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 Bone Marrow (BM) Metabolism and Tumor Immune Environment

Because there is a cross talk between the 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 cell activity, and 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 remain 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 gynecologic cancer, high BM glucose metabolism was mainly due to the production of granulocyte colony-stimulating factor (G-CSF) by tumor cells (*8*). Patients with high BM glucose metabolism displayed an im-munosuppressive 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 physiopathologic 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, preimmunotherapy ^{18}F-FDG PET/CT that explores bone marrow might be a relevant assay to predict response to MDSCs-blockade therapies, in combination with ICI (*10*).

In conclusion, the scientific community has demonstrated that BM glucose metabolism measured on ^{18}F-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

No potential conflict of interest relevant to this article was reported.

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Published online May 28, 2021.
DOI: 10.2967/jnumed.121.262361

Is ^{18}F-FDG PET/CT Effective in Identifying True Residual Disease After Treatment of Pediatric PTLD?

TO THE EDITOR: Limited data are available describing the role of ^{18}F-FDG PET/CT in assessing treatment response in pediatric posttransplant lymphoproliferative disease (PTLD). In this journal, Montes de Jesus reported 8 patients who underwent end-of-treatment ^{18}F-FDG PET/CT. Of 4 positive scans, 1 was true-positive and the remaining 3 were false-positive. There were 4 true-negative and 1 false-negative results. In 2 of the false-positive cases, a 2-y follow-up did not reveal PTLD, and in 1 case a biopsy revealed no evidence of PTLD. For the false-negative end-of-treatment ^{18}F-FDG PET/CT, a biopsy 2 mo later revealed residual monomorphic PTLD (*1*). Similar data were reported in adult PTLD. Van Keerberghen reported positive predictive values (PPVs) and negative predictive values (NPVs) for disease recurrence of 13% and 85% for interim and 33% and 87% for end-of-treatment ^{18}F-FDG PET/CT, respectively. Negative interim or negative end-of-treatment ^{18}F-FDG PET/CT correlated with durable remissions (*2*). A lower false-positive rate was

reported at assessment of treatment response in 20% of cases in a recent metanalysis evaluating the performance of ^{18}F-FDG PET/CT either at interim or end-of-treatment assessments (*3*).

A 12-y-old with history of heart transplant in infancy presented with bowel obstruction and was found to have an abdominal mass. Tumor biopsy revealed monomorphic PTLD/diffuse large B-cell lymphoma (DLBCL) subtype, Epstein-Barr virus–negative. After 4 cycles of immune-chemotherapy, ^{18}F-FDG PET/CT showed avid uptake in a segment of the small bowel (Deauville 4). Because of the limited data about interpreting a positive end-of-treatment ^{18}F-FDG PET/CT in a child with PTLD, he underwent a biopsy, which was negative for PTLD/DLBCL. This case illustrates the problem of a false-positive uptake on ^{18}F-FDG PET/CT and therefore the limitations of a positive ^{18}F-FDG PET/CT in the assessment of treatment response, similar to the report in this journal (*1*). In another child, an 8-y-old with Burkitt lymphoma postcardiac transplant, a residual mediastinal mass at end of therapy was ^{18}F-FDG PET/CT–negative; therefore, no biopsy was performed and no further therapy was administered. This child remains in remission 9 mo after the end of therapy. This decision was guided by the relatively high NPV reported by Van Keerberghena and Montes de Jesus (*2*,*3*). In a metanalysis by Montes de Jesus, inactive metabolic lesions on ^{18}F-FDG PET/CT were considered to be in complete remission. Treatment was stopped in half of the cases to minimize treatment-related complications. Patients in whom treatment was stopped remained in complete remission throughout the study follow-up (*3*).

In pediatric non-Hodgkin lymphoma (NHL), a high NPV was reported in 2 studies (*4*,*5*). This remains to be studied further in patients with post–solid organ transplant Burkitt lymphoma (PSOT-BL), as in our second patient. Post solid organ transplant Burkitt lymphoma is considered a separate entity of PTLD and is treated similarly to Burkitt lymphoma in immunocompetent children. This raises an important point concerning the clinical and pathologic spectrum of pediatric PTLD and the implications this variability may have on the metabolic response by ^{18}F-FDG PET/CT based on the subtype of PTLD. Even in studies of pediatric NHL, a high false-positive rate was reported. In the study by Minard et al., only 2 of 26 patients who underwent biopsy, after chemotherapy, for positive ^{18}F-FDG PET/CT had evidence of residual lymphoma. None of the 62 patients with negative ^{18}F-FDG PET/CT had viable cells at biopsy, and none experienced relapse (*4*). In a study of 18 children with NHL who underwent ^{18}F-FDG PET to assess treatment response, the sensitivity and NPV were 100%, but the specificity and PPV were 60% and 25%, respectively (*5*).

The question is: what is the value of ^{18}F-FDG PET/CT in assessing treatment response and identifying true-positive residual PTLD? The limited data available indicate low sensitivity and a high false-positive rate (*1*–*3*). Therefore, as a screening tool for response assessment, ^{18}F-FDG PET/CT appears to have limited value in identifying true-positive residual disease in pediatric PTLD. The value of performing ^{18}F-FDG PET/CT to assess treatment response is its high specificity and its ability to predict true-negative residual PTLD.

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Published online May 14, 2021.
DOI: 10.2967/jnumed.121.262414