Original Article

CYFRA 21-1 predicts efficacy of combined chemoimmunotherapy in patients with advanced non-small cell lung cancer: a prospective observational study

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Background: Tumor markers such as serum carcinoembryonic antigen (CEA) and cytokeratin fragment 19 (CYFRA 21-1) are utilized for assessing the effectiveness of chemotherapy in non-small cell lung cancer (NSCLC) patients. Yet, it remains uncertain whether these markers can reliably forecast responses to combined chemoimmunotherapy. Our study aimed to examine the significance and effectiveness of these markers in predicting responses among NSCLC patients undergoing combined chemoimmunotherapy.

Methods: This two-part observational study involved patients with NSCLC who were treated with combined chemoimmunotherapy in Japanese hospitals. An initial retrospective study of these patients, with serum CEA and CYFRA 21-1 as prognostic factors for combined chemoimmunotherapy outcomes, served as a discovery cohort. Patients in a subsequent prospective study served as a validation cohort, where we assessed the prognostic accuracy of CEA and CYFRA 21-1 cut-off points determined by the discovery cohort.

Results: In total, 121 patients treated with combined chemoimmunotherapy were included, with 44 and 77 patients in the discovery and validation cohorts, respectively. Serum CYFRA 21-1 levels >3.0 ng/mL were significantly associated with progression-free survival (PFS) in both the discovery and validation cohorts (P=0.01, P=0.04, respectively). PFS did not differ significantly by CEA levels (P=0.21).

Conclusions: After combined chemoimmunotherapy treatment, serum CYFRA 21-1 stands out as a potentially valuable biomarker for predicting the prognosis of NSCLC.

Keywords: Combined chemoimmunotherapy; cytokeratin fragment 19 (CYFRA 21-1); non-small cell lung cancer (NSCLC); prospective observation study

Submitted Mar 01, 2024. Accepted for publication Jul 17, 2024. Published online Aug 20, 2024.
doi: 10.21037/tlcr-24-190
View this article at: https://dx.doi.org/10.21037/tlcr-24-190

Introduction

Background

Lung cancer has become the leading cause of cancer-related deaths (1). Nevertheless, the therapeutic landscape for advanced lung cancer has experienced a significant upturn with the advent of immune checkpoint inhibitors (ICIs) (2-4). Furthermore, innovative combination therapies, such as combined chemoimmunotherapy, are supplanting platinum-based chemotherapy as the standard of care for advanced non-small cell lung cancer (NSCLC) patients (5,6). Numerous biomarkers have been identified for predicting response to ICIs in NSCLC patients, encompassing programmed death ligand 1 (PD-L1) expression levels, neutrophil-to-lymphocyte ratio, microbiome composition, and tumor mutation burden (7-10). However, comprehensive exploration of predictive factors for combined chemoimmunotherapy outcomes in NSCLC patients remains ongoing.

Rationale and knowledge gap

Tumor markers like serum carcinoembryonic antigen (CEA) and cytokeratin fragment 19 (CYFRA 21-1) have primarily been explored as prognostic or predictive indicators for chemotherapy outcomes (11). CEA is a serum glycoprotein that plays a role in cell adhesion. In individuals without cancer, CEA levels are typically low. However, in patients with colorectal, ovarian, breast, and lung cancers, CEA levels are elevated. CEA is one of the most widely used tumor markers (12). Elevated CEA levels are often noted in smokers and in non-neoplastic conditions (13). CYFRA 21-1, predominantly found in pulmonary tissue, exhibits heightened serum concentrations, especially in cases of carcinoid tumors and squamous cell carcinoma of the lung. Furthermore, serum levels of CYFRA 21-1 are often elevated in oropharyngeal squamous cell carcinoma, oral squamous cell carcinoma, and colorectal cancer (14,15). CYFRA 21-1 is a crucial protein for maintaining the structural integrity of epithelial cells and is overexpressed in the cytoplasm of epithelial tumors. CYFRA 21-1 can be released into the bloodstream when tumor necrosis occurs (16). Studies indicate that serum CYFRA 21-1 levels correlate with tumor size, lymph node involvement, and disease stage (17). CEA and CYFRA 21-1 are reported to be elevated in both tissues and serum. The expression levels of both CEA and CYFRA in tissues may influence the efficacy and prognosis of treatment (18,19). Further, serum CEA and CYFRA 21-1 have also been identified as useful predictors of the efficacy of chemotherapy and ICI (20-22). However, the predictive value of CEA and CYFRA-21 for the efficacy of combined chemoimmunotherapy in patients with NSCLC is unclear.

Highlight box

Key findings

- Cytokeratin fragment 19 (CYFRA 21-1) is a potentially useful biomarker for non-small cell lung cancer (NSCLC) prognosis after combined chemoimmunotherapy treatment.

What is known and what is new?

- CYFRA 21-1 is abundant in pulmonary tissue, and its serum concentrations are particularly elevated in the presence of carcinoid tumors and squamous cell carcinoma of the lung. It has been reported that serum concentrations of CYFRA 21-1 are associated with tumor size, lymph node status, and stage of disease. However, the predictive value of CYFRA-21 for the efficacy of combined chemoimmunotherapy in patients with NSCLC is unclear.
- The results of our study show that lower levels of CYFRA 21-1 were associated with better progression-free survival with combined chemoimmunotherapy in patients with NSCLC.

What is the implication, and what should change now?

- Larger and more diverse studies are needed to fully determine the predictive value of CYFRA 21-1 for the effectiveness of combined chemoimmunotherapy for patients with NSCLC.

Objective

This study was designed to assess the effectiveness of serum CEA and CYFRA-21 as prognostic biomarkers for combined chemoimmunotherapy in patients with NSCLC within a real-world context. We present this article in accordance with the REMARK reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-190/rc).

Methods

Study design

This observational study consisted of two parts. The initial part involved a discovery cohort, which constituted a retrospective analysis of patients. Here, we examined the potential of baseline serum CEA and CYFRA 21-1 levels as prognostic indicators for combined chemoimmunotherapy outcomes and determined optimal cutoff values. We

retrospectively enrolled patients diagnosed with advanced or recurrent NSCLC who had undergone combined chemoimmunotherapy treatment between January 2019 and December 2019 at three medical institutions in Japan (Kyoto Prefectural University of Medicine, Japanese Red Cross Kyoto Daini Hospital, and Japanese Red Cross Kyoto Daiichi Hospital). Patients who had not been tested for PD-L1 or CYFRA 21-1 were excluded. Patients in the discovery cohort were followed-up through September 2020. Serum samples were analyzed on a commonly available electrochemiluminescence immunoassay analyzer (Cobas e801; Roche Diagnostics, Tokyo, Japan) for CEA and a chemiluminescent enzyme immunoassay (Lumipulse L2400; FUJIREBIO, Tokyo, Japan) for CYFRA 21-1.

The validation cohort was a prospective study testing the hypotheses generated by the discovery cohort. We prospectively enrolled patients diagnosed with advanced or recurrent NSCLC who received first-line combined chemoimmunotherapy at 1 of 10 medical institutions in Japan (Kyoto Prefectural University of Medicine, Japanese Red Cross Kyoto Daini Hospital, Saiseikai Suita Hospital, Japanese Red Cross Kyoto Daiichi Hospital, Uji-Tokushukai Medical Center, Otsu City Hospital, Matsushita Memorial Hospital, Fukuchiyama City Hospital, Kyoto City Hospital, and Saiseikai Shigaken Hospital) between November 2019 and March 2021. Eligible patients met the following criteria: (I) histologically and cytologically confirmed unresectable advanced or recurrent NSCLC and (II) no prior exposure to chemotherapy or immunotherapy. Patients for whom evaluation using residual specimens after a pathological diagnosis was challenging or impossible were excluded. Follow-up for patients in the validation cohort was conducted until November 2021.

Ethics declarations

All participating hospitals were informed and agreed with the study, and patients in the validation cohort provided written informed consent, while for those in the discovery cohort, consent was waived by the Ethics Committees of the Kyoto Prefectural University of Medicine and each participating hospital due to the retrospective nature of the study. The study protocol received approval from the Ethics Committee of the Kyoto Prefectural University of Medicine (Kyoto, Japan; approval number: ERB-C-1545, 1803) and adhered to the principles outlined in the Declaration of Helsinki (as revised in 2013). Additionally, the protocol was registered in the University Medical Hospital Information Network (UMIN) Clinical Trials Registry (No. UMIN000043958).

Statistical analysis

In both cohorts, the clinical endpoints included progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and disease control rate (DCR), assessed according to RECIST v1.1 criteria. PFS and OS were calculated utilizing the Kaplan-Meier method, with differences assessed via the log-rank test. Optimal cutoff levels for CEA and CYFRA 21-1 in the discovery cohort were determined using a receiver operating characteristic (ROC) curve, based on the status of the compounds at 6 months of PFS. Cox proportional hazards models were employed to estimate univariate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs); OS and PFS were censored at the date of the last survival confirmation for patients without documented disease progression. Covariates for Cox multivariate regression included patient sex, age (≥75 years), smoking status, PD-L1 tumor progression score (PD-L1 TPS) of ≥50% or above, and histology, selected based on previous literature reports (23,24). Efficacy results for CEA and CYFRA 21-1 in the discovery cohort were used to determine biomarkers tested in the validation cohort, and significant results were used in Cox regression analyses of the combined cohorts. All statistical analyses were performed using EZR statistical data analysis and interpretation version 1.40 (25), with a significance level of $P<0.05$.

Results

Discovery cohort

Forty-four patients who had been treated with combined chemoimmunotherapy at the participating hospitals met the eligibility criteria for the discovery cohort (*Figure 1*). The median age was 69.5 (range, 43–79) years; 31 (70.5%) patients were male and 36 (81.8%) had a history of smoking. Only three patients (6.8%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) higher than 1. One (2.3%) patient had an epidermal growth factor receptor (EGFR) mutation, and 11 (25.0%) had a PD-L1 TPS ≥50%. Thirty-seven (84.1%) patients had received a pembrolizumab regimen and 21 (47.7%) had received pemetrexed (*Table 1*). The median duration of follow-up was 13.0 months, with a median PFS of 7.3 months [95%

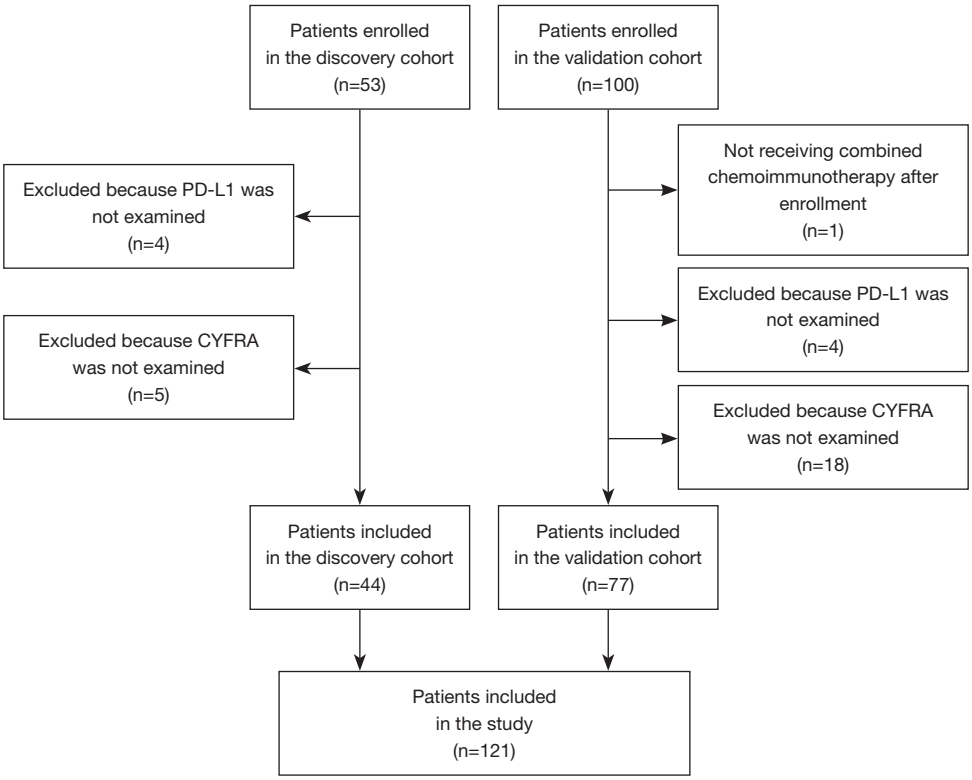

Figure 1 Flow diagram of the study. PD-L1, programmed death ligand 1; CYFRA, cytokeratin fragment.

confidence interval (CI): 4.6–10.1]. The median OS was not reached [95% CI: not evaluated (NE)–NE] (Figure S1). The ORR of patients was 43.2% (95% CI: 28.3–59.0%), and the DCR was 77.3% (95% CI: 62.2–88.5%).

The ROC analyses showed areas under the curve of 0.666 for CYFRA 21-1 and 0.557 for CEA. Consequently, we opted for a cutoff of 3.0 ng/mL for serum CYFRA 21-1 (sensitivity 86%, specificity 56%) and 9.7 ng/mL for serum CEA (sensitivity 74%, specificity 50%) based on these findings (Figure S2).

Patients with serum CYFRA 21-1 levels above the cut-off experienced a significantly shorter PFS of 3.9 months (95% CI: 1.4–6.2) *vs.* 9.1 months (95% CI: 6.6–14.7) for patients with lower values (P=0.01; *Figure 2A*). Conversely, there was no notable disparity in PFS based on the serum CEA cut-off level (P=0.40; *Figure 2B*). The Cox regression analyses showed that serum CYFRA 21-1 levels >3.0 ng/mL predicted significantly shorter PFS in both univariate (HR =2.51; 95% CI: 1.19–5.32; P=0.02) and multivariate models (HR =2.97; 95% CI: 1.24–7.13; P=0.02) (Table S3). Among patients with CYFRA 21-1 levels exceeding the cut-off, the proportion with adenocarcinoma was significantly lower compared to those with levels at or below the cut-off (P=0.04). However, no significant differences were observed in other characteristics based on the CYFRA cut-off level (Table S1).

Validation cohort

During the specified period, one hundred patients with advanced NSCLC received combined chemoimmunotherapy across the participating institutions. Of these patients, 77 were eligible for analysis in this study (*Figure 1*). The median age upon enrollment was 70 (range, 44–86) years, with 67 patients (87.0%) being male. Additionally, 65 patients (84.4%) had a history of smoking, while five patients (6.5%) exhibited an ECOG PS above 1. Four (5.2%) patients had EGFR mutations, and 26 (33.8%) had a PD-L1 TPS greater than 50%. Pembrolizumab and atezolizumab were administered to 56 (72.7%) and 21 (27.3%) patients, respectively. Thirty-six (46.8%) patients received pemetrexed and 41 (53.2%) received paclitaxel or nab-paclitaxel regimens (*Table 1*). Patients with serum CYFRA 21-1 levels above the cut-off had a significantly higher history of smoking compared to those with CYFRA

Table 1 Characteristics of patients

Characteristics	Discovery cohort (n=44)	Validation cohort (n=77)
Age (years), median (range)	69.5 (43–79)	70 (44–86)
Sex, n (%)		
Male	31 (70.5)	67 (87.0)
Female	13 (29.5)	10 (13.0)
ECOG PS, n (%)		
0	25 (56.8)	30 (39.0)
1	16 (36.4)	42 (54.5)
2	3 (6.8)	5 (6.5)
Histology, n (%)		
Adeno	25 (56.8)	49 (63.6)
Squamous	12 (27.3)	19 (24.7)
Others	7 (15.9)	9 (11.7)
Stage, n (%)		
III/IV	38 (86.4)	75 (97.4)
Recurrence	6 (13.6)	2 (2.6)
Oncogenic driver, n (%)		
EGFR mutation positivity	1 (2.3)	4 (5.2)
Smoking status, n (%)		
Current/former	36 (81.8)	65 (84.4)
Never	8 (18.2)	12 (15.6)
PD-L1 TPS, n (%)		
≥50%	11 (25.0)	26 (33.8)
1–49%	17 (38.6)	29 (37.7)
<1%	16 (36.4)	22 (28.6)
Regimen, n (%)		
Pembrolizumab regimen	37 (84.1)	56 (72.7)
Atezolizumab regimen	7 (15.9)	21 (27.3)
Pemetrexed regimen	21 (47.7)	36 (46.8)
Paclitaxel or nab-paclitaxel regimen	23 (52.3)	41 (53.2)
Response assessment, n (%)		
CR	0 (0.0)	2 (2.6)
PR	19 (43.2)	49 (63.6)
SD	15 (34.1)	15 (19.5)
PD	4 (9.1)	6 (7.8)
NE	6 (13.6)	5 (6.5)
Overall response rate (%) (95% CI)	43.2 (28.3–59.0)	66.2 (54.6–76.6)
Disease control rate (%) (95% CI)	77.3 (62.2–88.5)	85.7 (75.9–92.6)

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; PD-L1 TPS, programmed death ligand 1 tumor progression score; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; CI, confidence interval.

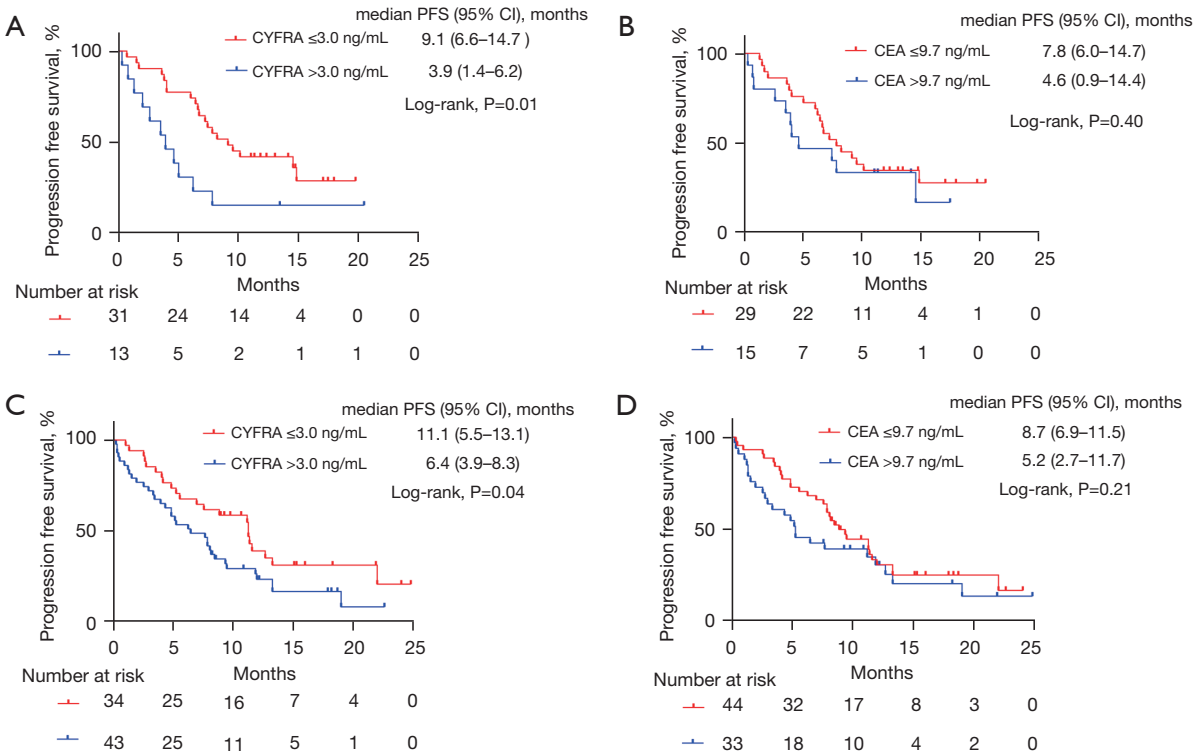

Figure 2 PFS based on the status of CYFRA 21-1 and CEA in the discovery and validation cohorts. PFS outcomes were stratified according to the levels of CYFRA 21-1 (A) and CEA (B) in the discovery cohort and CYFRA 21-1 (C) and CEA (D) in the validation cohort. PFS, progression-free survival; CI, confidence interval; CYFRA, cytokeratin fragment; CEA, carcinoembryonic antigen.

21-1 values at or below the cut-off (P=0.03). However, no significant differences were observed in other characteristics, including histology, based on the CYFRA cut-off level (Table S2). The median follow-up duration was 12.0 months. The median PFS was 8.0 months (95% CI: 5.3–11.1); the median OS was not reached (95% CI: NE–NE) (Figure S3). The ORR of patients was 66.2% (95% CI: 54.6–76.6%) and the DCR was 85.7% (95% CI: 75.9–92.6%).

Patients with CYFRA 21-1 levels above the cut-off had a significantly shorter PFS (6.4 months, 95% CI: 3.9–8.3) than patients with CYFRA 21-1 values at or below the cut-off (11.1 months, 95% CI: 5.5–13.1) (P=0.04; *Figure 2C*). However, there was no significant difference in PFS based on the CEA cut-off level (P=0.21; *Figure 2D*). In the univariate Cox regression analysis, patients with serum CYFRA 21-1 levels exceeding 3.0 ng/mL exhibited significantly shorter PFS compared to those with lower levels (HR =2.51; 95% CI: 1.19–5.32; P=0.02). This finding was consistent in the multivariate analysis (HR =1.89; 95% CI: 1.02–3.48; P=0.04) (*Table 2*).

As an exploratory analysis, we then combined the discovery and validation cohorts to investigate the prognostic value of serum CYFRA 21-1 for PFS according to patients' histology and chemotherapy regimen. Among patients with non-squamous cell carcinoma, those with low CYFRA 21-1 levels exhibited significantly longer PFS compared to those with high levels (11.0 *vs.* 4.8 months, P=0.01) (Figure S4). In contrast, patients with squamous cell carcinomas showed no significant differences in PFS based on CYFRA 21-1 levels (P=0.13; Figure S4). Among patients treated with a pemetrexed regimen, those with low CYFRA 21-1 levels experienced significantly longer PFS (11.1 *vs.* 6.4 months, P=0.01; Figure S5). However, PFS did not vary significantly by CYFRA 21-1 level for patients following a paclitaxel/nab-paclitaxel regimen (9.5 *vs.* 5.1 months, P=0.09; Figure S5).

Discussion

Key findings

Prognostic biomarkers for assessing the therapeutic efficacy

Table 2 Cox proportional-hazards models for time to progression-free survival in patients with non-small cell lung cancer in validation cohort

Items (comparator)	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
CYFRA 21-1 >3.0 ng/mL (*vs.* ≤3.0 ng/mL)	1.72 (1.01–2.95)	0.04	1.89 (1.02–3.48)	0.04
CEA >9.7 ng/mL (*vs.* ≤9.7 ng/mL)	1.39 (0.82–2.36)	0.22	–	–
Age ≥75 years (*vs.* <75 years)	0.94 (0.53–1.67)	0.83	1.16 (0.63–2.14)	0.64
Male sex (*vs.* female sex)	1.29 (0.58–2.85)	0.54	1.46 (0.60–3.58)	0.40
Smoker (*vs.* never smoker)	1.04 (0.51–2.13)	0.91	0.89 (0.35–2.24)	0.80
PD-L1 TPS ≥50% (*vs.* <50%)	0.36 (0.20–0.66)	<0.01	0.33 (0.18–0.61)	<0.01
Squamous (*vs.* non-squamous)	0.90 (0.50–1.62)	0.72	1.04 (0.56–1.95)	0.90
Pembrolizumab regimen (*vs.* atezolizumab regimen)	0.69 (0.38–1.25)	0.22	–	–

HR, hazard ratio; CI, confidence interval; CYFRA, cytokeratin fragment; CEA, carcinoembryonic antigen; PD-L1 TPS, programmed death ligand 1 tumor progression score.

of combined chemoimmunotherapy are essential for the continued development of effective treatments. Our results showed that serum CYFRA 21-1 had significant predictive value for clinical outcomes of combined chemoimmunotherapy in patients with NSCLC.

Strengths and limitations

The strength of this study lies in the fact that, to the best of our knowledge, this is the first report to demonstrate this effect. This study had several limitations. First, the sample size was small. Further, the relatively small sample size allowed only a limited number of clinical and non-clinical covariates in the regression models. Second, all the patients in the cohort were Japanese. Finally, the follow-up time was insufficient to calculate OS.

Comparison with similar researches

Various serum CYFRA 21-1 cut-offs have been used in previous retrospective studies. A study of 70 patients treated with ICI monotherapy reported that CYFRA 21-1 levels <3.3 ng/mL were associated with better OS (21). In another investigation, baseline CYFRA 21-1 levels exceeding 8 ng/mL were strongly associated with lower DCR and shorter OS in both ICI monotherapy- and chemotherapy-treated patients (22). Our study supports the value of a cut-off at approximately 3 ng/mL, as determined through a retrospective discovery cohort and validated in an independent prospective cohort. However, further research is needed to determine the optimal cut-off values.

Explanations of findings

In this study, serum CYFRA 21-1, but not serum CEA, was significantly associated with the efficacy of immunotherapy. This suggests that CYFRA 21-1 reflects more than tumor volume. Notably, the predictive value of CYFRA 21-1 was particularly pronounced in patients with non-squamous cell carcinomas and those receiving pemetrexed regimens. CYFRA 21-1 is a known marker of squamous cell carcinoma and may have been indirectly marking intratumor heterogeneity by detecting squamous cell components within non-squamous cell tumors (26). Furthermore, a recent study reported a significant association of CYFRA 21-1 with circulating tumor DNA (ctDNA; a potent biomarker of ICI), in NSCLC (27), and CYFRA 21-1 may have acted as a convenient indicator of ctDNA. However, the study found no significant correlation between CEA and ctDNA.

Implications and actions needed

At present, our findings do not provide conclusive evidence regarding whether elevated CYFRA levels can be deemed predictive specifically of the efficacy of combined chemoimmunotherapy or more broadly prognostic of a poor outcome, irrespective of the treatment modality administered. Nevertheless, investigating the association of serum CYFRA21-1 with intratumoral heterogeneity

and ctDNA may help clarify the role of tumor markers as predictors of combined immunotherapy.

Conclusions

We found that lower levels of serum CYFRA 21-1 were associated with better PFS with combined chemoimmunotherapy in patients with NSCLC. Larger and more diverse studies are needed to fully determine the predictive value of CYFRA 21-1 for the effectiveness of combined chemoimmunotherapy for patients with NSCLC.

Acknowledgments

We thank the patients, their families, and all the investigators involved in this study. We also thank Editage (https://www.editage.com/) for their help with English language editing.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-190/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-190/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-190/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-190/coif). Tadaaki Yamada serves as an unpaid editorial board member of *Translational Lung Cancer Research* from October 2023 to September 2025. Tadaaki Yamada reports receiving research grants from Pfizer Inc., Ono Pharmaceutical, Janssen Pharmaceutical, AstraZeneca PLC, and Takeda Pharmaceutical and personal fees from Eli Lilly. K.T. reports receiving research grants from Chugai-Roche Co., and Ono Pharmaceutical Co., and personal fees from AstraZeneca Co., Chugai-Roche Co., MSD-Merck Co., Eli Lilly Co., Boehringer-Ingelheim Co., and Daiichi-Sankyo Co. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Ethics Committees of Kyoto Prefectural University of Medicine (Kyoto, Japan; approval number: ERB-C-1545, 1803) and was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013). All participating hospitals were informed and agreed with the study. Written informed consent was obtained from patients in the validation cohort and was waived for those in the discovery cohort owing to its retrospective nature.

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Cite this article as: Kataoka N, Katayama Y, Yamada T, Morimoto K, Takeda T, Okada A, Shiotsu S, Chihara Y, Hiranuma O, Yamada T, Ota T, Harada T, Hasegawa I, Nishioka N, Iwasaku M, Tokuda S, Takayama K. CYFRA 21-1 predicts efficacy of combined chemoimmunotherapy in patients with advanced non-small cell lung cancer: a prospective observational study. Transl Lung Cancer Res 2024;13(8):1929-1937. doi: 10.21037/tlcr-24-190