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CHRONOTHERAPY IN PERSONALIZED CANCER TREATMENT: CLINICAL EVIDENCE AND FUTURE DIRECTIONS

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ABSTRACT

This narrative review is concerned with the clinical impact of chronotherapy, the timing of cancer treatment based on the natural 24-hour circadian clock of the body, on efficacy, toxicity, and overall outcome in adult patients with solid tumors. The circadian clock regulates cellular processes such as drug metabolism, DNA repair, and apoptosis, which can be disturbed by cancer. Accumulating evidence suggests that chronotherapy can enhance treatment efficacy while reducing treatment-related toxicity. Chronomodulated chemotherapy has been shown to improve progression-free survival (PFS) and reduces toxicity. Several observational studies have reported improved survival outcomes when immunotherapy is administered earlier in the day. Morning radiotherapy has also been associated with reduced toxicity, such as oral mucositis in head and neck cancer. However, the field faces major challenges, such as a lack of standardized circadian measures, the absence of large-scale multicenter trials, and irregular recording of precise treatment time. Future efforts should prioritize the integration of wearable technologies and precise treatment-time documentation to support individualized circadian-based therapy. The shift of population-averaged schedules to patient-specific chronotherapy can be used to address the existing limitations and enhance clinical outcomes.

KEYWORDS: Chronotherapy; Circadian rhythm; Cancer treatment timing; Radiation oncology; Immunotherapy; Radiotherapy.

INTRODUCTION

The circadian clock is an inherent biological time mechanism that controls the physiological functions in a close 24-hour cycle. Its primary purpose is to ensure the appropriate sleep-wake cycle and physiological processes, ensuring that high-level, energy-dependent processes are optimally maintained throughout the day. Endocrine and cellular function rhythms are maintained in hormone secretion and the cell cycle, coordinating important functions necessary for cell growth and chemical signaling.[1] Circadian timing consists of a molecular clock that controls 24-hour changes in drug metabolism, detoxification, DNA repair, apoptosis, and the formation of new blood vessels. When anticancer therapies are administered at suboptimal circadian phases, that is, when they are most harmful, the body's natural pattern is disturbed. It can also affect the dose that can be administered to the patient. Better results can be obtained by timing drug administration to exploit the differences in rhythmic activity between the tumor and host.[2] Chronotherapy in cancer involves administering treatment at times that align with the body's natural daily clock to improve efficacy and reduce adverse effects.[3] In the clinical practice, treatment timing is often determined by convenience rather than biological optimization.[4] The scheduling of treatment based on circadian rhythms is gaining more and more significance in cancer therapy, especially in radiation oncology where DNA repair and normal tissue radiosensitivity are time dependent. Chronotherapy improves the timing of existing therapies to enhance patient survival and well-being.[5] Clinical trials have shown that administering anticancer drugs or targeted immunotherapy according to the body's natural clock can improve efficacy and reduce complications. In contrast, radiotherapy timing primarily reduces treatment-related symptoms rather than directly affecting tumor growth or survival.[6] For example, the administration of oxaliplatin in the evening has shown improved outcomes and reduced toxicity in patients with colorectal cancer. The strongest finding of chronotherapy is that it can reduce serious side effects in healthy tissues, especially in fast-growing tissues, such as the bone marrow and digestive system. In various cancer chronotherapy trials, patients had a 41% lower risk of toxicity and ADRs than those who did not.[7] Clinical trials and reviews have shown that this approach helps patients receive better treatment and improves their quality of life.[8] The timing of radiation therapy can also influence outcomes. This can affect the survival rate and local tumor control. Good evidence lies in the research work done on the application of stereotactic radio-surgery (SRS) on the treatment of brain metastases associated with small cell lung cancer. Earlier SRS patients report improved survival and disease control when they are treated in the morning as compared to the afternoon.[9]

MECHANISTIC BACKGROUND

Molecular clock genes and tumor biology

Molecular clock genes belong to the body's internal clock, which operates inside each cell. This internal clock keeps track of time and controls body functions in a regular cycle that lasts approximately 24 hours.[10] Two important feedback loops that regulate gene and protein activities control the mammalian circadian system.[11] The circadian clock is controlled by two main proteins: Circadian Locomotor Output Cycles Kaput (CLOCK) and Brain and Muscle Arnt Like Protein-1 (BMAL1) regulate transcriptional-translational feedback loops; NPAS2 is used as a replacement for CLOCK when needed. Period (PER1 and PER2) and cryptochrome (CRY) proteins form the negative feedback limb of the circadian clock, inhibiting CLOCK-BMAL1 activity.[12] Most studies have shown that changes in the circadian rhythm are linked to cancer growth.[13] Disruption of the circadian clock affects the daily activities of genes and cells, yet results in the imbalance of the metabolism, oxidative stress, and altered DNA damage repair pathways that influence tumor response to radiotherapy.[14]

Table No. 1: Core circadian clock proteins and their functions.

Component	Function
CLOCK (Circadian Locomotor Output Cycles Kaput)	Regulates transcriptional-translational feedback loops (positive limb)
BMAL1(Brain and Muscle ARNT-Like Protein-1)	Regulates transcriptional-translational feedback loops (positive limb)
PER1 & PER2	Proteins form the negative feedback limb which inhibit CLOCK-BMAL1 activity
CRYPTOCHROME (CRY)	Proteins form the negative feedback limb which inhibit CLOCK-BMAL1 activity

Circadian influence on drug metabolism

When the natural 24-hour clock of the body is disrupted, cells fight hard to carry out normal functions, which also includes the detoxification of harmful substances, and this can enhance the increase of the growth of the tumor. Many cancers show changes in clock genes, and the exact effects may vary with the type of cancer. Drugs that target clock disruption may kill specific cancer cells, offering a new treatment option.[15] Circadian rhythms cause regular differences in drug metabolism and transport, leading to daily changes in drug exposure and pharmacokinetics (PK). These variations arise from the regular patterns of drug-metabolizing enzymes and transporters in organs such as the liver, intestine, and kidney. As a result, drug effects and toxicity also show a circadian pattern. Knowledge of these processes can be utilized to advance time-based dosing to enhance the efficacy and reduce the adverse effects.[16]

Immune system circadian variation

The circadian clocks have a role in the operation of the immune system, which has an impact on the control of tumors and checkpoints. Single-cell RNA sequencing studies in colorectal cancer demonstrate that circadian regulation influences rhythmic PD-L1-expressing myeloid-derived suppressor cells (MDSC), which suppress CD-8 T-cells activity. Disruption of the epithelial circadian clock alters cytokine profiles, increases inflammation, and promotes MDSC accumulation.[17] CD8+ T cells quality and quantity are essential for tumor control and immunotherapy response, and they also show clear circadian changes. These daily changes arise from the internal clock of T-cells and the regular pattern of endothelial cells to allow their entry into tumors. Adjusting therapy according to this pattern improves outcomes and may enhance the synergistic effects of radiotherapy combined with immunotherapy. The anti-PD-L1 therapy can be most effective when these PD-L1 cells are higher in number every single day because then it can be possible to treat people at the time when the target immune cells are most functionally active.[18]

CURRENT EVIDENCE

Chemotherapy chronotherapy evidence

Organized cancer drug delivery in sync with natural body cycle demonstrates greater efficacy, lesser toxicity, and less adverse effects in various types of cancers comprising lung, colon, breast, head and neck cancers.[19] Clinical studies have revealed that chrono-modulated chemotherapy can enhance progression-free survival and treatment outcomes compared to conventional chemotherapy.[20] Anticancer drugs achieve peak efficacy when administered at times of highest patient tolerance, thereby improving the quality of life of patients.[21] In early-phase clinical trials, fewer complications and enhanced tumor response were noted with chronotherapy administration of doxorubicin in the morning and cisplatin in the evening in patients with ovarian cancer.[22] "Meta-analyses show that men often experience greater survival benefits from chronotherapy than women, indicating sex-specific responses to treatment timing".[23] The positive outcomes indicate that chronotherapy is effective, but bigger studies are needed to establish regular treatment schedules and improve patient targeting.[19]

Immunotherapy timing evidence

The effectiveness of cancer treatment can be influenced by the delivery of immunotherapy based on the biological clock of the body in cancer patients.[24] Data from 18 different studies from different countries suggest that patients with different cancers, including melanoma, kidney, lung, bladder, stomach, oesophagus, and liver cancers, who receive immune checkpoint inhibitors earlier in the day significantly improved survival than those treated later.[25] Recent laboratory and patient studies suggest that administering immune checkpoint inhibitors in the morning instead of the afternoon can improve survival.[26] Infusion of immunotherapy in the daytime or early afternoon enhances treatment outcomes, including overall survival (OS), progression-free survival (PFS), and response to treatment, improving patient tolerability.[27] To come up with clear guidelines on the most appropriate time to administer immune checkpoint inhibitor therapies, prospective randomised clinical trials should be well designed to validate these studies and offer standardisation of treatment schedules.[28]

Radiotherapy timing evidence

Radiation therapy harms cancer cells by breaking their DNA, resulting in cell death.[29] The biological clock of the body controls the repair and death of cells of the body; thus, cancer treatment is more effective when radiation is timed to these rhythms.[30] Clinical evidence suggests that morning (8:00-9:30 am) radiotherapy reduces oral mucositis in patients with head and neck cancer[31], whereas afternoon (11 am–3 pm) radiotherapy may improve bone metastasis responses in female patients.[32] Most patients prefer to receive radiation therapy from 8 am to 4:30 pm on weekdays.[33] More prospective and randomised trials are required to standardise the timing strategies in radiation oncology and enable routine implementation of chronoradiotherapy.[34]

Targeted and hormonal therapy

Hormonal therapy is significant in the treatment of breast and prostate cancer since it can slow down the growth of the tumor and reduce the risk of the disease recurrence.[35] A study showed that women taking tamoxifen in the evening or at night remained healthier than those who took it earlier in the day. However, timing did not significantly affect the aromatase inhibitor.[36] Endocrine-disrupting chemicals can disturb the natural hormone rhythm, especially during life. A study showed that liquorice root extract can protect cells by reducing hormone disturbance.[37] Multikinase inhibitors are important for patients with radioactive-iodine-resistant thyroid cancer, but the right time to begin treatment is not clearly known.[38] Tyrosine kinase inhibitors can help treat cancer, but they may cause serious heart problems, such as hypertension and weak heart function, and affect multiple organs, including the lungs, liver, gastrointestinal tract, thyroid, skin, and kidneys.[39] Targeted and hormone therapies help fight cancer by focusing on the part of the cancer that makes it grow. They are able to slow down the growth or kill the cancer cells, but only when the cancer has the target, otherwise it becomes resistant.[40]

CLINICAL IMPLICATIONS

Impact on efficacy

Circadian cancer therapy has proven effective in improving outcomes across various cancers, with growing clinical relevance for radiation oncology practice.[41] Many studies have reported improved outcomes, increased efficacy, and reduced toxicity with chrono-chemotherapy.[42] For example, first-line chrono-modulated chemotherapy with irinotecan, oxaliplatin, 5-fluorouracil, and leucovorin achieved an Objective Response Rate of 62.3 %, median progression-free survival of 8.7 months, and Overall Survival of 19.9 months.[43] Majority of the retrospective studies indicate that morning delivery of chrono-immunotherapy is more effective than evening delivery, but randomised controlled trials are needed to standardise regimens.[44] Several studies have confirmed that chronoradiotherapy maintains tumor response rates while reducing toxicities with morning sessions; for example, in nasopharyngeal carcinoma, reduction of haematological toxicities.[45] Targeted therapies have shown improved outcomes, leading to improved response rates and PFS.[46] For example, in advanced NSCLC, drugs such as loratinib have shown a 5-year progression-free survival.[47] Hormonal therapy improves the survival outcomes of patients with breast and prostate cancers. For example, administering letrozole for 5 more years after completing tamoxifen lowers the risk of recurrence in postmenopausal women.[48] Circadian rhythms play an important role in controlling the toxicity and safety of anticancer treatments, influencing both patient safety and the ability to treat safely.[49] Cancer treatment can be more effective and less side effects can be achieved by administering it at the appropriate time of the day.[50]

Impact on toxicity and treatment

Chrono-modulated chemotherapy is designed to reduce toxicity and improve effectiveness compared to conventional chemotherapy.[51] Cisplatin is one of the chemotherapy drugs that may cause serious nausea and vomiting, which may result in toxicity that may affect cancer patients and affect their quality of life.[52] Individuals who survive cancer can have long-term health problems, such as heart or kidney issues, tiredness, and depression, compared to others.[53] Epidermal growth factor receptor (EGFR)-targeting treatment for non-small cell lung cancer (NSCLC) is more effective but can have side effects; combining them with other therapies has shown mixed results.[54] Completing the full chemotherapy dose is important in triple-negative breast cancer, and supportive care helps manage side effects.[55] There may be strong side effects from cancer treatment that can delay therapy and affect well-being. Therefore, it should be carefully managed by doctors.[56] The treatment and cancer may have an impact on the mind, resulting in cognitive difficulties and toxicity, which may affect the capacity of patients to finish treatment. Supportive therapies, such as cognitive rehabilitation, can help meet the need for stronger proof. Better studies can predict issues and improve treatment completion.[57]

PRACTICAL CONSIDERATIONS IN CLINICS

Current healthcare systems, including radiation oncology departments with fixed scheduling workflows, are not built for the precise timing demands of chronotherapy making it difficult to smoothly fit into daily work.[22] Chronotherapy may be applied through training personnel to detect issues with circadian rhythms, through simple devices to monitor rhythms, and low-cost habits, including light and meal timing, to reset clocks.[58] Scheduling healthcare workers' shifts to match natural sleep patterns can improve their health and care given to patients.[59] Many studies provide evidence that the patient chronotype influences treatment efficacy; administration of drugs according to the body's natural clock improves outcomes.[60] The research should be conducted in the future to test chronotype-specific interventions to develop individual healthcare policies.[61]

Table no. 2: Factors that may influence treatment timing in cancer care.

Therapy type	Optimal timing	Effect
Chemotherapy	Coordinated with the natural body cycle.	Shows increased efficacy, reduced toxicity and minimized adverse effects in several cancers.
Oxaliplatin (colorectal cancer)	Evening administration	Has shown improved outcomes and reduced toxicity in patients with colorectal cancer.
Doxorubicin/ cisplatin (ovarian cancer)	Doxorubicin in morning and cisplatin in evening.	Fewer complications and enhanced tumor response were noted with chronotherapy dosing.
Immunotherapy (ICI)	Earlier in the day/ morning	Patients receiving immune checkpoint inhibitors earlier in the day has demonstrated significantly improved overall survival compared to those treated later.
Radiotherapy (head and neck cancers)	Morning (8:00-9:30am)	Reduces oral mucositis in head and neck cancer patients.
Hormonal therapy (tamoxifen)	Evening or at night	Those women who took tamoxifen in the evening or at night stayed healthier.

CHALLENGES AND LIMITATIONS

A major challenge in using real-world data in chronotherapy is the lack of accuracy and consistency in recording treatment time, leading to high variability in timestamps. Many hospitals and clinics, including radiotherapy units, do not consistently record the exact time of treatment delivery limiting chronotherapy research. Thus, the right time of chronotherapy is hard to define. Patients tend to take medicines at a time that fits their day-to-day routine and not necessarily the most appropriate time medically. This leads to irregular time intervals.

Gaps in electronic health records timing precision: Electronic health records (EHR) are primarily designed for clinical documentation and billing rather than precision timing studies. EHR generally lack precise timing information and do not capture patients' chronotherapy or the exact minute of drug administration. In the absence of this, researchers will not be able to achieve the timing accuracy needed to analyze time-specific treatment. Since the existing EHR data are not detailed enough, future studies should be designed to gather comprehensive data, accurate, and standard timing data to evaluate chronotherapy. Proper data collection will help researchers understand how timing can affect treatment effectiveness.

Lack of circadian standardization: Research in human chronobiology faces challenges owing to the absence of standardized circadian measures. There are no standard protocols for the measurement of parameters such as melatonin, cortisol, or activity, leading to inconsistent results in circadian studies. This makes it difficult to compare studies or merge data, slowing the progression of circadian medicine. These variations hide each patient's unique body clock type, making custom chemotherapy or radiation therapy timing difficult.

Inconsistent wearable data processing: Practical issues, such as strict sampling rules and person-to-person differences, limit clinical trials. Wearables help track daily rhythms, but the analysis varies, causing issues. Global rules would allow the best-timed personalized drugs to be effective.

Limitations of single-center trials: The existing literature on chronotherapy, particularly with real-world data, is scarce due to the small size of most studies and the fact that they are carried out in one hospital or in one type of cancer. There are not enough large multi-center studies that include different hospitals, patient groups and treatment settings. Because of this timing, results found in one place are not applicable or vary across populations. In addition, much existing research focuses only on a few cancers, such as colorectal cancer and melanoma. This implies that the evidence on the most appropriate time to treat a cancer is highly specific to certain cancers and may not be applicable to others. Multi-center studies on a large scale are challenging to perform in chronotherapy due to the fact that various hospitals have different approaches. As there is no common method for recording data, it becomes difficult to combine and analyze information from different sources. Because of these differences, many studies use only small, single-center data, which do not represent all types of patients. Important factors such as age, sex, health condition, and other factors can affect a person's body clock, but smaller studies cannot include all of these. Consequently, the timeline of treatment proposed by small studies might not be effective in all patients, and it is hard to implement in clinical practice.

Table no. 3: Barriers and research gaps in clinical implementation of chronotherapy.

Challenge	Underlying issue	Impact on clinical practice
Inconsistent treatment time recording	Lack of standardized timestamp documentation in oncology units	Limits reliability of outcome analysis
Limitations of EHR timing	Electronic systems designed for billing, not circadian precision	Prevents accurate chronotherapy research
Absence of standard circadian biomarkers	No standard protocol for melatonin, cortisol, or activity assessment	Reduces comparability across studies
Small single-center trials	Limited patient population and sample size	Poor generalizability of findings
Inter-individual circadian variability	Age, sex, comorbidities influence body clock patterns	Requires personalized scheduling strategies
Wearable data processing	Variations algorithms and sampling methods	Reduces reproducibility
Fixed hospital scheduling systems	Real-world challenges in radiation and chemotherapy schedules	Difficult real-world implementation

FUTURE DIRECTIONS

There are no significant examples of real-world prospective studies that use Electronic Health Records to monitor treatment times, which are vital in chronotherapy, particularly in cancer. They record the exact cancer therapy timing and results, which helps us find the best daily time for different patients, something that is impossible in laboratory trials that ignore daily rhythms. These studies evaluate millions of patients in clinics to determine how morning or evening cancer therapies improve survival or cause fewer adverse effects. To address these issues, it is possible to launch the standardization of circadian stamps, linking wrist trackers, and artificial intelligence to map the types of patient body clocks, as well as simple studies that combine health data and online sign-ups to receive more timely cancer treatments. These methods can provide quick and widely applicable evidence for body-clock-scheduled treatments, directly addressing the standardization issues. Chronotherapy in radiation oncology needs to shift from average population timing to personalized, circadian-guided radiotherapy scheduling for each patient. To overcome this, advanced digital health technologies, particularly wearable devices, must be used. Wearable technologies, such as smartwatches and fitness trackers, are important tools for future healthcare because they can collect continuous information about a person's daily activities and body functions. These devices can provide time-based measurements, such as how active someone is, how well they sleep, body temperature, and heart rate patterns. These measurements indicate the natural body clock of a person. Having the correct real-time data of wearables, we will be able to know precisely when the medication is taken and align it with the body rhythm. This helps us understand how timing affects treatment results and provides a good database for improving personalized therapy. Digital phenotyping can provide a more accurate way to understand each patient's natural body clock by using continuous data from wearable devices. Instead of depending on questionnaires, it provides real and continuous information. Using machine learning, researchers can study these data and determine a patient's exact circadian rhythm. This helps create a personal profile for each person; with this information, doctors can choose the best time to administer treatment, such as chemotherapy, so the medicine works better and matches the patient's own biology. Future directions in personalized circadian timing should combine new gene tests that read the body clock with AI tools to pick optimal drug times based on each patient's natural rhythm. Simple blood tests from one drop can quickly identify a person's inner body clock, making cancer treatments easier to time precisely. Nanomaterial hybrids release cancer drugs at the optimal body clock.

Table no. 4: Frame work for implementing personalized chronotherapy in oncology practice.

Step	Component	Practical strategy	Expected outcomes
Step 1	Circadian assessment	Questionnaire on chronotherapy and wearable activity monitoring	Identification of patient-specific biological timing
Step 2	Biomarker integration	Single-time blood sampling for circadian phase estimation	Objective rhythm validation
Step 3	Treatment scheduling	Align therapies with peak tolerance phase	Improved efficacy and reduced toxicity
Step 4	Digital monitoring	Continuous wearable-based rhythm tracking	Adaptive timing adjustments
Step 5	Data standardization	Precise timestamp documentation in EHR	Reproducible research and multicenter validation

CONCLUSION

Chronotherapy is an encouraging method of enhancing cancer therapy with the help of natural patterns of the body, and there is a high translational potential in radiation oncology to increase treatment efficacy and improve treatment tolerability. Research shows that administering chemotherapy, immunotherapy, and radiotherapy at the right time can help treatments work better and reduce side effects, making patients experience improved well-being. Chronotherapy is not widely used because healthcare systems lack precise treatment timing records, and there are few large studies or standardised methods to measure patients' body rhythms. The possible solutions are to record the time of treatment in the medical records correctly, wearable devices to monitor the body clock of every patient, and advanced computational tools to personalise the time of treatment of every patient. With improved timing documentation, digital health tools, and patient-specific circadian assessment, chronotherapy has the potential to become a practical and effective component of routine care.

AUTHOR CONTRIBUTIONS

Both authors contributed to the study conception, literature review, manuscript drafting, and final approval.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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