LETTER TO THE EDITOR

TITLE

Potential theranostic role of bone marrow glucose metabolism on baseline [18F]-FDG PET/CT in metastatic melanoma

RUNNING TITLE

Theranostic value of bone marrow glucose metabolism

AUTHORS

Romain-David Seban, MD, MSc [1,2], Laurence Champion, MD MSc [1,2], Izza Muneer, MD [3], Shwe Synn, MD [3], Lawrence H. Schwartz, MD [4], and Laurent Dercle, MD, PhD [4,*]

AFFILIATIONS

1 Department of Nuclear Medicine, Institut Curie, 92210 Saint-Cloud, France;

romain.seban@gmail.com, laurence.champion@curie.net

2 Laboratoire d'Imagerie Translationnelle en Oncologie, Inserm, Institut Curie, 91401, Orsay, France

3 Department of Internal Medicine, Montefiore/Albert Einstein College of Medicine, Bronx, NY, USA; dr.shwesynn@gmail.com, drizzamuneer@hotmail.com

4 Department of Radiology, New York Presbyterian Hospital, Columbia University Medical Center, New York, New York; lhs2120@cumc.columbia.edu, ld2752@cumc.columbia.edu

CORRESPONDING AUTHOR

Laurent Dercle

Department of Radiology

New York Presbyterian Hospital - Columbia University Medical Center

New York, NY, 10039, USA

ld2752@cumc.columbia.edu

WORDS

798/800 words

KEYWORDS

[18F]-FDG PET/CT; metastatic melanoma; bone marrow metabolism; tumor immune environment; theranostic approach.

TO THE EDITOR

We have read with great interest the manuscript "*Prognostic value of bone marrow metabolism on pretreatment 18F-FDG PET/CT in patients with metastatic melanoma treated with anti-PD-1 therapy*" from Nakamoto et al. (*1*). While *The Journal of Nuclear Medicine* has published several papers highlighting the clinical value of sequential [18F]-FDG PET/CT for response assessment (*2,3*), this new manuscript showed that baseline [18F]-FDG PET/CT could also be used to guide treatment decisions.

To this end, the authors studied a population of 92 patients with a diagnosis of metastatic melanoma treated with immune checkpoint inhibitors (ICIs) (*1*). ICIs included anti-PD1 as single-agent (88%) or in combination (12%) with anti-cytotoxic T-lymphocyte antigen-4 or anti-lymphocyte activation gene-3. The authors have evaluated if patients' overall survival (OS) could be predicted by biomarkers such as demographic or clinical (n = 4), biological (n = 1), pathological (n=1), and imaging variables extracted from baseline and on treatment [18F]-FDG PET/CT (n = 6).

Confirming the prognostic significance of BM metabolism

In this population, the authors confirmed that noninvasive measurement of glucose metabolism on non-tumoral bone marrow can be used to predict OS in patients with a diagnosis of advanced melanoma treated with ICIs (*4*). They demonstrated that mean bone marrow-to-liver uptake ratio (BLRmean = bone marrow SUVmean/liver SUVmean) was the most valuable prognostic imaging biomarker. High baseline BLRmean predicted a significantly poor progression-free survival (PFS) and OS. The finding that bone marrow glucose metabolism is an imaging biomarker correlated with survival is of interest and aligns with findings in existing literature (*4,5*). Hence, this letter aims to share with the readership of *The Journal of Nuclear Medicine* recent publications in the field to provide a deeper understanding on the relationship between bone marrow and clinical outcomes.

Association between BM metabolism and systemic inflammation

In a recent review published in *The Journal of Nuclear Medicine*, tumor & bone marrow glucose metabolism were analyzed in 12 studies including 2,588 cancer patients who had both [18F]-FDG PET/CT scans and biochemical assessments with blood samples (*6*). Most studies showed that these imaging biomarkers were associated with clinical outcomes as well as systemic inflammatory responses (high C-reactive protein, low albumin, high neutrophils or leukocytes or platelets).

Association between BM metabolism and tumor immune environment

Since there is a cross talk between tumor immune environment and BM, our team evaluated the association between bone marrow glucose metabolism and transcriptomics in patients with a diagnosis

of metastatic cutaneous melanoma treated with ICIs (*4*). To this end, we assessed the tumor immune microenvironment using transcriptomics analysis on tumor tissues. Strikingly, high bone marrow metabolism was associated with an upregulation of genes related to dendritic cells, regulatory T cells activity, as well as memory T cells phenotypes (*4*).

Of note, this was a pilot study and the major molecular pathways determining the cross talk between the BM and tumor immune environment remains to be elucidated. For now, preclinical studies showed that tumor growth in melanoma seems to play a critical role in reprogramming the host immune system by regulating hematopoiesis, which might be associated with the expansion of immunosuppressive cells such as tumor associated macrophages, regulatory T cells and Myeloid-Derived Suppressor Cells (MDSCs) (*7*).

In patients with gynecological cancer, high BM glucose metabolism was mainly due to the production of G-CSF by tumor cells (*8*). Patients with high BM glucose metabolism displayed an immunosuppressive phenotype with increased MDSCs and decreased CD8+ T-cells (*8*).

Prospective studies and translational studies correlating BM glucose metabolism with antitumor immunity are warranted. Continued efforts need to be made and should focus on improving our understanding of physiopathological concepts. We have to clarify the association between baseline bone marrow glucose metabolism and the presence of an immunosuppressive environment. This is necessary to unravel further cancer-related inflammation and immunosuppressive phenotypes associated with immunotherapy resistance through the use of quantitative transcriptome analyses of tumor, lymphoid tissue biopsies, and immuno-PET imaging.

Potential theranostic approaches

The demonstration of the prognostic value of BM glucose metabolism and of its association with tumor immune environment offers a springboard to exciting, new theranostic research. Novel therapies blocking immunosuppressive agents, such as MDSCs, are indeed under investigation (*9*) to potentiate ICIs. The underlying assumption is that glucose metabolism on tissues with medullary and extramedullary hematopoiesis could be associated with tumor-induced immune suppression. For instance, pre-immunotherapy [18F]-FDG PET/CT that explores bone marrow might be a relevant assay to predict response to MDSCs-blockade therapies, in combination with ICI (*10*).

Conclusion

In conclusion, the scientific community has demonstrated that BM glucose metabolism measured on [18F]-FDG PET is associated with immunotherapy outcomes in patients with metastatic melanoma. The next step is to pursue efforts with prospective and large multicenter studies that would ensure a deeper understanding on how this specific biomarker could be used as a clinical decision support tool in patients with metastatic melanoma treated with ICIs.

DISCLOSURE

The authors have no conflict of interest to disclose.

REFERENCES

1. Nakamoto R, Zaba LC, Liang T, et al. Prognostic value of bone marrow metabolism on pretreatment [18] F-FDG PET/CT in patients with metastatic melanoma treated with anti-PD-1 therapy. *J Nucl Med*. February 2021:jnumed.120.254482.

2. Seban R-D, Schwartz LH, Bonardel G, Dercle L. Diagnosis of Hyperprogressive Disease in Patients Treated with Checkpoint Inhibitors Using 18F-FDG PET/CT. *J Nucl Med*. 2020;61:1404-1405.

3. Dercle L, Seban R-D, Lazarovici J, et al. 18F-FDG PET and CT Scans Detect New Imaging Patterns of Response and Progression in Patients with Hodgkin Lymphoma Treated by Anti-Programmed Death 1 Immune Checkpoint Inhibitor. *J Nucl Med*. 2018;59:15-24.

4. Seban R-D, Nemer JS, Marabelle A, et al. Prognostic and theranostic 18F-FDG PET biomarkers for anti-PD1 immunotherapy in metastatic melanoma: association with outcome and transcriptomics. *Eur J Nucl Med Mol Imaging*. 2019;46:2298-2310.

5. Prévost S, Boucher L, Larivée P, Boileau R, Bénard F. Bone marrow hypermetabolism on 18F-FDG PET as a survival prognostic factor in non-small cell lung cancer. *J Nucl Med*. 2006;47:559-565.

6. Dolan RD, McLees NG, Irfan A, et al. The Relationship Between Tumor Glucose Metabolism and Host Systemic Inflammatory Responses in Patients with Cancer: A Systematic Review. *J Nucl Med*. 2019;60:467-471.

7. Kamran N, Li Y, Sierra M, et al. Melanoma induced immunosuppression is mediated by hematopoietic dysregulation. *Oncoimmunology*. 2018;7:e1408750.

8. Shimura K, Mabuchi S, Komura N, et al. Prognostic significance of bone marrow FDG uptake in patients with gynecological cancer. *Sci Rep*. 2021;11:2257.

9. Holtzhausen A, Harris W, Ubil E, et al. TAM Family Receptor Kinase Inhibition Reverses MDSC-Mediated Suppression and Augments Anti-PD-1 Therapy in Melanoma. *Cancer Immunol Res*. 2019;7:1672-1686.

10. Liu Y, Wei G, Cheng WA, et al. Targeting myeloid-derived suppressor cells for cancer immunotherapy. *Cancer Immunol Immunother*. 2018;67:1181-1195.