High-Dose Statin Flash-Potentiation of Cancer Chemotherapy

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Abstract

In low micromolar concentrations, statins have been shown to boost the apoptotic response to a wide range of cytotoxic agents, in a wide range of cancers. This effect appears to be mediated by inhibition of protein geranylgeranylation, leading to an up-regulation of apoptotic mechanisms. Statin intakes at least an order of magnitude higher than those used standardly for serum lipid modulation may be required to evoke this phenomenon clinically, and such high intakes would evidently entail toxic risk. Nonetheless, several phase I and phase II studies indicate that lovastatin intakes of around 30 mg/kg/day, given for 7 consecutive days once monthly, are reasonably tolerable for most patients. This suggests that it may be feasible to employ high-dose statins as an adjuvant to chemotherapy, if the statins are administered for only several days at a time prior to and following administration of the cytotoxin. Concurrent administration of tocotrienols, which can down-regulate expression of HMG-CoA reductase in cancers, could be expected to amplify the impact of statins on isoprenylation, while likely promoting chemosensitization by independent mechanisms.

Cancer Chemosensitizing Activity of Statins

A number of cell culture studies have demonstrated that, in low micromolar concentrations, statins can dose-dependently potentiate the cell killing efficacy of various cytotoxic agents (e.g. carboplatin, cisplatin, docetaxal, doxorubicin, gemcitabine, 5-fluorouracil, mitomycin C) in a range of cancer cell lines (hepatoma, colon, melanoma, leukemia, breast, pancreatic, non-small cell lung, ovarian, nasopharyngeal, gastric, osteosarcoma).[1-20] This phenomenon hence appears to be of some generality, and may reflect a statin-mediated up-regulation of apoptotic mechanisms. In some of these studies, co-administration of geranylgeranyl diphosphate, but not farnesyl diphosphate, abrogates this phenomenon, suggesting that impaired function of G proteins requiring geranylgeranylation, such as those of the Rac/Rho family - and/or other soluble proteins which require post-translational geranylgeranylation for proper integration into cell membranes, such as lamins - mediates the impact of statins in this regard.[2, 10] A handful of studies in mouse xenograft models indicate that high-dose statin co-administration can boost the cancer-retardant efficacy of cytotoxic agents *in vivo*.[4, 7, 13, 20] The interaction of statins with doxorubicin is of especial interest, as statins have the potential to decrease the cardiotoxicity of this agent while enhancing its cancer-killing efficacy; this may reflect a key role for Rac1 activity in mediation of this cardiotoxicity.[13, 21, 22]

How suppressed activity of isoprenylated proteins translates into an up-regulation of chemosensitivity remains unresolved. In statin-treated cancer cell lines, modulated expression of proteins that regulate apoptosis has been described, as well as a reduction in Akt phosphorylation and NF-kappaB activity;[13, 15, 19, 23-25] why these effects would be downstream consequences of decreased geranylgeranylation requires clarification. Another key consideration that, by and large, is not addressed by the statin chemosensitizaion literature is whether these effects of statins are relatively specific to transformed cells, as opposed to healthy tissues. However, a report that simvastatin boosts the growth retardant impact of

carmustine in rats bearing gliomas, without however influencing the myelotoxicity of this drug, provides a measure of reassurance.[20]

An effect of lovastatin independent of its impact HMG-CoA reductase activity that may boost the chemosensitivity of some cancers is inhibition of the ABCB1 (a.k.a. MDR1) drug transporter;[9, 12] over-expression of this transporter, which can extrude a range of cytotoxic agents from cancer cells, is a common cause of chemoresistance in advanced cancers.[26] Lovastatin's impact in this regard is only meaningful at low micromolar concentrations.

The relevance of these findings to standard clinical use of statins is dubious, as the statin dose schedules recommended for controlling LDL cholesterol typically produce statin serum levels in the low to mid nanomolar range; for example, 40-200 mg lovastatin daily is reported to produce serum concentrations of lovastatin equivalents in the 50-250 nM range.[27] This cautious dosing is intended to minimize risk for the myotoxicity which is the most important potential adverse effect of statin therapy; this risk is clearly dose-dependent. A number of investigations have suggested that inhibition of geranylgeranylation in muscle fibers plays a key role in the muscle pain and necrosis that occasionally is induced by statin therapy.[28-32] It is notable that few if any of the studies demonstrating potentiation of cytotoxin cancer cell killing with statins have demonstrated such as effect with nanomolar statin levels – likely because such concentrations have too modest an impact on geranylgeranylation to be useful in this regard. This accords well with the fact that statin-induced myotoxicity is only observed in a minority of patients treated with standard clinical doses.

Moreover, a recent meta-analysis of prolonged randomized controlled studies of standard statin therapy has failed to observe any impact on cancer mortality during the trials.[33] On the other hand, epidemiological evidence does suggest that survival in cancer patients receiving statins may be modestly better overall, and that outcomes in breast and prostate cancer in particular may be benefited.[34-38] Even if standard statin usage does have a favorable impact on survival in some cancers, it is not clear whether chemosensitization contributes to this effect – and in any case, it is reasonable to conclude that standard clinical statin doses would be unlikely to optimize the impact of statins on chemosensitivity.

Some cell culture investigations conclude that the concentration of statin capable of markedly inhibiting cholesterol synthesis is considerably lower than the micromolar concentrations which notably inhibit geranylgeranylation – likely because geranylgeranyl transferase has a very high affinity for its substrate.[39, 40] On the other hand, there is growing body of evidence that inhibition of isoprenylation reactions may be a key mechanism whereby clinical statin doses provide protection from vascular events, independent of their impact on lipoprotein levels.[41-43] It is not clear why these lines of research are in seeming conflict – perhaps the impact of clinical statin levels on isoprenylation in certain types of cells is more meaningful than in others. Presumably, effective inhibition of geranylgeranylation would require higher levels of statins in cell types which maintain relatively high intracellular pools of geranylgeranyl diphosphate, and/or high expression of geranylgeranyl transferase.

Practical Regimens for Statin Chemosensitization

In any case, the available cell culture data suggest that low micromolar concentrations of statins may be required to potentiate the cell-killing efficacy of cytotoxic agents. Since the pharmacokinetics of statins tend to show a linear dose-dependence, it seems likely that some sufficiently high oral intake of statins

could achieve low micromolar serum concentrations of these agents. However, it is reasonable to presume that such a high intake, if continued for prolonged periods, would be highly likely to evoke important myotoxicity. For this reason, the most clinically feasible way to achieve statin-mediated potentiation of cancer chemotherapy may be to administrate high doses of statins for just several days at a time, just prior to and for two to three days following administration of a cytotoxin; the title of this essay refers to this strategy as "flash-potentiation" of cancer chemotherapy. As an example, when chemotherapy is administered once weekly, three times per month, it might be reasonable to give high-dose statins for three days three times monthly – for one day prior to and two days following each dose of cytotoxin. Such a regimen would likely mitigate risk for myotoxicity, as high statin levels would only be present about 30% of the time.

This "flash-potentiation" proposal is not novel – back in 1999, Holt and colleagues wrote that "lovastatin might therefore be used in cycles with chemotherapeutic agents to increase tumor cell kill, rather than being used over prolonged periods to inhibit tumor proliferation. This would minimize the adverse effects of high-dose lovastatin administered over prolonged periods and would increase its utility in cancer chemotherapy."[2]

Fortunately, several phase I or II clinical trials of high-dose statins in cancer patients have already been conducted, in an effort to determine what dose ranges might be clinically tolerable.[44-48] These investigations were ultimately intended to determine whether intermittent administration of statins *alone* could achieve clinically worthwhile cancer control – since micromolar statin doses by themselves have slowed cellular proliferation or enhanced apoptosis in some cancer cell lines. Few objective responses were noted in these investigations – in a handful of cases, temporary stasis of cancer growth was reported – likely in part because statins could only be administered intermittently at the doses tested. It thus seems to have been concluded that statin therapy *per se* was unlikely to have clinically important utility in oncology, as phase III studies have not been reported. Nonetheless, these studies established that various high-dose intermittent statin protocols could be administered with an acceptable side effect profile. In particular, lovastatin administered in the range of 25-35 mg/kg daily, in multiple divided doses, for seven consecutive days, once monthly, appears to be reasonably well tolerated, with nausea, diarrhea, myalgia and muscle weakness, typically of grade 1 or 2 intensity, as the most common side effects.[44-46] In the study by Thibault et al., peak serum concentrations of active lovastatin metabolites as high as 3.9 μM were measured; in light of cell culture data, it seems likely that such concentrations would be sufficient to achieve a measure of chemosensitization in many cancers.[44] This is not unreasonable, given that the doses employed were about 10-fold higher than the highest dose of lovastatin used for cholesterol control. When administered for 21 consecutive days, every 28 days, the maximal tolerated dose of lovastatin was found to be 7.5 mg/kg.[48]

Concurrent supplementation with ubiquinone was employed with some of these protocols, and in one such study the investigators had an impression that this reduced the incidence and severity of muscle symptoms;[44] however, this conclusion is hard to square with the cited evidence that suppressed geranylgeranylation may be largely responsible for statin-induced myopathy. In any case, concurrent supplementation with ubiquinone appears prudent during high-dose statin therapy, to alleviate any concern that induced ubiquinone deficiency might compromise cardiac performance or lead to other adverse effects; there is no reason to suspect that ubiquinone deficiency plays a role in the chemosensitizing impact of statins.

This author has been able to trace only two studies in which high-dose statins were administered in conjunction with chemotherapy. In a dose-finding study enrolling patients with relapsed or refractory myeloma or lymphoma, simvastatin was administered for 7 days, following which chemotherapy with VAD or CHOP was commenced.[49] The maximal tolerated dose was found to be 15 mg/kg; the dose-limiting toxicities were grade 3 gastrointestinal effects and neutropenic fever. 30% of the patients achieved a clinical response; 3 of these 7 patients had been previously judged refractory to the chemotherapy regimen they received – suggesting that simvastatin may have aided their subsequent response. However, in a follow-up study by this same group, which enrolled 12 patients with refractory or relapsed myeloma, only one of the patients achieved remission with the simvastatin-VAD regimen, and further study was discontinued.[50] It is not unlikely that the efficacy of this regimen was compromised by the fact that statin administration was discontinued before the cytotoxic agents were given; in the cell culture studies demonstrating synergism between statins and cytotoxins, these agents have been present simultaneously.

In light of these considerations, it would seem worthwhile to evaluation a flash potentiation regimen in which 30 mg/kg/day lovastatin, administered orally in divided doses, is given for three consecutive days in conjunction with chemotherapy, the lovastatin administration to commence one day prior to the chemotherapy.

In light of the nausea and diarrhea occasionally observed with high-dose statin regimens – likely reflecting privileged access of intestinal epithelium to oral statins – the possibility that high-dose statins might potentiate the gastrointestinal toxicity of concurrent chemotherapy merits consideration. Indeed, in a phase II trial evaluating continual normal-dose pravastatin (40 mg/day) as an adjuvant to a chemotherapy regimen in patients with advanced gastric carcinoma, a non-significant trend toward increased GI side effects was noted in the active pravastatin arm.[51]

Adjunctive Potential of Tocotrienols

Some investigators have proposed that a somewhat more tumor-selective suppression of HMG-CoA reductase activity might be achieved if statin therapy is complemented by administration of certain naturally occurring isoprenoids, such as tocotrienols.[52, 53] Cancers, particularly those that are aggressive, tend to express high HMG-CoA reductase activity because they are resistant to sterol-mediated suppression of reductase expression;[54, 55] this phenomenon mandates the use of high, potentially toxic statin doses if isoprenylation reactions in cancers are to be minimized. However, cancers retain sensitivity to another feedback mechanism controlling reductase activity. Farnesol and various other isoprenoid compounds serve as a feedback signal that decreases the translation of HMG-CoA reductase mRNA while also promoting accelerated degradation of the reductase protein; tocotrienols have this effect, and some evidence suggests that their action in this regard may be somewhat cancer-selective.[52, 56, 57] Hence, it has been suggested that co-administration of a statin and tocotrienols may achieve a more potent inhibition of HMG-CoA reductase activity in tumors than in healthy cells, thereby down-regulating isoprenylation more selectively in tumors while minimizing toxic risk.[52, 53] Whereas statin administration tends to up-regulate HMG-CoA reductase expression by relieving feedback inhibition, tocotrienols block this up-regulation in cancer cells.[58] Anti-proliferative synergism between statins and tocotrienols has indeed been reported in cancer cell lines.[53, 58-61]

Prolonged administration of high-dose tocotrienols (which owing to their lipid solubility require a number of days to achieve equilibrium tissue levels), in conjunction with intermittent administration of high-dose statins, might ultimately be a preferable approach to flash-potentiation of chemotherapy if the impact of tocotrienols on HMG-CoA reductase expression is indeed tumor-selective. Inclusion of tocotrienols in the regimen could either be used to enable a dose reduction for the lovastatin – presumably lessening toxicity; to amplify the net impact of the regimen on isoprenylation within the cancer; or preferably both. And, propitiously, tocotrienols have cancer-retardant and chemosensitizing effects of their own, unlikely to be fully attributable to isoprenylation inhibition, that could well complement the chemosensitizing impact of isoprenylation suppression.[62-67] The pharmacokinetics of high-dose tocotrienol supplementation are now being studied in humans.[68, 69]

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