Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Clinical Efficacy of Taxol Plus Platinum (TP) Chemotherapy Combined with Delayed Administration of PD-1 Inhibitors in Patients with Locally Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma: A Retrospective Study

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Purpose: Immune checkpoint inhibitors (ICIs) combined with chemotherapy have become the first-line standard treatment for locally advanced or metastatic esophageal squamous cell carcinoma (ESCC). The evidence also demonstrates improved synergistic effects of chemotherapy when combined with delayed administration of ICIs. In this study, we conducted a retrospective investigation into the treatment efficacy of taxol plus platinum (TP) chemotherapy combined with delayed administration of PD-1 inhibitors for ESCC patients.

Patients and Methods: Clinical data of ESCC patients who received PD-1 inhibitors 3–5 days after TP chemotherapy as first-line treatment was retrospectively reviewed between January 2019 and April 2023. Clinical outcomes and treatment safety were analyzed. The potential roles of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and pan-immune-inflammation value (PIV) were investigated.

Results: A total of 34 locally advanced, recurrent or metastatic ESCC patients received PD-1 inhibitors 3–5 days following TP chemotherapy were included. The objective response rate (ORR) and disease control rate (DCR) were 85.3% and 97.1% respectively. The median progression-free survival (PFS) and overall survival (OS) were 13.2 and 19.1 month respectively. Seven patients received radical surgery, 1 patient achieved pathologic complete response (pCR) and 3 patients achieved major pathologic response (MPR). Among the 27 patients without surgery, the median PFS and OS were 9.7 and 19.1 month respectively. A more favorable prognosis was correlated with NLR less than 3 at the 3rd and 4th cycle of immunochemotherapy. No significant correlations between other parameters (PLR, MLR and PIV) and prognosis were observed. A total of 22 patients developed grade 3–4 toxicity events.

Conclusion: The optimized sequence of PD-1 inhibitors administered 3–5 days after TP chemotherapy as the first-line treatment of ESCC demonstrated favorable treatment efficacy. Pretreatment NLR of less than 3 at the 3rd and 4th cycle of immunochemotherapy is associated with a better prognosis.

Keywords: immune checkpoint inhibitors, chemotherapy, rational sequence, esophageal squamous cell carcinoma, peripheral blood parameters

Received: 3 February 2024
Accepted: 19 June 2024
Published: 3 July 2024

Introduction

Esophageal cancer (EC), a widespread type of cancer worldwide, ranks seventh in cancer incidence (estimated 604,100 new cases) and sixth in cancer mortality (approximately 544,100 deaths) according to the GLOBOCAN 2020 database.[1,2] Furthermore, there are an estimated 957,000 new EC cases and 880,000 deaths worldwide in 2040 if current incidence and mortality rates did not change.[2] EC is particularly prevalent in Eastern Asia. Approximately 59.2% of new EC cases were reported in Eastern Asia, with China accounting for 53.7% of these cases alone.[2] Similarly, 58.7% of cancer-related deaths occurred in Eastern Asia with 55.3% of all deaths occurring in China alone.[2] Despite of the non-stopped development of different treatments, the survival rate for EC remains very low, with less than 30% of 5-year survival rates except for Japan (36%), China (34%) and Korea (31%).[3,4]

Esophageal squamous cell carcinoma (ESCC) was the most common histological type of EC, contributing to about 85% of all cases, followed by esophageal adenocarcinoma (EAC) and others.[2,5] Traditional treatments for ESCC includes surgery, radiotherapy, and chemotherapy. However, these strategies may not always provide satisfactory efficacy. In recent years, immune checkpoint inhibitors (ICIs) have shown great promise in improving the prognosis of ESCC patients, particularly in those with advanced or metastatic disease.[6] Currently, the combination of chemotherapy and ICIs has become the standard first-line treatment for patients with ESCC and is widely used during clinical practices.[7] A series of Phase III clinical trials, such as KEYNOTE-590,[8] CheckMate 648,[9] ESCORT-1ST,[10] JUPITER-06,[11] ORIENT-15,[12] ASTRUM-007[13] and RATIONALE 306,[14] have demonstrated that the combination of anti-PD-1 antibody significantly improved progression-free survival (PFS) and overall survival (OS) as compared with chemotherapy alone in patients with advanced or metastatic ESCC.[15] Furthermore, several studies have indicated that platinum in combination with taxol (TP) + ICIs may offer advantages over platinum in combination with fluorouracil (PF) + ICIs for advanced or metastatic ESCC.[7,16]

Besides enhancing treatment efficacy by optimizing different chemotherapeutic drugs in the treatment of ESCC, evidences suggested that the administration schedule of chemotherapy and anti-PD-1 antibody may also influence the treatment efficacy of immuno-chemotherapy.[17–19] Induction chemotherapy may establish an immune-stimulating environment within the tumor, potentially making it more responsive to immunotherapy.[20,21] Previous study showed that a second- or later-line treatment of administering anti-PD-1/anti-PD-L1 antibodies 1 to 10 days after chemotherapy, especially within 3 to 5 days, was more effective compared to giving anti-PD-1/anti-PD-L1 antibodies before or concurrently with chemotherapy in lung cancer patients.[17] Patients receiving anti-PD-1/anti-PD-L1 antibodies 3–5 days after chemotherapy had a significantly prolonged OS compared with patients receiving anti-PD-1/anti-PD-L1 antibodies 0 to 2 days before chemotherapy (median OS 40.9 vs 12.7 months; HR=0.27, P=0.021). Multivariable analysis also showed that administering anti-PD-1/anti-PD-L1 antibodies 3–5 days after chemotherapy strategy was an independent indicator for better OS compared with 0 to 2 days before chemotherapy, with the lowest HR among all the subgroups (HR=0.23, 95% CI 0.07–0.73; P = 0.013). In an open-label randomized Phase II study exploring the rational sequence of immunochemotherapy from a small group of locally advanced ESCC,[19] results showed that patients in the experiment group (toripalimab was administered two days after paclitaxel and cisplatin) had higher rates of pathologic complete response (pCR) than patients in the control group (toripalimab, paclitaxel and cisplatin were administered on the same day), with a nearly significant in statistics (pCR rates: 36.4% vs 7.7%, p = 0.079). In patients with PD-L1 CPS ≤ 1, pCR rates were 33.3% (2/6) in the experimental group and 0.0% (0/6) in the control group.

In this study, we retrospectively investigated the treatment efficacy and safety of optimized strategy of anti-PD-1 antibodies 3–5 days after TP chemotherapy as first line immunochemotherapy in patients with locally advanced, recurrent or metastatic ESCC. Furthermore, we also evaluated the potential roles of peripheral blood parameters including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR) and pan-immune-inflammation value (PIV) in ESCC patients treated with anti-PD-1 antibodies.

Materials and Methods

Patient Population, Inclusion and Exclusion Criteria

Patients with locally advanced, recurrent or metastatic ESCC who were treated at the Affiliated Hospital of Yangzhou University between January 2019 and April 2023 were reviewed retrospectively in this study. Inclusion criteria were as follows: (1) patients with pathologically confirmed unresectable and locally advanced, recurrent or metastatic ESCC; (2)

no previous systemic treatment for tumors or relapse of disease at least 6 months after the last dose of chemotherapy or (neo)adjuvant chemo(radio) treatment; (3) receiving immunotherapy 3–5 days after TP chemotherapy as first-line treatment; and (4) Eastern Cooperative Oncology Group (ECOG) performance status score less than 3. Exclusion criteria were as follows: (1) other tumor was previously or concurrently diagnosed; (2) pathology with non-squamous esophageal carcinoma; (3) lack of complete medical documents. This study was approved by the Ethics Committee of the Affiliated Hospital of Yangzhou University (approval No.2023-YKL04-05). The present study was conducted in accordance with the guidelines outlined in the Declaration of Helsinki.

Chemotherapy Regimens

All patients received immunotherapy in combination with TP chemotherapy as first-line treatment. Drugs of taxol included paclitaxel, docetaxel and albumin-bound paclitaxel, and drugs of platinum included cisplatin and carboplatin. Immunotherapeutic drugs, including Camrelizumab, Sintilimab, Pembrolizumab, Toripalimab and Tislelizumab, were given 3 to 5 days after TP chemotherapy for each cycle. Treatments were given every 21 days for each cycle.

Treatment Efficacy and Safety Evaluation

Clinical response was assessed every two cycles of treatment or at the time when new symptoms occurred with suspicious disease progression according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST1.1). Adverse events were assessed according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 5.0. Objective response rate (ORR), PFS, and OS were further analyzed. ORR was defined as the ratio of patients with complete response (CR) or partial response (PR). Disease control rate (DCR) was defined as the ratio of patients with CR, PR, or stable disease (SD).

Exploring of Hematologic Parameters

Peripheral blood test results of absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, and absolute platelet count were recorded and the data of NLR, PLR, MLR and PIV were further calculated, where PIV was calculated as (neutrophils count × monocytes count × platelets count)/lymphocytes count. According to previous reports, the threshold value of the NLR, PLR, and MLR were 3.0, 173.0 and 0.4, respectively.[22–24] The threshold of PIV is set at the median value.

Follow Up

Patients were followed up continuously and the last follow-up time was on July 1st, 2023. PFS is defined as the time from the first cycle of treatment to first documentation of disease progression or death, and OS is defined as the time between initiation of immunochemotherapy and patient's death from any cause.

Statistical Analysis

All the clinical data were processed using SPSS 23.0 statistical software for statistical analyses and GraphPad Prism 9.0 software for graphing. Categorical data were presented as frequencies (n) and percentages (%). Non-normally distributed data were expressed as median and the range. Kaplan Meier's method and the Log rank test were used to calculate PFS and OS for each group. $P < 0.05$ was considered as a statistically significant difference.

Results

Characteristics of Patients and Treatment Summary

From January 2019 to April 2023, a total of 478 ESCC patients were screened and 34 patients with locally advanced, recurrent or metastatic ESCC were included in this study. The flow chart of patient selection was shown in Figure 1. The baseline of clinical characteristics was summarized in Table 1. There were 25 male and 9 female, with a median age 66 years old (49–80 years). ECOG performance status scores ranged from 0 to 1. There were 11 patients with locally advanced diseases and 23 patients with recurrent or metastatic diseases. The common metastatic sites included

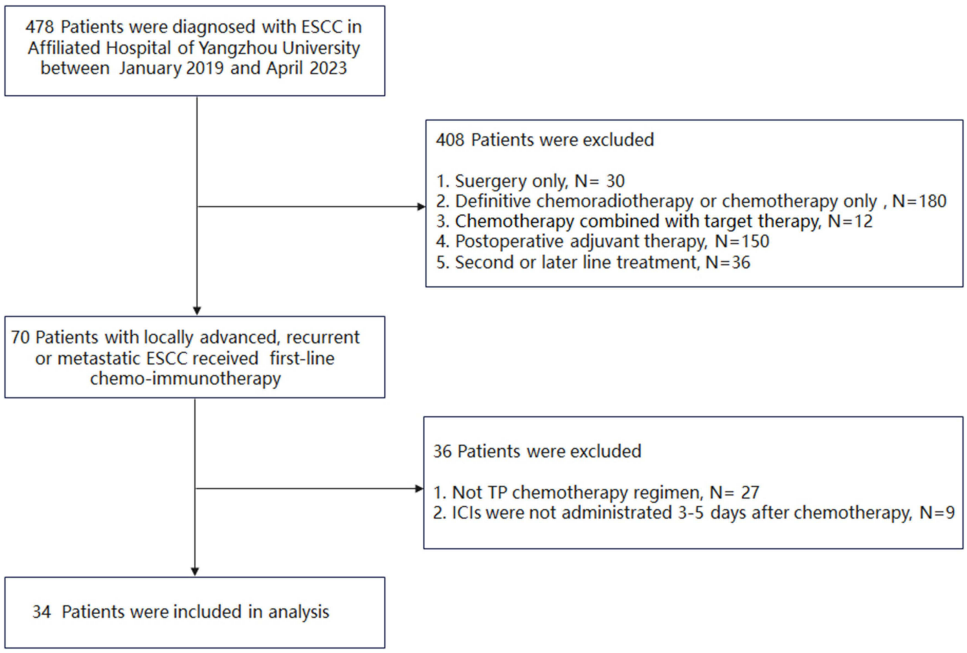

Figure 1 Flow chart of patient's selection.

mediastinal lymph nodes (34 patients), abdominal lymph nodes (11 patients), supraclavicular lymph nodes (8 patients), liver (5 patients), lung (2 patients) and bone (2 patients).

All patients were treated with anti-PD-1 antibodies 3 to 5 days after the first dose of TP for each cycle. Albumin-bound paclitaxel (25 patients) was the most commonly used for chemotherapy followed by docetaxel (5 patients) and paclitaxel (4 patients). Anti-PD-1 regimes included sintilimab (18/34, 53.0%), camrelizumab (10/34, 29.4%), tislelizumab (4/34, 11.8%), pembrolizumab (1/34, 2.9%) and toripalimab (1/34, 2.9%). A total of 138 cycles of chemotherapy were administered, and the median treatment cycle was 4 (range 2–6 cycles). All patients received at least of 2 cycles of TP+ICIs treatment and 7 patients were granted surgical opportunities after 2 to 3 cycles of immune-chemotherapy.

Table 1 Patient Characteristics of the 34 ESCC Patients

Characteristic	TP+ICIs (N=34)
Gender, n (%)	
Male	25 (73.5%)
Women	9 (26.5%)
Age (year)	
Median	66
Range	49–80
ECOG performance-status score, n (%)	
0	13 (38.2%)
1	21 (61.8%)
Tumor Location, n (%)	
Middle esophagus	16 (47.1%)
Lower esophagus	18 (52.9%)

(*Continued*)

Table 1 (Continued).

Characteristic	TP+ICIs (N=34)
T stage, n (%)	
T2	8 (23.5%)
T3	18 (53.0%)
T4	8 (23.5%)
N stage, n (%)	
N1	16 (47.0%)
N2	14 (41.2%)
N3	4 (11.8%)
M stage, n (%)	
M0	12 (35.3%)
M1	22 (64.7%)
Baseline clinical stage, n (%)	
III	7 (20.6%)
IV	27 (79.4%)
Number of sites with metastases, n (%)	
Single	12 (35.3%)
Multiple	22 (64.7%)
Sites of metastases, n (%)	
Mediastinal lymph-nodes	34 (100.0%)
Abdominal lymph-nodes	11 (32.4%)
Supraclavicular lymph-nodes	8 (23.5%)
Liver	5 (14.7%)
Bone	2 (5.9%)
Lung	2 (5.9%)
Other	5 (14.7%)
Immunotherapy drugs, n (%)	
Sintilimab	18 (53.0%)
Camrelizumab	10 (29.4%)
Tislelizumab	4 (11.8%)
Pembrolizumab	1 (2.9%)
Toripalimab	1 (2.9%)

Abbreviations: ESCC, esophageal squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group.

Efficacy Assessment

Changes in lesion size were summarized in Figure 2. There was no early treatment-related death in our study. A total of 11 patient (32.4%) achieved CR, 18 patients (52.9%) achieved PR, 4 patients (11.8%) achieved SD, and 1 patient (2.9%) had PD. The ORR and DCR were 85.3% and 97.1%, respectively. Among 7 patients who underwent surgery, all patients received margin-negative (R0) resection. There was 1 patient who achieved pCR and 3 patients achieved major pathologic response (MPR) including 1 patient with pCR of the primary tumor.

After a median follow-up of 9.4 months (3.0–26.7 months), 12 patients had disease progression, and 8 patients died. The median PFS and OS were 13.2 months and 19.1 months (Figure 3A and B), respectively. The 6-month, 12-month and 18-month PFS rates were 96.7%, 50.9%, 37.3%, respectively. The 6-month, 12-month and 18-month OS rates were 100.0%, 95.1%, 65.5%, respectively. Among the 7 patients who received radical surgery, all patients alive. Among the 27 patients without radical surgery treatment, the median PFS and OS were 9.7 months and 19.1 months (Figure 3C and D), respectively. The 6-month, 12-month and 18-month PFS rates were 96.0%, 37.0%, 18.6%, respectively. The 6-months, 12-months and 18-months OS rates were 100.0%, 93.8%, 53.1%, respectively.

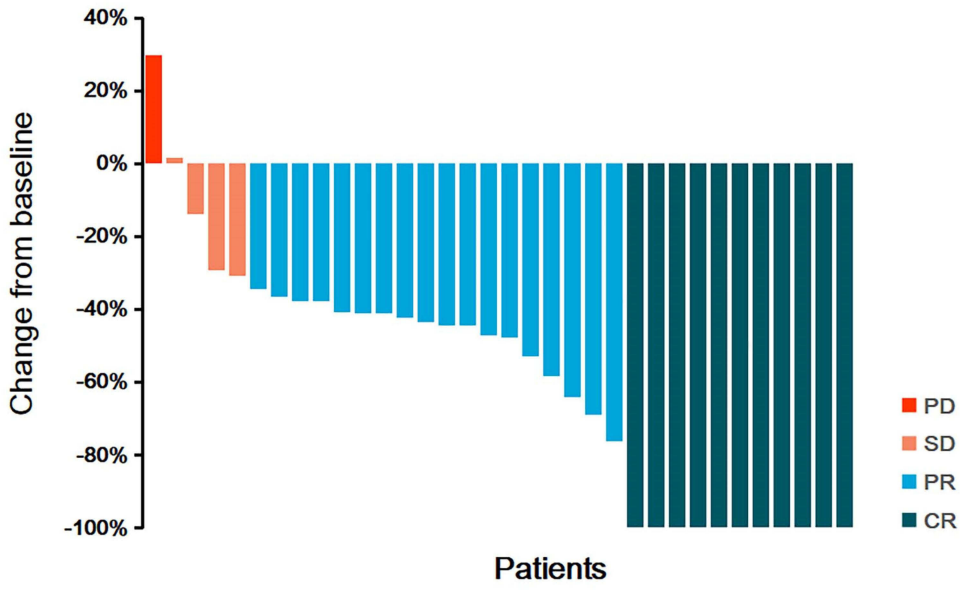

Figure 2 Percentage change of tumor size after the treatment. Each bar represents one patient with the best response in the dimension of target lesions.

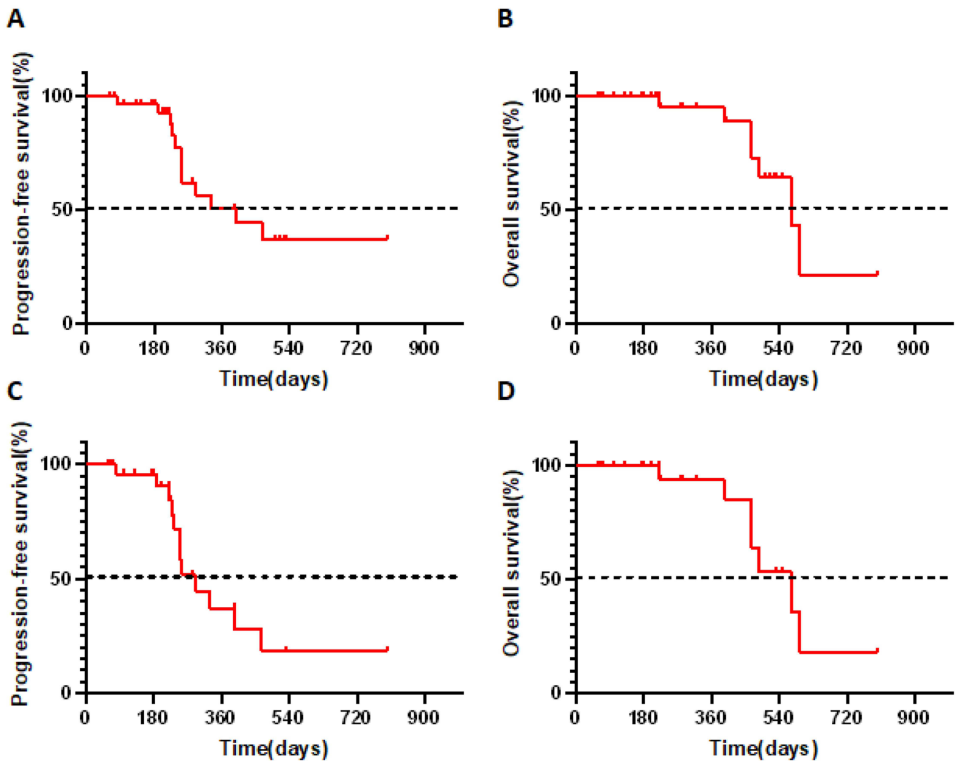

Figure 3 Kaplan–Meier curves of PFS and OS. PFS (**A**) and OS (**B**) for all patients (n=34). PFS (**C**) and OS (**D**) for patients who did not receive radical surgery treatment (n=27). PFS, progression-free survival; OS, overall survival.

Relationship Between Survival and Peripheral Blood Parameters

In the present study, we conducted a further analysis to analyze the relationship between patient survival and dynamic changes in peripheral blood parameters (NLR/PLR/MLR/PIV) in 27 patients without radical surgery. The results showed that NLR at the baseline and the second cycle of treatment did not exhibit a significant correlation with PFS and OS

(Figure 4A, B, E and F). However, a more favorable prognosis was closely correlated with a pretreatment NLR of less than 3 at the 3rd and 4th cycle of immunochemotherapy (Figure 4C, D, G and H). Our results did not show any significant correlations between other peripheral blood parameters (PLR, MLR and PIV) and prognosis of patient both at baseline and throughout the various cycles of immunochemotherapy (Figures 5-7).

Adverse Events (AEs)

All the 34 patients were included in the safety analysis. Table 2 showed the incidence of AEs. Treatment-related AEs of any grade occurred in 30 patients (88.2%). The most common treatment-related AEs included neutropenia in 29 patients (85.3%), leukopenia in 28 patients (82.4%), anemia in 27 patients (79.4%), thrombocytopenia in 20 patients (58.8%), nausea-vomiting in 18 patients (53.0%), fatigue in 15 patients (44.1%), rash in 13 patients (38.2%), and hypothyroidism in 8 patients (23.5%). A total of 22 patients developed grade 3–4 toxicity events, including leukopenia in 17 patients

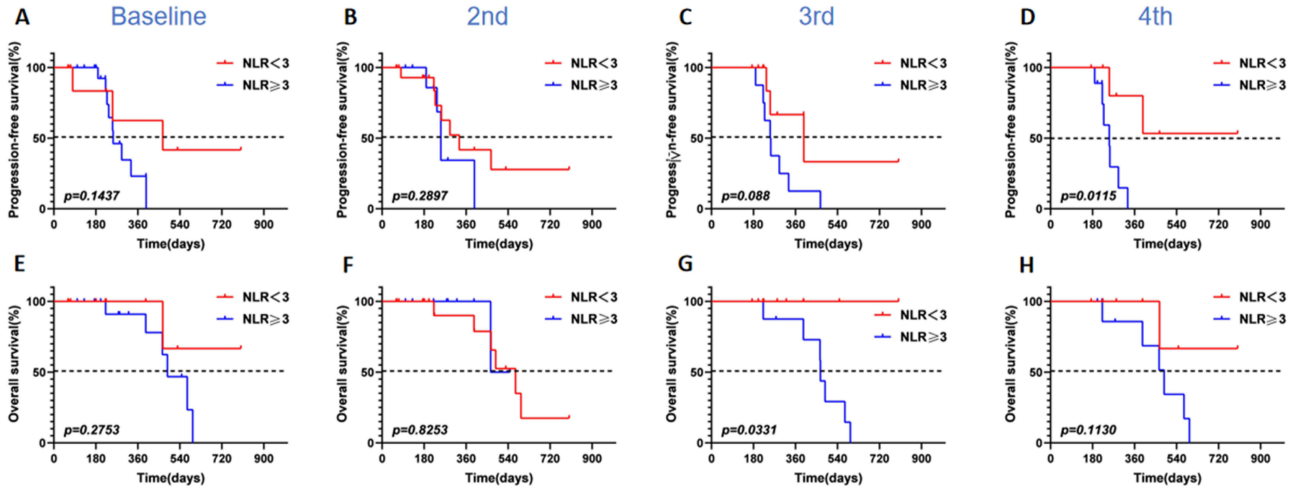

Figure 4 Kaplan–Meier curves of PFS and OS between different groups of NLR at different cycle of treatment. Kaplan–Meier curves of PFS at baseline (**A**), at second (**B**), third (**C**) and fourth (**D**) cycle of treatment. Kaplan–Meier curves of OS at baseline (**E**), at second (**F**), third (**G**) and fourth (**H**) cycle of treatment. PFS, progression-free survival; OS, overall survival; NLR, neutrophil-to-lymphocyte ratio.

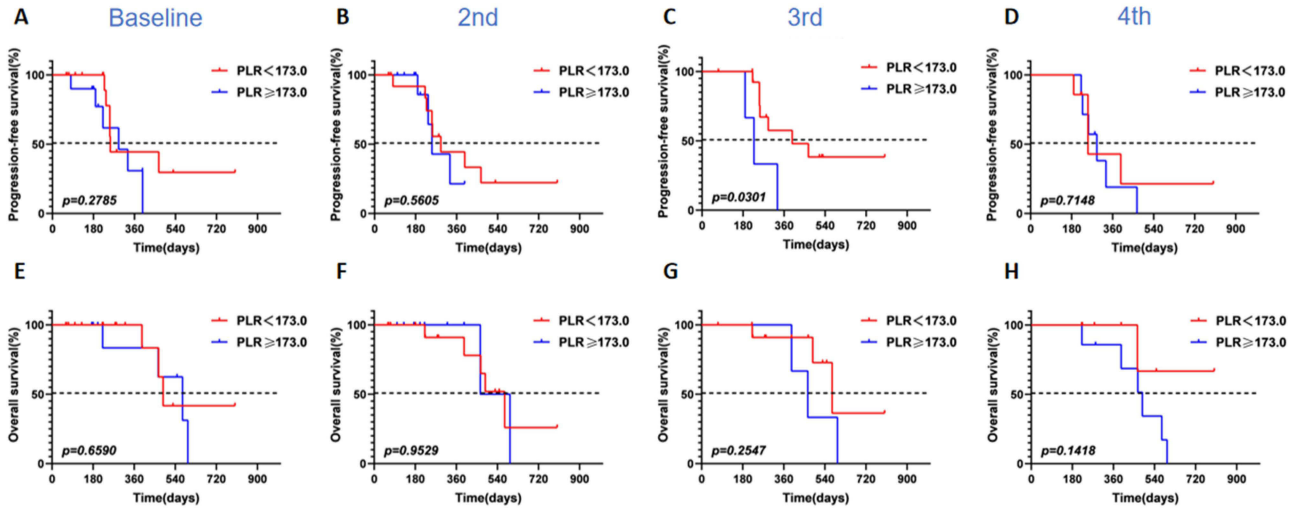

Figure 5 Kaplan–Meier curves of PFS and OS between different groups of PLR at different cycle of treatment. Kaplan–Meier curves of PFS at baseline (**A**), at second (**B**), third (**C**) and fourth (**D**) cycle of treatment. Kaplan–Meier curves of OS at baseline (**E**), at second (**F**), third (**G**) and fourth (**H**) cycle of treatment. PFS, progression-free survival; OS, overall survival; PLR, platelet-to-lymphocyte ratio.

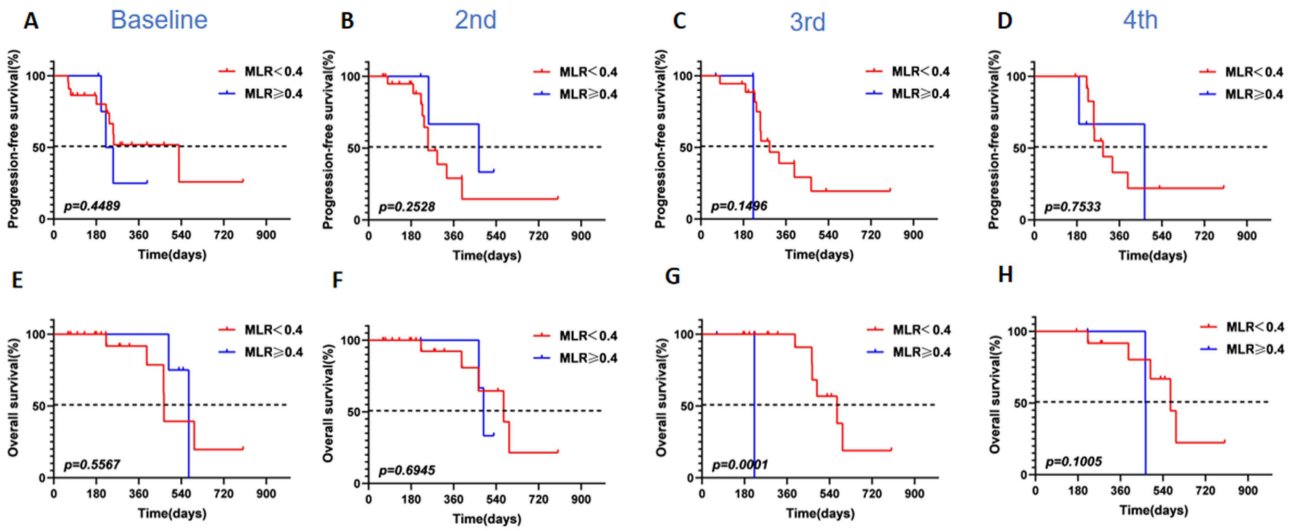

Figure 6 Kaplan–Meier curves of PFS and OS between different groups of MLR at different cycle of treatment. Kaplan–Meier curves of PFS at baseline (**A**), at second (**B**), third (**C**) and fourth (**D**) cycle of treatment. Kaplan–Meier curves of OS at baseline (**E**), at second (**F**), third (**G**) and fourth (**H**) cycle of treatment. PFS, progression-free survival; OS, overall survival; MLR, monocyte-to-lymphocyte ratio.

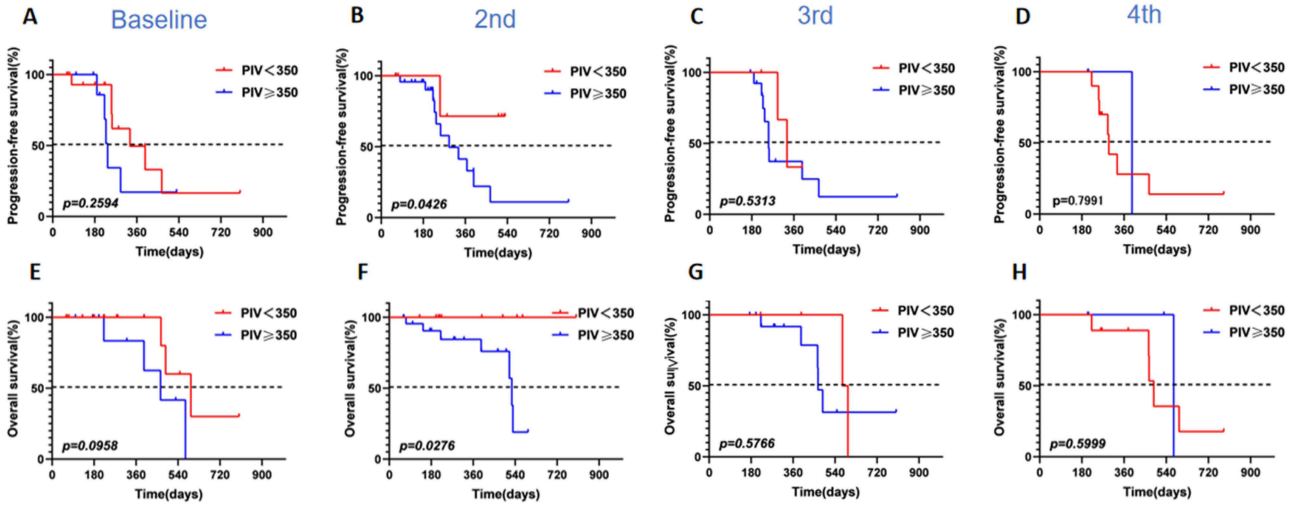

Figure 7 Kaplan–Meier curves of PFS and OS between different groups of PIV at different cycle of treatment. Kaplan–Meier curves of PFS at baseline (**A**), at second (**B**), third (**C**) and fourth (**D**) cycle of treatment. Kaplan–Meier curves of OS at baseline (**E**), at second (**F**), third (**G**) and fourth (**H**) cycle of treatment. PFS, progression-free survival; OS, overall survival; PIV, pan-immune-inflammation value.

(50.0%), anemia in 5 patients (14.7%), neutropenia in 3 patients (8.8%), thrombocytopenia in 3 patients (8.8%), nausea-vomiting in 3 patients (8.8%), lymphopenia in 2 patients (5.9%), rash in 2 patients (5.9%) and fatigue in 1 patient (2.9%).

Discussion

In this retrospective real-world study, our results demonstrated the synergistic antitumor effect through an optimized strategy involving anti-PD-1 antibodies administered 3–5 days after TP chemotherapy as a first-line immunochemotherapy for patients with locally advanced, recurrent or metastatic ESCC. The observed ORR reached as high as 85.3%. The median PFS and OS were 13.2 months and 19.1 months respectively. Additionally, a more favorable prognosis was closely correlated with a pretreatment NLR of less than 3 at the 3rd and 4th cycles of immunochemotherapy.

As compared with chemotherapy, the current approach of simply combining standard chemotherapy with immunotherapy does have brought significant changes to clinical practice, but it is crucial to acknowledge that the components within

Table 2 Incidence of Adverse Events in 34 ESCC Patients Receiving Immunochemotherapy

Adverse Events	Grade	TP+ICIs (N=34)
Neutropenia	Any grade	29 (85.3%)
	Grade≥3	3 (8.8%)
Leukopenia	Any grade	28 (82.4%)
	Grade≥3	17 (50.0%)
Anemia	Any grade	27 (79.4%)
	Grade≥3	5 (14.7%)
Thrombocytopenia	Any grade	20 (58.8%)
	Grade≥3	3 (8.8%)
Lymphopenia	Any grade	6(17.6%)
	Grade≥3	2 (5.9%)
Nausea	Any grade	18 (53.0%)
	Grade≥3	3 (8.8%)
Vomiting	Any grade	11 (32.4%)
	Grade≥3	2 (5.9%)
Fatigue	Any grade	15 (44.1%)
	Grade≥3	1 (2.9%)
Rash	Any grade	13 (38.2%)
	Grade≥3	2 (5.9%)
Hypothyroidism	Any grade	8 (23.5%)
	Grade≥3	0 (0.0%)

these combinations, including drugs, doses and sequence of administration, may not have been fully optimized.[25] Phase III randomized controlled trials (KEYNOTE-590,[8] CheckMate-648,[9] ESCORT-1ST,[10] JUPITER-06,[11] ORIENT-15,[12] ASTRUM-007[13] and RATIONALE 306[14]) have clinically confirmed synergistic treatment efficacy of chemotherapy combined with ICIs, and the standard of care for locally advanced, recurrent or metastatic ESCC has been built up. Since TP+ICIs has demonstrated superior treatment efficacy compared to PF+ICIs,[7,16,26] the current study focused on a retrospective analysis specifically investigating the therapeutic efficacy of combining TP with ICIs as a first-line treatment for patients diagnosed with locally advanced, recurrent, or metastatic ESCC. In addition, we went a step further by refining the sequence of chemotherapy and anti-PD-1 antibody administration based on insights from prior researches.[17,19]

In this study, we used a treatment protocol where anti-PD-1 drugs were administered 3–5 days following TP chemotherapy, inspired by a retrospective analysis of refractory lung cancer patients[17] and initially implemented by one of our oncologists. The successful PR achieved by the first patient underscored the potential of this refined treatment schedule, prompting its adoption for subsequent cycles. Notably, a phase II study, released at the 2021 ASCO annual meeting[27] and subsequently published,[19] demonstrated that delayed Toripalimab administration on day 3 led to a higher pCR compared to simultaneous administration with chemotherapy as neoadjuvant therapy in locally advanced ESCC. This modification gained attraction among more of our oncologists, who tried to adopt this modification and observed promising treatment efficacy in more patients. Therefore, we retrospectively analyzed a total of 34 patients, recognizing that this well-intentioned effort of optimization by our oncologist did have brought tangible benefits to patients.

Theoretically, an optimized sequencing of chemotherapy and anti-PD-1 drugs holds the potential to amplify treatment efficacy because induction chemotherapy or neoadjuvant chemotherapy have the potential to create an immune-stimulating environment within the tumor. This immune-stimulating environment could be characterized by increased T cell infiltration and upregulated expression of immune-related gene sets, including those associated with IFN-γ response, IL-6–JAK–STAT3 signaling, complement, IL-2–STAT5 signaling, Inflammatory response, TGF-α signaling via NF-κB, IFN-α response, and etc.[20,21] This priming of the tumor microenvironment could render it more amenable to immunotherapy, thereby augmenting the probability of favorable responses to PD-1 inhibitors. Previous in vivo study has

indicated that optimal treatment efficacy is often achieved when ICIs are administered subsequent to chemotherapy interventions.[28] Another study found that administering cyclophosphamide before initiating anti-cytotoxic T lymphocyte antigen 4 protein (CTLA-4) therapy resulted in substantial tumor regression in CT26 tumor-bearing mice (7/8), whereas the curative effect was observed in only 4 out of 8 mice when cyclophosphamide was given after anti-CTLA-4 therapy.[28] Notably, a comparison of administering cyclophosphamide before versus after anti-CTLA-4 therapy revealed that the percentage of apoptotic tumor-specific $CD8^+$ T cells increased when cyclophosphamide was administered after anti-CTLA-4 therapy, leading to a decline in treatment efficacy. This increased apoptosis and diminished antitumor effect were potentially linked to cyclophosphamide's potential to eliminate actively proliferating tumor-specific T cells induced by anti-CTLA-4 therapy.[28] In a separate experiment involving B16 (mouse melanoma) and CT26 (mouse colon carcinoma) tumor-bearing mice, the administration of DTX-VNS (a lipid nanoparticle encapsulating docetaxel) two days prior to anti-PD-1 treatment resulted in the greatest therapeutic effects which was evidenced by the smallest tumor volumes, the least lung metastatic nodules, and the highest survival rates when compared to scenarios involving DTX-VNS administered two days after anti-PD-1 treatment, or the simultaneous administration of DTX-VNS and anti-PD-1.[18] The TONIC clinical trial showed that induction strategies using cisplatin or doxorubicin followed by nivolumab increased ORRs as compared with non-induction group in metastatic triple-negative breast cancer (ORRs: doxorubicin 35%; cisplatin 23% and non-induction 17%).[20] As reported in ESCC and lung cancer, the administration of chemotherapy 2–5 days before anti-PD-1/PD-L1 drugs appeared to offer supplementary potential benefits when juxtaposed with administering the anti-PD-1/PD-L1 drugs prior to or simultaneously with chemotherapy.[17,19] In our study, we employed more potent inducers of ICD with TP regimens, administered 3–5 days prior to initiating anti-PD-1 treatment. This approach yielded remarkable results, with an ORR reaching an impressive 85.3%, coupled with a DCR of 97.1%. Among all the 34 patients diagnosed with ESCC, the median PFS and OS were 13.2 months and 19.1 months, respectively. A total of 4 patients who received radical surgery achieved MPR. In the subgroup of 27 patients who did not undergo radical surgery treatment, the median PFS and OS were 9.7 months and 19.1 months, respectively. Our study, despite having a limited number of patients, indicated that optimizing chemotherapy drugs and the sequence of immunochemotherapy administration resulted in an increased effectiveness of clinical treatment.

Currently, reliable biomarkers for predicting the effectiveness of anti-PD-1 therapy in ESCC are lacking. Among the various possibilities, peripheral blood parameters such as NLR, PLR, MLR and PIV have garnered significant attention as plausible biomarkers with potential predictive value.[29–34] Previous study has shown that an elevated pretreatment NLR was significantly associated with shortened PFS with a hazard ratio (HR) of 1.61, as well as reduced OS with a hazard ratio of 1.70.[35] In the ORIENT-2 trial, which focused on exploring sintilimab as second-line therapy for advanced or metastatic ESCC, the data suggested that patients with a baseline NLR < 3 experienced notably prolonged OS, with a median OS of 14.0 months compared to 6.2 months for those with a baseline NLR of ≥ 3.[22] Besides the NLR, cancer patients with lower PLR, MLR or PIV exhibited a higher response rate and improved prognosis concerning both PFS and OS compared to those with higher PLR MLR or PIV,[34,36,37] indicating the potential significance of peripheral blood parameters as valuable biomarkers capable of predicting both the clinical response and prognosis of patients undergoing anti-PD-1 treatment. In the present study, we further explored the relationship between peripheral blood parameters, specifically NLR, PLR, MLR and PIV, and the prognosis of ESCC patients undergoing anti-PD-1 treatment. Our data once again reaffirmed predictive potential of NLR in this particular cohort of ESCC patients. Similar with previous study,[32] a more favorable prognosis was closely correlated with a pretreatment NLR of less than 3 at the 3rd and 4th cycle of immunochemotherapy. However, it is worth noting that the baseline NLR did not exhibit a significant correlation with PFS and OS. In addition, our study did not identify any significant correlations between other peripheral blood parameters (PLR, MLR and PIV) and prognosis of patient both at baseline and throughout the various cycles of immunochemotherapy.

In this study, a total of 22 patients developed grade 3–4 toxicity, including leukopenia, anemia, neutropenia, thrombocytopenia, nausea-vomiting and fatigue. In comparison to previous reports,[16] our study exhibited a reduction in grade 3/4 neutropenia (8.8%) and lymphopenia (5.9%). Because chemotherapy was initially designed with a principle of administering doses at the highest level of toleration, such high level of dose might induce immune cell toxicity.[28] Therefore, balancing the benefits of chemotherapy with its potential impact on the immune system is essential for

optimizing the treatment approach and improving patient outcomes when combined with immunotherapy. A meta-analysis comparing one-week and three-week paclitaxel regimens for advanced pan-cancers revealed that the weekly paclitaxel treatment exhibited improved PFS, comparable OS, and a lower incidence of both hematological and non-hematological toxicities as compared to the three-week paclitaxel regimen.[38] In non-small-cell lung cancer, the use of weekly paclitaxel resulted in a significantly reduced incidence of grade 3/4 hematologic events and improved survival compared to the three-weekly paclitaxel regimen.[39] In our study, among the 34 patients, 25 patients received the weekly albumin-bound paclitaxel treatment. This approach might be associated with a decrease in grade 3/4 hematological toxicities. Taken together, these findings imply that adopting a weekly taxol treatment regimen might potentially exert a positive impact on the immune system, possibly resulting in an enhanced synergistic effect when combined with immunotherapy. In the future, various aspects such as the selection of chemotherapeutic drugs, appropriate dosages, the sequence of agent administration and strategies for immune system protection require further optimized during immunochemotherapy treatment.

There were several limitations existed in this study. Firstly, the relatively small number of patients included in this study underscores the importance of conducting more comprehensive research in the future, particularly prioritizing randomized controlled studies with larger sample sizes and long-term follow-up. Secondly, the wide range of anti-PD-1 antibodies utilized in our study presents a challenge in accurately determining the specific efficacy and potential toxic effects of each individual drug. Thirdly, our study did not delve into potential distinctions in treatment efficacy and safety between weekly Taxol administration and the three-weekly taxol administration, primarily due to the limitations imposed by the available data. Finally, this study did not assess the PD-L1 expression levels among the included patients, potentially introducing bias into the outcomes.

Conclusion

This study highlights the optimized sequence of TP chemotherapy and immunotherapy for the first-line treatment of ESCC. The results derived from this retrospective clinical study showed that a favorable treatment efficacy is achieved when PD-1 inhibitors are administered subsequent to chemotherapy. A pretreatment NLR of less than 3 at the 3rd and 4th cycles of immunochemotherapy is associated with a more favorable prognosis. Further investigations focused on optimizing the administration strategy of components within immunochemotherapy are warranted.

Ethics Approval and Informed Consent

Ethical approval (No. 2023-YKL04-05) was obtained from the Ethics Committee of the Affiliated Hospital of Yangzhou University. The present study was conducted in accordance with the guidelines outlined in the Declaration of Helsinki. Informed consent was not required because of the retrospective nature of our study. Patient privacy and data confidentiality were strictly maintained throughout the study. Patient data were anonymized before analysis to ensure confidentiality. All analyses in this retrospective study were conducted using anonymized patient data.

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.

Funding

This work was supported by Project of Jiangsu Provincial Natural Science Foundation (BK20191218), Projects of Yangzhou Social Development (YZ2021081 and YZ2021086), Project of Yangzhou key discipline in oncology therapeutics (YZYXZDXK-013), and Project of Industry-University-Research (BY20221106).

Disclosure

The authors report no conflicts of interest in this work.

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