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Review Article

High-dose nicotinamide, a histone deacetylase inhibitor (Sirtuin-1), can prevent emergence of treatment resistance in chronic myeloid leukemia – A perspective

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ABSTRACT

Chronic myeloid leukemia (CML) is now widely treated using tyrosine kinase inhibitors (TKI). These TKIs can annihilate dividing cells, but they have no effect on quiescent stem cells. These quiescent stem cells slowly give rise to treatment resistance in the form of mutations. T315I is one such mutation that is resistant to most of the TKI's and treating this acquired kinase domain mutation i.e T315I, is often costly. Nicotinamide is histone deacetylase inhibitor. It inhibits SIRT-1(Sirtuin-1). High dose nicotinamide, when used with TKI, will not only potentiate TKI action, but also annihilate quiescent stem cells thereby preventing the emergence of treatment resistance in CML. We propose a perspective article on using high dose nicotinmaide along with TKI to prevent emergence of treatment resistance. Thus going by the famous idiom "prevention is better than cure",we suggest trial on high dose nicotinamide with TKI in CML.

Keywords: Nicotinamide, Sirtuin-1, Histone deacetylase inhibitor, Chronic myeloid leukemia, Tyrosine kinase inhibitors

INTRODUCTION

Chronic myeloid leukemia (CML), a disease as a result of BCR-ABL fusion protein, is treated by tyrosine kinase inhibitors (TKIs). However, even these TKIs cannot kill quiescent stem cells, and thus, there is an emergence of resistant strains leading to disease progression.[1] Hence, those quiescent stem cells need to be targeted.[1]

Nicotinamide or Vitamin B-3 deficiency can cause pellagra. This is a well-known fact, but very few know that it is also a poly ADP ribose polymerase 1 (PARP-1) inhibitor.[2] Besides, it also causes inhibition of Sirtuin-1 (SIRT-1).[3] SIRT-1 inhibitors have been studied in CML as SIRT-1 is over-expressed in CML cells.[3] Not only its action on SIRT-1 but also its action to decelerate telomerase shortening rate also potentiates the action of second-generation TKI like nilotinib.[4]

Hence, nicotinamide, an amide derivative of Vitamin B3, also has myriads of effects to potentiate the effect of TKIs apart from itself having anti-leukemia activity as far as BCR-ABL inhibition is concerned. It also increased the sensitivity of doxorubicin and reduced its cardiotoxicity in one of the published studies on CML cell lines.[5] Nicotinamide is a non-competitive inhibitor of SIRT-1.

Regarding SIRT-1, they are nicotinamide adenine dinucleotide-dependent histone deacetylases[5] and promote leukemogenesis and mutagenesis in CML, including T315I, which is an acquired mutation.[6] SIRT-1 is a member of the Sirtuin family responsible for the regulation of cell senescence by its action on telomere shortening, DNA repair through PARP-1, cell cycle,

metabolism, and cell survival.[7] Some older studies suggested over-expression of SIRT-1 in blast crisis.[8] SIRT-1 overexpression and consequent de-acetylation of P53 results in a dysregulated cell cycle and consequent mutations.[9]

NICOTINAMIDE AS AN ADJUNCT TO TKI TO PREVENT THE EMERGENCE OF T315I

T315I mutation is the most frequent mutation. It is located in the ATP binding domain[10]. It is not only frequent, but is also difficult to treat by first- and second-generation TKI.

The question is, can we prevent the emergence of such mutations in CML clones? In preclinical studies, the use of heat shock protein 90 (HSP-90) inhibitors can prevent the emergence of imatinib-resistant mutations like T315I.[11] SIRT-1 and HSP-90 α are linked functionally in controlling cell viability, although in diffuse large B cell lymphoma (DLBCL).[12]

Although imatinib mesylate has changed the way we treat CML, we know that imatinib has little, if not any, effect on quiescent CML stem cells.[13] However, these quiescent stem cells can shuffle between quiescence and dividing stem cells. Once they enter the cycling phase, they may acquire mutations, including T315I.[14] Nicotinamide riboside supplementation decreased the aging of hematopoietic stem cells and promoted their engraftment.[15] Together, if we combine nicotinamide with TKI, we can affect the hematopoietic stem cells. Increased aging of HSCs can promote mutagenesis.

T315I mutation is difficult to treat, and the means to prevent its emergence should be our goal to achieve sustained molecular remission and deep molecular remission in CML.

NICOTINAMIDE - DOSE REQUIRED IN CML?

Nicotinamide, although at a high dose, has shown its action on SIRT-1 and PARP-1 inhibition[2,4-6] and increases telomerase activity.[6] *In vitro* studies suggest PARP-1 inhibition action by nicotinamide at a dose concentration of 10 mm when used as a single agent, while when used with some anticancer agent, PARP-1 inhibition occurred at a much lower dose. Clinically, a dose of 6 g of nicotinamide transcends into a dose of >2 mm. Such a high dose of nicotinamide has mild nausea and vomiting as side effects.[16] Clinical trials like NCT00580931 on Alzheimer's disease used a dose of 1500 mg twice a day for six months and considered such dose as safe for the elderly population.[17] Thus, it is proven that nicotinamide in doses up to 1500 mg BD can be safely given in clinical practice. We have published our perspective on nicotinamide as a potential PARP-1 agent at the dose mentioned above to be used as maintenance in BRCA mutated ovarian cancer patients post-chemotherapy.[18] The telomerase activity of nicotinamide is due to its action as a PARP-1 inhibitor.

Thus, at a high dose, nicotinamide exerts its effect on PARP-1 as an inhibitor of PARP-1 activity and, thus, can be used as a supplement to TKI in CML.

NICOTINAMIDE WITH OTHER TKIs

In preclinical studies, replacing the benzamide moiety of ponatinib with nicotinamide resulted in enhanced activity against leukemia (acute myeloid leukemia). It can be potentially less toxic than ponatinib as well.[19]

Of course, it is a preclinical study and cannot be extrapolated, as idiosyncratic toxicity can occur when used in clinical scenarios. In other pre-clinical studies done on cell lines – K 22 IR-imatinib resistant CML cell lines with ABL-1 mutation (T315I) have shown anti-ABL-1 activity in addition to anti-FLT3 activity by compounds containing water-soluble nicotinamide moiety.[20]

T315I is a type of mutation ABL-1 mutation, and it develops after prolonged drug treatment.[19] Ponatinib is the drug that has an action against ABL-1 mutation and is currently approved for the treatment of T315I mutated CML. Ponatinib has a cardiovascular side effect profile as its main side effect and carries a black box warning for the same. Hence, ponatinib is used as a last resort in treating CML. Thus, a potent drug that inhibits ABL-1 activity is usually used late in the course of this disease. This paves the need for some drugs in addition to conventional imatinib to prevent the emergence of T315I ABL-1 mutation from emerging.

We suggest nicotinamide derivatives to be used with imatinib to prevent the emergence of ABL-1 mutations. As shown in preclinical studies, nicotinamide at a high dose has the potential to inhibit ABL-1 activity, at least in pre-clinical studies.

It is hypothesized that nicotinamide potentiates the inhibition of telomerase activity of nilotinib through PARP-1 inhibition.[3] Nilotinib and dasatinib, in particular, have an action on telomerase inhibition.[21]

In a pre-clinical study done on cell lines that are BCR-ABL positive (K 562) and negative (HL 60), both nilotinib and dasatinib demonstrated telomerase inhibition, suggesting that their telomerase inhibition activity is independent of BCR-ABL inhibition. Nicotinamide, in addition to nilotinib, has an action on K562 cell lines [22], which are imatinib-resistant.

We can add nicotinamide or else make nicotinamide derivatives in addition to imatinib to prevent the emergence of kinase domain mutations, including T315I.

NICOTINAMIDE CLINICAL USES AND SIDE EFFECT PROFILE

The recommended daily allowance for nicotinamide is 20 mg a day for an adult. The dose used to treat diabetic and pre-diabetic patients has ranged from 25 to 50 mg/kg/day

Table 1: Pharmacokinetics of nicotinamide.

Absorption	Readily absorbed parenterally and all parts of the GI tract.
Peak plasma concentrations	One hour of oral ingestion
Distribution	Distributed in all tissues
Clearance	High hepatic extraction ratio and plasma clearance
Metabolism	At high doses, methylated to n methyl nicotinamide – which is oxidized in the liver to n–methyl two pyridone–5 carboxylic acid amide(2 pyr) Even oxidation to nicotinamide n–oxide

GI: Gastrointestinal

Table 2: Toxicity.

Toxicity	Human data
Liver toxicity	Jaundice with a frequency of 1: 2000
Teratogenicity	No evidence
Oncogenicity	No evidence
Growth retardation	No growth retardation
Insulin response	25 mg/kg (1.2 g/m^2) – no effect in normal subjects. 25 mg/kg: 1 g/day – improved stimulated C-peptide secretion in newly diagnosed type-1 diabetic patients. 1.2 g/m2 dose – decreased first-phase insulin response in pre-diabetic subjects.

Table 3: Side effects of high-dose nicotinamide.

Side effects	Frequency(%)
Flushing	≤1.5
Facial erythema	≤0.5
Hives	≤0.4
Sore mouth	≤0.4
Dull headache	≤0.5
Heartburn	≤1.6
Nausea (with radiotherapy)	17–65
Nausea (without radiotherapy)	≤1.5
Other gastrointestinal symptoms	≤0.8
Inability to focus the eyes	≤0.4
Dry hair	≤0.4
Fatigue	≤0.4

(1.75–3.5 g/day), approximately the same dose that we propose for using it in CMl (1500 mg BD), such a high dose requires evaluation of its toxicity. Doses in excess of 3 g/day should be considered as potentially toxic, and unsupervised use should be discouraged.[23]

As shown in Table 1, nicotinamide can be absorbed orally; peak plasma concentration is one hour after the oral intake. Nicotinamide is metabolized by methylation reactions.[24] As shown in Tables 2 and 3, side effect profile is manageable.

High-dose nicotinamide is a relatively safe option for its use in CML, especially in high-risk CML, with second-generation TKIs such as nilotinib or dasatinib so as to prevent the emergence of T315I mutation.

CONCLUSION

We need to study in detail nicotinamide and its role in addition to the conventional treatment of TKI in CML. Nicotinamide and its inhibitory action on SIRT-1 will help in eliminating quiescent stem cells. These quiescent stem cells are responsible for drug resistance and disease progression. It has been proven that histone deacetylase inhibitors help in annihilating these quiescent stem cells. Thus, we suggest nicotinamide, in addition to conventional TKIs, be added to the treatment armamentarium to prevent the emergence of resistance to TKI.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient consent was 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 writing or editing of the manuscript and no images were manipulated using AI.

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