Prevention of radiation induced lung injury after chemoradiation with simvastatin
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Radiation pneumonitis is a known toxicity of thoracic radiation therapy (RT) characterized by a non-productive cough, dyspnea, and pleuritic chest pain. Moderate to severe pneumonitis can occur in 10-20% of lung cancer patients treated with radiotherapy. A recent analysis by the Radiation Therapy Oncology Group (RTOG) in these patients found that baseline global quality of life, physical functioning, and dyspnea scores were all independently predictive for survival at 5 years and outweighed classical prognosticators such as performance status, stage, age, and histology. Therefore, attempts should be made to reduce decline in lung function. Currently, the most common method to reduce the risk of radiation pneumonitis involves minimizing the volume of lung that is irradiated above a threshold value of radiation. However, even when these constraints are met, some patients may still experience pulmonary symptoms. Therefore, alternative methods to prevent toxicity from thoracic RT must be developed.

While the exact mechanism for the development of radiation pneumonitis is unclear, it is thought to be due to an inflammatory process. Therefore, the anti-inflammatory properties of simvastatin may be useful in preventing RT induced lung injury. In pre-clinical studies, administering a statin prior to RT reduces the presence of pro-inflammatory markers and recruitment of inflammatory cells. Additionally, mice exposed to a statin prior to RT also have decreased change in lung architecture compared to mice treated with RT alone. While pre-clinical data support this concept, there are no clinical studies to date that have verified these findings in patients. Our broad objective is to test the hypothesis that simvastatin can decrease the incidence of radiation induced lung injury without increasing other toxicities of treatment with chemoradiotherapy.

Specific Aims:
1. Define the maximum tolerated dose (MTD) of simvastatin in combination with chemoradiotherapy by escalating the dose of simvastatin in 20 mg increments from 40 mg po daily to 100 mg po daily. The first cohort of lung cancer patients will receive the lowest dose of simvastatin and the dose will be escalated to the next dose level only if an acceptable number of patients (<2/6) develop dose-limiting toxicities.

2. Assess whether the addition of simvastatin decreases the rate of radiation pneumonitis. Symptomatic and radiographic pneumonitis will be assessed based on history and CT imaging at 1,4,7, and 11 months following treatment. The pneumonitis rates in the patients treated with simvastatin will be compared with contemporary patients treated off-protocol who are not receiving simvastatin.

3. Compare the quality of life in patients treated with simvastatin with patients who are not receiving simvastatin (off-protocol) by administering global quality of life and lung-specific quality of life surveys at 1,4,7, and 11 months following treatment.
4. Assess a series of biomarkers of lung injury to determine if there is a predictable correlation between changes in the biomarkers and the development of radiation pneumonitis. Determine if this is altered in patients who are treated with simvastatin.