Received: 13 April 2022 | Accepted: 16 June 2022

DOI: 10.1111/1759-7714.14568

ORIGINAL ARTICLE

WILEY

The rest period between chemotherapy and immunotherapy influences the efficacy of immune checkpoint inhibitors in lung cancer

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Funding information
Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Science and Technology, Grant/Award Numbers: NRF-2019R1C1C1008864, NRF-2021R1A2C2011603, NRF-2022R1C1C1007301; Chungnam National University Hospital Research Fund, Grant/Award Number: 2021; Chungnam National University Hospital; Ministry of Science and Technology; National Research Foundation of Korea

Abstract

Background: The use of immune checkpoint inhibitors (ICIs) as first-line treatment rather than as second-line treatment makes a big difference in the drug efficacy and progression-free survival. However, the mechanism for this is still not clear. This study aimed to analyze the effects of the rest period between chemotherapy and immunotherapy on the efficacy of ICIs.

Methods: This study included 100 patients with advanced NSCLC treated with PD-1/PD-L1 inhibitors at Chungnam National University Hospital (CNUH) between May 2016 and August 2019. The rest period was defined from the last dose of cytotoxic chemotherapy to the first dose of ICIs. We retrospectively reviewed patients' clinical data and blood test records and analyzed lymphocyte subsets using flow cytometry.

Results: The median rest period was 64 days. The long rest period group (≥36 days) showed significantly higher clinical benefits than the short rest period group (<36 days) (69.4% vs. 39.5%, $p = 0.003$). White blood cell (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and neutrophil-lymphocyte ratio (NLR) just before chemotherapy were not different between the two groups. However, the blood test after chemotherapy immediately before immunotherapy showed significantly higher ANC and NLR in the short rest period group than in the long rest period group. The frequency of the Th1 subset and PD-1 + $CD8^+$ T cells were significantly higher in the long rest period group than in the short rest period group.

Conclusion: Time interval from chemotherapy to immunotherapy may affect immune cell status and efficacy of ICIs.

KEYWORDS
chemotherapy, immunotherapy, lung cancer, PD-1/PD-L1 inhibitor, time interval

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide.[1] For decades, treatment options for patients diagnosed with advanced non-small cell lung cancer (NSCLC) have been limited to cytotoxic chemotherapy. Over the last decade, different types of drugs, including targeted therapy and immunotherapy, have become available, resulting in a shift in the treatment paradigm for patients with NSCLC.[2] Immune checkpoint inhibitors (ICIs) bind to the programmed death 1 (PD-1) receptor or programmed death ligand 1 (PD-L1) and allow activated T cells to induce tumor cell death by blocking the binding of the PD-1 ligand of tumor cells to the PD-1 receptor of immune cells.[3–6] In recent years, immunotherapy has become the standard of care for NSCLC.

Checkmate 017, 057, KENOTE-010, OAK, and POLAR reported the superior efficacy and survival benefit of nivolumab, pembrolizumab, and atezolizumab in patients

with previously treated NSCLC.[7–12] In KENOTE-024, pembrolizumab was associated with significantly longer progression-free survival (PFS) and overall survival (OS) than platinum-based chemotherapy in previously untreated advanced NSCLC patients with high PD-L1 expression (tumor proportion score [TPS] ≥ 50%).[13] The PFS in patients treated with pembrolizumab as first-line treatment was 10.3 months, significantly longer than 5.2 months in patients who had previously received cytotoxic chemotherapy and received pembrolizumab as second-line treatment. The effects of the first- and second-line settings of ICI single agents in the same patient population are very different, but the mechanism for this remains unclear.

Conventional cytotoxic agents can modulate the tumor immune microenvironment through various mechanisms, such as inhibiting tumor-induced immune suppression, direct stimulation of T- and B cell responses, and immunogenic cell death.[14,15] Platinum, which has been used as the first-line treatment for lung cancer for a long time, can induce neutropenia and lymphopenia.[16] Changes in the immune cell population are different for each patient, even with the same drug. It has been reported that chemotherapy changes the neutrophil-lymphocyte ratio (NLR) of patients after urothelial cancer and pancreatic cancer treatment, affecting the efficacy of the next treatment and prognosis.[17,18] The NLR, a predictive and prognostic marker in various cancers, may be changed by cytotoxic chemotherapy. This change may also affect the efficacy of subsequent immunotherapy but is yet to be elucidated. In addition, although it takes time to recover host immunity after cytotoxic chemotherapy, the optimal timing for administering ICIs after chemotherapy is unknown.

In this study, we aimed to analyze the effects of the rest period between chemotherapy and immunotherapy on the efficacy of ICIs and the immune cell population in lung cancer patients.

METHODS

Patients

This study included patients with advanced NSCLC who had received previous cytotoxic chemotherapy regimens and were treated with PD-1/PD-L1 inhibitors at Chungnam National University Hospital (CNUH) between May 2016 and August 2019. Patients were given intravenous nivolumab (3 mg/kg bodyweight every 2 weeks), pembrolizumab (2 mg/kg bodyweight or 200 mg every 3 weeks), or atezolizumab (1200 mg every 3 weeks). Treatment was continued until the patient experienced serious adverse events (AEs), had confirmed investigator-assessed disease progression, or withdrew informed consent. Patients expected to experience clinical benefit were permitted to continue treatment beyond radiological disease progression.

In some patients who provided informed consent, peripheral blood was collected before they received the first dose of the PD-1/PD-L1 inhibitor. Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood using standard Ficoll-Paque (GE Healthcare) density gradient centrifugation.

This retrospective study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the institutional review board of CNUH (2018-04-014).

Data collection

The following clinicopathological data were collected: age, sex, smoking history, cell type, PD-L1 expression of tumor cell, first-line chemotherapy regimen, number of previous chemotherapy, date of last administration of cytotoxic chemotherapeutic agent immediately before immunotherapy, date of administration of the first dose of ICI, and best objective response to ICI treatment according to Response Evaluation Criteria in Solid Tumors version 1.1.

Blood test data, including white blood cell (WBC) count, absolute neutrophil count, absolute lymphocyte count, absolute platelet count, and hemoglobin were collected just before initiating chemotherapy and immunotherapy treatment. The NLR was calculated by dividing the number of neutrophils by that of lymphocytes.

Rest period was defined as the period from the last day of administration of cytotoxic chemotherapeutic agent immediately before immunotherapy to the first day of administration of ICI.

PFS was defined as the time from the first date of ICI treatment to the date of documented progression or death from any cause. The OS was measured from the first day of ICI treatment to the date of death or the last day of follow-up.

Multicolor flow cytometry

Multicolor flow cytometry of PBMCs was performed at CNUH. The following human antibodies were used for multi-color flow cytometry: APC-Cy7-conjugated anti-CD3, PE-CF594-conjugated anti-PD1 (both from BD Pharmingen), PE-conjugated anti-CXCR3 (CD183), PerCP-Cy5.5-conjugated anti-CD4, APC-conjugated anti-CCR6 (CD196), BV421-conjugated anti-CCR4 (CD194), and BV605-conjugated anti-CD8 (all from BioLegend). To exclude dead cells, single-cell suspensions were first incubated for 20 min in viability dye (LIVE/DEAD Fixable Aqua, Thermo Fisher Scientific). Stained cells were analyzed using BD LSR Fortessa X-20 flow cytometry (BD Biosciences). Fluorescence-activated cell sorting (FACS) analysis was performed using FlowJo software (Tree Star).

Statistical analysis

To calculate the sensitivity and specificity of biomarker, conventional receiver-operating characteristic (ROC) curves

TABLE 1 Baseline characteristics of total patients ($N = 100$)

Variables		Number of patients (%)
Sex	Male	77 (77.0)
	Female	23 (23.0)
Age, years	Mean ± standard deviation	65.0 ± 9.9
Smoking history	Nonsmoker	31 (31.0)
	Former	37 (37.0)
	Current	32 (32.0)
Histopathology	Adenocarcinoma	39 (39.0)
	Squamous cell carcinoma	50 (50.0)
	Others[a]	11 (11.0)
PD-L1 expression[b]	High (TPS ≥ 50%)	47 (47.0)
	Low (TPS 1–49%)	21 (21.0)
	No (TPS <1%)	17 (17.0)
	Unknown	15 (15.0)
Agent of ICI	Atezolizumab	13 (13.0)
	Nivolumab	36 (36.0)
	Pembrolizumab	51 (51.0)
Treatment line	Second line	57 (57.0)
	≥third line	43 (43.0)
Response for ICI	PR	28 (28.0)
	SD	30 (30.0)
	PD	42 (42.0)
Cycles of ICI	Median (times)	5.3
First-line chemotherapy	Platinum + gemcitabine	49 (49.0)
	Platinum + paclitaxel	10 (10.0)
	Platinum + pemetrexed	31 (31.0)
	Platinum + vinorelbine	4 (4.0)
	Others[c]	6 (6.0)
Follow-up time	Median (month)	16.9
Rest period	Median (days)	64

[a]Adenosquamous, three large cells, one large cell neuroendocrine, five NSCLC NOS.
[b]PD-L1 expression was assessed using qualitative immunohistochemical (IHC) staining with the in vitro diagnostic PD-L1 IHC 22C3 pharmDx test (Agilent Technologies) on the Dako Autostainer (Dako) and PD-L1 IHC SP263 test on the Ventana BenchMark platform (Ventana Medical Systems).
[c]Two platinum + etoposide, two weekly vinorelbine, one platinum + docetaxel, one afatinib.
Abbreviations: ICI, immune checkpoint inhibitor; PD-L1, programmed death ligand-1; PD, progressive disease; PR, partial response; SD, stable disease; TPS, tumor proportion score.

were generated, and the area under the curve (AUC) was calculated. The optimal cutoff value was determined as the point at which the Youden index was maximized by the ROC curve. Statistical comparisons were performed using two-tailed chi-square and independent *t*-tests. Survival was estimated using the Kaplan–Meier method, and survival rates were compared using the log-rank test. A *p*-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22 (IBM Corp.) and MedCalc Software (version 19, Ostend, Belgium).

RESULTS

Baseline characteristics of patients

In total, 100 patients were enrolled in this study. The baseline characteristics and response of ICI treatment are summarized in Table 1. The mean age was 65.0 ± 9.9 years, 77% of the patients were male, and 69% were former/current smokers. The major histological types were squamous cell carcinoma (50.0%) and adenocarcinoma (39.0%). All patients had received at least one previous systemic treatment. In almost all patients, the platinum doublet was administered as first-line chemotherapy. A total of 38.0% (38/100) of patients had no/low expression of PD-L1, and 47.0% (47/100) of patients had high PD-L1 expression. The best responses for ICI treatment were PR in 28 patients (28.0%), SD in 30 patients (30.0%), and PD in 42 patients (42.0%).

Rest period

The distribution of the rest period among the patient population is shown in Figure 1a. The median value was 64 days. In the ROC curve for distinguishing patients with disease control from the total population, the AUC for the rest period was 0.634 ($p = 0.019$) based on a 36-day cutoff (Figure 1b). Based on the cutoff value for the rest period determined by the ROC curve analysis (36 days), all patients were classified as short period group (38 patients) or long period group (62 patients). Baseline characteristics (sex, age, disease stage, histological type, PD-L1 expression, type of agents, and type of first-line chemotherapy regimens) were not significantly different between the two groups. The response to previous chemotherapy before immunotherapy was not different between the two groups. The median time-to-progression (TTP) of previous chemotherapy in the short rest period group was 137 days (range 33–647 days), which was not significantly different from 166 days (range 51–389 days) in the long rest period group (Table 2).

Clinical outcomes according to rest period

In the short rest period group, the responses to ICI were PR 21.1%, SD 18.4%, PD 60.5%, which were significantly different from the 32.3, 37.1, and 30.6% of the long rest period group ($p = 0.012$). The DCR of the long rest period group was 69.4%, which was significantly higher than the DCR in the short rest period group (39.5%, $p = 0.003$). The median number of cycles of ICI treatment in the long rest period group was 7.75, which was significantly higher than 2.83 in the short rest period group (Table 3).

The median PFS of the long rest period group was 189 days (95% confidence interval [CI]: 81–297), which was significantly longer than the PFS in the short rest period group (78 days, 95% CI: 0–163, $p = 0.006$; Figure 2a). The

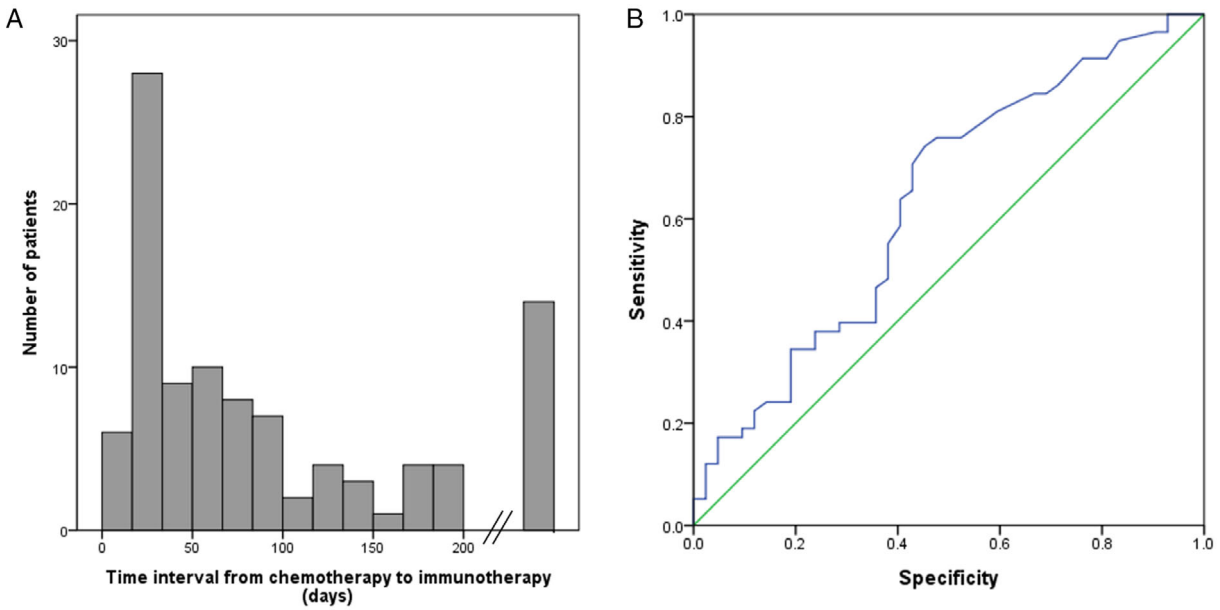

FIGURE 1 Predictive value of the rest period for clinical benefit in lung cancer patients treated with PD-1/PD-L1 inhibitors. (a) Histogram of rest period (time interval from chemotherapy to immunotherapy) in all patients. (b) The AUC for the rest period was 0.634 ($p = 0.019$) based on a 36 day cutoff in the ROC curve for the disease control rate. AUC, area under the curve; ROC, receiver-operating characteristic

median OS of patients in the long rest period group was significantly longer than the OS in the short rest period group (not reached vs. 171 days, 95% CI: 38–284, $p < 0.001$; Figure 2b).

CBC subpopulation according to rest period

WBC count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), NLR, hemoglobin (Hb), and platelet count before chemotherapy were not significantly different between the short rest period group and the long rest period group. However, before immunotherapy, the neutrophil count was significantly higher in the short rest period group than in the long rest period group, and the NLR was also significantly higher. There was no difference in ALC, Hb, and platelet count (Table 4).

Circulating T cell subsets according to rest period

In 20 patients with preimmunotherapy peripheral blood mononuclear cells (PBMC) samples, we examined the relative frequency and phenotypes of subpopulations of peripheral blood $CD4^+$ T cells and $CD8^+$ T cells. There were no significant differences in the proportion of $CD3^+$, $CD4^+$, and $CD8^+$ T cells in total PBMCs. We divided the $CD4^+$ T cell subset using CXCR3, CCR4, and CCR6. The gating strategy to identify Th1, Th2, and Th17 in $CD4^+$ T cells is shown in Figure 3a. The proportion of Th1 cells (CXCR3 + CCR4-CCR6- $CD4^+$ T cells) on $CD4^+$ T cells was significantly higher in patients with long rest periods than in patients with short rest periods (Figure 3b). The proportion of PD-1 + $CD4^+$ T cells in $CD4^+$ T cells was not significantly different between the long and short rest period group. The proportion of PD1 + $CD8^+$ T cells in the $CD8^+$ T cells was significantly higher in the long rest period group than the short rest period group (Figure 3c).

DISCUSSION

This is the first study to demonstrate that the rest period between chemotherapy and immunotherapy affects the efficacy of ICIs. The long rest period group showed a significantly higher disease control rate than the short rest period group. The median PFS and OS in the long rest period group were significantly longer than in the short rest period group. There is no difference in TTP after previous chemotherapy in the two groups. Therefore, we think that there will be no significant difference in the rate of tumor progression between the two groups. However, the response rate in the two groups showed a slight difference even though not significant, and some patients with rapid tumor progression are likely to start the next therapy quickly, so the tumor progression rate may have a slight effect on the PFS and OS according to the rest period.

In this study, the CBC subpopulation just before chemotherapy was not different between the long rest period and short rest period groups. However, the blood test after chemotherapy immediately before immunotherapy showed significantly higher ANC and NLR in the short rest period group than in the long rest period group. Cytotoxic

TABLE 2 Baseline characteristics of patients according to the rest period

Variables		Short rest period group ($N = 38$)	Long rest period group ($N = 62$)	*p*-value
Sex	Male	27 (71.1)	50 (80.6)	0.269
	Female	11 (28.9)	12 (19.4)	
Age, years	Mean ± standard deviation	64.5 ± 9.4	65.3 ± 10.3	0.686
Smoking history	Nonsmoker	15 (39.5)	16 (25.8)	0.287
	Former	11 (28.9)	26 (41.9)	
	Current	12 (31.6)	20 (32.3)	
Histopathology	Adenocarcinoma	17 (44.7)	22 (35.5)	0.207
	Squamous cell carcinoma	15 (39.5)	35 (56.5)	
	Others	6 (15.8)	5 (8.1)	
PD-L1 expression[a]	High (TPS[c] ≥50%)	17 (44.7)	30 (48.4)	0.461
	Low (TPS 1–49%)	11 (28.9)	10 (16.1)	
	No (TPS<1%)	5 (13.2)	12 (19.4)	
	Unknown	5 (13.2)	10 (16.1)	
Agent of ICI	Atezolizumab	3 (7.9)	10 (16.1)	0.142
	Nivolumab	18 (47.4)	18 (29.0)	
	Pembrolizumab	17 (44.7)	34 (54.8)	
First-line chemotherapy	Platinum + gemcitabine	16 (42.1)	33 (53.2)	0.526
	Platinum + paclitaxel	6 (15.8)	4 (6.5)	
	Platinum + pemetrexed	13 (34.2)	18 (29.0)	
	Platinum + vinorelbine	1 (2.6)	3 (4.8)	
	Others	2 (5.3)	4 (6.5)	
Best response to previous chemotherapy	PR	13 (34.2)	33 (53.2)	0.134
	SD	15 (39.5)	20 (32.3)	
	PD	9 (23.7)	6 (9.7)	
	Unknown	1 (2.6)	3 (4.8)	
TTP of the previous chemotherapy, days	Median (range)	137 (33–647)	166 (51–389)	0.191

[a]PD-L1 expression was assessed using qualitative immunohistochemical (IHC) staining with the in vitro diagnostic PD-L1 IHC 22C3 pharmDx test (Agilent Technologies) on the Dako Autostainer (Dako) and PD-L1 IHC SP263 test on the Ventana BenchMark platform (Ventana Medical Systems).
Abbreviations: ICI, immune checkpoint inhibitor; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; TPS, tumor proportional score.

TABLE 3 Clinical outcomes of patients according to the rest period

Variables		Short rest period group ($N = 38$)	Long rest period group ($N = 62$)	*p*-value
Response to ICI	PR	8 (21.1)	20 (32.3)	0.012*
	SD	7 (18.4)	23 (37.1)	
	PD	23 (60.5)	19 (30.6)	
Overall response rate		21.1%	32.3%	0.226
Disease control rate		39.5%	69.4%	0.003*
Cycles of ICI (median)		2.83	7.75	0.004*

*$p < 0.05$. Abbreviations: ICI, immune checkpoint inhibitor; PD, progressive disease; PR, partial response; SD, stable disease.

chemotherapy before immunotherapy affects neutrophil count and NLR, which may affect the efficacy of ICIs. It has been reported that prepembrolizumab NLR predicts the efficacy of second-line pembrolizumab in urothelial cancer regardless of prechemotherapy NLR.[17] A meta-analysis reported that chemotherapy-induced reduction of NLR is associated with better survival in pancreatic cancer.[18] In other words, the immune cell status just before immunotherapy is important for the efficacy of ICIs.

In this study, we identified differences in the Th subset proportion and the fraction of PD-1 + $CD8^+$ T cells, even though there was no difference in lymphocyte count before immunotherapy according to the rest period. In the additional PBMC analysis of patients not included in this study as well as patients included in this study, the proportion of Th1 cells in $CD4^+$ T cells and the proportion of PD-1 + $CD8^+$ T cell in $CD8^+$ T cells were significantly higher in the PR/SD group than the PD group (Figure S1). This suggests that the Th1 subset and PD-1 + $CD8^+$ T cells would be related to the response to treatment. In the long rest period group, patients had a

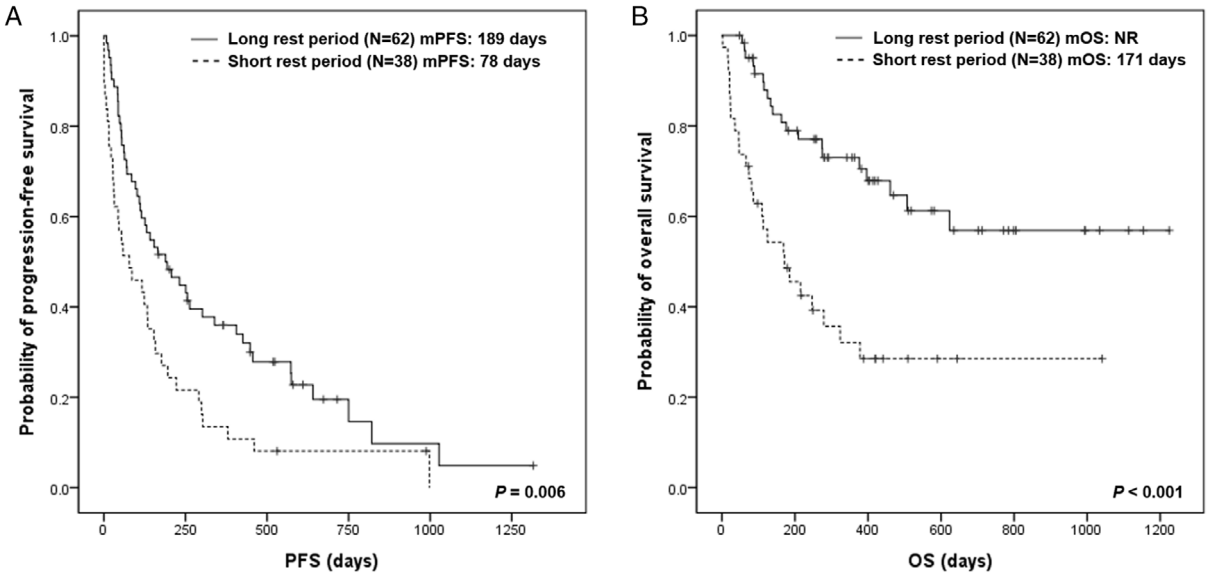

FIGURE 2 Survival analysis according to the rest period in lung cancer patients treated with PD-1/PD-L1 inhibitors. (a) Progression-free survival (PFS) according to the rest period. The median PFS of the long rest period group was 189 days (95% confidence interval [CI] 81–297), which is significantly longer than the PFS in the short rest period group (78 days, 95% CI 0–163, $p = 0.006$). (b) Overall survival (OS) according to the rest period. The median OS of patients in the long rest period group was significantly longer than the OS in the short rest period group (not reached vs. 171 days, 95% CI: 58–284, $p < 0.001$)

TABLE 4 CBC subpopulation according to the rest period

	Short rest period group ($N = 38$)	Long rest period group ($N = 62$)	*p*-value
Prechemotherapy WBC (mean)	8665	8129	0.512
Prechemotherapy neutrophil (mean)	6223	5401	0.241
Prechemotherapy lymphocyte (mean)	1734	1720	0.938
Prechemotherapy NLR (mean)	4.2	3.9	0.734
Prechemotherapy Hb (mean)	12.0	11.7	0.585
Prechemotherapy Plt (mean, 10^3)	292	275	0.533
Preimmunotherapy WBC (mean)	9389	7739	0.063
Preimmunotherapy neutrophil (mean)	6685	5131	0.026*
Preimmunotherapy lymphocyte (mean)	1701	1752	0.754
Preimmunotherapy NLR (mean)	5.0	3.3	0.016*
Preimmunotherapy Hb (mean)	11.6	11.5	0.765
Preimmunotherapy Plt (mean, 10^3)	297	285	0.595

*$p < 0.05$. Abbreviations: Hb, hemoglobin; NLR, neutrophil lymphocyte ratio; plt, platelets; WBC, white blood cells.

higher proportion of Th1 cells (CXCR3 + CCR4-CCR6-$CD4^+$ T cells) on $CD4^+$ T cells. Naïve $CD4^+$ T cells can differentiate into different subsets of T helper (Th) cells, including Th1, Th2, Th17, and Treg cells.[19] Th1 cells are generated when naïve T cells are activated in the presence of IL-12 and express the T-box transcription factor TBX21 (T-bet), which induces the Th1 cytokine IFN-gamma.[20] IFN-gamma plays a major role in anticancer immunity by promoting the activity of cytotoxic T lymphocyte and NK cells and by upregulating MHC expression and antigen presentation by dendritic cells.[21] Several studies have reported that IFN-gamma signaling is associated with the response and benefit of PD-1 blockade.[22] In our study, patients with long rest periods had higher proportions of PD-1 + $CD8^+$ T cells on $CD8^+$ T cells. It has been reported in the literature that the PD-1+ T-cell fraction is enriched for tumor-reactive T cells,[23] and proliferation of PD-1+ $CD8^+$ T cells in the blood after PD-1 blockade treatment has been reported to be associated with positive clinical outcomes.[24] Previous chemotherapy before immunotherapy may cause changes in the immune cell population. The rest period is associated with changes in helper and cytotoxic T cell subsets, and this is thought to affect the response to immunotherapy.

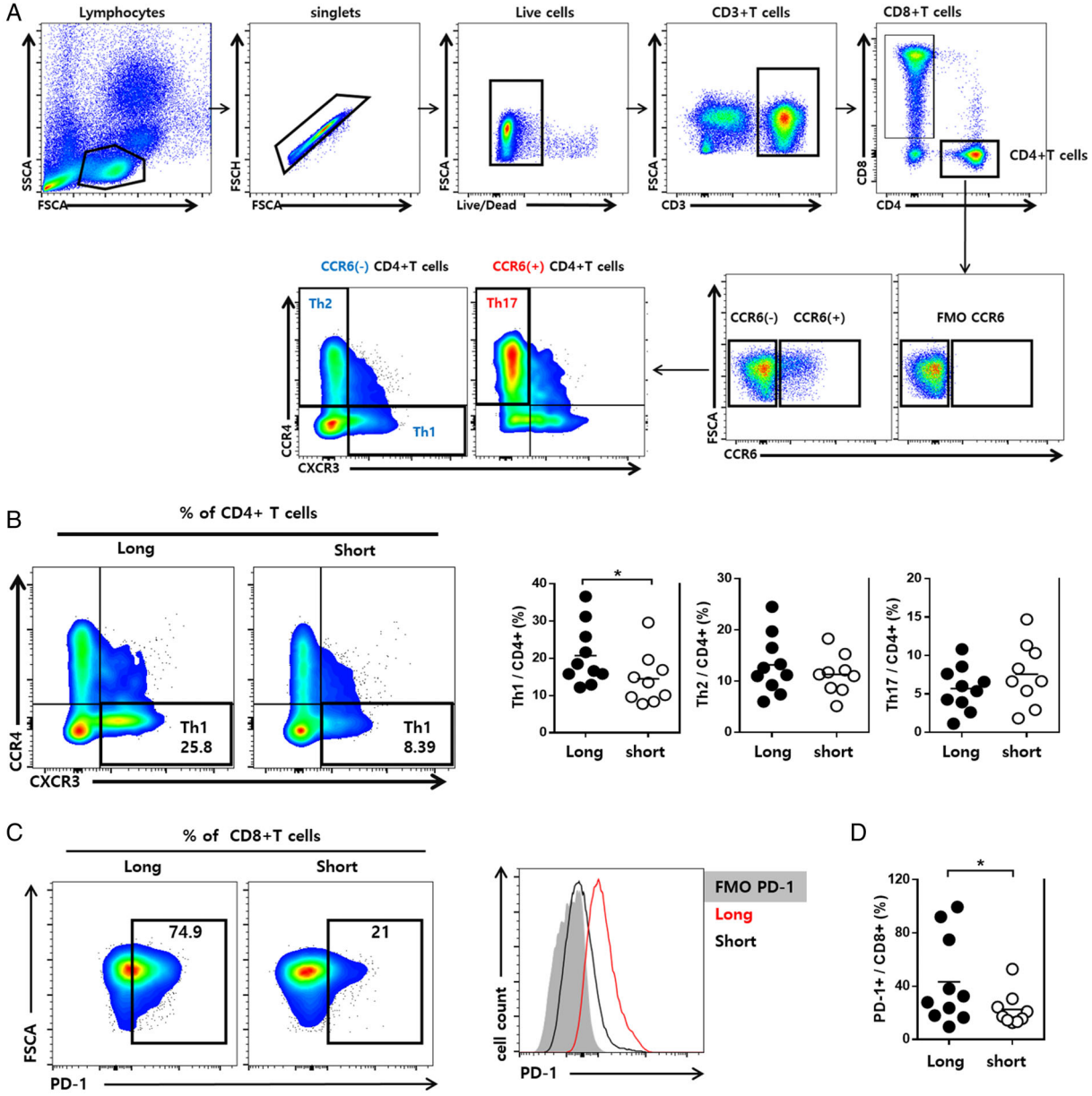

FIGURE 3 T cell subsets according to the rest period in lung cancer patients treated with PD-1/PD-L1 inhibitors. (a) Gating strategies of $CD4^+$ and $CD8^+$ T cells shown by flow cytometric analyses. (b) The frequency of Th1 cells is significantly higher in patients with long rest periods than in patients with short rest periods. (c) The proportion of PD1 + $CD8^+$ T cells in the $CD8^+$ T cells was significantly higher in the long rest period group than in the short rest period group

Several cytotoxic chemotherapeutic drugs can have cytotoxic effects on immune cells, such as lymphocytes or myeloid cells.[25] In the mice model, cisplatin used as the initial treatment for lung cancer is reported to eliminate myeloid-derived suppressor cells (MDSCs) and increase dendritic cells.[26] It is reported that docetaxel and gemcitabine kill MDSCs and induce the maturation of proinflammatory cytokines such as IL-1beta in MDSCs.[27] IL-1beta activates Th17 cells and recruits and activates neutrophils through IL-17A and IL-17F secreted from Th17 cells.[28] Cytotoxic chemotherapy changes the immunity of the host by various mechanisms and also affects lymphocytes and neutrophils. After cytotoxic chemotherapy, neutrophil and lymphocyte counts may change, and it is thought that the changed host immunity will vary depending on the rest period.

Immunotherapy is continuously changing the paradigm of lung cancer; it is currently recommended as the first-line treatment for advanced lung cancer as a single treatment or in combination with cytotoxic chemotherapeutic agents.[29] However, because the number of elderly lung cancer patients is increasing, it is not easy to treat with combination therapy with cytotoxic chemotherapeutic agents and ICIs. There are some cases where immunotherapy is administered as a second-line or further-line treatment after the administration

of cytotoxic chemotherapy due to adverse events and insurance problems. It is known that even in the same high PD-L1 expression group, the PFS was 10.3 months when pembrolizumab was administered as the first-line treatment. However, the PFS was 5.2 months when pembrolizumab was administered as the second-line treatment, showing a significant difference.[10,13] Until now, the reason for this has not been clearly elucidated. Our study findings supported that cytotoxic chemotherapy used before immunotherapy may have an effect on host immunity and ICI efficacy.

The limitations of this study are the retrospective design and that it was performed in a single institution. Future multicenter prospective studies will help to support these study findings. In addition, it is unclear whether the rest period directly affected the neutrophil count and NLR changes. It is necessary to experimentally confirm whether the immune cell status, including neutrophils, and lymphocytes, changes over time after exposure to the chemotherapeutic agent.

In conclusion, the time interval from chemotherapy to immunotherapy correlates with efficacy, PFS, and OS in patients treated with ICIs. Therefore, when starting immunotherapy in patients who have previously received chemotherapy, a rest period of 5 weeks or more should be considered before ICI treatment.

ACKNOWLEDGMENTS

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Science and Technology (NRF-2019R1C1C1008864, NRF-2021R1A2C2011603, and NRF-2022R1C1C1007301). This research was also supported by Chungnam National University Hospital Research Fund, 2021.

CONFLICT OF INTEREST

The authors have declared that there are no competing interests.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kang DH, Choi S, Sun P, Chung C, Park D, Lee S-I, et al. The rest period between chemotherapy and immunotherapy influences the efficacy of immune checkpoint inhibitors in lung cancer. Thorac Cancer. 2022;13(16):2346–54. https://doi.org/10.1111/1759-7714.14568