In vivo Molecular Prediction of Carbonic Anhydrase IX-G250MN Expression on Immunotherapy Outcome in Renal Cancer

To the Editor: It is with great interest that we read the article of Atkins et al. (1) and the accompanying commentary of Panelli et al. (2) about the possible usefulness of carbonic anhydrase IX-G250MN (CAIX) expression as a biomarker to predict responses to interleukin-2 therapy in renal cell carcinoma. Atkins et al. (1) showed that high-positively CAIX staining [according to Bui et al. (3)] of mostly primary renal cell carcinoma tumors correlated with a significantly better survival rate after interleukin-2 therapy. This is strikingly in line with a previous observation in a study in which we compared the usefulness of the diagnostic imaging modalities [18F]FDG-positron emission tomography and immunoscintigraphy with 131I-labeled chimeric anti-CAIX monoclonal antibody (mAb) G250 (mAb 131I-cG250) in patients with advanced metastasized renal cell carcinoma (4). We noticed that patients who showed poor accumulation of mAb 131I-cG250 in most of their metastatic lesions subsequently had rapidly progressive disease. The prognostic value of the molecular marker CAIX expression, as determined on specimens of primary tumors and renal cell carcinoma metastases by Atkins et al. (1) and Bui et al. (3), can be evaluated noninvasively with radioimmunoscintigraphy with the mAb 131I-cG250 (4). Thus, in vivo molecular imaging with a mAb targeting CAIX (e.g., radiolabeled mAb cG250) holds promise for patient selection [no treatment of non-immune-responsive tumors as suggested by Panelli et al. (2)] before initiation of therapy in metastatic renal cell carcinoma (4) and for response evaluation during and at the end of therapy. Another advantage of in vivo visualization of CAIX expression with radioimmunoscintigraphy is the possibility to assess the uptake of radiolabeled mAb for each individual lesion as metastases have a lower expression of CAIX than primary tumors (3). Apart from clinical relevance, this noninvasive procedure could add to our understanding of the role of CAIX up-regulation in tumorigenesis of clear cell renal cell carcinoma and its role in the responsiveness of renal cell carcinoma tumors to interleukin-2, other immunotherapies (e.g., IFN-α), or novel experimental treatments that have recently come available for patients with renal cell carcinoma (1, 2). Indeed, more research in this area is warranted.

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References

In Response: Brouwers et al. described an immunoscintigraphic approach to assessing tumor carbonic anhydrase IX (CAIX) expression in patients with advanced renal cancer. Although their data support the contention that low CAIX–expressing tumors are associated with poor prognosis, it is premature to link their results too closely with those reported in our study. For example, the G250 antibody used in their imaging study binds to a different epitope on CAIX than the MN75 antibody used in the University of California at Los Angeles and Dana Farber-Harvard Cancer Center Renal Cancer Program immunohistochemical studies. To date, no data exist that support a relationship between tissue G250 binding and either prognosis or response to interleukin-2 (IL-2) therapy. Furthermore, whereas data with the MN75 antibody relate high CAIX expression on the primary tumor specimen with subsequent response or survival in patients receiving IL-2 therapy, insufficient information is available to determine whether such a relationship would persist if exclusively metastatic lesions were evaluated as proposed with the imaging studies. Nonetheless, the investigators raise several intriguing points about the complementary information that could potentially be obtained through their imaging technique. Such information, if validated, may help to better dissect out the mechanisms of tumor response and resistance to IL-2-based immunotherapy and potentially other novel treatments currently under investigation in patients with advanced renal cancer. My co-authors and I agree that further exploration in the context of clinical trials is warranted.

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