Effect of antimicrobial therapy on progression free survival of patients with non-small-cell lung cancer receiving checkpoint-inhibitor- and chemotherapy

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Research Article

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Abstract

Background

Checkpoint-inhibitor therapy (CPI) has 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 by the microbiome. Little is known about the influence and timing of antimicrobial therapy (AMT) on the microbiome mediated effect on CPI therapy.

Patients and methods

We retrospectively analysed 70 patients (age 68 ± 9,2y) with NSCLC stage IV. Patients were treated according to the guidelines with either CPI alone (pembrolizumab, nivolumab, atezolizumab) or chemotherapy (platin doublet or docetaxel / nintedanib or pemetrexed). We registered patients' characteristics including presence and timing of AMT. Group 1 consisted of 27 patients with AMT in the month before CPI- or chemotherapy, group 2 were 30 patients with AMT during CPI- or chemotherapy, and group 3 were 43 patients without AMT.

Results

Group 1–3 showed comparable patients characteristics. Using cox-regression analysis, we found that AMT in the month before CPI resulted in a decreased progression free survival (PFS) compared to patients with CPI and no AMT (14 ± 1.56 vs. 5 ± 0.99, p = 0.005, 95% CI: 0.13–0.67). In patients, who were treated with chemotherapy alone, there was no difference in PFS in those with or without AMT in the month before therapy (5+/- 0,99 vs. 6 ± 0.81 months, p = 0.3). Interestingly, AMT during chemotherapy or CPI therapy showed no effect on PFS.

Conclusions

In a real-life setting, we found that AMT reduces PFS when given in the month before CPI therapy. AMT before chemotherapy and during CPI and chemotherapy seems not to influence PFS. The best PFS was seen in patients without AMT before CPI therapy. This implies the need for an even more restrictive use of AMT in the context of patients with NSCLC stage IV disease.

Highlights / Key Words

- AMT (antimicrobial therapy) given in the month before CPI (checkpoint inhibitor therapy) resulted in a median PFS (progression free survival) of 5 months, which is comparable to the median PFS of chemotherapy.
- AMT during CPI showed no influence on PFS.
- CPI patients without AMT had a remarkably higher median PFS of 14 months.

Background

Checkpoint-inhibitor therapy (CPI) with PD-L1 or PD-1 inhibitors has 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 by the microbiome. A gut dysbiosis due to antimicrobial therapy (AMT) is associated with a dysfunctional immune system[1]. In a mouse-model it has been shown that a dysbiosis in gut is associated with a worse outcome using antineoplastic therapy[2]. Some studies showed negative effects of AMT on outcome in patients with cancer therapy. This was more pronounced in patients with CPI therapy, but also present under chemotherapy[3].

In one large study with 1512 patients with NSCLC stage IV, Chalabi et al.[4] saw a significantly shorter PFS and overall survival (OS) in patients, who were treated with AMT. In this study there was no discrimination with respect to the timing of AMT. AMT could be given in the month before, during or the month after start of CPI- or chemotherapy. However, little is known about the influence and especially exact timing of AMT on the probable microbiome mediated effect on CPI therapy.

Therefore, the aim of our study was to analyse, if the effect of AMT is different, when given in the month before CPI therapy compared to AMT during CPI therapy.

Study Design And Participants

In a retrospective study design, we analysed 70 patients (age 68 +/- 9,2y) with NSCLC stage IV. All patients were treated in our lung cancer center in the Florence-Nightingale hospital in Düsseldorf / Germany. Patients were treated according to the guidelines with either CPI alone (pembrolizumab, nivolumab, atezolizumab) or chemotherapy (platin doublet or docetaxel / nintedanib or pemetrexed). Therapy regimen, that we used were: carboplatin + pemetrexed, cisplatin + pemetrexed, carboplatin + paclitaxel, carboplatin + vinorelbin, docetaxel + nintedanib, pemetrexed, nivolumab, pembrolizumab and atezolizumab.

We registered patients' characteristics including presence and timing of AMT. We accepted prior therapy lines 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.

Group 1 consisted of 27 patients with AMT in the month before CPI- or chemotherapy, group 2 were 30 patients with AMT during CPI- or chemotherapy, and group 3 were 43 patients without AMT.

Information about timing of AMT and PFS were taken from our electronic patient database. Only patients with all available data about AMT and PFS were included in the analysis.

AMT was defined as at least a five days treatment with AMT drugs. PFS was determined according to classical RECIST criteria in repeated restaging during antineoplastic therapy with computed tomography.

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 27, 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 70 patients. 57 were treated with CPI while 43 got chemotherapy. 10 patients with chemotherapy got AMT in the month before therapy and 10 patients during therapy. 17 patients with CPI were treated with AMT one month before therapy and 20 patients during therapy. At the time of final analysis 60 patients died and 10 patients have still been treated with CPI.

Median PFS with chemotherapy was 5 ± 0.5 months compared to 9 ± 2.3 months with CPI (p = 0.002).

Median PFS in group 1 (patients with AMT in the month before CPI- or chemotherapy) was comparable in those with CPI and chemotherapy (5 ± 0.99 vs. 4 ± 0.63 months, p = 0.27).

Median PFS in group 2 (patients with AMT during CPI- or chemotherapy) was comparable in those with CPI and chemotherapy (12 ± 3 vs. 5 ± 0.7 months, p = 0.399).

Median PFS in group 3 (patients without AMT) was significantly higher in those with CPI compared to chemotherapy (14 ± 1.56 vs. 6 ± 0.81 months, p = 0.002).

Thus, CPI patients without AMT compared to CPI patients with AMT in the month before start of therapy showed significantly higher PFS (14 ± 1.56 vs. 5 ± 0.99, p = 0.005, 95% CI: 0.13–0.67). The cox regression survival curve for PFS of patients with CPI and chemotherapy is shown in graph 1.

In addition to AMT in the month before CPI therapy, PFS was significantly negatively influenced by the presence of type II diabetes mellitus and might be positively influenced by PD-L1 status with a TPS > 50%.

Conclusions

The main finding of our study is that AMT before the start of CPI decreases PFS. Previous studies have shown the possible negative effect of AMT in patients with NSCLC and CPI. However, in these previous studies there was no focus on the timing of AMT with respect to its effect. To the best of our knowledge, we are first to demonstrate, that especially AMT in the month before CPI results in a lower PFS, whereas AMT during CPI showed no influence on PFS.

AMT given in the month before CPI resulted in a median PFS of 5 months, which is comparable to the median PFS of chemotherapy. Interestingly, CPI patients without AMT had a remarkably higher median PFS of 14 months.

The hypothesis for the explanation of our findings is as follows: AMT leads to relevant short-term changes in the microbiome, which might negatively influence the immunological answer of CPI. Once the immune system und the influence of CPI has started to produce specific T-lymphocyts to attack tumor cells, it might be not so vulnerable anymore. This could explain, why AMT given during CPI therapy, which also causes dysbiosis, showed no significant effect in our study. The negative effect of diabetes, that we found, might also be linked to dysbiosis[5] and could be associated with altered PFS under CPI therapy.

Our study has several limitations. First, it is a retrospective study with a moderate number of patients. Moreover, prior therapy lines were accepted. We did not analyse the microbiome and its possible changes under AMT during the study. In conclusion, our data is hypothesis generating and needs validation in a larger study collective.

Declarations

All authors have read the manuscript and agreed to publication. No author has got conflicts of interest.

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According to an ethics committee approval is not needed.

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Figures

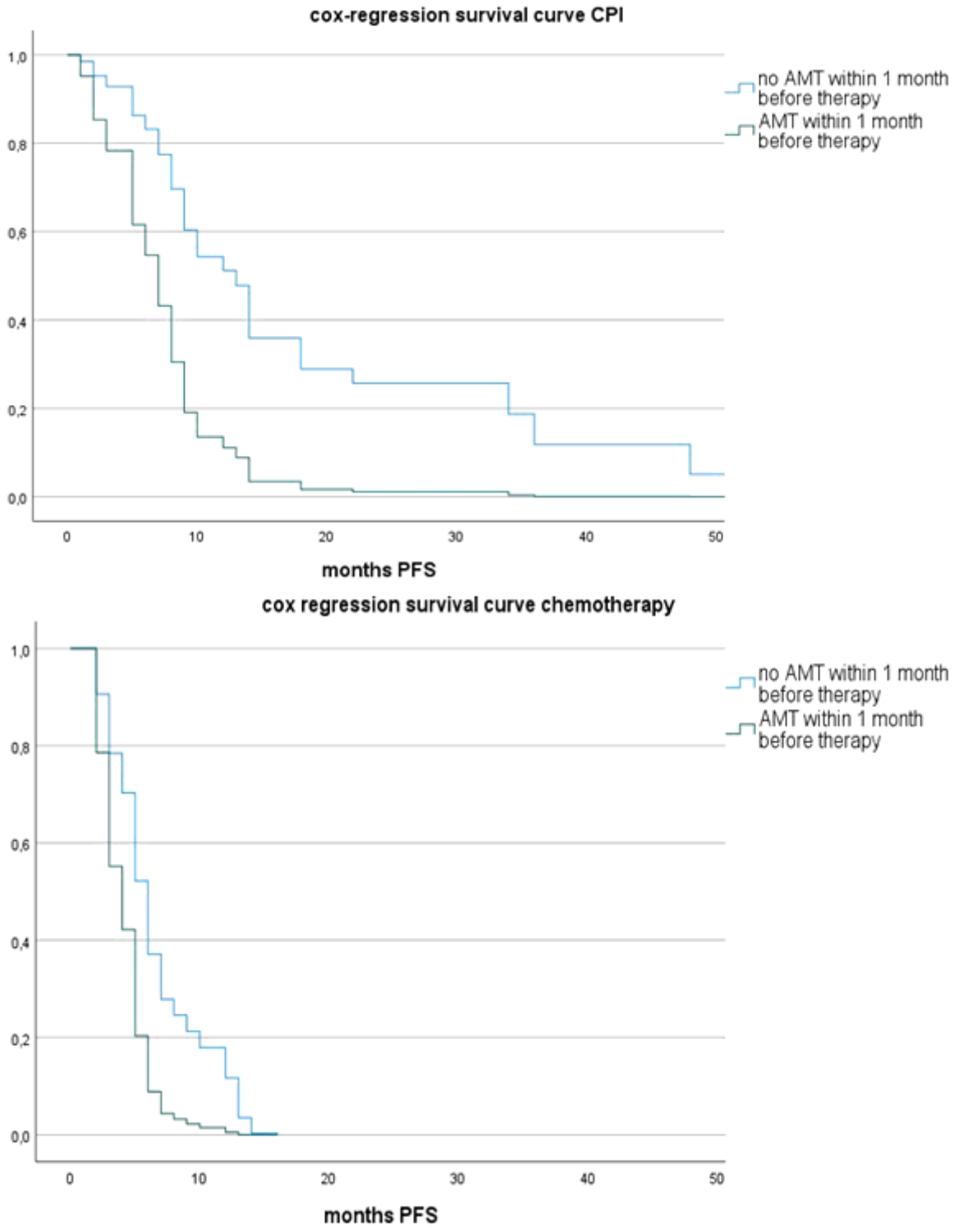

Figure 1

Cox regression survival curve for PFS of patients with CPI and chemotherapy. CPI: check point inhibitor, PFS: progression free survival; AMT: antimicrobial treatment