INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Immunotherapy in Head and Neck Cancer When, How and Why?

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Review question / Objective: **In patients with advanced or recurrent/metastatic head and neck cancer, immunotherapy alone or in combination with radiotherapy and chemotherapy, compared with standard therapy, can promote increased overall survival and progression-free survival by reducing associated adverse events?**
Condition being studied: **Patients with advanced or recurrent/metastatic head and neck cancer were the targets of the study. Based on the risk factors that promote the development of this neoplasm, head and neck cancer can be divided into two subtypes: non-associated Human Papilloma Virus (HPV) head and neck cancer and head and neck cancer associated with HPV. Therefore, the administration of immunotherapy (immune checkpoint inhibitors, vaccines, and oncolytic viruses) was explored in patients with head and neck cancer and, more strictly, in patients considering PD-L1 expression and HPV infection.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 August 2022 and was last updated on 03 August 2022 (registration number INPLASY202280016).

INTRODUCTION

Review question / Objective: **In patients with advanced or recurrent/metastatic head and neck cancer, immunotherapy alone or in combination with radiotherapy and chemotherapy, compared with standard therapy, can promote increased overall survival and progression-free survival by reducing associated adverse events?**

Rationale: **Check the effectiveness of immunotherapy in patients with head and neck cancer, based on the administration of monoclonal antibodies such as anti-**

PD-1, anti-PD-L1, anti-CTLA-4, anti-NKG2A, vaccines targeting Human Papilloma Virus and Epstein Barr, and, oncolytic viruses such as T-VEC.

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METHODS

Search strategy: The authors used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, to perform this systematic review to better understand role of immunotherapy in head and neck cancer. To achieve this objective, the literature search was carried out using the PubMed database. In this database, the keywords used for the research will be "head and neck neoplasms", "therapeutics", "immune checkpoint inhibitors", "cancer vaccines", and "oncolytic viruses". In this research, all selected articles will be properly identified, analyzed, and selected based on inclusion and exclusion criteria. Definition of these criteria ensures that all articles selected for study present accurate and relevant information about the theme addressed. According to the inclusion criteria, clinical trials, meta-analyses, randomized clinical trials, reviews and systematic reviews will be selected. It should also be noted that all information is obtained from free full texts, all of which are written in English and published between 2016 and 2022. In parallel, the exclusion criteria refer to all literature that doesn't meet the above-mentioned criteria.

Participant or population: Patients with advanced or recurrent/metastatic head and neck cancer. In addition, patients with head and neck cancer were also studied more narrowly based on PD-L1 expression and HPV infection.

Intervention: Efficacy of the administration of monoclonal antibodies directed to the blockade of PD-1, PD-L1, CTLA-4, and NKG2A as monotherapy or in combination. The combination of these agents with chemotherapy and radiotherapy was also investigated. In addition, the efficacy of therapeutic vaccines directed against the Human Papilloma Virus and Epstein Barr, as well as oncolytic viruses such as T-VEC, was also explored in patients with head and neck cancer.

Comparator: Overall survival rates, progression-free survival rates, objective response rates, median durations of responses and adverse events were compared between different immunotherapy strategies. Not applicable.

Study designs to be included: Clinical trials, randomized clinical trials, and Reviews

Eligibility criteria: According to the inclusion criteria, clinical trials, meta-analyses, randomized clinical trials, reviews and systematic reviews about patients with head and neck cancer will be selected. It should also be noted that all information is obtained from free full texts, all of which are written in English and published between 2016 and 2022. According to the inclusion criteria, clinical trials, meta-analyses, randomized clinical trials, reviews and systematic reviews will be selected. It should also be noted that all information is obtained from free full texts, all of which are written in English and published between 2016 and 2022.

Information sources: The literature search was carried out using the PubMed database.

Main outcome(s): Human Papilloma Virus-directed therapeutic vaccines have become a strategy on the rise, given their ability to

induce a durable cellular and humoral immune response. Therefore, these represent a possible therapeutic option for HPV-positive patients, as monotherapy, or combined with other agents to potentiate the antitumour response. The combination of T-VEC with Pembrolizumab didn't enhance the antitumour response in patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC), thus contrasting with results obtained in other tumours. However, monotherapy with immune checkpoint inhibitors is the most impactful strategy in this neoplasm scenario, due to its ability to induce a durable antitumour response, prolonging the survival of patients with locally advanced, recurrent, or metastatic disease in the face of standard therapy. In addition, this strategy was also correlated with a higher quality of life and lower toxicity index. Although the combination of anti-PD-L1 agents with anti-CTLA-4 reveals an increase in antitumour immunity, patients with R/M HNSCC don't seem to benefit from this strategy. However, in the neoadjuvant setting, the addition of Ipilimumab to an anti-PD-1 agent showed promising results in patients with untreated squamous cell carcinoma in the oral cavity. When combining immune checkpoint inhibitors with chemotherapy, in different scenarios, patients tend to reveal higher response rates and long-term clinical benefits, in contrast to the results obtained when combining immune checkpoint inhibitors with radiotherapy. Although it has proved to be an advantageous strategy for these patients, the toxicity associated with therapy is still a barrier to overcome.

Additional outcome(s): It should be noted, therefore, that immunological checkpoint inhibitors are the most impacting strategy in these patients, inducing variable response rates between 13% and 22%, in addition to promoting an increase in median overall survival at 2 months compared to standard therapy. In view of the associated adverse events, they are mild and easily manageable. With the objective of improving the antitumor response, the different immunological checkpoint inhibitors were combined, as well as their combination with chemotherapy and radiotherapy. However, it can be highlighted that only the addition of Ipilimumab and chemotherapy potentiated the increase in response rates (84.6% and 22.7% (chemotherapy) versus 33% (Ipilimumab)) and overall survival compared to monotherapy with immune checkpoint inhibitors. Therapeutic vaccines directed at HPV proved to be safe and capable of inducing cellular and humoral immunity, which is important for tumor regression. In turn, T-VEC combined with Pembrolizumab induced response rates (13.9%) similar to Pembrolizumab monotherapy, in addition to being unable to potentiate the medians rates of overall survival (5.8 months) and progression-free survival (3.0 months) compared to Pembrolizumab monotherapy.

Quality assessment / Risk of bias analysis: Quality control was performed individually, removing duplicates articles and information, as well as by only using published articles with impact factor and quartil, as well as indexed.

Strategy of data synthesis: The results were analyzed systematically, based on the previously defined inclusion criteria, and all studies that met these criteria were included. The most salient data from the studies were then collected, such as objective response rate, overall survival rate, progression-free survival rate, occurrence-free survival rate, median response duration and adverse events.

Subgroup analysis: HPV-positive patients versus HPV-negative patients and PD-L1 positive patients versus PD-L1 negative patients.

Sensitivity analysis: One-at-a-time (OAT).

Language restriction: Only english articles are accepted.

Country(ies) involved: Portugal.

Keywords: Head and neck neoplasms, therapeutics, immune checkpoint

inhibitors, cancer vaccines, oncolytic viruses.

Dissemination plans: Submission to a quartil 1 and High impact journal, as weel as present in Conferences trough poster or oral communication.

Contributions of each author:

Author 1 - Daniela Pereira - Author 1 developed the conceptualization, methodology, and investigation and wrote the manuscript.
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