Journal of Cancer Research and Clinical Oncology (2024) 150:394
https://doi.org/10.1007/s00432-024-05916-x

RESEARCH

Effect of TTF-1 expression on progression free survival of immunotherapy and chemo-/immunotherapy in patients with non-small cell lung cancer

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Received: 16 July 2024 / Accepted: 5 August 2024 / Published online: 22 August 2024

Abstract

Background The choice between immunotherapy with a checkpoint inhibitor (CPI) and chemo-/immunotherapy (CIT) in patients with NSCLC stage IV is often discussed. There is some data that the effect of chemotherapy is influenced by TTF-1 expression. Little is known about the influence of thyreoid transcription factor 1 (TTF-1) expression on CIT and CPI therapy. We aimed to investigate the relationship between tumor TTF-1 expression and efficacy of CIT and CPI therapy.

Patients and methods We retrospectively analysed 130 patients (age 68 ± 7 y) with NSCLC stage IV. Only patients with lung adenocarcinoma were included. Patients with ALK, ROS1, RET, MET, NTRK, EGFR, BRAF mutation were excluded. Patients were treated according to the guidelines with either CPI alone (pembrolizumab, nivolumab, atezolizumab, cemiplimab) or CIT (Carboplatin/Pemetrexed/Pembrolizumab, Carboplatin/Paclitaxel/Atezolizumab). We registered patients' characteristics including TTF-1 expression. Group 1 consisted of 40 patients with CPI and TTF-1 expression, group 2 were 26 patients with CPI and with no TTF-1 expression. Group 3 consisted of 41 patients with CIT and TTF-1 expression, group 4 were 23 patients with CIT and with no TTF-1 expression.

Results Group 1–4 showed comparable patients characteristics. Using cox-regression analysis, we found that TTF-1 expression resulted in an improved progression free survival (PFS) compared to patients with CPI and no TTF-1 expression (18 ± 3,15 vs. 5 ± 0,85 months, $p = 0.004$, 95% CI: 0,23 − 0,984). In patients, who were treated with CIT, PFS was also increased in patients with TTF-1 expression (9 ± 3,17 vs. 3 ± 0,399 months, $p = 0.001$, 95% CI: 0,23 − 0,85).

Conclusions In a real-life setting, we found that TTF-1 expression is associated with an increased PFS. Patients with chemo-/immunotherapy and immunotherapy seem to have a better therapy response in pulmonary adenocarcinoma with TTF-1 expression.

Keywords Chemo-/immunotherapy · Immunotherapy · NSCLC · Prognostic factor for therapy · TTF-1 expression

Background

Immunotherapy with a checkpoint inhibitor (CPI) and chemo-/immunotherapy (CIT) have significantly changed therapy in non-small cell lung cancer (NSCLC) in recent years. There is some data that the effect of CPI therapy is influenced multiple factors. Some are associated by the microbiome (Giannone et al. 2020) and antimicrobial therapy (Chalabi et al. 2020; Uhlenbruch and Kruger 2022, 2023). Other are associated with tumor mutations such as EGFR and ALK (Singh et al. 2022).

Thyreoid transcription factor 1 (TTF-1) expression is used to distinguish adenocarcinoma from the lung to other organs (Schilsky et al. 2017). TTF-1 is expressed in thyroid

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follicular cells and type 2 alveolar epithelial cells (Civitareale et al. 1989).

Concercning chemotherapy, TTF-1 expression is used to choose the most effective chemotherapy. Tumor TTF-1 expression is a positive prognostic parameter for using pemetrexed or docetaxel in patients with pulmonary lung cancer (Frost et al. 2020).

Nowadays CPI therapy und CIT have improved the treatment of NSCLC a lot (Reck et al. 2021).

Some studies show that CPI therapy could be influenced by TTF-1 expression on tumor cells as well (Nakahama et al. 2022).

However, little is known about its effect on PFS of patients treated with CIT or CPI in real life setting. Therefore, the aim of our study was to analyse the effect of TTF-1 expression in tumor cells on the PFS of patients treated with CIT or CPI therapy, who suffer from lung adenocarcinoma stage IV.

Study design and participants

In a retrospective study design, we analysed analysed 130 patients (age 68 ± 7 y) with NSCLC stage IV. Only patients with lung adenocarcinoma were included. Patients with ALK, ROS1, RET, MET, NTRK, EGFR, BRAF mutation were excluded. All patients were treated in our lung cancer centre in the Florence-Nightingale hospital in Düsseldorf / Germany. We collected data from 06/2017 to 01/22.

Patients were treated according to the guidelines with either CPI alone (pembrolizumab, nivolumab, atezolizumab, cemiplimab) or CIT (Carboplatin/Pemetrexed/Pembrolizumab, Carboplatin/Paclitaxel/Atezolizumab).

We registered patients' characteristics including TTF-1 expression and comorbidities.

TTF-1 expression was measured immunohistochemically using the SPT24 antibody. We accepted prior therapy lines of NSCLC according to guidelines.

We chose variables, based on their prognostic impact in NSCLC and risk factors for infections. This included age, sex, BMI, ECOG performance status, lung cancer pathology (squamous and non-squamous NSCLC), comorbidities (COPD, diabetes mellitus, hypertension), PD-L1 status, AMT use and timing of AMT.

The AMT prescription and the timing of its intake were recorded in the medical history.

Group 1 consisted of 40 patients with CPI and TTF-1 expression, group 2 were 26 patients with CPI and with no TTF-1 expression. Group 3 consisted of 41 patients with CIT and TTF-1 expression, group 4 were 23 patients with CIT and with no TTF-1 expression. Patient characteristics are shown in Table 1.

Information about TTF-1 expression and the other variables were taken from our electronic patient database. Only patients with all available data about TTF-1 expression and PFS were included in the analysis.

PFS was determined according to classical RECIST criteria in repeated restaging with computed tomography during antineoplastic therapy.

Table 1 Patient characteristic

		CPI ($n=66$)		Chemo-/Immuntherapy ($n=64$)	
variable		TTF-1 pos. ($n=40$)	TTF-1 neg. ($n=26$)	TTF-1 pos. ($n=41$)	TTF-1 neg. ($n=23$)
		n(%)	n(%)	n(%)	n(%)
Age		71 ± 8 y	71 ± 8 y	67 ± 7 y	65 ± 10 y
sex	male	18 (45%)	19 (62%)	27 (66%)	14 (65%)
ECOG	0	14 (35%)	7 (27%)	17 (41%)	10 (48%)
	> 1	26 (65%)	32 (73%)	24 (59%)	11 (52%)
BMI		22,8 ± 4 kg/m2	24,7 ± 5 kg/m2	25,9 ± 4 kg/m2	24,5 ± 4 kg/m2
COPD	GOLD E	4 (10%)	4 (15%)	8 (20%)	4 (17%)
active smoker		10 (25%)	5 (18%)	13 (32%)	5 (26%)
pack years		35 ± 20 py	42 ± 27 py	41 ± 16 py	30 ± 21 py
arterial hypertension		26 (60%)	14 (54%)	20 (49%)	9 (43%)
atrial fibrillation		6 (15%)	2 (8%)	4 (10%)	2 (9%)
diabetes mellitus		5 (13%)	2 (8%)	7 (17%)	1 (5%)
coronary heart disease		13 (32%)	9 (35%)	12 (29%)	8 (39%)
PD-L1	TPS > 50%	14 (35%)	6 (25%)	9 (21%)	5 (21%)
	TPS 1–50%	22 (55%)	18 (70%)	23 (56%)	11 (46%)
	TPS 0%	4 (10%)	2 (5%)	9 (23%)	7 (33%)

Statistics

Continuous variables are expressed as mean ± SD or median and compared using t-test unless stated otherwise. Statistical analysis was performed using SPSS (Version 28, IBM, Armonk, NY).

Cox proportional-hazards regression was used to analyse the effect of several factors on progression free survival in uni- and multivariable analyses.

Cox regression survival curves were generated to visualize the distribution of times from baseline to disease progression. All statistical tests were 2-tailed and a p-value < 0.05 was considered statistically significant.

Results

We included 130 patients in our analysis. 66 patients were treated with CPI while 64 received CIT. 40 patients with CPI had TTF-1 expression on their tumor cells. 26 patients with CPI suffered from NSCLC with no TTF-1 expression. 41 patients with CIT had TTF-1 expression on their tumor cells. 23 patients with CIT suffered from NSCLC with no TTF-1 expression. At the time of final analysis 90 patients had died and 40 patients were still treated with either CPI or CIT.

Median PFS with CIT was 6 ± 3.2 months compared to 8 ± 2.7 months with CPI ($p = 0.226$).

Comparing group 1 and 2 (patients with CPI with and without TTF-1 expression) PFS was better in patients with TTF-1 expression on their tumor cells. (18 ± 3,15 vs. 5 ± 0,85 months, $p = 0.004$, 95% CI: 0,23 − 0,984).

Comparing group 3 and 4 (patients with CIT with and without TTF-1 expression) PFS was better in patients with TTF-1 expression on their tumor cells (9 ± 3,17 vs. 3 ± 0,399 months, $p = 0.001$, 95% CI: 0,23 − 0,85). Thus, TTF-1 expression was associated with a better PFS in patients treated with CPI and CIT as well.

Antimicrobial treatment one month (AMT) before treatment also showed a significant effect on PFS in patients with CPI ($p = 0,001$) but not in patients with CIT ($p = 0,12$).

The frequency of comorbidities in patients with or without TTF-1 expression showed no significant differences.

Cox proportional-hazards regression demonstrated no significant effect of any other comorbidity on PFS.

The cox regression survival curve for PFS of patients with CPI and CTI is shown in graph 1.

Discussion

The main finding of our study is that TTF-1 expression on lung adenocarcinoma cells is associated with a better PFS in patients treated with CPI and CIT.

Previous studies have shown the possible positive effect in patients receiving pemetrexed. Only few studies showed an effect on immunotherapy.

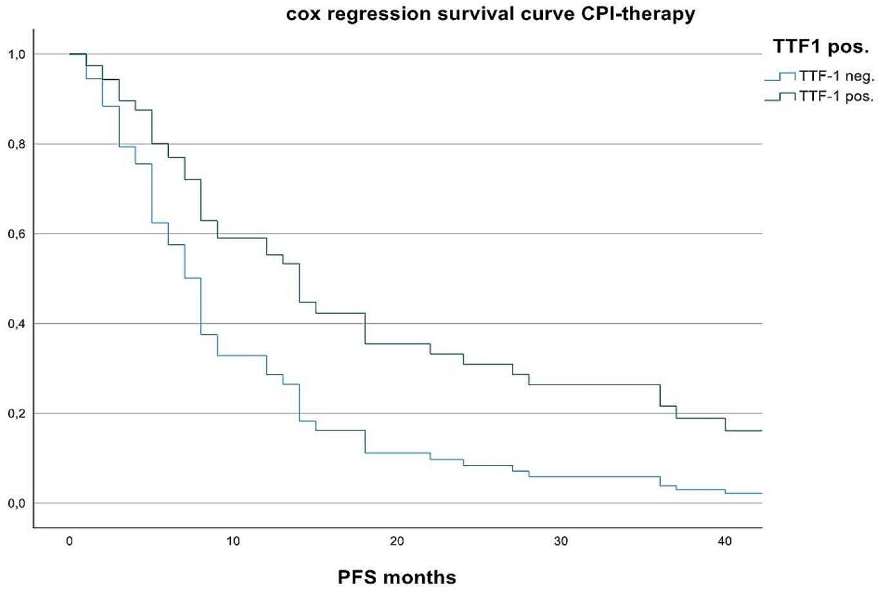
However, in these previous studies there was no focus on chemo-/immunotherapy and comorbidities. To the best of our knowledge, we are first to demonstrate, that TTF-1 expression is a prognostic parameter for chemo-/immunotherapy and immunotherapy as well. This is surprising because chemotherapy and immunotherapy have a different pharmacodynamic. Moreover, parameters influencing CPI have no effect on chemotherapy. A good example is AMT within one month therapy. In our study as well as in other studies AMT one month before therapy influences CPI but not chemotherapy (Chalabi et al. 2020; Uhlenbruch and Kruger 2023).

The hypothesis for the explanation of our findings might be that a negative TTF-1 expression on lung adenocarcinoma cells is associated with STK11 and KEAP 1 mutation (Nakahama et al. 2022). Both mutations are associated with a worse PFS and OS in NSCLC patients treated with chemotherapy and PD-L1/PD-1 inhibitortherapy (Karthikeyan et al. 2021; Johnson et al. 2023).

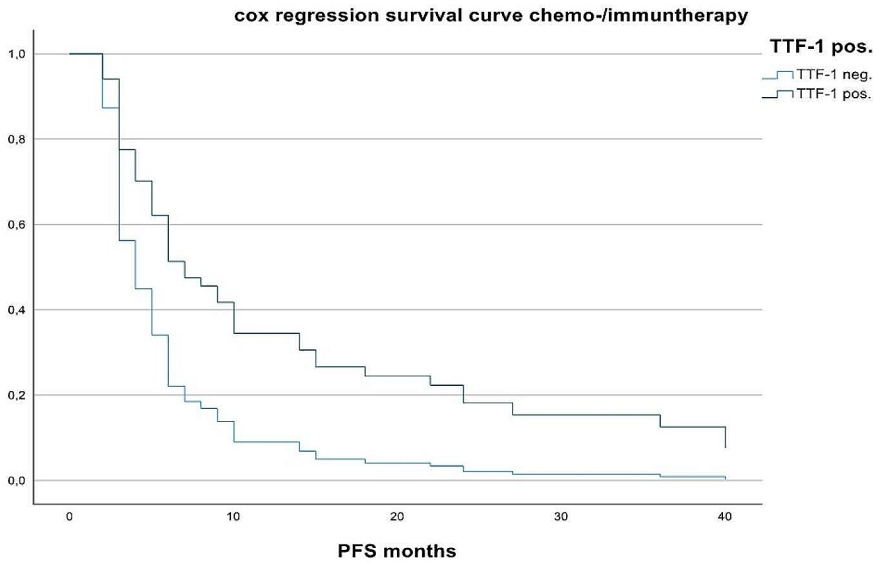
Thus, missing TTF-1 expression could be a predactive parameter using chemotherapy in combination with PD-L1 and CTLA-4 inhibitortherapy.

Our study has several limitations. First, it is a retrospective study with a moderate number of patients. We did not analyse rare mutations like STK 11 und KEAP 1.

In conclusion, our data is hypothesis generating and needs validation in a larger study collective.



Number at risk					
TTF-1 neg.	26	13	6	5	2
TTF-1 pos..	40	31	20	11	7



Number at risk					
TTF-1 neg.	23	13	3	1	0
TTF-1 pos..	41	31	21	11	1

Graph 1 Survival curve of progression free survival based on TTF-1 expression

Author contributions The named authors were alone and there were no further contributions. Both authors shared planning. Data collection and analysis, writing was performed by Mark Uhlenbruch. Prof. Krüger served as scientific adviser. Mark Uhlenbruch is guarantor.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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