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Review Article

Use of five-day chronomodulated prescription of palbociclib as myelopreservation drug along with Topotecan in recurrent extensive stage small cell lung carcinoma - A perspective article

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ABSTRACT

Myelopreservation is always a good option when prescribing myelotoxic chemotherapy like Topotecan. Bone marrow toxicity is one of the main hindrances in prescribing such chemotherapy. Cyclin-dependent kinase 4/6 inhibitors (CDK4/6 inhibitors) are known to inhibit the Cell cycle in the G1-S phase. Inhibition of hematopoietic stem cells was the reason for CDK4/6 inhibitor – trilaciclib to be prescribed with Topotecan as a myelopreserving agent. Trilaciclib is an intravenous CDK4/6 inhibitor with a short half-life and can be co-prescribed with chemotherapy. Trilaciclib is currently not available in India. We propose the use of palbociclib, an oral CDK4/6 inhibitor, for the same indication. We suggest the use of a short course of palbociclib for five days, along with chemotherapy, as a myelopreserving agent. We also propose to chronomodulate the dose to maximize the effect.

Keywords: Cyclin-dependent kinase 4/6 inhibitor, Myelopreservation, Chronomodulation, Topotecan, Myelotoxicity

INTRODUCTION

Topotecan, a topoisomerase I enzyme inhibitor, is used in relapsed extensive-stage small-cell lung carcinoma (SCLC). But it's highly myelotoxic. Recently, a cyclin-dependent kinase 4/6 inhibitor (CDK4/6 inhibitor), trilaciclib, got approval as a myeloprotectant when given along with Topotecan.[1] However, trilaciclib is not available in India. We suggest the use of widely available CDK4/6 inhibitor palbociclib although as a short course therapy as a chronomodulated prescription to prevent myelotoxicity when used along with Topotecan. Let us now compare the pharmacokinetics of trilaciclib with palbcociclib so as to bring some semblance to the topic. Trilaciclib is an intravenous short-acting CDK4/6 inhibitor.

A PK/PD study of trilaciclib noted its therapeutic effects at 192 mg/m^2 (240 mg/m^2 – dose approved) and dose-dependent inhibition of CD45+/CD3+ lymphocytes (a surrogate marker of CDK4/6 inhibition in bone marrow). The maximal inhibition was 60% and was four hours after infusion; recovery of peripheral lymphocytes was seen eight hours after infusion. However, the results of recovery were variable with few results did not show recovery even 24 hours post infusion.[2] It is almost the same as palbociclib! The only logic put forward for not using oral

CDK4/6 inhibitors for myelopreservation has a chronic effect on hematopoietic stem cells.[3] But what if we use a short course of palbociclib? A short course of palbociclib in a chronomodulated way[4] will have a myelopreservant effect and hence can be given with myelotoxic chemotherapy.

Bone marrow stem cells (BMSC), when exposed to CDK4/6 inhibitors, will have cell cycle arrest in the G1-S phase, rendering them incapable of dividing and hence immune to chemotherapy-induced cytotoxicity.[5] SCLC cells have Rb gene mutations (Retinoblastoma gene) in particular, which makes them resistant to the inhibitory effect of CDK4/6 inhibitors. Thus, CDJK4/6 inhibitors will not affect SCLC cells as such.[2]

Chronomodulation of CDK4/6 inhibitors[4] will help specifically in ensuring BMSCs are in the G1-S phase when CDK4/6 inhibitors are administered. Usually, oral CDK4/6 inhibitors follow T max-, that is, the maximum concentration is reached after 4–5 hours of its administration and a half-life of 24–26 hours.[6] Our BMSCs are under the aegis of circadian rhythm.[7] We are all solar bodies, and our cell cycle is also regulated by circadian rhythm.[4,8] If we give a short course of chronomodulated CDK4/6 inhibitors, we can ensure myelopreservation in the presence of cytotoxic chemotherapy such as Topotecan.

As shown in Table 1, trilaciclib is widely studied for its use as a myelopreservant, but even palbociclib can be repurposed for the same purpose as it matches with trilaciclib in almost every aspect of pharmacokinetics. If we give palbociclib as a short course for 5–7 days with Topotecan in extensive-stage SCLC, we can repurpose it to be used as a myelopreservant.

Table 1: Comparison of trilaciclib and palbociclib.

Drug profile	Trilaciclib	Palbociclib
Mode of administration	IV	PO
T max	4–5 h[2]	4–6 h[6]
t 1/2	8–24[2]	24–26 h[6]
Duration of administration	During chemotherapy session	21/28 days in hormone-sensitive metastatic breast cancer.
Indication	Along with Topotecan as myelopreservation agent	Along with hormonal therapy in
Dose	240 mg/m^2	125 mg PO
Timing of administration	Four hours before chemo	Not specified by any trial, given once a day

h: Hours, IV: Intravenous, PO: Per os (oral).

CHRONOMODULATION OF PALBOCICLIB TO REPURPOSE IT AS MYELOPRESERVANT

Every individual has a circadian rhythm or oscillatory rhythm, which is synchronized according to day/night cycle. The central control of this rhythmicity is in the suprachiasmatic nucleus.[9] There are peripheral oscillators at every tissue level. This biological clock is approximated to a 24 hour day/night cycle.[10] Chronotherapy is the administration of chemotherapy based on the timings of the day.[11] It was based on the study that chemotherapy becomes toxic only at particular times of the day;[12] however, phase III trial conducted on colorectal cancer patients being given chronomodulated FOLFOX, there was a beneficial trend for chronotherapy in men but not in women.[13] However, chronomodulation improved treatment tolerance.[14]

CDK4/6 inhibitors such as palbociclib cause cell cycle arrest of BMSC, which, over a period of time, leads to cytopenia as the main side effect of CDK4/6 inhibitors, and it is reversible.[15] Whenever it comes to BMSC, one must be aware of the impact of the light and dark cycle on BMSC.[16,17] Even the phases of the cell cycle are regulated by the light and dark cycle. We are all solar bodies, and our bone marrow also follows the same.[16,17] BMSC express core clock genes such as BMAL1 and PER2 in accordance with the circadian daylight cycle of approximately 20–26 hours.[17]

In one of the studies, CDK4/6 inhibitor happened to reduce the growth of cultured cells and mouse tumors in a time-of-day-specific manner underlying the importance of

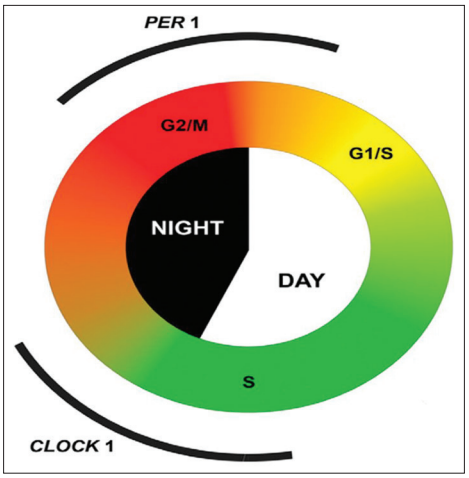

Figure 1: Exact correlation of day night cycle and cell division in adult neurogenic niche of diurnal vertebrates. PER1- Period gene-1, CLOCK-1 gene.

chronomodulation.[18] Thus light and dark cycle influences stem cells and their proliferation;[19] hence, chronomodulated prescription of palbociclib will arrest the BMSC and preserve them from myelotoxic chemotherapy like Topotecan.

As shown in Figure 1, in a study done on the adult neurogenic niche of diurnal vertebrates, it was seen that cells start in the morning, gradually transiting from the G1 to S phase of the cell cycle. This process lasts for several hours, with a peak number of cells undergoing the S phase at dusk time, that is, the time of light-dark transition. At night, cells are prevented from entering the S phase, roughly due to activation of the cyclin-dependent kinase inhibitor p20 around that time. This is followed by cells gradually shifting from the S phase and transiting into the G2/M phase throughout the night, with the peak in G2/M at dawn time.[20] We didn't come across any study showing a detailed cell cycle in hematopoietic stem cells. We presume it to be the same as in Figure 1. It gives a rough idea of the chronomodulation of CDK 4/6 inhibitors to be given in the early hours of the day to maximize the G1-S arrest of hematopoietic stem cells.

SCLC AND CDK4/6 INHIBITORS

Small cell lung cancer cell proliferation is dependent on the deletion of the RB-1 gene, Rb gene inactivation, or inactivating mutations in the RB-1 gene, and p53 is the hallmark of SCLC,[21] RB-1 inactivation. Mutation renders these cells resistant to CDK4/6 inhibitors.[22,23] Almost 90–100% of the SCLC cases have a biallelic loss of P53 and Rb-1 gene.[21] Thus, CDK4/6 inhibitors will have theoretically no or minimal action on SCLC cells as such.

DISCUSSION

Topotecan is known as myelotoxic chemotherapy. Trilaciclib, an intravenous CDK4/6 inhibitor, recently got approval as a myelopreserving agent. Trilaciclib is currently unavailable in India. If we study in detail the perspective that we are presenting, we may use palbociclib in a short course, chronomodulated or non-chronomodulated way. We may use an economical option as a myelopreserving agent in association with Topotecan. We may also use it along with any other myelotoxic chemotherapy as a myelopreservation agent.

It's high time to start a trial on the use of palbociclib as a myelopreservation agent. It's ironic! That palbociclib, a CDK4/6 inhibitor known for its effect on BMSC[15] can be repurposed for this indication. Palbociclib-induced myelosuppression–can be rapidly reversed as well,[15] it is different from other cytotoxic chemotherapy. While cytotoxic chemotherapy causes DNA damage cell toxicity, CDK4/6 inhibitors cause G1-S phase arrest. The recovery is rapid and fully reversible. It's also the reason why febrile neutropenia is rare in CKD4/6 inhibitors.[15]

The question remains: whether a short course, that is, 5–8 days of palbociclib results in BMSC arrest?

Well, there are two explanations that we would like to propose. One is the pharmacology of palbociclib suggests that palbociclib achieves steady-state concentration within 7–8 days of its initiation.[24] Secondly, there are alternative regimens of 5-day palbociclib/week, and they have also demonstrated clinical effects.[25] Five-day palbociclib had a similar effect and less grade 3 absolute neutrophil count, again supporting our argument that a cumulative dose of palbociclib results in more time to recovery of marrow. The short course will have a rapid recovery.

Besides, when used along with myelotoxic drugs like Topotecan, these actions of CDK4/6 inhibitors will help BMSCs in early recovery due to cell cycle arrest. It will also prevent harmful side effects like febrile neutropenia. Palbociclib, if repurposed for this indication, can be of great help to India as it will decrease the cost of CKD4/6 inhibitor and admission due to febrile neutropenia. Palbociclib is available in India as a generic medicine and can be very economical if used for this purpose as well.

We do agree that this is just a perspective; the clinical trial is highly recommended for this new indication of palbociclib.

CONCLUSION

We conclude that a clinical trial can be initiated to repurpose palbociclib as myelopreservation agent with Topotecan in recurrent extensive stage small cell lung carcinoma patients. palbociclib will be the most economical option for this indication.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of Artificial Intelligence (AI)-Assisted Technology for manuscript preparation

The authors confirm that there was no use of Artificial Intelligence (AI)-Assisted Technology for assisting in the

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