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ADVANCES IN THE TREATMENT OF MELANOMA: THERAPEUTIC INNOVATIONS AND CLINICAL RESULTS IN THE FIGHT AGAINST SKIN CANCER

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Abstract: The treatment of melanoma has advanced significantly, transforming a scenario of low expectations into a model of success in precision oncology. The aim of this study is to develop a study on advances in the treatment of melanoma, identifying therapeutic innovations and clinical results in the fight against skin cancer. The methodological approach adopted in the study was a literature review, using databases of scientific articles that contributed to the theoretical basis of the work. The results indicate that immunotherapy , particularly with immune checkpoint inhibitors such as anti-CTLA-4 and anti-PD-1/PD-L1, has profoundly changed the prognosis of patients with metastatic melanoma, promoting long-lasting response rates and significantly extending overall survival in many cases. Similarly, target therapy, especially BRAF and MEK inhibitors, has proved effective in patients with specific mutations, offering a personalized and more precise approach to dealing with the disease. The conclusion is that therapeutic advances in the treatment of melanoma have had a positive and transformative impact, not only in clinical terms, but also in terms of patients' quality of life. However, the fight against skin cancer remains a constantly evolving field, requiring the continued commitment of the scientific community, health professionals and public policies.
Keywords: Melanoma. Skin cancer. Immunotherapy.

INTRODUCTION

Cutaneous melanoma represents approximately 5% of skin cancers, but is responsible for more than 80% of deaths related to the disease. Traditionally treated with surgery and chemotherapy, the results were limited, especially in metastatic cases. A deeper understanding of tumor biology and the immune system has paved the way for more effective approaches (Bernardi et al., 2024).

The discovery of specific mutations, such as the BRAF V600E mutation, present in around 40 to 60% of melanomas, has led to the development of selective inhibitors such as vemurafenib and dabrafenib. In combination with MEK inhibitors (e.g. trametinib), a significant increase in response rate and progression-free survival has been observed. However, acquired resistance is still a challenge, which has stimulated research into therapeutic combinations and new molecules (Corrales et al., 2022).

Immunotherapy has revolutionized the treatment of advanced melanoma. Antibodies that block immune checkpoints, such as anti--CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab, pembrolizumab), promote long-lasting responses in a significant proportion of patients. Clinical studies show a consistent increase in overall survival, with objective response rates of between 30% and 50% in monotherapy and over 60% in combination. Despite this, immune-mediated adverse events require specialized management (Alves *et al*., 2024).

Combining target therapies with immunotherapy has been investigated as a way of overcoming resistance and boosting responses. Ongoing clinical trials are evaluating the efficacy of triple or sequential regimens. In addition, the genomic and immunological characterization of tumours has made it possible to personalize treatment, optimizing patient selection and therapeutic response (Bernardi *et al.,* 2024).

Therapeutic advances have translated into a significant improvement in clinical outcomes. Studies show that median overall survival in metastatic melanoma, which used to be less than one year, now exceeds 36 months in certain subgroups. Patients' quality of life has also improved, especially with the use of immunotherapies, due to the sustained response and lower long-term toxicity (Angrish *et al*., 2021).

Despite advances, major challenges remain: resistance to treatment, still limited predictive biomarkers and unequal access to therapies. New lines of research include therapeutic vaccines, cell therapy (such as tumor-infiltrating lymphocytes - TILs) and the use of messenger RNA. The integration of molecular data, artificial intelligence and precision medicine is likely to further refine melanoma management (Zuqui *et al.,* 2023).

The treatment of melanoma has advanced significantly, transforming a scenario of low expectations into a model of success in precision oncology. Continued efforts in translational research, equitable access to innovations and combined strategies will be crucial to consolidate these advances and extend the benefits to patients (Dika *et al*., 2020).

The aim of this work is therefore to develop a study on advances in the treatment of melanoma, identifying therapeutic innovations and clinical results in the fight against skin cancer.

MATERIAL AND METHODS

This study is a narrative literature review with the aim of identifying, analyzing and summarizing the main therapeutic advances in the treatment of cutaneous melanoma, with an emphasis on recent innovations, clinical efficacy and the impact on survival and quality of life of patients.

The search for scientific articles was carried out in the *PubMed, Scopus, Web of Science, SciELO and LILACS* databases, covering publications between 2019 and 2024. The choice of time interval aimed to cover the main developments in the field, especially after the introduction of immunotherapies and target therapies.

The following descriptors and keyword combinations were used, with Boolean operators: "*melanoma" AND "treatment"; "targeted therapy" AND "melanoma"; "immunotherapy" AND "clinical outcomes"; "skin cancer" AND "therapeutic advances"; "checkpoint inhibitors" AND "survival" AND "melanoma" AND "therapeutic resistance*". The descriptors were applied in English, Portuguese and Spanish, where possible, and were based on the Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS).

Articles were included that presented clinical results on the use of immunotherapy or targeted therapies in the treatment of melanoma; clinical studies, systematic reviews, narrative reviews and meta-analyses and publications between January 2019 and March 2024.

Duplicate articles were excluded, as were studies dealing exclusively with ocular or mucosal melanoma and pre-clinical studies (in vitro or in animal models), unless they were directly related to mechanisms of therapeutic action;

The selection of articles was carried out in three stages: reading the titles and abstracts for initial screening; full reading of the selected articles to assess their suitability for the inclusion criteria; and extraction and systematization of the relevant data, including: type of treatment, mechanism of action, study design, population evaluated, response rates, overall survival and adverse effects.

Therefore, the analysis was carried out qualitatively, with an emphasis on comparing the different treatments and their clinical outcomes.

RESULTS AND DISCUSSION

In recent decades, significant progress has been made in melanoma therapies. Although the incidence of the disease has shown continuous growth, the mortality rate associated with advanced-stage melanoma has fallen significantly in the last decade, driven by recent therapeutic innovations (Ahmed *et al*., 2020).

Genetic factors related to the development of melanoma include mutations in genes such as BRAF, NF1 and NRAS. Traditionally, treatment involved surgery, radiotherapy and systemic chemotherapy. However, the introduction of target therapy and immunotherapy has substantially changed the therapeutic landscape of the disease (Henley *et al.,* 2020).

The management of advanced melanoma, in particular, requires the joint action of different medical specialties and the use of combined therapies. Strategies that combine different therapeutic modalities, such as immunotherapy and targeted treatments, have demonstrated synergistic effects and better clinical outcomes in certain patient profiles (Sabag *et al*., 2020).

Currently, several clinical trials are investigating innovative pharmacological agents, with a special focus on immunotherapy and targeted therapies. In this context, pre-clinical studies play an essential role, as they allow the identification of new molecular targets with therapeutic potential. Among the most promising targets are CD126, CSPG4, CD70 in combination with B7-H3, and the αvβ3 integrin (Ernst Giubellino, 2022).

In addition, emerging therapies have been consolidated as innovative therapeutic approaches, such as the use of oncolytic viruses and interventions aimed at intensifying immunotherapy efficacy. However, it remains a challenge to accurately assess and predict the efficacy of each therapeutic approach in individual patients (Carlino; Larkin, 2021).

Although immunotherapy represents a transformative milestone in the fight against melanoma, especially in patients who did not respond to previous therapies, its effectiveness still varies substantially between individuals. It is estimated that around half of melanoma patients achieve prolonged survival with this type of treatment (Steininger *et al.,* 2021). For this reason, current research efforts are focused on identifying biomarkers that are predictive of immunotherapy response and strategies to increase its effectiveness in refractory cases (Steininger *et al*., 2021).

Even so, there are still significant challenges associated with conventional therapies. Due to its aggressive and adaptable nature, melanoma can develop resistance to current treatments, favoring recurrence and tumor progression (Lazaroff; Bolotin, 2023).

Furthermore, interventions such as chemotherapy have high toxicity, since they also affect healthy cells, resulting in adverse effects such as nausea, hair loss, fatigue, among others (Sood *et al*., 2021). In this sense, the search for therapies that preserve efficacy while minimizing side effects continues to be a priority in improving melanoma treatment.

Conventional treatments have shown limited efficacy in cases of advanced melanoma and are often associated with unfavorable prognoses. This scenario highlights the urgent need for more effective therapeutic approaches, capable of increasing survival rates and providing patients with a better quality of life (Massand; Neves, 2021).

The treatment of advanced melanoma generally requires interdisciplinary action, with the application of combined therapies or the incorporation of new therapeutic agents in order to achieve more satisfactory clinical responses. The integration of different therapeutic strategies, such as immunotherapy and target therapies, has shown synergistic effects and superior results in certain patient profiles (Sabag *et al.,* 2020).

Currently, several clinical trials have been dedicated to investigating combined therapeutic regimens, with the aim of identifying the most effective strategies for different subgroups of patients affected by melanoma (Dal'ava *et al*., 2022).

The therapeutic field of melanoma has undergone a remarkable transformation, driven by the introduction of immunotherapies and targeted therapies, which have reshaped the clinical approach to the disease. Although traditional interventions such as surgery, radiotherapy and chemotherapy are still used, their limitations in the management of advanced cases reinforce the need for ongoing research into innovative and integrated approaches (Silva *et al.,* 2023).

In this context, there is a pressing need to develop new pharmacological agents that act on specific molecular pathways related to the growth and progression of melanoma (Barros *et al*., 2024).

Targeted therapies have emerged as a promising alternative by exploiting the genetic and molecular singularities of melanoma tumors. As research advances and clinical trials are carried out, a more effective and personalized therapeutic future is in sight, with the potential to increase survival and quality of life for patients affected by the disease (Teixido *et al*., 2021).

CONCLUSION

Throughout this work, it has become clear that advances in the treatment of melanoma represent a significant milestone in modern oncology, especially with regard to the evolution of therapeutic strategies and the improvement of clinical outcomes for patients affected by this aggressive form of skin cancer. The current panorama is the direct result of intense efforts in translational research, pharmacological development and integration between different therapeutic modalities.

Immunotherapy, particularly with immune checkpoint inhibitors such as anti-CTLA-4 and anti-PD-1/PD-L1, has profoundly changed the prognosis of patients with metastatic melanoma, promoting long-lasting response rates and significantly extending overall survival in many cases. Similarly, targeted therapy, especially BRAF and MEK inhibitors, has proved effective in patients with specific mutations, offering a personalized and more precise approach to dealing with the disease.

Although these innovations have represented great achievements, tumor heterogeneity, acquired resistance mechanisms and associated adverse effects continue to challenge clinical practice, requiring constant review and refinement of therapeutic strategies. In this context, precision medicine, studies with combined therapies and the development of predictive biomarkers are emerging as promising ways to maximize the benefits of treatment and reduce its limitations.

In addition, the incorporation of new diagnostic technologies, the strengthening of early screening policies and population awareness of melanoma risk factors are fundamental pillars for reducing mortality and ensuring greater therapeutic efficacy. The future points to an increasingly integrated, interdisciplinary and patient-centred approach, in which science, innovation and humanization go hand in hand.

In conclusion, therapeutic advances in the treatment of melanoma have had a positive and transformative impact, not only in clinical terms, but also in terms of the quality of life of patients. However, the fight against skin cancer remains a constantly evolving field, requiring the continued commitment of the scientific community, health professionals and public policies so that progress is consolidated and reaches all individuals affected by this disease in an equitable manner.

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