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SPECIAL ARTICLE

National Comprehensive Cancer Network Recommendations on Molecular Profiling of Advanced Bladder Cancer

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INTRODUCTION

In the 2015 State of the Union address, President Barack Obama called for a push toward personalized medicine.[1] In the context of oncology, this can be broadly interpreted as the use of molecular profiling tools to define treatment for individual patients. Personalized medicine is already well established in the treatment paradigm for specific targets in certain malignancies, such as lung and breast cancer. Patients with advanced lung cancer are frequently assessed for alterations in genes that code for epidermal growth factor receptor and anaplastic lymphoma kinase.[2] Each of these alterations has specific therapeutic implications, with a targeted therapy available for either scenario. Molecular profiling has long been incorporated into the management of all stages of breast cancer, for which characterization of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 may lead to personalized options for adjuvant therapy and therapy for metastatic disease.[3]

Management of advanced bladder cancer represents a sharp contrast to the more sophisticated approach to breast and lung cancer. The current algorithm for the management of bladder cancer is a rather dichotomous decision of cisplatin or no cisplatin. Level 1 evidence supports the use of cisplatin-based chemotherapy regimens in the neoadjuvant setting and for front-line therapy of patients with metastatic disease.[4,5] In the second-line setting and beyond, there are no US Food and Drug Administration–approved treatment options. The National Comprehensive Cancer Network (NCCN) guidelines list a variety of cytotoxic regimens, such as pemetrexed, paclitaxel, and docetaxel, all of which are supported by phase II trials.[6] These trials showed minimal benefit, with progression-free survival and overall survival generally ranging from 3 to 6 months and 6 to 9 months, respectively.[7]

The landscape of bladder cancer therapy, however, is evolving. There is accumulating evidence for the activity of programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors, immunotherapeutic agents that reduce T-cell anergy.[8,9] Gene expression profiles of bladder tumors suggest there are several prognostic gene signatures present,[10,11] which may predict benefit from systemic chemotherapy[12] and may also predict response to immunotherapy.[9] Furthermore, the fundamental biology represented by gene expression may provide a context for mutationally driven tumors. One example is the enhanced peroxisome proliferator-activated receptor-γ expression observed in the luminal subtype, which is also enriched for fibroblast growth factor receptor 3 (FGFR3) mutations.[11] Several data sets also support the activity of specific targeted agents in a mutation-dependent context.[13,14] This latter finding supports the recent recommendation by the NCCN Bladder Cancer Guidelines panel, which supports molecular profiling of advanced bladder cancer.

BLADDER CANCER: A DIVERSE MOLECULAR PROFILE

The Cancer Genome Atlas Research Network has provided valuable insights into the genomic diversity of bladder cancer.[10] In a series of 131 patients with pT2-4aNxMx disease, detailed genomic characterization revealed that up to 69% of patients had actionable therapeutic targets. The preponderance of these targets was in the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway, which was found in 42% of patients in this series. Approximately 17% of patients had inactivating mutations in *PIK3CA*, and 9% of patients had mutation or deletion of *TSC1* or *TSC2*. Other notable pathway alterations were in *FGFR3*, with activating mutations found in 17% of patients. Amplification of epidermal growth factor receptor and mutation or amplification of human epidermal growth factor receptor 2 was seen in an equal proportion of patients (9% for both groups).

Ultimately, however, The Cancer Genome Atlas data reflects a cohort of patients with muscle-invasive bladder cancer. Among these patients, it is unclear how many will progress to metastatic disease, for which genomic profiling would theoretically be more relevant to clinical practice. Ross et al[15] have reported outcomes from a cohort of 295 patients with advanced bladder cancer, of whom all were high grade and had advanced stage. The Clinical Laboratory Improvement Amendments–certified platform in this experience interrogated 236 cancer-related genes, as well as 47 introns and 19 rearrangements. In this series, all patients had at least one genomic alteration, with a mean of 6.4 genomic alterations per patient. The most common genomic alterations in this cohort were *TP53* (55.6%), *CDKN2A* (34.2%), *CDKN2B* (26.8%), *ARID1A* (25.8%), *MLL2* (23.4%), *KDM6A* (21.7%), *FGFR3* (21.4%), and *PIK3CA* (20%). A subset of these alterations were labeled actionable, in particular, those alterations for which an associated anticancer drug was approved by the US Food and Drug Administration or was in registered clinical trials. With this in mind, 93% of patients in the cohort had at least one actionable mutation. Of note, the extent of sequencing may have implications for yield. In an analysis of 95 high-grade urothelial carcinoma specimens from Memorial Sloan Kettering Cancer Center, interrogation of 15 oncogenes and tumor suppressor genes yielded mutations in just 65% of patients.[16]

RESPONSE TO TARGETED THERAPIES IN MUTATION-DEFINED COHORTS

Several studies to date have identified a profound response to targeted therapies in subsets of patients that bear specific genomic alterations. An often-cited example is a report from Iyer et al,[14] in which 14 patients with advanced bladder cancer who were enrolled on a trial of everolimus were analyzed for genomic alterations. Five patients were identified with mutations in *TSC1*, a negative regulator the mTOR complex, and patients who bore these mutations derived varying degrees of clinical benefit from everolimus. A patient with mutation in both *TSC1* and *NF2*, the latter also a regulator of the mTOR complex, had the most profound benefit, with a near complete response that lasted 23 months. The observation of everolimus sensitivity in the context of an *NF2* mutation has also been made in a separate report.[17]

Compelling data has also been reported for FGFR3 antagonists. FGFR3 is thought to play a key role in bladder pathogenesis, and levels of the moiety seem to diminish in more advanced stages of the disease.[13] Early phase I trials of FGFR3 antagonists suggest objective response rates (partial and complete responses) in 50% of patients, with the additional benefit of disease stabilization in many more patients with FGFR3 mutated urothelial cancer.[13] Most recently, Choudhury et al[18] have reported clinical benefit with afatinib, an irreversible ErbB family inhibitor, in the context of relevant mutations. In *HER/ERRB3* altered patients, a significant improvement in progression-free survival was observed (6.6 months *v* 1.4 months).

ANTICIPATED EFFECT OF RECOMMENDATIONS FOR MOLECULAR PROFILING

NCCN recommendations for comprehensive molecular profiling will likely broaden the scope of use of these diagnostic tests in patients with advanced bladder cancer. As a consequence, patients with salient alterations, for example, *TSC1* alteration, may be guided toward more rational therapies. The purist may suggest that randomized trials are necessary to demonstrate the benefit of this approach over cytotoxic therapy alone. In fact, such studies have been conducted in the setting of advanced lung cancer; however, similar trials are unlikely to be feasible in advanced bladder cancer, a much less prevalent disease. The more abundant use of molecular profiling in the community will almost surely lead to greater identification of clinical trial candidates. Studies are currently ongoing to assess agents that abrogate signaling through *FGFR3*, *CDKN2A*, *CREBBP*, and *EP300*.[19-21] These are bladder cancer–specific trials; multiple other studies are ongoing in a histology-agnostic fashion. There is also emerging evidence that suggests that factors such as mutational load and intrinsic molecular subtypes may predict outcome with novel immune strategies, such as PD-1 and PD-L1 inhibition.[22] Many novel genomic profiling platforms will ultimately be equipped to discern mutational load and, therefore, may serve a dual purpose: to identify single mutations that predispose to targeted therapy sensitivity and to identify a comprehensive mutational profile that could be associated with immunotherapy responsiveness.

Although many ongoing studies afford an opportunity to obtain molecular profiling in an investigational setting, these studies—conducted largely at academic centers—are often inaccessible to the community-based oncologist. It is often a large expenditure in terms of time and effort for the patient to pursue a consultation at an academic center, and the yield may be low if a relevant study is examining an infrequent molecular alteration. Broadening access to molecular profiling will allow for patients in the community to be screened pre-emptively for salient alterations and may facilitate a more fruitful interaction between community and academic oncologists.

In conclusion, the noted recommendations from the NCCN panel will hopefully reconcile the apparent paradox that exists today—a push toward personalized medicine, but a lack of support for the platforms that facilitate their use. As use of molecular profiling expands, more patients will be discovered to have potentially actionable mutations, many of whom may proceed to relevant clinical trials. Furthermore, use of newer cell-free or circulating tumor DNA platforms may facilitate mutational analysis in patients for whom tissue acquisition is a challenge.[23] In this feed-forward loop, more robust enrollment in clinical trials could facilitate a broader spectrum of targeted therapeutic options for advanced bladder cancer. As previously noted, histology-specific trials for molecular subsets of bladder cancer are emerging; however, there are also other opportunities, such as the National Cancer Institute Molecular Analysis for Therapy Choice trial and other basket trials, which are histology agnostic and would allow for enrollment of patients with salient alterations.[24]

There is substantial evidence mounting for PD-1– and PD-L1–directed therapies, and a vigorous debate surrounds the use of PD-L1 immunohistochemical assessment to identify appropriate patients for therapy.[8,9,25] Data from the phase II assessment of atezolizumab hints at the potential use of mutational load as a predictor of response, furthering the argument for more widespread assessment of genomic profiles. Even with refinement of biomarker selection for checkpoint inhibition, there will remain

a large proportion of nonresponders who require other novel therapies. To address this emerging population, a paradigm shift toward personalized medicine may be in order.

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