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Brief Communication

Frequency of HLA-A*02:01 in the Brazilian population and its impact on uveal melanoma systemic treatment

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Abstract

Uveal melanoma is a rare malignancy originating from extracutaneous melanocytes on the uveal layer of the eyes. The incidence varies depending on the ethnic and racial global distribution, as uveal melanoma is more frequently diagnosed in non-Hispanic White subjects when compared with Hispanic, Asian, or Black individuals. Despite all the local effective management of uveal melanoma, roughly 50% of the cases will develop distant metastases. For these cases, the historical median overall survival is around 12 months. Recently, tebentafusp became the first therapy to receive Food and Drug Administration approval following a phase 3 trial demonstrating a continued long-term benefit for overall survival among adult HLA-A*02:01-positive patients with previously untreated metastatic uveal melanoma. Since 2021, high-resolution sequence-based HLA typing has been considered the gold standard for determining HLA alleles and haplotypes for the Brazilian Bone Marrow Donor Registry (REDOME) donors. To depict the HLA-A*02:01-positivity in Brazilian individuals, the REDOME database was queried out for the donors included from 2021 to 2023 and tested for HLA in high-resolution platforms. A total of 203, 44 donors were included and the frequency of the HLA-A*02:01 was 21.01%, much lower compared to the frequency in North Americans and Europeans (around 45%). Despite tebentafusp has demonstrated promising results in the treatment of uveal melanoma, the number of patients to benefit from this new approach can strongly vary by ethnic and racial issues. New strategies for the systemic treatment of advanced uveal melanoma have to be developed and tested as this disease still represents an unmet medical need.

Key words: HLA; Brazil; uveal melanoma.

Uveal melanoma is a rare malignancy that originates from extracutaneous melanocytes on the uveal layer of the eyes. Approximately 90% of the cases reside primarily in the choroid, 6% in the ciliary body, and less commonly in the iris (around 4%).[1] Despite being infrequent, uveal melanoma is the most common primary intraocular neoplasm representing nearly 5% of all melanoma cases, including the cutaneous and mucosal melanomas.[2]

The incidence varies depending on the ethnic and racial global distribution. Uveal melanoma is more frequently diagnosed in non-Hispanic White subjects when compared with Hispanic, Asian, or Black individuals. Incidence rates are greater than 8.0 cases per million person-years in Western/Northern Europe and Oceania, between 2.0 and 7.9 in North America and Eastern/Southern Europe, and lower than 2.0 in South America, Asia, and Africa.[3]

Considering the Brazilian Hospital-Based Cancer Registries, between 2000 and 2016, 2166 uveal melanoma cases were identified. Of these, 80.2% of the patients were younger than 69 years old,[2] which is a highly active population taking into account the labor force.

At the time of diagnosis, the vast majority of patients present ocular symptoms and have uveal melanoma restricted to the eye, with less than 2% at stage IV disease.[4] However, despite all the local effective management of uveal melanoma, which may involve brachytherapy, stereotactic radiosurgery, transpupillary thermotherapy, local resection, or enucleation, roughly 50% of the cases will develop distant metastases to the liver and less commonly to the lungs, soft tissue, lymph nodes, and bones.[5]

The aggressive clinical behavior of uveal melanoma is distinct from cutaneous melanoma, probably due to distinguishable molecular drivers and a different tumor-immune microenvironment. For patients diagnosed with metastatic uveal melanoma, a limited efficacy of the systemic therapy, including immune checkpoint inhibitors, is observed leading to a disappointing historical median overall survival of around 12 months.[6]

Recently, tebentafusp, a soluble affinity-enhanced HLA-A*02:01-restricted T-cell receptor that is specific for the glycoprotein 100 peptide and is fused to an anti-CD3 single-chain variable fragment, became the first therapy to receive Food and Drug Administration approval following the phase 3 trial over the investigator's choice control group (single-agent pembrolizumab, ipilimumab, or dacarbazine).[7] The T-cell receptor-bispecific molecule tebentafusp demonstrated a

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continued long-term benefit for overall survival among adult HLA-A*02:01-positive patients with previously untreated metastatic uveal melanoma.[8]

Despite showing unprecedented results, tebentafusp use is restricted to HLA-A*02:01-positivepatients. This accounts for 45% of people in the United States and Europe.[7]

The Brazilian Bone Marrow Donor Registry (REDOME) is coordinated by the Brazilian National Cancer Institute (INCA) and was created in 1993 to gather information from people willing to donate bone marrow to those in need of a bone marrow transplant. With more than 5 million registered donors, REDOME is the third largest bone marrow donor bank in the world and belongs to the Brazilian Ministry of Health, being the largest bank of bone marrow funded exclusively by public financing.[9]

Since 2021, high-resolution sequence-based HLA typing has been considered the gold standard for determining HLA alleles and haplotypes for REDOME donors. To determine the frequency of HLA-A*02:01-positivity in Brazilian individuals, the REDOME database was analyzed to identify donors who had been included from 2021 to 2023 and had tested for HLA in high-resolution platforms. Race/skin color was self-declared and followed the Brazilian Institute of Geography and Statistics (IBGE) classification defined as white, black, brown/mixed race, yellow or indigenous.[10] Since the study exclusively relied upon consolidated and de-identified information obtained from accessible governmental sources, the approval of the Institutional Review Board was not required.

A total of 203 744 donors were included and the frequency of the HLA-A*02:01 was 21.01%. Considering the race of the patients tested, 22.5% of white individuals, 17.5% of black, 22.8% of indigenous, 20.4% of yellow, and 20.2% of brown/mixed were HLA-A*02:01-positive.

HLA typing is a useful tool to assist in identifying suitable potential bone marrow and tissue donors. It will be frequently tested for systemic treatment of patients with metastatic uveal melanoma in Brazil by the regulatory approval of tebentafusp. According to the presented data, the positiveness of HLA-A*02:01 in the Brazilian population is much lower when compared to the frequencies in North Americans and Europeans.

Even though tebentafusp has ushered in a new era of promise in the treatment of uveal melanoma, the number of patients to benefit from this new approach varies greatly depending on ethnic and racial issues. New strategies for the systemic treatment of advanced uveal melanoma need to be developed and tested because for many patients this disease still represents an unmet medical need.

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Author contributions

All authors contributed to conception/design, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript.

Conflicts of interest

A.C.d.M. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Bristol Myers Squibb, GSK, MSD, Novartis, and Roche and also received for the participation on an Advisory Board from AstraZeneca, Bristol Myers Squibb, GSK, MSD, Novartis, and Roche. The other authors do not have conflicts to declare.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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