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The dawn of personalized medicine

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Abstract

Long awaited data from the clinical investigation of bladder cancer in both the neoadjuvant and adjuvant settings were released in 2011, setting the stage for the next generation of work in this area. The findings of a number of studies provide the first steps towards a personalized approach to this disease.

2011 was a year of progress in the field of bladder cancer. Efforts to set the context for more definitive, practice-changing studies of targeted agents in bladder cancer were reported. Updated analysis of a large European phase III trial of neoadjuvant chemotherapy confirmed a significant survival advantage, and mutations that define potential drivers of disease, as well as a gene signature that predicts lymph node involvement before cystectomy, are now available. Taken together, these advances make significant strides in our understanding of bladder cancer and begin to pour the foundation for a more personalized approach to the assessment and treatment of affected patients.

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Competing interests

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Currently, no targeted therapies are utilized in the routine clinical care of advanced bladder cancer, and this is largely due to lack of study rather than negative results. Two notable studies published in 2011 addressed this dearth of evidence. The importance of angiogenesis in oncogenesis is widely accepted and several antiangiogenic agents have been approved for cancer treatment in recent years. Preclinical evidence indicates that the vascular endothelial growth factor (VEGF) axis is important in urothelial carcinoma, but there has been little clinical investigation of vascular inhibition in patients with urothelial cancer. This year, the Hoosier Oncology Group published a single-arm, phase II study of a 21-day cisplatin–gemcitabine regimen for advanced urothelial carcinoma with addition of the VEGF-directed antibody bevacizumab, in 43 patients.¹ The overall radiographic response rate was 72% (19% were complete responses), with a median overall survival of 19.1 months. Both of these outcomes are encouraging and suggest improvement over historical series, in which overall survival has ranged from 14 to 18 months. Pulmonary embolism or deep vein thrombosis was observed in 21% of the study cohort, prompting a dose reduction of gemcitabine midway through the trial. The Cancer and Leukemia Group B is sponsoring a randomized, phase III study of this regimen in patients with advanced urothelial carcinoma (Clinical trials.gov identifier: NCT00942331).

Adding to our insight of targeted therapy, a new understanding of the mechanism of pulmonary metastasis in bladder cancer was described in 2011. Endothelin-1 (ET-1) is a vasoconstrictor, expression levels of which correlate positively with muscle invasion and negatively with bladder cancer-specific survival. In new preclinical findings, ET-1 and its receptor were determined to be necessary for lung metastasis in bladder cancer, and this process was shown to be dependent on macrophage activity in the lung.² Importantly, pharmacologic inhibition of the ET-1 axis, using orally bioavailable ET-1 receptor inhibitors, prevented the development of lung metastases, but had little effect on established primary or metastatic tumors. Attempting to translate these findings into a clinical context suggests that the use of ET-1 receptor inhibitors will be most efficacious in the adjuvant setting, not in the metastatic setting. This information may guide the future development of ET-1 inhibitors for bladder cancer, given their availability and tolerability for chronic use.

An important update to the large European phase III neoadjuvant chemotherapy trial was reported in 2011.³ This trial included patients with T2 grade 3, T3 or T4a bladder cancer (N0 M0) planning to undergo radical cystectomy or definitive radiation therapy. A total of 976 patients were randomized to either three cycles of a 21-day cisplatin, methotrexate and vinblastine (CMV) chemotherapy regimen or no chemotherapy before undergoing cystectomy or radiation therapy. The initial reports of this study in 1999 revealed a trend toward chemotherapy benefit that did not reach significance. In the updated report, there was a 16% reduction in the risk of death and an absolute increase in the 10-year survival (from 30% to 36%) with CMV chemotherapy. Of note, the reduction in the risk of death was 26% in patients treated with cystectomy, which is comparable to that reported in the neoadjuvant findings with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy reported by SWOG.⁴ Importantly, there is now evidence of a survival advantage with the use of neoadjuvant chemotherapy in two randomized, phase III studies, so a discussion of neoadjuvant chemotherapy should take place in all fit patients with muscle-invasive disease preparing for definitive local bladder cancer therapy.

Despite these positive findings, which are based on pathological risk stratification, it is clear that the majority of patients treated with neoadjuvant chemotherapy do not benefit. A robust prognostic test is needed that would facilitate the use of chemotherapy in those at highest risk of recurrence, with a predictive test to select the therapy most likely to elicit a response in each patient. We did see some progress in the search for better prognostic markers for bladder cancer in 2011. In one new study, gene expression was assessed in three separate cystectomy cohorts and evaluated in the context of pathologic lymph node status at the time of surgery.⁵ Two cohorts (including 90 and 66 patients) were used as training sets and a 20-gene signature was developed, which was validated in a larger group ($n = 185$). Patients in the validation cohort were prospectively collected in an earlier clinical trial and analyzed retrospectively. The 20-gene expression model yielded an RR for the discovery of lymph node metastases of 1.74 in the designated 'high-risk' group compared to an RR of 0.70 in 'low-risk' patients, and was independent of stage and lymphovascular invasion. Conceivably, with further validation, patients at high risk of node-positive disease could be identified using this algorithm and then strongly encouraged to undergo neoadjuvant chemotherapy before definitive treatment.

Whole-exome sequencing of paired tumoral and peripheral blood samples was recently performed in a small set of patients with bladder cancer, in an attempt to identify prognostic biomarkers.⁶ The initial findings from this cohort were then tested in a larger cohort of 88 patients. Several previously defined mutations were observed (in *TP53*, *RBI* and *HRAS*), as well as a number of novel mutations. Of these, *UTX* was the most commonly mutated gene, identified in 21% of tested individuals, with 17 nonsense, 5 missense and 1 synonymous mutation noted when combining the discovery and validation screens. Of particular note, eight of the newly identified mutated genes were related to chromatin remodeling, suggesting a potential area for bladder cancer investigation. Interestingly, mutations in chromatin remodeling genes have been commonly found in several other cancer types, suggesting a fundamental contribution to carcinogenesis.

Results of retrospective studies have suggested that p53 is both a marker of prognosis⁷ and potentially predictive of response to cytotoxic chemotherapy.⁸ However, the results of a much anticipated phase III trial testing p53 as a biomarker in patients after radical cystectomy were somewhat disappointing.⁹ Notably, these patients had early stage disease (pT1–2 N0 M0), and based on current pathologic risk stratification they would frequently not receive adjuvant chemotherapy. Patients whose tumors were negative for p53 overexpression—with <10% nuclear reactivity on immunohistochemical analysis—were observed, while those with p53-positive tumors were offered randomization to MVAC chemotherapy or observation. A total of 521 patients were registered, 272 were positive for p53, and 42% of these consented to randomization for chemotherapy. The findings of the trial were negative: the 5-year rate of recurrence was 20% regardless of p53 status, and p53-positive patients randomized to chemotherapy had a similar recurrence rate to p53-positive patients who did not receive chemotherapy. In other words, the immunohistochemical assessment of p53 is not useful in this setting. This study highlights both the challenge of successfully completing large-scale clinical trials in bladder cancer, with a trial accrual

period of more than 8 years despite the participation of many academic institutions, and also the ongoing need for robust prognostic biomarkers for urothelial carcinoma.

In summary, building on the findings described here should result in a better understanding of the underlying science of bladder cancer and possible clinical applications in the years to come. A future is approaching in which we can rationally and scientifically apply many of the targeted agents that are currently in development, based on a personalized assessment of patients with bladder cancer.

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Key advances

- Encouraging results have been obtained from studies of targeted therapies in bladder cancer,¹ laying the groundwork for future investigation in this area
- The reporting of a second randomized phase III trial of neoadjuvant chemotherapy³ confirms a survival advantage for patients with muscle-invasive bladder cancer
- A 20-gene expression model has been developed⁵ that can identify patients, before cystectomy, at high risk of lymph node involvement
- Evidence suggests a number of chromatin remodeling genes are involved in bladder cancer,⁶ representing a novel area for future investigation
- The immunohistochemical assessment of p53 is not a useful marker of prognosis or predictive of response to chemotherapy⁹