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Review Article

Post-chemotherapy maintenance treatment by nicotinamide riboside, a poly ADP ribose polymerase 1 inhibitor, in BRCA mutated advanced ovarian cancer – A perspective

Mukul Arvind Gharote[1], Amruta Ashok Deshpande[1]

[1]Department of Medical Oncology, Nashik, Maharashtra, India.

***Corresponding author:**
Mukul Arvind Gharote,
Department of Medical Oncology, MF-70,
Sundarban Colony, Nashik,
Maharashtra - 440 009, India.

mukul.gharote@gmail.com

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ABSTRACT

Poly ADP ribose polymerase 1 (PARP-1) inhibitors are approved for post-chemotherapy maintenance in BRCA mutated ovarian carcinoma. Various PARP-1 inhibitors such as olaparib, rucaparib, niraparib, and veliparib are approved for this indication. These PARP-1 inhibitors are costly as well as having toxic potential, anemia, and neutropenia is the major side effects. Most of the middle-aged women in Indian subcontinent are anemic and prescription of PARP-1 inhibitors is tricky in such conditions, besides their cost is at times unaffordable as maintenance chemotherapy. Hence, we need an affordable yet lesser toxic PARP-1 inhibitor to solve this problem. Nicotinamide, a vitamin B3 amide can be re-purposed as PARP-1 inhibitor. Nicotinamide, albeit at a higher dose, can be efficacious as well as economical in its use as maintenance chemotherapy. It has toxic potential but the toxicity is both rare and manageable. We need a clinical trial for this purpose. Following perspective is on the current evidence on high dose nicotinamide and it is re-purposing as PARP-1 inhibitor.

Keywords: Poly ADP ribose polymerase 1 inhibitor, Nicotinamide, BRCA mutated Ca ovary, Repurposing drugs

INTRODUCTION

Poly ADP ribose polymerase 1 (PARP-1) inhibitors are now approved as front line treatment either with conventional chemotherapy, bevacizumab or as maintenance in BRCA mutated epithelial ovarian cancers.[1-4] Niraparib,[1] olaparib,[2,3] and veliparib[4] are the approved PARP-1 inhibitors as maintenance[1-4] or with front line chemotherapy.[4] All these four phase III trials (SOLO-1, PAOLA-1/ENGOT-OV25, PRIMA/ENGOT-OV26, and VELIA/GOG-3005) have demonstrated significant improvements in progression-free survival with PARP inhibitors (olaparib, niraparib, or veliparib) for newly diagnosed ovarian cancer. All these trials demonstrated PFS benefits.

Repurposing existing drugs is a safe strategy for drug development wherein safety pharmacology studies have already been done, which reduces the time and cost for their clinical approval. With this in mind, we need to focus on economical PARP-1 inhibitor for the treatment of ovarian cancer. Nicotinamide is an economical known inhibitor of PARP-1 and source of NAD+ source, an enzyme with multiple cellular functions, including regulation of cell death, energy/metabolism, and inflammatory response.[5]

NICOTINAMIDE AS ANTINEOPLASTIC AGENT

Regarding its antineoplastic activity, nicotinamide is studied to sensitize human breast cancer cells to cytotoxic effect of cisplatin.[6] Nicotinamide, which is similar to FDA-approved olaparib and rucaparib[7] and a source of NAD+ and PARP-1 inhibition helps in inhibition of single-strand break DNA repair by base excision DNA repair mechanism.

ARCON

This phase III trial may have failed in achieving its primary goal, but the failure can be attributed to the low dose of radiation when combined with carbogen and nicotinamide.[8] This trial established a fact that nicotinamide enhances radiation-induced cell damage when used with carbogen. This clinical fact, especially in the hypoxic condition, is basically due to nicotinamide being a source of NAD+, which reduces hypoxia-inducible factor, which causes radiation and chemoresistance. Nicotinamide showed decreased chemoresistance in various pre-clinical trials [Table 1]. Another phase III randomized trial of nicotinamide for skin cancer prevention proved that nicotinamide was safe and effective in reducing new non-melanoma skin cancers and actinic keratoses in high-risk patients.[9]

Nicotinamide, when given at a high dose 60 mg/kg with carbogen inhalation, increased 5 FU deliveries to colorectal metastasis in liver.[10] Based on current evidences, nicotinamide can be repurposed as antineoplastic drug, for chemoprevention and as an adjunct to conventional chemotherapy[11] Nicotinamide, in a pre-clinical study done on human leukemia cell lines, enhanced inhibition of telomerase by nilotinib through PARP-1 inhibition.[12]

Following is the list of pre-clinical clinical trials of high-dose nicotinamide in cancer chemotherapy.

NICOTINAMIDE – MECHANISM OF ACTION

Nicotinamide is chemically part of the coenzymes nicotinamide adenine dinucleotide NAD+ and NADH,[13] used in oxidation-reduction reactions in the body. Among these activities is the production of adenosine triphosphate,[14] which fuels cellular metabolic activities.

As shown in Table 2, nicotinamide acts by inhibiting nitric oxide synthase and by doing so acts a free radical scavenger. It has a pivotal role in innate immunity by suppressing MHC class II expression. PARP-1 inhibition in the whole organism needs a higher dose of nicotinamide. Nicotinamide as an endogenous inhibitor of PARP-1 plays a significant role in apoptosis and cell senescence in response to DNA damage.[19]

Table 1: Evidence on role of nicotinamide in cancer chemotherapy.[11]

Organ	Remark on action of nicotinamide
Breast	• Various animal, cell lines demonstrated tumor growth inhibition with NAM, especially intraperitoneal tumor growth • Rate of apoptosis was increased • In view of its action as PARP inhibitor, STUDY done on TNBC cell lines showed suppressed DNA repair, replication • Inhibition of SIRT-1 was demonstrated in animal models as suppressed metastasis to lung and brain – boosting overall survival re-established chemo sensitivity – as a result of its action as NAD+source and reduced hypoxia, a known cause of tumor cell resistance
Skin/ melanoma	• As it inhibits SIRT-1 – it suppressed metastasis in melanoma cell lines and animal models • Demonstrated more CD4+and CD8+cytotoxic lymphocytes when treated with NAM
Colon	• Improved chemosensitivity to 5-FU in colon cancer human trial, especially to metastasis
Leukemia	• Enhances action when used with nilotinib, as its role in telomerase inhibition[12]
Lymphoma	• Synergistic action with vorinostat

NAM: Nicotinamide, PARP: Poly ADP Ribose polymerase

Table 2: Mechanism of action nicotinamide – a amide derivative of Vitamin B3.[14]

Inhibition of inducible NO synthase[15]
Free radical scavenging[16]
Suppression of MHC class II expression[17]
Intracellular adhesion molecule ICAM-1 expression on endothelial cells[18]
Inhibit poly (ADP ribose) polymerase[19]

HIGH-DOSE NICOTINAMIDE: DOSE, SAFETY, DRUG INTERACTION, PHARMACOKINETICS, AND PHARMACODYNAMICS

The recommended daily intake of nicotinamide is 20 mg a day for an adult. Any dosages of nicotinamide higher than 3 g/day are considered unsafe;[20] however, therapeutic actions of nicotinamide are seen within 500 mg–2 g/day, thus having a wide therapeutic window.

Nicotinamide in high dose has shown various beneficial effects in reducing the incidence of diabetes when taken in a dose of 550 mg twice a day for 2.5 years.[21] Nicotinamide supplementation reduced the incidence of various types of skin cancers and actinic keratoses when given at dose of 500 mg twice a day for 4 months.[22] Nicotinamide treated patients demonstrated more CD4+ and CD8+ infiltrating

lymphocytes than placebo in melanoma lesions.[23] Nicotinamide has anti-angiogenic properties.[24]

Main side effects of high-dose nicotinamide are hepatotoxicity, which is reversible and thrombocytopenia post-hemodialysis.[25] In children, transaminitis is seen, it take 4–6 weeks to remit[26] Animal studies document oncogenicity, no human data available,[20] nicotinamide along with PARP-1 acts on SIRT-1, and the role of SIRT-1 as proto-oncogenic gene is controversial.[27]

CONCLUSION: NICOTINAMIDE AS PARP-1 INHIBITOR

The majority of currently available PARP-1 inhibitors are NAD competitors and are congeners of nicotinamide moiety[28] Nicotinamide was the first PARP inhibitor identified.[29] FDA-approved PARP-1 inhibitors may cause anemia, neutropenia conversely, nicotinamide helps in bone marrow recovery through its action on hematopoietic stem cells.[30]

We need an economical PARP-1 inhibitor for such patients in Indian subcontinent. In the current scenario, PARP-1 inhibitors are indicated as maintenance therapy after primary chemotherapy in BRCA mutated or BRCA wild type with genomic instability score of $\geq 42^3$ or $\geq 33^4$ on my choice Cdx assay (myriad genetic laboratories). If nicotinamide is repurposed as PARP-1 inhibitor in BRCA mutated ovarian, prostate, and breast cancers, then patient compliance and cost-effectiveness can be improvised.

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.

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