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Review

The potential of statins as part of anti-cancer treatment

Stefan Sleijfer *, Ate van der Gaast, André S.Th. Planting, Gerrit Stoter, Jaap Verweij

Department of Medical Oncology, Daniel den Hoed Cancer Center, Erasmus University Medical Center, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands

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Abstract

Statins are known to reduce mortality related to cardiovascular diseases. In recent years, evidence has accumulated that statins also exert anti-tumour activity for which numerous potential underlying mechanisms of action have been suggested. Accordingly, several case-control studies showed a reduction in cancer incidence in patients treated with statins. Furthermore, statins interact synergistically with several anti-tumour treatments in preclinical studies. Until now, only a few clinical studies are available that explore the optimal dose, feasibility, and efficacy of statins applied as single agents to control the growth of existing tumours. Studies investigating statins as part of a multi-drug regimen are completely lacking. Nevertheless, the interesting pre-clinical anti-tumour activity of statins combined with a favourable toxicity profile warrant their further development as anti-tumour agents, in particular as part of multi-drug regimens.

Keywords: Statins; Anti-tumour activity; Solid tumours; Drug combinations

1. Introduction

Statins are known to decrease cholesterol levels, which results in a substantial reduction of cardiovascular mortality in patients with hypercholesterolaemia. Because of this, statins currently belong to the most widely prescribed drugs. In addition, they also improve endothelial function, reduce free radical formation, stabilise plaques, and inhibit endothelial inflammatory reactions thereby yielding other potential benefits for patients at risk for cardiovascular disease, regardless of cholesterol levels. Consequently, statins are now also used in patients with a prior cardiovascular event and diabetes mellitus, and their use has increased exponentially over recent years. In view of the large number of patients for which statins are indicated and the favourable toxicity profile, simvastatin has acquired, albeit controversial [1], an ''over-the-counter'' status in the United Kingdom. Other statins currently in clinical use are lovastatin, pravastatin, fluvastatin, rosuvastatin, and atorvastatin.

Statins reduce cholesterol levels by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which converts HMG-CoA to mevalonate, the precursor of cholesterol. In addition, they inhibit synthesis of other products downstream from mevalonate. Since some of these products are involved in important cellular processes such as proliferation, differentiation, and apoptosis, investigators were prompted to assess the anti-tumour activity of statins. This review addresses the potential application of statins in oncology, in particular their mechanisms of action, activity as single agents, and potential to be combined with other anti-tumour agents.

2. Mechanisms of action

Mevalonate synthesis is decreased by statins through the inhibition of the enzyme HMG-CoA reductase. Next

* Corresponding author. Tel.: +31 10 4391733; fax: +31 10 4391003.
E-mail address: s.sleijfer@erasmusmc.nl (S. Sleijfer).

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to cholesterol, several other products are derived from mevalonate such as ubiquinone, dolichol, geranylpyrophosphate and farnesylpyrophosphate. Ubiquinone, also known as co-enzyme Q, plays an important role in the mitochondrial respiratory chain and reduction of ubiquinone is thought to account for the occurrence of myopathy, the most common side-effect of statins. Dolichol is involved in the synthesis of glycoproteins and probably also in growth regulation [2]. Geranylpyrophosphates and farnesylpyrophosphates, collectively known as isoprenoids, bind to several important cellular proteins including Ras and other guanidine triphosphate (GTP)-binding proteins by a reaction called isoprenylation (Fig. 1). Isoprenylation is essential for membrane attachment of these proteins and thereby crucial for their function. GTP-binding proteins regulate the signal transduction from several membrane receptors. After activation of these receptors, a cascade of downstream messengers is initiated through GTP-binding proteins. This subsequently leads to altered transcription of genes involved in processes such as proliferation, differentiation, and apoptosis. In many tumour types, increased activity downstream from GTP-binding proteins has been demonstrated and implicated in malignant behaviour. Such increased activity can be induced through several mechanisms including activating mutations in GTP-binding proteins. The importance of disturbances in these systems in cancer pathogenesis is underscored by the finding that 30% of the human cancers harbour mutations in k-Ras, one of the GTP-binding proteins [3]. As malignant cells often depend more strongly on increased activity of GTP-binding proteins than normal cells do, GTP-binding proteins form an attractive target for anti-tumour therapy. Through inhibition of isoprenylation [4], statins impair the function of several GTP-binding proteins and thereby affect several important cellular processes, predominantly in tumour cells [5–7]. In addition, mevalonate-derived products other than isoprenoids are also involved in the effects of statins. This is based on observations that most statin-mediated effects can be abrogated by administration of mevalonate, while this can not always be achieved by co-administration of isoprenoids [8]. Furthermore, some statin-mediated effects appear to be completely independent of HMG-CoA reductase [9].

Anti-tumour effects exerted by statins include growth inhibition, inhibition of angiogenesis, stimulation of anti-tumour immunity and impairment of metastatic potential (Table 1). In preclinical models, statins were shown to induce growth inhibition in a wide range of

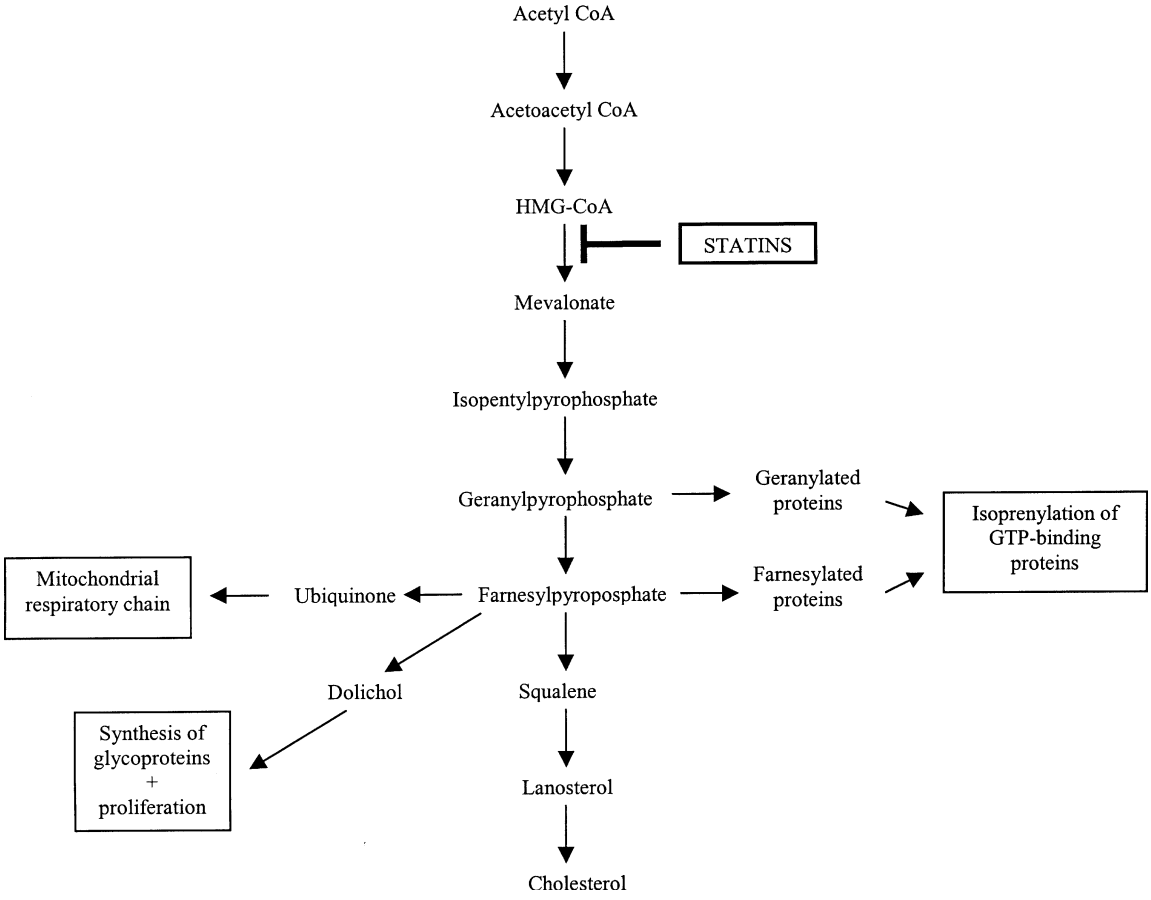

Fig. 1. The mevalonate pathway. GTP, guanidine triphosphate.

Table 1
Mechanisms of action

Inhibition of tumour growth	Cell cycle arrest Induction of apoptosis
Inhibition of angiogenesis	Reduction of pro-angiogenic factors Inhibition of endothelial cell growth Impairment endothelial cell adhesion
Attenuation of metastatic potential	Reduction of adhesion molecules Inhibition of tumour cell migrating factors
Stimulation cellular immunity	Attenuation of resistance mechanisms

different tumour types. Sensitivity to statins was highly dependent on the tumour cell line assessed [5], but in particular cell lines derived from acute myeloid leukaemia, neuroblastoma, rhabdomyosarcoma, squamous cell carcinoma of the cervix and head and neck appeared to be sensitive to statins [5]. Other cell lines reported to be susceptible to statins are derived from melanoma, high-grade glioma, and cancer of the kidney, testis, breast, stomach and prostate [5,10]. Presently, various mechanisms have been identified that may account for the anti-proliferative effects of statins. They arrest the cell cycle by downregulation of cell cycle-promoting factors such as certain cyclin-dependent kinases [8] or upregulation of the levels of the cell-cycle inhibitors, p21 or p27 [8,9,11]. Increase of p21 levels can occur through stimulation of transcription [12] and/or impairment of degradation by hindering proteasome function [9]. Induction of apoptosis contributes to growth inhibition as well. In recent years, it has been shown that apoptosis can occur through two pathways, an intrinsic and extrinsic one. The intrinsic pathway is activated as a response to severe cellular stress such as DNA-damage. It involves a shift in the balance between pro- and anti-apoptotic members of the Bcl-2 superfamily in favour of the former, which is followed by a release of apoptosis-inducing factors from the mitochondria. Activation of the extrinsic pathway is induced through members of the tumour neurosis factor (TNF)-superfamily including Fas-ligand and TNF-related-apoptosis-inducing-ligand (TRAIL). This pathway has been implicated in apoptosis by among others chemotherapy and cellular immunity. Statins may have an impact on both pathways as they can upregulate Fas, the receptor for Fas-ligand [13], and also induce apoptosis through mitochondrial effects [14]. However, it has to be emphasised that, in general, much higher statin doses are required to induce apoptosis than are needed for the induction of cell cycle arrest [5].

Another anti-tumour effect of statins is mediated through inhibition of angiogenesis. There is much controversy about the exact effects of statins on angiogenesis since both inhibition and stimulation have been demonstrated. Probably, pro- or anti-angiogenic effects of statins depend on the exact cell type exposed and the drug concentration [15]. Anti-angiogenic activity can occur by reducing cytokine-induced production of the pro-angiogenic factor vascular endothelial growth factor (VEGF) [15]. In addition, pravastatin can inhibit endothelial cell proliferation and hinder adhesion of endothelial cells to extracellular matrix [16].

Statins can impair the metastatic potential of tumour cells [17]. Underlying mechanisms include prevention of cytokine-induced expression of adhesions molecules such as E-selectin on endothelial cells [18]. Such adhesion molecules are necessary for the attachment of tumour cells to the endothelium, one of the first events required for the development of metastases. Another mechanism is inhibition of the synthesis of factors stimulating the migration of tumour cells towards the bone [19] and inhibition of epithelial-derived growth factor (EGF)-induced tumour cell invasion [7].

Improved efficacy of anti-tumour immunity may also play a role. Statins reduce the expression of Fas-ligand on tumour cells [20], a factor known to confer resistance against cellular immunity.

In summary, numerous mechanisms by which statins may yield anti-tumour activity have been identified, but the list is still likely to be incomplete.

3. Cancer incidence in statin users

Several studies have assessed the association between statin use and cancer. In a randomised-controlled study conducted in elderly subjects, a higher incidence of newly diagnosed cancers was shown in users of statins [21]. In the first four years of this study, 199 new cancer cases were observed in the 2913 patients allocated to placebo and 245 in the 2891 patients receiving pravastatin (hazard ratio 1.25 (95% Confidence Interval (CI), 1.04–1.51)). This increased risk, which obviously contrasts with the suggested anti-tumour effects of statins, may be due to the fact that statins strongly reduced mortality related to cardiovascular events, as a consequence of which the mortality in these elderly patients due to other disease conditions including cancer increased. In contrast with this study are findings from meta-analyses of randomised-controlled trials and case-control studies specifically designed to establish the effects of statin use on cancer incidence. These revealed either no association [21–24] or even a decreased cancer incidence among patients receiving statins [25–28] (Table 2). A nested case-control study with 542 first cancer cases and 5420 controls found a 28% (95% CI, 0.57–0.92) lower rate of cancer in statin users compared with those receiving bile-acid binders [28]. The largest case-control study with 3129 cancer cases and 16 976 controls demonstrated that statin use is accompanied by a 20% (95% CI, 0.66–0.96) reduced cancer rate compared with

Table 2
Case-control studies and meta-analyses of randomised statin trials assessing the risk of cancer incidence in statin users

Reference	Tumour type	Patients/controls	Odds Ratio (OR) (95% CI)	Comments
Case-control studies.				
[23]	Breast	1132/1331	1.5 (1.0–2.3)	
	Prostate	1009/1387	1.2 (0.8–1.7)	
[24]	Breast	224/1009	1.0 (0.6–1.6)	
[25]	Breast	975/1007	0.9 (0.7–1.2)	Postmenopausal women; in >5 years statins 0.7(0.4–1.0)
[26]	All	3129/16976	0.8 (0.66–0.96)	Controls use cardiovascular drugs
[27]	Colorectal	1608/1734	0.46 (0.35–0.60)	
[28]	All	542/5420	0.72 (0.57–0.92)	Controls use resins
Reference	Risk treatment group (cases/total)	Risk placebo group (cases/total)	OR (95% CI)	
Meta-analyses of placebo-controlled statin trials; all cancer incidence				
[21]	2082/29,424	2041/29,410	1.02 (0.96–1.09)	
[22]	1510/18,742	1523/18,698	0.99 (0.9–1.07)	

95% CI, 95% Confidence Interval.

patients using other cardiovascular drugs [26]. Another case-control study carried out in postmenopausal women included 975 cases diagnosed with primary invasive breast cancer and 1007 controls. It was shown that there is no difference in risk between women using statins and those who do not. However, in those patients receiving statins for more than 5 years, a decreased risk was demonstrated (Odds Ratio 0.7 (95% CI, 0.4–1.0)) [25]. A study that has been published only in abstract form demonstrated a 54% (95% CI, 0.35–0.60) reduction in the risk of colorectal cancer in statin users. This reduction remained unaltered (0.49 (95% CI, 0.36–0.68)) after adjustment for age, ethnicity, aspirin or non-steroidal anti-inflammatory drug (NSAID) use, hypercholesterolaemia, and presence of the susceptibility allele *APCI*1307K [27].

Collectively, these studies provide evidence that statins do not augment cancer incidence and may even exert a protective effect. However, it should be noted that data from prospective studies, for instance in patients at risk to develop cancer, are lacking. Clearly, further studies are needed, but if statins can really reduce cancer incidence by approximately 20–30%, this would have a major impact on general health in view of the high incidence of both cardiovascular and malignant diseases.

4. Single agent anti-tumour activity

Most tumour cell lines *in vitro* are not susceptible to statins at serum concentrations reached, by doses applied for the treatment of hypercholesterolaemia. For example, the lovastatin dose for treating hypercholesterolaemia is approximately 1 mg/kg/day yielding steady-state serum concentrations of 0.15–0.3 μM [29]. Although a lovastatin concentration of 0.3 μM yields growth inhibition in some tumour cell lines, most tumour cell lines are only sensitive to higher concentrations [5,10]. This prompted investigators to establish the feasibility, and efficacy of high-dose statins in cancer patients.

Unfortunately, only a few studies have been performed up to now. Thibault and colleagues [29] performed a phase I study with oral lovastatin administered at doses ranging from 2 to 45 mg/kg/day for 7 consecutive days, at monthly intervals. The most severe toxicity was myopathy, which only occurred at doses higher than 25 mg/kg/day. However, above that level, there was a lack of correlation between the occurrence of myopathy and doses administered. Subsequently, patients were co-administered ubiquinone, which significantly decreased the severity of myopathy. Combined with ubiquinone, a maximum tolerated dose of lovastatin was never reached. Systemic drug concentrations reached ranged from 0.10 to 3.92 μM. Drug concentrations achieved and the extent of mevalonate pathway inhibition reflected by reductions in cholesterol and ubiquinone levels, were not associated with the doses administered. HMG-CoA reductase was temporary blocked as is suggested by the observation that cholesterol levels return to pre-treatment values within 14 days after cessation of the 7-day course. Of the total 88 patients that were treated, one patient with a recurrent high-grade glioma achieved a minor response. It was concluded that 25 mg/kg/day lovastatin for 7 consecutive days at 4-weeks intervals was feasible without ubiquinone [29].

In a phase I/II study in patients with high-grade glioma, the feasibility of lovastatin alone or combined with radiotherapy was established [30]. *In vitro*, lovastatin exhibits anti-proliferative effects against glioma cell lines at doses ranging from 0.2–2.0 μM. Patients with recurrent disease after radiotherapy were treated with 30 mg/kg/day lovastatin for 7 days at 4-week intervals

alone, while newly diagnosed patients received radiotherapy with various doses of lovastatin. Of the 18 patients included in this study, 9 were allocated to receive lovastatin alone. In these 9 patients, toxicity was mild with only 2 patients experiencing mild joint pain. Despite the fact that ubiquinone was not administered, no myopathy was encountered. A partial response was observed in 1 patient, 1 patient experienced a minor response, while a durable stable disease lasting more than 402 days was seen in another patient [30].

A phase II trial with lovastatin 35 mg/kg/day given orally for 7 days at 4-week intervals in combination with ubiquinone was conducted in patients with irresectable gastric cancer [10]. Lovastatin concentrations yielding growth inhibition of gastric cancer cell lines range from 0.8 to 3.5 μM. In the 14 patients evaluable for toxicity and response, toxicity was relatively mild. Only 1 stable disease for 16 weeks was obtained. The authors concluded that lovastatin in the dose and schedule examined is not active against gastric cancer [10].

Although in these studies doses were used that were known to result in serum concentrations inducing growth inhibition of cancer cell lines *in vitro*, no relevant clinical activity was demonstrated. Since statins transiently suppress the mevalonate pathway and do not induce irreversible damage using these schedules and doses, it was hypothesised that longer exposure to statins may yield better activity. A study assessing a more prolonged administration of oral lovastatin was conducted in patients with recurrent or metastatic squamous cell carcinoma of the head and neck or of the cervix [31,32]. In a previous study, it was shown that, cell lines derived from these tumour entities in particular, are susceptible to statins at relatively low doses [5]. In this phase I study, 26 patients were initially treated at 5 and 10 mg/kg/day for 14 consecutive days repeated every 3 weeks. Dose-limiting toxicity (DLT) consisting of transient rises of creatine kinase was seen in patients receiving 10 mg/kg/day. Thereafter, the treatment schedule was changed to 7.5 mg/kg/day for 2 weeks followed by a 1-week break, which was well-tolerated. Subsequently, it was aimed to prolong treatment duration. At 7.5 mg/kg/day for 3 weeks followed by a 1-week break, 2/9 patients experienced DLT consisting of transient elevated creatine kinase. Since DLT was only encountered in patients with a relative renal dysfunction (creatinine clearance between 60–70 ml/min), it was concluded that the recommended dose for phase II studies should be 7.5 mg/kg/day for 3 weeks followed by a 1-week break, provided the patient had adequate renal function (creatinine clearance >70 ml/min). Cholesterol levels declined during active treatment, but returned to 70% of baseline values during the break. No responses were seen, but 5/26 patients achieved stable disease for more than 3 months. From 6/26 patients, baseline as well as on-treatment tumour biopsies were obtained. No signs of either apoptosis induction or decreased proliferation were demonstrated. Unfortunately, tumour samples from patients achieving durable disease stabilisation were not available [31].

Kawata and colleagues [33] reported on the efficacy of pravastatin applied continuously at low doses in patients with unresectable hepatocellular carcinoma. Patients initially underwent transcatheter arterial embolisation followed by 2 months of oral 5-fluorouracil (5-FU). Subsequently, patients were randomly allocated to a control or treatment group. The latter received daily pravastatin, initially at a dose of 20 mg and after 2 weeks this was escalated to 40 mg. Pravastatin was continued until progressive disease or unacceptable pravastatin-related toxicities. The control and treatment groups comprised 42 and 41 patients, respectively. None of the patients had to stop pravastatin due to toxicity. Cholesterol levels in the treatment group were significantly lower than in the control group at 2 and 6 months indicating suppression of HMG-CoA reductase. Median survival differed significantly between the two groups in favour of the treatment group (18 versus 9 months). In addition in multivariate analysis, pravastatin treatment was a significant factor for prolonged survival. No responses were observed during pravastatin administration, but increases in the maximal diameters of the main lesions at 6 and 12 months were significantly less in the patients receiving pravastatin. This study may suggest that continuously giving pravastatin in low doses could contribute to sustaining stable disease in hepatocellular carcinoma. However, it should be noted that the study lacked a statistical design and confirmation of this finding is therefore required in properly designed trials.

Thus, using high doses of oral statins, serum concentrations that are known to exert growth inhibition *in vitro* can be reached. However, such high doses are only feasible for a limited period of time, while most cell lines tested *in vitro* are only sensitive to these higher doses. In view of the mechanisms of action and the concentrations reached, statins should regarded as cytostatic rather than cytotoxic, thus prolonged administrations may be more effective. Accordingly, the most promising responses, albeit the data are preliminary, have been observed in patients treated continuously with lower doses.

5. Statins combined with other anti-tumour treatments

Since statins can affect several important cellular functions, studies have been initiated to explore the interaction between statins and other treatments used in oncology. Although not universal [34], synergistic interactions were observed, both *in vitro* and *in vivo*, using various cytotoxic drugs including cisplatin, doxorubicin, 5-FU, and carmustine [14,35–39]. Importantly,

potentiation of cytotoxic agents by statins is seen at much lower statin doses than are required for anti-proliferative effects [36–38]. The underlying mechanisms are not known exactly, but statin-induced downregulation of Nuclear Factor-κB (NF-κB) [36] and bcl-2 [37], factors known to confer resistance against chemotherapeutic agents, are thought to be involved. Anti-tumour effects of cytokines such as interferon-α [40] and TNF-α [6] are also enhanced by statins. In addition, lovastatin partially overcomes resistance against radiotherapy in Ras-transformed tumour cells [41].

Presently, there are no results from clinical studies prospectively exploring combinations of statins and cytotoxic agents. One study in patients with rectal cancer showed a trend towards improved anti-tumour effects of pre-operative chemoradiation in patients concurrently receiving statins [42]. However, this study has to be interpreted with great caution because of its non-randomised, retrospective nature and the low number of patients studied. Larner and colleagues [30] performed a phase I study of the combination of radiotherapy and lovastatin in 9 patients with high-grade glioma. It was found that this combination was well tolerated using standard doses of radiotherapy and lovastatin at 30 mg/kg/day. Unfortunately, the number of patients included and the design of this study does not allow any conclusions to be drawn on the efficacy of this approach.

In addition to potential synergistic effects, another beneficial effect when combining statins with the cytotoxic drug, doxorubicin, is the finding that statins seem to protect against cardiomyopathy in animals [38], the cumulative DLT of doxorubicin.

In view of these data, randomised studies examining statin-containing multidrug treatments, have been initiated, but results are not yet available.

6. Conclusions

In recent years, evidence has emerged that statins possess anti-tumour activity and various potential underlying mechanisms of action have been elucidated (Table 1). Until now, only a few clinical studies have attempted to assess the optimal dose, feasibility, and single agent activity of statins. To establish the optimal dose and scheme, it is necessary to find parameters that properly reflect effects leading to anti-tumour activity. Up to now, it is uncertain whether measuring products such as cholesterol and ubiquinone could serve this purpose since pathways other than those downstream from mevalonate may be involved [9]. Therefore, better insight into the mechanisms by which statins exert their anti-tumour activity is required.

Furthermore, the exact doses at which statins should be applied remains to be defined. Lovastatin given at high doses resulted in serum concentrations known to exert anti-proliferative effects *in vitro* against several tumour cell lines [29,31]. However, doses administered are not clearly related to the serum concentrations reached and suppression of HMG-CoA reductase-derived products. In addition, administration of such high doses is only feasible for a relatively short period of time yielding transient suppression of the mevalonate pathway [29,31]. In view of the mechanism of action and the fact that apoptosis will not occur at the concentrations achieved, more prolonged administration may yield better efficacy. Accordingly, low-dose statins given continuously seem to exhibit some anti-tumour activity that might explain the protective effect observed in case-control studies [25–28] and in a study performed in hepatocellular carcinoma [33]. However, results are preliminary and more data are needed.

The most attractive application of statins is probably as part of multidrug therapy. In preclinical models, statins have been demonstrated to interact synergistically with various anti-tumour treatments at doses much lower than are needed for their anti-proliferative effects [14,35–39]. In addition, the mild toxicity profile and various working mechanisms render statins attractive drugs to explore in combination with chemotherapy, immunotherapy, or radiotherapy. In such combinations, prolonged administration of statins should be assessed.

In conclusion, our knowledge on statins as anti tumour agents is still in its infancy given that most of the clinical studies performed to date suffered from methodological flaws. Nevertheless, statins possess numerous intriguing features that suggest further efforts to explore their potential application in oncology, in particular as part of multidrug therapies, should be made. To appropriately assess statins, well-designed studies are needed.

Conflict of interest statement

None declared.

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