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Chronomodulation of cyclin-dependent kinases 4/6 inhibitor may reduce hematological toxicities? A review of literature

Mukul Arvind Gharote

Department of Medical Oncology, Mukta Cancer Clinic, Nashik, Maharashtra, India

Correspondence to: Dr. Mukul Arvind Gharote, Mukta Cancer Clinic, Bunglow No. 61, Teerthroop Bunglow, Sundarban Colony, Near Deccan Petrol Pump, Nashik – 422 009, Maharashtra, India. E-mail: Mukul.gharote@gmail.com

ABSTRACT

Nucleotide excision repair, DNA damage checkpoints, and apoptosis are under the influence of the circadian rhythm1. Circadian rhythm is defined as oscillations in the behavior and biochemical changes in an individual that repeats itself after the span of 24 h approximately. Cyclin-dependent kinase (CDK) inhibition causes cell cycle arrest and subsequent circadian stage-dependent gating of cells at G2-M interface of the cell cycle. Few anecdotes have suggested that chronomodulation reduces hematological toxicity in cell cycle-specific chemotherapy, especially S1-specific chemotherapy. In a study conducted by Boucher *et al*., 2016, circadian rhythm plays a role in the regulation of human mesenchymal stem cells (hMSCs) differentiation and division and likely represents key factor in maintaining hMSCs properties. If we apply the knowledge of circadian clock, then we know the fact that bone marrow stem cells (BMSCs) are under the control of circadian rhythm and G1-S phase of cell division cycle occurs at the early morning period of solar day. If CDK4/6 plasma peak level coincides with G1-S phase of BMSCs, then theoretically cytopenia may occur, which again is the sign of CDK4/6 action but is also the reason of its toxicity. Chronomodulation studies of CDK4/6 inhibitor may reduce hematological toxicity of CDK4/6 inhibitor.

Key words: Chronomodulation, Hematological toxicity, Circadian rhythm, CDK4/6 inhibitors

Introduction

Most of the regulatory systems and DNA repair mechanisms are under the control of circadian rhythm. It has a possible role in affecting cancer treatment outcomes. It acts by modulating the pharmacokinetics and pharmacodynamics of chemotherapeutic drugs, as well as the activity of the DNA repair enzymes which repair the DNA damage caused by chemotherapy.[1]

Not only this but also the nucleotide excision repair, DNA damage checkpoints, and apoptosis are under the influence of the circadian rhythm.[1]

Definition of Circadian Rhythm

Circadian rhythm is defined as oscillations in the behavior and biochemical changes in an individual that repeats itself after the span of 24 h approximately.

Three important properties of the circadian rhythm are as follows:

i. Its innate nature, rhythm is devoid of any sensory input from the external environment.
ii. Its capacity for temperature compensation, that is, the maintenance of the intrinsic period, phase, and amplitude of the rhythm despite external fluctuations in temperature, so long as these fluctuations do not interfere with physiological thermoregulation.
iii. Its photoentrainment, that is, it synchronizes, phases of the rhythm with the external light and dark cycles of the solar day [Figure 1].[2]

Circadian Rhythm and Its Role in Cell Cycle

Vascular endothelial growth factor (VEGF) protein level peaks at 2–6 h after light onset, leading to variations in the *in vivo* response to several angiogenesis inhibitors according to the circadian time of administration. Thus, VEGF protein is also controlled by the circadian clock. Cell cycle progression is regulated by the circadian clock through WEE1, which modulates cyclin-dependent kinases (CDKs). CDK inhibition causes cell cycle arrest and subsequent circadian stage-dependent gating of cells at G2-M interface of the cell cycle.[3,4]

Optimal timing of the cancer chemotherapy can be modulated if there is precise information of the cell cycle division or cell reproducibly produce targets, relevant to the chemotherapy prescribed such prescription of chemotherapy, at the optimal time, is called chronochemotherapy.

Chronotoxicity: Implications in Chemotherapy-induced Toxicity

Many anticancer agents induced toxicities can be alleviated by chronochemotherapy. Since PK and PD are influenced by

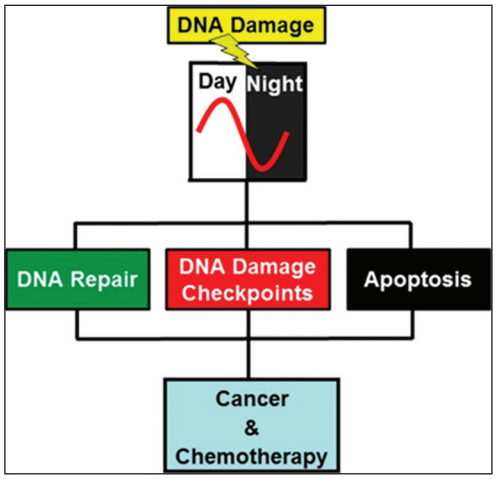

Figure 1: Cancer chemotherapy and circadian rhythm

the circadian rhythms in the biological functions, the circadian timing of drug administration might be very important in decreasing the toxicity of anticancer medications;[5] studies in rodents have revealed that the dose of the drug may be lethal when given at the certain times of the day, whereas the same dose may have only little adverse effects when given at other times of the day.[5]

Circadian Rhythm and G1-S Transition

Role of circadian rhythm and palbociclib was studied in the diurnal vertebrates showing cell cycle progression in neurogenic niches, the study established a hypothesis that to preserve neural stem cell reserve timing of administration of cytostatic chemotherapy is of utmost importance. Differences between neurogenic niches in the phase and degree of S-phase entrainment to the clock suggest additional roles for niche-specific regulatory mechanisms.[6]

Bone Marrow Stem Cells (BMSCs) and Circadian Rhythm: Focus on G1-S Phase

In a study conducted by Boucher *et al*., 2016,[7] circadian rhythm plays a role in the regulation of human mesenchymal stem cells (hMSCs) differentiation and division and likely represents key factor in maintaining hMSCs properties. In mammals, the master circadian clock that maintains 24 h rhythmicity in circadian rhythm is located in the suprachiasmatic nucleus (SCN) within the anterior hypothalamus. It has been shown that a bilateral SCN lesion abolished the circadian rhythmicity and SCN transplantation has the ability to restore this daily rhythm.

In cell division cycle (CDC), transitions between different phases of the cell cycle (i.e., G1, S, G2, and M) are regulated by cyclins, CDKs, and CDK inhibitors (CKIs), mainly by the cip/kip and the INK4 families.

There are enough evidences that progression through the cell cycle occurs at specific times of the day/night cycle, suggesting that a function of the circadian clock system is to control this fundamental process. Microarray analyses revealed that chief elements of the cell cycle machinery including cyclin D1, cyclin B1, cyclin E, cyclin A, P53, Wee1, c-myc, MDM2, and GADD45 exhibit circadian-dependent expression [Tables 1 and 2].[7]

G1/S phases

G1-S progression is negatively regulated by the p21 gene (p21Waf1/CIP1 [p21]) and is rhythmically expressed in numerous peripheral organs. p21 promoter region possesses two conserved RORE elements and the circadian expression of p21 directly results from an alternative activation or repression mediated by RORα and REV-ERBα, respectively. Activation of p21 by RORα leads to subsequent inhibition of G1 phase progression. Contrarily, REV-ERBα binding directs the inhibition of p21 that promotes G1 phase progression.

Cyclin D1 is also under circadian control. Expression of cyclin D1 is significantly elevated in PER1-/- and PER2Brdm1 mutant mice, leading to the shortening of the cell cycle and to an increase in cell proliferation. In this context, PER1 and PER2 genes indirectly promote cyclin D1 expression by inhibiting the transcription of c-myc. C-myc promoter contains multiple E-box sequences and can be controlled by circadian clock transcription factors.[7]

In PER1-/- and PER2Bdrm1 mutant mice, the repression of c-myc expression is canceled, resulting in elevated cyclin D1 expression and increased proliferation. Conversely, it was demonstrated *in vitro* that overexpression of PER2 leads to cell cycle arrest.[7]

G2/M phases

Wee1 is a tyrosine kinase that phosphorylates CDK1 and therefore inactivates the CDK1-cyclin B complex, a key regulator of G2/M transition.

The promoter of Wee1 contains three E-boxes that are activated by BMAL1/CLOCK or BMAL1/NPAS2 heterodimers and repressed by CRYs. Therefore, high levels of BMAL1/CLOCK or BMAL1/NPAS2 activate Wee1 expression, which consequently phosphorylates CDK1/cyclin B complex and inhibits G2-to-M transition of the cell cycle.

Disruption of circadian gene expression has a direct impact on Wee1 expression. Both Cry1 and Cry2 deficient mice exhibit a high level of WEE1, leading to impairment of cell proliferation.[3,8] Conversely, in clock-deficient mice, Wee1 mRNA level decreased considerably. These data indicate that circadian clock function is required for efficient cell proliferation *in vivo*.

Expression of Circadian Genes and Protein in hMSCs

Boucher *et al.,* 2016, demonstrated expression of cell cycle-specific molecules on the surface and cytoplasm of the hMSCs. Expression of CLOCK, BMAL1, PER1, PER2, GSK-3β, PPAR-γ, and osteocalcin by immunofluorescence staining

Table 1: G1-S phase and circadian rhythm[7]

Molecular links between circadian genes and cell cycle			
Cell cycle phase	**Circadian genes**	**Target genes**	**Effect**
G1-S	REV-ERBα	P21	Inhibition of p21→Induction of G1-S transition
	RORα	P21	Activation of p21→Repression of G1-S transition
	PER1	Cyclin-D1	Inhibition of cyclin D1→Repression of G1-S transition
	PER2	C-myc	Inhibition of c-myc → Cell cycle arrest

Table 2: G2-M phase and circadian rhythm

Molecular links between circadian genes and cell cycle			
Cell cycle phase	**Circadian genes**	**Target genes**	**Effect**
G2-M	BMAL1/CLOCK BMAL1/NPAS2	Wee1	Activation of Wee1→inhibition of cyclin B/CDK1→Repression of G2-M transition.
	Cry1	Wee1	Inhibition of Wee1→Activation of cyclin B/CDK1→Induction of G2-M transition
	CK1ε	Cyclin B1 Cyclin A2	Phosphorylation of cyclin B1, A2 → Activation G2-M transition

CLOCK and BMAL1 was predominantly in the cytoplasm, whereas PER1 was detected both in nucleus and cytoplasm. PER2 was peculiarly noted in the nucleus only that too in nucleoli.[9] Not only these factors were present on the hMSCs but also were regulating its migration and differentiation, as well as their cell division was also regulated by these factors, which were eventually under the control of circadian rhythm.

In Figure 2, 24 h cellular rhythms are driven by an autoregulatory feedback loop. During the subjective day, RORα contributes to the expression of Bmal1 through its retinoic acid-related orphan receptor response element. The resulting CLOCK/BMAL1 complex activates transcription of the negative regulators, Per and Cry. By the evening, PER and CRY levels accumulate to form a protein complex, which then becomes active as a CLOCK/BMAL1 inhibitor. During the subjective night, REV-ERBα suppresses the expression of Bmal1, while the newly formed PER/CRY complex blocks CLOCK/BMAL1 activity, thereby preventing further transcription from the Per and Cry genes. During this time, the phosphorylated PER/CRY complex gradually degrades.[10]

Thus, it is more than speculated that the BMSCs are under the control of the circadian rhythm. This fact may play an important role in the hematotoxicity of the cell-specific chemotherapy agents. There are anecdotes that suggest that S1-specific gemcitabine shows less hematotoxicity (10% less) when given in early hours of the day (0900 h) as compared to late in the day (1500 h).[2,11]

Coupling between Circadian Clock and Cell Cycle

In Figure 3, the cell cycle phases G1, S, G2, and M are indicated. Non-dividing cells are in G0. The specific complexes of cyclin/cyclin-dependent kinases (CDK) and the CKIs p15 and p21 are indicated in specific cell cycle phases. The proto-oncogene c-Myc is also shown.[12]

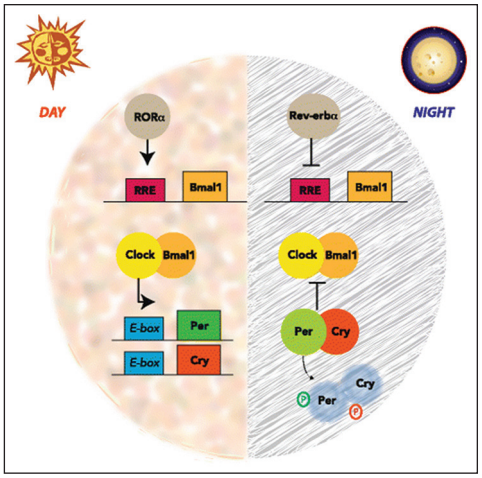

Figure 2: The core molecular circadian clock mechanism

Figure 4 represents, Image acquisition, fluorescence quantification, period, and phase dynamics in non-synchronized NIH3T3-REVERBα:VENUS_FUCCI cells. (A) Time series of a representative single cycle for the various fluorescent reporters and respective quantified traces: from top to bottom: Cell Cycle_G1 (red) = CDT1:mKO2, Cell Cycle_S/G2/M (blue) = GEMININ:E2CRIMSON, Circadian Clock (green) = REVERBα:VENUS, Merge = fluorescent channels combined with the corresponding brightfield image. Arrows point to tracked cell nuclei. Images are 2.5 h apart. Traces at the bottom have been plotted from measured intensities extracted from tracking with the LineageTracker plugin for ImageJ. (B) Histograms showing distribution of periods for both the clock (green) and cell cycle (red) in the whole population. In non-synchronized cells, mean clock period (19.4 ± 0.5 h) is not significantly different from mean cell cycle period: (18.6 ± 0.6 h). (C) Phase histograms for the same cells. Gray histogram and trace show random background densities. Colored histogram and trace show the observed phase of the clock at division.

G1-S Transition in Healthy Cells and Interaction by CKIs

G1-S transition occurs strikingly in the early hours of the daytime (early quarter of the day), Figures 3 and 5 describe the same in zebrafish and mammalian cell, respectively. Strikingly, it looks similar.

qBest example is the BMSCs, which are controlled by the genes regulated by circadian rhythm, if CDK4-6 inhibitor is given in the time period when BMSCs are in the G1-S phase, then theoretically there is a chance to inhibit their division, leading to BMSCs cell arrest and consequently lead to cytopenia, which is the chief side effect of CDK4-6 inhibitor.

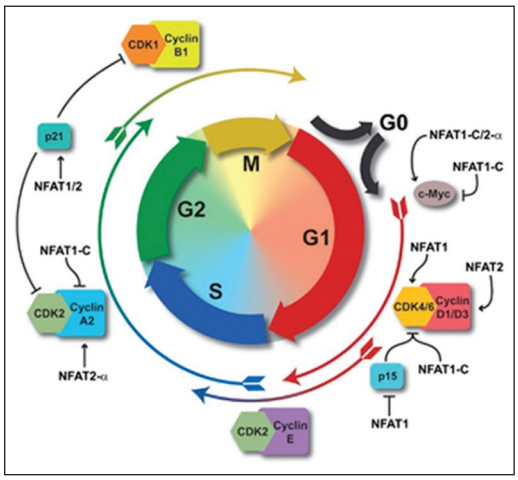

Figure 3: Schematic representation of the cell cycle regulation

Cytopenia was not severe in both PALOMA and MONALEESA trials, but still the chief side effects of CDK 4/6 inhibitors is anaemia, thrombocytopenia, and leukopenia as chief side effects of CDK4/6 inhibitors.

In India, leukopenia, even of mild grade can put our patient at serious risk of countering community acquired illness like Tuberculosis, community acquirCytopenia was not severe in both PALOMA and MONALEESA trials, but still the chief side effects of CDK 4/6 inhibitors is anaemia, thrombocytopenia, and leukopenia as chief side effects of CDK4/6 inhibitors.ed pneumonia.

If we study the timing of administration of oral palbociclib or ribociclib, it is possible that majority took the pills during peak of G1-S transition of the healthy cells, possibly leading to cytopenia due to same reason.

Will it Affect the Cancerous Cells?

Cancerous cells are not under the control of circadian rhythm. In fact, disrupted expression of circadian genes can alter breast biology and may promote cancer.[10]

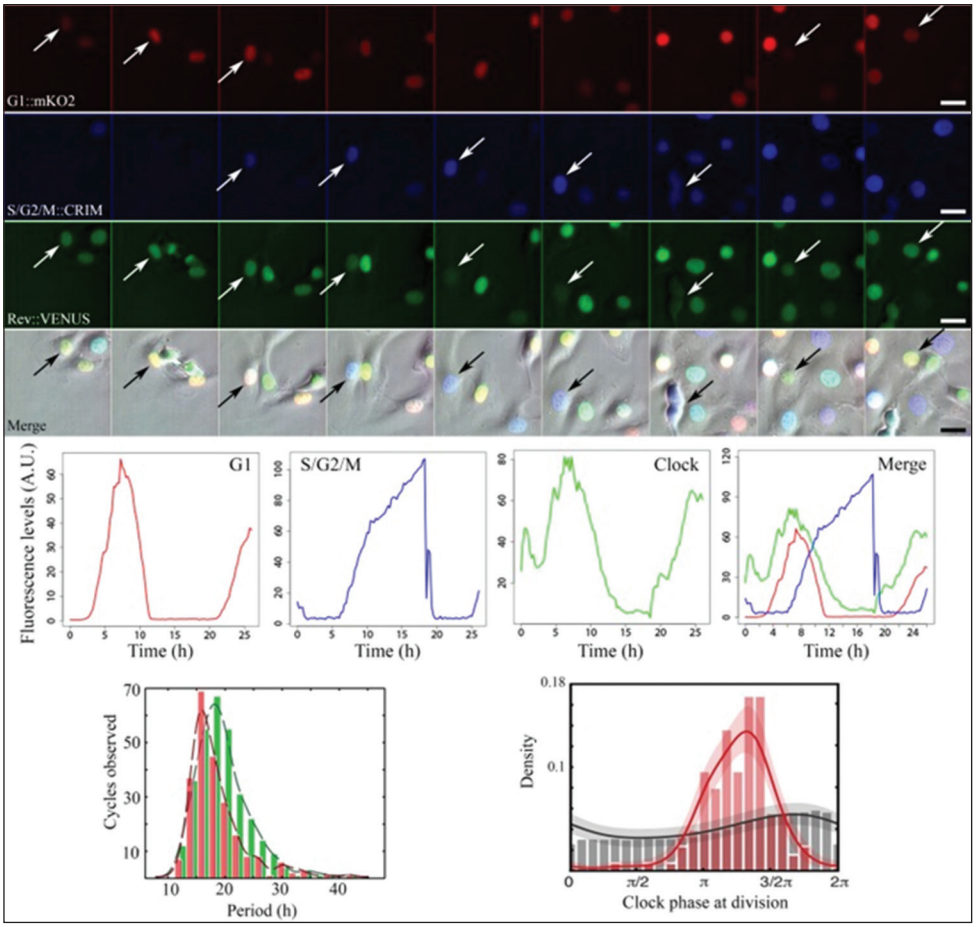

Figure 4: Schematic representation of cell cycle duration and biological clock (circadian clock)[13]

Various studies suggest that Clock gene defects in mammary epithelium can lead to cell cycle disruption. This disruption causes unregulated cell division, increased susceptibility to breast cancer, and results in more aggressive tumors.[10]

Following Table 3 clearly depicts that genes regulating circadian rhythm may be mutated in breast cancer patients.

Few genes are also implicated in the disease progression or metastasis. Whereas hypermethylation of the same genes, may render patient at reduced risk of having breast cancer. For example, hypermethylation of CLOCK gene promoter leads to reduced risk of breast cancer.

Some of the genes overexpression (PER1/PER2) helps in reduced proliferation of the breast cancer in general. Same applies to BMAL1 overexpression.

Whereas, knockout of the same gene leads to increased risk of invasion and metastasis of the breast cancer.

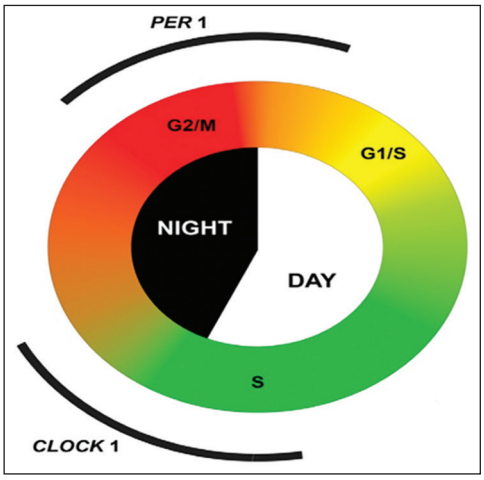

Figure 5: Schematic of the typical cell cycle progression in adult brain of a diurnal vertebrate, zebrafish, maintained under regular light–dark conditions. At early morning hours of Night 1, upregulation of cyclin D1 expression initiates gradual G1/S transition in the population of cycling neuronal stem and progenitor cells. Throughout the day, S-phase initiation and DNA replication continue, with a gradual surge in cyclin A2 expression and the number of S-phase cells peaking late in the day

Circadian mutations covered in this review and their links to cancer. Both epidemiological and experimental data are included, along with possible mechanisms and resultant phenotypes were known.

KO Knockout, SNP Single Nucleotide Polymorphism

There is still a long way to define the molecular basis of, how the circadian system influences breast cancer, and which of the different genetic types of breast cancer are most influenced by altered clocks. Further, details of the mechanisms linking Clock genes to cancer are needed to fully understand how an altered circadian system and how rotating shift work influence the disease. This molecular mechanism will help to improve future therapeutic interventions.

Can We Reduce the Hematological Toxicity of the G1-S Phase Inhibition by CDK4/6 Inhibitors?

If we apply the knowledge of circadian clock, then we know the fact that BMSCs are under the control of circadian rhythm and G1-S phase of CDC occurs at the early morning period of solar day. If CDK4/6 plasma peak level coincides with G1-S phase of BMSCs, then theoretically cytopenia may occur, which again is the sign of CDK4/6 action but is also the reason of its toxicity.

The target cells/cancerous cells are not under the whims of circadian rhythm and may be in G1-S phase at any given time. Thus, we may alleviate the toxicity to some extent if the dosing time is changed to late evening time instead of early morning or midday time of dose administration.

Cause peak plasma concentration of CDK4/6 inhibitor coincides with the G1-S transition phase of the healthy BMSCs.

Regarding pharmacokinetics of CDK4/6 inhibitor, its peak plasma concentration was achieved in 2–3 h after oral intake.[16] Hence, dosing schedule may alter the toxicity profile, this question needs to be answered by a large-scale data on timing of palbociclib administration and degree of neutropenia.

Table 3: Mutation in circadian clock genes and their impact on breast cancer process/progression

Mutations/SNP	Possible mechanism	Phenotype
CLOCK		**Self-renewal capacity of mammary progenitor cells becomes compromised (our unpublished data)**
Hypermethylation of *CLOCK* promoter	Mediates CCL5 expression	Reduced breast cancer risk
NPAS2 Ala394Thr SNP	Altered NPAS2 protein structure	Increased breast cancer risk
PER1 deficient	Alters expression of checkpoint proteins ATM and Chk2	Increased proliferation
PER1 overexpression	Impairs p53 leading to decreased apoptosis, deregulation of c-*myc*/*CyclinD1*/*GADD45*	Reduces proliferation in colon, lung, and breast cancer cell lines
PER2 overexpression	Cell cycle arrest, growth inhibition, apoptosis induction	Suppresses breast cancer *in vivo*
PER3 deficient		Higher probability of cancer recurrence
Cry deficient	Disrupted cell cycle regulation through deregulation of *Wee-1* and *CyclinD1*	
BMAL1/Era/*PER2*KO	Prevents mammary acinar formation	Facilitates invasion and metastasis
BMAL1 overexpression	Binds to *p53* promoter	Tumor suppression

At the end, we have to prove the pharmacokinetic modulation, respecting the circadian rhythm to reduce toxicity of cell cycle-specific drugs, especially G1-S phase active chemotherapeutics.

Chronological Modulation in Oncology

Chronological modulation is used in oncology, especially for FOLFOX regimen in colon/rectal carcinoma. If 5FU and oxaliplatin are given in chronomodulated fashion, then the tolerability. There was overall improvement in quality of life with chronochemotherapy affecting indirect costs such as reduction of work.[17]

Professor Levi conducted up to three trial of the first line 5FU and oxaliplatin with chronomodulation versus conventional delivery for metastatic colorectal cancer. His trial showed consistent benefit in terms of reduced toxicity. The first trial showed benefit in median survival,[18] but not median progression-free survival, the second showed a benefit in tumor shrinkage and disease control,[19] and the third showed 3-month survival advantage in males but not in women.[20]

Why Not in Women?

As the toxicity of the drug is 25% higher in females,hence chronomodulation didn't impact much, as toxicity itself was limiting the effects of the drug. But in CDK4/6 inhibitors, toxicity is uniform and not gender specific.[20] A meta-analysis has also proved that men are benefitted by chronomodulation in 5FU, leucovorin, and oxaliplatin regimen than females.[21]

Conclusion

Chronomodulation of chemotherapy, in oncology, through personalized circadian-timed therapy may reduce hematological toxicity as far as 5FU is considered. In our case of hematological toxicity which is correlated with cell cycle of the BMSCs, there is high chance of avoiding or minimizing the hematological toxicity of the CDK4/6 inhibitors, a cell cycle-specific chemotherapy.

5-FU is an antimetabolite as against CDK4/6 inhibitors, which are more cell cycle specific. We do understand that previous studies and meta-analysis on chronomodulation did not prove any substantial benefit on survival but as far as quality of life, tolerance, or pharmacoeconomics are concerned, chronomodulation has definitely beneficial as compared to conventional ways of drug administration.

To conclude, we can have a larger data collected on timing of administration of CDK4/6 inhibitors and its impact on hematological toxicity. Later half of the day administration seems to be theoretically beneficial. Larger data are needed to prove this hypothesis.

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