"Missing the Target" in Urothelial Cancer

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Advanced urothelial cancer remains, along with pancreatic cancer, one of the last solid tumors for which essentially no progress has been made for 25 years. It’s time to think out of the box, and to develop novel and creative ways of overcoming the real, but not insurmountable, logistical challenges to carrying out the needed clinical trials.

Dr. Verdoorn and colleagues have provided a concise summary of the efforts thus far to investigate several classes of targeted agents in patients with advanced urothelial cancers. The urothelial cancer literature is awash with frequent references to the presence of bountiful numbers of therapeutic molecular targets and the relative ease of obtaining tissue (bladder sampling) to do translational science. Despite these theoretical advantages, to date the clinical results from trials of targeted agents, drugs that have established therapeutic value in a number of other solid tumors, could be charitably characterized as extremely disappointing.

When we take a closer look at the trials done to date, essentially all have enrolled all comers—ie, no effort has been made to enrich the trial with the purported key target. This approach is understandable given our insufficient understanding of most of the compounds and their true target or targets and the well-documented difficulty in accruing patients to urothelial cancer trials. Many of the agents currently being evaluated are, in fact, multitargeted, and attempts to restrict patients based on an inadequate understanding of the biology may in some settings actually be the wrong approach.

Recent attempts to narrow eligibility to those patients with tumors expressing the target of interest include a multicenter phase II trial of trastuzumab (Herceptin) in combination with chemotherapy that enrolled only human epidermal growth factor receptor 2 (HER2)/neu-expressing patients. Accrual to this trial was challenging, and in fact it was not designed or powered to evaluate the utility of enriching for HER2/neu expression in response to therapy.[1]

Several newer trials are underway that are specifically designed to assess activity in patients selected for expression of the target. The European Organisation for Research and Treatment of Cancer (EORTC) has completed accrual to a phase I/II trial (NCT00623064) of lapatinib (Tykerb) in combination with gemcitabine (Gemzar) and cisplatin in patients with locally advanced or metastatic urothelial cancer who overexpress HER1 and/or HER2. Investigators from the Hoosier Oncology Group have recently activated a phase II trial (NCT01732107) of dovitinib, a multi-targeted receptor tyrosine kinase inhibitor with activity against both the vascular endothelial growth factor receptor (VEGFR) and fibroblast growth factor receptor (FGFR) pathways in patients with bacillus Calmette-Gurin (BCG)-refractory non–muscle-invasive bladder cancer. FGFR3 mutations are highly associated with early-stage low-grade urothelial cancer, and overexpression of FGFR3 has been observed in up to 42% of muscle-invasive urothelial tumors.[2] Eligibility for the trial will be limited to patients with tumors that demonstrate FGFR3 mutations or overexpression.

As clearly outlined by Verdoorn and colleagues, the clinical experience to date using single-targeting approaches in advanced urothelial cancer has been inadequate, suggesting that a more sophisticated therapeutic paradigm needs to be considered.

The differences in molecular pathogenesis between non–muscle-invasive and invasive disease have long been recognized.[3] Mutations of the receptor tyrosine kinase (RTK)/Ras pathway components, which occur in over 90% of low-grade, noninvasive transitional cell carcinomas (TCCs), are relatively uncommon in high-grade invasive disease. In contrast, invasive TCCs are frequently associated with mutations and allelic loss of p53, and aberrant expression of retinoblastoma protein (pRb), which are rare events in low-grade disease.[4]

Recent work by Zhou and colleagues may provide a rationale for a more integrated approach.[5] Using a transgenic mouse model, the investigators demonstrated that inhibition of mammalian target of rapamycin (mTOR), a downstream effector of AKT, by a 2-week course of rapamycin (Rapamune) significantly reduced the size of high-grade papillary TCCs; however, they observed that despite antitumor activity, there was evidence of considerable residual disease and little, if any,
impact on survival. Molecular analysis revealed a marked induction of activated mitogen-activated protein kinase (MAPK) in rapamycin-treated tumors, which provided a theoretical rationale for the relative ineffectiveness of single-agent therapy. These studies by Zhou and colleagues suggest that in urothelial cancer, targeting one pathway signal could result in compensatory activation of another signaling pathway, resulting in drug resistance; these studies also suggest that more significant antitumor activity (i.e., significant enough to have an impact on the natural history of the disease) might be achievable through the inhibition of several targets in multiple signaling pathways. The concept of attempting to target several pathways is obviously not new but unfortunately remains problematic. Efforts in renal cancer to combine some of the newer targeted agents (e.g., an agent that targets VEGF plus an agent that targets mTOR, etc) have been limited by toxicity issues, and to date there is little evidence that this approach provides synergistic/additive activity. Future efforts that attempt to take advantage of the existence of other reasonably well-defined targets by using drugs with demonstrated on-target activity in studies in patients with advanced urothelial cancer will be complicated by the lack of phase I data for many of the novel combinations. Among the greatest logistical hurdles will be the need to overcome the elephant in the room—i.e., the fact that many of these novel compounds have been and will continue to be developed by a range of companies. The development programs of these companies typically don’t involve urothelial cancers; moreover, a joint effort between companies would be required to do early studies of combinations of these investigational agents. Advanced urothelial cancer remains, along with pancreatic cancer, one of the last solid tumors for which essentially no progress has been made for 25 years. It’s time to think out of the box, and to develop novel and creative ways of overcoming the real, but not insurmountable, logistical challenges to carrying out the needed clinical trials. **Financial Disclosure:** The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**


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