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Statins and Lung Cancer: A Review of Current Literature

W Kurtis Childers DO[1,*], Nathaniel Melton MD[1], Daniel Goldman MD[1], Troy Moritz DO[2]

[1]Department of General Surgery, Pinnacle Health System Harrisburg PA

[2]Department of Cardiovascular and Thoracic Surgery, Pinnacle Health System Harrisburg PA

Abstract

Cardiovascular disease and lung cancer are two of the most common causes of death in the United States. The cardioprotective benefits of statin class drugs is predominantly mediated through the inhibition of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase, decreasing available mevalonate, and thus limiting in vivo cholesterol biosynthesis. Mevalonate and its metabolites have significant roles in cellular membrane synthesis, which is dysregulated during tumorigenesis, and is therefore a potential source for anti-tumor effects of statins. Similarly, dysregulation of cellular signaling is a hallmark of tumorigenesis. In vitro studies of EGFR, RAS, and AKT signaling pathways in cancer cells can all be reformed back to states more indicative of normally functioning cells when treated with statins. Statins have also been shown to exert beneficial properties in the presence of chemotherapeutic medications and radiation therapies by modulating the deleterious effects of reactive oxygen species, decreasing tumor cell resistance, and minimizing damage to surrounding native tissues. There is abundant of in vitro evidence to support the beneficial effects of statins on lung cancer patients. Prospective studies to determine the value of statin therapy on lung cancer prevention could lead to a significant change in lung cancer treatment.

Corresponding Author: W. Kurtis Childers DO, 205 S. Front St, Brady Hall 9th Floor, Harrisburg, PA 17104, E-mail: wchilders@PINNACLEHEALTH.org

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History and Epidemiology of Lung Cancer

The impact lung cancer has on global health is well known. Lung carcinoma is the leading cause of cancer-related deaths with >1 million deaths worldwide attributable to the disease.[1] The American Cancer Society has projected 224,390 Americans will receive a new diagnosis of lung cancer in 2016. This represents a dramatic increase in both incidence and prevalence of the disease, as the United States had approximately 157,426 deaths attributable to lung cancer in 2012.[2] While the incidence of lung cancer has increased across all demographics, male mortality from lung cancer actually saw a reduction between 1990 and 2007 while women saw an increase of 6.31% in mortality over that same time span.[1,2] This is likely attributable to the early peak of smoking rates in men compared to women. Increasing pack-years, African-American race, low income, lesser education, and occupational exposures are all associated with increased lung cancer rates as well.

History and Information about Statins

In 1971, Dr. Akira Endo set out to develop a medication that would theoretically decrease coronary artery disease by decreasing cholesterol production. By 1992, >1 million people had been prescribed a statin class medication.[3] 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitors, or statins, work at the level of cholesterol precursor biosynthesis inhibition. HMG-CoA reductase is the rate limiting enzyme in the production of mevalonate, a major precursor of cholesterol production. The functional group of statin class drugs competitively binds the active site of the enzyme resulting in a significant decrease of mevalonate biosynthesis, subsequently significantly inhibiting hepatic cholesterol production. Low-density lipoprotein (LDL) receptors must be upregulated, effectively decreasing circulating blood cholesterol levels.[3-5]

The Role of Statins in Lung Cancer Incidence and Mortality

Cancer causation and prevention remains an area of much interest and research. As more medications become commercially available, long-term effects of medication use, and possible epidemiology of cancer prevention or development becomes extrapolated. As being one of the most prescribed medications in the United States, statins remain under constant scrutiny for possible malignancy development.[5]

In 2007, a large case-control study was conducted using the database from the Veterans Affairs (VA) Health Care System. Among the 7,280 patients diagnosed with primary lung cancer, the use of statins >6 months was associated with a 55% decrease in lung cancer incidence (OR 0.45; 95% CI 0.42-0.48)[6]. This initiated a detailed investigation about the pleotropic effects of statins, and their purported benefits of lung cancer incidence.

Multiple meta-analytic studies have been conducted to correlate the incidence of lung cancer in patients taking statins. In 2008, a meta-analysis consisting of 42 studies was published: 17 randomized control trials, 10 cohort studies, and 15 case-control studies. The study concluded that statins had no effect on the overall incidence of cancer (RR 0.96 CI 0.72-1.2), or lung cancer (RR 0.92, CI 0.83-3.0)[7]. In 2013, an updated meta-analysis consisting of 20 studies was published: 5 randomized control trials, 8 cohort studies, and 7 case-control studies. As the number of studies was much less than prior, it renders itself to more specific inclusion criteria, and less study variable. Results showed a non-significant decrease of total lung cancer risk among all statin users (RR 0.89, CI 0.78-1.02). The findings of this meta-analysis suggested that there was no significant association between statin use and risk of lung cancer[8].

In respect to lung cancer mortality after diagnosis, only one study was identified to this sort. A retrospective cohort study was conducted consisting of 3,638 lung cancer patients. In patients who had at least 12 prescriptions of statins prior to mortality, endpoint showed a HR of 0.81 (95% CI 0.67-0.98) in cancer-specific mortality. Furthermore, in 11,051 lung cancer patients, statin use before diagnosis was associated with reduced lung cancer-specific mortality (adjusted HR 0.88; 95% CI 0.83-0.93)[9]. The use of statins extends beyond the role of lipid lowering. As numerous meta-analysis studies have shown no increase or decrease in the incidence of lung cancer among statin users, the use of statins after diagnosis was shown to decrease lung cancer mortality.

Mevalonate Pathway and Receptors

Mevalonate is the byproduct of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) via HMG-CoA reductase. Recent studies have regarded malignant cells to be highly dependent on the end products of the mevalonate pathway[10,11].

Mevalonate is the precursor of two classes of functioning molecules: isoprenoid and prenyl molecules. Mevalonic acid is the precursor for the biosynthesis of isoprenoid molecules such as cholesterol, dolichol, and ubiquinone[12]. Prenyl groups comprise of farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), which facilitate essential intracellular functions of various proteins such as Ras and Rho[11,12].

Isoprenoid molecules provide essential systemic functions. Cholesterol is a structural component of plasma membranes. Ubiquinone is part of the electron transport chain in mitochondria, and dolichol is a carrier molecule in glycoprotein synthesis[4, 13].

The prenyl molecules FPP and GGPP undergo a process called isoprenylation. This process involves attachment of the FPP and GGPP for key intermediates for post-translational cell signaling. This is fundamental for activation and intracellular transport[5].

Maintenance of cholesterol within the cell membrane continues to be the foundation of fluidity within the cell membrane. One of the hallmark features of all malignancies is rapid cell division, thus increasing the demand for cholesterol for cellular membrane synthesis . Cholesterol within the cell membrane was found to directly interact with EGF receptors, and influence the binding of EGF upon the EGF receptor in a concentration-dependent manner[14]. Pravastatin has been demonstrated to down-regulate signal transduction through the cell membrane in more than 300 genes of Calu-1 lung cancer cells[15]. However, simvastatin did not lower the cell cholesterol content, but was found to increase Δ5-desaturase activity, the enzyme necessary for the synthesis of unsaturated fatty acids[16].

The presence of mevalonate, and its metabolites has been proven vital for optimal cell structure and cellular function. The production of isoprenoid and prenyl molecules may be the subject of a possible target of future antitumor medication. Further evidence is supported by the use of statins in *in vivo* lung cancer cells.

Lung Cancer Receptors and the Influence of Statins

EGFR

Epidermal growth factor receptor (EGFR) is a tyrosine kinase cell membrane receptor, and a key receptor in cell growth, differentiation, migration, and survival[17]. When EGFR is activated, phosphorylation of the receptor tyrosine kinase triggers a series of downstream signaling for cell proliferation and survival[17]. This cascade of events is dysregulated in malignant cells, leading to hyperproliferation, and metastatic potential[17-19]. Most recent guidelines from the NCCN recommend testing for the presence of EGFR in all newly diagnosed NSCLC[20]. EGFR mutations are present in approximately 5-15% of adenocarcinoma and <5% of squamous-cell carcinoma or the lung[21]. When the receptor is present, potent tyrosine kinase receptor inhibitors can be added to the chemotherapy regimen, with a documented increase in survival in non-metastatic NSCLC[19]. Mevalonate metabolites have been shown to play a role in transducing EGFR-mediated signaling[14]. *In vitro* studies have demonstrated lovastatin to inhibit EGF-induced EGFR autophosphorylation. In multiple studies, when lovastatin was combined with the tyrosine kinase inhibitor gefitinib, synergistic inhibition was demonstrated, inducing a potent apoptotic response in NSCLC[22, 23]. As the results exhibit synergistic inhibition, there is some suggestion that HMG-CoA reductase and EGFR may act cooperatively to target the same receptor[23].

Though EGFR tyrosine kinase inhibitors (TKI) are highly efficacious, acquired resistance is almost inevitable. However, this was shown to be attenuated when gefitinib was combined with simvastatin, as an enhanced caspase-dependent apoptosis was demonstrated in previously EGFR-TKI resistant NSCLC[24]. Further investigation revealed simvastatin inhibited AKT activation, leading to suppression of beta-catenin activity and thus down-regulation of survivin[25].

RAS

The RAS family plays a key role in oncogenesis. Family members include HRAS, KRAS, and NRAS. RAS

activation triggers a cascade of downstream events, with subsequent phosphorylation, and activation of MEK1/2 and ERK[26]. KRAS encodes a GTP-binding protein involved in many cellular processes including proliferation, differentiation, and apoptosis[27]. Carcinogenic mutations of KRAS are detected in approximately 20% of NSCLC, and leads to dysregulated activation[28].

Cells from adenocarcinoma (GLC-82) and squamous cell carcinomas (CALU-1) were exposed to increasing concentrations of simvastatin. Simvastatin significantly inhibited ERK1/2 phosphorylation, and induced caspase-2 activated apoptosis in the GLC-82 and CALU-1 cell lines[26].

The tyrosine kinase inhibitor, gefitinib, is effective at inhibiting KRAS and its progression in NSCLC. Approximately 25% of lung adenocarcinomas exhibit a KRAS mutation, offering resistance to gefitinib, and ultimately rendering the chemotherapy unsuccessful. Mevalonate and its metabolites are essential substrates in the downstream signaling of KRAS. Atorvastatin has been demonstrated in multiple *in vitro* studies to overcome the gefitinib resistance of the KRAS mutation in NSCLC[29, 30]. Further investigation demonstrated the combination to decrease the expression of RAS protein and inhibit EGFR, an effect not shown in NSCLC cells treated with gefitinib alone. This resulted in proliferation inhibition, and an increase in apoptosis[30].

The progression-free survival (PFS) and overall survival (OS) in patients with stage 3 or 4 lung cancer harboring KRAS mutations was evaluated by investigators. All patients were treated with an EGFR-TKI (erlotinib or gefitinib), while 12 patients were additionally treated with a statin in addition to the EGFR -TKI, and 55 patients were not. The median PFS survival was 1.0 month, and 2.0 months for the EGFR-TKI and EGFR-TKI+statin, respectively (p=0.025). The OS was 5.4 and 14.0 months for the EGFR-TKI and EGFR-TKI+statin, respectively (p=0.130). Suggesting a longer PFS in patients treated with a statin added to the existing therapy[31].

In a study performed by Falcone et al., normal, and lung cancer tissues were exposed to increasing concentrations of simvastatin and rosuvastatin. This study showed a dose-dependent reduction on RAS protein expression when exposed to the 2 trial drugs. This was found to further inhibit the production of MMP-2, MMP-9, and NF-κB, suggesting potential anti-tumor activities of simvastatin and rosuvastatin in NSCLC[32].

AKT

AKT is a serine/threonine kinase receptor that serves as a common intermediary for downstream signaling of many cellular stimuli.. Activation of AKT serves to stimulate cell survival by inhibition of apoptosis, and promotion of proliferation and angiogenesis[33]. Much attention has been garnered at the continuing downstream effects of AKT, and its malignant potential.

Lovastatin treatment diminished tumor growth *in vivo* and *in vitro* through inhibition of both the PI3K/ AKT, and MAPK pathways[34]. Simastatin has been suggested to induce apoptosis in A549 lung cancer isolates via AKT singnaling-dependent cell survial[35]. The combination of atorvastatin and carboplatin is shown to inhibit AKT activity in H1299 lung carcinoma cell lines, both *in vivo,* and *in vitro*[36].

Oxidative Stress

Accumulation of oxidants and free radicals contribute to increased macrophages, neutrophils, and thus, reactive oxygen species (ROS) production. ROS may contribute to various signaling pathways, including MAPK activation. Recent evidence supports this activation to contribute to the development and progression of lung cancer[37]. Simvastatin has been shown to inhibit the effects of ROS on lung cancer cells *in vitro*. Inducing an antiproliferative, proapoptotic and antinflammatory effects[38].

Chen et al. demonstrated atorvastatin to decrease VEGF production in NSCLC *in vitro* and *in vivo*. Under further investigation, atorvastatin could upregulate the activity of glutathione peroxidase and catalase, prompting elimination of hydrogen peroxide[39]. Hydrogen peroxide has been shown to increase cellular expression of MMP-2 and MMP-9, which are also components of EGFR activation[32]. Simvastatin and lovastatin have both been able to inhibit the effects of

hydrogen peroxide on surrounding cells[38, 40].

Another important defense to antagonize the effects of ROS is superoxide dismutase (SOD), an enzyme functioned to scavenge free radicals in the mitochondria. Simvastatin was shown to inhibit the proliferation of A549 lung cancer cells through oxidative stress by upregulating SOD[41]. When the same A549 lung cancer cells were exposed to simvastatin in combination with sulindac, there was an induced caspase-dependent apoptosis in the A549 cells, activity greater then that induced with either drug alone[35].

Apoptosis is a known major function of normal cells within the human body. Evasion of apoptosis is another hallmark characteristic of malignant cells. Some chemotherapeutic agents target and activate the normal apoptotic activating proteins, caspase. A549 lung cancer cells were incubated with simvastatin, which exhibited a dose-dependent increase in inducing cell apoptosis. Through its downstream effects, simvastatin blocked cells in the G1 phase, downregulated cyclin D1, and increased caspase-3, -8, and -9 protein expression[42, 43].

Radiation Therapy

The use of radiotherapy is a useful adjunct for the treatment of NSCLC. Despite its useful capacity to treat malignant disease, its impact on surrounding normal tissue remains elusive. Recent studies have demonstrated a gain of motility and invasiveness of tumor cells in the radiated field[44]. *In vitro* studies have demonstrated lovastatin to block the irradiation stimulated adhesion and subsequent pro-metastatic effect of radiation therapy[45]. In a study by Sanli et al., lovastatin inhibited proliferation of A549 lung cancer cells, and induced radiosensitivity[46].

In a recent retrospective cohort study of 252 patients with diagnosed lung cancer and 55 (22%) patients subsequently developed brain metastasis. The risk of brain metastasis from lung cancer was significantly higher in young patients ($p<0.0007$). The multivariable Cox model did not show a significant association between statin use and brain metastasis from lung cancer (HR 1.20; 95% CI 0.68-2.13)[47]. Though the available literature is limited on the effects of statins and radiation on lung cancer progression, it supports the antitumor effects. Though antimetastatic properties showed no benefit for brain metastasis of lung cancer, in vivo and in vitro data demonstrated simvastatin prevented proliferation and osteolytic bone metastases of lung adenocarcinoma cells[48].

Chemotherapy

A minority of patients with diagnosed lung cancer are actually candidates for surgical and curative resection. Even with surgical resection, tumor size, the presence of visceral invasion, or positive lymph nodes can be factors which stage a patient where adjuvant chemotherapy is recommended. A majority of lung cancer patients, who can medically tolerate, will receive some form of chemotherapy. Research has examined the effects of common medications on the antitumor effects of chemotherapy. As stated previously, tyrosine kinase inhibitors remain very important therapeutic medications in patients with susceptible receptors.

In a phase 2 study, patients with NSCLC were randomized to receive gefitinib plus simvastatin (52 patients) versus gefitinib alone (54 patients)[49]. Primary endpoints were response rate, and secondary end points were toxicity, progression-free survival (PFS), and overall survival (OS). The response rate was 38.5% and 31.5% for the gefitinib+simvastatin and gefitinib, respectively. PFS survival exhibited a hazard ratio (HR) of 0.891 (95% CI, 0.604-1.315, $p=0.549$). OS exhibited a HR of 0.876 (95% CI, 0.567-1.354, $p=0.491$). However, when a subgroup analysis was performed comparing patients with EGFR-mutant tumors versus wild-type EGFR, the response rates and PFS was statistically and significantly in favor for patients treated with gefitinib+simvastatin who had the wild-type EGFR[49]. Receptor resistance to tyrosine kinase inhibitors has been described as 'inevitable' and remains a constant frustration. Atorvastatin has been demonstrated in multiple *in vitro* studies to overcome the gefitinib resistance of the KRAS mutation in NSCLC[29, 30].

Platinum-based chemotherapy is commonly used in the various types of chemotherapy regimens for treatment of lung cancer. Similar to tyrosine kinase inhibitors, resistance developed from malignant cells against platinum-agents is an all to common occurrence. In NSCLC, atorvastatin was found to antagonize platinum-resistance and enhance the efficiency of apoptosis induced by carboplatin[36].

Medical Comorbidities

Multiple chronic medical conditions are associated with hypercholesterolemia, atherosclerotic disease, and the indicated use of statins. Much investigation continues to be conducted to investigate the pleotropic effects of statins when exposed to medical illnesses where statins are not typically prescribed.

Chronic obstructive pulmonary disease (COPD) is a debilitating pulmonary disease affecting millions of adults worldwide[50]. Interestingly, almost one quarter of patients with COPD expire from cancer related deaths[50]. Van Gestel et al. investigated whether the risk of COPD increased lung cancer mortality, and if lung cancer mortality can be modulated with statins. Of the 1310 patients with COPD in the study, COPD was associated with an increased risk of lung cancer mortality (HR 2.06; 95% CI 1.32-3.20). In the COPD patients who used statins, there was a trend toward a lower risk of cancer mortality among patients who used statins (HR 0.57; 85% CI 0.32-1.01)[51]. Although this is not statistically significant, it prompts further investigation to determine whether statins affect the natural disease process, the lung cancer, or both.

Diabetes has been associated with an increased risk of cancer occurrence[52]. The development and progression of atherosclerosis is also a common occurrence in patients with diabetes, usually indicating the use of statins. In a large cohort study, there is an associated decreased incidence of squamous cell lung cancer in diabetic patients who have ever taken statins (HR 0.69; 95% CI 0.60-0.81). Interestingly, there was no difference in the incidence of adenocarcinoma lung cancer in diabetic patients (0.97; 95% CI 0.88-1.07)[53]. Common diabetic medications have been combined with statins for possible antitumor potential. Troglitazone and lovastatin were combined in vitro with CL1-0 lung cancer cells. Observed effects demonstrated dramatic synergistic effects with cell cycle regulating proteins CDK2, cyclin A, and RB phosphorylation[54].

Conclusion

Lung carcinoma is responsible for most malignancy related deaths in the United States, and is an important area for development of preventative therapies. While the cessation of smoking would potentially lead to the greatest risk reduction of lung cancer, a common pharmacologic medication with inherent anti-tumor properties would be extremely valuable to the medical community. Meta-analyses performed have demonstrated that statin class medications are safe with no increase incidence in cancer development. Through knowledge of receptors and the impact of the mevalonate pathway in lung cancer cells, statins have demonstrated potential anti-tumor properties *in vivo*. It is therefore hypothesized that statin medications could prove to help minimize the morbidity and mortality of lung cancer patients. Prospective clinical trials should be utilized to elucidate the potential clinical impact.

Compliance with Ethical Standards

Author WK Childers declares that he has no conflicts of interest. Author N Melton declares that he has no conflicts of interest. Author D Goldman declares that he has no conflicts of interest. Author T Moritz declares that he has no conflicts of interest.

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