Exploring the Impact of Circadian Timing and TIL Status on Immunotherapy Response in Breast Cancer

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Background

- Circadian rhythms regulate immune responses, but their clinical relevance in cancer immunotherapy remains underexplored.
- Clinical trial results indicate that in advanced non-small cell lung cancer, patients receiving immune checkpoint inhibitors (ICI) at early time of day improve better prognosis compared to those treated at later time of day. [1)2)]
- However, it remains unclear whether the timing of administration affects efficacy in breast cancer treatment.
- We investigated whether the timing of immune checkpoint inhibitor (ICI) administration, in conjunction with tumor-infiltrating lymphocyte (TIL) status, influences treatment efficacy in breast cancer.

Methods

- We conducted a retrospective analysis of two cohorts: a perioperative cohort receiving neoadjuvant ICI (n=22, early-stage) and a metastatic cohort treated with ICI in the advanced setting (n=18).
- For each patient, the median time of ICI administration was determined and dichotomized as morning (<12:00) or afternoon (≥12:00).
- In the perioperative cohort, pathological complete response (pCR) was assessed; in the metastatic cohort, progression-free survival (PFS) was analyzed.
- Pre-treatment stromal TIL levels were evaluated and stratified by median value (TIL-high vs. TIL-low).
- Associations between administration time, TIL status, and treatment outcomes were explored.
- TILs were evaluated based on the International TILs Working Group's proposal using the percentage of area occupied by TILs within the tumor stroma.[3)]

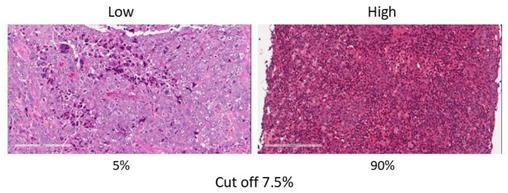


Figure 1. Representative images for TIL assessment in breast cancer.The cutoff value is set at 7.5%, with (A) showing low TILs (5%) and (B) showing high TILs (90%).

Results

Table 1. Patient characteristics in cohort 1.

Factor		N	(%)
		22	
Age	Median (range)	53.5 (34 - 76)	
Clinical T	cT1	2	(9.1)
	cT2-4	20	(90.9)
Clinical N	cN0	14	(63.6)
	cN1-3	8	(36.4)
cStage	Ⅱ	17	(77.3)
	Ⅲ	5	(22.7)
Histology	IDC	19	(86.4)
	ILC	0	(0.0)
	Others	3	(13.6)
Ki-67	< 20	0	(0.0)
	≧ 20	17	(77.3)
	unknown	5	(22.7)
TIL	high	11	(50.0)
	low	11	(50.0)
	unknown	0	(0.0)
pCR	Yes	14	(63.6)
	No	8	(36.4)
Time of administration	< 12:00	6	(27.3)
	≧ 12:00	16	(72.7)
irAE	Yes	9	(40.9)
	No	13	(59.1)

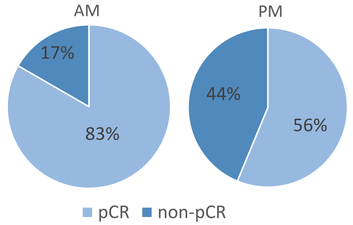


Figure 2. There was no significant association between the time of ICI administration and the pCR rate in cohort 1. (p=0.351)

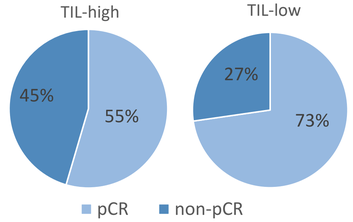


Figure 3. There was no significant association between TIL status and the pCR rate in cohort 1. (p=0.659)

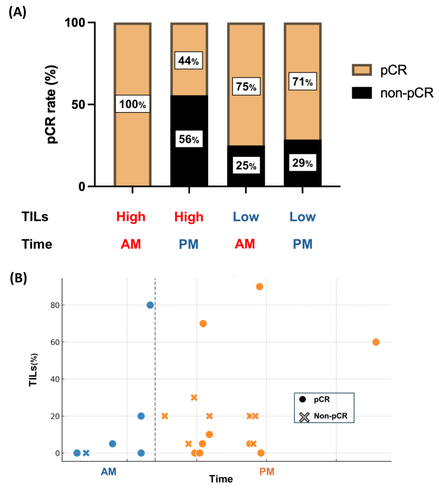


Figure 4. (A) Among patients with high TILs, the group receiving treatment in the morning achieved a 100% pCR rate, whereas the group receiving treatment in the afternoon had a non-pCR rate of 55.6%. In contrast, patients with low TILs demonstrated high pCR rates regardless of the time of administration. (B) Even with high TIL status, afternoon administration tends to be less effective.

Table 2. Patient characteristics in cohort 2.

Factor		N	(%)
		18	
Age	Median(range)	68.0(39 - 78)	
ECOG PS	0	8	(44.4)
	1	10	(55.6)
Disease setting	De novo	8	(44.4)
	metastatic	10	(55.6)
Metastatic sites	Liver	4	
	Lung	11	
	Brain	2	
	Bone only	1	(5.6)
Histology	IDC	16	(88.9)
	ILC	0	(0.0)
	Others	2	(11.1)
Ki-67	< 20	0	(0.0)
	≧ 20	17	(94.4)
	unknown	1	(5.6)
Time of administration	< 12:00	9	(50.0)
	≧ 12:00	9	(50.0)
irAE	Yes	8	(44.4)
	No	10	(55.6)

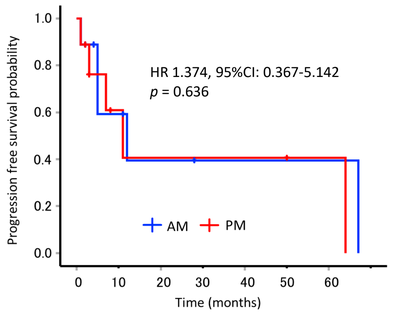


Figure 5. PFS did not significantly differ between morning and afternoon administration in cohort 2.

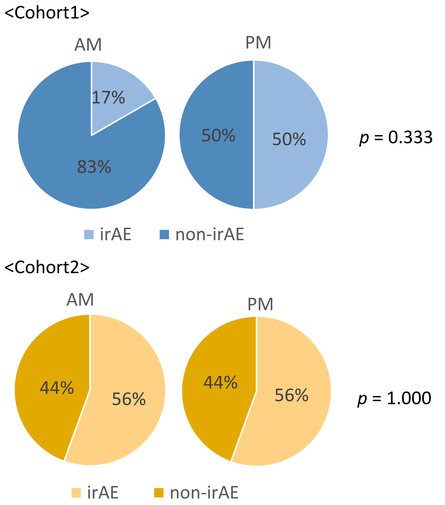


Figure 6. No meaningful association was observed between time of administration and irAE in either cohort 1 (p=0.333) or cohort 2 (p=1.000).

Conclusions

- While overall efficacy was not significantly influenced by ICI administration time, subgroup analysis revealed a paradoxical pattern among TIL-high patients in the perioperative setting: afternoon administration was associated with reduced pCR rates.
- This finding suggests that the functional phenotype of TILs—and possibly their interaction with circadian immune modulation—may shape response to immunotherapy.
- Further studies incorporating spatial and functional profiling of the tumor immune microenvironment are warranted to clarify the clinical implications of circadian timing in ICI treatment.

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References

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