Use of Immunotherapy In Laryngeal Squamous Cell Carcinoma (LSCC)

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Cancer occurs when cells grow and divide uncontested and spread (metastasizes). The immune system is a collection of cells, tissues, and organs that send signals and work together to fight off infection or disease. Thus, in cases where the immune system should intervene to bring together its efforts in incremental growth to fight cancerous cell growth and return to homeostasis, it does not. Either the cancerous growth is too strong to permit immune intervention against it, or the cancerous growth can send immune system signals to suggest nothing is wrong, which leads to decreased immune response or total immune response shutdown. One method of using the immune system against cancer is called immunotherapy; it relies on the patients' response to immune engagement. Since immunotherapy activates T cells, this would be an appropriate method to reduce cancer immune evasion, as the immune system is very good at detecting and singling out cells. In addition, it is frequently used in conjunction with other cancer treatment methods. This article reports reasons why immunotherapy is a beneficial treatment option due to immune response engagement based on LSCC treatment.

Recently, innovations in immunotherapy have provided new treatment avenues for LSCC, giving hope to those with recurrent or metastatic lesions. LSCC falls under Head and Neck Malignancies. LSCC arises from squamous cells of the vocal cords larynx, an essential structure for respiration and speaking. The typical mutations associated with LSCC include TP53, CDKN2A, and RB1 (Febres-Aldana 2022). Relative risk factors include prolonged exposure to drinking and smoking alcohol. LSCC primarily occurs in males aged 50-70 years; the ratio between male and female is 4:1 (Talamini 2002). This is because men are more sensitive to becoming active tobacco and alcohol users; however, tobacco use has significantly declined in recent years. According to the WHO, in 2022, approximately 1 in every 5 adults are global tobacco users; in 2000, it was 1 in every 3 (WHO 2024). Furthermore, alcohol use increased by 20% for heavy drinking, and all alcohol-related consumption increased by 4% from 2018-2020 in the United States before the COVID19 pandemic. Regardless of whether they are used in combination or separately, alcohol and tobacco use increases the statistics of risk factors to develop laryngeal cancer. Increased permeabilities of alcohol in mucosal cells cause subsequent activation of microsomal enzymes which creates alcohol carcinogens from tobacco that degrades DNA (Agrawal 2016). In addition, while early diagnosis of LSCC has a 5 year survival rate of 70-90%, late-diagnosed individuals only survive 30% (Zhang 2021). Treatments for LSCC normally include surgery, radiotherapy, and chemotherapy. These treatments, while shown to be effective in early stages of LSCC, often result in reduced quality of life because around 16-36% of patients need a Laryngectomy (the surgical removal of the voice box) (Victor 2024).

LSCC is a laryngeal (voice box) malignancy that escapes immune surveillance through immune checkpoint dysregulation. LSCC escapes immune surveillance through immune checkpoint protein upregulation. For instance, PDL1 upregulation occurs with a dysregulated approach to determining LSCC by T-cells; thus, LSCC can proliferate on its own without being recognized. The immune system cells that are dysregulated here are cytotoxic T-cells, making the immune response ineffectual (Chen 2024). Therefore, there is an effective treatment intervention to enhance an immune response so that these tumor cells can be found and destroyed. The LSCC standard of immunotherapy is immune checkpoint inhibition. Immune checkpoint inhibition inhibits PD1 or its receptor, PDL1, from operating within the LSCC tumor microenvironment. Such treatments allow for induced awareness and subsequent destruction from the immune system. The immune system components most influenced by this treatment are the T-cells, mostly activated cytotoxic T-cells during the initial cancer-fighting reaction. The effectiveness of LSCC for immunotherapy is variable. However, two types of immunotherapy, pembrolizumab and nivolumab, are PD1 and PDL1 inhibitors that have high efficacy among LSCC patients regarding increased overall survival rates. Yet not every patient is suited for such an ideal course. For some, the tumor microenvironment compensates for the immune control attempt that the treatment conveys. In other instances, immunotherapy causes autoimmune responses where inflammation occurs in previously healthy areas of tissue. Nevertheless, LSCC has numerous FDA-approved immunotherapies that focus on PD1 or related PD1 and PDL1 axis interactions (Outh-Gauer 2018). Moreover, EZH2 inhibitors are in the works which could impact time to response with further increased awareness of LSCC (DuCote 2024). Therefore, such findings transform accidents that would otherwise induce fear into manageable occurrences with effective prognoses.

There are several clinical trials underway concerning LSCC treatment. One direction is immunotherapy combined with standard treatment. For instance, there is a phase I trial of pembrolizumab. It studies the effectiveness and dosing schedules of pembrolizumab in combination with cisplatin and intensity modulated radiation therapy in patients with stage III-IV head and neck squamous cell carcinoma; it seeks to determine immune therapeutics effectiveness through integration with standard treatment modalities (NCT02609503). Inclusion criterias involve 18 years of age and older, a diagnosis of LSCC (minimum stage II), adequate organ function, and no previous treatment with immune checkpoint inhibitors. Exclusion criterias involve positive autoimmune disorders, untreated infections, and previous treatment with immunotherapy resulting in major adverse side effects. In addition, there is a study involving viral treatment of LSCC. There is a phase I trial of viral therapy. It studies the dose determination and side effects of a viral therapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck; it seeks to determine whether oncolytic (modified) viruses can preferentially kill LSCC cells (NCT04163952). Finally, there is an assessment of neoadjuvant chemoimmunotherapy for locally advanced laryngeal and hypopharyngeal squamous cell carcinoma. There is a

single-arm phase II clinical trial that assesses neoadjuvant chemotherapy and immunotherapy to see if it reduces tumor size before surgical intervention, noting good efficacy (NCT02296684).

LSCC is a malignant tumor that arises from the epithelial cells of the larynx, it is often associated with risk factors such as smoking and alcohol consumption. Recently immunotherapy rose as a promising treatment option for LSCC, offering an approach to cancer treatment by harnessing the immune system to target cancer cells. Immune checkpoint inhibitors such as PD1 and PDL1, have shown encouraging results in improving survival and disease control in some patients. Scientists are actively exploring combination therapies and biomarkers to enhance immunotherapies efficacy and expand its benefits to a larger patient population. With continuing advancements, immunotherapy holds great potential to change the future for LSCC treatment.

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