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CHRONOimmunoTOX: Does time play a role in toxicity?

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Background

Immune checkpoint inhibitors (ICIs) are standards of care in metastatic melanoma. (1)There is growing evidence that the time of administration (ToA) influences patient outcomes due to direct and indirect effects of the 24-hour circadian rhythm on immune system. Indeed circadian rhythm tightly regulates the immune composition and proliferation of blood cells and melanoma patients often show down-regulation of clock genes, which may interfere with the antigen presentation machinery. (3,4) Retrospective studies have demonstrated improved progression-free survival (PFS) and overall survival (OS) in patients receiving morning or early afternoon ICIs.(5,6) Although immunochronotherapy could potentially affect immune-related adverse events (IRAEs), no evidence has been reported.

Methods

We analysed a retrospective cohort of stage IV melanoma patients treated with first-line nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) at our center between 2014 and 2024. We included 41 patients and categorised an administration as “morning” if the infusion was before 2:00 pm. Patients receiving at least two morning doses were categorized into the AM group. Only the time of the four administration of Nivo/Ipi was analysed, based on pharmacokinetics and pharmacodynamics data (3)The primary endpoint was PFS, with secondary endpoints including OS, adverse event rates, toxicity type and grade, and the need of systemic immunosuppressive therapy to treat toxicities.

Results

21 patients were in the AM group and 20 in the PM group. The median PFS in the AM group was not

reached (95% CI 23.23-NR), compared to 7.8 months in the PM group (95% CI 3.10-NR), showing a significant benefit for the AM group (HR 3.45, 95% CI 1.42-8.40, p=0.006). This remained significant in multivariate analysis. A similar trend was observed for OS, but it was not statistically significant (HR 3.04, p=0.121) due to the small sample size and follow-up. No differences in IRAEs were observed between the groups in terms of rate, grade, or type of toxicity. However, PM group patients were more likely to require immunosuppressive treatment for G≥2 toxicity (80% vs. 52%, p 0,06), potentially indicating greater IRAE morbidity.

Conclusion

In melanoma patients treated with first line Nivo/Ipi combination therapy the AM group showed a significant PFS benefit, with a positive trend for OS. While IRAE rates and grades were similar, the PM group was more likely to require treatment with systemic steroids or other immunosuppressive drugs-

Table 1.

PFS forest plot		**n (%)**	**HR (univariable)**	**HR (multivariable)**
ToA	AM	21 (51)		
	PM	20 (49)	3.45 (1.42-8.40, p=0.006)	6.53 (1.88-22.72, p=0.003)
PS ECOG	0	37 (90)		
	1-2	4 (10)	1.81 (0.53-6.15, p=0.341)	3.69 (0.75-18.16, p=0.109)
Age	<60y	22 (53)		
	≥60y	19 (46)	1.33 (0.57-3.10, p=0.510)	2.39 (0.70-8.19, p=0.167)
≥3 sites of mts	No	28 (68)		
	Yes	13 (32)	2.55 (1.09-5.96, p=0.030)	1.63 (0.52-5.04, p=0.400)
SEX	F	16 (39)		
	M	25 (61)	0.56 (0.24-1.30, p=0.177)	0.88 (0.35-2.17, p=0.776)
BRAF mut.	No	18 (44)		
	Yes	23 (56)	1.75 (0.73-4.17, p=0.210)	0.94 (0.33-2.72, p=0.912)
SNC mts	No	22 (54)		
	Yes	19 (46)	1.58 (0.68-3.70, p=0.289)	0.41 (0.11-1.49, p=0.176)
LDH	≥2x ULN	8 (20)		
	UPN	33 (80)	0.49 (0.19-1.26, p=0.139)	0.17 (0.05-0.63, p=0.008)

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