Jornal de Assistência Farmacêutica e Farmacoeconomia
v.10, n.2, 2025.
Original Article

Patient profile and treatment pattern characterization of advanced melanoma at two private cancer centers in brazil: a real-world study

Perfil do paciente e caracterização do tratamento do melanoma avançado em dois centros privados de câncer no brasil: um estudo de mundo real

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How to cite: Finardi Roubik, C., Casagrande D. Oliveira, A. P., Mirandola, D., Herrero Geraldino, T., Maria Neves De Carvalho, L., Luiz Cunha De Sousa Martins, C., & Alves Ladislau, L. (2025). Patient profile and treatment pattern characterization of advanced melanoma at two private cancer centers in brazil: a real-world study. JAFF, 10(2). https://doi.org/10.22563/2525-7323.2025.v10.e00171e

Received: November 22, 2024

Accepted for publication: April 7, 2025

ABSTRACT

Objective: To analyze the profile of advanced melanoma patients and treatment patterns at two private oncology centers in Brazil. **Methods:** This retrospective observational study analyzed the profile of advanced melanoma patients and treatment patterns at two private oncology centers in Brazil: COI Américas – RJ and Hospital Paulistano - SP. Patients with a diagnosis of advanced melanoma (stage III or IV) who received at least one systemic treatment between 2012 and 2020 were included. Demographic and clinical information was collected from medical records and analyzed using SPSS v25.0 software. Results: The study included 185 patients, with a mean age of 62.8 years and an average weight of 78 kg. Throughout the study period, the predominant first-line treatment was anti-PD-1 monotherapy, followed by dacarbazine. For patients treated up until 2015, dacarbazine was the primary first-line choice; however, starting in 2016, immunotherapy became the most common initial therapeutic approach. The combination of anti-PD-1 with anti-CTLA-4 was also a relevant option. **Conclusion:** The study highlights the shift in treatment patterns for advanced melanoma in Brazil with the introduction of immunotherapy and suggests that the evolution of treatment should continue to be monitored in the future with more comprehensive studies.
Keywords: Melanoma; Melanoma Treatment; Patient Profile; Real-World Study

RESUMO:

Objetivo: Analisar o perfil dos pacientes com melanoma avançado e os padrões de tratamento em dois centros oncológicos privados no Brasil. **Métodos:** Este estudo observacional retrospectivo analisou o perfil dos pacientes com melanoma avançado e os padrões de tratamento em dois centros oncológicos privados no Brasil: COI Américas – RJ e Hospital Paulistano SP. Foram incluídos pacientes com diagnóstico de melanoma avançado (estádio III ou IV) que receberam ao menos um tratamento sistêmico entre 2012 e 2020. Informações demográficas e clínicas foram coletadas dos prontuários e analisadas utilizando o software SPSS v25.0. **Resultados:** O estudo incluiu 185 pacientes, com média de idade de 62,8 anos e peso médio de 78 kg. Durante todo o período do estudo, o tratamento de primeira linha predominante foi a monoterapia com anti-PD-1, seguida pela dacarbazina. Considerando apenas pacientes tratados até 2015, a dacarbazina foi a principal escolha de primeira linha; contudo, a partir de 2016, a imunoterapia se tornou a abordagem terapêutica inicial mais comum. A combinação de anti-PD-1 com anti-CTLA-4 também foi uma opção relevante. **Conclusão:** O estudo destaca a mudança no padrão de tratamento do melanoma avançado no Brasil com a introdução da imunoterapia e sugere que a evolução do tratamento continue a ser monitorada em estudos futuros de maior abrangência.
Palavras-chave: Melanoma; Tratamento do Melanoma; Perfil de Paciente; Estudo do Mundo Real

Introduction

Melanoma represents a type of skin cancer that originates from the malignant transformation of melanocytes, the cells responsible for pigmentation.[1,2] In addition to the skin, melanocytes are also present in the eyes (uveal and conjunctival mucosa), ears, gastrointestinal tract (upper esophagus and anorectal mucosa), meninges, and the oral, nasopharyngeal, anorectal, and genital mucosae.[2] Although melanoma accounts for only 4% of all skin cancer cases, it is responsible for 75% of deaths caused by this type of cancer.[3]

Cutaneous melanoma is the 16th most common type of cancer worldwide, with an age-adjusted incidence rate of 3.2 per 100,000 individuals.[4] In Brazil, according to the National Cancer Institute (INCA) of the Ministry of Health, the estimated number of new melanoma cases for each year of the 2023-2025 triennium is 8,980, corresponding to a risk of 4.13 per 100,000 Brazilians.[5] BRAF gene mutations are frequently associated with melanoma, occurring in approximately 50% of cases.[6]

Generally, the diagnostic process begins with the clinical evaluation of a suspicious skin lesion, followed by histopathological analysis and the possibility of molecular testing.[1] The extent of tumor spread within the skin and adjacent tissues defines the staging, which is based on both clinical and pathological parameters. The stage of cutaneous melanoma is determined through the assessment of the tumor (T), number of metastatic lymph nodes (N), and presence of distant metastases (M).[1] In general, the lower the stage, the better the prognosis and patient outcomes.[7]

Brazilian data from 2018 indicate that melanoma is diagnosed at more advanced stages, with 26.1% and 20.6% of patients diagnosed at stages IV and III, respectively.[8] Advanced-stage melanoma, characterized by unresectable and/or metastatic disease (stage III or IV), is associated with lower survival rates compared to localized disease.[9] The five-year survival rate for metastatic melanoma is estimated at 35%.[9]

However, the treatment landscape for advanced disease has been revolutionized over the past decade. In Brazil, targeted therapy for BRAF mutation inhibition (iBRAF) was introduced in 2011,[10] while immunotherapies with anti-PD-1 agents and the combination of MEK inhibitors with BRAF inhibitors (iBRAF + iMEK) were approved by ANVISA in 2016,[11-14] followed by the approval of the anti-PD-1 + anti-CTLA-4 combination in 2017.[15] More recently (2023), the anti-PD-1 + anti-LAG-3 immunotherapy combination was also approved.[16]

Long-term outcomes with immuno-oncology (IO) agents and targeted therapies provide evidence of durable survival for a substantial number of patients, in contrast to the limited efficacy achieved with traditional chemotherapy.[17,18] The five-year overall survival rate for patients with advanced melanoma, as observed in randomized clinical trials, was 8.8% for dacarbazine, 34% for combined targeted therapy, 44% for monotherapy immunotherapy (anti-PD-1), and 52% for combination immunotherapy (anti-PD-1 + anti-CTLA-4).[19]

Despite the significant progress demonstrated in clinical trials with the introduction of these new therapies, there remains a lack of published data assessing whether this paradigm shift and the new standard of care for advanced melanoma have been reflected in the Brazilian supplementary healthcare system.

Objectives

To characterize the treatment patterns and their evolution, as well as to describe the clinical and demographic characteristics of patients diagnosed with advanced melanoma who received care at two private oncology centers in Brazil.

Methods

An observational, non-interventional, retrospective real-world study was conducted based on the medical records of patients with advanced melanoma who were treated and followed at two private oncology centers in Brazil: COI Américas and Hospital Paulistano. The study population consisted of patients diagnosed with advanced melanoma (stage III or IV), registered and treated at both hospitals, according to the inclusion and exclusion criteria.

The inclusion criteria were: age ≥ 18 years at the time of inclusion, diagnosis of advanced (unresectable or metastatic) melanoma, receipt of at least one systemic treatment for advanced melanoma, and treatment initiation between January 2012 and December 2020. The exclusion criteria were: patients with another primary cancer diagnosed before the inclusion date, and patients who were participating in or had previously participated in clinical trials involving melanoma or immunotherapy.

Patient data were collected from medical records and transferred to a Case Report Form (CRF) containing information on treatments received, as well as demographic and clinical characteristics. All included patients were followed until death or until the date of the last recorded visit in their medical charts at the time of data collection. To ensure data confidentiality, neither patients nor researchers were identified in the CRF.

The study was approved by the Ethics Committees of both institutions (approval numbers: 4.500.371, 4.763.399, 5.174.074, 5.143.621, and 4.724.991). Qualitative variables were described using absolute (n) and relative (%) frequencies, and the analyses were performed using the SSP software, version 25.0.

Results

Clinical and Demographic Characteristics:

The study included 185 patients, of whom 62.7% were male and 37.3% were female. The age at diagnosis of advanced disease ranged from 28 to 93 years (median: 62 years), and the weight at the start of first systemic therapy ranged from 46 to 180 kg (mean: 78 kg).

The majority of patients (80%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The BRAF mutation test was positive in 30.3% (n = 56) and negative in 40% (n = 70) of patients. The test was not performed or not reported for 55 patients (29.7%).

Metastatic disease (stage IV) was the initial melanoma-related diagnosis for 39 patients (21.1%), whereas 182 patients (98.4%) had stage IV disease when the advanced condition was identified (Table 1).

Table 1. Clinical and Demographic Characteristics

Characteristic	Total (n = 185)
Age - Mean (SD)	62.8 (14.2)
Sex - n (%)	
Male	69 (37.3)
Female	116 (62.7)
Mean Weight (SD)	78 (16.7)
Treatment Center - n (%)	
Center I - Rio de Janeiro	148 (80.0)
Center II - São Paulo	37 (20.0)
Median time between advanced melanoma diagnosis and treatment initiation - months	1.9
Primary Diagnosis - n (%)	
C43 - Malignant melanoma of the skin	119 (64.3)
C43.1 - Malignant melanoma of the eyelid, including canthus	2 (1.1)
C43.3 - Malignant melanoma of other and unspecified parts of the face	5 (2.7)
C43.4 - Malignant melanoma of scalp and neck	14 (7.6)
C43.6 - Malignant melanoma of upper limb, including shoulder	2 (1.1)
C43.7 - Malignant melanoma of lower limb, including hip	1 (0.5)
C43.8 - Overlapping malignant melanoma of skin	7 (3.8)
C43.9 - Malignant melanoma of skin, unspecified	35 (18.9)

Characteristic	Total (n = 185)
Stage at first melanoma diagnosis - n (%)	
Stage I	14 (7.6)
Stage II	21 (11.3)
Stage III (unspecified)	5 (2.7)
Stage IIIa	6 (3.2)
Stage IIIb	3 (1.6)
Stage IIIc	11 (5.9)
Stage IIId	1 (0.5)
Stage IV	39 (21.1)
Data not available	85 (45.9)
Stage at advanced melanoma diagnosis - n (%)	
Stage III	2 (1.1)
Stage IV	182 (98.4)
Data not available	1 (0.5)
Recurrence - n (%)	
Yes	101 (54.6)
No	75 (40.5)
Data not available	9 (4.5)
BRAF Status - n (%)	
Positive	56 (30.3)
Negative	74 (40.0)
Not reported	55 (29.7)
ECOG Performance Status - n (%)	
ECOG 0	68 (36.8)
ECOG 1	80 (43.2)
ECOG 2	10 (5.4)
ECOG 3	2 (1.1)
Not reported	25 (13.5)

ECOG: Eastern Cooperative Oncology Group; SD - Standard Deviation.

Treatment Pattern

All patients received first-line (1L) therapy for advanced disease, with the most common regimens being anti-PD-1 monotherapy (39.5%), dacarbazine (18.4%), vemurafenib (10.8%), and the anti-CTLA-4 + anti-PD-1 combination (10.3%). Less than half of the patients underwent second-line therapy (n = 85; 45.9%), while 35 patients (18.9%) proceeded to third-line therapy.

Among patients who initiated 1L treatment up to 2015 (n = 59), dacarbazine predominated as the main 1L therapy (47.5%). However, for those who started 1L treatment from 2016 onward (n = 118), the treatment landscape changed following the approval of immunotherapy (anti-PD-1 ± anti-CTLA-4), which became the predominant choice for first-line therapy (78.8%).

Information regarding the treatments administered is presented in Tables 2, 3, and 4.

Table 2. Proportion of Patients by Treatment Line

Treatment Line	Patients - n (%)
First Line (1L)	185 (100.0)
Second Line (2L)	85 (45.9)
Third Line (3L)	35 (18.9)
Fourth Line (4L)	12 (6.4)
Fifth Line (5L)	2 (0.0)
Sixth Line (6L)	1 (0.0)

Table 3. Therapeutic Regimens Used in First-Line Treatment (1L)

Therapeutic Regimen	Patients - n. (%)
Anti-PD-1	73 (39.5)
Dacarbazine	34 (18.4)
iBRAF	20 (10.8)
Anti-PD-1 + anti-CTLA-4	19 (10.3)
Anti-CTLA-4	10 (5.4)
iBRAF + iMEK	6 (3.4)
Others*	18 (9.7)
Data not available#	5 (2.4)

iBRAF - BRAF inhibitor; iMEK - MEK inhibitor; iBRAF + iMEK - BRAF inhibitor + MEK inhibitor; Anti-PD-1 - PD-1 inhibitor; Anti-CTLA-4 - CTLA-4 inhibitor; Anti-PD-1 + Anti-CTLA-4 - PD-1 inhibitor + CTLA-4 inhibitor. * Other treatments: Interferons (n = 11), Temozolomide (n = 2), Fotemustine (n = 1), Cisplatin + Temozolomide (n = 1), Dacarbazine + Vinblastine + Cisplatin (n = 3). # Unspecified immunotherapy (n = 4) and unspecified chemotherapy (n = 1).

Table 4. First-Line (1L) Treatment Pattern According to BRAF Mutation Status and Year of Treatment Initiation

	Positive (n= 55)		Negative or Not Reported (n = 122)		Total (n = 177)	
	Up to 2015 (n = 23) - n (%)	**From 2016 (n=32) - n. (%)**	**Up to 2015 (n=36) - n. (%)**	**From 2016 (n=86) - n. (%)**	**Up to 2015 (n=59) - n. (%)**	**From 2016 (n=118) - n. (%)**
Anti-PD-1 + anti-CTLA-4	0	3 (9.4)	0	16 (18.6)	0	19 (16.1)
Anti-PD-1	0	16 (50.0)	0	55 (63.9)	0	71 (60.2)
Anti-CTLA-4	4 (17.4)	0	3 (8.3)	3 (3.5)	7 (11.9)	3 (2.5)
Dacarbazine	4 (17.4)	1 (3.1)	24 (66.7)	2 (2.3)	28 (47.5)	3 (2.5)
iBRAF	9 (39.1)	7 (21.9)	2 (5.6)	0	11 (18.7)	7 (5.9)
iBRAF + iMEK	0	4 (12.5)	0	2 (2.3)	0	6 (5.1)
Others	6 (26.1)	1 (3.1)	6 (16.7)	4 (4.6)	12 (20.3)	5 (4.2)
Data not available	0	0	1 (2.8)	4 (4.6)	1 (1.7)	4 (3.4)

iBRAF - BRAF inhibitor; iMEK - MEK inhibitor; iBRAF + iMEK - BRAF inhibitor + MEK inhibitor; Anti-PD-1 - PD-1 inhibitor; Anti-CTLA-4 - CTLA-4 inhibitor; Anti-PD-1 + Anti-CTLA-4 - PD-1 inhibitor + CTLA-4 inhibitor. 8 patients were excluded from the analysis due to missing medical record data that prevented inclusion in the proposed evaluation.

Discussion

The results of this study highlight significant changes in the treatment of advanced melanoma in recent years across two private oncology centers in Brazil. With the regulatory approval of immunotherapies and targeted therapies in the country, a clear shift in the treatment landscape has occurred. The introduction of PD-1 and CTLA-4 inhibitors, regardless of BRAF mutation status, along with BRAF and MEK inhibitors for patients with BRAF-positive mutations, demonstrates a clear evolution in first-line (1L) treatment patterns. Overall, a wide variety of treatment choices was observed, with up to 63 different therapeutic protocols identified.

This study underscores that, before 2016, the year when anti-PD-1 agents (nivolumab and pembrolizumab) were approved in Brazil for this indication,[11,12] dacarbazine was widely used as first-line therapy, which reflected the limited therapeutic options available at that time, offering poor overall survival outcomes (median overall survival: 6.4 months with dacarbazine).[20,21] With the approval and broader use of innovative therapies, a clear transition was observed toward PD-1 inhibitors, alone or in combination with CTLA-4 inhibitors, establishing immunotherapy as the new standard of care in this study.

Furthermore, the data from this study reveal an important scenario regarding late-stage melanoma diagnosis in Brazil. A substantial number of patients were initially diagnosed at stages III and IV, illustrating the ongoing challenge of improving early detection and prevention practices. The high rate of patients diagnosed with metastatic disease as their first melanoma diagnosis (21.1%) reinforces the need for greater awareness and more effective screening, particularly among fair-skinned populations, where incidence has been increasing.[1]

Despite the late diagnosis, only a small proportion of patients (6.5%) presented with an ECOG performance status greater than 1, indicating that most maintained relatively preserved physical function, even with advanced disease. This profile contrasts with that typically observed in randomized clinical trials,[22] which generally include only patients with ECOG $\leq$ 1, that is, those with minimal functional impairment. The BRAF mutation was identified in 30.3% of patients in this study, a proportion similar to that reported in other Brazilian studies (34.1% and 40%).[23,24] However, the percentage observed here may be underestimated, as 29.7% of patients had no BRAF mutation data available in their records.

It is important to note that, while these results show notable progress in treatment patterns within these two centers, a broader study including patients from different regions of the country is needed to ensure a more representative picture of the population treated within Brazil's supplementary healthcare system. Additionally, efficacy data of the therapies used could not be assessed due to limited patient numbers per treatment regimen and missing data in medical records.

Although this study represents an advance in understanding the treatment patterns of advanced melanoma in two private oncology centers, its results may not reflect the reality of public oncology centers that treat patients through the Unified Health System (SUS). Regarding advanced melanoma treatment in the SUS, the Diagnostic and Therapeutic Guidelines for Cutaneous Melanoma,[1] currently guide High-Complexity Oncology Care Centers (CACONs) and High-Complexity Oncology Units (UNACONs). This document was updated following the incorporation of anti-PD-1 monotherapy in 2020,[25] based on a positive recommendation from CONITEC.[19] This incorporation led to the revision of the reimbursement value for the procedure 03.04.02.023-0 - Chemotherapy for Advanced Malignant Melanoma, from R$1,080.00 to R$7,500.00.[26] However, under the current decentralized procurement model of oncology care, it cannot be stated that anti-PD-1 therapy is fully implemented in the SUS.[19,26]

Finally, the continuation of real-world studies in Brazilian institutions is essential to monitor the evolution of treatment patterns and their impact on survival and quality of life for patients with advanced melanoma. Although anti-PD-1 monotherapy was the predominant approach in this study, the current standard of care for advanced melanoma is combina-

tion immunotherapy, regardless of BRAF mutation status, given its superior clinical outcomes.[17,18,27,28] Additionally, new immunotherapy combinations recently approved by ANVISA, such as anti-PD-1 + anti-LAG-3, were not assessed in this study but may already be used in clinical practice. This underscores the need for new studies to track ongoing therapeutic innovations in advanced melanoma treatment in Brazil.

Conclusions

This study demonstrates the significant transformation in the management of advanced melanoma across two private oncology centers in Brazil, highlighting the transition from conventional chemotherapy to modern immuno-oncology and targeted therapies. However, persistent challenges remain, such as late diagnosis and potential disparities in treatment access between the supplementary healthcare system and the public health system (SUS), where the effective use of therapies such as anti-PD-1 may face practical and financial barriers. Therefore, it is essential to expand research nationwide to validate these findings in diverse care settings and to evaluate the inclusion of newer therapeutic combinations already entering clinical use. Continuous monitoring of the effectiveness and applicability of these therapies in real-world scenarios is crucial to ensure improved outcomes in the treatment of advanced melanoma throughout the country.

Authors' Contributions

CFR, APCDO, THG, DM, LMNDC, CLCDSM, and LL: Conception and study design, or data analysis and interpretation; drafting or critical revision of the article for important intellectual content; final approval of the version to be published; and responsibility for all aspects of the work, ensuring the accuracy and integrity of any part of it.

Conflicts of Interest

Camila Finardi Roubik, Ana Paula Casagrande D. Oliveira, Daniela Mirandola, Thais Herrero Geraldino, and Leandro Ladislau are employees of Bristol Myers Squibb.

Funding

This study was funded by Bristol Myers Squibb Brazil.

Data Availability Statement

The data will be made available upon request. Data generated in the current study are available from the corresponding author upon reasonable request.

Responsible editor

Lindemberg Assunção Costa.

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