Minireview

The Statins as Anticancer Agents

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Abstract

3-Hydroxy-3-methylglutaryl CoA reductase inhibitors, commonly referred to as the statins, have proven therapeutic and preventative effects in cardiovascular diseases. Recently, there are emerging interests in their use as anticancer agents based on preclinical evidence of their antiproliferative, proapoptotic, anti-invasive, and radiosensitizing properties. Inhibition of 3-hydroxy-3-methylglutaryl CoA reductase by the statins interferes with the rate-limiting step of the mevalonate pathway, leading to reduced levels of mevalonate and its downstream products, many of which play important roles in critical cellular functions such as membrane integrity, cell signaling, protein synthesis, and cell cycle progression. Perturbations of these processes in neoplastic cells by the statins may therefore result in control of tumor initiation, growth, and metastasis. The statins have demonstrated growth inhibitory activity in cancer cell lines and preclinical tumor models in animals. Phase I trials of statins in humans have demonstrated myotoxicity as their main dose-limiting toxicity, and Phase II trials in various tumor types are ongoing to evaluate their efficacy. Potential future directions in the development of the statins as anticancer agents include combinations with chemotherapeutic or other molecular-targeted agents, combinations with radiotherapy, maintenance therapy in minimal disease status, and as chemopreventive therapy.

Introduction

HMG-CoA reductase inhibitors are a class of drugs that inhibit the rate-limiting step of the mevalonate pathway (1), essential for the synthesis of various compounds, including cholesterol. Since the discovery of the first HMG-CoA reductase inhibitor (ML-236A) from Penicillium citrinum and its cholesterol-lowering properties in rats (2), these agents have emerged as the dominant class of compounds for the treatment of hypercholesterolemia. Among them, lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin are currently commercially available. Ruvastatin is the newest agent in this class but awaits approval for use in the United States.

HMG-CoA reductase inhibitors decrease hepatic cholesterol production, which in turn leads to increased LDL receptor turnover, enhanced hepatic LDL-cholesterol uptake, and ultimately decreased plasma LDL-cholesterol level (3). Overall, plasma LDL-cholesterol levels are substantially decreased by 20–60%, along with mild elevation in high-density lipoprotein-cholesterol and reduction in triglyceride levels.

Numerous multicentered trials have demonstrated the efficacy of HMG-CoA reductase inhibitors in reducing mortality and morbidity in both primary (4, 5) and secondary prevention (6–8) of coronary artery disease. Furthermore, four meta-analyses also discovered their use to be associated with long-term reduction in cerebrovascular events particularly after an initial coronary event (9–12). More recently, these agents were also shown to have pleiotropic cardiovascular and antiatherosclerotic effects, including reversal of endothelial dysfunction, inhibition of monocyte recruitment, antioxidant activity, down-regulation of angiotensin II receptors, immunomodulation, reduction in inflammatory response, plaque stabilization, reduction in ventricular arrhythmias, and decrease in thrombogenicity (13–15). Indeed, recent clinical studies have shown that treatment with HMG-CoA reductase inhibitors in acute coronary syndrome decreases short-term recurrent ischemia (16), and similarly after a transient ischemic attack they may suppress recurrences (17). Other proposed beneficial effects of HMG-CoA reductase inhibitors also include stimulation of bone formation and inhibition of growth of tumor cells (18). The potential antitumor effect of this class of agents is the main subject of this review.

The Mevalonate Pathway and Its Products

The rate-limiting step of the mevalonate pathway is the conversion of HMG-CoA to mevalonate, which is catalyzed by HMG-CoA reductase. The mevalonate pathway (Fig. 1) produces various end products that are important for many different cellular functions. These products include isoprene units incorporated into sterol and nonsterol compounds such as cholesterol, dolichol, ubiquinone, isopenentenylamine, GGPP, and FPP (1). Cholesterol is essential in maintaining cellular membrane structure and integrity. It also serves as a precursor for the synthesis of steroid hormones and bile acid (19). Dolichol works as a carrier molecule of oligosaccharides in N-linked protein glycosylation for the production of glycoproteins. Ubiquinone is involved in mitochondrial respiration and may also play a significant role in the inhibition of lipid peroxidation (20). Isopenentenylamine is an essential substrate for the modification of certain tRNAs. Geranylgeranyl transferase and farnesyl transferase use GGPP and FPP, respectively, for posttranslational modifications of cellular proteins. These include Ras, nuclear lamins, and many small GTP-binding proteins such as members of the Rab, Rac, and Rho families (21). For some of these...
proteins to be active, they must first undergo prenylation (e.g., farnesylation or geranylgeranylation) to associate with the plasma membrane. This association is achieved by the addition of a farnesyl moiety (e.g., Ras) or a geranylgeranyl moiety (e.g., Rho) to the COOH terminus of the proteins. Blockade of the rate-limiting step of the mevalonate pathway by HMG-CoA reductase inhibitors results in decreased levels of mevalonate and its downstream products and, thus, may have significant influences on many critical cellular functions.

Pharmacology
Lovastatin, simvastatin, and pravastatin are all fungal derivatives, whereas fluvastatin and atorvastatin are synthetic. Lovastatin and simvastatin are prodrugs and are converted into their active forms (β-hydroxy acid) in the liver, whereas the others are active in their parent forms. The differences in metabolism among the various statins lead to different distributions of the drugs in the liver (via enterohepatic circulation) or peripheral tissues (via systemic circulation) at equivalent doses. For example, pravastatin was found in lower concentrations in the liver (50%) but in higher concentrations (300–600%) in the peripheral tissues, including kidney, spleen, testis, adrenal gland, and nonglandular stomach as compared with lovastatin or simvastatin (22). It was thought that the lipophilic properties of the prodrugs confer their selectivity to liver. Similarly, lovastatin and simvastatin were shown to cross the blood-brain and placental barriers but pravastatin and fluvastatin do not (23). Table 1 summarizes the pharmacokinetic properties of the five commercially available HMG-CoA reductase inhibitors (24).

The bioavailability of the HMG-CoA reductase inhibitors is limited by extensive first-pass metabolism. The CYP system is responsible for the majority of the clearance of this class of drugs, with the exception of pravastatin where renal clearance also plays a major role in its elimination. Therefore, inhibitors to isozymes of CYP may significantly elevate the serum levels of HMG-CoA reductase inhibitors. Lovastatin, simvastatin, and atorvastatin are primarily oxidized by CYP3A4. Fluvastatin is predominately (50–80%) inactivated by CYP2C9, but CYP3A4 and CYP2C8 also contribute to its biotransformation. Pravastatin is not metabolized extensively by CYP isozymes but is selectively taken up by the sodium-independent bile acid transporter. Caution must be exercised with the concurrent administration of drugs that interfere with the CYP system in the presence of HMG-CoA reductase inhibitors.

Myotoxicity from HMG-CoA Reductase Inhibitors
HMG-CoA reductase inhibitors generally are well tolerated and have a safe side effect profile. The most concerning adverse

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**Table 1** The pharmacokinetic properties of five commercially available HMG-CoA reductase inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Form</th>
<th>Absorption of oral dose (%)</th>
<th>Bioavailability (%)</th>
<th>Plasma protein bound (%)</th>
<th>Plasma half-life (h)</th>
<th>Urinary excretion (%)</th>
<th>Time to plasma max conc (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>Acid</td>
<td>34</td>
<td>10.0–26.0</td>
<td>40–55</td>
<td>1.8</td>
<td>43–48</td>
<td>1</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Acid</td>
<td>&gt;90</td>
<td>25</td>
<td>98</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;5</td>
<td>0.6</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Lactone</td>
<td>30</td>
<td>&lt;5</td>
<td>&gt;95</td>
<td>1.1–1.7</td>
<td>&lt;13</td>
<td>2–4</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Lactone</td>
<td>85</td>
<td>&lt;5</td>
<td>&gt;95</td>
<td>1.9</td>
<td>&lt;13</td>
<td>1–2</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Acid</td>
<td>NA</td>
<td>40.7</td>
<td>NA</td>
<td>12–57.6</td>
<td>2.3</td>
<td>2–4</td>
</tr>
</tbody>
</table>

<sup>a</sup> NA, not applicable.
effects include hepatotoxicity and myotoxicity. Increases in serum liver enzymes are dose dependent and occur at a reported frequency of 1–33% (25). The majority of cases of clinically significant transaminis occur within the first 3 months of therapy and therefore monitoring of liver enzymes is required (25). The majority of cases of clinically significant transaminis occur within the first 3 months of therapy and therefore monitoring of liver enzymes is required (25). Myotoxicity, including myalgia and elevated serum creatine kinase (>10 times the upper limit of normal), occurs in 0.5% of patients treated with lovastatin (27). Rhabdomyolysis occurs in ~0.1% of patients who receive HMG-CoA reductase inhibitor monotherapy (26). In its extreme form, rhabdomyolysis can lead to myoglobinuria and acute renal failure.

Various hypotheses have been proposed for the pathogenic mechanisms that account for the spectrum of muscle dysfunction related to HMG-CoA reductase inhibitors. Although contributing to better understanding of this toxicity, none of the hypotheses has sufficiently or completely elucidated the underlying pathophysiology (28). The focuses of research on this toxicity revolve around the effects of HMG-CoA reductase inhibitors on ubiquinone, membrane function, calcium regulation, and drug interactions.

Ubiquinone, also known as coenzyme Q, is a polyisoprenylated quinoid cofactor of the electron transport chain, which accepts electrons from complexes I and II. It is a lipophilic compound composed of redox-active quinoid moieties as well as a hydrophobic prenylated tail. These features provide the physiochemical properties enabling mobility within the phospholipid bilayer of the inner mitochondrial membrane. The predominant form of coenzyme Q in human is coenzyme Q10, containing 10 isoprenoid units in its tail. As discussed before, ubiquinone is one of the end products of the melanovate pathway and therefore is at risk of being depleted by treatment with HMG-CoA reductase inhibitors.

Case reports seemingly describe the efficacy of coenzyme Q10 supplementation in patients on HMG-CoA reductase inhibitors who developed myalgia and even signs and symptoms resembling mitochondrial encephalomyopathy, lactic acidosis and stroke-like syndrome (29, 30). Despite numerous studies confirming that HMG-CoA reductase inhibitors decrease serum ubiquinone concentration, its effect on the i.m. content of ubiquinone is the subject of continual debate. Only one study has found depleted muscle ubiquinone (30). On the contrary, other muscle biopsy studies suggested that ubiquinone concentrations were increased by treatment with HMG-CoA reductase inhibitors in humans (31, 32). It is important to note that none of the study subjects experienced signs and symptoms of myotoxicity when muscle biopsies were performed. It was speculated that only patients who have intrinsic latent mitochondrial diathesis or partial defect in coenzyme Q10 synthesis would become clinically symptomatic with the administration of HMG-CoA reductase inhibitors (28).

In addition, HMG-CoA reductase inhibitors have also been reported to affect skeletal muscle membrane physiology by producing changes in cholesterol content, membrane fluidity, membrane electrical properties (33), Na/K pump density (34), excitation-contraction coupling (35), and tyrosine phosphorylation in signal transduction (36). The latter three mechanisms may lead to increase in cytosolic calcium levels resulting in membranolysis. The relative importance of these effects contributing to clinical myotoxicity is unclear.

The coadministration of HMG-CoA reductase inhibitors with other medications that interfere with their metabolism through inhibition of CYP450 system further potentiates the risk for the development of myotoxicity. As discussed above, CYP3A4 is the major isoform responsible for the biotransformation of most of the HMG-CoA reductase inhibitors. Given that CYP3A4 is also the most common isoform (60%) of the CYP450 system in humans and that many drugs are also metabolized by this isoform, myotoxicity may be precipitated by inhibition of CYP3A4 by another drug causing marked elevation of serum HMG-CoA reductase inhibitor levels. For example, erythromycin, antifungals, or cyclosporin A, which inhibit CYP3A4, have all been associated with myopathy or rhabdomyolysis when taken concomitantly with HMG-CoA reductase inhibitors. Drugs that cause cholestasis (e.g., cyclosporin A) may also increase the serum levels of HMG-CoA reductase inhibitors and contribute to their myotoxicity (37). The other major drug interactions of statins occur with fibric acid derivatives and niacin. A potential mechanism of such interactions involves a dual membrane-cholesterol lowering effect that increases sarcolemmal fluidity and leads to destabilization (38).

Besides the dose-effect relationship of HMG-CoA reductase inhibitors and their interactions with other CYP450 inhibitors, their lipophilicity may also be an important risk factor for drug-induced myotoxicity. For example, in vitro, pravastatin is less myotoxic than lovastatin and simvastatin, which may be related to its relatively poor uptake by muscle cells (39). Other conditions that may predispose to the occurrence of myopathy and rhabdomyolysis are electrolyte disturbances, major trauma,
defective lipid metabolism, seizures, hypothermia, metabolic acidosis, hypoxia, viral infections, and drug abuse (40).

**Epidemiological Link between HMG-CoA Reductase Inhibitors and Cancer**

With the exponential increase in the use of HMG-CoA reductase inhibitors in the past 15 years, their long term safety has become more apparent. The initial concerns about their long term safety were 2-fold. First, there was concern whether substantial lowering of serum cholesterol may be associated with higher rates of cancer death because studies have shown a possible U-shaped association among men relating all-cause mortality and serum cholesterol (41). Second, there was also concern that HMG-CoA reductase inhibitors have intrinsic carcinogenic properties.

These concerns originated from studies of HMG-CoA reductase inhibitors in animal models and from epidemiological data in humans. Newman et al. (42) reviewed the potential carcinogenicity of lipid lowering drugs on rodents and concluded that HMG-CoA reductase inhibitors and fibrates initiate or promote cancer in rodents. This observation is additionally supported by human cohort studies, which seemingly demonstrated that low cholesterol levels were associated with an increase in cancer deaths (41, 43). These studies are generally limited by confounding variables, including the effect of preexisting cancer and their retrospective nature (44). Despite the anxiety arising from these studies, meta-analyses of randomized controlled trials of cholesterol reduction did not reveal any significant increase in cancer mortality (45, 46).

Long-term follow-up data from major trials on secondary prevention of coronary artery disease with HMG-CoA reductase inhibitors provide reassurance regarding the risk of cancer from low serum levels of cholesterol or the use of HMG-CoA reductase inhibitors. An 8-year follow up of the Scandinavian Simvastatin Survival Study (4S) reported a decrease in overall mortality (relative risk, 0.70; P = 0.00002) with no significant difference in cancer deaths (relative risk, 0.73; P = 0.087; Ref. 47). In addition, two meta-analyses of major randomized controlled trials demonstrated no association between the use of HMG-CoA reductase inhibitors and the risk of fatal and nonfatal cancers (9, 48).

Therefore, on the population level, HMG-CoA reductase inhibitors appear to be safe without associated increases in cancer incidence. Furthermore, a recent nested case-control study demonstrated that users of HMG-CoA reductase inhibitors were 28% less likely than users of bile acid-binding resins to be diagnosed with cancer (rate ratio, 0.72; 95% confidence interval, 0.57–0.92; Ref. 49). All specific cancer sites under study were found to be not or inversely associated with the use of HMG-CoA reductase inhibitors. In addition to providing additional reassurance about the safety of HMG-CoA reductase inhibitors, this result also serves to generate the hypothesis that these agents may have chemopreventive properties, which merit additional evaluation in this area.

**Potential Mechanisms of the Antiproliferative Effects of HMG-CoA Reductase Inhibitors**

HMG-CoA reductase inhibitors have been shown to synchronize tumor cells by blocking the transition of G1-S in the cell cycle, thereby exerting its antiproliferative effect (50). This effect is reversed with the addition of mevalonate. In primary cultures of human glioblastoma cells, inhibition of Ras farnesylation by lovastatin is associated with reduction of proliferation and migration (51). However, the inhibition of cell growth by lovastatin may be independent of Ras function (52). In C6 glioma cells treated with lovastatin, free geranylgeranion overcomes the arrest of cell proliferation, whereas the rescue effect was significantly lower with farnesol (53). These findings suggest that geranylgeranylated proteins (but to a much lesser degree, farnesylated proteins such as Ras) are essential for progression of C6 glioma cells into the S phase of the cell cycle. In addition, N-Ras mutated, primary AML cells were no more sensitive to simvastatin than AML cells without the mutation, suggesting that the inhibition of AML cell proliferation by HMB-CoA reductase inhibitors may be independent of the Ras signaling pathway (54). On a murine prostate tumor cell line, it was also shown that H-Ras is capable of only inducing cell spreading but incapable of supporting cell proliferation in the absence of geranylgeranylated proteins such as RhoA (55). Recently, the antiproliferative effects of HMG-CoA reductase inhibitors on G1-S arrest are thought to be attributable to an increase in p21\(^{WAF1/CIP1}\) and p27\(^{KIP1}\), two cyclin-dependent kinase inhibitors (56–58). Rho small GTPase(s), geranylgeranylated by GGPP, were shown to be important for the degradation of p27\(^{KIP1}\) (59).

**Potential Mechanisms of Apoptosis Induction by HMG-CoA Reductase Inhibitors**

The mechanism of HMG-CoA-induced apoptosis also appears to be mediated predominantly through depletion of geranylgeranylated proteins (60). Add-back experiments of downstream products of the mevalonate pathway were conducted on lovastatin-pretreated human AML cells. Apoptosis induced by lovastatin was abrogated by mevalonate and GGPP and was partially reversed by FPP. However, other products of the mevalonate pathway, including cholesterol, squalene, lanosterol, desmosterol, dolichol, dolichol phosphate, ubiquinone, and isopentenyladenine, did not affect lovastatin-induced apoptosis in AML cells. Furthermore, the use of a geranylgeranyl transferase inhibitor mimicked the effect of lovastatin on apoptosis, whereas the use of a farnesyl transferase inhibitor was much less effective in triggering apoptosis in AML cells *in vitro*. These findings are also supported by a study in colon cancer cells, which showed that addition of GGPP prevented lovastatin-induced apoptosis, whereas cotreatment with FPP had no effect (61). This study also showed that lovastatin treatment resulted in decreased expression of the antiapoptotic protein Bcl-2 and increased the expression of the proapoptotic protein Bax.

**Potential Mechanisms of the Anti-invasive Effects of HMG-CoA Reductase Inhibitors**

HMG-CoA reductase inhibitors have also been shown to inhibit cell signaling pathways associated with the invasive and metastatic properties of cancer. In an *in vitro* study investigating the effect of HMG-CoA reductase inhibitors on the invasion of human pancreatic cancer PANC-1 cells, fluvastatin markedly attenuated EGF-induced translocation of RhoA from the cytosol.
to the membrane fraction and actin stress fiber assembly without inhibiting the tyrosine phosphorylation of EGF receptor or c‐erbB‐2. This was associated with a dose‐dependent inhibition of invasion by fluvastatin or lovastatin on EGF‐stimulated cancer cells. The invasion was also reversed by the addition of all‐trans‐geranylgeraniol but not by the addition of all‐trans‐farnesol (62). Similarly, the anti‐invasive effect of cerivastatin on an aggressive breast cancer cell line (MDA‐MB‐231 with spontaneous activation of Ras and nuclear factor κB, and overexpression of RhoA) was observed with RhoA delocalization from the cell membrane, resulting in disorganization of the actin fibers and disappearance of focal adhesion sites (56). The importance of RhoA inactivation in both of these inhibitory effects was additionally supported by their reversal by GGPP but not by FPP. Moreover, cerivastatin was also shown to induce inactivation of nuclear factor κB in a RhoA inhibition‐dependent manner, resulting in a decrease in urokinase and matrix metalloproteinase‐9 expressions, which are important for cell migration. As consistent with other studies on the effect of HMG‐CoA reductase inhibitors on antiproliferation and apoptosis, the participation of Ras inactivation is considered a subsidiary mechanism for the effects of cerivastatin on anti‐invasiveness because they were not rescued by FPP.

**Potential Mechanisms of Radio‐Sensitization of HMG‐CoA Reductase Inhibitors**

Cells located in different phases of the cell cycle have a wide variation in sensitivity to ionizing radiation (63, 64). Cells located in late G1 and G2/M phases of the cell cycle are most sensitive to ionizing radiation‐induced cell death, whereas cells located in the S phase are the most resistant. The effect of HMG‐CoA reductase inhibitors on arresting cells in late G1 located in the S phase are the most resistant. The effect of HMG‐CoA reductase inhibitors on arresting cells in late G1 phase potentially sensitizes cells to radiation. In addition, it has been shown that Ras potentially confers intrinsic radiation resistance (65) and that Ras‐associated increase in radiation resistance can be reversed by lovastatin in osteosarcoma cells (66).

**Preclinical Safety and Efficacy**

Preclinical data of lovastatin on animals, including mouse, rat, rabbit, and dog, revealed linear pharmacokinetics. Doses close to 200 mg/kg/day would produce serum concentrations in the range of 2–20 μM. Circulating concentrations of 2–4 μM were well tolerated for months in all models, whereas levels of 20–25 μM were associated with progressive anorexia and death in rabbits (67). The therapeutic dose for the treatment of hypercholesterolemia is ~1 mg/kg/day, which yields serum levels of ~0.1 μM (68).

When the cytostatic activity of lovastatin was compared among a variety of cell lines, including melanoma, adenocarcinoma, and neuroblastoma, the IC50s were in the range of 0.3–2.0 μM (69). This would seem to make lovastatin a promising drug to be administered as a cytostatic agent in conjunction with other cytotoxic agents or radiation.

However, the concentration of lovastatin required to achieve apoptosis may be as high as 30–100 μM for various tumor‐derived cell lines, including glioma and prostate cancer (70, 71). Such high concentrations were not compatible with life in animal models, which seemingly preclude lovastatin to be used as a single agent.

New optimism regarding the use of HMG CoA reductase inhibitors as antineoplastic agents emerges from recent studies. On the basis of the identification of HMG Co‐A reductase as a biological mediator of the effects of retinoids, an evaluation of the sensitivity of tumor cell lines to lovastatin‐induced apoptosis was undertaken (72–74). These studies demonstrated that various retinoid‐responsive cancers, including neuroblastoma, AML, juvenile monomyelocytic leukemia, pediatric solid malignancies (rhabdomyosarcoma, medulloblastoma), and squamous cell carcinoma of the cervix and of the head and neck, are susceptible to lovastatin‐induced apoptosis within therapeutically achievable levels. Similar results were demonstrated in medulloblastoma and mesothelioma (75, 76). This rekindles the interests of developing new therapeutic approaches using HMG‐CoA reductase inhibitors as anticancer compounds.

In addition, HMG‐CoA reductase inhibitors have also been shown to interact additively or synergistically with other chemotherapy agents such as 5‐fluorouracil (61), N,N′‐bis(2‐choloroethyl)‐N‐nitrosourea (77), cisplatin (78), doxorubicin (79), and 1‐β‐ti‐arabinofuranosylcytosine (80, 81). The interaction with other chemotherapeutic agents potentially enables the use of HMG‐CoA reductase inhibitors in lower doses in the treatment of cancers that previously were only susceptible to lovastatin‐induced apoptosis at unacceptably high doses.

The development of more potent HMG‐CoA reductase inhibitors provides additional options in the search of antitumor agents with better therapeutic indices. For example, cerivastatin was shown to be 10 times more potent than lovastatin at inducing apoptosis in AML cell lines (82). However, cerivastatin was withdrawn from the market in 2001 for the treatment of hypercholesterolemia because of 23 deaths from fatal myopathy, an incident that was not reported before with the other HMG‐CoA reductase inhibitors. Whether the concomitant administration of ubiquinone can prevent this life‐threatening complication remains to be evaluated.

Besides their in vitro efficacy, HMG‐CoA reductase inhibitors have also been shown to have in vivo antitumor effects in different animal models. Efficacy in chemoprevention has been demonstrated in radiation‐induced mammary tumorigenesis (83) and chemical‐induced colon tumorigenesis in rodent models (84, 85). HMG‐CoA reductase inhibitors were also shown to have significant antiproliferative effect on human myeloid leukemia cells in severe combined immunodeficient mice (54), glioma cancer cells inoculated in nude mice (86), or syngeneic murine lung tumor (87). Inhibition of metastasis was also demonstrated on rat lymphoma (88), rat fibrosarcoma (89), mouse mammary tumor (90), hepatic metastasis of murine colon tumor (91), and mouse melanoma (92). In addition, HMG‐CoA reductase inhibitors were shown to potentiate the antitumor effect of doxorubicin in three tumor models in vivo while attenuating its cardiotoxicity (79). They were also able to potentiate the antitumor effect of tumor necrosis factor α via inhibition of tumor‐induced angiogenesis in a murine tumor model (93).

Because HMG‐CoA reductase inhibitors exhibit such diverse effects on various aspects of carcinogenesis in vivo, numerous clinical trials are under way to assess whether these actions will translate into significant clinical benefit.
Clinical Safety and Efficacy

There were at least two Phase I clinical studies evaluating the maximum tolerable dose and toxicity of lovastatin in advanced malignancies (Table 2). Thibault et al. (94) conducted a Phase I trial to characterize the safety and tolerability of lovastatin administered at progressively higher doses in 88 cancer patients with advanced solid tumors. Most patients had prostate cancer or central nervous system tumor. Myopathy was found to be the dose-limiting toxicity. Use of ubiquinone was associated with reversal of lovastatin-induced myopathy, and its prophylactic administration prevented the development of this toxicity in a cohort of 56 patients. Without ubiquinone supplementation, lovastatin given at an oral dose of 25 mg/kg/day for 7 days followed by 3 weeks of rest was well tolerated. The maximum-tolerated dose for the combination of lovastatin and ubiquinone was not reached in this study. An indirect assay of drug concentrations was used to measure peak serum HMG-CoA reductase inhibitory activity. At doses of 4 mg/kg/day lovastatin and above, peak drug concentrations of 0.1–3.9 μM were reached, with or without ubiquinone supplementation. One patient with anaplastic astrocytoma who progressed after surgical resection, radiation therapy, and two cycles of carmustine had a minor response (45% reduction in tumor size) that was maintained for 8 months.

Similarly, Larner et al. (95) conducted a Phase I-II trial of lovastatin in anaplastic astrocytoma and glioblastoma multiforme. Eighteen patients received lovastatin at doses between 20 and 30 mg/kg/day for 7 days followed by 3 weeks of rest. Only 2 patients developed mild joint pain. None of the study patients experienced myalgia, and therefore ubiquinone supplementation was not required. Serum levels of lovastatin were not reported. Of interest, 9 of 18 patients received concurrent radiation with no neurological toxicity observed, which suggests that concurrent administration of high dose lovastatin and radiation is potentially safe. For the 9 patients treated with lovastatin and concurrent radiation, there were two minor responses and two partial responses. The response durations for these 4 patients ranged from 160 to 236 days. For the remaining patients treated with lovastatin alone, there was one partial response, one minor response, and 1 patient with stable disease. Interestingly, the patient who had a partial response achieved a response duration in excess of 405 days, at which time lovastatin was discontinued because of cost.

Regarding clinical efficacy of lovastatin, two published disease-specific Phase II studies reported mixed results (Table 2). A Phase II study in gastric adenocarcinoma was disappointing. Sixteen patients with advanced gastric adenocarcinoma received lovastatin 35 mg/kg/day for 7 consecutive days followed by 3 weeks of rest, with prophylactic ubiquinone (60 mg p.o. q.i.d.) to prevent rhabdomyolysis. The treatment was repeated every 28 days. No objective responses were seen, although 1 patient achieved stable disease for 16 weeks. Anorexia was the most common toxicity with decreased oral intake observed only in 3 of 28 cycles (96). Two patients developed mild and reversible myalgia with elevated muscle enzymes, but no rhabdomyolysis was observed.

In contrast, Kawata et al. (97) reported encouraging results of a randomized trial of pravastatin in patients with advanced...
hepatocellular carcinoma. Eighty-three patients were randomized to standard treatment with or without pravastatin (40 mg/day). The standard treatment included transcatheter arterial embolization followed by oral 5-fluorouracil (200 mg/day) for 2 months before randomization. The median survival was 18 months in the pravastatin group versus 9 months in the control group (P = 0.006). The frequency of myalgia did not differ between the two groups. Although this study was not done in a placebo-controlled, double-blinded fashion, the cytostatic effect of pravastatin seemed to produce a significant survival benefit with excellent tolerability in advanced hepatocellular carcinoma.

On the basis of the in vitro sensitivity of retinoid-responsive cancers to HMG-CoA reductase inhibitors (74), a Phase I/II study of lovastatin in recurrent or metastatic squamous cell cancers of the head and neck and of the cervix is ongoing (98). This study explores a prolonged oral administration schedule with dose- and duration-escalation steps and includes pharmacokinetic and pharmacodynamic evaluations. Five of 19 patients enrolled thus far showed disease stabilization of ≥2 months, and accrual continues at 7.5 mg/kg/day for 4 weeks followed by 1 week of rest. Steady-state plasma concentrations of lovastatin ranged from 0.2 to 1.0 μM at doses of 5 mg/kg/day to 0.5–3.5 μM at doses of 10 mg/kg/day. LDL cholesterol levels demonstrated a nadir to 50% of baseline by 2 weeks with uniform recovery to >80% of baseline by the start of each subsequent cycle. Preliminary data suggest a correlation between pretreatment ubiquinone levels and muscle toxicity.

Future Directions

Although the beneficial effects of HMG-CoA reductase inhibitors in the cardiovascular field are well established, their importance in the area of cancer therapeutics has recently gained recognition. Increased appreciation of their effects on apoptosis, proliferation, and invasion has supported their applications as molecular targeted agents, and future efforts should focus on improving their specificity while avoiding depletion of essential isoprenoids. There are emerging interests to explore the anticancer potentials of HMG-CoA reductase inhibitors in the clinical setting, particularly in tumor sites sensitive to these agents in vitro. In locally advanced or recurrent metastatic disease where the tumor burden is high, statins are more likely to be effective if given in combination with cytotoxic or other novel molecular-targeted agents, especially those combinations that yield additivity or synergism in preclinical models. Furthermore, the role of the statins as radiosensitizers and their interactions with Ras-associated radiation resistance should be evaluated, ideally along with molecular correlations. In cases of localized disease where tumor burden is low after definitive cytoreductive therapy, the use of statins as maintenance therapy seems promising. Finally, their chronic application as chemopreventive agents such as in premalignant lesions of oropharyngeal leukoplakia and cervical squamous intraepithelial neoplasia merit additional investigation (Fig. 3).

Because myotoxicity is the dose-limiting toxicity of HMG-CoA reductase inhibitors, it is important to elucidate the mechanisms, as well as methods to treat and prevent this adverse effect, therefore enabling the safe use of statins at high doses. In vivo models and clinical studies are needed to determine whether supplementation with ubiquinone reliably rescues statin-induced myotoxicity. Although in vitro add-back experiments in AML cells have shown that ubiquinone yielded no protective effects on lovastatin-induced apoptosis (60) and serum lovastatin levels achieved in patients also appeared to be unaffected by ubiquinone (94), the impact of this antidote on antitumor activity awaits clarification. Newer generations of statins with higher potency, better toxicity profile, and fewer drug interactions are likely candidates for future clinical evaluations. The goal of extending the scope of HMG-CoA reductase inhibitors beyond their cholesterol-lowering capacity might soon be within reach.

References


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