

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Bladder Cancer: Advances in Treatment and Research

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H&O What is the background on bladder cancer and the current state of this disease?

MG Bladder cancer affects approximately 70,000 patients a year in the United States and accounts for approximately 14,000 deaths yearly. Superficial, or non-muscle invasive, bladder cancer accounts for the vast majority of diagnoses. Non-muscle invasive bladder cancer presents in various forms but is generally treated with transurethral resection and followed by installation of immunotherapy or chemotherapy into the bladder.

For muscle invasive bladder cancer, surgical removal of the bladder is standard treatment, although for some patients there are bladder sparing approaches involving the appropriate combination of chemotherapy and radiation. Approximately 40–50% of patients undergoing surgical resection of the bladder will experience metastatic recurrence. For these patients, chemotherapy is the mainstay of treatment.

In the late 1980s, the methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) regimen was developed, and after a series of phase III trials, it became a standard chemotherapy regimen for patients with metastatic disease. The MVAC regimen is associated with response rates of 50–60% but also with some significant toxicities. Subsequently, MVAC was compared to newer generation cytotoxic regimens such as gemcitabine and cisplatin; a large trial comparing gemcitabine and cisplatin to MVAC found similar outcomes between the regimens, but fewer adverse events with gemcitabine and cisplatin. Therefore, gemcitabine plus cisplatin is the more commonly used current standard regimen for metastatic bladder cancer.

H&O What advancements have been made in the past few years in prevention, early detection, and quality of life outcomes?

MG In terms of prevention, there have not been many significant advances. However, in terms of early detection, novel urine-based molecular tests that are more sensitive but less specific than conventional urine cytology have been developed.

There have been developments to improve quality of life in patients with all stages of bladder cancer. For patients with muscle invasive disease who require surgery, there have been dramatic advances in surgical techniques, such as the formation of orthotopic neobladders, which is an internal reservoir connected to the native urethra that eliminates the need for an ostomy. Furthermore, bladder-sparing procedures, such as partial cystectomy, are now available to patients; this procedure also eliminates the need for an ostomy. There have also been developments in bladder-sparing therapies such as combining chemotherapy and radiation therapy in order to leave the native bladder intact. For patients with advanced or metastatic disease, the advances in quality of life have to do with chemotherapeutic regimens associated with less toxicity than traditional regimens.

H&O What is photodynamic therapy?

MG Photodynamic therapy involves intravesical installation of a porphyrin, a light-sensitive molecule, which is taken up by cancer cells. Fluorescence endoscopy is then performed; when cancer cells are exposed to the light, the porphyrins are activated and cause cell death. Photodynamic therapy can potentially aid in the treatment of multifocal non-muscle invasive bladder cancers.

There has been a randomized phase III study comparing the use of photodynamic therapy with conventional cystoscopy and resection. The integration of photodynamic therapy appeared to decrease the amount of residual tumor and improved the relapse-free survival in patients with non-muscle invasive disease. This technology is not approved by the US Food and Drug Administration but is available in other countries.

H&O What is the focus of current research?

MG There are several major focuses of research in bladder cancer. For the treatment of advanced disease, targeting angiogenesis has been a big theme. Several phase II studies have explored anti-angiogenic therapies both as single agents and in combination with cytotoxic chemotherapy. Single agent sunitinib (Sutent, Pfizer) has been associated with modest activity in chemotherapy refractory bladder cancer in a phase II study published by Gallagher and colleagues in the *Journal of Clinical Oncology*. We presented initial results of the combination of gemcitabine, cisplatin, and sunitinib at the American Society of Clinical Oncology Genitourinary (ASCO GU) Cancers Symposium this year. This regimen demonstrated intriguing preliminary activity but was associated with significant hematologic toxicities at the dose and schedule tested, and this study is ongoing with a revised dose and schedule. Hahn and colleagues from the Hoosier Oncology Group reported the results of a phase II trial of gemcitabine, cisplatin, and bevacizumab (Avastin, Genentech) at ASCO in 2009. This regimen has been moved forward in an ongoing phase III study conducted by the Cancer and Leukemia Group B. This is the first phase III study in bladder cancer integrating an anti-angiogenic agent.

Another main focus of research, similarly to other solid tumors, is to identify the molecular mechanisms of tumor growth and progression in individual patients, which will ultimately allow a personalized approach to treatment. Ongoing studies are selecting patients with HER-2 amplification or fibroblast growth factor receptor (FGFR) mutations for treatment with the relevant “targeted” therapy.

H&O What are the challenges in the treatment of bladder cancer?

MG There are some challenges unique to bladder cancer, and there are other challenges that are common to all solid tumors. The general challenge applicable to all solid tumors is that these tumors are heterogeneous. Often times the molecular mechanisms driving cancer growth in one metastatic site may be different than in another site. We often do not have available tumor tis-

sue from multiple metastatic sites and may only have it from the primary tumor. Hence, really getting to the molecular mechanisms that drive growth and progression of cancer in an individual patient is challenging and is frequently limited by the lack of tissue.

A challenge somewhat unique to bladder cancer is that the patient population is generally older, with multiple comorbidities, and frequently with some element of renal dysfunction.

H&O What role do molecular markers and predictors of recurrence play in the management of bladder cancer?

MG Molecular markers currently provide only a limited role in the management of bladder cancer. The urine molecular and fluorescence in situ hybridization studies may aid in detecting recurrent superficial bladder cancer; however, for the treatment of patients with muscle invasive disease and advanced disease, molecular markers do not yet play a role in the everyday management. There have been many attempts to integrate molecular markers in the treatment and prognostication of patients with bladder cancer, and ultimately that is where the field is headed, but at this time there is nothing that is integrated into clinical management on a regular basis.

With regard to predictors of recurrence, there are clinical nomograms integrating prognostic information such as tumor stage and grade, which can aid in predicting the risk of recurrence after surgical removal of the bladder. There have been several studies examining a variety of molecular markers, both individually and in combination, such as altered p53 status, that are promising, but so far nothing has been validated to the point of being incorporated into daily management.

H&O What were some of the interesting findings at the 2010 ASCO GU Symposium?

MG Some of the noteworthy studies include 15-year outcomes of selective bladder preservation for muscle invasive bladder cancer at the Massachusetts General Hospital, presented by Dr. Jason Efstathiou. The investigators presented the 15-year outcomes of 348 patients treated at their institution from 1986–2002. The analysis showed that the 5-year overall survival in these patients was 52%, which is similar to what we see with radical cystectomy in patients with muscle invasive disease. In this series, approximately 70% of patients retained their native bladder. Overall, the results were sobering in that there is still a significant risk for distant recurrence and ultimately for bladder cancer-related death. However, a large number of patients who

opted for this type of strategy and survived were able to retain their native bladder.

Another interesting study, which was presented by Dr. Edward Messing, examined whether mixed histologic features affected the survival benefit from neoadjuvant platinum-based combination therapy in patients with locally advanced bladder cancer. This was a secondary analysis of the Southwest Oncology Group trial S8710—a trial integrating neoadjuvant chemotherapy prior to cystectomy versus cystectomy alone in muscle invasive bladder cancer. This was one of the 2 large trials that have established a survival benefit for neoadjuvant chemotherapy in bladder cancer. A large proportion of patients with bladder cancer have transitional cell carcinoma, but often times there is a mixed component of squamous cell cancer or adenocarcinoma in the tumor.

There has been some controversy as to whether or not patients with mixed histologies benefit from chemotherapy, though this analysis found that the survival benefit from chemotherapy was greater in patients with mixed histologies compared to those with pure urothelial carcinoma. Furthermore, the investigators concluded that the presence of squamous or glandular differentiation in bladder cancer is a strong indication for the use of neoadjuvant chemotherapy prior to cystectomy. There will not likely be a prospective trial to address this question, and these data, though retrospective in nature, will be important in routine clinical practice.

H&O Where do you think future research is headed?

MG Future research is focused on identifying the molecular drivers of cancer progression in individual patients and matching the appropriate treatment to the appropriate molecular perturbations. There are ongoing efforts in this regard. A presentation by Iyer and colleagues at the ASCO GU Symposium reported on their efforts to characterize the frequency of “druggable” gene mutations in invasive bladder cancer specimens. They demonstrated that small subsets of patients harbored mutations in BRAF, FGFR3, and PI3K. There are currently drugs in clinical development, which potentially mitigate the effects of activating mutations in these genes, and evaluating these drugs in the appropriate patient populations may mean the difference between failure and success.

Suggested Readings

Efstathiou JA, Coen J, Spiegel DY, et al. 15-year outcomes of selective bladder preservation for invasive bladder cancer: the Massachusetts General Hospital experience. Abstract presented at: American Society of Clinical Oncology Genitourinary Cancers Symposium; March 5–7, 2010, San Francisco, CA. Abstract 273.

Messing EM, Ely B, Scosyrev E, et al. Do mixed histologic features affect survival benefit from neoadjuvant platinum-based combination chemotherapy in patients with locally advanced bladder cancer? Abstract presented at: American Society of Clinical Oncology Genitourinary Cancers Symposium; March 5–7, 2010, San Francisco, CA. Abstract 274.

Clinicaltrials.gov. Gemcitabine Hydrochloride and Cisplatin With or Without Bevacizumab in Treating Patients With Advanced Urinary Tract Cancer. Identifier: NCT00942331