

Statins and immune checkpoint inhibitors: a strategy to improve the efficacy of immunotherapy for cancer?

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ABSTRACT

In the past decade, immune checkpoint inhibitor (ICI) therapy significantly improved the prognosis of patients with cancer. Despite impressive and often unprecedented response rates, a significant portion of the patients fails to benefit from this treatment. Additional strategies to improve ICI efficacy are therefore needed. The widespread clinical use of ICIs has increased our knowledge on the effects of the concomitant use of commonly prescribed drugs on the outcome of ICI treatment. A particular interesting class of drugs in this context are statins. These HMG-CoA reductase inhibitors, which are used to treat hypercholesterolemia and reduce the risk for atherosclerotic cardiovascular disease, are frequently used by patients with (advanced) cancer. This paper addresses the hypothesis that statins improve the efficacy of ICI therapy.

The introduction of immune checkpoint inhibitor (ICI) therapy targeted at the checkpoint proteins cytotoxic T lymphocyte-associated protein 4 (CTLA4), programmed cell death protein 1 (PD1) and programmed death ligand 1 (PDL1), significantly improved the prognosis of patients with advanced melanoma, renal cell cancer and non-small-cell lung cancer (NSCLC) in the past decade. Driven by these successes, ICI therapy is becoming a standard of care for the neoadjuvant, adjuvant and palliative treatment of a rapidly increasing number of other cancer types, including gastrointestinal cancer, urothelial cell cancer and hematological malignancies. Despite promising and often unprecedented response rates following ICI treatment, further improvement of the efficacy of ICI therapy is required as a substantial portion of patients fails to benefit from this therapy. For example, up to 50% of the patients with advanced melanoma will not have a durable survival benefit following ICI therapy.¹ Additional strategies to improve the outcome of this therapy may include the development of novel ICI targeted at other coinhibitory molecules, for example, lymphocyte activation gene 3 (LAG3) or

T-cell immunoglobulin and mucin-domain containing 3 (TIM3) or novel combination therapies. Additionally, an increasing number of studies suggest that the concomitant use of commonly prescribed drugs affects the outcome of ICI therapy. An interesting class of drugs in this context are lipid-lowering agents, in particular 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase inhibitors (statins), which are used to treat hypercholesterolemia and reduce the risk for atherosclerotic cardiovascular disease. Treatment with statins is often continued in patients with advanced cancer, for example, >20% of the patients with NSCLC concomitantly use these agents.² This paper addresses the hypothesis that statins may improve the efficacy of ICI therapy in patients with cancer.

One of the first clinical studies that evaluated the effect of concomitant medication on the outcome of ICI therapy is the multicenter observational retrospective study by Cortellini *et al.*³ This study assessed the impact of various classes of drugs on the oncological outcome of patients with advanced NSCLC, melanoma or renal cell carcinoma following PD(L)1 targeting therapy.³ Statins were being used by 19.4% of the 1012 patients.³ Multivariate analysis demonstrated that the baseline use of statins was independently related to an increased objective response rate (statin users vs non-users; HR 1.60 (95% CI 1.14 to 2.25), p=0.0064), but not with progression-free survival (PFS) and overall survival (OS).³ The concomitant use of non-statin lipid-lowering agents did not affect these clinical outcomes in this study.³ A meta-analysis of Zhang *et al.*, which included four studies in patients with advanced solid tumors who received CTLA4 and/or PD(L)1 inhibitors, provided further insight in the potential effects of statins on ICI therapy.² Here, it was demonstrated that the concomitant use of statins improved both OS (HR 0.76 (95% CI



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0.63 to 0.92), $p=0.005$) and PFS (HR 0.86 (95% CI 0.75 to 0.99), $p=0.36$).² Subgroup analysis demonstrated that the favorable effects of statins were limited to patients who received PD(L)1 targeting agents.² Additionally, the beneficial effects were most prominent in patients with malignant pleural mesothelioma, where statin use was associated with improvement of both OS and PFS, and in patients with NSCLC, who showed improved PFS.^{2,4} In accordance, a recent retrospective study, which was not included in this meta-analysis, also demonstrated that statin use correlated with improved OS in 390 PD(L)1 inhibitor-treated patients with NSCLC.⁵ Although direct cytotoxic effects of statins on malignant cells have previously been described, statins did not affect the oncological outcome of chemotherapy-treated patients, suggesting that statins specifically affect the outcome of ICI therapy.⁵ In contrast to these data, other retrospective studies failed to demonstrate any beneficial effect of lipid-lowering agents in ICI-treated patients. These conflicting reports may at least partly be explained by heterogeneity of patient populations, follow-up periods and variations in statin use. For example, favorable effects of lipid-lowering agents were most pronounced in patients who received high-dose statin treatment (eg, atorvastatin (80 mg) or rosuvastatin (40 mg)).⁴ Moreover, other prognostic factors or comorbidities may have steered the concomitant use of statins in patients with cancer, this comorbidity bias may have affected treatment outcome.⁶ Together, the published clinical data suggest that high-intensity statin treatment may affect the oncological outcome of selected cancer patients who received PD(L)1 targeting therapies, but prospective studies are undoubtedly required to confirm these findings. Interestingly, it has also been demonstrated that statins attenuated ICI-related atherosclerotic cardiovascular disease, potentially by modifying the chronic inflammatory response that drives atherosclerosis.⁷ Whether statins affect the incidence of immune-related adverse events of ICI therapy, such as endocrinopathies, pneumonitis, or colitis, is incompletely understood and conflicting findings have been reported.

A large number of preclinical studies identified immunomodulatory effects of statins in the context of cancer, which may provide biological plausibility for the potential beneficial effects of statins on the outcome of ICI therapy. In addition to direct antiproliferative effects, statins promoted immunogenic cell death of KRAS-mutated cancer cells by enhancing the expression of 'eat me' signals (eg, the calreticulin/ERP57 complex) and damage-associated molecular patterns signals (eg, heat shock protein 70 (HSP70)), while reducing the expression of coinhibitory proteins that suppress T cell-driven antitumor responses.⁸ Statins also enhanced the immunogenic profile of dendritic cells in mice with KRAS mutated tumors, characterized by increased expression of several key costimulatory immune checkpoint proteins and a gene expression profile that was

associated with antigen uptake and processing, DC activation and DC maturation, thereby enhancing CD8⁺ T cell responses.⁸ In a syngeneic KRAS-mutated tumor model, which is resistant to PD-1 blockade, combined treatment with simvastatin, oxaliplatin and anti-PD1 antibodies suppressed tumor development and increased survival compared with mice that received oxaliplatin and anti-PD1 antibodies.⁸ Interestingly, antibody-mediated depletion of CD8⁺ T cells, and not CD4⁺ T cells, abrogated the antitumor effects of simvastatin in tumor-bearing mice.⁸ Comparable beneficial effects were also reported in mice with head and neck squamous cell carcinoma following triple therapy with cisplatin, PD1 inhibitors and statins, as compared with mice that received the chemoimmunotherapy combination without statins. Together, these data indicate that the immunomodulatory effects of statins sensitize tumors to ICI therapy by enhancing tumor-specific cytotoxic T cell responses, at least in these preclinical models. Other studies also demonstrated that statins may affect T cell functioning in the tumor microenvironment. Prolonged antigen exposure and the hostile tumor microenvironment may induce a dysfunctional state of cytotoxic T cells, known as exhaustion. Phenotypically, exhausted cytotoxic T cells are characterized by an increased expression of co-inhibitory molecules, including CTLA4, PD1, LAG3, TIM3 and SLAMF4 (9). Both human and mouse studies demonstrated that elevated cholesterol levels in tumor-infiltrating T cells was associated with increased expression of inhibitory checkpoint proteins, as well as impaired T cell-driven antitumor immunity.⁹ Genetic or pharmacological (simvastatin-mediated) reduction of cholesterol content reversed the exhausted T cell phenotype and restored T cell-mediated antitumor responses in B16 melanoma tumor-bearing mice.⁹ In contrast to these solid preclinical studies, others reported that a genetic or pharmacological increase in membrane cholesterol content enhanced TCR-mediated signaling and subsequent activation in CD8⁺ T cells, thereby potentiating antitumor responses. This highlights that the role of cholesterol in T cell biology is incompletely understood and may vary depending on the presence of other T cell regulating factors, such as immune checkpoint proteins, nutrients or cytokines. Consequently, the effects of statin-mediated cholesterol modulation on T cell-driven antitumor immunity and ICI efficacy may depend on specific genetic alterations of the tumor, tumor type and type of statins. Further studies are undoubtedly required to elucidate the underlying mechanisms of these interesting preclinical studies and to confirm these findings in humans.

In addition to statins, other lipid-lowering drugs, in particular proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, may also potentiate ICI therapy.¹⁰ PCSK9 inhibitors prevent the degradation of the low-density lipoprotein receptor, resulting in increased cholesterol clearance. PCSK9 is highly expressed in

several human cancers and negatively impacts disease progression.¹⁰ In preclinical models, it was shown that PCSK9 inhibition enhanced intratumoral recruitment of cytotoxic T cells as well as TCR-mediated T cell activation and effector functions.¹⁰ Future studies should investigate if these immunomodulatory effects of PCSK9 attenuate the efficacy of ICI therapy in patients. Interestingly, several studies suggest that other classes of lipid-lowering drugs (eg, fibrates and ezetimide) also affect the outcome of ICI treatment, but this should be further explored.

In conclusion, solid preclinical studies in conjunction with heterogeneous retrospective clinical studies suggest that statins may improve the efficacy of ICI therapy in patients with cancer. Our viewpoint is that this findings warrant further investigation in prospective and well-controlled clinical trials. Especially as statins have well-known safety profiles and are readily available and could therefore be rapidly implemented as additive strategy to boost the efficacy of ICI in patients with cancer.

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