Chrono-immunotherapy in genitourinary oncology: From emerging evidence to clinical translation (Review)

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Received January 7, 2026; Accepted May 15, 2026

DOI: 10.3892/ol.2026.15799

Abstract. The intersection of immunotherapy and circadian biology represents a promising translational frontier in genitourinary (GU) oncology. Immunotherapy has reshaped the treatment landscape and markedly influenced patient outcomes in renal cell carcinoma (RCC) and urothelial carcinoma (UC), yet therapeutic responses remain variable, highlighting the necessity for strategies that can further enhance therapeutic efficacy. Notably, the circadian regulation of immune cell trafficking plays a central role in immune function and tumor biology. Retrospective analyses have suggested that earlier time-of-day administration of immunotherapy improves patient outcomes in RCC and UC. To facilitate the translation of chrono-immunotherapy from a theoretical concept to a clinical standard for patients, the present review assesses the biological rationale behind chronotherapy, summarizes clinical and scientific evidence regarding its therapeutic potential and provides a method for the prospective validation of chronotherapy in GU oncology. The present review also identifies current limitations in chrono-immunotherapy data and proposes potential solutions to validate this data and guide its translation into clinical practice.

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Abbreviations: GU, genitourinary; UC, urothelial carcinoma; RCC, renal cell carcinoma; ICIs, immune checkpoint inhibitors; OS, overall survival; VEGF, vascular endothelial growth factor; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; TME, tumor microenvironment; P, pembrolizumab; EV, enfortumab vedotin; MSI-H, microsatellite instability-high; SCN, suprachiasmatic nucleus; HR, hazard ratio; NSCLC, non-small cell lung cancer; RCT, randomized controlled trial; MEQ, morningness-eveningness questionnaire; DLMO, dim light melatonin onset; AR, androgen receptor; ADT, androgen deprivation therapy

Key words: chrono-immunotherapy, time-of-day administration, GU oncology, circadian rhythm, UC, RCC

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1. Introduction

Immunotherapy revolution in genitourinary (GU) oncology. The therapeutic landscape for GU malignancies has been reshaped over the last decade, which has largely been driven by the advent of immunotherapy, particularly immune checkpoint inhibitors (ICIs) (1,2). This class of agents, which boost the antitumor immune response in patients by suppressing inhibitory immune pathways, have established new standards of care and have demonstrated the potential to promote durable, long-term survival in a subset of patients with cancer (1,2). However, the success of immunotherapy remains inconsistent across GU cancer types, emphasizing the necessity for strategies to optimize immunotherapeutic efficacy, broaden its applicability and overcome mechanisms of therapeutic resistance (1).

The most notable effects of ICI-based treatments within GU oncology have been observed in renal cell carcinoma (RCC) and urothelial carcinoma (UC). In metastatic RCC, ICIs have become the foundation of first-line therapeutic strategies (1,2). Landmark clinical trials have demonstrated the improved efficacy of ICI-based combinations compared with previous standard treatments. The CheckMate-214 trial established that cotreatment with nivolumab, an anti-programmed cell death protein 1 (PD-1) antibody, and ipilimumab, an anti-cytotoxic T-lymphocyte protein 4 antibody, represents a more effective therapeutic option than sunitinib for patients with intermediate- and poor-risk RCC, leading to a marked improvement in overall survival (OS) (3,4). Subsequently, trials such as the KEYNOTE-426, CheckMate-9ER and CLEAR trials have validated the therapeutic efficacy of the combination of an ICI with a vascular endothelial growth factor (VEGF)-tyrosine kinase inhibitor (TKI) in RCC, demonstrating superior OS

and progression-free survival (PFS) compared with TKI alone (5-7). The rationale for these combinations extends beyond the additive effects of individual therapeutic agents; VEGF inhibitors may help to normalize tumor vasculature and modulate the tumor microenvironment (TME) to be more permissive to immune cell infiltration, potentially contributing to a synergistic antitumor effect (2). Similarly, immunotherapy has reshaped the treatment paradigm for UC. For patients with advanced or metastatic UC, pembrolizumab (P) and avelumab have demonstrated therapeutic efficacy in platinum-refractory and first-line maintenance settings, respectively (8,9). More recently, the EV-302 trial provided evidence that the combination of enfortumab vedotin (EV), an antibody-drug conjugate, with P represented a new standard of care in the first-line treatment of unresectable or metastatic UC, doubling the median PFS and OS of patients compared with chemotherapy (10). This treatment regimen has also been studied in the perioperative setting, demonstrating improved patient outcomes, including an increase in the pathological complete response rate of patients with UC (11,12).

Despite these transformative advancements, an important challenge remains: A notable proportion of patients with RCC or UC do not respond to ICI-based therapies, and numerous patients that initially respond to ICI-based treatments eventually develop acquired resistance (13). Primary progressive disease occurs in up to 30% of patients with RCC who are treated with dual ICIs and 10-20% of those receiving ICI-TKI combination therapies (14). This challenge is magnified in patients with prostate cancer, which is the most prevalent GU malignancy in male patients; notably, prostate cancer is largely considered to be immunologically cold and therefore unresponsive to ICIs (15). Although ICIs have been approved for treating patients with microsatellite instability-high (MSI-H) malignancies, ICI-based treatments have failed to improve outcomes for the majority of patients (16). These challenges in GU cancer treatment highlight the necessity of optimizing treatment strategies. One promising yet underexplored mechanism of optimizing cancer treatment involves the endogenous circadian clock, a system that controls the circadian rhythms of the body, including the activity of the immune system and its interactions with cancer cells. This review provides a roadmap for translating the concept of the circadian clock into clinical practice by examining its biological rationale, summarizing emerging clinical evidence supporting its influence on patient outcomes and outlining a path for prospective validation of the therapeutic potential of the circadian clock in GU oncology.

Circadian clock: An endogenous conductor of the antitumor immune response. The efficacy of the immune system is not a static property, but is dynamically sculpted by the 24-h cycle of day and night, a phenomenon governed by a highly conserved internal timekeeping system known as the circadian clock (17,18). These fluctuations in the immune system provide a biological rationale for chronotherapy, which refers to the practice of timing medical treatments to align with the endogenous rhythms of the body to maximize their efficacy and minimize toxicity. The emerging field of chronotherapy has been built upon the foundational understanding that the circadian clock is a master conductor of the antitumor immune response, orchestrating its components spatially and temporally (17-19).

At the molecular level, the circadian clock is driven by a cell-autonomous transcription-translation feedback loop present in the majority of cells in the body. The core mechanism of this feedback loop involves the heterodimerization of key transcription factors, such as circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like protein 1 (BMAL1), which drives the expression of their own repressors; for example, period circadian regulator (PER) and cryptochrome (CRY) (20-23). This feedback loop generates a robust, 24-h oscillation in gene expression that rhythmically regulates a range of cellular processes, including DNA repair, cell cycle progression and metabolism, which are fundamental to cancer biology. Although this molecular clock operates within individual cells, it is synchronized system-wide by the suprachiasmatic nucleus (SCN) of the hypothalamus, which operates as a central pacemaker by interpreting external factors in order to align internal physiological processes with the external environment (Figs. 1 and 2) (24). This hierarchical control ensures that the functions of the immune system are orchestrated over the course of a 24-h circadian cycle.

The influence of the circadian clock on the immune system is multi-layered, affecting a range of factors, from the systemic availability of immune cells to their local function within the TME. A foundational manifestation of this control is the daily oscillation of immune cells in circulation. Naive CD4 and CD8 T-cells have demonstrated notable circadian rhythms with a daytime nadir, whereas mature effector CD8 T-cell counts have been shown to peak during daytime hours. Notably, daytime increases in cortisol mediated by C-X-C chemokine receptor type 4 (CXCR4) have demonstrated the potential to redirect naive T cells from the bloodstream into tissues rich in the corresponding ligand, C-X-C motif chemokine ligand 12 (CXCL12), to the lymph nodes and bone marrow (25,26). This rhythm of T-cell activity is primarily driven by the morning surge of cortisol from the hypothalamic-pituitary-adrenal axis (27).

Furthermore, T-cell infiltration in the tumor is governed by a more complex, dual-layered control system. Beyond the systemic availability of circulating lymphocytes, the vasculature of the tumor itself exerts a local gatekeeping function (28). Preclinical models have demonstrated that the endothelial cells lining tumor blood vessels possess their own intrinsic circadian clock, which rhythmically modulates the expression of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1) (29). This local endothelial rhythm directly controls the extravasation of T cells, which is influenced by hormones and the endothelial clock-mediated permeability of local vasculature, from the bloodstream into the TME, creating a specific time window for the immune infiltration of tumors. As such, this dual control system and the resulting immune infiltration window establishes a notable framework for immune surveillance. The existence of two layers of control suggests an evolutionarily conserved, redundant system. This dual control also presents a notable therapeutic consideration; it is unlikely that the optimal window for immunotherapy administration is solely dependent on when T cells are most abundant in the circulation, but instead when their systemic availability is synchronized with the opening of the local endothelial gate

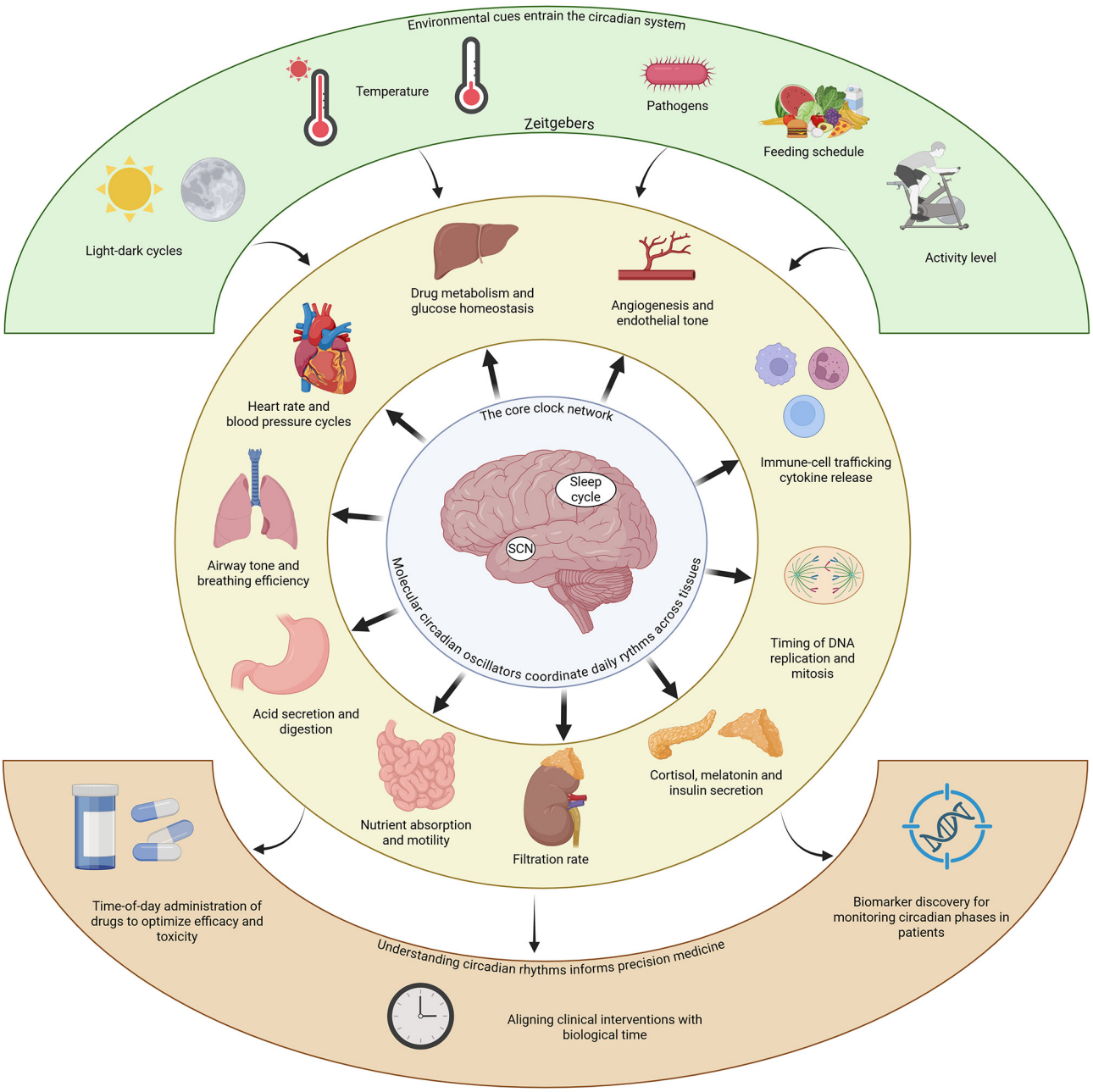

Figure 1. Multi-layered organization of the human circadian system. Created in BioRender. Ozgun, G. (2026) https://BioRender.com/sqawr62. The figure illustrates the hierarchical structure and clinical relevance of circadian biology. The central ring represents the core neural clock network, with the SCN acting as the master pacemaker that synchronizes peripheral clocks across tissues via the rhythmic expression of core clock genes, such as brain and muscle ARNT-like protein 1, circadian locomotor output cycles kaput, period circadian regulator and cryptochrome. The central ring depicts key physiological processes that are subject to circadian regulation, including metabolism, cardiovascular function, immune activity, endocrine secretion and cell cycle control; each of these processes follow tissue-specific circadian patterns. The upper outer ring integrates environmental cues, such as light, temperature, pathogens, eating schedule and activity, which entrain internal clocks. The lower outer ring highlights the clinical and translational implications of the circadian clock, including the implementation of a chronotherapeutic approach in clinical practice, which may pave the way for circadian biomarker discovery and time-based optimization of treatment efficacy and safety, as well as the development of personalized medicine. SCN, suprachiasmatic nucleus.

at the tumor site. The phase relationship between these two rhythms may vary between individuals and tumor types, suggesting that a one-size-fits-all timing strategy may be suboptimal.

The optimal window for immunotherapy administration and temporal differences in therapeutic response have been attributed to multiple factors studied in preclinical settings, resulting from SCN-mediated regulation of the aforementioned biological clock genes of the immune system. As the circadian clock controls the availability of immune cells, such as $CD4^+$ and $CD8^+$ T cells, dendritic cells and macrophages, in the TME, immune-cell depletion is expected to occur in the afternoon and peak a few hours after midnight (30). $CD8^+$ T cells exhibit natural day-night fluctuations in their function and infiltration of tumor tissues, and these rhythms can influence the therapeutic efficacy of immunotherapy. The activity of these cells varies not only due to their own internal clocks but also as tumor blood vessels respond differently to immune

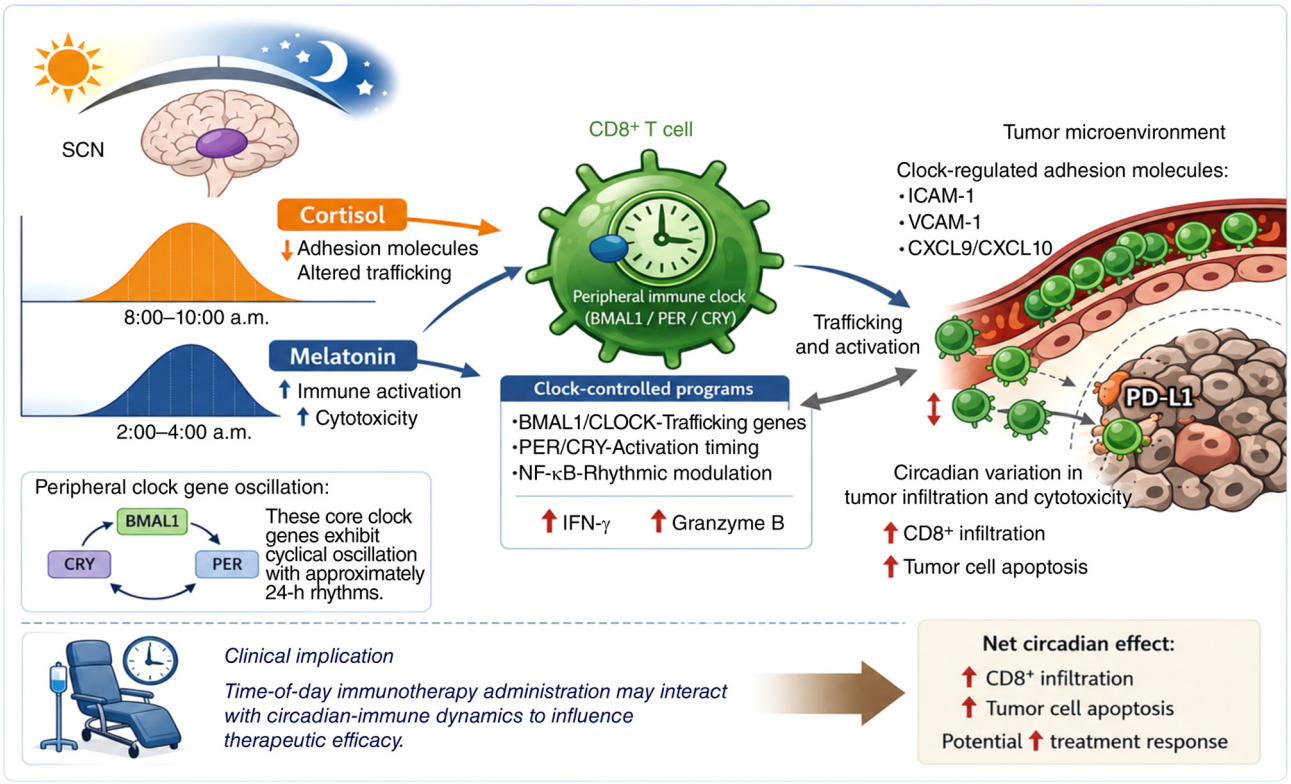

Figure 2. Circadian regulation of CD8+ T-cell infiltration and antitumor activity in genitourinary malignancies. Created in BioRender. Ozgun, G. (2026) https://BioRender.com/r2hqu0u.The suprachiasmatic nucleus (purple) drives rhythmic systemic oscillations in cortisol and melatonin, which provide temporal cues to peripheral immune cells. Circulating CD8+ T cells contain intrinsic circadian clock machinery, which includes BMAL1, CLOCK, PER and CRY, that regulates trafficking programs and effector functions, such as IFN-γ and granzyme B production. Within the tumor vasculature, circadian variation in adhesion molecules, such as ICAM-1 and VCAM-1, and chemokines, for example CXCL9 and CXCL10, may influence T-cell adhesion and extravasation. In the tumor microenvironment, rhythmic modulation of CD8+ infiltration and cytotoxicity intersects with PD-1/PD-L1 signaling. The net circadian effect may result in time-of-day-dependent variation in tumor immune infiltration and apoptosis, providing a mechanistic rationale for chrono-immunotherapy. CLOCK, circadian locomotor output cycles kaput; BMAL1, brain and muscle ARNT-like protein 1; PER, period circadian regulator; CRY, cryptochrome; ICAM-1, intercellular adhesion molecule 1; VCAM, vascular cell adhesion protein; PD-1, programmed cell death protein 1; PD-L1, programmed cell death 1 ligand 1; CXCL, C-X-C motif chemokine.

cell trafficking throughout the day. In a number of preclinical models, chimeric antigen receptor T-cell therapy or treatment using ICIs has been shown to result in improved outcomes when CD8+ T cells reach their peak count and activation status (29,31-33). Chronic disruption of this complex system, whether through environmental factors, such as shift work or jet lag, or internal factors, such as aging, represents a recognized risk factor for cancer development as well as a direct impediment to therapeutic efficacy (34). Circadian disruption fosters a pro-tumorigenic, immunosuppressive TME and can directly dysregulate the molecular clock within tumor cells, leading to the upregulation of immune checkpoint molecules, such as programmed cell death 1 ligand 1 (PD-L1) (35). This creates a deleterious cycle in which a disrupted circadian clock promotes oncogenesis, and the dysregulated circadian clock of tumor tissues arms the tumor with potent mechanisms of immune evasion, rendering it intrinsically more resistant to treatment with ICIs (35).

2. Clinical evidence and emerging frontiers in GU oncology

Clinical signal: Retrospective evidence in RCC and UC. In previous years, there has been a growing interest in the therapeutic potential of chronotherapy, with research investigating the timing of chemotherapy dating back decades and including a large body of work examining the timing of multiple chemotherapy drugs in both experimental and human studies (36-38). The largest prospective trial investigating chronotherapy was a randomized trial involving 564 patients with colon cancer who received 5-fluorouracil/oxaliplatin chemotherapy on either a standard schedule or via timed administration, which was based on optimal administration times predicted by male mouse studies (39). The risk of mortality was reduced by 25% in male patients subject to chronotherapy but increased by 38% in female patients. Notably, there was no sex-based difference in survival among patients subject to the standard administration schedule; this schedule involved the administration of drugs at random times, which is common in chemotherapeutic regimens. Thus, the consistent timing of therapeutic administration highlighted sex-based differences in survival outcomes.

Despite a compelling biological rationale, immunotherapeutic studies focused on GU cancers rarely evaluate the effects of treatment timing and sex together; additionally, women remain underrepresented in numerous trials, limiting the ability to identify clinically meaningful interactions (40-43). Furthermore, a growing body of retrospective evidence has suggested that earlier administration of ICIs associates with improved patient survival, although the causality of this

association remains to be elucidated in patients with metastatic RCC and UC (44). As summarized in Table I (45-52), multiple studies using international cohorts have reported notably consistent findings regarding the therapeutic effects of chrono-immunotherapy. However, only three studies from Table I explicitly adjusted for sex in multivariable models; for the remaining studies, inclusion of sex as a covariate was not specified in the described methods. As evidence suggesting that time-of-day administration influences ICI-based treatment outcomes continues to accumulate, investigations into the role of sex in chrono-immunotherapy studies is necessary to advance the clinical translation of chrono-immunotherapeutic strategies (46,53).

Furthermore, several retrospective studies have demonstrated that morning or early-day infusions were associated with improved PFS and OS in patients with metastatic RCC. For example, a 2024 multi-center analysis reported a 43% reduction in mortality risk for patients receiving infusions before noon [hazard ratio (HR), 0.57] (51). These findings were corroborated by studies on Mexican and European cohorts, which showed that earlier infusions could more than double median PFS and extend median OS (45,51).

The therapeutic benefits of early-day infusions in UC have been shown to be of similar notability. A retrospective study of patients receiving avelumab maintenance therapy published in 2025 demonstrated that morning infusions were associated with a 65% reduction in mortality rate, extending the median OS of patients from 14.4 to 39.5 months (HR, 0.35) (52). An earlier study in a cohort of patients with metastatic UC reported that early-day infusions more than doubled the median OS and tripled the median PFS (47). The consistency and magnitude of these findings provide a strong impetus for prospective validation. Our previous study, which was conducted using a limited cohort of patients with metastatic UC who received P as a second line treatment, also demonstrated that OS and PFS were markedly improved in patients whose average infusion time for the first two treatment cycles was before 2:00 p.m. compared with the late-time-of-day infusion group (54). A larger retrospective cohort analysis is currently underway.

Chrono-immunotherapy in prostate cancer: Biological rationale. Despite the relative paucity of clinical data evaluating chrono-immunotherapy in prostate cancer, several converging lines of evidence support a biologically plausible role for circadian timing in modulating tumor-immune interactions for this disease.

The interaction between circadian biology and androgen signaling represents a notable consideration for the implementation of chronotherapy in prostate cancer treatment. The circadian clock gene PER1 has been revealed to be downregulated in human prostate cancer samples and its protein product has been shown to physically interact with androgen receptors (ARs), resulting in a decrease in AR transactivation (55). Coordination of the circadian clock and androgen signaling is important for maintaining the rhythmic expression of androgen-regulated genes. Furthermore, androgens have been shown to regulate the structure and function of the SCN circadian clock, where ARs are highly present (56,57). Androgen levels have also been shown to exhibit diurnal variation. Notably, single nucleotide polymorphisms associated with variable prostate cancer risk have been identified in several clock genes (29,33).

Androgen deprivation therapy (ADT), a foundational therapeutic strategy for prostate cancer management, has been shown to exert notable immunomodulatory effects that may be temporally dynamic (58). ADT has also been shown to notably aggravate the prostate TME, resulting in an inflamed milieu that exhibits increased activated $CD8^+$ T cell counts, expansion of pro-inflammatory M1-like tumor-associated macrophages, upregulation of major histocompatibility complex class I and II antigen presentation and downregulation of CD47 (59,60). ADT also restores thymic output, with newly generated thymic emigrants trafficking to tumors where they become activated (61). However, a proportional increase in regulatory T cell count and PD-L1 expression has been shown to accompany the $CD8^+$ T-cell infiltrate, suggesting that ADT contributes to the development of adaptive immune resistance (62). Anti-PD-1 immunotherapy combined with ADT has been shown to induce robust immune infiltration in patients with metastatic castration-sensitive prostate cancer (63). Given the established circadian oscillations in $CD8^+$ T-cell tumor infiltration and function, as well as the aforementioned circadian expression of PD-L1 on myeloid suppressor cells, the immunological effects of ADT and its synergy with immunotherapy could plausibly be influenced by treatment timing (64,65).

Notably, the chronotherapeutic rationale in prostate cancer extends beyond the use of ICIs, which only benefits the small subset of patients with MSI-H prostate cancer. Testosterone levels have been shown to peak in the early morning, and AR-driven transcriptional activity, including prostate-specific antigen expression, also follows this diurnal pattern (66,67). This creates a pharmacodynamic window during which AR pathway inhibitors may achieve maximal target engagement by blocking the AR signaling pathway at its point of greatest activity (68). Furthermore, circulating lymphocyte counts reach a nadir in the daytime, which reflects the active redistribution of immune cells into tissues, including lymph nodes and tumors, where they are optimally positioned for antigen encounter and activation (69). Dendritic cells exhibit peak lymphatic migration and enhanced antigen processing during this redistribution period, and $CD8^+$ T-cell tumor infiltration and effector function also oscillate in a circadian manner (29,55). The convergence of peak androgen signaling vulnerability with tissue-positioned immune readiness suggests that morning-timed treatments could simultaneously optimize both hormonal blockade and immune-mediated tumor clearance. This rationale applies broadly across the prostate cancer treatment landscape, including: i) ADT and next-generation AR pathway inhibition; ii) radiation therapy, for which preclinical data have demonstrated superior therapeutic efficacy with morning-timed administration than standard scheduling; and iii) combination strategies employing poly(ADP-ribose) polymerase (PARP) inhibitors, which target DNA damage repair genes that also exhibit circadian expression patterns (70,71). Together, this suggests that the administration of treatments in the morning could improve their overall effectiveness by aligning therapies with hormonal and immune rhythms.

Overall, the complex interplay between the circadian clock, androgen signaling and cellular senescence represents

Table I. Key retrospective studies of chrono-immunotherapy in renal cell and urothelial carcinoma.

First author, year	Cancer type	Regimen	Time of day cut-off	Primary endpoints	Number of patients	Sex adjustment or stratification	Key findings	(Refs.)
Molina-Cerrillo *et al*, 2022	mRCC	Immune checkpoint inhibitor combinations, including PD-1 + CTLA-4, PD-1 + VEGF-TKI, nivolumab + ipilimumab and pembrolizumab + axitinib	4:30 p.m.	PFS	61	NR	Median PFS doubled with earlier infusion (before 4:30 p.m.) at 12.3 vs. 5.6 months (HR, 2.28; 95% CI, 1.1-5.15; P=0.048); trend to improved OS, but data was immature	(45)
Nelson *et al*, 2022	Advanced solid tumors (14.4% renal cell carcinoma)	Immune checkpoint inhibitors and immuno-modulatory combinations, including PD-1, PD-L1 inhibitors ± other investi-gational agents.	One cohort was treated from 8 a.m. to 8 p.m. Another cohort was treated from 8 p.m. to 8 a.m.	OS and PFS	4,441	Yes, there were adjustments for sex in the models	Poorer OS with overnight time-of-day infusion for lung, renal and breast cancer; specific daytime TOI in melanoma and H&N cancers also associated with lower survival	(46)
Ortego *et al*, 2022	mUC	Immune checkpoint inhibitor monotherapy using PD-1 or PD-L1 inhibitors	4:30 p.m.	PFS, OS and RR	92	NR	<20% late infusions associated with improved PFS (11.38 vs. 3.58 months), OS more than doubled (14.04 vs. 6.8 months; HR, 2.62; P=0.001); RR markedly improved (59.3% vs. 16.0%)	(47)
Fernandez-Mañas *et al*, 2023	mRCC	Immune checkpoint inhibitor-based regimens ± VEGF-targeted therapy,for 2nd line treatment	4:30 p.m.	OS	104	NR	Late infusions of ICIs in 2nd line treatments and beyond in the late group were linked to shorter OS and treatment duration, as well as higher progression rates	(48)
Dizman *et al*, 2023	mRCC	Immune checkpoint inhibitors, including PD-1 monotherapy or PD-1 + CTLA-4,	≥20% infusions occurred after 4:30 p.m. This	TTF, OS and ORR	135	NR	The early TOI group exhibited improved ORR (36% vs. 29.5%), longer TTF (9.5 vs. 4.6 months) and longer	(49)

Table I. Continued.

First author, year	Cancer type	Regimen	Time of day cut-off	Primary endpoints	Number of patients	Sex adjustment or stratification	Key findings	(Refs.)
		as well as nivolumab ± ipilimumab, in 1st or 2nd line treatments	defined the late TOI group				OS (46.3 vs. 41.7 months); TTF significance was confirmed	
Arroyave Ramirez *et al*, 2024	mRCC	Immune checkpoint inhibitor combinations, such as PD-1 + CTLA-4 and nivolumab + ipilimumab, in 1st line treatments	4:30 p.m.	OS and ORR	127	NR	The early TOI group (<20% infusions after 4:30 p.m.) had markedly longer OS (64.8 vs. 46.3 months; HR, 0.67; P=0.03)and higher ORR (32.8% vs. 22.4%; P=0.04); stronger impact in inter-mediate- and poor-risk groups	(50)
Patel *et al*, 2024	mRCC	Immune checkpoint inhibitors, for example PD-1 monotherapy or PD-1 + CTLA-4 combi-nation therapy, nivolumab, nivolumab + ipilimumab and pembrolizumab	12:00 p.m.	PFS, OS	201	Yes	Patient who received ≥20% infusions before noon (Group A) demonstrated markedly improved PFS (HR, 0.70; P=0.04) and OS (HR, 0.57; P=0.043); greater peripheral $CD8^+$ T-cell activation compared to those who received <20% of infusions prior to noon (Group B)	(51)
Gonçalves *et al*, 2025	aUC	Immune checkpoint inhibitor maintenance via PD-L1 inhibitors or avelumab	2:00 p.m.	PFS, OS and ORR	105	Yes	Morning infusions, which were defined as those before 2:00 p.m., led to markedly improved OS (39.5 vs. 14.4 months; HR, 0.35); trend toward improved PFS (9.8 vs. 6.6 months; HR, 0.43)	(52)

mRCC, metastatic renal cell carcinoma; aUC, advanced urothelial carcinoma; mUC, metastatic urothelial carcinoma; PFS, progression-free survival; OS, overall survival; RR, response rate; ORR, objective response rate; TOI, time of infusion; TTF, time to treatment failure; NR, not reported; HR, hazard ratio; PD-1, programmed cell death protein 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; VEGF-TKI, vascular endothelial growth factor-tyrosine kinase inhibitors; CI, confidence interval; PD-L1, programmed death-ligand 1.

a promising yet underexplored subject in prostate cancer research (33,72). Future studies should take this into account in clinical trial design to explore whether temporal optimization of ADT or immunotherapy can enhance treatment efficacy in this immunologically cold malignancy (58,73).

3. From hypothesis to clinical standard: A roadmap for translation

Critical appraisal: The indispensable caveat of retrospective data. Although basic scientific data exists to explain the influence of the circadian rhythm on immunotherapy, the underlying mechanisms of this interaction remain incompletely elucidated. It is important to recognize that almost all current human evidence is retrospective and, therefore, hypothesis-generating at best, despite the consistency of results across clinical studies (74-76). Retrospective analyses are highly susceptible to selection bias and confounding factors that cannot be fully adjusted for. It is also possible that patient-related factors, rather than the timing of the treatment itself, were responsible for the results of the aforementioned retrospective studies. For instance, patients who receive immunotherapeutic infusions earlier in the day may be healthier, employed and demonstrate improved therapeutic outcomes, whereas frail patients or those with a poorer prognosis may require more time to prepare for appointments and consequently receive treatment later in the day (74).

Furthermore, chronotype is shaped by a mix of biology, environment and lifestyle, and represents another consideration regarding the applicability and efficacy of chronotherapy (77). Genetics play a notable role in determining chronotype, as sleep onset time is influenced by a number of rare mutations in core clock genes and numerous common variants, whereas age and sex have also been shown to contribute to chronotype; individuals tend to exhibit chronotypes favoring later sleep onset times during puberty and gradually shift chronotype towards earlier sleep onset with aging, and men generally exhibit more evening-typed chronotypes than women until menopause (78-80). Women exhibit stronger circadian immune rhythms and sex hormone-dependent regulation of clock genes compared with men, as well as distinct cortisol patterns, yet the majority of chronotherapy studies lack sex-stratified analyses (44,81,82). Female patients also demonstrate greater hormonal amplitude than male patients, as well as sex-specific circadian-immune interactions, which may influence optimal treatment timing (83-90). Sex-based differences in cortisol dynamics and generally stronger baseline immune responses in women further support this, with clinical data suggesting greater timing sensitivity in women (75,91-95). Hormones, homeostatic sleep pressure and individual circadian traits further shape these chronotype patterns (78). Environmental factors, particularly light exposure and screen use, strongly affect chronotype: High exposure to bright lights at night and limited exposure to daylight have been shown to affect sleeping patterns, with light sensitivity varying widely between individuals (96).

Geography has also been shown to contribute to chronotype; individuals living farther from the equator or in locations that experience later sunsets tend to display later sleep onset times than individuals located in equatorial regions (97). Finally, social and behavioral factors, including work schedules, education level, physical activity, alcohol consumption, smoking, childcare responsibilities, religious practices and even sleep quality, can shift or mask intrinsic circadian preferences, often widening the gap between desired and true sleep onset time (98,99).

Meanwhile, the manner in which clinics and healthcare systems operate can introduce additional biases into practice. Logistical constraints and clinical workflow primarily govern appointment scheduling in oncology centers. Clinical scheduling is influenced by a number of practical issues, for example: i) How complex an appointment is expected to be; ii) how predictable patient flow is; iii) the experience level of individuals responsible for curating schedules; and iv) the limits of the information technology system used by the clinic (100). Clinics may implicitly or explicitly assign complex or potentially time-consuming appointments to periods with lower workload, which are often later in the day. All of the aforementioned factors, as well as variations in study design, such as the definitions of timing for morning and afternoon infusions, treatment type and the line of therapy studied, complicate the interpretation of retrospective studies and may explain the observed differences in patient survival outcomes between studies.

Notably, a retrospective analysis of the single-center, multi-cohort investigator-initiated phase II study of pembrolizumab immunological response evaluation (INSPIRE) study evaluated whether the timing of P administration influenced clinical outcomes in 106 patients with diverse malignancies, including GU malignancies. The median infusion start time was 3:06 p.m. for the first treatment dose and 3:11 p.m. across all doses, and the range of infusion start times extended from 09:19 a.m. to 6:34 p.m. Multiple predefined timing thresholds were assessed, including: i) Administration before vs. after noon; ii) administration before vs. after the median start time; iii) the proportion of doses delivered after 4:30 p.m. (≥20% threshold); and iv) the season of treatment initiation. Across all analyses, infusion timing was not associated with PFS, OS or the incidence of grade ≥2 immune-related adverse events according to Common Terminology Criteria for Adverse Events, and findings were consistent across tumor-specific subgroup analyses. However, the initial study demonstrated a median follow-up of only 11.5 months, which was notably shorter than positive studies in the literature, such as the MEMOIR trial, which extended OS monitoring to 5 years, Retro TIMing trial, which lasted 29 months, and a trial on a Japanese non-small cell lung cancer (NSCLC) cohort, which lasted for 62.5 months. With only 106 patients fragmented across five cohorts of patients with cancer, containing as few as 12 patients with melanoma per subgroup, the INSPIRE study was too underpowered to derive a sufficient conclusion on chronotherapeutic efficacy. Additional limitations of the INSPIRE study included: i) Tumor heterogeneity inherent to the basket design of the study; ii) the possibility that lower overall response rates in a mixed tumor population may have diluted potential chronotherapy signals observed in more immunotherapy-responsive cancers; and iii) the single-center Canadian setting, which raises the possibility that geographical or seasonal differences not observed within the study may limit treatment generalizability (75,76,101,102).

Negative trials are important for defining the boundaries of chrono-immunotherapy. A detailed comparison of the INSPIRE study and GU-specific retrospective analyses is provided in Table SI (45-51,76,103), highlighting key differences in study design, patient populations, timing definitions and statistical reporting. Furthermore, several features of prior retrospective analyses have raised the possibility of false-positive findings in chrono-immunotherapy studies, including: i) Residual confounding factors, for example patients with higher fitness levels may have been preferentially treated earlier in the day; ii) the use of operational rather than biologically defined timing cut-offs; and iii) multiple hypothesis testing across different time thresholds without correction. All of these factors may inflate type I error rates (44,91-93). These features raise the possibility of publication bias and serve as a reminder that biological rationale on its own is not sufficient to support the efficacy of a treatment. A prime example of this is the Cardiac Arrhythmia Suppression Trial, which demonstrated higher mortality rates in patients treated with anti-arrhythmic drugs (compared with placebo) after myocardial infarction despite strong biological reasoning supporting their therapeutic potential, further supporting the necessity of prospective trials (74).

Path forward: A methodological framework for prospective validation. The convergence of a strong biological rationale and consistent retrospective data has generated an important hypothesis regarding the efficacy of chrono-immunotherapy. To translate this concept into a clinical standard of care, well-designed pragmatic, prospective, randomized controlled trials (RCTs) are needed (74).

However, emerging research has revealed an important layer of complexity that should inform the design of future studies: The plasticity of human chronotype. Chronotype is not a fixed trait but a dynamic state resulting from continuous interactions between the endogenous circadian system and external environmental cues (104). A number of external signals have been shown to influence the circadian system, which are known as zeitgebers. The most implicated zeitgebers with the largest reported effects are light-dark cycles, temperature, exercise, pathogens and nutrition (105). Prior analyses have shown that societal factors, particularly work schedules, markedly shape the internal time of an individual. Occupationally active individuals exhibit chronotypes that are markedly earlier than those of non-working individuals, and internal rhythms can shift measurably between workdays and weekends (106,107). This plasticity provides a mechanistic explanation for potential confounding effects in prior retrospective studies; patients available for morning infusions may have more structured daily routines; therefore, the improved patient outcomes observed in early-administration cohorts may have been linked to the more robust underlying circadian health of these individuals, rather than the treatment timing itself. As such, a randomized trial design is required to definitively isolate the therapeutic effect of administration time (37,108), including: i) Randomized treatment timing; ii) standardized definitions of exposure windows; iii) tumor-specific stratification factors; and iv) sex and individual circadian measures, such as chronotype.

Historically, the morningness-eveningness questionnaire (MEQ), a subjective assessment tool, has been used to assess circadian phases, with important limitations. Notably, this questionnaire reflects self-reported preference rather than true biological circadian phase and can be influenced by social factors. As such, MEQ may misclassify circadian timing and should be interpreted cautiously in chronotherapy studies (109). Subsequently, the dim light melatonin onset (DLMO) assay was developed, which measures the increases in melatonin level in saliva observed during evening hours (109,110). Although the DLMO assay represents the physiological benchmark for circadian phase assessment, routine implementation of this assay in high-volume oncology practice is unrealistic due to the resulting logistical burden, complicated technique and cost (110-112). Therefore, more powerful and feasible tools are required for the identification of patients who may respond more effectively to morning or afternoon treatment schedules, thereby helping to align therapy with the circadian rhythm of each patient for improved outcomes.

Molecular clock-based assays, such as TimeTeller, which estimate internal circadian time via RNA sequencing of tissues such as the oral mucosa, offer a robust and feasible approach (113,114). In parallel, actigraphy and consumer-grade wearable devices provide low-cost, minimally invasive longitudinal estimates of activity-rest cycles and chronotype that could serve as practical surrogates for circadian phase (112). Notably, initial implementation of circadian rhythm data for chrono-immunotherapy studies may not require individualized phase assessment; the standardization of therapeutic infusions to a defined morning window could serve as a pragmatic first step, with biomarker-guided refinement reserved for further research settings. This tiered approach may balance biological precision with clinical feasibility and therefore enhance the translational viability of chrono-immunotherapy.

Moving forward, a combination of clinical and molecular tools could enable the capture of multidimensional information to examine the real-time effects of the circadian rhythm and its effects on the immune system. Within this context, integrated translational studies may represent an important method of elucidating immune biology mechanisms and TME changes that are influenced by circadian time, helping to distinguish true circadian effects from experimental noise and generate evidence that will markedly influence clinical practices. Incorporating longitudinal sampling into the design of future studies may help to capture dynamic changes in the immune system over time, revealing daily oscillations in key immune cell populations and clarifying the mechanisms (115). The ultimate goal is to determine optimal treatment timing, for example morning versus afternoon, and the appropriate number or proportion of treatment cycles to mandate for improved therapeutic efficacy.

On another note, circadian amplitude, which is the magnitude of oscillation between peak and trough values in circadian rhythms, is another important factor in chronobiology and represents an important indicator of health that often declines with age and disease. The circadian amplitude of an individual patient could represent an important predictive biomarker, identifying patients with a robust, coordinated immune system who are most likely to benefit from timed immunotherapy (110).

Overall, the combination of advanced technologies could help determine whether the timing of a therapy influences patient outcomes, paving the way for personalized chronotherapy approaches.

From bench to bedside: Considerations for clinical application. It is important to determine a cut-off time for grouping patients for early- or late-time-of-day drug administration (116). However, this was not standardized in the available retrospective data, and cut-off times for patient stratification were predominantly based on data from Qian *et al* (75), which were modified according to practical or clinical considerations. Across retrospective studies, the cut-off time to determine early and late treatment groups varies, including noon, 2:00, 3:00 or 4:30 p.m. (75,101,117). As such, an optimal cut-off time has yet to be determined. A portion of this variability may reflect practical scheduling constraints within clinical infusion centers, whereas this variation also partially reflects attempts to align treatment timing with different interpretations of circadian immune biology.

The MEMOIR study, for example, selected 4:30 p.m. as the cut-off time for treatment groups based on data suggesting that circulating naïve CD4 and CD8 T cells approach a late-day nadir at this approximate time (75). Due to the differential classification of patients treated between midday and late afternoon across studies, some degree of exposure misclassification remains unavoidable, which likely contributes to variability in the reported outcomes.

More broadly, these differences in cut-off time highlight the absence of a consensus regarding the biologically optimal treatment window. Similar challenges have been identified in earlier chronotherapy research involving chemotherapy, which uncovered promising biological signals that were difficult to translate into clinical practice (37). An additional layer of complexity regarding temporal stratification stems from the growing recognition that circadian phases vary widely between individuals. Differences in chronotype may shift the biologically relevant treatment window by several hours, raising the possibility that fixed clock-time cut-off values only represent a practical approximation of chronotherapeutic efficacy rather than a physiologically precise strategy (30,37,53,118).

Toward a biologically informed treatment window. Circadian physiology provides a useful framework for elucidating how treatment timing might influence immunotherapy outcomes. Cortisol levels have been shown to reach their peak in the early morning and then decline gradually over the course of the day, and lymphocyte trafficking and T-cell activation capacity have also been shown to follow coordinated daily rhythms (95,119-123). Circadian variation in circulating T cells is subset-specific: Naïve $CD4^+$ and $CD8^+$ T cells show a daytime decrease, potentially due to cortisol/CXCR4-driven redistribution to the bone marrow, while terminally differentiated effector $CD8^+$ T cells are increased during daytime hours (75). Although these findings require validation in well-designed trials, they support the broader concept that immunotherapy delivered during periods of greater immune activation capacity may produce more effective antitumor responses.

Taken together, available physiological and early clinical data suggest that the late-morning to early-afternoon period may represent a reasonable biologically aligned window for ICI administration. Furthermore, the circadian phase and chronotype of an individual may shift the optimal timing of ICI administration. Future studies incorporating simple circadian assessments may help to progress chrono-immunotherapy translation to create more personalized scheduling approaches aligned with the intrinsic biological rhythms of each patient (30,37,118).

Other clinical considerations for determining the optimal treatment window. Another aspect of treatment timing to consider is the type of ICI used, as there may be differences in therapeutic responses to variable time-of-day administration among different treatments and diseases, which should be addressed in future research (124). The number of treatment cycles required for immune priming represents another aspect of chronotherapy that remains poorly defined.

Rodent studies have shown that after initial treatment cycles, the response to the timing of administration diminished. The reasons behind this reduction in response intensity over the course of treatment remains poorly understood. The reason may partly have been due to the potentially long half-lives of drugs used, resulting in the maintenance of relatively constant systemic drug levels and therefore a reduction in patient sensitivity to dosing time (125-128). Notably, an immunotherapy trial conducted in patients with NSCLC reported improved median PFS and OS in patients who received at least one of the first four treatment cycles prior to noon compared with those who received only late-day drug administration (129). As such, investigations into the optimal number of treatment cycles or the percentage of cycles that should be mandated to achieve a meaningful difference in treatment response will play an important role in translation.

In the rapidly evolving field of chronotherapy, well-designed prospective RCTs are required to validate retrospective findings and to further elucidate the mechanisms underlying chronotherapy and chronobiology in GU oncology. Building on our retrospective research project that supported the findings reported in the literature, two investigator-initiated phase III RCTs have been initiated by our research group: i) An RCT investigating the impact of time-of-day administration of EV and P in metastatic UC (ClinicalTrials.gov identifier NCT07346053); and ii) an RCT examining the impact of time-of-day administration on dual immune checkpoint inhibition in advanced RCC (ClinicalTrials.gov identifier NCT07338981). As the opposite sex-specific effects were observed in the literature, we have incorporated sex as a stratification factor in the trial design. Treatment timing was determined according to existing literature and expert opinion. Additionally, the assessment of different timing groups in the morning and afternoon, as well as correlation analyses on the observed outcomes, to improve the analysis of the therapeutic benefits associated with different administration times, will be included. Furthermore, the chronotype information of trial participants has been incorporated into the study design. We have also intentionally included a gap between the morning and afternoon groups to capture potential differences in

outcomes with improved accuracy and to avoid potential overlap between treatment groups. These studies aim to reshape the field of GU oncology by providing insights into the relationship between tumor biology and chronotherapy, guiding the design of prospective trials and accelerating progress toward determining whether chronotherapy can optimize treatment outcomes in GU cancers.

Practical considerations for clinical implementation. In the event that prospective RCTs support the influence of time-of-day administration on immunotherapy outcomes, the most notable challenge for clinical translation will be implementing chronotherapy into routine oncology practice. Unlike pharmacological innovations, the clinical translation of treatment-timing strategies requires health-system workflow adjustments, staffing considerations and careful attention to equitable patient access (44). Implementation planning should therefore be considered early in the translation process.

Clinical workflow and capacity. The majority of oncology infusion centers already experience peak activity during morning hours, which is driven by patient preference, laboratory processing workflows and staffing patterns (130). A shift toward preferential morning delivery of immunotherapy could exacerbate existing clinical bottlenecks associated with chair availability, pharmacy preparation timelines and nursing support. Health systems may therefore need to adopt a range of operational strategies if early treatment administration demonstrates improved efficacy (130).

One approach to implementing chronotherapy in clinical practice would involve the expansion of morning infusion capacity through earlier opening hours and increased staffing support. Although this may be feasible in some clinical centers, its implementation could incur substantial financial costs and, if not carefully managed, may markedly increase workload demands and contribute to fatigue among nursing staff. Although treatment-timing interventions have often been described as 'low-cost' or 'cost-neutral', rigid scheduling recommendations could unintentionally create access barriers for some patient populations (53). Patients living in rural or geographically remote areas may need to travel several hours to reach clinical infusion centers; as such, mandatory early-morning appointments could necessitate overnight accommodation or departures during the early pre-dawn hours. Notably, transportation barriers and limit paratransit servies have been associated with delayed follow-up, reduced accessibility of specialized medical care and treatment inconsistent with established guidelines in remote areas (131-133). Considering chronotherapy from a health economics perspective, formal cost-effectiveness analyses would be necessary before implementing widespread timing-based clinical scheduling changes. Cost-effectiveness frameworks should therefore incorporate not only potential survival benefits, but also operational costs, patient-incurred expenses, such as transportation and accommodation, and equity impacts. Notably, even interventions with minimal drug-related costs may not be cost-effective if they exacerbate access barriers or disproportionately burden vulnerable populations (134,135).

An alternate strategy for synthesizing optimal therapeutic timing with clinical practice involves staggered morning scheduling, for example 07:00, 09:00 and 11:00 a.m. start times within medical centers, to distribute patient flow more evenly while preserving early-day drug administration (130). A third approach may involve biologically targeted prioritization, in which patients most likely to benefit from chrono-immunotherapy, based on evaluations using biomarkers, chronotype assessments or disease-specific evidence, are preferentially allocated to the appropriate clinical time slots.

Collectively, these strategies highlight the fact that the practical implementation of chrono-immunotherapy would likely require adaptive, institution-specific scheduling solutions rather than uniform mandates across all infusion centers (130). Additionally, given that retrospective data suggest that the timing of initial treatment cycles exerts the greatest impact on therapeutic efficacy, focusing the allocation of early-day clinical time slots to patients undergoing initial treatment cycles may simplify the practical implementation of chronotherapy, as this strategy would not require timing adjustments for the entire course of therapy.

4. Conclusions: Translating biological rhythms into standard of care

The field of chrono-immunotherapy in GU oncology stands at an important juncture. The study of chrono-immunotherapy has progressed from a biological concept rooted in the fundamental role of the circadian clock in regulating immunity to a tangible clinical signal supported by consistent retrospective data, with ongoing prospective trials attempting to validate the concept. Ultimately, chrono-immunotherapy represents a paradigm shift in therapeutic rationale. This therapeutic strategy does not involve a new drug, but a new dimension of care: A readily accessible strategy that leverages the physiology of a patient to enhance the efficacy of existing treatments. Although chrono-immunotherapy involves no additional drug costs, implementation into clinical practice would require upfront investment in clinical workflow optimization and may therefore impose indirect costs on patients. Formal cost-effectiveness analyses comparing these implementation costs against the potential survival benefits associated with chrono-immunotherapy will be necessary before widespread adoption of this therapeutic strategy.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

OZD, BE and GO conceived and designed the present review. OZD, XY and GO wrote the original draft of the manuscript. OZD, XY, PL, RA, GB, CK, BE and GO revised the manuscript.

Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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