced postoperative recurrence and improved survival outcomes, particularly when

administered in combination with interferon or immunotherapy.[19,20] In breast, gastric, and colorectal cancers, Tα1 used as an adjunct to chemotherapy was associated with reduced myelosuppression, preservation of immune function, and improved treatment tolerance and quality of life.[21–23] These findings collectively suggested that Tα1 enhanced immune resilience and potentiates antitumor responses across various malignancies.

Importantly, several potential confounders factors may have influenced the observed treatment effects. *BRCA mutation status* and *prior PARP inhibitor exposure* are known to affect immune responsiveness in PROC, as BRCA-mutated tumors usually display higher genomic instability and immunogenicity, while PARP-pretreated cases may show immune exhaustion.[24] These data were unavailable in our cohort, which may have introduced bias. Nevertheless, both groups were balanced in prior chemotherapy lines, suggesting that the observed benefit of Tα1 is unlikely due to BRCA or PARP imbalance.[25] In addition, repeated chemotherapy can induce lymphopenia and T-cell dysfunction, potentially compromising ICI efficacy.[26] The immune-restorative effect of Tα1—such as enhancement of CD4+ and NK cells—may partly counteract this suppression, providing a plausible explanation for the improved outcomes observed in the Tα1 group.

To explore the basis of the observed clinical benefit, we analyzed immune changes associated with Tα1 treatment. Post-treatment assessments showed significant increases in serum immunoglobulins, CD3+ and CD4+ T lymphocytes, NK cells, and the CD4+/CD8+ ratio in patients receiving Tα1, indicating broad activation of adaptive and innate immunity. These findings align with the known immunostimulatory effects of Tα1, which promotes T-cell maturation, Th1 cytokine production, and NK cell cytotoxicity.[27–31,] The rise in immunoglobulin levels suggests enhanced humoral defense, potentially strengthening antitumor and anti-infective responses. Moreover, Tα1 may mitigate tumor-induced immunosuppression by reducing regulatory T cells and inhibitory cytokines, thus favoring a more proinflammatory immune milieu.[32–37] Given that platinum- and taxane-based chemotherapy often causes leukopenia and immune depletion, Tα1 could help maintain hematopoietic and immune integrity during treatment.[15,38] Overall, these effects provide a plausible immunologic basis for the improved clinical outcomes observed with Tα1-assisted therapy in platinum-resistant recurrent ovarian cancer.

Taken together, these findings suggested that Tα1 exerts multifaceted immunomodulatory effects, including restoration of immune function, enhancement of antitumor immunity, and remodeling of the tumor microenvironment. These biological activities provide a strong rationale for incorporating Tα1 into ICI-based chemotherapy regimens for platinum-resistant ovarian cancer and may underlie the observed improvements in clinical outcomes.

Nevertheless, several limitations of this study should be acknowledged. First, the retrospective design inherently carries the risk of selection bias and potential confounding, despite efforts to balance baseline characteristics. In particular, requiring complete immune marker data before and after treatment may have excluded patients with rapid disease progression, early death, or poor clinical condition, which could have led to an overestimation of treatment efficacy. Second, the use of non-standardized chemotherapy regimens across patients could introduce additional confounding effects. Third, immunological analyses were not uniformly performed in all patients, which may further contribute to selection bias. Moreover, the absence of overall survival data and long-term follow-up limits assessment of the durability of clinical benefits. Prospective randomized controlled trials with larger sample sizes, standardized treatment protocols, and comprehensive immune profiling are warranted to validate these findings and clarify the mechanisms by which Tα1 modulates the immune response in ovarian cancer.

Conclusion

This retrospective study suggests that the addition of thymosin α1 to PD-1/PD-L1 inhibitor-based chemotherapy may improve response rates and prolong progression-free survival in patients with platinum-resistant recurrent ovarian cancer. The observed immunomodulatory and protective effects of Tα1 provide a rationale for further investigation. Prospective studies with longer follow-up and overall survival data are warranted to confirm these findings and assess the clinical feasibility of this combination strategy.

Data Sharing Statement

This research data can be obtained from the corresponding author or the first author.

Ethics Approval and Informed Consent

This study has been approved by the Academic Ethics Committee of the Second People's Hospital of Neijiang (No. 2024RP-806-05). Written informed consent was obtained from patients or their family members. Our study complies with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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