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Quality of Life in Patients with Metastatic or Unresectable Melanoma: Is Monotherapy with Nivolumab Preferred Over Combination Therapy?

Calidad de vida en pacientes con melanoma no resecable o metastásico: ¿es la monoterapia con Nivolumab preferible frente a la terapia combinada?

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RESUMEN

Introduction: Immune checkpoint inhibitors have ushered in the melanoma treatment revolution. The aim of this review lies in evaluating whether the therapeutic combination of nivolumab and relatlimab leads to an improvement in both survival and quality of life compared to the exclusive use of nivolumab in patients suffering from metastatic or unresectable melanoma. **Methods:** Narrative review based on evidence published in PubMed, Scopus, Scielo and Embase databases. **Results:** The analysis demonstrates substantial benefits in terms of progression-free survival, and furthermore, this therapeutic combination is well-tolerated by patients. Various risk factors, including genetic predisposition, intermittent exposure to solar radiation, and the number of nevi present, contribute to the development of melanoma. To address this disease, the TNM staging system stands as a crucial tool in classification and prognostic estimation. It is important to note that, in localized cases, surgery plays an essential role, while in more advanced situations, pharmacological modalities, especially those involving immune checkpoint inhibitors, emerge as fundamental. The assessment of quality of life finds its expression through Patient-Reported Outcome (PRO) questionnaires, playing a pivotal role in medical decision-making. Patients who receive detailed information about the risks and benefits associated with adjuvant anti-PD1 immunotherapy express greater satisfaction with their medical choices. **Conclusions:** This review provides evidence that the therapeutic combination of nivolumab and relatlimab yields significant improvements in the survival of patients with metastatic melanoma.

Key words: Melanoma, Neoplasm Metastasis, Quality of Life, Nivolumab, Combination Drug Therapy. (Source: MeSH).

SUMMARY

Introducción: Los inhibidores de puntos de control inmunológico han inaugurado una revolución en el tratamiento del melanoma. El objetivo de esta revisión radica en evaluar si la combinación terapéutica de nivolumab y relatlimab conduce a una mejora tanto en la supervivencia como en la calidad de vida en comparación con el uso exclusivo de nivolumab en pacientes que padecen melanoma metastásico o irresecable. **Métodos:** Revisión narrativa realizada basada en evidencia publicada en las bases PubMed, Scopus, Scielo y Embase. **Resultados:** El análisis demuestra beneficios sustanciales en términos de supervivencia libre de progresión y, además, esta combinación terapéutica es bien tolerada por los pacientes. Varios factores de riesgo, incluida la predisposición genética, la exposición intermitente a la radiación solar y el número de nevos presentes, contribuyen al desarrollo del melanoma. Para abordar esta enfermedad, el sistema de estadificación TNM se erige como una herramienta crucial en la clasificación y estimación pronóstica. Es importante señalar que, en casos localizados, la cirugía desempeña un papel esencial, mientras que en situaciones más avanzadas, las modalidades farmacológicas, especialmente aquellas que involucran inhibidores de puntos de control inmunológico, surgen como fundamentales. La evaluación de la calidad de vida encuentra su expresión a través de cuestionarios de Resultados Reportados por el Paciente (PRO), desempeñando un papel fundamental en la toma de decisiones médicas. Los pacientes que reciben información detallada sobre los riesgos y beneficios asociados con la inmunoterapia adyuvante anti-PD1 expresan una mayor satisfacción con sus elecciones médicas. **Conclusiones:** Esta revisión proporciona evidencia de que la combinación terapéutica de nivolumab y relatlimab produce mejoras significativas en la supervivencia de pacientes con melanoma metastásico.

Palabras clave: Melanoma, Metástasis de la Neoplasia, Calidad de Vida, Nivolumab, Quimioterapia Combinada. (Fuente: DeCS).

INTRODUCTION

Cancer stands as the leading cause of global mortality, accounting for approximately 10 million deaths in the year 2020. This figure translates to roughly one in every six reported fatalities. According to data provided by the World Health Organization (WHO), during the same year, skin cancer ranked fifth in terms of prevalence, with an estimated 1.2 million cases worldwide [1].

Globally, the decision has been made to primarily classify skin cancer into two categories: melanoma and non-melanoma skin malignancies (squamous cell carcinoma and basal cell carcinoma). Addressing the topic of skin cancer, particularly melanoma, is essential due to its significant impact on public health and the necessity to raise awareness about its prevention and early detection. Despite constituting only 2% of all skin cancer diagnoses, melanoma's significance lies in the fact that it accounts for most fatalities associated with this disease. Approximately 325,000 cases of melanoma are estimated to have been recorded worldwide in the year 2020. These statistics underscore the importance of specifically addressing melanoma, as its high mortality rate despite its low incidence highlights the need for increased awareness, prevention, and early detection efforts to mitigate its impact on public health [2-4].

Increasingly, the significance of assessing quality of life (QoL) as a pivotal patient-reported indicator is being recognized, as it can enhance communication between physicians and patients, identify symptoms requiring attention, and influence medical decisions. QoL is a multidimensional concept encompassing physical, functional, emotional, social, and familial well-being [5].

Within this context, physical well-being pertains to disease-related symptoms (such as pain, nausea, and fatigue) and treatment side effects. On the other hand, functional well-being refers to the ability to perform daily activities (like walking, bathing, and dressing) and fulfill social roles. Emotional well-being is linked to coping capacity and reflects a spectrum of emotions ranging from pleasure to distress. Lastly, social and familial well-being mirrors the quality of relationships with friends and family, as well as the level of engagement in social activities [6].

The assessment of QoL holds paramount importance, particularly in clinical studies related to cancer. This is because self-perceived QoL has been shown to independently predict survival in patients afflicted with various cancer types. Furthermore, quality of life-related outcomes can be a pivotal consideration in medical decision-making within clinical trials where survival differences are modest. In this regard, a broad array of tools is available for evaluating QoL [6].

METHODS

A bibliographic search was conducted, including articles in both English and Spanish, indexed in the PubMed, Scopus, Scielo, and Embase databases. The search included articles published up to the year 2024. MeSH terms and synonyms such as "metastatic melanoma," "unresectable melanoma," "nivolumab," "relatlimab," and "quality of life" were employed. These terms were combined using Boolean operators (AND, OR) to maximize the precision and relevance of the results. The search strategy was adapted for each database to capture observational studies, clinical trials, systematic reviews, and meta-analyses, as available.

Inclusion criteria were defined to encompass any full-text scientific article whose primary or secondary objective was directly related to the outcome of interest in metastatic or unresectable melanoma and the use of nivolumab or relatlimab.

DEFINITIONS

Melanoma Definition:

Melanoma is a malignant neoplasm originating from melanocytes, cells primarily located in the basal layer of the epidermis. This type of cancer can arise from pigment-producing cells in various parts of the body, such as the eye, gastrointestinal tract, genitals, paranasal sinuses, and meninges. However, its most common manifestation occurs in the skin, especially in areas affected by ultraviolet (UV) radiation [7]. Upon UV light exposure, genetic mutations accumulate that activate oncogenes, deactivate tumor suppressor genes, and disrupt DNA repair. This process can lead to uncontrolled proliferation of melanocytes and ultimately result in melanoma.

In the history of clinical oncology research, randomized trials have predominantly prioritized traditional efficacy measures such as overall survival and progression-free survival. However, a positive trend is currently emerging where more and more clinical trials and studies in the field of oncology are being conducted in real-world healthcare contexts, incorporating assessments of patients' overall QoL and Health-Related Quality of Life (HRQoL) into their designs. This inclusion provides a valuable complement to clinical decisions [8].

Research has demonstrated that certain aspects of HRQoL in patients can act as independent predictors of their survival in advanced melanoma cases. In the context of melanoma, around one-third of patients have reported clinically relevant distress levels [9]. Generally, lower levels of HRQoL and overall self-perceived health are observed in the acute survival phase immediately following diagnosis. These levels can be attributed in part to exacerbated physical symptoms such as pain, decreased energy, and increased physical effort. Additionally, emotional stress impacts patients' social activities during this period [8].

Genetics Features of Melanoma:

The transformation of melanocytes into melanoma results from a complex interplay between exogenous and endogenous influences. The first genetic indications emerged through the identification of germ line changes in families with multiple members affected by melanoma. Approximately 8% of melanoma patients have family histories, and among them, 40% carry high-risk germline mutations in the CDKN2A gene, encoding the tumor suppressors P16 and p14, as well as in the BAP1 gene, responsible for an enzyme influencing DNA damage response and chromatin modification [10]. However, most sporadic melanomas, accounting for 90% of total cases, are often driven by low or moderate-risk alleles, which have a high prevalence but low penetrance. This suggests a significant role for environmental factors in malignant transformation, such as exposure to UV radiation and other risk elements [11].

Epidemiology:

Melanoma persists as a malignant neoplasm with lethal potential. While the incidence of many tumor types is decreasing, melanoma continues to rise [12]. Although most patients are diagnosed with localized disease and undergo surgery to remove the primary tumor, a substantial number experience metastasis [13]. According to the Global Cancer Observatory, approximately 325,000 people worldwide were diagnosed with melanoma in 2020 (174,000 males and

151,000 females), and the disease claimed the lives of around 57,000 individuals (32,000 males and 25,000 females). Out of all new cases in 2020, 79.7% (259,000) were in individuals aged over 50, and in terms of deaths, 87.7% (50,000) were over 50.

The highest incidence rates, both in males (42 per 100,000 person-years) and females (31 per 100,000 person-years), were recorded in Australia/New Zealand, followed by Western Europe (19 per 100,000 person-years for both sexes), North America (18 per 100,000 person-years for males and 14 per 100,000 person-years for females), and Northern Europe (17 per 100,000 person-years for males and 18 per 100,000 person-years for females). In contrast, the lowest rates were observed in most regions of Africa and Asia, with values below 1 per 100,000 person-years, except for Central and Southern Africa, as well as Western Asia.

The highest mortality rates (4 per 100,000 person-years for males and 2 per 100,000 person-years for females) were found in Australia/New Zealand, whereas in most other regions of the world, they were considerably lower, ranging from 0.2 to 1.0 per 100,000 person-years. Most melanoma-related deaths were concentrated in Central and Eastern Europe (16.3%), followed by North America (14.7%) and Western Europe (13.0%). While 5.9% of melanoma cases occurred in Oceania, this region contributed 3.4% of global melanoma deaths. This contrasts with Asia, where 7.3% of cases resulted in 21.0% of all melanoma deaths, and with Africa, which contributed 2.1% of cases but accounted for 4.7% of global melanoma deaths.

Globally, melanoma was more prevalent in males (174,000 cases) than females (151,000 cases). Male predominance in incidence remained in all regions of the world, except in Eastern and Western Africa, as well as Northern Europe and Melanesia, where melanoma rates in females exceeded those in males. The cumulative risk of developing melanoma was highest in Australia/New Zealand [4,14].

Risk Factors:

Today, melanoma is recognized as a multifactorial disease arising from the interplay between genetic predisposition and environmental exposure. Pigmentation undeniably and significantly impacts the skin's vulnerability to malignant transformation. The melanocortin 1 receptor (MC1R), present on the surface of melanocytes, triggers pigment production. The various polymorphisms of the MC1R gene, determining distinct skin phenotypes, lead to variants such as red hair and fair skin phenotype displaying low pigmentation. This results in heightened sensitivity to UV light and an increased risk of associated melanoma.

Apart from its role in phototype classification, melanin also shields melanocytes and keratinocytes from harmful UV ray effects. This explains why phototypes I and II face a greater risk of developing melanocytic and keratinocytic cancers due to their higher susceptibility to UV damage. The presence of numerous acquired melanocytic nevi, the red hair phenotype, and certain alleles of the MC1R gene, known as R alleles, independently elevate the risk of melanoma [15].

Numerous studies have evidenced that primary factors linked to melanoma development include the number of melanocytic nevi, family history of melanoma, and genetic predisposition. In most cases, melanoma arises on seemingly healthy skin. However, a quarter of melanoma cases are associated with previous nevi, supporting the observation of a doubled incidence of nevus-associated melanoma in both young and older individuals [16].

Most cutaneous melanomas originate in skin areas intermittently exposed to sunlight, rather than continuously. This is especially true for individuals and areas prone to sunburn. The highest rates of melanoma are observed in those repeatedly exposed to intense sunlight. This theory gains strength from the observation that melanoma patients who actively reduce sun exposure after the initial diagnosis have a lower risk of developing a second primary melanoma [17]. In contrast, individuals with dark skin or those who tan easily in response to sunlight but rarely experience burns exhibit notably lower melanoma rates [15]. However, it's important to note that sun exposure isn't directly tied to melanoma development. This is evident from the fact that melanoma can also arise in areas that haven't been chronically exposed to sunlight.

Exposure to UV rays stands as the most relevant and modifiable environmental factor in malignant melanoma development due to its genotoxic capacity. Studies investigating the connection between melanoma and sun exposure have concluded that intermittent sun exposure is a key determinant of melanoma risk [18]. Past episodes of sunburn can serve as indicators of intense intermittent sun exposure, particularly sunburns suffered during childhood are linked to an increased risk [19, 20]. Additionally, the total count of nevi (pigmented marks on the skin) shows a positive correlation with melanoma risk, varying based on the number, size, and type of nevi. A meta-analysis conducted by Gandini et al. showed that individuals with more than 100 nevi have a sevenfold higher risk of developing melanoma [21].

Melanoma Classification:

Initially, melanoma categorization was based on its origin, whether from a pre-existing nevus, an acquired melanocytic lesion, or seemingly flawless skin. However, in the 1960s, an influential dermatologist named Wallace Clark proposed an innovative approach: classifying melanoma based on its histological features. This insightful idea revolutionized the way this condition was diagnosed [22,23].

Currently, there are four main subtypes of cutaneous melanoma [3]:

- **Superficial Spreading Melanoma (70%):**
  This is the most common type of melanoma. It is characterized by initial lateral (radial) growth before developing vertical (invasive) growth.

- **Nodular Melanomas (15%–30%):**
  These lesions are elevated or polypoid, rapidly increase in size, and often exhibit blue or black coloration. They show an early vertical growth phase.

- **Lentigo Maligna Melanoma (4%–10%):**
  Primarily seen in older patients with chronic sun exposure. It typically starts as a small macule resembling a freckle. Over time, it grows, darkens, becomes asymmetrical, and shows a vertical growth phase.

- **Acral Lentiginous Melanoma (<5%):**
  These lesions commonly appear on the palms, soles of the feet, subungual areas, and occasionally on mucous membranes.

Melanoma has the ability to arise in non-cutaneous sites where melanocytes reside, such as the eyes, gastrointestinal tract, genitourinary areas, and nasopharynx. However, these occurrences are significantly less frequent than cutaneous melanoma, as data from a review of the National Cancer Database shows. Among 84,836 patients with melanoma (both cutaneous and non-cutaneous), 91.2% were cutaneous melanomas. Ocular melanoma accounted for 5.2%, while 1.3% had primary origin in mucosal tissues. The remaining 2.2% were classified as melanoma of unknown primary site [24].

The American Joint Committee on Cancer (AJCC) has played an essential role in shaping the TNM (Tumor, Node, Metastasis) staging system [25]. The underlying database is continuously analyzed and used to update the AJCC's TNM staging system for melanoma. This system provides pathologists and physicians with guidelines for classifying patients diagnosed with melanoma. By integrating primary tumor histological features (T), the presence and extent of disease in regional lymph nodes (N), and the presence and extent of distant metastasis (M), medical professionals can assign patients a stage closely linked to survival and prognosis. Apart from Breslow depth, the AJCC staging system for melanoma has incorporated other attributes of the primary tumor, such as ulceration, mitotic rate, tumor-associated inflammation, and regression [25], which have demonstrated correlation with outcomes and thus contribute to staging accuracy.

Despite the existence of a comprehensive staging system, it has long been a reality that accurate and consistent diagnosis of melanoma remains a significant challenge [26]. Surprising variability has been observed both among different observers and within the same observer when diagnosing melanocytic neoplasms, especially when ambiguous histological features are present.

Treatment:

The surgical removal of the tumor and surrounding healthy tissue constitutes the primary approach for localized melanoma. In patients with tumors thicker than 0.8 mm or, even if thinner, with ulceration (stage pT1b or higher), sentinel lymph node biopsy is performed. If melanoma cells are detected in the sentinel lymph nodes, additional lymph nodes in the region are occasionally removed. Under certain circumstances, surgically removing metastasized tumors is also possible. However, it's important to emphasize that surgical intervention in the context of recognized metastatic disease does not aim for cure, and other therapeutic modalities will be necessary.

In the case of patients with metastatic disease, isolated surgery does not lead to a curative effect, and pharmacological therapies emerge as the next level of approach. In 1968, pioneering clinical trials of chemotherapy for metastatic melanoma were conducted using the compound 1-phenylalanine mustard, known as melphalan. However, this approach proved ineffective and was characterized by high toxicity [22].

In 1975, dacarbazine became the first and only chemotherapeutic drug approved by the FDA for melanoma treatment [22,27].For a time, dacarbazine held its position as the standard approach for metastatic melanoma, but the responses it achieved were at best partial, with a median survival of 5 to 11 months and a one-year survival rate of 27% [22,27,28]. However, since then, no other chemotherapeutic developed for melanoma treatment has shown to be more effective or less toxic.

Until 2010, no medically examined treatment in a randomized clinical trial had achieved a significant improvement in overall survival for patients with advanced unresectable melanoma. Less than half of all patients diagnosed with stage IV metastatic melanoma survived beyond 1 year, and only 20% of patients managed to live beyond 3 years. Before the development of current medical therapies aimed at extending life, only a small percentage of people with advanced melanoma experienced long-term survival of more than 5 years [29].

To date, immune checkpoint inhibitors have emerged as the most successful treatments for metastatic melanoma. The first of these inhibitors was approved for clinical use in 2011 [30]. Manipulating immune checkpoint pathways by melanoma can be overcome by treatment with antibodies against PD-1, PD-L1/2, and CTLA-4 [27]. Three immune checkpoint inhibitor drugs have received approval for use in melanoma treatment: the anti-CTLA-4 antibody ipilimumab and two anti-PD-1 antibodies, nivolumab and pembrolizumab. Additionally, several PD-L1/2 antibody drugs are in clinical trials, and some have been approved for clinical use in other indications, though not yet for melanoma [30].

Treatment with ipilimumab has demonstrated long-term survival of up to 10 years in 20% of cases; this represents a significant advance compared to the median survival rate of less than one year in patients with stage IV melanoma [30-32]. In patients with metastatic melanoma, pembrolizumab exhibits an approximate response rate of 37-38%, along with a 74% survival rate at 12 months [33]. On the other hand, nivolumab treatment yields a response rate of around 40%, accompanied by a 73% overall survival rate at 12 months, in contrast to the 43% observed in patients treated with dacarbazine [27]. Additionally, the combination of ipilimumab and nivolumab led to a response rate close to 57% and a progression-free survival duration of 11.5 months [30].

Side effects resulting from immune checkpoint blockade are commonly known as immune-related adverse events (irAEs). The most frequent irAEs affect the skin, liver, gastrointestinal organs, lungs, and endocrine system. Additionally, cases of autoimmune diabetes and side effects involving the cardiovascular, renal, and musculoskeletal systems have been recorded. Most cutaneous, gastrointestinal, and hepatic adverse effects occur within the first two months, while endocrine, pulmonary, and renal effects tend to appear after around nine weeks. Early diagnosis and treatment are recognized as essential to reduce the severity of irAE [34].

Comparison of Monotherapy with Nivolumab or Combination Therapy:

In recent years, presented preclinical data have outlined a clear synergy between LAG-3 (Lymphocyte-activation gene 3) inhibitory receptors and PD-1 (Programmed cell death protein 1). This synergy possesses the ability to control immune homeostasis, prevent autoimmunity, enhance tumor-induced tolerance, reduce tumor growth, and boost anti-tumor immunity [35-38]. Furthermore, the combination therapy was generally well tolerated, with no adverse clinical signs [35].

Relatlimab is a monoclonal antibody that blocks the LAG-3 IgG4. Its function lies in restoring effector activity in T cells that are in an exhausted state. It has been investigated in two contexts: in resistant metastatic melanoma (registered as

NCT01968109) and in cases where no checkpoint inhibitor therapy has been applied (registered as NCT03470922) [39].

The efficacy and safety of combined therapy with relatlimab and nivolumab have been demonstrated in the phase II/III clinical trial RELATIVITY-047. This trial showcased a significantly extended progression-free survival benefit with the combined therapy compared to nivolumab monotherapy in patients with metastatic or unresectable melanoma (HR 0.78 [95% confidence interval (CI), 0.64–0.94]). Additionally, the combination was well tolerated, and 21.1% of patients experienced grade 3/4 treatment-related adverse events. Given its effectiveness and favorable toxicity profile, this combined therapy received approval from the U.S. Food and Drug Administration for use in patients with metastatic melanoma on March 18, 2022 [39,40].

Quality of Life:

The assessment of HRQoL is carried out through the utilization of validated patient-reported outcome (PRO) questionnaires. This approach encompasses a multidimensional concept that encapsulates the patient's perception of how the disease and its treatment impact the physical, psychological, and social aspects of their life.

In a systematic review of seven studies (involving 4,246 patients, comprising 6 cross-sectional studies and 1 prospective study), it was revealed that various factors influenced worse HRQoL (in both psychological, physical, and overall aspects). Among these factors are marital status, age, gender, lack of social support, severity of melanoma at the time of diagnosis, and the presence of comorbidities [41].

Given that treatment-derived toxicity can have negative repercussions on HRQoL, it is crucial to compare this among treatments with varying toxicity rates. In the RELATIVITY-047 study, HRQoL, evaluated from the patient's perspective, was considered an exploratory endpoint. Preliminary results obtained from the analysis of the main database up until March 9, 2021, indicated that both the use of NIVO + RELA and NIVO alone maintained stable HRQoL during treatment (i.e., at levels close to baseline values). This was evident despite the combination of NIVO + RELA presenting higher toxicity in comparison, and HRQoL remained similar in both treatments [39,42]. Additionally, it has been observed that when patients receive comprehensive and quantitative information about the risks and benefits associated with adjuvant anti-PD1 immunotherapy, those who chose this form of treatment experienced lower regret about their choice and displayed greater satisfaction over time. This held true even in cases where treatment outcomes were not as favorable [43].

CONCLUSIONS

Melanoma poses a significant threat to global health, with a consistent rise in its incidence despite the decline of many other types of tumors. While constituting only a small fraction of skin cancer cases, its lethal impact is disproportionate, underscoring the need to specifically address this type of cancer. The interplay between genetic and environmental factors, such as UV radiation exposure, plays a pivotal role in melanoma development. Despite existing histological classification and staging systems, accurate diagnosis remains a challenge. Treatment has evolved over the years, from ineffective and toxic approaches to modern immune checkpoint inhibitors that have shown significantly improved survival rates.

Combination therapy, like that of relatlimab and nivolumab, has proven particularly effective, enhancing progression-free survival compared to monotherapies. The approval of this therapeutic combination marks a milestone in metastatic melanoma treatment, offering hope to patients and a new way to approach this complex and deadly disease.

Furthermore, HRQoL has been demonstrated to remain stable in patients who have received combination therapy. To date, there are no records of potential long-term emotional, physical, and cognitive impacts arising from the use of immune checkpoint inhibitors in individuals with metastatic melanoma. Future research focusing on the early assessment of psychosocial, neurocognitive, and HRQoL issues is crucial to better understand the care needs of individuals who have survived advanced melanoma. Improving patients' subjective well-being could hold the potential to mitigate the possible emotional, physical, and socio-economic ramifications of this devastating disease.

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