Impact of Concomitant Medication Administered at the Time of Initiation on the Outcome of Nivolumab Therapy in Non-small Cell Lung Cancer

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Aim

To investigate potential association between administration of corticosteroids, antibiotics, probiotics, proton pump inhibitors, non-steroidal anti-inflammatory drugs (NSAID), statins and metformin and the outcome in patients with non–small cell lung cancer (NSCLC) treated with nivolumab.

Patients and Methods

- multicentric Czech retrospective study based on TULUN registry
- 224 patients with advanced NSCLC treated with nivolumab
- concomitant medications were followed one months before and one months after the initiation of nivolumab treatment
- Overall response rate (ORR) was defined as best response defined by RECIST 1.1
- ORR – Pearson Chi-Square Test and in case assumption of this test was not met, Fisher's Exact Test
- PFS and OS – Kaplan–Meier method
- statistical significance of the differences in Kaplan–Meier – by using the log-rank test
- multivariate Cox proportional hazards model was used to evaluate the effect of all potential prognostic factors on the survival measures
- statistical significance, $\alpha = 0.05$ was used

Results

Baseline patients characteristics

Parameter	Category	n	%
Age	Median	67	Years
Sex	Male	133	59.4
	Female	91	40.6
Smoking status	Smoker	109	48.7
	Former smoker	72	32.1
	Non-smoker	43	19.2
ECOG PS	0	56	25
	1	164	73.2
	2	4	21.8
Line of therapy	First	9	4
	Second	108	48.2
	Third	55	24.6
	Fourth	36	16.1
	Fifth	14	6.3
	Sixth	2	0.9
Histology	Adenocarcinoma	137	61.2
	SCC	86	38.4
	Other	1	0.4
Stage	III	24	10.7
	IV	200	89.3
CRP	< 10 mg/l	76	36.2
	≥ 10 mg/ l	134	63.8

Characteristics of concomitant medication

Parameter	Category	n	%
Corticosteroid use	Yes	22	9.8
	No	202	90.2
Corticosteroid dose (prednisone equivalent)	>10mg	14	63.7 %
	≤10mg	5	22.7 %
	Unknown	3	13.6 %
Antibiotics	Yes	27	12.1
	No	197	87.9
Route of antibiotics administration	Intravenous	3	11.1
	Oral	21	77.8
	Combined	3	11.1
Probiotics (Lactobacillus)	Yes	6	2.7
	No	218	97.3
PPI	Yes	64	28.6
	No	160	71.4
NSAID	Yes	46	20.5
	No	178	79.5
Statins	Yes	31	13.8
	No	193	86.2
Metformin	Yes	18	8
	No	206	92

Univariate analysis of PFS and OS

Parameter	Taking drug	Not taking drug
Corticosteroids		
PFS	p = 0.398	
Median (95% CI)	3.6 (1.7; NA)	6.0 (4.1; 7.0)
OS	p = 0.485	
Median (95% CI)	6.2 (3.6; NA)	13.1 (11.3; 16.9)
Antibiotics		
PFS	p = 0.152	
Median (95% CI)	4.4 (2.7; 10.6)	6.0 (4.0; 7.2)
OS	p = 0.191	
Median (95% CI)	12.8 (6.1; NA)	13.1 (11.0; 20.0)
Probiotics		
PFS	p = 0.821	
Median (95% CI)	6.3 (4.4; NA)	5.9 (3.9; 7.0)
OS	p = 0.837	
Median (95% CI)	7.5 (6.1; NA)	13.0 (11.0; 16.9)
PPI		
PFS	p = 0.117	
Median (95% CI)	3.7 (2.8; 8.8)	6.1 (4.3; 7.2)
OS	p = 0.101	
Median (95% CI)	9.9 (7.5; 33.9)	14.6 (11.7; 20.0)
NSAID		
PFS	p = 0.120	
Median (95% CI)	6.9 (4.8; 24.9)	5.3 (3.7; 6.8)
OS	p = 0.297	
Median (95% CI)	16.8 (8.7; NA)	12.8 (9.9; 16.8)
Statins		
PFS	p = 0.320	
Median (95% CI)	7.2 (3.2; 10.6)	5.4 (3.8; 6.9)
OS	p = 0.426	
Median (95% CI)	16.8 (9.6; NA)	12.9 (10.6; 16.9)
Metformin		
PFS	p = 0.562	
Median (95% CI)	3.3 (2.9; NA)	6.0 (4.1; 7.0)
OS	p = 0.44	
Median (95% CI)	10.6 (3.3; NA)	13.1 (11.3; 17.7)

Multivariate Cox proportional hazard model

	OS		PFS	
Category	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender				
Male	Ref. Cat.		Ref. Cat.	
Female	1.278 (0.779; 2.095)	0.331	1.045 (0.714; 1.529)	0.822
Age	0.963 (0.940; 0.987)	**0.003**	0.972 (0.953; 0.991)	**0.004**
Smoking status				
Non-smoker	Ref. Cat.		Ref. Cat.	
Former-smoker	1.431 (0.715; 2.862)	0.312	1.455 (0.867; 2.442)	0.156
Smoker	0.784 (0.400; 1.536)	0.478	0.762 (0.457; 1.270)	0.297
ECOG PS				
0	Ref. Cat.		Ref. Cat.	
1	1.980 (1.074; 3.651)	**0.029**	1.507 (0.959; 2.368)	0.076
2	0.888 (0.180; 4.383)	0.884	1.263 (0.362; 4.404)	0.714
Line of therapy				
First	Ref. Cat.		Ref. Cat.	
Second	0.884 (0.340; 2.297)	0.801	0.805 (0.343; 1.892)	0.619
Third	0.753 (0.286; 1.985)	0.567	1.064 (0.445; 2.546)	0.888
Fourth	0.794 (0.292; 2.161)	0.651	1.179 (0.476; 2.923)	0.722
5th or 6th	0.563 (0.166; 1.913)	0.358	0.691 (0.243; 1.961)	0.487
Histology				
AC	Ref. Cat.		Ref. Cat.	
SCC	0.577 (0.334; 0.995)	**0.048**	0.592 (0.383; 0.914)	**0.018**
Stage				
III	Ref. Cat.		Ref. Cat.	
IV	1.546 (0.743; 3.218)	0.244	1.211 (0.689; 2.129)	0.505
CRP concentration	1.016 (1.010; 1.023)	**< 0.001**	1.005 (1.000; 1.010)	**0.048**
Corticosteroids				
Yes	Ref. Cat.		Ref. Cat.	
No	0.737 (0.344; 1.580)	0.433	0.933 (0.502; 1.733)	0.826
Antibiotics				
Yes	Ref. Cat.		Ref. Cat.	
No	1.513 (0.717; 3.193)	0.277	1.182 (0.642; 2.178)	0.591
Probiotics				
Yes	Ref. Cat.		Ref. Cat.	
No	1.086 (0.279; 4.232)	0.905	0.765 (0.272; 2.152)	0.611
PPI				
Yes	Ref. Cat.		Ref. Cat.	
No	0.822 (0.487; 1.388)	0.463	0.737 (0.485; 1.121)	0.154
NSAID				
Yes	Ref. Cat.		Ref. Cat.	
No	1.744 (0.946; 3.216)	0.075	1.596 (1.018; 2.503)	**0.042**
Statins				
Yes	Ref. Cat.		Ref. Cat.	
No	1.324 (0.679; 2.584)	0.41	1.251 (0.748; 2.093)	0.393
Metformin				
Yes	Ref. Cat.		Ref. Cat.	
No	0.521 (0.250; 1.089)	0.083	0.714 (0.383; 1.329)	0.287

Overall response rate (ORR)

- Only association between *ORR and corticosteroids* was significant (p = 0.019). Among the patients treated with corticosteroids (n=16), partial response (PR) was observed in 4 patients (25%), stable disease (SD) in 5 patients (31%), and progressive disease (PD) in 7 patients (44%). Among patients not treated with corticosteroids (n=165), PR was seen in 27 patients (16.4%), SD in 106 (64.2%) and PD in 32 patients (19.4%).
- There is no relation between ORR and administration of antibiotics (p = 0.359), probiotics (p = 0.515), PPI (p = 0.655), NSAID (p = 0.504), metformin (p > 0.999) and statins (p = 0.875).

Conclusion

- present retrospective exploratory analysis underscore the importance of detailed knowledge of concomitant medications, including the route of administration or dose in evaluating the effect on the outcome of nivolumab therapy
- significantly higher progression rate was evident in patients treated with corticosteroids
- positive effect of NSAID on PFS (in multivariate Cox model) use at the time initiation of nivolumab treatment was observed