The Role of Targeted Therapy in the Management of Sinonasal Malignancies

Lawrence Kashat, MD, MSc, Christopher H. Le, MD, Alexander G. Chiu, MD*

KEYWORDS

• Targeted therapy • Immunotherapy • Sinonasal malignancy
• Head and neck squamous cell carcinoma • Sinonasal tumors
• Cell-mediated immunity • Head and neck melanoma • Mucosal melanoma

KEY POINTS

- Malignancy arises when cancer cells evade detection and destruction by immune system cells. The cell-mediated immune response, particularly that involving $CD8^+$ cytotoxic T lymphocytes, is a critical component of the antitumor response.
- Activation of the cell-mediated immune response is a complex process involving interactions between tumors and the immune system. This process involves foreign proteins expressed and/or shed by cancer cells (tumor antigens), APCs (including dendritic cells and macrophages), $CD4^+$ helper T lymphocytes, and $CD8^+$ cytotoxic T lymphocytes.
- Cancers evade the immune response by numerous mechanisms, including expression of inhibitory immune checkpoint proteins, release of cytokines, and interactions with inhibitory cells in the tumor microenvironment.
- Cancers may prevent their own destruction through the exploitation of several inhibitory pathways found on T lymphocytes, including the CTLA-4 and PD-1 pathways. These inhibitory cell-surface interactions between cancer cells, APCs, and lymphocytes are an important therapeutic target.
- Several targeted immune therapies that block these inhibitory interactions have resulted in unprecedented clinical efficacy in the treatment of numerous malignancies and may present a novel therapeutic approach to the treatment of sinonasal and ventral skull base malignancies.

Department of Otolaryngology, University of Kansas School of Medicine, 3901 Rainbow Blvd, MS 3010, Kansas City, KS 66160, USA
* Corresponding author.
E-mail address: alexchiumd@gmail.com

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INTRODUCTION

The notion that the immune system is important in defending against malignancy had first been postulated more than 100 years ago by Robert Ehrlich, who suggested that cancer would occur with high frequency if not for host immune defense preventing tumor growth.[1] Cancers arise secondary to genetic and epigenetic changes that provide the cell with a survival advantage that promotes cellular immortality. Cells that undergo these changes often express foreign antigens on their surface that would ordinarily be expected to stimulate a host immune response to destroy them. Malignancy arises when tumors use mechanisms to evade detection and destruction by the immune system.

Following the discovery of T cells in the 1940s came the concept of "immunosurveillance," the process by which the immune system is able to identify and destroy transformed cells to prevent formation of neoplastic disease. For several decades, scientists have worked to find ways to harness the power of the host's own immune system in the fight against cancer.[2] Many malignancies seem to elicit an immune response, yet somehow manage to avoid destruction by the cells of the immune system. For example, several studies have shown that large subsets of head and neck squamous cell carcinomas (HNSCCs) demonstrate the presence of $CD8^+$ cytotoxic T lymphocytes and that their presence may be associated with improved response to chemotherapy.[3] Because these tumor-infiltrating lymphocytes function in the immune system to destroy abnormal cells, the question arises: how did these cancers avoid destruction by the host immune system? Furthermore, is there a way to exploit this immune response and make it reactive to the malignant cells?

In recent years there have been unprecedented advances in targeted cancer immunotherapy that are dramatically improving outcomes for several different malignancies, including advanced metastatic cancers that previously had minimal hope for long-term survival. This article discusses some of these remarkable clinical findings and explores their potential for use in treatment of various sinonasal and ventral skull base malignancies.

Immunology Basics

To understand the role of the immune system in the development of malignancy and the mechanisms by which tumors evade the immune system, it is important to understand some essential principles of immunology. Broadly, the immune system is divided into innate and adaptive components (**Tables 1** and **2**).

Innate Immunity

Innate immunity refers to an always-present system that can immediately defend against the development of infections and neoplasia. The components of innate immunity include epithelial cells that act as a barrier to infection; complement proteins; and a variety of cell types, such as monocytes, macrophages, dendritic cells, natural killer cells, eosinophils, mast cells, and basophils. Some of these pertinent components are described in more detail in **Table 1**.

Adaptive Immunity

Adaptive immunity specifically refers to lymphocytes and their products, such as antibodies. This powerful component of the immunity system is not immediately available to defend against pathologic states, but requires additional steps to become active. This includes presentation of a foreign antigen to B or T lymphocytes by antigen presenting cells (APCs), such as dendritic cells and macrophages. After antigen