Association of concomitant medications on survival outcomes in cancer patients treated with immune checkpoint inhibitors: analysis of Health Insurance Review and Assessment database

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Soojung Hong[1*], Ju Hyun Lee[2*], Ja Yoon Heo[1], Koung Jin Suh[2,3], Se Hyun Kim[2,3], Yu Jung Kim[2,3], Jee Hyun Kim[2,3], Jong-Seok Lee[2,3].

1. Division of Oncology-Hematology, Department of Internal Medicine, National Health Insurance Service, Ilsan Hospital, Goyang, Republic of Korea
2. Division of Hematology/Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
3. Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

* Soojung Hong and Ju Hyun Lee are co-1st authors

BACKGROUND

Recent evidence suggested that medications regulating immune homeostasis and gut microbiota could affect the efficacy of immune checkpoint inhibitors (ICI). This study aimed to investigate the impact of concomitant medications on the survival outcomes in cancer patients treated with ICI in the Korean population data.

METHODS

The study population was selected from the Health Insurance Review and Assessment Service (HIRA) database in Korea. We identified patients newly treated with ICI for non-small cell lung cancer (NSCLC), urothelial carcinoma (UC), and malignant melanoma (MM) from Aug 2017 to June 2020. ICI was reimbursed as 2nd line in NSCLC and UC and as 1st line in MM. Concomitant medication use was defined as prescribed medication within 30 days before the date of ICI initiation. We assessed the association of concomitant medication (antibiotics (ATB), corticosteroids (CS), proton-pump inhibitors (PPI), and opioids) on treatment duration and survival. In this study, we aimed to analyze the association of concomitant medications with the clinical outcomes such as treatment duration and overall survival (OS) of cancer patients receiving ICI treatment.

RESULTS

We identified 8,870 patients as ICI cohort; 7,128 with NSCLC, 960 with UC, and 782 with MM. The median age was 66 years (range, 60-73), and two-thirds of patients were male. The patients were prescribed baseline ATBs (33.8%), CS (47.8%), PPIs (28.5), and Opioids (53.1%), respectively (Table 1). Median ICI treatment durations were 72 days in NSCLC, 85 days in UC, and 127.5 days in MM. ICI treatment duration was significantly shorter in patients with concomitant medications except in melanoma patients treated with ATB(Table2).

Table 1. Baseline characteristics of ICI cohort patients by cancer types.

	ICI cohort	NSCLC	UC	MM
Number of patients (%)	**8870 (100.00)**	**7128(80.36)**	**960(10.82)**	**782(8.82)**
Age				
Mean age(SD)	66(9.91)	65.8(9.53)	68(10.06)	64.8(12.51)
Age Group				
< 70	5409(60.98)	4425(62.08)	495(51.56)	489(62.53)
70~	3461(39.02)	2703(37.92)	465(48.44)	293(37.47)
Gender				
Male	6694(75.47)	5569(78.13)	714(74.38)	411(52.56)
Female	2176(24.53)	1559(21.87)	246(25.63)	371(47.44)
Type of comorbidity				
Myocardial Infarction	236(2.66)	197(2.76)	27(2.81)	12(1.53)
Congestive Heart Failure	1020(11.5)	854(11.98)	111(11.56)	55(7.03)
Peripheral Vascular Disease	1389(15.66)	1098(15.4)	166(17.29)	125(15.98)
Cerebrovascular Disease	1354(15.26)	1123(15.75)	139(14.48)	92(11.76)
Dementia	193(2.18)	127(1.78)	43(4.48)	23(2.94)
Chronic Pulmonary Disease	6025(67.93)	5250(73.65)	472(49.17)	303(38.75)
Connective Tissue Disease-Rheumatic Disease	400(4.51)	297(4.17)	59(6.15)	44(5.63)
Peptic Ulcer Disease	3334(37.59)	2726(38.24)	382(39.79)	226(28.9)
Mild Liver Disease	3140(35.4)	2520(35.35)	358(37.29)	262(33.5)
Diabetes without complications	3365(37.94)	2747(38.54)	365(38.02)	253(32.35)
Diabetes with complications	1077(12.14)	846(11.87)	123(12.81)	108(13.81)
Paraplegia and Hemiplegia	162(1.83)	129(1.81)	18(1.88)	15(1.92)
Renal Disease	507(5.72)	296(4.15)	180(18.75)	31(3.96)
Moderate or Severe Liver Disease	62(0.70)	52(0.73)	8(0.83)	2(0.26)
Number of comorbidity				
0-1	2718(30.64)	2058(28.87)	297(30.94)	363(46.42)
2-3	3571(40.26)	2979(41.79)	339(35.31)	253(32.35)
4~	2581(29.10)	2091(29.34)	324(33.75)	166(21.23)
Type of ICI				
Pembrolizumab	3502(39.48)	2856(40.07)	20(2.08)	626(80.05)
Nivolumab	2355(26.55)	2145(30.09)	54(5.63)	156(19.95)
Atezolizumab	3013(33.97)	2127(29.84)	886(92.29)	0(0)
Antibiotics				
None	5875(66.23)	4845(67.97)	604(62.92)	426(54.48)
Yes	2995(33.77)	2283(32.03)	356(37.08)	356(45.52)
Broad Spectrum	2816(94.02)	2183(95.62)	340(95.51)	293(82.30)
Narrow Spectrum	179(5.97)	100(4.38)	16(4.49)	63(17.70)
Comedications				
Corticosteroids	4240(47.8)	3758(52.72)	308(32.08)	174(22.25)
PPIs	2529(28.51)	2125(29.81)	247(25.73)	157(20.08)
Opioids	4703(53.02)	3854(54.07)	491(51.15)	358(45.78)
ICI treatment setting				
1st line	887(10.00)	173(2.43)	28(2.92)	686(87.72)
2nd line	4970(56.03)	4194(58.84)	686(71.46)	90(11.51)
3rd line	1854(20.90)	1649(23.13)	201(20.94)	4(0.51)
4th line and beyond	1156(13.07)	1112(15.60)	45(4.68)	2(0.26)
Post ICI treatment (number)				
None	5443(61.36)	4206(59.01)	757(78.85)	480(61.38)
1	2283(25.74)	1831(25.69)	169(17.6)	283(36.19)
2 ~	1144(12.90)	1091(15.31)	34(3.54)	19(2.43)

Table 2. Median Treatment Duration and Overall Survival

	NSCLC (n=7128)			UC (n=960)			MM (n=782)		
Median ICI TD*	72(22-1218) days			85(22-1051) days			127.5(22-1017) days		
Median OS	11.12 (10.63-11.68) months			12.24 (10.82-14.54) months			22.17 (19.54-26.09) months		
	ATB user (n=2283)	ATB non-user (n=4845)	p-value	ATB user (n=356)	ATB non-user (n=604)	p-value	ATB user (n=356)	ATB non-user (n=426)	p-value
Median ICI TD	64(22-162)	85(44-218)	<.0001	68.5(22-202.5)	87(44-248)	0.009	133(65.5-317.5)	127(64-292)	0.972
Median OS	7.24(6.35-7.96)	12.90(12.07-13.71)	<.0001	8.09(6.02-11.61)	15.13(12.57-17.43)	<.0001	22.17(17.76-30.79)	22.47(18.62-26.41)	0.905
	CS user (n=3758)	CS non-user (n=3370)	p-value	CS user (n=308)	CS non-user (n=652)	p-value	CS user (n=174)	CS non-user (n=608)	p-value
Median ICI TD	65(22-1218)	89(22-1213)	<.0001	67(22-942)	86(22-1051)	0.0004	92(22-755)	136.5(22-1017)	0.005
Median OS	8.65(8.06-9.18)	14.38(13.39-15.07)	<.0001	7.30(5.76-9.84)	14.70(12.80-17.04)	<.0001	15.26(10.43-20.46)	24.41(20.95-28.78)	0.001
	PPI user (n=2125)	PPI non-user (n=5003)	p-value	PPI user (n=247)	PPI non-user (n=713)	p-value	PPI user (n=157)	PPI non-user (n=625)	p-value
Median ICI TD	65(22-1218)	80(22-1213)	<.0001	65(22-757)	87(22-1051)	<.0001	93(22-1017)	148(22-1007)	0.0008
Median OS	7.73(7.03-8.36)	12.63(11.94-13.39)	<.0001	7.43(5.72-11.58)	14.54(11.84-16.28)	<.0001	16.45(10.49-21.35)	25.13(20.79-30.10)	0.002
	Opioid user (n=3854)	Opioid non-user (n=3274)	p-value	Opioid user (n=491)	Opioid non-user (n=469)	p-value	Opioid user (n=358)	Opioid non-user (n=424)	p-value
Median ICI TD	64(22-1218)	94(22-1213)	<.0001	64(22-1051)	121(22-942)	<.0001	104.5(22-1017)	148(22-1007)	0.0005
Median OS	7.30(6.74-7.83)	16.28(14.90-17.99)	<.0001	6.68(5.59-8.42)	16.41(14.14-23.91)	<.0001	19.34(14.31-22.17)	26.18 (21.41-NA)	0.0001

*Median ICI treatment duration (day, min-max)

**Median OS (month, 95% Confidence Interval): log-rank test p value

Table 3. Cox Regression analysis for Overall Survival

	NSCLC		UC		MM	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age Group						
< 70						
≥ 70	1.15 (1.08-1.23)	<.0001	1.25(1.05-1.50)	0.015	1.46(1.16-1.82)	0.001
Gender						
Male						
Female	0.96 (0.89-1.04)	0.339	0.90(0.73-1.11)	0.32+8	0.88(0.71-1.08)	0.219
Number of Comorbidity		0.238		0.205		
0-1						
2-3	1.07(0.99-1.15)	0.095	0.86(0.69-1.08)	0.190	1.08(0.85-1.38)	0.536
4~	1.05(0.97-1.15)	0.234	1.04(0.83-1.30)	0.749	1.05(0.79-1.40)	0.736
Type of ICI		<.0001				
Pembrolizumab						
Nivolumab	1.20(1.11-1.29)	<.0001				
Atezolizumab	1.33(1.23-1.44)	<.0001				
Antibiotics						
No						
Yes	1.29(1.21-1.38)	<.0001	1.24(1.03-1.50)	0.023	0.79(0.62-1.00)	0.054
Corticosteroids						
No						
Yes	1.32(1.24-1.41)	<.0001	1.43(1.19-1.72)	0.0002	1.38(1.07-1.78)	0.014
Proton Pump Inhibitors						
No						
Yes	1.18(1.10-1.26)	<.0001	1.22(1.00-1.50)	0.054	1.27(0.97-1.66)	0.078
Opioids						
No						
Yes	1.59(1.49-1.70)	<.0001	1.68(1.39-2.03)	<.0001	1.57(1.23-1.99)	0.0002
ICI treatment setting						
1st line & 2nd line						
3th line over	1.17 (1.10-1.25)	<.0001	1.11(0.91-1.36)	0.307	1.56(1.15-2.12)	0.004

Median overall survivals were 11.1m in NSCLC, 12.2m in UC, and 22.1m in MM. In the multivariable analysis, opioids and CS were strongly associated with poor survival across all three cancer types (Table 3). In NSCLC, ATB and PPI use were associated with inferior OS (6.3 vs. 12.1 months, HR=1.29, 95% CI 1.21-1.38 and 8.1 vs. 13.4 months, HR-1.18, 95% CI 1.10-1.26). In UC, ATB use was associated with poor OS (8.1 vs. 12.6 months, HR=1.24, 95% CI 1.03-1.50). However, ATB and PPI use did not affect survival in the MM cohort.

CONCLUSION

Our real-world data demonstrate that opioid and CS use are associated with poor prognosis in NSCLC, UC, and MM patients treated with ICI. However, the effect of ATB and PPI use on survival differed significantly depending on the type of cancer.

suzzy901@nhimc.or.kr