Advanced Urothelial Carcinoma: Moving the Field Forward

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Current efforts utilizing genomic strategies to unravel the biology of urothelial carcinoma will undoubtedly lead to rational targets, new therapies, and a renewed enthusiasm among researchers and clinicians working in this field—which ultimately will improve the lives of patients with this devastating disease.

Advanced urothelial carcinoma (UC) is a devastating illness with limited effective chemotherapy options for patients with metastatic disease. Molecularly targeted therapy has demonstrated substantial activity in many malignancies, including non-small-cell lung cancer (NSCLC), melanoma, breast cancer, colorectal cancer, and others. Over the past several years, the biology of UC has been better defined, with novel tumor subgroups elucidated by means of integrated genomic analysis.[1] The recognition that many of the same genetic alterations that represent potential targets in other malignancies also exist in UC has led to a renewed interest in clinical trials research in UC. Verdoorn, Kessler, and Flaig provide an excellent discussion of many of these potential targets as well as a comprehensive review of studies incorporating novel therapeutics.

The authors highlight several important molecular targets, including the epidermal growth factor receptors 1 and 2 (EGFR and HER2/neu), vascular endothelial growth factor receptor (VEGFR), and insulin-like growth factor (IGF) pathways. In spite of the fact that more than 50% of UCs overexpress EGFR, the studies evaluating EGFR-targeted therapy have demonstrated limited activity to date. In NSCLC, response to EGFR inhibitors is associated with mutations in exons 19 and 21 of the EGFR tyrosine kinase domain. A recent study demonstrated that EGFR overexpression in UC (as determined by immunohistochemistry) is not associated with EGFR mutations in exons 19 and 21, suggesting that other mechanisms for overexpression may exist in UC.[2] This finding may also relate to the modest activity of EGFR inhibitors in patients with UC vs patients with NSCLC who harbor activating mutations.[3]

Novel agents targeting HER2/neu have changed the landscape in the management of women with breast cancer. More recently, a phase III trial of trastuzumab (Herceptin) for gastric cancer (ToGA) demonstrated a survival benefit for trastuzumab plus chemotherapy in patients with HER2-positive advanced gastric or gastro-esophageal junction cancer.[4] Although there is uncertainty regarding the true level of HER2/neu expression in UC, there is no question that both protein overexpression and gene amplification are present in a subset of patients, creating a strong biologic rationale for the investigation of HER2/neu-targeted therapy in patients with advanced UC. HER2/neu amplification exists in both non–muscle-invasive and advanced UC and may be associated with a more aggressive phenotype.[5-7] The authors present an excellent summary of the trials performed to date, and they appropriately address the need for a randomized trial in order to truly understand the potential role of trastuzumab in HER2/neu-positive UC. In addition, HER2/neu represents an ideal candidate for inclusion in a biomarker-integrated approach in a targeted therapy phase II trial in patients with advanced UC. Such trials have successfully been performed in lung and breast cancers: BATTLE (the Biomarker-integrated Approaches of Targeted Therapy for Lung cancer Elimination trial) and the I SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2).[8,9] The VEGF axis represents a rational target in UC; the authors provide a thorough discussion of the data supporting the significant role that angiogenesis plays in UC biology, and they review the trials utilizing bevacizumab (Avastin), as well as several trials exploring the use of VEGFR tyrosine kinase inhibitors. Although the majority of trials have shown only modest activity, the Hoosier Oncology Group phase II trial evaluating gemcitabine plus cisplatin (GC) and bevacizumab demonstrated a promising survival outcome, which led to the important ongoing multicenter phase III trial (Cancer and Leukemia Group B [CALGB] 90601; NCT00942331) comparing GC + placebo and GC + bevacizumab. The authors appropriately comment on the difficulty that the oncology community has had in completing phase III trials in UC. This is no longer acceptable if we are to change outcomes for patients with advanced UC; CALGB 90601 must be a major priority for the oncology community.
The authors also review the IGF pathway as a target of interest in UC. This pathway is active in many malignancies; however, to date, targeting the pathway in a range of tumors has not demonstrated widespread clinical activity. Nonetheless, there is hope that combination treatment with inhibitors of other signaling pathways will ultimately lead to success.[10] Additional potential targets in UC include fibroblast growth factor receptor (FGFR)-3 and the phosphoinositide-3 kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway, as well as epigenetic events (a recent report describes frequent mutations in a variety of chromatin remodeling genes, including UTX, MLL-MLL3, CREBBP-EP300, NCO1, ARID1a, and CHD6).[11] Rapid advances in genomics, along with The Cancer Genome Atlas (TCGA) in bladder cancer,[12] will lead to the identification of novel molecular alterations in UC, with the promise of a better understanding of tumor biology that holds potential for the development of new therapies. For example, when whole-genome sequencing was used to investigate a complete and durable response in a patient with metastatic bladder cancer treated in a phase II clinical trial with the mTOR pathway inhibitor everolimus (Afinitor), it showed a loss of function mutation in TSC1 (tuberous sclerosis complex 1), a regulator of mTOR pathway activation.[13]

Verdoorn and colleagues have correctly commented on the lack of progress in advanced UC over the past 2 decades. Nonetheless, this is an extremely exciting time in oncology: molecular pathways have been elucidated, and targeted therapeutics have been developed that have led to dramatic improvements in outcomes for patients with many malignancies. Current efforts utilizing genomic strategies to unravel the biology of UC will undoubtedly lead to rational targets, new therapies, and a renewed enthusiasm among researchers and clinicians working in this field—which ultimately will improve the lives of patients with this devastating disease.

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