The action of Palbociclib on the Cell Cycle of Head and Neck Squamous Cell Carcinoma: A Systematic Review

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Abstract

This study evaluates the action of Palbociclib in the cell cycle of HPV-negative head and neck squamous cell carcinoma. Initially approved for HER2- and HR + breast cancer. Palbociclib induces cellular senescence, increases the efficacy of Cetuximab, restores p16 function and decreases phosphorylated Rb, suggesting an improvement in survival in both cancers.

Keywords

- cyclin-dependent kinase inhibitor proteins
- tumor agnostic therapy
- squamous cell carcinoma of head and neck
- palbociclib
- medical oncology

Introduction

Tumor cells have various molecular characteristics, which, due to their abundance, end up hindering the effectiveness of traditional cancer treatments, whose approach, in most cases, is tissue-based rather than molecular. From the moment it became possible to know the molecular alterations of the cells, and to carry out genetic sequencing of the tumor, more specific treatments were created, the so-called tumor-agnostic treatments, aimed at this cellular information, and not dependent on the type of tissue the cell is part of. Thus, it is necessary to monitor the progression of the tumors and its molecular alterations throughout treatment, since it ends up being highly selective to certain specific molecular alterations, so the drugs used in this type of treatment are active against different subtypes of oncogene-dependent cancers.[1–6]

In head and neck squamous cell carcinoma, there is usually activation of the epidermal growth factor receptor (EGFR). In human papillomavirus (HPV)-negative head and neck squamous cell carcinoma (HNSCCs) cases, which show a better response to cyclin inhibitors, the development pattern is usually based on inactivation of p16INK4A and overexpression of cyclin D1, resulting in hyperactivation of cyclin-dependent kinase 4 and 6 (CDK4/6). This is because the loss of p16 functionality allows CDK4/6 to complex with cyclin D and then phosphorylate and inactivate Rb, releasing E2F and progressing to the G1 phase, after the first checkpoint, and advancing to the S phase of the cell cycle. Thus, loss of checkpoint regulation leads to uncontrolled cell proliferation, allowing cancer cells to multiply exacerbatedly.[7–13]

Increased expression of cyclin or CDKs or decreased levels of endogenous CDK inhibitors, such as INK4 or CIP/KIP, is found in many cancers, while mutations in genes encoding CDKs that cause cancer are rare. In this way, CDKs end up becoming targets for cancer therapies.[14,15]

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Dual CDK4/6 inhibitors have shown significant efficacy in preclinical and clinical cancer therapies, especially in breast cancer, as single agents or combined with hormonal treatments, chemotherapy, radiotherapy, or immunotherapy. It is, therefore, considered necessary to review the action of these drugs on the cell cycle of cancer cells, to provide us with therapeutic possibilities[14,15]

Although CDK4/6 inhibition results in a decrease in cell multiplication and leads to an interruption of the cell cycle, it is likely that cell senescence or senescence-like activity is a crucial mechanism associated with the clinical efficacy of this medication. Cellular senescence is the phenomenon in which a cell experiences a permanent and irreversible interruption of its growth in response to cellular stresses, such as unrepaired DNA damage, which renders it resistant to mitogenic stimulation and oncogenic challenges.[8]

An example of a CDK4/6 inhibitor is palbociclib, which is currently approved by the Food and Drug Administration (FDA) only for the treatment of breast cancer, but has been the subject of several clinical trials in other types of cancer, including head and neck squamous cell carcinoma.[14,16] Palbociclib is a highly effective and selective oral inhibitor of the cyclin-dependent kinase CDK4/6, with robust preclinical data supporting its effectiveness in tumors that show retinoblastoma protein expression.[17]

This inhibitor acts on cells in such a way as to decrease phosphorylated Rb, and consequently restore the function of p16, bringing back the effectiveness of the first G1 checkpoint, causing cell replication to occur only in healthy cells, and preventing the exacerbated multiplication of mutant cancer cells. In other words, this drug inhibits the progression from G1 to S in defective cells, leaving them in what is known as a senescent state, which allows these cells to respond more effectively to conventional treatments.[8,12,13]

The present study aims to understand how the genetic composition of head and neck squamous cell carcinoma cells is affected by CDK4/6 cyclin inhibitors, especially palbociclib, to understand, based on a comparison between the cellular alterations that trigger this cancer, how the aforementioned drug, currently used in HER-negative breast cancers, has been responding in the therapy of cancers of other systems.

Materials and Methods

The current systematic review, conducted without a meta-analysis, is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42024539528.

Sources of Information

A systematic search was performed in the PubMed and LILACS databases from 2013 to 2024. In addition, clinical trial registries, including ClinicalTrials.gov, were searched. The articles included were in Portuguese and English. In addition, the bibliography of articles and reviews from the present study was manually selected for additional study eligibility.

Eligibility Criteria

The study characteristics are expressed in the population, intervention, control group, outcome format (PICO):

Population: Patients diagnosed with HPV-negative head and neck squamous cell carcinoma.

Intervention: To evaluate the effectiveness of palbociclib's response in head and neck squamous cell carcinoma, taking into account the drug's effect on the tumor's cell cycle.

Control: Cells with a regular cell cycle, without defects or overexpression of the factors involved, and cells with alterations in the factors involved resulting in head and neck squamous cell carcinoma.

Outcome: To understand how palbociclib acts, and how it can help in the regression of head and neck squamous cell carcinoma.

In addition, only articles that met the inclusion criteria and did not include the exclusion criteria were eligible.

Inclusion criteria: Articles in Portuguese or English with the keywords *squamous cell carcinoma of the head and neck*, *palbociclib/palbociclib*, *CDK4/6 inhibitors*, or *tumor-agnostic/-tumor agnostic* in their title or abstract.

Exclusion criteria: Articles outside the periodicity of 2013 to 2024, or that present studies on HPV-positive head and neck squamous cell carcinoma, or that bring any drug association other than palbociclib associated with cetuximab.

Data Collection Process

A total of 37 articles of interest to the research were obtained from the LILACS and PubMed databases. During screening, 24 articles were obtained, 13 of which were excluded due to duplication between the databases. All texts were actively searched and reviewed by two reviewers. If there was no agreement, the conflict was resolved by discussion and consensus. In the event of disagreement over the inclusion of a citation, the article was independently assessed and revised by another reviewer. If disagreement persisted, a fourth reviewer decided whether or not to include the article. The article selection process is outlined in ►**Fig. 1**, describing the reasons that led to the exclusion of some of the articles.

As for the eligibility criteria, 14 articles were excluded due to incompatible study design, 4 were excluded due to incompatible population, and in 4, the study medication was not compatible. Of the remaining 4 articles, 2 were included for study analysis, and the other 2 were excluded due to incompatible drug combinations.

Risk of Bias between Studies

The methodological quality of the study was assessed using the Joanna Briggs Institute (JBI) tool, so that the two studies included in this article underwent a thorough assessment, following the criteria instructed by the tool in question. They were then placed in the Risk-Of-Bias VISualization (Robvis) system, thus generating ►**Fig. 2**, which shows results related to:

Bias due to the randomization process, which presented a low risk of bias in both articles.

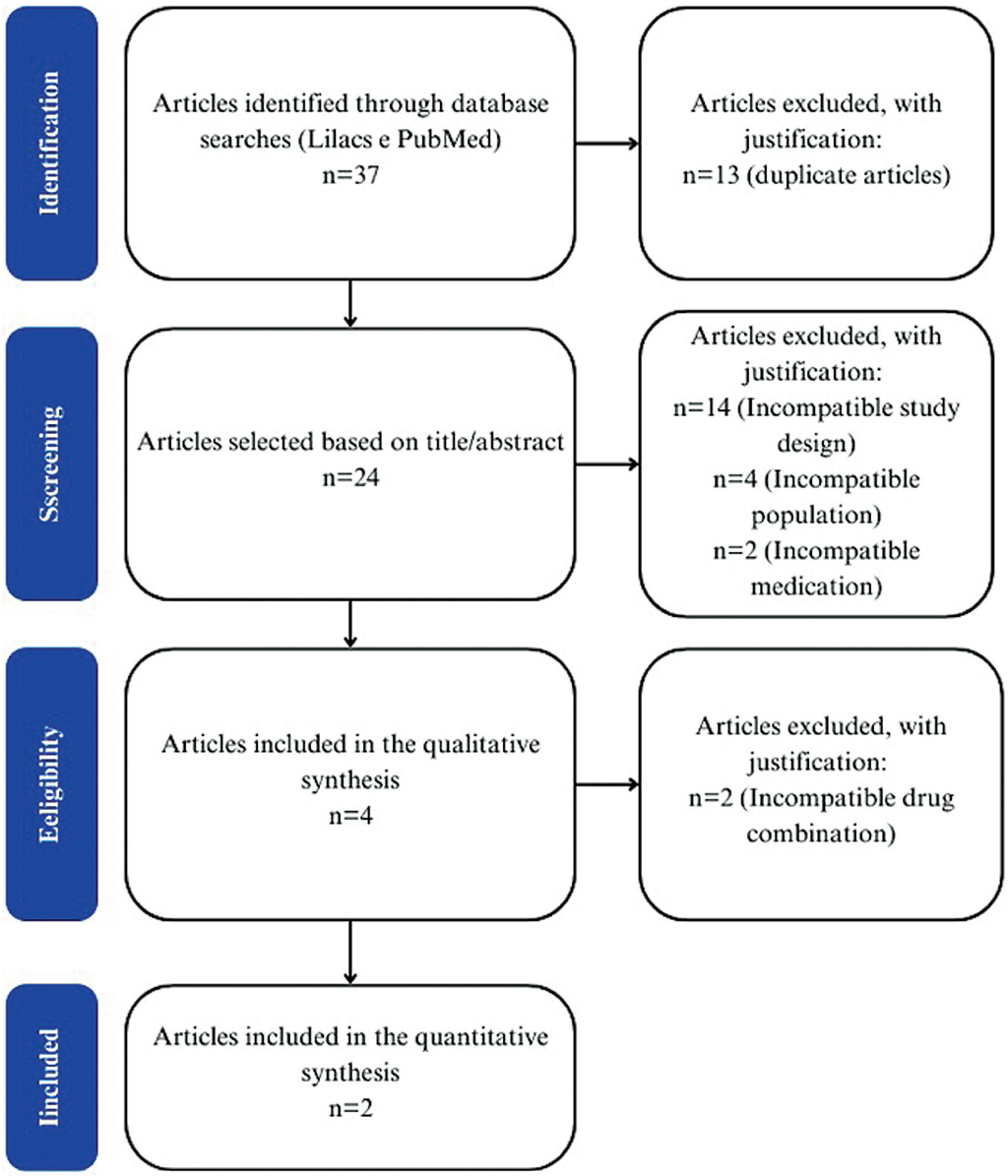

Fig. 1 Flowchart of the systematic review process.

Bias due to deviations from the intended interventions, which showed high bias in both studies, since the deviations were not very well elucidated in the studies, which could lead to an ambiguous interpretation of the results.

Bias due to lack of outcome data was low in the study by Adkins et al (2019) and worrying in the study by Michel et al (2016), since the latter did not provide results for the partial response criterion.

Finally, measurement and selection bias were low in both studies, leading to an overall study bias considered to be low.

For both studies, palbociclib was administered at a dose of 125 mg/day orally, taken on days 1 to 21 of each 28-day cycle. Cetuximab was administered at a dose of 400 mg/m^2 intravenously on the first cycle day 1 and then once a week at a dose of 250 mg/m^2.

Results

The study by Michel et al. (2016)[7] shows that of the 9 patients included in the study, 6 were resistant to Cetuximab, and 4 were resistant to platinum, with 1 of the 9 being resistant to both medications. It is worth noting that most of the patients had a history of smoking. As for the response to the combination treatment of palbociclib and cetuximab, the best tumor response was seen in two patients, and there was no description of the patients who had a partial response. Stable disease was seen in 6 patients and disease progression was observed in only 1 patient. In the present study, the average duration of response was 112 days.

The study by Adkins et al. (2019)[9] assessed 62 patients diagnosed with HNSCC, most commonly in the larynx and oral cavity. They were divided into 2 groups, the 1st with 30 patients with HPV-negative HNSCC without previous use of

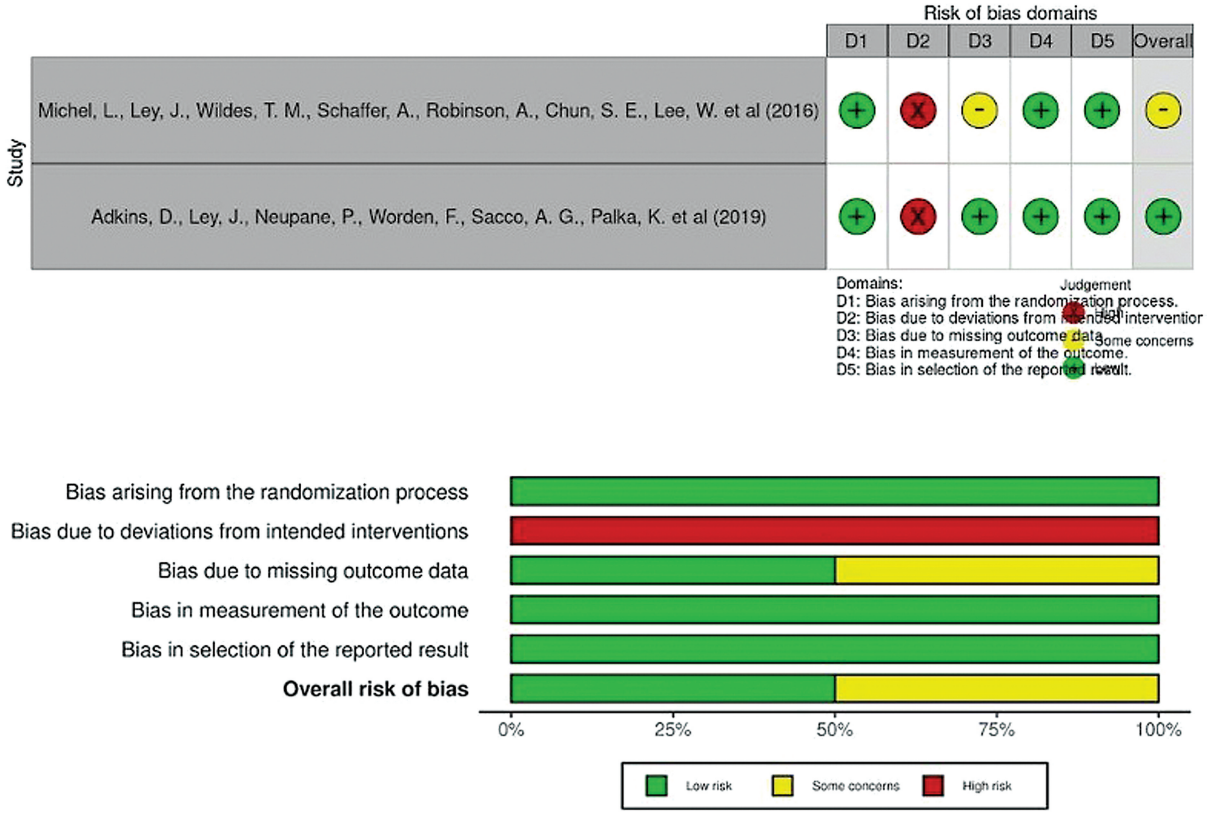

Fig. 2 Bias risk analysis using the Risk-Of-Bias VISualization (robvis) platform.

cetuximab, but resistant to platinum, 2 of whom died early. Of the 28 evaluated in this group, 3 showed the best response and 8 showed a partial response, 14 maintained stable disease, and 3 progressed. The median duration of response for this group was 4 months.

In the 2nd group, 32 patients were selected who were resistant to the use of cetuximab in monotherapy; of these, 5 were not evaluable. Of the remaining 27, 1 showed a better response and 4 a partial response, 13 showed disease stability, and the other 9 progressed. The median duration of response for this group was 6 months. The groups were followed up for an average of 5.4 months, making it possible to extract the results described. ►**Table 1**.

Discussion

The present systematic review shows that the use of a CDK4/6 cyclin inhibitor, palbociclib, is capable of bringing a cancer cell to a state of senescence, regulating cell proliferation, which is out of control, and restoring the function of the G1 to S checkpoint of the cell cycle, which was lost during the mutation that turned the cell into a cancer.[8]

The drug in question is part of the treatment protocol for HR+ breast cancer only and is not approved by the FDA for any other type of tumor. However, clinical trials show relative evidence of this drug in other cancers, including HPV-negative HNSCC, which was the focus of the current study.

Looking at other systematic reviews, the similarities between the most common defects found in the cell cycle of head and neck squamous cell carcinoma and HR+ breast cancer are clear. Van Caloen et al. (2019)[10] shows that HNSCC is driven by inactivation of the p16-INK4a and TP53 proteins, as well as amplification of the CCND1 protooncogenes and inactivation of the CDKN2A tumor suppressor gene. Similarly, Clark et al. (2016)[17] found that palbociclib showed greater antiproliferative effects in HR+ breast cancer cells through the loss of p16 or the increase in CCND1, and, thus, after completing the 3 phases of the Palbociclib: Ongoing Trials in the Management of Breast Cancer (PALOMA) study, was included as a therapeutic option for this type of tumor, in association with antiestrogens, including letrozole and fulvestrant.

This similarity gives rise to the guiding question of this systematic review, which asks how palbociclib, approved only for HR+ breast cancer, can also be effective in head and neck squamous cell carcinoma. There are no studies in the literature that clearly demonstrate this mechanism, but some describe results that allow us to think about a future inclusion of palbociclib, in association with an EGF2 inhibitor, cetuximab, to prolong the prognosis of HNSCC.

Billard-Sandu et al. (2020)[12] point out that HPV-negative HNSCC generally has a poor prognosis, which encourages the search for new treatment strategies. Given that EGFR inhibitors show a satisfactory response in the treatment of this cancer, the pattern of genetic alterations found in the pathology in question has the potential to cause a decrease in the effectiveness of EGFR inhibitors, corroborating with the lower survival of patients.

Table 1 Results of selected articles relevant to the study

Author (year)	Title	Study country	Number of patients	Number of platinum-resistant patients	Number of patients resistant to cetuximab	Number of evaluable patients	Best response (n = patients)	Partial response (n = patients)	Stable disease (n = patients)	Disease progression (n = patients)
Michel, L., Ley, J., Wildes, T. M., Schaffer, A., Robinson, A., Chun, S. E., Lee, W. et al. (2016)[7]	Phase I trial of palbociclib, a selective cyclin dependent kinase 4/6 inhibitor, in combination with cetuximab in patients with recurrent/metastatic head and neck squamous cell carcinoma.	USA	9	3	6	9	2	–	6	1
Adkins, D., Ley, J., Neupane, P., Worden, F., Sacco, A. G., Palka, K. et al. (2019)[9]	Palbociclib and cetuximab in platinum-resistant and in cetuximab-resistant human papillomavirus-unrelated head and neck cancer: a multicenter, multigroup, phase 2 trial.	USA	62	30	32	55	4	12	27	12

For this reason, new medications are being studied to improve the prognosis of HNSCC, including palbociclib, which allows for slower disease progression, possibly explained by its action at a different stage of the cell cycle of these cells, when compared with cetuximab in monotherapy. The CDK4/6 cyclin inhibitor decreases phosphorylated Rb and, consequently, restores the function of p16, bringing back the effectiveness of the first G1 checkpoint, causing cell replication to occur only in healthy cells, and preventing the exacerbated multiplication of mutant cancer cells. In other words, this drug inhibits the progression from G1 to S in defective cells, leaving them in what is known as a senescent state, which allows these cells to respond more effectively to conventional treatments, including cetuximab.[8,12]

To confirm the hypothesis discussed in this paper, clinical trials were analyzed that studied the clinical response of several patients with HPV-negative HNSCC, using palbociclib associated with cetuximab. Analyzing the results of Adkins et al. (2019),[9] we see that of the 62 patients studied, only 12 showed disease progression, the others showed a complete or partial response, or kept the disease stable, bringing a favorable result, in relation to disease progression, when compared with the isolated use of drugs or even in relation to patients who underwent chemotherapy with platinum derivatives.

In this same study, it was shown that the duration of response, although satisfactory, was shorter with the use of the combination of palbociclib and cetuximab than with PD-1 inhibitors, but progression-free survival was higher in patients who used the combination compared with those who used monotherapy.

Looking at the results of the clinical trial by Michel et al. (2016),[7] of the 9 patients evaluated, only one showed disease progression, with the others showing a complete response or stabilization of the disease. Thus, it is argued that both the rate of disease control and the duration of response were superior in relation to the same parameters in monotherapy.

Finally, this systematic review presents important aspects, showing a clear correlation between the genetic alterations found in HNSCC and HR+ breast cancer, allowing the same CDK4/6 cyclin inhibitor to be used in both pathologies in association with the conventional medications already known for each of them. Therefore, the effectiveness of palbociclib in HNSCC is not clearly described, due to the lack of studies in the area, but the few that were found show that there is a possibility of including this medication in the therapeutic regimen for this cancer, requiring further clinical studies to strengthen this hypothesis.

Conclusion

The present systematic review indicates that the CDK4/6 inhibitor palbociclib has promising potential to induce senescence in tumor cells and modulate cell proliferation and is currently approved only for the treatment of HR+ and HER2- breast cancer. The preliminary studies discussed in this review suggest a possible applicability in other types of cancer, such as HPV-negative HNSCC, given the similarity in the mechanisms of cell cycle deregulation.

The clinical studies analyzed report that the combination of palbociclib with cetuximab demonstrated relevant antitumor activity, especially in cases resistant to platinum and to cetuximab itself, with superior results to monotherapy in terms of progression-free survival. However, the exact mechanisms by which palbociclib acts in this context are not yet fully elucidated. Furthermore, the scarcity of studies on this subject in the literature limits the strength of the conclusions, reinforcing the need for further clinical and preclinical investigations to validate the role of palbociclib in this therapeutic scenario.

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Authors' Contributions
MEBT: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, validation, writing – original draft; JPFdS: formal analysis, investigation, resources, validation, writing – original draft; ACdSAH: writing – review & editing, supervision, validation.

Conflict of Interests
The authors have no conflict of interests to declare.

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