


Repurposing Statin Drugs to Decrease Toxicity and Improve Survival Outcomes in Head and Neck Cancer

OTO Open
 2021, Vol. 5(4) 1–4
 © The Authors 2021
 Article reuse guidelines:
sagepub.com/journals-permissions
 DOI: 10.1177/2473974X211065715
<http://oto-open.org>


Richard O. Bourguillon, BS¹, William A. Stokes, MD²,
 Jennifer Dorth, MD³, and Nicole C. Schmitt, MD⁴

Abstract

Objective. The rising incidence of head and neck squamous cell carcinoma (HNSCC) calls for the assessment and improvement of currently available therapies that may enhance the therapeutic ratio in these patients. Statin drugs are one of the most widely used drug classes in the world for their lipid-lowering properties. As such, statins have been widely studied and found to possess pleiotropic effects that may make them effective in cancer treatment and toxicity mitigation. The aim of this review is to examine the potential use of statin drugs as adjunctive therapy in patients with HNSCC.

Data Sources. PubMed.

Review Methods. Any preclinical or clinical articles pertaining to the effects of statin drugs on treatment-related toxicity or survival outcomes in patients with head and neck cancer were included in this narrative review.

Conclusions. Emerging data suggest that statins may improve survival and reduce toxicities associated with chemotherapy and radiotherapy in patients with head and neck cancer, by mechanisms that are poorly understood at present.

Implications for Practice. Given their affordability and safety, statins deserve further study as a tool to improve oncologic outcomes and enhance survivorship in patients with HNSCC.

Keywords

statin drugs, head and neck cancer, radiation therapy, ototoxicity

Received November 4, 2021; accepted November 21, 2021.

Since isolated from fungi by Akira Endo and later approved for medical use by the Food and Drug Administration (FDA), statin drugs have become one of the most widely used drug classes in the world for treatment of hyperlipidemia.¹ Statins are inhibitors of the hydroxymethylglutaryl-CoA (HMG-CoA) reductase enzyme, a key molecule in the biosynthetic pathway of cholesterol. By

inhibiting this enzyme, statins decrease the hepatic cholesterol concentration. Moreover, statins initiate the upregulation of low-density lipoprotein (LDL) receptor in the liver to take up more LDL cholesterol from the blood, further decreasing blood cholesterol levels. Statins have a higher affinity for the HMG-CoA reductase enzyme than the natural HMG-CoA substrate, making it a highly effective drug class.² Over the years, extensive study has revealed that statins possess additional properties beyond lowering lipids. Mohammad et al reviewed the literature concerning the pleiotropic effects of this class and found it to exert anti-inflammatory and immunomodulatory effects that may be of benefit in treating many other diseases, including cancer.³

Head and neck squamous cell carcinoma (HNSCC) is a relatively common cancer in developing countries and the sixth-most common cancer in the world. The etiology of HNSCC is multifactorial, but strong associations have been identified with tobacco, alcohol, and the high-risk subtypes of human papilloma virus (HPV). HPV-related HNSCC has a unique biology and better prognosis in comparison with non-HPV-related HNSCC due to its relatively favorable response to treatment. However, the incidence of HPV-related HNSCC is increasing.⁴ Currently, the treatment for both subtypes of HNSCC includes surgery, chemotherapy, and radiation or various combinations of these 3 treatment modalities, depending on the stage and location of the tumor. Despite advances in these modalities, the prognosis for HPV-negative HNSCC remains poor, and treatment often entails considerable short-

¹Morehouse School of Medicine, Atlanta, Georgia, USA

²Department of Radiation Oncology and Winship Cancer Institute, Emory University, Atlanta, Georgia, USA

³Department of Radiation Oncology, Case Western Reserve University, Cleveland, Ohio, USA

⁴Department of Otolaryngology–Head and Neck Surgery and Winship Cancer Institute, Emory University, Atlanta, Georgia, USA

Corresponding Author:

Nicole C. Schmitt, MD, Winship Cancer Institute, School of Medicine, Emory University, 550 Peachtree Street NE, 11th Floor Otolaryngology, Atlanta, GA 30308, USA.

Email: nicole.cherie.schmitt@emory.edu



Table 1. Studies Relevant to the Effects of Statins on Toxicity and Survival in HNSCC.

Study	Type of study	Relevant findings
Survival outcomes/anticancer activity		
Getz, <i>International Journal of Cancer</i> (2020) ⁷	Retrospective cohort study from a single institution	Inverse association between statin use and death; inverse association between statin use and cancer-specific death seen only in HPV+ cohort
Gupta, <i>Oral Oncology</i> (2019) ⁸	Retrospective cohort study based on SEER Medicare database	Patients with hyperlipidemia taking a statin at diagnosis had improved overall and cancer-specific survival vs patients not taking a statin
Lebo, <i>Head and Neck</i> (2018) ⁶	Retrospective cohort study based on Ontario Cancer Registry	Patients taking statins upon diagnosis of HPV– squamous cell carcinoma of the larynx, hypopharynx, or nasopharynx had superior overall and disease-specific survival vs patients not taking statins
Mehibel, <i>Scientific Reports</i> (2018) ⁹	Preclinical murine study	Simvastatin prevented growth of head and neck cancer cells in vitro and delayed formation of tumor xenografts in vivo
Treatment-related toxicities		
Addison, <i>Journal of Stroke</i> (2018) ¹⁶	Retrospective cohort study from a single institution	Reduced incidence of ischemic stroke after radiation (hazard ratio, 0.4)
Bourgier, <i>International Journal of Radiation Oncology Biology Physics</i> (2019) ¹²	Prospective phase 2 study of pravastatin as an antifibrotic agent for head and neck cancer treated with radiation	Pravastatin reduced radiation fibrosis by >30% in half of patients after 12 mo of use
Fernandez, <i>Hearing Research</i> (2020) ¹⁰	Preclinical murine study	Lovastatin mitigated cisplatin-induced hearing loss in adult mice, with more pronounced effects in female mice
Fernandez, <i>Journal of Clinical Investigation</i> (2021) ¹¹	Prospective/retrospective observational study of hearing loss in HNSCC treated with cisplatin chemoradiation	Patients taking atorvastatin were 53% less likely to develop hearing loss after cisplatin chemoradiation
Lee, <i>Journal of Stroke</i> (2018) ¹⁷	Retrospective cohort study based on National Health Insurance Research Database (Taiwan) with propensity matching	No significant difference in incidence of ischemic stroke among statin users vs nonusers

Abbreviations: HNSCC, head and neck squamous cell carcinoma; HPV, human papilloma virus; SEER, Surveillance, Epidemiology, and End Results.

and long-term toxicities.⁵ This narrative review examines the use of statin drugs as adjunctive therapy in patients with head and neck cancer by highlighting effects on oncologic outcomes, analyzing effects on toxicities associated with chemotherapy and radiotherapy, and describing the future work needed to evaluate the validity of incorporating statin drugs into treatment regimens for HNSCC.

Methods

A search was performed in PubMed for any articles pertaining to the use of statin drugs in head and neck cancer (keywords “head and neck cancer,” or “squamous cell carcinoma” combined with “statins”). Nine studies relevant to the effects of statins on treatment-related toxicities and/or survival were included in this narrative review (Table 1). Preclinical/animal and clinical/human studies were included.

Discussion

Impact of Statins on Survival Outcomes

Emerging preclinical and clinical data suggest that statin drugs may have some activity against HNSCC. Statin use has shown promising results in a few large retrospective database studies that investigated effects on survival and recurrence in HNSCC. In a study of 1194 patients from the Ontario Cancer Registry, patients with HPV-negative HNSCC of the larynx, hypopharynx, and nasopharynx who were taking a statin had better overall and disease-specific survival than those who were not taking a statin at or before cancer diagnosis.⁶ When statin use was adjusted to have a more stringent timeline of 1 year before diagnosis and 4 months after diagnosis, these results held.⁶ A large single-institution retrospective study showed similar results.⁷ When subgroup analyses were done to assess the effects of HPV status with HNSCC, overall

survival was increased for patients taking a statin who were HPV positive or negative, while disease-specific survival was increased by statins only in patients with HPV-positive disease.⁷ In a retrospective study using the SEER Medicare database, Gupta et al classified patients with HNSCC as having hyperlipidemia plus using a statin, having hyperlipidemia but not using a statin, or not having hyperlipidemia. Patients with hyperlipidemia who were taking a statin had increased overall and disease-specific survival versus those with hyperlipidemia not taking a statin and those without hyperlipidemia. Interestingly, improvement in disease-specific survival was disproportionately greater than the improvement in overall survival, suggesting that the cancer might be targeted by statin drugs.⁸

The mechanisms by which statins may target HNSCC cells are not well understood. In a preclinical study, simvastatin, but not pravastatin, inhibited the proliferation of HNSCC cell lines and delayed the formation of tumors after subcutaneous inoculation of tumor cells in mice, in part via the upregulation of MCT1 (monocarboxylate transporter 1), an important mediator of lactate metabolism.⁹ A systematic review found that multiple preclinical studies demonstrated evidence that statins exert anticancer effects on HNSCC cell lines, including inhibition of growth, invasion, and metastasis of tumor cells.⁹ Additional preclinical studies might elucidate the mechanisms of statin activity in HNSCC and assist in determining its usefulness in combined modality therapy for HNSCC. The enhanced survival in HNSCC among patients taking statins under a variety of circumstances suggests that the use of statin drugs deserves further study in preclinical models and prospective clinical studies of HNSCC.

Impact of Statins on Toxicities of Chemotherapy and Radiation

In addition to prolonging the survival of patients with HNSCC, statin drugs have gained interest due to their potential to ameliorate some treatment-related toxicities that may affect quality of life among survivors. For example, cisplatin is an effective chemotherapeutic drug for HNSCC that may cause ototoxicity, presenting as tinnitus and/or a high-frequency sensorineural hearing loss.¹⁰ In a study of HNSCC treated with cisplatin chemoradiation, statin users had reduced incidence of hearing loss when compared with those who were not on a statin, even though the nonusers were younger and had better hearing at baseline. Subgroup analyses revealed a 53% lower incidence of hearing loss among patients taking atorvastatin, regardless of the dose. When hearing loss did occur, the severity by Common Terminology Criteria for Adverse Events was milder in atorvastatin users versus nonusers.¹¹

Many patients with HNSCC are at risk of developing radiation-induced cutaneous and subcutaneous fibrosis (RIF), which can lead to dysphagia, trismus, lymphedema, and/or restricted range of motion in the neck. In a prospective study of patients with HNSCC and grade 3 or 4 RIF, pravastatin (40 mg/d) was started at a mean interval of 17 months after radiation and then continued for 12 months. The use of pravastatin

in this setting led to a decrease in thickness and severity of RIF, improved quality of life, and minimal toxicity for the duration of 12 months in most patients.¹²

Radiation can also adversely affect the cardio- and cerebrovascular systems, resulting in stroke and myocardial infarction. Among survivors of HNSCC, there is an increased risk for stroke due to radiation-related damage to the carotid artery. The rate of stroke is reported to be as high as 24% at 20 years after completing radiation therapy, as opposed to <5% in the general population.^{13,14} There is some evidence that statins may mitigate radiation-related vascular injury. A prospective study investigating the effect of radiation therapy on the carotid arteries found a significant increase in intima-media thickness, which is an early biomarker of radiation injury. Interestingly, the degree of change in carotid artery intima-media thickness was directly correlated to the baseline level of LDL cholesterol.¹⁵ In a retrospective study by Addison et al, statin use in patients with HNSCC treated with radiation resulted in a 60% relative risk reduction in stroke events.¹⁶ Of note, these differences were highly significant despite statin users having higher vascular comorbidities, such as older age, diabetes, and hypertension. The anti-inflammatory and antioxidative effects of statin drugs are thought to play a role in reducing the endothelial dysfunction of blood vessels induced by radiation therapy.¹⁶ However, in a retrospective study that included patients with nasopharyngeal cancer from Taiwan, propensity score matching showed no significant effect of statin use on the incidence of stroke,¹⁷ suggesting that the study population and anatomic subsite may influence the effects of statins on radiation-induced cerebrovascular events.

Limitations of the Current Literature

The effects of statin drugs on survival outcomes and treatment-related toxicities in patients with head and neck cancer is an emerging topic, with insufficient published data to perform an unbiased systematic review or meta-analysis. Furthermore, the studies to date, summarized in this narrative review, consist of preclinical and retrospective clinical studies, which introduce further bias. Indeed, such studies can show associations but do not accurately demonstrate a causative relationship between statin use and outcomes. The ability to adjust for possible confounding factors may be limited in cohort studies where clinical information on each subject is limited. Last, immortal time bias can produce results that favor the treatment group, which has likely influenced large cohort studies investigating the effects of statins on cancer risk or outcome studies.¹⁸

Implications for Practice

Statin drugs represent a promising strategy for improving the treatment of head and neck cancer. Studies have shown that statins may enhance survival outcomes while abating the toxicities of chemoradiation therapy, thereby reducing morbidity and enhancing quality of life. However, further research is necessary to determine whether statin drugs should be incorporated into the treatment of HNSCC. Several important questions remain:

- What are the mechanisms by which statins convey anticancer activity?
- Do statins exhibit anticancer activity in all forms of head and neck cancer? The retrospective cohort studies summarized in this review suggest that statin activity may be variable according to the anatomic subsite and/or HPV status.
- Which statins are most efficacious? Would lipophilic statins, with their broader extrahepatic distribution, prove more effective than hydrophilic statins? Are high-intensity statins, which have stronger lipid-lowering effects, more effective than moderate-intensity statins? Since there are 7 commercially available FDA-approved drugs in this class, it would be valuable to identify the statin (or statins) that provides the most benefit if there is such distinction. Some of the studies described here and others in the literature suggest that off-target effects can vary dramatically among high-intensity statin drugs.
- What dose should be used?
- When should statins be started, and how long should they be continued?

Although these mysteries remain, there is growing evidence that these inexpensive, well-tolerated FDA-approved drugs deserve further study in preclinical and prospective clinical studies for HNSCC and other cancers.

Author Contributions

Richard O. Bourguillon, literature search, drafting and revision of the review; **William A. Stokes**, revision of the review; **Jennifer Dorth**, revision of the review; **Nicole C. Schmitt**, study supervision, literature search, drafting and revision of the review.

Disclosures

Competing interests: Nicole C. Schmitt: advisory board—Checkpoint Surgical, Sensorion; book royalties—Plural Publishing; research funding—Astex Pharmaceuticals.

Sponsorships: None.

Funding source: Supported in part by Winship Cancer Institute.

References

1. Stossel TP. The discovery of statins. *Cell*. 2008;134(6):903-905.
2. Sirtori CR. The pharmacology of statins. *Pharmacol Res*. 2014; 88:3-11.
3. Mohammad S, Nguyen H, Nguyen M, et al. Pleiotropic effects of statins: untapped potential for statin pharmacotherapy. *Curr Vasc Pharmacol*. 2019;17(3):239-261.
4. Alfouzan AF. Head and neck cancer pathology: old world versus new world disease. *Niger J Clin Pract*. 2019;22(1):1-8.
5. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. *Mayo Clin Proc*. 2008;83(4): 489-501.
6. Lebo NL, Griffiths R, Hall S, Dimitroulakos J, Johnson-Obaseki S. Effect of statin use on oncologic outcomes in head and neck squamous cell carcinoma. *Head Neck*. 2018;40(8):1697-1706.
7. Getz KR, Bellile E, Zarins KR, et al. Statin use and head and neck squamous cell carcinoma outcomes. *Int J Cancer*. 2020; 148:2440-2448.
8. Gupta A, Stokes W, Eguchi M, et al. Statin use associated with improved overall and cancer specific survival in patients with head and neck cancer. *Oral Oncol*. 2019;90:54-66.
9. Mehibel M, Ortiz-Martinez F, Voelxen N, et al. Statin-induced metabolic reprogramming in head and neck cancer: a biomarker for targeting monocarboxylate transporters. *Sci Rep*. 2018;8(1): 16804.
10. Fernandez K, Spielbauer KK, Rusheen A, et al. Lovastatin protects against cisplatin-induced hearing loss in mice. *Hear Res*. 2020;389:107905.
11. Fernandez KA, Allen P, Campbell M, et al. Atorvastatin is associated with reduced cisplatin-induced hearing loss. *J Clin Invest*. 2021;131(1):e142616.
12. Bourgier C, Auperin A, Rivera S, et al. Pravastatin reverses established radiation-induced cutaneous and subcutaneous fibrosis in patients with head and neck cancer: results of the biology-driven phase 2 clinical trial pravacur. *Int J Radiat Oncol Biol Phys*. 2019;104(2):365-373.
13. Asplund K, Karvanen J, Giampaoli S, et al. Relative risks for stroke by age, sex, and population based on follow-up of 18 European populations in the MORGAM Project. *Stroke*. 2009; 40(7):2319-2326.
14. Lam TC, Choi HCW, Yeung I. Progressive increase in the risk of stroke among survivors of nasopharyngeal cancer treated with radical radiation therapy: 13-year follow-up of the 1998-2004 cohort. *International J Radiat Oncol Biol Phys*. 2019;105:S212.
15. Pereira EB, Gemignani T, Sposito AC, Matos-Souza JR, Nadruz W Jr. Low-density lipoprotein cholesterol and radiotherapy-induced carotid atherosclerosis in subjects with head and neck cancer. *Radiat Oncol*. 2014;9:134.
16. Addison D, Lawler PR, Emami H, et al. Incidental statin use and the risk of stroke or transient ischemic attack after radiotherapy for head and neck cancer. *J Stroke*. 2018;20(1):71-79.
17. Lee BC, Lin CL, Tsai HH, Kao CH. Statin and the risk of ischemic stroke or transient ischemic attack in head and neck cancer patients with radiotherapy. *J Stroke*. 2018;20(3):413-414.
18. Gormley M, Yarmolinsky J, Dudding T, et al. Using genetic variants to evaluate the causal effect of cholesterol lowering on head and neck cancer risk: a Mendelian randomization study. *PLoS Genet*. 2021;17(4):e1009525.