New Strategies in...

New Strategies in Muscle Invasive Bladder Cancer: On the Road to Personalized Medicine

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Abstract

Bladder cancer remains one of the most deadly and most expensive diseases affecting modern society. The options currently available to patients with muscle invasive bladder cancer have remained essentially unchanged for the last generation. As the roles for surgery and chemotherapy in the management of this lethal disease have become better defined, so too have the limitations of these two treatment modalities. Despite the lack of groundbreaking clinical advances over the past two decades, the recent years have witnessed a notable increase in the amount of promising preclinical and early translational research that will greatly improve our understanding of the molecular underpinnings of bladder cancer. As this momentum in bladder cancer research continues to build, the next five to ten years show considerable potential for achieving the goal of bringing bladder cancer treatment into the age of personalized medicine.

Background

Urothelial carcinoma of the bladder is the fifth most common cancer affecting the American population with 70,530 new cases estimated for 2010. It is also the ninth deadliest cancer in American men with 14,680 deaths estimated for 2010. Urothelial cancers develop along two major “tracks” (non-invasive and muscle-invasive) that pose distinct challenges for clinical management. For patients with non-invasive
urothelial carcinoma, the very high recurrence rate (~70-80%) mandates frequent and prolonged cystoscopic surveillance and thus makes bladder cancer the most expensive malignancy in terms of lifetime dollars spent per patient.(2) For patients with muscle-invasive disease, the traditional standard of care has been radical surgery (cystoprostatectomy in men or anterior exenteration in women) with regional lymphadenectomy. For those patients with advanced urothelial carcinoma of the bladder (defined as local extension to adjacent organs, regional lymphadenopathy, distant metastases, or disease recurrence after radical surgery), options for durable disease control are limited. For patients presenting with metastatic disease and for patients with disease recurrence after radical surgery, the median survival has been estimated to be only slightly over one year.(3)

**Multi-modality approach to bladder cancer**

To improve upon the survival of patients with advanced bladder cancer, chemotherapy has been integrated into various treatment paradigms. Early large-scale randomized clinical trials showed that the combination of methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) had activity in patients with advanced bladder cancer.(4) In the ensuing two decades since this discovery, the role of chemotherapy for patients with clinically localized muscle-invasive bladder cancer has been tested by multiple investigators.(5, 6) It has been shown that administration of cisplatin-based chemotherapy in the neoadjuvant setting can prolong survival for patients with muscle-invasive bladder cancer. In a randomized controlled trial of patients with clinical stage ≥
T2 urothelial carcinoma of the bladder, the median survival for patients receiving neoadjuvant chemotherapy prior to cystectomy was markedly greater than for patients proceeding directly to cystectomy (77 months versus 46 months). This survival improvement was attributed to the significantly greater likelihood of having no residual cancer in the cystectomy specimen for the combination therapy group than in the surgery alone group (38% versus 15%, p < 0.001).

Despite the existence of level 1 evidence showing that neoadjuvant chemotherapy is beneficial, it remains grossly underutilized. Many clinicians counsel their patients to proceed directly to surgery with the rationale that neoadjuvant chemotherapy overtreats many patients and that adjuvant chemotherapy can be selectively administered to those patients with unfavorable findings at cystectomy. The literature for adjuvant chemotherapy is less compelling than that for neoadjuvant chemotherapy, but a direct meaningful comparison between the two modalities has yet to be undertaken. While it is not known if there is a difference between the neoadjuvant and the adjuvant setting, it is becoming increasingly clear that chemotherapy does have a role in the treatment of clinically localized muscle invasive bladder cancer. The fact that systemic chemotherapy is actually given, rather than the specific timing of administration, may be the most critical aspect.

To address the concern about overtreatment with nonselective use of neoadjuvant chemotherapy, the current practice at MD Anderson Cancer Center is to selectively administer neoadjuvant chemotherapy only to patients with a palpable mass on exam under anesthesia, lymphovascular invasion in the TURBT specimen,
hydronephrosis, or aberrant histology (micropapillary, small cell carcinoma, adenocarcinoma, etc)—those patients thought to be at highest risk for harboring loco-regionally advanced bladder cancer. Patients without any of these features are counseled to proceed to immediate cystectomy and those patients found to have pathologic upstaging at cystectomy are treated with adjuvant chemotherapy, without sacrificing survival.(14) Patients who receive neoadjuvant chemotherapy and are found to have lymph node-positive disease at cystectomy are also treated with adjuvant chemotherapy, albeit with a different regimen.

On the Horizon

The evolution of muscle invasive bladder cancer from being a purely surgical disease to a disease best managed with a multimodal approach has been the key transformation in our conceptualization of this lethal cancer over the last decade. The biggest challenges now are i) to improve our ability to accurately stage patients (eg, identify patients who need chemotherapy because cystectomy alone will be insufficient for cure), and ii) to improve our ability to predict which patients will respond to which chemotherapy regimens. In the current paradigm, there is no reliable way to distinguish between those patients who have clinically occult locoregionally advanced disease—and should therefore receive neoadjuvant chemotherapy—and those patients with truly localized low risk disease that would be best managed with immediate
cystectomy. Various investigators are actively engaged in better understanding the biology of bladder cancer to develop biomarkers that can predict disease aggressiveness (to improve staging) and response to specific therapies (to allow for development of personalized treatment plans). The neoadjuvant paradigm as described below represents a promising step toward the personalization of therapy for invasive bladder cancer. Within the next five to ten years, current research efforts will likely have identified accurate predictive markers of response to chemotherapy that will allow us to construct highly specific treatment plans tailored to each individual patient.

**Understanding the biology of bladder cancer**

Since it is well known that patients die not from the regional effects of bladder cancer within the pelvis but rather from the sequela of metastatic disease, a major research focus has been to understand the basic biologic mechanisms that promote cancer progression. Specifically, what is the biologic switch that triggers bladder cancer cells to invade through the detrusor muscle and/or gain access to the lymphatic and vascular channels of the systemic circulation? What mechanisms allow tumor cells to colonize distant sites to establish metastases? Furthermore, what are the mechanisms that allow some cancers to be resistant to conventional chemotherapy?

To understand the biologic switch that allows bladder cancer progression, investigators have taken differing approaches. The Berman lab at Johns Hopkins University has focused on identifying bladder cancer stem cells in the basal cell compartment of the urothelial lining.(15) This group has posited that these cancer stem
cells are ideally situated for escaping immune surveillance and surviving cytotoxic therapy by interacting with the neighboring stroma.(16) Using preclinical models, Theodorescu and colleagues have identified proteins that may be involved in both local escape from the bladder as well as metastatic colonization of distant sites. Using the UMUC-3 bladder cancer cell line, they showed that RalBP-1, an effector protein for the Ras pathway target RalA, is necessary for metastasis of human cancer cell lines.(17) Additionally, they have shown that tumor endothelin-1 facilitates metastatic colonization of the lung in a mouse xenograft model of bladder cancer.(18) Other molecules that have been implicated in bladder cancer aggressiveness include src (which is paradoxically downregulated in muscle-invasive cancers), caveolin-1, galectin-1, p53, PTEN, and choline kinase-alpha.(19-22)

Gene expression profiling has also been used to find molecular signatures that are predictive of patterns of metastasis and drug sensitivity. Building on previous work that established that epithelial-to-mesenchymal transition (EMT) is involved in bladder cancer progression and metastasis, we used global gene expression profiling of human bladder cancer cell lines as well as primary patient tumors to define molecular signatures of tumor heterogeneity.(23) Tumor cells naturally segregated into epithelial and mesenchymal subsets. The epithelial subset contained all of the non-muscle invasive and approximately half of muscle-invasive tumors. The epithelial subset expressed high levels of the p53 family member, p63, a marker of the basal “stem cell” compartment of the urothelium. It also contained all of the bladder cancer cell lines that were sensitive to inhibitors of epidermal growth factor receptor or fibroblast
growth factor receptor-3. The mesenchymal subset was composed entirely of muscle invasive tumors, and mesenchymal tumors tended to express lower levels of the PTEN tumor suppressor than did the epithelial tumors. These results are consistent with recent studies demonstrating that loss of PTEN drives the development of muscle-invasive disease in genetically-engineered mice and is associated with muscle-invasive disease in patients. (21) Preclinically, RNAi-mediated knockdown of the EMT-associated transcription factors Zeb-1 or Zeb2 inhibits tumor cell invasion, whereas knockdown of the “epithelial” transcriptional regulator p63 increases Zeb1 expression in some bladder cancer cells and promotes tumor cell invasion. (24) These findings are in keeping with the widely accepted two-track theory of bladder cancer development and suggest that EMT is a critical determinant of overall bladder cancer biology. (25) Strikingly, however, high level expression of p63 identified a particularly lethal subset of muscle-invasive bladder cancers, despite p63’s apparent role in suppressing EMT. Our ongoing experiments are focused on more precisely defining the roles of p63 and EMT in muscle invasion and metastasis and its influence on sensitivity to conventional and investigational cancer therapies.

Improving selection of patients

Since it is likely that not all patients with invasive bladder cancer benefit from neoadjuvant chemotherapy, better stratification of “high” and “low” risk cancers will be a key focus of emerging research efforts. Over the past two decades, our definition of stage has expanded beyond simple anatomical staging (EUA, three-dimensional imaging)
to incorporate adverse histologic features (variant histology, lymphovascular invasion) that reflect the virulent biology of bladder cancer. While we have been modestly effective at distinguishing between high- and low-risk tumors, we still understage 40% of patients and 15% die of bladder cancer. To improve upon these disappointing statistics, investigators are adopting a systems biology approach to incorporate molecular and genetic features into the staging paradigm to identify the relevant features of tumor biology that mediate bladder cancer pathogenesis. This understanding will allow for improved distinction of “favorable” and “unfavorable” cancers and therefore, more informed and objective selection of neoadjuvant therapy.

Ongoing preliminary studies suggest that it is possible to refine our current “staging” scheme by integrating gene expression and micro-RNA profiling information with clinical parameters to classify risk. These results are being verified on larger cohorts of specimens from low-risk patients to determine if it is possible to identify a “signature” from the arrays that can be used prospectively to help determine which patients will benefit most from neoadjuvant chemotherapy. Similarly, investigators are evaluating whether global gene expression patterns can identify patients likely to respond to specific therapies. Early work suggests that in addition to regulating disease progression, EMT also appears to be associated with sensitivity to cisplatin-based chemotherapy.

Theodorescu and colleagues have developed a novel algorithm that may predict tumor cell sensitivity to various conventional and investigational agents.(26) The COXEN (for COeXpression ExtrapolatioN) algorithm, uses baseline gene expression profiling and
drug sensitivity data from the NCI-60 panel of human cancer cell lines and baseline gene expression profiling data from bladder cancer cell lines to isolate lists of co-expressed genes that are associated with sensitivity or resistance to a given drug. COXEN has been used in several recent studies to successfully predict tumor sensitivity to cisplatin-based therapy.(26-28) Intriguingly, our preliminary data indicate that the expression of most of the COXEN-defined cisplatin resistance genes overlap with molecular markers of EMT.

**The neoadjuvant platform for development of personalized therapy**

The efficacy of chemotherapy for more advanced bladder cancer has been stranded on a modest plateau for nearly a generation with no seminal advances since the advent of combination chemotherapy in the early 1980’s. Reliable symptom palliation and routine prolongation of life have been achieved, but relapses are still swift, devastating, and all but inevitable. In this setting, there is a pressing need to “expand the paradigm.” Many of the newer “biologic” agents have yet to be explored fully in bladder cancer. The neoadjuvant platform represents a very attractive method of developing “personalized” therapy for bladder cancer and it may have implications for the treatment of other solid tumors. As compared with other solid tumors that may rely upon a diagnostic needle biopsy, larger volumes of tumor for diagnosis and for research can be obtained during staging cystoscopy and transurethral resection of tumor. Following treatment additional tumor may be collected at a repeat cystoscopy or upon cystectomy providing the opportunity to evaluate the impact of a targeted agent on specific pathways. This may also allow us to explore avenues of tumor biology
and pathways related to chemo-sensitivity and chemo-resistance of tumor cells. Developing new agents in the setting of patients with intact bladders provides an ideal opportunity to explore these agents and to collect tissue specimens before and after therapy to measure receptor phosphorylation and other downstream targets, as well as to measure response.

At MD Anderson Cancer Center, we have adopted a unique two-pronged paradigm to incorporate the study of novel agents both with and without cytoreductive chemotherapy (Figure). The benefits of this strategy are clear; we can collect tissue before treatment by routine cystoscopy, with residual post-treatment tissue collected at cystectomy. This approach allows us to study the effects of novel agents on the downstream receptor pathways in the hopes of developing molecular markers that will predict response or resistance to treatment. Previous studies in the neoadjuvant setting suggest that overexpression of VEGF is associated with a higher rate of relapse despite surgery and MVAC in these high-risk patients. Based on these data, we are currently conducting a trial combining dose-dense MVAC with bevacizumab with the goal of enhancing pathological response (pT0) and improving survival of patients with locally-advanced bladder cancer.(29)

The second approach in our neoadjuvant paradigm has been to study new agents in patients who may not require cytoreductive chemotherapy. While it is clear that neoadjuvant chemotherapy improves the survival of patients undergoing cystectomy, the overall benefit is modest.(6) For patients with low-volume muscle invasive disease or recurrent high-grade non-invasive or T1 tumors, there is a high
likelihood of cure with cystectomy alone – with disease specific survival at 10 years approaching 85% (unpublished data). Traditionally, we have taken these patients to cystectomy first and then offered adjuvant chemotherapy selectively to patients with pathologic upstaging with no sacrifice in survival. As part of our neoadjuvant paradigm, these patients are now offered inclusion in a novel proof-of-principle phase II neoadjuvant trial of erlotinib to identify a “signature” of tumors likely to respond to EGFR-based therapy. The hypothesis is that quantification of markers of EMT (e-cadherin, miR-200, Zeb-1/2) in pretherapy biopsies and correlation with changes in Ki-67 will allow us to prospectively identify tumors likely to respond to EGFR-based therapy. As with the neoadjuvant bevacizumab trial, tumor tissue is collected at baseline, with residual tumor collected at cystectomy. Knowledge gained from this trial may have substantial impact by establishing a paradigm that sets the stage for personalized therapy for bladder cancer.

Conclusion

For both clinicians and laboratory investigators alike, the ultimate goal of bladder cancer research is to reduce the morbidity and mortality of this aggressive disease through innovative translational research in early detection, risk assessment, and personalized treatment. If we are to succeed, the foundation for this goal must be based on an improved understanding of the underlying genetic and molecular
aberrations that contribute to the pathogenesis of this lethal disease. Our significant advances in bladder cancer research over the past decade have led to the development of molecular markers of risk, progression, and therapeutic response; as well as the development of new therapeutic and preventive strategies based on this molecular information. The research advances on the horizon promise to simultaneously expand our armamentarium of treatment options for patients with invasive bladder cancer as well as improve our ability to select patients most likely to respond to therapy. It is our hope that the momentum from these developments will boldly propel the field of bladder cancer therapy forward into the age of personalized medicine.
References

Figure 1. The MDACC neoadjuvant paradigm for patients with invasive bladder cancer. All patients with invasive urothelial cancer are clinically stratified as either “low risk” or “high risk” for locoregionally advanced disease. Patients in the “low risk” category – to whom chemotherapy is not typically administered – are offered enrollment in single-agent studies with medications such as erlotinib. Erlotinib is given for 5 days prior to cystectomy. Pre-treatment tissue (obtained at TURBT) and post-treatment tissue (obtained at cystectomy) are then used for pharmacodynamic and molecular profiling studies. Patients in the “high risk” category are offered enrollment in clinical trials that call for adding a novel agent (e.g., bevacizumab) to conventional chemotherapy. For all patients with resectable invasive bladder cancer, the neoadjuvant paradigm allows for the testing of novel agents as well as the acquisition of pre- and post-treatment tissue without compromising patient care.
Resectable urothelial cancer  

Low risk  
Pharmacodynamic studies (erlotinib)  

High-risk  
- lymphovascular invasion  
- hydronephrosis  
- 3-D mass on EUA (cT3b)  
- cT4a  
- variant histology  

Radical cystectomy  
M-VAC/bevacizumab  
Radical cystectomy
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