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The Urokinase Plasminogen Activator System in Metastatic Papillary Thyroid Carcinoma: A Potential Therapeutic Target

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AQ: 2 Although distant metastases occur in a minority of papillary thyroid cancer (PTC) patients, their impact on disease course and survival rates is profound, with aggregate 10-yr survival rates of 40% (1). Limited treatment options further complicate management of metastatic PTC. Radioiodine (RAI) remains the standard of care for most distant metastases in PTC. Of particular concern, however, is the significant prevalence of PTC metastases unable to trap RAI; such metastases are termed RAI-refractory (RAIR). Because thyroid cancer loses differentiated features of normal thyroid tissue, one feature commonly lost is sodium iodide symporter expression, which is the entire basis for the use of RAI therapy in thyroid malignancies. This phenomenon can occur in a heterogeneous manner: in a given patient, RAI uptake can vary between individual metastases, and it can even vary within a metastasis at the cellular level.

Because radiation dose to the tumor and successful outcome of RAI therapy are directly correlated, this has a significant negative impact on the ability to treat metastatic disease. One recent study on RAIR metastases' impact on survival (1) showed that 23% of PTC patients had distant metastases that were unable to trap RAI at all, whereas another 23% of PTC patients had distant metastases that trapped RAI but were nonetheless unable to achieve remission (both groups were designated as RAIR). Ten-year survival rates (among all differentiated thyroid cancers) were decreased to 10% for the patients with no RAI uptake and 29% for those with metastases that trapped RAI but did not achieve remission, compared with the 92% 10-yr survival rate of metastatic thyroid cancer patients with RAI uptake who achieved remission (1). The large disparity between survival rates of these groups underscores the extraordinary impact of RAIR metastases in PTC prognosis.

Given the high prevalence of BRAFV600E mutations (and other activating mutations in the RET-Ras-Raf-MAPK pathway) in PTC and RAIR metastatic PTC, one experimental therapy that has been studied is the use of synthetic tyrosine kinase inhibitors (TKI), such as sorafenib, to block this pathway (2). Originally developed as specific inhibitors of BRAFV600E, these drugs have since been shown to have a less specific range of targets. These compounds are approved by the U.S. Food and Drug Administration for the treatment of unresectable hepatocellular carcinoma, gastrointestinal stromal tumors, and advanced renal cell carcinoma. Recently, phase II clinical trials have shown that sorafenib had significant efficacy against RAIR metastatic thyroid cancers, including PTC; sorafenib has since moved forward to phase III clinical trials. These drugs are currently being used off-label at cancer centers for the treatment of RAIR metastatic thyroid malignancies (2, 3).

Although treatment of RAIR metastatic thyroid cancer with sorafenib in clinical trials has yielded some positive results thus far, concerns have been raised regarding several aspects of TKI treatment. The first is the disparity in response according to the site of the metastases. Lung metastases were more responsive than those in lymph nodes, and bone metastases are highly refractory to sorafenib treatment (2, 3). Additionally, there were several adverse side effects resulting from sorafenib treatment. These ranged from mild to severe and included diarrhea, hypertension, fatigue, weight loss/anorexia, thyroiditis, and

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Abbreviations: PTC, Papillary thyroid cancer; RAI, radioiodine; RAIR, RAI-refractory; TKI, tyrosine kinase inhibitor; uPA, urokinase plasminogen activator; uPAR, uPA receptor.

hand-foot reaction syndrome; in some cases, the side effects were severe enough to warrant discontinuation or reduction of therapy. More dangerous side effects reported included pericardial effusion and reversible neutropenia (2, 3).

Perhaps most distressing, however, was the subsequent development of new primary cancers in a subset of patients receiving sorafenib therapy. Cabanillas *et al.* (3) reported that 27% of their patients developed squamous cell carcinoma of the skin or inflammation of actinic keratoses; this trend has been observed in other clinical studies dealing with sorafenib (4). This effect (as well as the lack of responsiveness of some tumors to sorafenib) has been speculated to be the result of the TKI ability to activate CRAF (another member of the RAF family of kinases, with functions similar to BRAF) in cells with wild-type BRAF or mutant RAS, which in turn gives rise to continued activation of MAPK signaling (2, 5). Furthermore, BRAFV600E has been shown to confer antiapoptotic phenotypes to PTC cells (and transformed thyroid cells) via ERK-independent interactions with the mitochondria. Treatment of the cells with sorafenib and the MEK inhibitor U0126 was unable to induce responsiveness to apoptotic stimuli, despite inhibiting ERK signaling; this phenomenon may further explain the ineffectiveness of sorafenib on some metastatic thyroid tumors (6).

Given the apparent shortcomings of both conventional RAI and experimental TKI like sorafenib, we propose that inhibitors of other molecular targets be explored in clinical trials. One attractive target is the urokinase plasminogen activator (uPA) and the uPA receptor (uPAR) system, a key mediator of tumor invasion. uPAR converts pro-uPA to its active form, which then cleaves plasminogen to plasmin. Plasmin can then degrade extracellular matrix components, a prerequisite for tumor invasion and metastasis (7). Previous work by our group has shown that uPAR and uPA are consistently up-regulated in PTC tissue, and the degree of up-regulation positively correlates with metastasis. Furthermore, we have demonstrated that inhibition of uPA and uPAR significantly reduces degradative and invasive potential of BRAFV600E-positive PTC cells (8). Finally, our group has also shown that uPAR (which we showed was induced by BRAFV600E-induced ERK hyperactivity) mediates focal adhesion kinase/phosphatidylinositol 3-kinase/Akt signaling, which coordinates various functions critical to metastatic behavior, including migration, invasion, and proliferation in BRAFV600E-positive PTC cells (9). Our data corroborate studies showing similar importance of this system in other malignancies (7).

Given the importance of the uPA/uPAR system in PTC invasion and metastasis, we submit that uPA/uPAR inhibitors are attractive alternatives in the treatment of metastatic PTC, especially RAIR disease. Potent, orally bioavailable inhibitors of uPA have recently been developed and may hold great potential for the treatment of any metastatic tumor expressing this marker, including PTC (10, 11). One such agent, designed by Wilex (Mesupron, WX-671), is currently being studied in clinical trials for other cancers. In cellular and animal models, Mesupron has been shown to effectively inhibit tumor growth and metastatic spread. Early clinical studies in head and neck carcinoma revealed that Mesupron achieved therapeutic concentrations in tumor tissue while causing no significant side effects, beyond minor gastrointestinal effects (10). This lack of serious side effects corroborates early studies demonstrating the normal life spans/phenotypes of uPA/uPAR-knockout mice (7). A phase II clinical trial in non-metastatic pancreatic cancer has yielded further promising results. In this trial, addition of Mesupron to conventional chemotherapy (gemcitabine) was well tolerated, causing no specific toxicities (beyond those attributed to gemcitabine) and improving response rates (partial or complete remissions), progression-free survival, and overall survival rates (12). Additionally, a phase II clinical trial in HER2-negative metastatic breast cancer is currently ongoing (13).

Mesupron (and other uPA/uPAR system inhibitors) would enable the direct inhibition of a system that is a significant contributor to biological processes underlying the metastatic phenotype of PTC (proteolysis, invasion, and migration, growth and proliferation), as well as metastatic phenotypes of other thyroid malignancies. Furthermore, it would avoid therapy-limiting side effects and the potential risk of skin cancer development seen in sorafenib and other TKI. We therefore advocate that clinical trials involving such inhibitors of the uPA/uPAR system be explored for the treatment of metastatic PTC (particularly RAIR cases) and other thyroid cancers.

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