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## Potential Association of Nicotinamide on the Telomerase Activity and Telomere Length Mediated by PARP-1 Mechanism in Myeloid Cancer

(Potensi Perkaitan Nikotinamida ke atas Aktiviti Telomerase dan Panjang Telomer Disebabkan oleh Mekanisme PARP-1 pada Kanser Mieloid)

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### ABSTRACT

*Administration of nicotinamide is affecting various types of cells through its survival, maturation, and differentiation. Nicotinamide as part of vitamin B3, plays an important role in DNA repair and maintenance of the genomic stability which related to its function as a NAD<sup>+</sup> precursor that involve in many biological processes. During DNA breaks, PARP-1 mechanism will be activated and use NAD<sup>+</sup> as a substrate in process of DNA damage and repair that will result to either cell repair and cell death. In the meantime, in presence of nicotinamide that is also acting as a PARP-1 inhibitor, causing inability of the repair mechanism to fix the entire DNA damage which also lead to the cell death. Therefore, loss of PARP-1 enzyme will cause disturbance in the DNA repair process. Telomere shortening rate was reduced in the presence of nicotinamide that might related with telomerase enzyme which able to maintain the telomere length of the cell. Other than that, telomere also can be influenced by PARP-1 activity where it might show some correlation between nicotinamide, telomere and telomerase that could related with PARP-1 mechanism. Currently, there is no treatment options that respond effectively in chronic myeloid leukemia (CML) in blast crisis (BC) phase without any side effect and it is require an identification of new drug therapies to treat the CML patients. By understanding the role and potential of nicotinamide relation with PARP-1 mechanism in telomere and telomerase status may improve the therapeutic strategy for chronic myeloid leukemia.*

*Keywords: Nicotinamide; PARP-1; telomerase; telomere*

### ABSTRAK

*Pengambilan nikotinamida menjejaskan pelbagai jenis sel melalui kelangsungan hidup, kematangan dan pembezaannya. Nikotinamida sebagai sebahagian daripada vitamin B3 memainkan peranan penting dalam pembaikan dan penyelenggaraan kestabilan genom DNA yang berkaitan dengan fungsinya sebagai prakursor NAD<sup>+</sup> yang melibatkan banyak proses biologi. Semasa DNA pecah, mekanisme PARP-1 akan diaktifkan dan menggunakan NAD<sup>+</sup> sebagai substrat dalam proses kerosakan dan pembaikan DNA yang akan menyebabkan pembaikan sel dan kematian sel. Sementara itu, dengan adanya nikotinamida yang juga bertindak sebagai perencat PARP-1, menyebabkan ketidakupayaan mekanisme pembaikan untuk memperbaiki keseluruhan kerosakan DNA yang juga membawa kepada kematian sel. Oleh itu, kehilangan enzim PARP-1 akan menyebabkan gangguan dalam proses pembaikan DNA. Kadar pemendekan telomer berkurang dengan kehadiran nikotinamida yang mungkin berkaitan dengan enzim telomerase yang dapat mengekalkan panjang telomer sel. Selain itu, telomer juga boleh dipengaruhi oleh aktiviti PARP-1 dan ia mungkin menunjukkan beberapa korelasi antara nikotinamida, telomer dan telomerase yang boleh dikaitkan dengan mekanisme PARP-1. Pada masa ini, tiada pilihan rawatan yang bertindak balas dengan berkesan dalam leukemia mieloid kronik (CML) dalam fasa krisis blas (BC) tanpa sebarang kesan sampingan dan memerlukan pengenalan terapi ubat baru untuk merawat pesakit CML. Dengan memahami peranan dan potensi hubungan nikotinamida dengan mekanisme PARP-1 dalam telomer dan status telomerase dapat meningkatkan strategi terapeutik untuk leukemia mieloid kronik.*

*Kata kunci: Nikotinamida; PARP-1; telomerase; telomer*

### INTRODUCTION

Nicotinamide or known as niacinamide or nicotinic acid amide is an active form of vitamin B3 which is also a water soluble amide of nicotinic acid with many physiological

and pharmacological functions in various organisms. It acts as precursors of nicotinamide adenine dinucleotide (NAD) (Audrito et al. 2011) which is an important molecule involve in energy metabolism and also in chemical

reaction in the body including ADP-ribosylation that related to DNA repair, cell death, transcription, DNA replication, and cell cycle (Ida et al. 2009). Nicotinamide has also shown to be a free radical scavenger and been used in cyclic ADP ribose synthesis (Surjana et al. 2010) and its phosphorylated derivative, nicotinamide adenine dinucleotide phosphate (NADP<sup>+</sup>). The dietary sources of nicotinamide and niacin are readily available in plant and animal food such as in liver, yeast, dairy product, bean, green vegetable, bread and coffee. NAD<sup>+</sup> and NADP<sup>+</sup> can be enzymatically hydrolyzed to nicotinamide from the uncooked food during the process of cooking (Jacob & Swendseid 1996).

Nicotinamide have been used for years by many people and it was shown to have low toxicity and side effects (Knip et al. 2000). Deficiency of nicotinamide in human can cause pellagra (Bogan & Brenner 2008) which is a nutritional disorder to cause dermatitis, diarrhea, dementia, and also death (Karthikeyan & Thappa 2002). It also had been used in the therapy of pellagra even in high levels of the drugs. According to Paul (2011), nutrient deficiency such as folate, zinc and magnesium, can cause the DNA damage from various causes possibly results to shorter telomeres in rats and cells.

Cancer patients were found to be at risk of niacin deficiency in a few studies due to the suppressed NAD<sup>+</sup> levels from chemotherapy and maintaining an optimum level of nicotinamide is therefore important to these patients (Surjana et al. 2010). On the other hand, nicotinamide also functions as sensitizing agent and counteract chemotherapy and radiation therapy by increasing blood flow that will allow the elevated oxygen supply to the tumors (De Soto et al. 2006). Thus, tumors hypoxia is reduced.

Based on the study by Chen et al. (2015), this one type of vitamin B3 has also been shown to have the ability to preserve from the effects caused by the UV radiation and thus decrease the proportion for new premalignant skin cancer. They have found that nicotinamide has reduced the rate of various type of skin cancers when treated with nicotinamide from 11-30% compared to other type of treatment and no evidence benefit after discontinuation of nicotinamide. They also have come to agree that the intake of oral nicotinamide was safe and effective to be used in the treatment of high-risk patient of skin cancer. UV radiation can cause damage to DNA, disturb the immunity system (Yarosh 2004) and depleting the cellular ATP thereby inhibiting the DNA repair (Park et al. 2010). The production of ATP that can be used for DNA repair requires NAD<sup>+</sup> which can be obtain from nicotinamide that also act as a precursor of NAD<sup>+</sup>. Therefore, glycolytic blockade, ATP depletion and also the level of immunosuppression caused directly by the UV radiation can be reduced and prevented by nicotinamide (Park et al. 2010; Surjana et al. 2013; Thompson et al. 2014; Yarosh 2004). Nicotinamide has been proven to play a beneficial role in inhibiting liver fibrosis in rats and at the same time able to induce apoptosis by reducing the

expression in cell cycle related proteins (Jin et al. 2011; Traister et al. 2005).

Over years, nicotinamide has been used within required doses with minimal side effect that does not cause flushing, itching, hypotension or headaches under doses of consumption (Knip et al. 2000; Ranchoff & Tomecki 1986). Nicotinamide is also an inexpensive supplement that widely accessible in any pharmacies which can be taken as an additional supplement for consumption.

Moreover, nicotinamide also play an important role in poly (ADP-ribose) polymerase (PARP-1) which has a part in reassembling the DNA strand breaks caused by radiation and chemotherapy (Kjellen et al. 1985). Its function as NAD<sup>+</sup> precursor and also a substrate for PARP-1 has been an important player in DNA repair and also maintenance of the genomic stability as the increase of NAD<sup>+</sup> level by addition of nicotinamide will also increase and improve the capacity in DNA repair. It has been studied that a certain amount of nicotinamide increase the intracellular NAD<sup>+</sup> and enhance the repair of DNA damage in cultured primary human mammary epithelial cells (Jacobson et al. 1999). It is essential to have adequate NAD<sup>+</sup> for the increase in ADP-ribose polymer metabolism due to the DNA damage. Hence, it showed that increasing level of NAD<sup>+</sup> by addition of nicotinamide therefore improved the capacity of DNA repair. Even a poor diet can fulfill the standard requirement for NAD<sup>+</sup> synthesis since NAD<sup>+</sup> has various precursors (Belenky et al. 2007). As in the case of pellagra, it is clear it could be harmful in a shortage of NAD, yet it remains to be seen whether high dosages of NAD precursors can be applicable as a therapeutic or as beneficial diet supplements. This review aims to highlight better understanding of the potential association of nicotinamide on the telomerase activity and telomere length mediated by PARP-1 mechanism particularly in myeloid cancer and to initiate further investigation of tyrosine kinase inhibitors such as nilotinib in relation to nicotinamide supplementation effects.

#### NICOTINAMIDE AND PARP-1 MECHANISM

Administration of poly (ADP-ribose) polymerase 1 (PARP-1) has been developed to be one of the promising molecular targets as an anticancer drug where it involves in many biological process from DNA repair to cell death. PARP-1 is also known as NAD<sup>+</sup> ADP-ribosyltransferase is a nuclear enzyme encoded by PARP-1 gene which used in DNA damage and repair, where it binds to the DNA single or double strand breaks and used NAD<sup>+</sup> as a substrate to form a nicotinamide and ADP-ribose (De Lorenzo et al. 2013; Surjana et al. 2010). One of the earliest events that occur when DNA breaks is the recognition of DNA damage by PARP-1 enzyme (Malyuchenko et al. 2015). DNA breaks will activated the PARP-1 which can lead to three cellular pathways depend on the intensity of DNA damage stimuli (Virag & Szabo 2002). PARP-1 activation in minimal genotoxic damage will enhance the DNA repair by interacting with

p53 protein, signaling cell-cycle arrest, and facilitating DNA repair enzymes to access the damaged DNA. PARP-1 activation induces apoptotic cell death when DNA damage is irreparable or stronger damage happened. However, in an extensive DNA damage will cause over activation of PARP-1 that will lead to deplete of intracellular NAD, and therefore, trigger cell to undergo necrosis (Burkle 2001). When the cells are severely deficient in energy, it is unable to proceed through apoptotic cell death since apoptosis is an energy-dependent process (Surjana et al. 2010). Nicotinamide plays an important role in PARP-1 activity for DNA repair and maintenance of the genomic stability and it is related to its function as a NAD<sup>+</sup> precursor that involve in many biological processes (Litwack 2018) such as regulation of energy metabolism, DNA repair and transcription.

Inhibition of PARP-1 also currently been studied to act as antitumor agent since PARP-1 inhibitors are able to boost the cytotoxic effects of alkylating agents (Rouleau et al. 2010) which they can enhance the chemo-sensitizers and radio-sensitizers in tumors therapy (Malyuchenko et al. 2015). Inhibition of PARP-1 may lead to the destruction of abnormal cells by suppressing the repair mechanism involved in DNA damage and cause failure to DNA repair. Thus, it will help to increase the effect of alkylating agent in causing breakage of DNA strands and eventually the death of the cell. PARP-1 inhibitors can be used as independent drug against tumors but the inhibitions do not always have direct cytotoxic effect on cell and it can be used with administration of other drug to treated several reported tumor such as in mice lymphoma, Hela cell, and lung cancer cell (Holl et al. 2000; Magan et al. 2012; Mason et al. 2008). Moreover, it also have been reported that one of the PARP-1 inhibitors were shown to prevent recovery of the tumor cell after the potentially lethal damage and surpass the resistance (Liu et al. 2008). Based on Malyuchenko et al. (2015), the first generation of typical PARP-1 inhibitor is nicotinamide which is one of the products of PARP-1 catalyzed reaction that can cause moderate inhibition to its activity. It has been reported in several studies that nicotinamide has inhibit PARP-1 activity (Allende-Castro et al. 2012; Knip et al. 2000; Lee et al. 2008; Park et al. 2010; Virag & Szabo 2002) in many type of disease and tumors in relation with NAD<sup>+</sup> and ATP level cause by DNA strand breaks. Therefore, nicotinamide as an inhibitor of PARP-1 plays an important role in determining the cellular fate in response to DNA damage (Turunc Bayrakdar et al. 2014). By inhibition of PARP-1, NAD levels can be manipulated for the therapeutic potential. Since PARP-1 play an important role in detection and repair of both single-stranded and double-stranded DNA breaks, its inhibition has been considered as a treatment to sensitize tumor cells to genotoxic stress such as induced by radiotherapy or chemotherapy. Moreover, telomere stability might also be influenced by PARP-1 activity (Boesten et al. 2013; Paul 2011) and since nicotinamide has been shown as

PARP-1 inhibitor (Kjellen et al. 1985), therefore there might be some association between nicotinamide on the telomerase activity and telomere length mediated by PARP-1 mechanism.

#### EFFECTS OF NICOTINAMIDE ON TELOMERE AND TELOMERASE IN MYELOID CELLS

Telomerase activity have been studied and widely explored for their respond toward different kind of drug (Opitz 2005). These enzyme activities and the telomere maintenance are the markers of the proliferative potential of cells and have shown to be involved in cell immortalization and malignant transformation (Shay & Wright 2004). It is believed that increased telomerase activity found in human cancers prevents telomere length from shorten gradually and this allow the cancer cell to further proliferate out of the normal limits of cellular proliferation (Cao et al. 2008).

Telomere is the repetitive DNA sequence that located at each end of the chromosome in order to maintain the chromosome stability and protect the chromosome from degradation or end-to-end fusion with the nearby chromosome (Bouffler et al. 1996). At each round of cell division, telomeres shorten progressively and according to limit the number of division for a cell to replicate. In the present study, the rate of telomere shortening was reduced in the presence of nicotinamide (Kang et al. 2006) and it is possibly due to the shortening or damaged telomere that will activate the DNA-damage signal to lead to the cell life span extension.

While, telomerase is a ribonucleoprotein enzyme complex consisting of reverse transcriptase (hTERT), protein (hTP1) and RNA template for telomeric DNA synthesis (hTERC). This enzyme stabilizes telomere length and it has been suggested as a useful tumor marker for malignancy. hTERT is the major mechanism to regulate telomerase activity in human cells and in most cancer cells, it is specifically overexpressed (Horikawa & Barrett 2003; Matsubara et al. 2006). While, telomerase activity is present in over 90% of human tumors and it is absent in most somatic cells.

According to study by Ida et al. (2009), nicotinic acid related compound including nicotinamide has inhibited the K562 cell proliferation by 50-90% and also induced differentiation in human acute promyelocytic leukemia HK-60 cells. Other than that, it was also shown to induce apoptosis in human cancer cells (Kauppinen et al. 2013). Several other studies have shown the effect of nicotinamide on the human SIRT1 which was completely inhibited and it leads to reduce the cell proliferation and activated the apoptosis (Audrito et al. 2011; Vaziri et al. 2001). In normal and cancerous cell in existence of damaged DNA will automatically activated the PARP-1 mechanism and by induction of nicotinamide will facilitated the DNA repair process while at the same time also affecting telomerase activity and telomere length regulation (Figure 1).

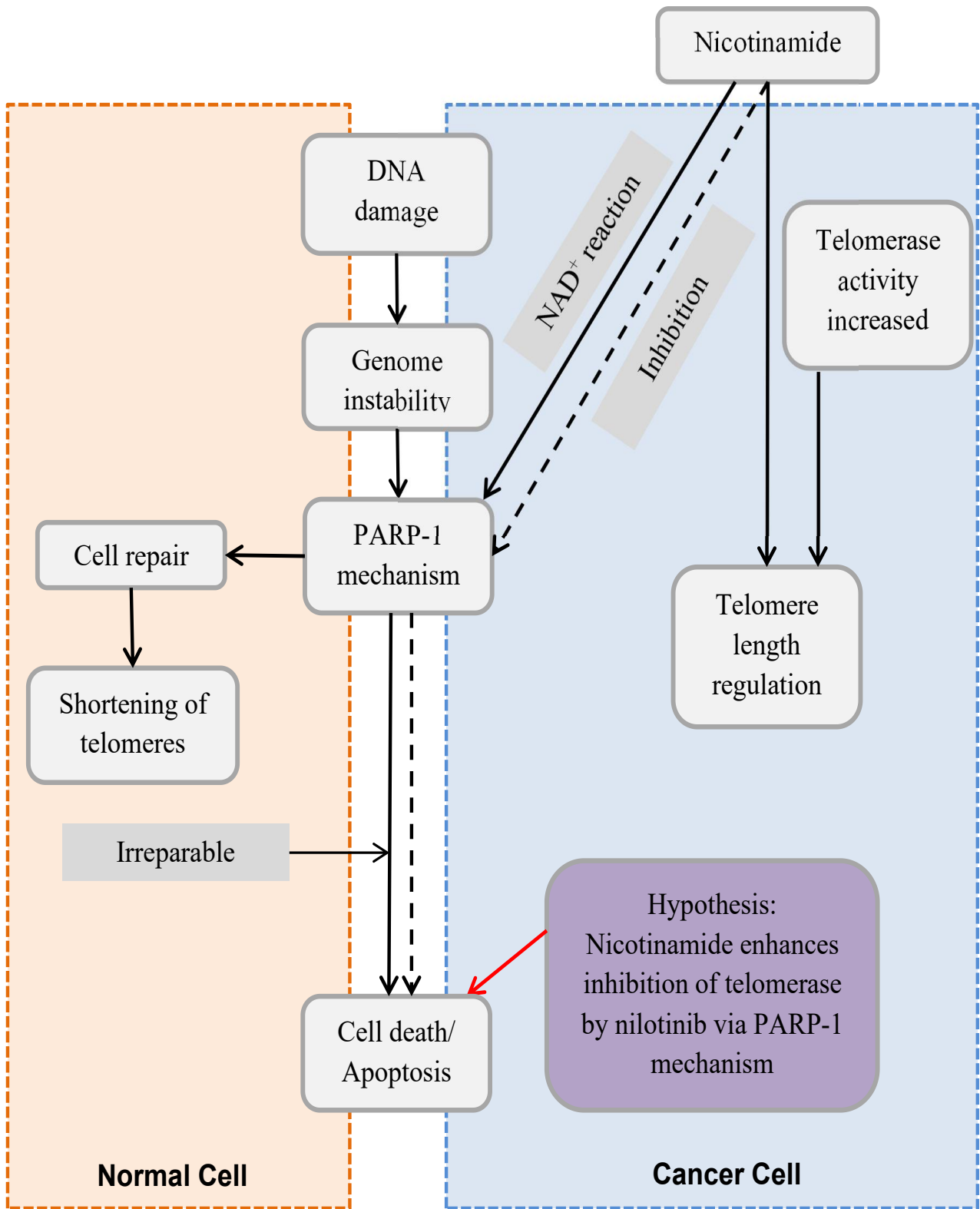


FIGURE 1. Potential effects of nicotinamide towards telomerase and telomere regulation and association with PARP-1 mechanism in normal and cancer cells

K562 cell lines are the human cells that derived from 53 years old female who was a patient with blastic

crisis of chronic myelogenous leukemia (CML) (Lozzio & Lozzio 1975). CML is one of the four major types of

leukemia disease that affects the myeloid cell. It has been reported as a myeloproliferative disorder due to the reciprocal translocation between chromosome 9 and 22 called Philadelphia chromosome (Ph) that carried by the hematopoietic cell. These Ph chromosomes encode the BCR-ABL with constitutively active protein tyrosine kinase that is required for cell transformation. The fusion between these two chromosomes forming BCR-ABL oncogene has leading to uncontrolled cellular proliferation and also reduced apoptosis (Hazlehurst et al. 2009). CML cells are unable to function properly to fight infections and disease because they are not fully mature but when the bone marrow produces too much CML cells, it can interfere with the normal cell production and spill out of the bone marrow into the blood stream. It will prevent the bone marrow to make an adequate number of red blood cells, normal white blood cell and platelets that can cause the patient to be more susceptible to anemia, infection or to brushing and bleeding easily.

More than 90% of patient with CML were found to have the BCR-ABL tyrosine kinase and it can be as a targeted molecular therapy in order to inhibit the oncogene activity from further proliferate out of control (Druker 2008; Melo & Barnes 2007; Yildirim et al. 2016). During chronic phase, CML can be effectively treated with tyrosine kinase inhibitor (TKI) which is a type of drug that target the mutant BCR-ABL protein by blocking its effects that have been found in CML cell and it have been approved in clinical trial (Quintas-Cardama et al. 2007). It is referred as molecular targeted therapy due to the specific approach to block the effect of a specific protein that causes transformation of leukemia cell.

The therapy started with imatinib, is widely used as the standard first-line treatment (Druker et al. 2001, 1996; Kantarjian et al. 2002) and has resulted in outstanding responses in the patient. Nevertheless, despite the excellent results with imatinib, a substantial fraction of patients eventually develop resistance to the drug and have to switch to the second-line therapy of TKI such as nilotinib and dasatinib to treat patient who become resistant or intolerant to imatinib (Hughes & White 2013; Leitner et al. 2011). It is debatably the best example of successful targeted CML treatment.

However, it is continued to exist as a challenging disease in order to treat the CML patient in a blast crisis (BC) phase even though the advance TKI therapy have been introduced (Pietarinen et al. 2015). When the TKI treatment are significantly less effective, it is causing the patient to be less favorably to respond toward the therapy is due to the more aggressive nature of advanced phase of CML. Even the original TKI such as imatinib did not show any toxicity effect to the body after the prolonged contact, but still the intake of imatinib gives several side effects to the patients and by switch the highly potent TKI such as nilotinib and dasatinib also could not be able to improve the overall survival (Hughes & White

2013). Currently, there is no treatment options that are responding effectively in CML BC and it is require an identification of new drug therapies to treat the CML patients in a blast crisis.

A study by Shapira et al. (2012), have shown that the effect of these TKIs on telomerase activity is not necessarily dependent on their effect on BCR-ABL even though the telomerase activity have been reduced by 90% after been introduced with those TKIs agent compared to the untreated control. They are suggesting that the telomerase is not affected directly by these TKIs but rather through other so far unknown cellular proteins. Nilotinib have shown to have direct effect on telomerase activity where it have been reported to reduce telomerase activity and cause substantial decrease in hTERT expression which is part of enzyme telomerase (Shapira et al. 2012).

#### CONCLUSION

The role of nicotinamide as cancer preventive agent will be studied by investigating its effect in enhancing the effect of nilotinib which is the current treatment for patient with resistant to first-line treatment in CML. It has potential as a PARP-1 inhibitor and the ability to decelerate telomere shortening rate without detectable increase in telomerase activity may help to enhance the effect of nilotinib that have shown to have direct effect on telomerase activity. Nicotinamide may boost the effects of nilotinib in K562 cell line and this may reduce the tumor growth or promote the tumor cells death. Therapeutic strategy for CML may be improved by understanding the role and potential of nicotinamide in telomere and telomerase status association with PARP-1 mechanism in myeloid cell line.

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