

Immunotherapy in head and neck cancer: A review

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Abstract

Immunotherapy is one of the newer entities which is promising, at least can be very much helpful as an adjuvant therapy. This newer modality of the treatment in the field of cancer treatment may be the fourth pillar supporting surgery, chemotherapy, and radiotherapy. Careful selection of patient is the key for success of immunotherapy, which is based on patient's immunological contexture. In this article we will try to give idea about the immunotherapy in treatment of head and neck cancer and it is a ongoing research.

Keywords: Immunotherapy, Natural killer cells, Human papiloma virus, Chemotherapy.

Introduction

Head-and-neck squamous cell malignant growths are one of the most well-known tumours worldwide and represent the greater part million new cases and 480,000 passing for each year.¹ Major etiological hazard factor incorporates tobacco use, betel-quid and areca-nut biting, liquor utilization, human papillomavirus (HPV) contamination (oropharyngeal disease), and Epstein–Barr infection disease (nasopharyngeal cancer).² An enormous number of patients are determined to have privately propelled ailment and require multimodal treatment approaches.³ Despite progresses in radiation and careful procedures and the utilization of chemotherapy and monoclonal antibodies in cutting edge ailment, the greater part of all patients repeat remotely.

Tumor cells from different strong malignancies, including HNSCC, over-express PD-L1 to habituate the safe checkpoint pathways to sidestep insusceptible surveillance.⁴ Pembrolizumab and nivolumab are PD-1 antibodies that intrude on the immunosuppressive pathway of inhibitory checkpoints, which are utilized by tumor cells to anticipate the carcinoma.

Mechanism Responsible for Carcinogenesis

Immune evasion

Maintaining a strategic distance from insusceptible devastation is one of the signs of cancer.⁵ Tumors sidestep invulnerable reaction through various immunologic opposition systems: advancement of T-cell resistance, tweak of fiery and angiogenic cytokines, downregulation of antigen processing machinery (APM), and the outflow of safe checkpoint ligand end receptors.⁶ Tumor cells additionally build up a safe suppressive microenvironment by advancing the emission of immunosuppressive cytokines, for example, tumor growth factor-beta (TGFβ) and interleukin 10 (IL-10) which smother T-cell multiplication and cytotoxic capacity and downregulate articulation of co-stimulatory particles and MHC.⁷ These cytokines repress dendritic cell development, macrophage enactment, cytolysis by normal killer cells, and Cytotoxic T lymphocytes. There are three kinds of immunosuppressive hematopoietic cells that are selected in the tumor microenvironment and assume a significant job in

insusceptible getaway: myeloid-inferred silencer cells (MDSCs), tumor-related macrophages (TAMs), and administrative T-cells (Tregs). Penetrating MDSCs produce arginase-I to utilize L-arginine (which is a basic amino corrosive that is critical for the capacity of T-cells) to hose T-cell response.⁸⁻¹⁰

HPV malignant growth is a key model for understanding tumor safe evasion.¹¹ Although HPV disease is normal, HPV-related malignancy is very rare.¹² Various investigations have demonstrated that HPV-contaminated cells effectively advance stromal irritation and collaborate with nearby microenvironment to advance oncogenesis.¹³ In HPV-related malignancy, there is a feeble T-cell reaction to HPV early antigens in blood alongside elevated levels of TILs that need cytotoxicity and expanded quantities of IL-10 creating Tregs.¹⁴ HPV+ Head-and-neck squamous cell cancers additionally has significant levels of T-invaded lymphocytes with high PD-1 articulation, and significant levels of PD-L1 articulation on tumor cells, and TAMs.¹⁵ These outcomes mean that a characteristic immunologic reaction is produced against HPV Head-and-neck squamous cell cancers which incite PD-1/PD-L1 pivot and may confine the limit of TILs to come full circle an immunologic assault.

Immune tolerance

Immune toerance is characterized as inability to mount a resistant reaction to antigen. Tumor cells are heterogeneous with nonuniform articulation of tumor-related antigens and tumor-explicit antigens (TSAs).¹⁶ Head and neck cancer cells with elevated levels of tumor-explicit antigens are bound to be recognized by the safe framework and wiped out when contrasted with Head-and-neck squamous cell cancers cells with no or low degrees of tumor-explicit antigens which display low immunogenicity and break from resistant surveillance.^{17,18} The interchange between tumor antigen and TA-explicit is important for Cytotoxic T lymphocytes acknowledgment and tumor cell pulverization. antigen processing machinery segments work pair to produce antigenic peptides, translocate into endoplasmic reticulum, load MHC Class I H chain with peptides, lastly transport MHC Class I particles to the cell surface to display the

peptide to T-lymphocytes.¹⁹ Tumor cells can possibly diminish T cell-interceded acknowledgment by downregulating or changing HLA I atoms or potentially antigen processing machinery segments to constrict antigen introduction.

Disruption of T cell regulation

T cell receptors associate with co-investigating ligands and co-stimulatory receptors to give T-cell signal acknowledgment. Malignant growth cells repress T-cell-interceded acknowledgment and initiation by downregulating MHC I antigen introduction to endogenous T cell receptors and furthermore through the inhibitory co-stimulatory receptor pathways.²⁰ Two of the most usually included checkpoint inhibitory components are CTLA-4 and PD-1/PD-L1, which act at prior and later phases of insusceptible reaction to tumors. CTLA-4 rivals CD28 receptor, an initiating co-stimulatory receptor, for authoritative to B7 ligand (CD80 and CD86) found on APCs, bringing about T-cell inactivation. In ordinary cells, PD-1 ties to its ligands PD-L1/PD-L2 to lessen T-cell effector movement and end invulnerable reaction. In any case, PD-L1 is overexpressed in most of tumors, and this resistant brake signal is embraced by cells to avoid invulnerable elimination.

Different types of Immunotherapy in Head and Neck Cancer

Checkpoint Inhibitor

Allison made a major leap forward in the field of invulnerable oncology by setting up another idea that, aside from antigen introduction, enactment of cytotoxic T cells required an optional costimulatory sign to accomplish antitumor invulnerability. The revelation of inhibitory pathways, which stifle T-cell movement prompting tumor development, made a major transformation in the field of immunotherapy. Obstructing these inhibitory pathways by means of monoclonal antibodies, which are generally called checkpoint inhibitors, has demonstrated to be probably the most ideal approaches to relapse tumor.²¹⁻²³

Checkpoint hindrance has an assortment of utilizations in resistant oncology running from lung malignant growth to oral cancer.²⁴⁻²⁷ Among checkpoint inhibitors, hostile to CTLA-4 and against PD-1 antibodies are generally utilized for helpful purposes. Hostile to CTLA-4 antibodies have more extensive T cell work contrasted with against PD-1 antibodies, which reestablishes that enemy of CTLA-4 has more reactions than hostile to PD-1. As of late, against PD-L1 ligand is in the late period of business improvement for clinical practice with name durvalumab. Ipilimumab was endorsed by the European Organization for Research and Treatment of Cancer (EORTC) for the adjuvant treatment in patients with high-chance melanoma.²⁸ The blend of nivolumab and ipilimumab was affirmed in the United States for the treatment of BRAF-negative melanoma. Apart from hostile to PD-1 and against CTLA-4 antibodies, other checkpoint inhibitor receptors, for example, lymphocyte-activation gene 3 (LAG3), mucin domain3 (TIM-3), and T-

cell immunoglobulin have shown restorative impacts in clinical preliminaries in mix with PD-1 agents.^{29,30} The mix of radiation and PD-1 barricade was demonstrated to be synergistic in the treatment of cancer.³¹

Targeted monoclonal bodies

Monoclonal antibodies are produced using either human or murine neutralizer parts that bound to tumor-related antigen prompting ADCC. The best model in this gathering which is utilized remedially is counter acting agent against epidermal growth factor. Deregulation of epidermal growth factor prompts the restraint of apoptosis, intrusion, metastasis, and angiogenic potential.^{32,33} Compared to typical mucosa, epidermal growth factor level is expanded in 95% of Head-and-neck squamous cell cancers.³⁴ In Head-and-neck squamous cell cancers, the statement of epidermal growth factor is expanded, which corresponds with hostility of the malignancy. EGFR is answerable for tumor movement in numerous strong tumors, particularly in Head-and-neck squamous cell cancers.³⁵ Monoclonal antibodies, for example, cetuximab and panitumumab are epidermal growth factor focused on treatments; they are demonstrated to be successful against either alone or in blend with radiotherapy.³⁶

Adoptive immunisation

The significance of T cells in the end of malignant growth cells is a settled marvel. Lymphocytes from tumor test or blood of the patient are collected, extended, and reintroduced for antitumor immunity.^{37,38} The viability of T cells can be emphasized by bringing explicit antigen receptor into the cells by hereditary building, consequently upgrading their capacity to perceive tumor antigen.³⁹ Encouraging outcomes were found in 93 patients treated for metastatic melanoma utilizing adoptive cell transfer. This procedure has demonstrated excellent to treat metastatic strong tumors, which are generally hard to treat with customary strategies. Adoptive cell transfer with human papillomavirus – directed tumor-penetrating T cells has indicated promising outcomes in patients with cervical cancer.⁴⁰ Improvements in adoptive cell transfer are picking up force as a result of its prosperity rate; presentation of explicit antigen receptor into T cells will slaughter disease cells specifically. Large-scale generation for clinical utilization of adoptive cell transfer is endeavored by building antigen receptors: one strategy is through complemented introduction of significant histocompatibility complex and the other is through chimeric antigen receptor.

Cytokine immunotherapy

Cytokines are sub-atomic delivery system that permit the cells of our resistant framework to speak with one another to create an organized reaction to an objective antigen (disease cell). This immunotherapy animates insusceptible cells through a convoluted pathway, in this way expanding coordination between tumor cells and stromal cells. As of late, various cytokines have been created for the treatment of malignant growth. Two cytokines as of now affirmed by the

FDA for clinical reasons for existing are interferon α (IFN α) and interleukin 2 (IL-2).

IFN α

These cytokines when infused subcutaneously in renal cell carcinoma have demonstrated tumor relapse. These have demonstrated magnificent outcomes in organize 3 melanoma. The blend of IFN α and IL-2 indicated fractional reaction and higher toxicity.⁴¹

IL-2- It is a FDA-endorsed cytokine for metastatic melanoma. These cytokines increment level of Natural Killer cells and tumor-infiltrating lymphocytes (TILs) in the lesion.^{42,43} Perilymphatic IL-2 organization has expanded the endurance pace of patients with Head-and-neck squamous cell cancers⁴⁴ expanded tumor receptive T cells were found in patients who experienced monoclonal counter acting agent treatment after surgery.⁴⁵

Conclusion

Cancer treatment is one of the difficult perspectives in the treatment modalities extending from medical procedure to chemotherapy and radiation are yielding blended outcomes. To defeat this obstacle, more up to date imaginative methodologies are expected to lessen the dreariness and mortality of the patients. The weaknesses of medical procedure, for example, repeat of tumor or non-resectable injury and poisonous quality of radiotherapy or chemotherapy can be significantly diminished by immunotherapy when utilized in blend with these treatment modalities. Principle issues with immunotherapy is the absence of strong prescient markers of viability, particularly when the expenses of these medications are considered. It is still ongoing test for the treatment of head and neck cancer.

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Conflict of Interest

None.

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