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Chrono-immunotherapy as a low-hanging fruit for cancer treatment? A call for pragmatic randomized clinical trials

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ABSTRACT

The share of immune checkpoint inhibitors (ICIs) used in cancer treatment has rapidly increased in recent years. Although ICIs have the potential to provide a durable survival benefit in a subset of patients, many patients do not respond to these costly and often toxic therapies. Recent retrospective clinical data indicate that the time of day of ICI infusion may be a powerful modulator of their efficacy. These observational studies suggest an enhanced efficacy of morning over evening infusion. However, randomized trials have not confirmed in other fields findings obtained by observational studies, possibly because of selection bias and residual confounding factors. Thus, while the data are intriguing, the time dependence of the efficacy of immunotherapy needs to be confirmed in pragmatic randomized clinical trials. Here, we provide an overview of the modulation of ICI efficacy by the timing of immunotherapy infusion and critically discuss the biological rationale for chrono-immunotherapy, the circadian regulation of the immune system, and the need for pragmatic randomized clinical trials to confirm an effect of the timing of immunotherapy infusions on patient outcomes.

CHRONO-IMMUNOTHERAPY: A BIOLOGICAL RATIONALE

Various physiological functions and pathological processes, including carcinogenesis[1] and metastatic cell shedding,[2] are affected by circadian rhythms. Our body's internal circadian clock is composed of a complex molecular network. The so-called master clock resides in the suprachiasmatic nucleus, which regulates the sleep-wake rhythm, body temperature, and food intake with a periodicity of approximately 24 hours.[3] The cells of the innate and adaptive immune system and their crosstalk with surrounding tissues are tightly controlled by the circadian clock at multiple levels that include leukocyte effector functions and trafficking, which influences the number of circulating immune cells.[4] This circadian regulation of immune functions might have evolved as an adaptation mechanism to cyclic differences in exposure to pathogens, although that remains speculative.[5]

Dendritic cells (DCs) are essential for anticancer immunity. Migration of DCs into the draining lymph node and expression of molecules important for antigen presentation and T cell priming/activation, such as the costimulatory molecule CD80, all occur in a circadian fashion.[6] Effector functions of T cells, including their priming, proliferation, and capacity to produce IFNγ, also differ in their magnitude depending on the time of day.[3] Thus, the circadian regulation of multiple cellular compartments involved in successful anticancer immunity has been shown to translate into differential efficacy depending on the time of day administration of immune checkpoint inhibitor (ICI) therapy in preclinical mouse models of cancer.[7] Mice are nocturnal, and cancer cells injected in the early morning grow more aggressively compared with injections performed in the afternoon. Furthermore, anti-cancer therapy by vaccination is most effective when administered to mice in the afternoon. Humans, in contrast, are diurnal or day-active, which means that their immune system is shifted by ~12 hours compared with mice,[8] pointing to a stronger immune response to vaccination in the morning. Indeed, a retrospective analysis of an antitumor vaccination trial in stage IV melanoma patients[9] indicated that vaccination had the strongest effect on the generation of antigen-specific $CD8^+$ T cells when administered in the morning compared with the afternoon[6] (figure 1). Still, preclinical models may fail to guide human immunotherapy research. For instance, key PD-1 differences between rodents and humans, due to evolutionary divergence, impacted immune function.[10] When exploring the

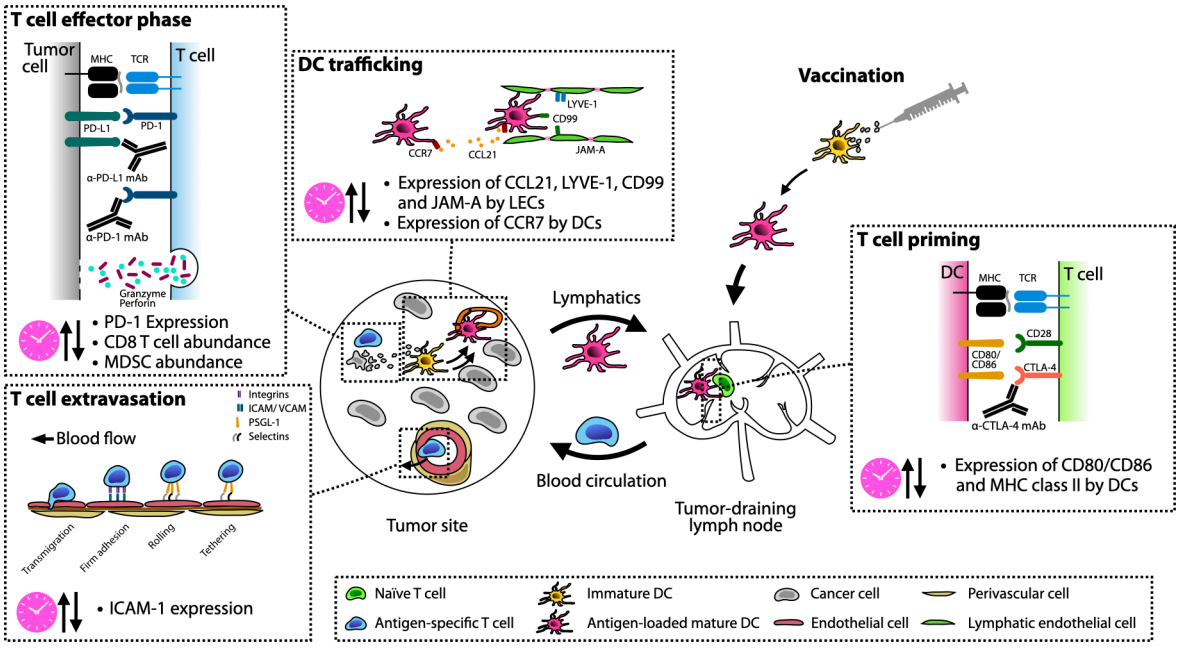

Figure 1 Circadian regulation of the cancer immunity cycle. Multiple steps of the cancer immunity cycle[37] are subjected to circadian oscillations. The molecules and cell types affected in their expression and abundance, respectively, are indicated by a clock symbol. Please note that although DC trafficking to the tumor draining lymph is altered depending on the time of day, the indicated molecules (CCR7, CCL21, LYVE-1, CD99 and JAM-A) have formally not been investigated in the tumor setting. However, the circadian regulation of their expression has been shown in the immunosurveillance of the skin.[38] DC, dendritic cell; MDSC, myeloid-derived suppressor cell.

temporal dynamics in the generation of circulating tumor cells (CTCs) in relation to the body's circadian rhythms, researchers found that most spontaneous CTC intravasation events in patients with breast cancer occurred during sleep, with these CTCs also being more prone to metastasize compared with those generated during active behavioral phases. This suggests that the body's rest phase plays a significant role in cancer metastasis, highlighting a potential for time-controlled treatment strategies.[2]

The concept of chronotherapy—timing the administration of drugs in concordance with the body's circadian rhythm to increase efficacy while minimizing potential adverse effects and toxicity—was proposed half a century ago.[11] In experimental models, the importance of dose timing for severe toxic outcomes has been demonstrated for more than 30 anticancer drugs. In a phase I/II trial enrolling patients with metastatic colorectal cancer, the optimal timing of irinotecan administration to minimize adverse events without impairing efficacy was found to be sex dependent. In male patients, receiving irinotecan in the morning yielded the lowest toxicity, while female patients experienced fewer adverse events when receiving it in the afternoon.[12] Sex differences in chronoefficacy and chronotoxicity may arise from sex-specific variations in circadian rhythms,[13] gut microbiome,[14] hormonal regulation of drug metabolism with distinct patterns in enzyme activity [15] and drug clearance[16] . For instance, in a recent population pharmacokinetics model of nivolumab, patient sex among other factors had a significant effect on nivolumab clearance.[17] Exploring different optimal dosing times for male and female patients is crucial for clinical practice and has the potential of improving outcomes for all, by tailoring treatments that are safer and more effective.

CHRONO-IMMUNOTHERAPY—DOES PHARMACOLOGY FIT THE NARRATIVE?

ICI antibodies are characterized by extended plasma half-lives (2–3 weeks) and low volume of distribution in humans. After administration, the initial tissue distribution of ICIs is very fast, rapidly reaching maximum concentration in plasma and extensive binding to target antigens in plasma and tissues. In preclinical models, radiolabeled pembrolizumab was distributed rapidly and largely to high-perfused (eg, liver, brain, kidney), low perfused (eg, skin), and lymphoid organs (eg, thymus and spleen). The high-affinity interaction between the drugs and surface receptors (ie, receptor-mediated endocytosis) contributes to the turnover of ICIs, which do not undergo metabolic degradation but proteolytic catabolism in plasma and tissue. ICI elimination fits biphasic or triphasic kinetics like conventional antineoplastics such as oxaliplatin and doxorubicin.[18] In addition, preclinical evidence suggests that anti-PD-1 antibodies can be rapidly removed when bound to CD8+T cells by macrophages, which further complicates the correlation between pharmacokinetics and pharmacodynamics.[19] Although a long elimination duration might suggest that the timing of infusion has limited impact on efficacy, other anticancer agents such as oxaliplatin, doxorubicin, and irinotecan demonstrate pronounced chronotoxicity and

chronoefficacy, even with their long half-lives and rapid distribution to leukocytes and organs within minutes.[19 20] Indeed, pharmacokinetic data from renal cell carcinoma (RCC) patients showed that nivolumab clearance and plasma concentration are associated with overall survival (OS),[21] confirming a clearance–response relationship for nivolumab reported previously.[17]

The pharmacokinetics of ICIs—their rapid distribution and slow unbinding from plasma and tissues—is, therefore, similar to that of chemotherapeutics. Although there might be a rationale for an effect of the timing of infusion during the rapid distribution phase, the fact that antibodies can exert their antitumoral effect over weeks diminishes the pharmacological rationale for the timing of infusion affecting efficacy. Therefore, if the time of day effects can be reproduced in randomized clinical trials, the underlying mechanism is likely not due to plasma pharmacokinetics. Instead, it is possible that initial infusion timing may affect circadian alterations that exist locally within the tumor immune microenvironment.[7 22] The precise mechanism at play still needs to be defined in molecular detail.

IMMUNOTHERAPY AND TIMING OF ADMINISTRATION: RETROSPECTIVE STUDIES

The share of ICIs used in cancer treatment has rapidly increased in recent years.[23] Various retrospective analyses have investigated whether the timing of immunotherapy infusion had an impact on clinical outcomes in different cancer types. Data from 18 studies, with various cutoffs or methods including metastatic melanoma, non-small cell lung cancer (NSCLC), RCC, urothelial, gastric, esophageal, or liver cancer from different countries found up to fourfold increased survival (either OS or progression-free survival (PFS)) in patients receiving more early time of day ICI infusions.[24]

As an example, the MEMOIR study—Melanoma Outcomes Following Immunotherapy—was a longitudinal study of patients with stage IV melanoma treated with nivolumab, pembrolizumab, or ipilimumab alone or in combination in a US tertiary center.[25] The investigators used both unmatched and propensity-matched methods to investigate whether receiving immunotherapy after 16:30 hours, a cut-off based on previous data from vaccine trials, could affect survival. In the matched analysis of 146 patients, they found that patients receiving at least 20% of their infusion after 16:30 hours had a shorter OS as compared with those who did not. The median OS was 4.8 years in those receiving more evening ICIs and not reached in those receiving treatment earlier during the day (HR=2.04, 95% CI 1.04 to 4.00, p=0.038). Notably, there were no differences in the toxicity rate between groups. In addition, subgroup analyses suggested that female patients benefited even more from earlier infusions. This finding could be of great clinical relevance given that female sex has already been identified as a poor predictive factor for response to ICIs in melanoma.[26]

In contrast, a retrospective analysis of the phase II INSPIRE study of pembrolizumab in solid tumors did not find any association of the timing of the infusion with patient outcome, possibly due to small sample size with high heterogeneity (n=106).[27]

Does the timing of the first ICI infusions matter even more? In a cohort of 121 advanced melanoma patients, the OS rate was significantly shorter when all first four infusions were administered in the afternoon compared with patients who received ≥1 of the first four infusions in the morning (HR 2.4, p=0.004).[28] For NSCLC patients receiving at least one of the first four ICI therapies (anti-PD1 alone or in combination with chemotherapy) before 12:00 hours was associated with a significant improvement in the median PFS and OS (16.1 months vs 7.4 months, p=0.003).[29] A similar effect was reported for esophageal cancer, where delivering the first infusion and those during the first 3 months before 13:00 hours, rather than receiving most infusions before 13:00 hours had the highest impact on PFS and response rate.[30]

Interestingly, the season of the year appears also to influence ICI efficacy. In a nationwide retrospective analysis, initiation of immunotherapy in summer (April–September) was associated with prolonged OS in patients with BRAF wild-type melanoma living in Denmark. Possible explanations for this finding are the seasonal changes in dietary, infectious, and hormonal factors, including vitamin D levels, which affect the immune system.[31] In fact, in a single-center analysis from the UK, vitamin D deficiency and supplementation were associated with OS, but season of ICI initiation was not.[32]

Given the retrospective and non-randomized analyses in these reports, several confounding factors such as differences in duration of treatment (ie, number of ICI infusions) and prognostic factors (ie, ECOG, LDH levels, driver mutations) could affect the results. Another concern, which is highlighted by the heterogeneity of time cutoffs, is the risk of data-dredging (or p-hacking).[33] In other words, by analyzing the data with various assumptions, the chance of finding statistically significant yet spurious results grows. Only prospective, randomized clinical trials can assess whether chrono-immunotherapy should find its way into clinical practice.

WHY A RANDOMIZED TRIAL?

When medical interventions are identified as ineffective or even detrimental by studies that may fill empirical lacunae, or are better designed, controlled, and/or powered than earlier research, this is what Prasad and Cifu call “medical reversal”.[34] Two classical pitfalls may be in play in medical reversal. One is the implementation of practice based (only) on biological or pathophysiological rationales; the other is basing practice on retrospective studies.

Even though biological discovery has exploded in our time, most of the complex intricacies of human body functioning still lie beyond current understanding. For

example, after a myocardial infarction, patients were often treated with medications known to reduce rhythm abnormalities known as tachyarrhythmias, a leading cause of death. Nonetheless, the Cardiac Arrhythmia Suppression Trial (CAST) was a randomized trial conducted to verify whether anti-arrhythmic medication was beneficial. The trial was difficult to conduct, and it sparked ethical debates among physicians, some of whom argued that withholding what was believed to be life-saving treatment for the sake of the trial was unethical. However, CAST found these medications increased mortality in myocardial infarction patients.[35] Bioplausibility alone is not enough.

Selection bias is another source of medical reversals. When a procedure—for example, a particular surgical intervention—appears beneficial in retrospective studies, the question is whether the observed benefit is driven by patient selection, that is, the fact that patients deemed eligible for surgery are in better condition than those who are not. Even after adjusting for various confounders, some of them—residual confounding—will remain retrospectively uncaptured. Thus, in the case of timing of ICI infusions, which are mostly administered in outpatient settings, it is possible that patients coming to the clinic for early infusion are healthier, and some might prefer early treatment slots because they still have active employment. On the other hand, frail patients, who have a poorer prognosis, may need more time to prepare and thus prefer later infusions. Additionally, some patients may be scheduled for emergency treatment the next day, making evening spots more available. Many other explanations could also be in play yet remain uncaptured or unadjusted for in retrospective observational studies.

Thus, the implementation of early during the day ICI infusions in clinical practice, solely based on a biological rationale and retrospective analyses, without prospective randomized data, may pose challenges for both patients and outpatient clinics. For outpatient clinics, concentrating treatments earlier in the day could limit appointment availability. For patients, this could negatively impact those with work or travel constraints, potentially affecting their adherence to treatment. Additionally, it may place a psychological burden on patients, as they might feel pressured to adhere to early-in-the-day schedules, knowing that failing to do so could result in inferior outcomes, which is ethically questionable in the absence of sound evidence.

WHAT IS A SUITABLE DESIGN FOR A PRAGMATIC RANDOMIZED TRIAL?

We suggest a pragmatic trial, that is, a trial intended to inform decision-makers including patients, physicians, and policy-makers on the clinical utility of the proposed intervention rather than elucidating a biological mechanism, and the trial enrolls a patient population representative of the real-world patients for whom the decision is relevant.[36] By definition, a positive pragmatic trial must have the potential to change practice. Conducting a randomized clinical trial to test the effect of the timing of ICI infusion needs careful planning to ensure meaningful results. The current data suggest equipoise, placing the burden of proof on the intervention's side, thus the trial should be designed to demonstrate the superiority of one time point over the other.[36] Given the many challenges posed by the research question, patient and public involvement will be key in the conduct of such a pragmatic trial.

Patients should be randomized parallel to two treatment time points, early and late. The time points should be spaced enough to avoid overlap of the treatment groups and to capture a significant difference in outcome. The treatment is ideally applied in the allocated group during the whole ICI treatment duration but at least during the first 3 months. While a single-blind or double-blind design is not feasible, patient involvement in trial design is key to addressing their concerns and ensuring maximal recruitment. In line with the definition of a pragmatic trial, exclusion criteria should be limited to contraindications for ICI treatment according to the treating physician (eg, autoimmune diseases requiring immunosuppression), and all patients who fulfill criteria for ICI treatment should be included in the study. Ideally, patients are randomized when they receive approved ICI (anti-PD1 monotherapy or in combination with CTLA4) as first-line therapy for advanced cancers such as melanoma, NSCLC, and RCC. To reduce heterogeneity, patients who had previous adjuvant ICI or who qualify for ICI in combination with chemotherapy or tyrosine kinase inhibitors should be excluded. Given the differences in prognosis or response to therapy, patients should be stratified at least according to therapy type (anti-PD1 monotherapy vs combination with CTLA) and sex. The number of stratification factors should be carefully limited, focusing on those with a substantial prognostic impact, as including additional factors does not always enhance or improve power and may impact feasibility in terms of sample size. In addition, the number of collected data points should be limited, and the monitoring requirements should be kept to a minimum and be in line with the standard of care tests and clinical evaluations.[36] This should ensure the feasibility of the trial in terms of costs.

Our suggested statistical design is a basket trial in which each cohort is designed and analyzed separately and independently, with an overarching Bayesian analysis over the whole trial. This approach enables maximal utilization of resources to conduct one clinical trial with different cancer types.

The ideal primary endpoint to assess for a practice-changing trial is OS. While PFS might be a more practical endpoint, we believe that OS is more clinically meaningful for first-line therapies, as it directly measures the ultimate benefit of prolonging life. OS avoids potential biases from variability in progression assessment and ensures the most definitive and impactful results. Despite requiring more time and resources, OS aligns with the priorities of both

patients and clinicians, making it the most appropriate endpoint for this type of study. However, given that subsequent therapies might significantly affect OS, ORR at 3 months, PFS at 12 months or time to subsequent treatment should be analyzed as secondary endpoints. ORR at 3 months may seem short for IO trials, yet it provides an early indication of efficacy. Also, while long-term endpoints like PFS at 3 years are important for assessing durability of response, they are resource-intensive and may delay change in clinical practice.

Toxicity rates and patient satisfaction with treatment (eg, using the FACIT-TS-G questionnaire) should also be assessed as secondary endpoints. The suggested statistical design also allows for using different primary endpoints for each patient cohort while using a common primary endpoint for the overarching Bayesian analysis.

Translational studies including characterization of immune cell populations immediately after the first ICI fusion and at subsequent time points and exploratory analyses of potential biomarkers based on routine blood samples (eg, neutrophil/lymphocyte ratio) should be considered to understand the biological basis of potential differences in outcome. The follow-up time should be 2–3 years.

Finally, the interest of the pharmaceutical industry in sponsoring a trial that does not investigate new compounds or indications might be limited. It is therefore critical that governmental funding bodies and private foundations provide the resources for pragmatic investigator-initiated, patient-centered clinical trials that have the potential to change clinical practice and improve patient survival solely via rearrangement of the time of administration of approved treatments without further patient exposure to additional drugs generating additional toxicity or costs. If immunotherapy alone is ultimately proven to be more effective at specific times of the day, all combination therapies incorporating such agents will need to be tested under the same principles.

CONCLUSIONS

Several retrospective observational studies suggest that morning infusion can enhance ICI efficacy. However, pharmacological data on the long half-lives of ICIs and the possibility that results of observational studies could be at least partly driven by residual confounding, with healthier patients possibly being more likely to come for morning infusion, both contribute uncertainty to whether time of infusion is a true modifier of ICI efficacy. We posit that equipoise remains, and although the prospect of improving patient survival solely by administering ICI early during the day is tempting, it should be explored with randomized trials before scheduling constraints are added to the burden of patients with cancer. We suggest performing a pragmatic basket trial in which each patient cohort is analyzed separately and independently, with an overarching Bayesian analysis.

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