

## Anticancer Agents in Combination with Statins

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### Abstract

Statins are 3-Hydroxy-3-methylglutaryl CoA (HMG CoA) reductase inhibitors and mainly used in cardiovascular diseases. However, they are also widely known for their anticancer activities mediated by antiproliferative, proapoptotic, anti-invasive, and radio sensitizing properties. They are tested alone in several clinical trials for their anticancer activity and the response is not satisfactory due to high dose requirements in humans. Tumor inhibitory concentration of statins is 10-100  $\mu\text{M}$  for different cancer cell lines when tested *in vitro*. But statins can cause anorexia and death in some individuals if concentration is reached to 20-25  $\mu\text{M}$  in serum. So, there is high risk factor. To avoid these unwanted harmful effects, we can give statins in combination with other chemotherapeutic drugs for synergism. It will reduce the concentration of statins in dosage, and can avoid unwanted toxic effects. When used along with the other chemo therapeutic agents like prenylation inhibitors, NSAIDs and standard chemotherapeutic agents, they have shown much better results at lower doses with little or no toxicity.

**Keywords:** Statins; Cancer; Vitamins; Doxorubicin; PSA; RAS

### Introduction

Statins are well known drugs to reduce cholesterol levels in the body by inhibiting HMG CoA reductase enzyme. Inhibition of HMG-CoA reductase is rate limiting step in mevalonate pathway. Intermediate and downstream products of this pathway including isoprenyl sub units are essential for critical cellular functions such as membrane integrity, cell signaling, protein synthesis, and cell cycle progression [1]. Cancer cells use this pathway to upregulate key essential molecules for tumor initiation, growth, and metastasis. By targeting the mevalonate pathway, statins exert growth inhibitory activity in cancer cells evident from *in vitro* and animal studies [2]. Protein prenylation is necessary for anchoring of proteins to cell membranes, protein-protein interactions and localization [3]. The isoprenoid intermediates of mevalonate pathway, farnesyl and geranyl-geranyl pyrophosphate are essential for post-translational modification of variety of intracellular proteins including Rho, Rac, and Ras. The two isoprenyl units activate different proteins in cells mediating cell proliferation and survival [4].

Post translational modifications of proteins determine their functionality in eukaryotic cells. Proteins undergo different kinds of post translational modification and lipid modifications are one of them [5,6]. It is found that prenylation (lipid modification) of proteins like Ras activates them and lead to cancer [2,7-9]. Prenylation occurs at carboxy terminal of protein and aids in binding or docking of the protein to the cell membrane or other cellular organelles. Prenylated proteins increase uncontrolled proliferation of cells and decrease apoptotic factors. Inhibition of specific proteins' prenylation may show better therapeutic values in cancer patients [10,11].

According to clinical studies, continuous supplementation of statins for more than 5 years reduced colorectal cancer risk by 47%. But, the patient factors like age, sex and ethnic groups are to be taken into consideration for better outcome [12]. In a similar study, statins were administered for a period of 4 years and it decreased cancer occurrence by 20% [13]. However, limitations are suggested to use statins for prolonged period of time due to their nonspecific toxicities in body. The high dose of statins may outweigh unwanted effects to the therapeutic outcomes [14]. As statins are critical regulators of many cell essential proteins and their activation, increasing evidence is available to show their use in cancer prevention and treatment. Statins demonstrated their anticancer activity in melanoma, glioma, neuroblastoma, and leukemia cell lines [1].

Cohort studies (pharmacoepidemiologic survey) in which patients were analyzed based upon their statins use indicate their pharmacological benefit of improving cancer patient survival [15]. More than 300,000 patients with cancer were identified for their statins use in a period and divided into groups as statin users, nonstatin users and nonusers. Leukemia, lung and renal cancer patients who have taken statins before diagnosis showed high overall survival rate. At the same time, statins and bisphosphonates combination used group of patients were also associated with increased survival compared to that of no treatment group. This indicates that the statins use alone or in combination can affect isoprenylation of compounds inside the cell to exert their anticancer activity [15]. Further clinical investigation is needed to better support the data and the pharmacological benefit of statins.

### Statins with Prenylation Inhibitors

Statins and prenylation inhibitors are the two different drugs used to inhibit the prenylation of proteins at different levels. The prenylated proteins which are important in cancer include Ras, Heterotrimeric G proteins and Rab proteins [16,17]. When statins and prenylation inhibitors are used in combination, statins decrease the pool of isoprenyl subunits in the cell and at the same time prenylation inhibitors decrease transfer of any isoprenyl units to the proteins. This action is synergistic [18,19]. Statins and prenylation inhibitors are acting at same pathway but at different stages. Synergistic combination also decreases the dose of individual compounds required for showing the therapeutic action and lesser associated toxicities.

Ras is a small G protein. The prenylation of Ras is important for its malignant action [20,21]. Ras undergoes lipid modifications (prenylation) at the carboxy terminal and further its oncogenic activity of Ras is increased leading to cancer. Ras undergoes two types of lipid

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modifications; they are farnesylation and geranylgeranylation [22]. Inhibition of Ras prenylation leads to anticancer activity. Farnesyl Transferase Inhibitors (FTIs) act competitively with farnesyl transferases and inhibit the farnesyl group attachment to the proteins and block the protein activity. FTIs can inhibit farnesylation of Ras, Rab and different proteins. FTIs inhibit the growth of Ras-dependent tumor cells [23,24]. And also, FTIs reduce Vascular Endothelial Growth Factor (VEGF) expression in mice and so reduces angiogenesis in cancer [25,26]. Statins when tested in clinical trials, the blood concentration was achieved in between 0.1-3.9  $\mu\text{M}$  [27]. But concentrations above 3.9  $\mu\text{M}$  are essential for anticancer activity of Statins. When given with FTIs the combination gave better therapeutic results in different types of cancers.

Cancer is heterogeneous group diseases and can originate from any part of the body [28-31]. It consists of uncontrolled proliferated cells that vary in morphology, biology, and response to therapy [32,33]. Even there are multiple treatment options for cancer, they are still not sufficient to treat all the types of cancer completely without tumor relapse, recurrence or metastasis. During progression, cancer involves several mutations and abnormalities resulting in multiple clones in same tumor [34-38]. Hence combination treatment is one of the better options to target the tumor at multiple points at same time. GTIs like GGTI-2Z [(5-nitrofurantolyl)methyl-(2Z,6E,10E)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl-4-chlorobutyl(methyl)phosphoramidate] were developed and tested *in vitro* with combination of Lovastatin [3]. GGTI-2Z is a geranylgeranyl phosphate derivative. This combination was able to inhibit the proliferation of STS-26T malignant peripheral nerve sheath tumor cells synergistically. The inhibition was due to the arrest of G0/G1 phase of cell cycle.

### Statins with $\gamma$ -tocotrienol

Vitamin E consists of eight isoforms and  $\gamma$ -tocotrienol is one of them bearing potent antitumor activity when tested *in vitro* [39-41]. It has very little or no toxicity on normal cells and so can be used in cancer treatment safely.  $\gamma$ -tocotrienol also showed its anticancer activity in combination studies with statins and celecoxib [42]. The combination acts synergistically and can avoid the myotoxicity associated with high dose statins monotherapy. Statins and  $\gamma$ -tocotrienol both act on HMG-CoA pathway. Statins are the inhibitors of HMG-CoA reductase enzyme and  $\gamma$ -tocotrienol causes down regulation of HMG-CoA by affecting post transcriptional modifications of enzyme [43]. Here,  $\gamma$ -tocotrienol showed its combination synergistic activity with simvastatin, lovastatin and mevastatin at low doses. Combination of tocotrienol with statins induced cell cycle is arrested at G1 phase, and decreased levels of cyclins and cyclin dependent kinases [43,44]. Combination of  $\gamma$ -tocotrienol with statins inhibited the cyclin D1, CDK2 and further hyperphosphorylated Rb protein. Cyclin D1 combines with CDK4 or CDK6 during the G1 to S transition phase, causes hyper phosphorylation of Rb protein. This leads to tumorigenesis [44]. In many breast cancers Cyclin D1 is over expressed [45]. As  $\gamma$ -tocotrienol with statins is reducing the levels of cyclin D1, this combination treatment may be a promising approach for treating breast cancer in women. This combination is also inhibiting the Akt and MAPK pathways.  $\gamma$ -tocotrienol along with statins is increasing the p27 expression and inhibiting the CDKs [44].

$\gamma$ -tocotrienol also works in colon cancer cells synergistically with atorvastatin when tested *in vitro* [46,47]. This combination decreased the RhoA protein concentration in the cell membrane by inhibiting the geranylgeranylation of RhoA and caused cell cycle arrest. Membrane binding of RhoA is essential for G1 to S phase transition of cells [48]. Instead of acting on RhoA protein, this combination also

induced apoptosis by caspase 3 activation, PARP cleavage and DNA fragmentation.

### Statins with NSAIDS

Non-steroidal Anti-inflammatory Agents (NSAIDS) are the cyclooxygenase inhibitors. Cyclooxygenase-2 (COX-2) inhibition can affect tumor cell survival, angiogenesis and metastasis [49,50]. NSAIDS also work through COX-independent mechanisms [51]. They can be used not only as anti-inflammatory agents but also as anticancer drugs, especially in colorectal cancer [52-54]. But the safety and efficacy are the two main factors which are not evaluated well [55,56]. NSAIDS can be used in cancers of breast, esophagus, stomach and prostate. Sulindac showed very good results when applied in adenomatous polyps [57]. It reduced the size and number of adenomatous polyps. Aspirin decreased the number of adenomas when tested in colorectal adenomas. However, NSAIDS required high dose administration to exert their anticancer activity. Long term use may cause gastro intestinal and cardiovascular adverse effects. To avoid this problem, we can combine the NSAIDS with other chemotherapeutic agents and can reduce their dose [58].

In a population based case control study, aspirin is used in combination with atorvastatin and simvastatin. This combination reduced the risk of colorectal cancer by 62% if used for 5 or more years [58]. Moreover, NSAIDS with statins also lowers the risk of prostate cancer if used for 5 years [59]. In immune deficient mice injected with androgen independent PC-3 prostate cancer cells, celecoxib and atorvastatin delayed tumor occurrence significantly and also decreased the tumor size in mice bearing tumors [60]. In azoxymethane induced colon carcinogenesis rat model, the low dose combination of atorvastatin and celecoxib decreased the incidence of adenocarcinomas by 71% [61]. Atorvastatin combination with celecoxib decreased the membrane association of RhoA [58,62]. Here, atorvastatin is preventing the prenylation of RhoA and celecoxib is synergizing the effect and causing cell cycle arrest. This may be due to inhibition of negative effect of RhoA on p27Cip1/waf1 and p27Kip1. The treatment also induces apoptosis in cancer cells by inhibiting PDK1, and PI3K phosphorylation [62].

### Statins with Doxorubicin

P-glycoprotein (P-gp) inhibitory property of statins is useful for its combination treatment with other chemo therapeutic agents [63]. P-gp is a glycosylated membrane associated multi drug resistant protein and responsible for the decreased drug concentration in multi-drug resistant cells [64]. P-gp mediated mechanism pumps drug out of the cell and the desired drug concentration inside the cell is regulated. Doxorubicin is an antibiotic and used in the chemotherapy of variety of cancers. When doxorubicin is used along with lovastatin in ovarian cancer cells, the statins sensitized the cells to doxorubicin and potentiated its anticancer activity synergistically. By blocking the drug efflux mediated by P-gp, Lovastatin increases the doxorubicin concentration inside the cells [63]. Simvastatin, atorvastatin or lovastatin inhibit the P-gp in high concentration [65,66]. Statins in combination with doxorubicin in human neuroblastoma cells (SH-SY5Y and STA-NB-10 cells) increased the concentration of doxorubicin inside the cancer cells [67]. Doxorubicin further caused the apoptosis. Lovastatin also decreased the P-gp levels in KG1a-leukemia cells and further increased the daunorubicin concentration inside the cell [68].

Statins are also able to decrease the glycosylation of P-gp. P-gp is present in two forms, fully glycosylated species (~180 kDa) and core glycosylated species (~140 kDa) [69]. Simvastatin and Atrovastatin are able to decrease the fully glycosylated form of P-gp. The core glycosylated

P-gp cannot be folded properly and cannot transport the drug out of the cell. The glycosylation inhibitory action of statins may be due to the inhibition of dolichol synthesis [2]. So, statins decrease the P-gp content of the cell by two mechanisms.

### Statins with FOLFIRI

In phase-II clinical study, simvastatin was tested in combination with FOLFIRI. FOLFIRI chemotherapy includes the administration of irinotecan, 5-fluorouracil and leucovorin. FOLFIRI treatment is used in colorectal cancer chemotherapy as a first line treatment. Combination increased the Time-to Progression (TTP) of colorectal cancer. At the same time, there is no increase in toxicity because of adding simvastatin [70].

### Statins Effect on PSA Levels

Prostate Specific Antigen (PSA) is present in the serum of healthy men. PSA levels are increased beyond certain level in several prostate disorders or prostate cancer. It is evident that use of higher doses of statins can reduce the risk of advanced prostate cancer in men [71,72]. In a study, long term use of statins decreased the PSA levels by 42% [73]. Statins dependent decline in PSA levels may be the reason for reduced risk of advanced prostate cancer. Statins may reduce the risk of advanced prostate cancer by altering the prostate biology [74]. Reduction in the cholesterol bodies decreases the amount of membrane signaling domains in prostate [75]. Statins when given reduced the LDL levels by 28-41% and PSA levels are decreased significantly at the same time. Further studies are needed to understand whether the statins are influencing prostate cancer diagnosis by altering PSA levels.

### Conclusion

Statins can be used as better chemotherapeutic agents in the future. Future directions should concentrate more on combination of statins with other anticancer agents, molecular targeted agents, and radiotherapy. They can also be used to prevent cancer occurrence, and in maintenance therapy.

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