Bladder Cancer: Advances in Diagnosis and Clinical Care

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STATEMENT OF NEED

In 2010, it was estimated there were 70,530 new cases of bladder cancer diagnosed in the United States, with 14,680 deaths occurring from the disease. Bladder cancer is the fourth most common type of cancer in men and the eighth most common in women. It ranks as the third most common cancer and the ninth leading cause of cancer death in men. Each year in the United States, more than 52,000 men and 18,000 women are diagnosed with bladder cancer. More than 9 out of 10 Americans with bladder cancer have a type called transitional cell cancer (TCC) — cancer that begins in cells that normally make up the inner lining of the bladder. TCC is the most common form of bladder cancer, accounting for more than 90% of all bladder cancers. There are no approved agents for the treatment of advanced or metastatic relapsed TCC of the urinary bladder.

It is expected that the incidence of bladder cancer will continue to increase concurrent with an increase in industrialization, lifestyle factors, and an aging population. In the United States, over 500,000 people are survivors of this cancer. Most of the patients with bladder cancer require frequent follow up and treatment, some as often as two to four times per year.

LEARNING GAPS

Bladder cancer is an underserved disease that is both difficult to detect and has a high rate of recurrence. The suboptimal performance of many current markers and the lack of proven markers for many urologic applications, such as the surveillance of bladder cancer, have led to an intensive search for new markers. Yet despite such intense research activity, relatively few molecular markers have been successfully integrated into clinical practice.

At only 14 months, the median survival for patients with metastatic bladder cancer has not changed significantly in the last 20 years. Few new therapies are being tested and research in bladder cancer has historically been under funded. In addition, several therapeutic interventions known to influence survival have not been widely adopted into practice.

Cystectomy is often delayed in patients with high-risk non–muscle-invasive bladder cancer. In muscle-invasive disease, mounting evidence supports a more extensive surgical approach and the beneficial role of neoadjuvant chemotherapy on survival. However, a wide gap remains between evidence and practice. A recent study using the National Cancer Database to evaluate the integration of chemotherapy for bladder cancer in the United States showed that only 11.6% of patients received any perioperative chemotherapy, most of those in the adjuvant setting. As at least 70% of all bladder initially is non–muscle-invasive disease, the urologist must determine a treatment strategy that balances the risk of recurrent, invasive disease (occurring in > 15% of patients), with the risk of overtreatment. Transurethral resection (TUR) with surveillance cystoscopy is sufficient therapy for most low-grade non–invasive tumors. However, most will recur within five years, but will rarely invade or result in death.

Certain subgroups of patients, however, have a higher risk and should be considered for intravesical therapy after TUR and perioperative chemotherapy. These subgroups include patients with tumors classified as high grade, and patients with carcinoma in situ. In addition, patients with large lesions (> 3 cm), multifocal tumors, evidence of lamina propria invasion, or recurrence within two years have been shown to be at increased risk. Although aggressive intervention with intravesical therapy in this high-risk group leads to response rates up to 85%, recurrence rates are more than 50% within the first year and 90% by five years. In addition, up to 50% of high-risk lesions will progress to muscle-invasive disease despite intravesical therapy.

Intravesical Bacillus Calmette-Guérin (BCG) is widely accepted as the most effective therapy for patients with high-risk non–muscle-invasive transitional-cell carcinoma compared with chemotherapy or TUR alone. It will delay recurrence and progression, thereby decreasing the need for immediate cystectomy. Intravesical BCG is administered usually as a six-week induction course. There is strong evidence that a course of induction therapy followed by a course of maintenance therapy leads to significantly better outcomes than induction therapy alone, though not all maintenance BCG schedules provide the same benefit. Unfortunately, up to 50% of patients may fail BCG therapy, particularly when longer follow-up is provided, due to several different factors — intolerance, resistance, relapse, and refractory.

Intravesical valrubicin and gemcitabine have been studied as second-line intravesical therapy for refractory superficial bladder cancer. Although complete response rates range from 20% to 50%, durable disease-free intervals have not been maintained. Intravesical taxane therapy has also met with some success when combined with a maintenance course where a 13-month disease-free rate of 46% has been reported. Interferon alfa-2b (IFN-α-2b) is well tolerated as monotherapy for superficial bladder cancer and has shown some dose-related clinical efficacy after BCG failure, although the durability of the response is limited.

Photodynamic therapy may also be effective in patients with refractory CIS, but the logistics and poor availability of equipment and expertise continue to render this therapy investigational. Mitomycin with microwave-induced hyperthermia is another approach that seems to be more effective than standard mitomycin when used as adjuvant therapy, but it has not been tested in refractory patients. Although intravesical BCG may be safely offered to many patients with high-risk disease,
early cystectomy should be considered in patients considered at high risk for progression, because survival may be compromised once progression occurs. Clearly, more effective intravesical therapies are necessary to improve overall survival and provide an alternative to radical cystectomy. A number of novel approaches are being tested, including intravesical maintenance gemcitabine, doublets of intravesical agents, and intravesical gene therapy.

The current standard approach for treating muscle-invasive bladder cancer in the United States is radical cystectomy and bilateral pelvic lymph node dissection (PLND). However, a preponderance of evidence indicates that the quality of the radical cystectomy and the extent of PLND affect staging and survival. Although there has been significant controversy regarding the importance of the extent of PLND in patients undergoing a radical cystectomy, patients undergoing a more extensive dissection seem to have a lower risk for disease recurrence and improved overall survival. The success of radical cystectomy is dependent upon the stage of the cancer. However, even in pathologically organ-confined bladder cancer, the five-year survival rate is approximately 68%. Outcome is worse for those with extra-vesicular extension or lymph node involvement, with approximately 25% to 30% five-year survival rates. Failures after radical cystectomy occur most frequently at distant sites, with systemic relapses being fatal in most patients.

Multiagent chemotherapy seems to improve outcomes of patients with muscle-invasive bladder cancer. Additional support for the role of neoadjuvant cisplatin-based combination chemotherapy is provided by long-term analysis of a large, randomized, phase III trial performed by the Medical Research Council/European Organisation for Research and Treatment of Cancer. At seven-year follow-up, survival was superior for those who received neoadjuvant chemotherapy compared with those undergoing cystectomy or radiation therapy alone.

There is an expectation a growing number of new markers and therapies targeting different pathways will revolutionize patient diagnosis and management strategies in bladder cancer. Today there are more clinical trial options for treatment, as well as many promising agents in late-stage clinical testing. Given the challenges of diagnosing and treating bladder cancer, it is imperative physicians learn to improve patient outcomes by defining and implementing optimal standards of care, and identify and prioritize specific strategies to advance development of more effective therapies for patients with bladder cancer.

LEARNING OBJECTIVES
Upon completion of this activity, participants will be able to:
• Examine the advances in diagnostic imaging of bladder tumors
• Discuss the emerging role and economics of new therapies in the treatment of bladder cancer
• Review the advantages and disadvantages of adjuvant and neoadjuvant therapy to treat bladder cancer
• Describe the most recent advances in chemotherapy, immunotherapy and targeted therapy for bladder cancer

TARGET AUDIENCE
This publication has been developed and is intended for urologists, oncologists, and other healthcare professionals involved in the diagnosis and treatment of bladder cancer.

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In this issue of *Grand Rounds in Urology*, two leading experts in the clinical area of bladder cancer will provide analysis of treating this common cancer and its future prospects. According to recent statistics, bladder cancer is the fourth most common type of cancer in men and the eighth most common in women. Each year in the United States, more than 70,000 men and women combined are diagnosed with bladder cancer. More than 90% of patients with bladder cancer (both men and women) have a transitional cell cancer (TCC), and unfortunately current chemotherapeutic agents for advanced or metastatic disease rarely result in cure. Additionally, bladder cancer is one of the most costly cancers to treat, more costly than lung cancer, more than breast cancer, and more costly than colon cancer. It is expected that the incidence of bladder cancer will continue to increase, and most of the surviving patients will require frequent follow up and treatment.

In the first article, Dr. Seth Lerner, from Baylor College of Medicine, discusses a number of challenges in managing localized disease, including intravesical therapy and endoscopic imaging. Since this field is moving fairly quickly, Dr. Lerner provides the reader with some tools that might answer the question as to why wouldn’t you want to see better at the time of cystoscopy. The discussion covers issues like fluorescence, narrow-band imaging, and optical coherence tomography as well as drug therapy, and we hope it will offer valuable ideas on how to provide a more complete diagnosis and comprehensive therapy.

The second article is from Dr. Daniel Petrylak, from Columbia University, who provides his analysis a systemic approach to treatment. Of important emphasis is how understanding biology can help in the development of future clinical trials. Dan discusses adjuvant and neoadjuvant therapy, antiangiogenetics agents, and the prospect of vaccines among the ongoing variety of approaches. His thorough review suggests there is an utmost need for collaborative clinical trials to find new ways to attack this difficult to treat and deadly disease.

We hope you will enjoy this latest issue of *Grand Rounds in Urology*, and that it will help you in your approach to patient care in 2012 and beyond.

Sincerely,

E. David Crawford, MD
INTRODUCTION

In 2011, an estimated 69,250 individuals were diagnosed with bladder cancer, and 14,990 died from the disease [1]. The incidence of bladder cancer is roughly 4-fold higher in men than in women, and nearly twice as high in white men compared with African American men. Approximately half of all bladder cancer patients are diagnosed with non-invasive urothelial cancer (Ta, Tis) of the bladder. Prognosis is typically excellent for these patients, with a 5-year survival rate of 97%. By comparison, the 5-year survival rates for bladder cancer diagnosed at local, regional, and distant stages are 73%, 36%, and 6%, respectively [1].

Given the importance of early detection and accurate staging, the urology community has significant interest in new optimal imaging technologies that address the diagnostic challenges of standard white-light cystoscopy (WLC). Furthermore, even in patients with non-muscle invasive bladder cancer (NMIBC) optimally managed with cystectomy and trans-urethral resection of the bladder tumor (TURBT) and intravesical chemotherapy and/or immunotherapy, and patients with refractory NMIBC or muscle invasive disease requiring cystectomy, high relapse rates are observed. New approaches to the adjuvant treatment of NMIBC, as well as options for second-line therapy in patients with recurrent disease, are major research priorities.

Bladder Cancer: A Local Approach

Seth Lerner, MD

PREVENTION

Cigarette smoking is a well-known risk for bladder cancer for both men and women. Bladder cancer incidence rates have been rising in the U.S. over the past several decades. Changes in smoking prevalence and cigarette composition suggest that the relationship between smoking and bladder cancer may be changing as well. According to new findings from the National Institutes of Health-American Association for Retired Persons (NIH-AARP) Diet and Health Study, smoking now accounts for approximately 50% of the population-attributable risk (PAR) of bladder cancer in both men and women [2]. This represents a sharp increase in smoking-related risk, particularly among women [2].

The NIH-AARP Diet and Health Study evaluated the association between tobacco smoking and bladder cancer in men (n = 281,394) and women (n = 186,134) between 1995 and 2006. Compared with never-smokers, the risk of bladder cancer was more than double for former smokers (HR, 2.22; 95% CI, 2.30-2.44) and more than 4-fold higher for current smokers (HR, 4.06; 95% CI, 3.66-4.50). In 7 earlier observational studies initiated between 1963 and 1987, the relative risk estimate for current smoking was 2.94 (95% CI, 2.45-3.52). Thus, compared with historical data, the relative risks for smoking were higher in the more recent NIH-AARP Diet and Health Study. Moreover, the PARs of bladder cancer for tobacco smoking were comparable for men (0.50) and women (0.52) [2].

The NIH-AARP Diet and Health Study investigators attribute the stronger relationship between smoking and bladder cancer to changes in cigarette composition [2]. Over the past 50 years, modifications in cigarette design have reduced the tar and
nicotine concentrations in cigarette smoke, but have also increased the concentrations of carcinogens such as betanaphthylamine and tobacco-specific nitrosamines [2]. Although the overall prevalence of tobacco smoking is declining, the increased exposure to bladder-specific carcinogens may contribute to slow inexorable rise in the incidence of bladder cancer [2].

The most significant long-term impact clinicians can have on bladder cancer is to prevent people from ever smoking. For current smokers, smoking cessation is a critical tool for cancer prevention, though the attributable risk reduction may take years to manifest.

ENDOSCOPIC IMAGING
Traditionally, WLC has been the preferred diagnostic tool for confirming the presence, location, and type of tumor. This imaging approach, however, is not useful for detecting subclinical abnormalities. For instance, CIS of the bladder is not visible by WLC in up to 50% of cases. Small papillary tumors and urothelial cancer in the prostatic urethra may also be missed with standard WLC. Using WLC alone, bladder tumors can be overlooked and inadequately resected during TURBT. Indeed, many so-called ‘recurrences’ of bladder cancer may not be true recurrences, but may instead reflect the growth of residual tumors or microscopic lesions unintentionally left behind at resection. Advances in endoscopic imaging improve the detection and treatment of subclinical tumors and other features that are not visible with standard imaging techniques.

Fluorescence Cystoscopy
Fluorescence-guided cystoscopy, which is also called photodynamic diagnosis (PDD), exploits the behavior of photoactive porphyrins to visualize bladder lesions. Following intravesical instillation, porphyrins such as 5-aminolevulinic acid (5-ALA) accumulate in tumor cells, where they emit a red color when exposed to blue light. In a typical fluorescence cystoscopy procedure, 50 cc of the photoactive porphyrin is instilled into the empty bladder, and emptied after 1 hour. Cystoscopy is then performed using a light source with a filter that allows passage of light in the blue spectral range (380 to 450 nm). The urologist can toggle between white light and blue fluorescence excitation light, allowing the operator to switch between standard and fluorescence cystoscopy. Currently, only rigid fluorescence cystoscopy is available.

One of the limitations of 5-ALA-guided fluorescence cystoscopy is the relative tissue insolubility of 5-ALA. This barrier has been addressed with the development of an hexyl ester derivative of 5-ALA, hexaminolevulinate (HAL), with increased lipophilicity [3]. Stenzl and colleagues demonstrated the benefits of HAL-guided fluorescence cystoscopy in a prospective, randomized study of 814 patients who were suspected of having NMIBC at increased risk for recurrence [4]. In the trial, all patients underwent WLC and TURBT when indicated. Patients randomized to the fluorescence group (n = 365) also received intravesical HAL at least 1 hour prior to cystoscopy and underwent additional evaluation with blue light before and after TURBT. Patients

<table>
<thead>
<tr>
<th>Study/Tumor Grade</th>
<th>White-Light Cystoscopy</th>
<th>Fluorescence Cystoscopy</th>
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<tbody>
<tr>
<td>Jichlinski (N = 52) [57]</td>
<td>46</td>
<td>76</td>
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<tr>
<td>All grades</td>
<td>78</td>
<td>97</td>
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<tr>
<td>Carcinoma in situ (CIS)</td>
<td>56</td>
<td>97</td>
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<tr>
<td>Schmidbauer (N = 211) [58]</td>
<td>68</td>
<td>95</td>
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<tr>
<td>All grades</td>
<td>68</td>
<td>95</td>
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<tr>
<td>CIS</td>
<td>68</td>
<td>92</td>
</tr>
<tr>
<td>Joacham (N = 146) [59]</td>
<td>68</td>
<td>92</td>
</tr>
<tr>
<td>All grades</td>
<td>83</td>
<td>95</td>
</tr>
<tr>
<td>CIS</td>
<td>83</td>
<td>95</td>
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<tr>
<td>Grossman (N = 108) [61]</td>
<td>56</td>
<td>95</td>
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<tr>
<td>pTa</td>
<td>56</td>
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<td>pT1</td>
<td>56</td>
<td>95</td>
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Within the fluorescence group, 16.4% of patients with Ta or T1 tumors and 46.3% of patients with CIS had at least 1 lesion that was visible only with fluorescence (P = .001). The within patient false-positive rate was comparable in the HAL and WLC groups (12.1% vs. 10.2%). During the 9-month follow-up period, 47% of patients in the fluorescence group had tumor recurrence compared with 56% in the WLC group (RR, 0.84; P = .026). Therefore, in this pivotal trial, HAL-guided fluorescence cystoscopy improved the detection of Ta and T1 tumors and, by influencing treatment decisions, reduced the rate of tumor recurrence at 9 months [4]. These findings led to the approval of HAL-guided fluorescence cystoscopy in May 2010, for the detection of non-muscle-invasive papillary cancer of the bladder.

Several additional studies have demonstrated that HAL-guided fluorescence cystoscopy is more sensitive than WLC for detecting bladder tumors, particularly CIS and papillary lesions. In a meta-analysis of 3 randomized trials, HAL increased the detection of CIS by approximately 12% compared

Table 1. Tumor Detection by White-Light Cystoscopy and Hexaminolevulinate (HAL)-Guided Fluorescence Cystoscopy

In a
with WLC [5]. In another recent review, Witjes and colleagues concluded that HAL provides clear advantages for the visualization of bladder tumors [6]. In particular, the addition of fluorescence cystoscopy to standard WLC improves the detection of CIS by approximately 20% (Table 1) [6].

Kausch and colleagues examined the completeness of TURBT with WLC compared with HAL-guided fluorescence cystoscopy [7]. In a meta-analysis of 3 trials, TURBT performed under fluorescence cystoscopy reduced residual tumor rates at second resection by 72% compared with WLC alone (OR, 0.28; P < .0001) [7]. Improved tumor detection and resection with fluorescence-guided cystoscopy appears to prolong time to recurrence [6, 7]. In 2 prospective trials, the median time to recurrence varied from 5 to 8 months with WLC, compared with 12 to 17 months with fluorescence-guided cystoscopy [7]. Patients with multifocal or recurrent tumors appear to benefit most from fluorescence-guided cystoscopy [6].

Current options for fluorescence-guided cystoscopy have important limitations. Photobleaching results in a loss of fluorescence and a corresponding decrease in the ability to detect bladder lesions. Even with improved lipophilicity relative to 5-ALA, HAL has limited tissue penetration. Fluorescence-guided cystoscopy has been associated with a higher rate of false-positive biopsy results compared with WLC, though this is also seen with WLC. The gap between techniques in false-positive rates is closing, however, as clinicians gain experience with fluorescence-guidance cystoscopy. To date, the reductions in disease recurrence rates that are attributable to fluorescence-guided cystoscopy have been modest and inconsistent.

Several options for addressing these limitations are currently under evaluation. Novel fluorophores such as hypericin show decreased susceptibility to photobleaching [8, 9]. Hypericin is insoluble in water, but solvents such as albumin and polyvinylpyrrolidone (PVP) are effective carriers [8, 9]. In a small study of 57 patients with suspected primary or recurrent bladder malignancies, fluorescence cystoscopy using PVP-hypericin was more sensitive in the diagnosis of CIS and dysplasia compared with WLC [10]. As this diagnostic technology evolves, novel photosensitizers may play an important role in fluorescence-guided cystoscopy.

**Narrow-Band Imaging**

Narrow-band imaging (NBI) is an emerging imaging technology for endoscopy that filters out the red light spectrum to provide two bandwidths of illumination centered on blue (415 nm) and green (550 nm) light [11]. Hemoglobin preferentially absorbs these wavelengths, thereby increasing the visibility of capillaries and submucosal blood vessels. Compared with standard white-light examination, NBI improves the visualization of capillaries on the mucosal surface and the deeper vasculature structures by enhancing contrast between them.

In prospective studies, NBI flexible cystoscopy significantly improved the detection of urothelial carcinoma (UC) tumors compared with standard white-light flexible cystoscopy with the same instrument [12, 13]. Kerr and colleagues evaluated 427 patients for bladder tumor recurrences with standard white-light cystoscopy [13]. Compared with WLC, NBI cystoscopy were treated by fulguration or TURBT. Compared with follow-up with WLC, NBI cystoscopy was associated with a lower rate of tumor recurrence (94% vs. 62%), a lower mean number of recurrent tumors (5.2 vs 2.8), and longer median recurrence-free survival (12 months vs 29 months; P = .001) [14].

The Clinical Research Office of the Endourological Society (CROES) has launched an international, multicenter, randomized trial to compared the safety and efficacy of white-light

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**Figure 1.** Comparison of mucosal lesions visually suspicious for carcinoma in situ (CIS) differentiated by optical coherence tomography (OCT) [16]. Under OCT imaging, the left lesion shows a combined bright urothelial and lamina propria layer, which is characteristic of CIS. By comparison, OCT imaging of the right lesion shows normal urothelium.
and NBI cystoscopy in the detection and treatment of bladder cancer recurrence [15]. The CROES Global Randomized NBI Bladder Cancer Study plans to randomly assign 764 patients to NBI-assisted TURBT (Arm A) or white-light-assisted TURBT (Arm B). The primary efficacy endpoint is recurrence rate at 1 year. Secondary endpoints will evaluate 3-month recurrence, perioperative (30-day) morbidity, risk factors for perioperative morbidity, and the association between recurrence rate and adjuvant therapy. The study estimates a 1-year recurrence rate of 45% in the white-light-assisted TURBT arm, and is powered to detect a 10% reduction in 1-year recurrence in the NBI-assisted TURBT arm. As of August, 2011, approximately 150 patients have been accrued. The CROES Global Randomized NBI Bladder Cancer Study remains open to investigators who are interested in enrolling patients (see www.croesoffice.org for more information).

**Optical Coherence Tomography**

Optical coherence tomography (OCT) is a high resolution, real-time imaging modality that uses near-infrared light to penetrate the surface of biological tissue. OCT measures the unique backscattering pattern of different tissue characteristics to generate a cross-sectional, 2-dimensional image of the underlying tissue microstructure. OCT initially gained FDA clearance for use in imaging retinal disorders in ophthalmology in 1996, and subsequently demonstrated utility for imaging esophageal and pancreatico-biliary diseases in gastroenterology and cutaneous diseases in dermatology.

In patients with bladder cancer OCT can characterize bladder lesions that are visually subtle, such as CIS, based on sub-surface microstructural detail (Figure 1). As an extension of conventional cystoscopy, OCT facilitates the noninvasive examination of bladder tissue at a resolution of 10 to 20 μm. This modality can distinguish structural features in the bladder wall with a depth of penetration of 1 to 2 mm, including changes involving the mucosa, lamina propria, and superficial muscularis propria and thus may be useful for determining the presence and depth of invasion of bladder tumors (Manyak MJ, Gladkova ND, Makari JH, Schwartz AM, Zagaynova EV, Zolfaghari L, Zara JM, Iksanov R, Feldchtein FI. J Endourol. 2005 Jun;19(5):570-4).

Lerner and colleagues evaluated OCT as an adjunct to conventional cystoscopy in a retrospective study of 32 patients undergoing bladder biopsy or TURBT [16]. Compared with biopsy findings, OCT imaging correctly identified tumors confined to the mucosa with a sensitivity of 90% and a specificity of 89%. In addition, OCT detected muscle-invasive lesions with 100% sensitivity, 90% specificity, and 92% accuracy. Erosion and scarring were the major sources of false-positive results. The mucosa and submucosa may be disrupted or absent in cases of erosion or scarring, resulting in microstructural features that may resemble invasion [16]. Accuracy may improve as clinicians gain experience interpreting OCT images.

At the 2011 Société Internationale d’Urologie (SIU) annual meeting, Lerner and colleagues described the use of OCT at Baylor College of Medicine, in Houston, Texas [17]. The single-institution study included 84 patients with a history of bladder cancer who were undergoing biopsy or TURBT. In total, 97 unique lesions were identified. Compared with pathology findings, OCT imaging detected bladder lesions confined to the mucosa (stage Ta or CIS) with a sensitivity of 89% and a specificity of 86%. In addition, OCT identified invasive tumors (stage ≥T1) with a sensitivity and specificity of 93% and 85%, respectively. By comparison, the sensitivity and specificity of bladder cytology for all tumors were 37% and 88%, respectively [17].

OCT is undergoing further evaluation in a multicenter study with participants from Baylor College of Medicine, University of Wisconsin, Cornell University, and the Cleveland Clinic. The trial will enroll approximately 100 patients with 1 or more papillary tumors that are amenable to complete resection (stage Ta or T1) and do not require a cystectomy, or positive cytology or fluorescence in situ hybridization (FISH) findings, with or without visible tumor. The trial is designed to validate tumor staging and margin-status assessment with OCT compared with WLC and pathology.

Future applications for OCT may involve multiple imaging modalities. Schmidbauer and colleagues found that OCT combined with HAL-directed fluorescence cystoscopy significantly reduces the false-positive rate of fluorescence cystoscopy alone, and therefore may reduce the need for unnecessary biopsies in patients with suspected UC [18]. Investigators are also testing algorithms for quantitative OCT image analysis, with the goal of real-time tumor detection and grading [19, 20]. Additional technological advances include the use of Doppler flow imaging in OCT to identify neovascular blood flow, and the use of time-lapse, ultrahigh-resolution OCT to improve the detection of nonpapillary bladder cancer [21, 22].

**Confocal Laser Endomicroscopy**

Confocal laser endomicroscopy (CLE) is an emerging imaging technique that allows for real-time in vivo microscopy of living tissues. CLE involves the use of fiberoptic probes inserted through standard endoscopes, including cystoscopes. Typically performed with fluorescein or fluorescently-labeled antibodies against tumor surface markers, CLE provides tumor visualization with micron-level resolution. The resulting images are similar to histology, revealing cellular morphology and tumor microarchitecture. Probe-based CLE is currently cleared for clinical use in the respiratory and gastrointestinal tracts, including the assessment of Barrett’s esophagus [23].
Probe-based CLE has been used in conjunction with both rigid and flexible cystoscopy. In 2011, Wu and colleagues from Stanford University, Stanford (should this be Menlo Park?), CA, described their experience using CLE in the assessment of 66 patients scheduled for TURBT or nephrectomy [23]. In the study, CLE images were compared with findings from WLC and standard hematoxylin and eosin analysis. Compared with histology, probe-based CLE enabled real-time interrogation of the entire urinary tract. To facilitate the adjunctive use of CLE imaging in bladder cancer, investigators are developing CLE-specific diagnostic imaging criteria to differentiate normal, inflamed, and low- and high-grade cancer [23].

INTRAVESICAL THERAPY

Perioperative single dose intravesical chemotherapy is the standard of care for patients with low and intermediate risk NMIBC undergoing TURBT [24]. Intravesical instillation has the benefit of limiting systemic uptake of cytotoxic agents while providing optimal contact with the target tissue. In a meta-analysis of 7 randomized trials, a single postoperative instillation of chemotherapy reduced the risk of recurrence by 39% compared with TURBT alone in patients with stage Ta/T1 bladder cancer (36.7% vs. 48.4%; P < .0001) [25]. Despite clear evidence supporting its use, however, perioperative intravesical chemotherapy has not been widely adopted by urologists in the U.S. for the treatment of NMIBC. Madeb and colleagues evaluated claims data from 16,748 patients who were diagnosed with bladder cancer between 1997 and 2004 [26]. Among those who underwent cystoscopic biopsy or TURBT (n = 14,677), only 0.33% received same-day intravesical instillation of chemotherapy [26].

In the US, Mitomycin-C (MMC) is the favored agent for both peri-operative and adjuvant intravesical chemotherapy. There are ongoing issues with shortages of MC in some parts of the country, which mandate the development of alternative chemotherapy agents. In addition, some patients have clear contraindications to MMC, including hypersensitivity, bladder perforation, myelosuppression, and thrombocytopenia [27]. For the majority of patients with NMIBC, however, intravesical therapy is a safe and effective option for reducing the risk of recurrence [24]. Researchers are evaluating options for enhancing the delivery of intravesical therapy toward improved efficacy and better tolerability.

Electromotive Mitomycin-C

Penetration of intravesical MMC into the mucosa and the deeper tissues of the bladder wall is driven in part by the concentration gradient of the drug. Indeed, some MMC failures may be attributable to inadequate drug delivery. Electromotive drug delivery is an emerging option for increasing MMC penetration into the urothelium, lamina propria, and superficial muscle layers of the bladder wall. The electromotive technique relies on the principles of iontophoresis, in which ions are driven down gradients induced by an electric field. Di Stasi and colleagues evaluated the safety and efficacy of preoperative intravesical electromotive MMC in patients with NMIBC [28]. In a prospective phase III trial, 352 patients with primary NMIBC were randomly assigned to 1 of 3 treatment groups: TURBT alone (n = 116), TURBT plus one immediate postoperative instillation of passive-diffusion MMC 40 mg with a dwell time of 60 minutes (n = 119), or one immediate pre-TURBT instillation of intravesical electromotive MMC 40 mg with a 20 mA electric current for 30 minutes (n = 117). Patients with intermediate- and high-risk NMIBC also received adjuvant intravesical therapy.

The median follow-up was 85.4 months. A single intravesical instillation of electromotive MMC immediately prior to TURBT was more effective in reducing tumor recurrence and prolonging disease-free survival than TURBT alone or post-TURBT passive-diffusion MMC (Table 2). In the post-TURBT passive-diffusion MMC group, 36.1% of patients had bladder symptoms and 23.5% discontinued treatment because of pain or bladder spasms. By comparison, no side effects were reported in the pre-TURBT electromotive MMC group [28].

The high tolerability of electromotive MMC suggests a potential future role in combination therapy. Intravesical electromotive MMC has been combined successfully with bacillus Calmette-Guerin (BCG) in patients with high-risk NMIBC, illustrating the potential benefits

![Table 2. Outcomes Following Transurethral Resection of Bladder Tumor (TURBT) Alone, TURBT Followed by a Single Intravesical Instillation of Passive Diffusion (PD) Mitomycin-C (MMC), or TURBT Plus a Single Preoperative Intravesical Instillation of Electromotive MMC in Patients with Non–Muscle-Invasive Bladder Cancer [28](n = 16) | PD/MMC Post-TURBT (n = 119) | Electromotive Drug Administration (EDMA) Pre-TURBT (n = 117) | P (EDMA/MMC Pre-TURBT versus other groups) |
---|---|---|---
| Tumor recurrence, % | | | |
| All patients (n = 352) | 63.8 | 58.8 | 37.6 | < .001 |
| Low-risk disease (n = 30) | 0 | 0 | 3.3 | .409 |
| Intermediate-risk disease (n = 225) | 62.7 | 59.7 | 36.5 | .001 |
| High-risk disease (n = 27) | 84.4 | 75.0 | 51.5 | .012 |
| Median disease-free survival, mo | 12.9 | 16.4 | 56.9 | < .001 |
of a multimodal approach that involves chemotherapy and immunotherapy [29].

**Gemcitabine**

Perioperative intravesical chemotherapy with gemcitabine is also being evaluated in bladder cancer. The phase III Southwest Oncology Group (SWOG) 0337 trial is testing the safety and efficacy of a single dose of 2 grams of intravesical gemcitabine immediately after TURBT in patients with newly diagnosed or recurrent grade 1 or 2 bladder cancer [30]. Approximately 408 patients will be randomly assigned to treatment with intravesical gemcitabine or placebo within 3 hours of TURBT. Patients will be stratified according to disease status (first occurrence vs. recurrent disease) and number of tumor sites (1 vs. ≥2). As of December 2011, 296 patients had been accrued to SWOG 0337. Moving forward, the target accrual is 14 patients per month.

The primary efficacy endpoint will be time to recurrence. The trial is powered to detect a 15% reduction in time to recurrence at 2 years. Additional sub-studies will examine the sensitivity and specificity of urine biomarkers, including the BTA Stat test and the NMP22 BladderChek, for follow-up monitoring. The trial will also examine whether gemcitabine preferentially reduces clonal recurrences of the index bladder cancer; whether gemcitabine activating or inactivating enzyme polymorphisms predict response to gemcitabine; and whether co-expression extrapolation (COXEN) modeling can be used to predict therapeutic response. The COXEN algorithm uses microarray analysis to evaluate tumor gene expression and predict drug sensitivity or resistance.

**Apaziquone**

Apaziquone was evaluated in a phase II trial of 46 patients with NMIBC [31]. In the study, patients underwent visible lesion resection, except for 1 marker tumor, and then treated with 6 intravesical instillations of apaziquone at weekly intervals. The histologic complete response rate, assessed 2 to 4 weeks after the last instillation, was 67% [31].

Apaziquone is currently undergoing evaluation in phase III clinical trials [32-34]. Two large phase III trials testing Apaziquone in the peri-operative setting have completed accrual and the results are pending. The international, multicenter, placebo-controlled phase III SPI-1011 trial will evaluate multiple instillations of apaziquone in approximately 658 patients with intermediate-risk NMIBC [32]. All patients will receive a single instillation of apaziquone 4 mg immediately following TURBT. Patients will then be randomly assigned to treatment with 6 additional weekly intravesical instillations of apaziquone or placebo. Patients will undergo cystoscopic and safety assessments every 3 months for 24 months. The primary endpoint is time to recurrence [32].

**nab-Paclitaxel**

Nanoparticle albumin-bound (nab)-paclitaxel is approximately 5-fold more soluble than traditional unbound taxanes, allowing higher concentrations to be administered intravesically. Recent research has focused on the use of tumor-secreted SPARC (secreted protein, acidic and rich in cysteine) to enhance the delivery of nab-paclitaxel to tumor cells. SPARC is a key regulator of cellular functions related to tumor progression, including survival, proliferation, and migration [35]. SPARC is overexpressed and secreted by many tumor types, including urothelial tumors, and has a high binding affinity to albumin [36]. The SPARC/albumin interaction facilitates the delivery of albumin-bound drug to tumor cells. As a result of this interaction, nab-paclitaxel shows increased antitumor activity compared with solvent-based paclitaxel in SPARC-expressing cancers. Thus, SPARC-mediated delivery mechanism increases the solubility of nab-paclitaxel and makes it an excellent candidate for intravesical therapy.

McKiernan and colleagues evaluated intravesical nab-paclitaxel in a phase I trial of 18 patients with BCG-refractory NMIBC [37]. In the trial, intravesical nab-paclitaxel demonstrated minimal systemic absorption and no grade ≥2 toxicities. After 12 weeks, 5 patients (27%) had a complete response to treatment. This included just 1 of 11 patients (9%) with CIS at baseline. Of the 13 patients who recurred, only 1 had evidence of stage progression at the post-treatment evaluation [37]. Future studies may evaluate tumor expression data to determine whether nab-paclitaxel uptake is dependent on SPARC expression levels.

**EXTENDED PELVIC LYMPHADENECTOMY**

Another emerging approach includes extended lymphadenectomy (LND) at the time of radical cystectomy. Standard LND includes complete resection of bilateral external and internal iliac and obturator lymph nodes. This strategy identifies at least 95% of patients with N1 disease. By comparison, extended LND includes the presacral, common iliac (CI), and in some centers distal aorta/inferior vena cava (IVC) nodes. Up to 40% of patients with locally advanced pT3-pT4a tumors have node metastasis above the CI bifurcation. Extended LND also increases the node yield by up to 40% and increases the likelihood of detecting N2 and N3 disease.

Launched in August, 2011, the NCI sponsored multicenter, randomized, phase III SWOG 1011 trial compares standard versus extended pelvic LND performed at the time of radical cystectomy for muscle-invasive urothelial cell cancer [38]. SWOG 1011 will test the hypothesis that extending the node dissection to include the pre-sacral and
CI nodes will improve progression-free survival compared with standard LND in patients with clinically node-negative bladder cancer. The trial will enroll approximately 620 patients with predominantly urothelial carcinoma of the bladder that is stage T2-T4a and clinically node negative. Following surgery, patients with node-positive disease will also receive adjuvant chemotherapy. Patients will be stratified according to prior neoadjuvant therapy (yes vs. no), clinical stage (T2 vs. T3 vs. T4a), and Zubrod performance status (0-1 vs. 2).

The primary endpoint of is progression-free survival at 3 years. The trial is assuming a 3-year survival of 55% in the standard LND group, and will consider a 10% to 12% improvement in the extended LND group to be clinically significant. The trial also assumes a 5-year overall survival rate of 55% in the standard LND group, and defines a 10% improvement in the extended LND group to be clinically significant. SWOG 1011 is powered to detect a 28% reduction in the hazard rate of disease progression or death in the extended pelvic LND group [38].

In SWOG 1011, several tissue-based sub-studies are also planned. Epithelial-mesenchymal transition (EMT) is thought to drive lymph node metastasis and systemic circulation of tumor cells in patients with muscle-invasive bladder cancer. The trial will evaluate the relationship between expression of EMT markers in the primary bladder tumor and local tumor stage, burden of lymph node metastasis, and disease progression. Tissue studies will also attempt correlate the expression of various EMT markers in primary bladder tumors; correlate the number of circulating tumor cells with adverse outcomes such as node metastasis and disease progression in patients undergoing radical cystectomy; and define the relationship between EMT marker expression in the primary bladder tumor and CTC number [38].

**New Drug Development in Bladder Cancer**

**Daniel P. Petrylak, MD**

Numerous single-agent cytotoxic therapies have been evaluated over the last 30 to 40 years in bladder cancer, including paclitaxel, gemcitabine, methotrexate, docetaxel, cisplatin, ifosfamide, vinblastine, doxorubicin, trimetrexate, 5-fluorouracil (5-FU), carboplatin, and gallium nitrate. Unfortunately, response to single-agent therapy has been unimpressive, with very few complete responses and overall response rates ranging from 10% to 42%.

**COMBINATION CHEMOTHERAPY REGIMENS**

The first durable complete responses in bladder cancer were observed with the advent of combination chemotherapy. A phase III Intergroup trial compared cisplatin alone or in combination with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) in 255 patients with advanced urothelial carcinoma [39]. Patients were randomly assigned to treatment with single-agent cisplatin (70 mg/m2 on day 1) (n = 122) or combination chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) in 255 patients with advanced urothelial carcinoma [39]. Patients were randomly assigned to treatment with single-agent cisplatin (70 mg/m2 on day 1) (n = 122) or combination chemotherapy with methotrexate (30 mg/m2 on days 1, 15, and 22), vinblastine (3 mg/m2 on days 2, 15, and 22), doxorubicin (30 mg/m2 on day 2), and cisplatin (70 mg/m2 on day 2) (n = 133) every 28 days. After a minimum follow-up duration of 6 years for all patients, overall survival was superior with MVAC compared with cisplatin (P = .0015). After 3 years, 4 patients were alive in the single-agent cisplatin arm, compared with 17 patients in the MVAC group. After 6 years of follow-up, only 2 patients in the cisplatin group and 9 patients in the MVAC group were alive and continuously disease free [39]. Even with combination chemotherapy, durable progression-free survival was rare.

Newer regimens have tried to improve upon MVAC in bladder cancer. In the European Organization for Research and Treatment of Cancer (EORTC) 30924 trial, Sternberg and colleagues compared high-dose-intensity MVAC (HD-MVAC) with the classic MVAC regimen in patients with advanced urothelial tract tumors [40]. In the phase III trial, 263 patients who had no prior chemotherapy were randomly assigned to treatment with HD-MVAC in 2-week cycles or standard MVAC in 4-week cycles. Patients in the HD-MVAC group also received treatment with recombinant human granulocyte colony-stimulating factor (G-CSF) for 7 consecutive days, beginning on day 4 after administration of MVAC, and continuing for up to 14 days as needed. All patients completed at least 2 cycles of chemotherapy.

The median follow-up was 38 months. Treatment with HD-MVAC, compared with standard MVAC, was associated with a higher overall response rate (62% versus 50%; P = .06) and a higher complete response rate (21% versus 9%; P = .009). HD-MVAC also extended the median progression-free survival compared with MVAC (9.1 months versus 8.2 months; P = .037). However, there was no difference between the treatment groups in overall survival (HR, 0.80; P = .122). The HD-MVAC regimen allows the administration of twice the dose of cisplatin and doxorubicin in half the time, with less toxicity and fewer dose delays compared with standard MVAC [40]. Based on these findings, several institutions have adopted the HD-MVAC regimen for use in the neoadjuvant treatment of bladder cancer.

Combination chemotherapy with gemcitabine/cisplatin (GC) is an alternative standard of care in advanced disease. In a phase III trial, von der Masse and colleagues compared GC with MVAC in 405 patients with advanced or metastatic transitional-cell carcinoma of the urothelium (TCCU) [41,42]. Patients were randomly assigned to treatment with gemcitabine 1000 mg/m2 on days 1, 8, and 15 and cisplatin 70 mg/m2 on
day 2 (n = 203) or standard MVAC (n = 202) every 28 days for a maximum of 6 cycles. Efficacy outcomes were similar in the GC and MVAC groups, with comparable overall response rates (49% versus 46%), equal complete response rates (12%), and similar median durations of response (9.6 months versus 11.0 months; P = .48). The median overall survival was 13.8 months in the GC group and 14.8 months in the MVAC group (HR, 1.04; P = .75) [41]. In a long-term follow-up analysis, the 5-year overall survival rates were 13.0% and 15.3% in the GC and MVAC groups, respectively (P = .53) [42].

Despite similar efficacy outcomes, the GC regimen may be preferable to MVAC for some patients due to a more favorable toxicity profile. In particular, grade 4 neutropenia was less common with GC compared with MVAC (29.9% versus 65.2%), as was grade 4 neutropenic infection (0.5% versus 5.2%). Of note, the Van der Masse study did not allow for the routine use of prophylactic growth factors, and such use could change the toxicity profiles. As a result, medical resource utilization for managing adverse events, including hospitalization and use of growth factors, parenteral antibiotics, and antiviral and antifungal medications, was generally higher in the MVAC group compared with GC [41]. In general, GC and MVAC are considered to be equivalent frontline standards of care for metastatic bladder cancer.

The phase III EORTC 30987 trial compared GC with paclitaxel/gemcitabine/cisplatin (PGC) in 627 patients with locally advanced or metastatic urothelial cell cancer [43]. The primary disease site was the bladder for most patients (81%), followed by the renal pelvis or ureter (13%), urethra (3%), or other site (1%). Approximately 80% of patients had metastatic disease, including visceral metastases in 47%. All patients were chemotherapy-naïve at enrollment. Patients were randomly assigned to treatment with gemcitabine 1000 mg/m2 on days 1 and 8 and cisplatin 70 mg/m2 on day 2 (n = 312) or gemcitabine 1000 mg/m2 on days 1 and 8, cisplatin 70 mg/m2 on day 2, and paclitaxel 80 mg/m2 on days 1 and 8 (n = 315) in 21-day cycles.

Median overall survival was 12.8 months with GC and 15.7 months with PGC (Table 3). This represents a non-significant trend in favor of treatment with PGC, with a 14% relative reduction in the risk of death (response rate [RR], 0.86; P = .10). The toxicity profiles of the PGC and GC treatment regimens differed considerably. PGC was associated with a significantly higher risk of grade 4 leukopenia (17% versus 5.1%; P < .001) and grade 4 neutropenia (34.9% versus 20.6%; P < .001) compared with GC. In contrast, treatment with CG significantly increased the risk of grade for thrombocytopenia (25.4% versus 15.7%; P = .003) relative to PGC [43]. Some treatment centers have also adopted the PGC triplet combination for the frontline treatment of advanced urothelial cell cancer.

### Table 3. Outcomes Following Paclitaxel/Gemcitabine/Cisplatin (PGC) Compared to Gemcitabine/Cisplatin (GC) in Advanced Urothelial Cancer [43]

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>PGC (n = 312)</th>
<th>GC (n = 315)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival, mo</td>
<td>15.7</td>
<td>12.8</td>
<td>.10</td>
</tr>
<tr>
<td>Grade 4 hematologic adverse events, %</td>
<td>17</td>
<td>5.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>34.9</td>
<td>20.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15.7</td>
<td>25.4</td>
<td>.003</td>
</tr>
</tbody>
</table>

In the primary tumor is associated with worse prognosis, including higher grade and accelerated disease progression. Vascular endothelial growth factor (VEGF) expression correlates with grade, stage, and survival, and higher serum VEGF levels predict vascular invasion and poor prognosis in patients with bladder cancer. Preclinical evidence supports the use of anti-VEGF therapy in combination with chemotherapy to inhibit angiogenesis, induce apoptosis, and prevent metastasis [44]. Options for antiangiogenic therapy include bevacizumab, a monoclonal antibody against VEGF; sunitinib and sorafenib, small-molecule tyrosine-kinase inhibitors (TKIs) that target VEGF; and VEGF Trap, a soluble decoy receptor that binds VEGF and blocks the VEGF signaling pathway.

### Bevacizumab

The phase II Hoosier Oncology Group GU 04-75 trial evaluated bevacizumab in combination with CG (CGB) in patients with metastatic urothelial carcinoma [45,46]. Patients were treated with cisplatin 70 mg/m2 on day 1, gemcitabine 1000-1250 mg/m2 on days 1 and 8, and bevacizumab 15 mg/kg on day 1 every 21 days for up to 8 cycles. After 7 of the first 17 patients developed venous thromboembolism (VTE), the gemcitabine dose was reduced to 1000 mg/m2 on days 1 and 8 and for all subsequent patients. Overall, 9 patients (21%) developed deep-vein thrombosis (DVT) or pulmonary embolism (PE). Grade 3 to 4 hematologic toxicity included neutropenia in 35%, thrombocytopenia in 12%, anemia in 12%, and neutropenic fever in 2%. Three treatment-related deaths included CNS hemorrhage, sudden cardiac death, and aortic dissection.

Among 43 patients evaluable for response, the overall response rate was 72%, including a complete response rate of 19% and a partial response rate of 53%. After a median follow-up of 27.2 months, median progression-free survival was 8.2 months, and median overall survival was
19.1 months. Treatment with CGB demonstrates promising survival outcomes at the expense of antiangiogenic treatment-related toxicity [46]. The triplet CGB regimen is undergoing further evaluation in metastatic UC in a phase III intergroup trial lead by the CALGB.

**Sunitinib**

Early promising findings from studies of single-agent sunitinib (SU011248) illustrate the potential role of small-molecule TKIs in the treatment of advanced UC. In a multicenter phase II trial, Bellmunt and colleagues assessed sunitinib as first-line treatment in patients with metastatic UC who were ineligible for cisplatin [47]. Patients received sunitinib 50 mg daily for 4 weeks every 6 weeks. Three patients (8%) had partial responses and 19 patients (50%) had stable disease, for a total clinical benefit rate of 58%. The median time to progression was 4.8 months, and the median overall survival was 8.1 months. Lower baseline interleukin (IL)-8 levels correlated with increased time to progression [47].

Another phase II trial evaluated single-agent sunitinib in 77 patients with metastatic UC who progressed after initial chemotherapy [48]. Patients were treated with 1 of 2 treatment schedules: 50 mg/day for 4 weeks on and 2 weeks off (cohort A; n = 45) or 37.5 mg/day continuously (cohort B; n = 32). Partial responses were observed in 3 patients (7%) in cohort A and 1 patient (3%) in cohort B. Overall, 33 patients (43%) experienced clinical regression or stable disease. There was no difference between dosing cohorts A and B with regard to overall survival (2.4 months versus 2.3 months) or progression-free survival (7.1 months versus 6.0 months) [48].

An ongoing phase II trial is evaluating maintenance sunitinib in patients with advanced UC [49]. Eligible patients included those who received 4 to 6 cycles of standard first-line chemotherapy for the treatment of locally advanced or metastatic UC and achieved stable disease, partial response, or complete response following frontline treatment. Patients will be randomly assigned to maintenance treatment with sunitinib 50 mg once daily or placebo for 4 consecutive weeks, followed by a 2-week drug holiday. Participants who show evidence of disease progression will be unblinded, and those in the placebo arm will be given the opportunity to crossover to the sunitinib arm. The primary endpoint is 6-month progression-free survival. Additional endpoints will include safety, response, overall survival, and the association between serum VEGF and VEGF2 levels and clinical outcomes. The sunitinib maintenance trial has been closed due to slow accrual and has an expected completion date of 2015 [49].

**Sorafenib**

Two phase II studies found that single-agent sorafenib has no clinically meaningful activity in advanced UC. The Princess Margaret Hospital Phase II Consortium evaluated the safety and efficacy of first-line sorafenib in 17 patients who had not had prior chemotherapy [50]. All patients were treated with oral sorafenib 400 mg twice daily until disease progression or unacceptable toxicity. No patients had objective responses. Only 1 patient had stable disease and remained on treatment for more than 3 months. Median overall survival was 5.9 months [50]. The phase II ECOG 1804 trial evaluated sorafenib in patients who were previously treated with 1 prior chemotherapy regimen [51]. A total of 27 patients were treated with oral sorafenib 400 mg twice daily. No treatment responses were observed. Three patients (14%) had stable disease, and 9 (41%) had progression as their best overall response. Median overall survival was 6.8 months [51].

**SECOND-LINE CHEMOTHERAPY**

No standard of care for the second-line treatment of bladder cancer has been
defined to date. Median survival in the second-line setting is 6 months, and median time to progression is 3 months. Several therapeutic strategies are currently under evaluation for patients with progressive disease following frontline treatment for bladder cancer.

**Pemetrexed**

Sweeney and colleagues evaluated the safety and efficacy of pemetrexed in patients with locally advanced or metastatic TCCU [52]. The phase II trial enrolled 47 patients who had received 1 prior chemotherapy regimen and whose disease had progressed at any time after therapy for advanced or metastatic disease, or within 12 months of neoadjuvant or adjuvant therapy. All patients received pemetrexed 500 mg/m² on day 1 every 21 days. The overall response rate was 27.7% and included complete responses in 3 patients (6.4%) and partial responses in 10 patients (21.3%). Grade 3 or 4 adverse events included thrombocytopenia in 8.5%, neutropenia in 4.3%, and anemia in 2.1%. These findings demonstrate the safety and efficacy of single-agent pemetrexed as second-line treatment in patients with advanced bladder cancer [52].

**Vinflunine**

Vinflunine is an investigational antitu- bulin agent developed from a vinca alka- loid base with higher antitumor activity compared with parent compounds [53]. In a multicenter phase II trial, Cüline and colleagues evaluated the safety and efficacy of vinflunine in 51 patients with advanced TCCU who were treated with 1 prior line of platinum-based chemotherapy. Nine patients (17.6%) had a partial response, and 25 patients had stable disease (49%), for a total disease-control rate of 66.6%. The median duration of response was 9.1 months. Median progression-free survival was 3.0 months, and median overall survival was 6.6 months [53].

A multicenter, randomized, phase III trial evaluated vinflunine as second-line therapy following platinum-based chemotherapy in 370 patients with advanced TCCU [54]. Patients were randomly assigned to treatment with vinflunine 280 mg/m² to 320 mg/m² every 3 weeks plus best supportive care (BSC) (n = 253) or BSC alone (n = 117) until disease progression. Treatment with vinflunine was associated with a greater overall response rate compared with BSC alone (8.6% versus 0%; P = .006) and a higher rate of disease control (41.1% versus 24.8%; P = .002).

In the intent-to-treat population (ITT), median overall survival was 6.9 months in the vinflunine, compared with 4.6 months in the BSC group (HR, 0.88; P = .287). When the analysis was limited to patients who were treated per protocol (n = 357), the survival advantage in the vinflunine group was statistically significant. Median overall survival was 6.9 months with vinflunine and 4.3 months with BSC (HR, 0.78; P = .040) (Figure 2) [54]. In a multivariate analysis, treatment with vinflunine was associated with a 33% reduction in the risk of death (P = .036). Neutropenia was the most frequent grade 3/4 adverse event in the vinflunine group, with neutrope- nia fever occurring in 6% of patients. Additional grade 3/4 adverse events included fatigue in 19.3% of patients, anemia in 19.1%, and constipation in 16.1% [54].

In summary, second-line vinflunine shows a significant advantage in terms of objective response and survival compared with BSC in patients with TCCU, but at the cost of increased toxicity. Median survi- val with vinflunine was not greater when compared with historical data of second- line single-agent docetaxel, paclitaxel, pemetrexed, or gemcitabine. Given these findings, however, vinflunine appears to be a reasonable option for second-line therapy in patients with TCCU who progress following platinum-based che- motherapy [54]. Vinflunine is approved in Europe, but remains investigational in the United States.

**Combination Therapy**

Docetaxel-based combination regimens have also been evaluated as second-line treatment for advanced bladder cancer. In a phase II trial, Choueiri and colleagues evaluated docetaxel plus vandetanib in patients with platinum-pretreated advanced UC [55]. A total of 142 patients were randomly assigned to treatment with docetaxel 75 mg/m² every 21 days with or without once daily oral vandetanib 100 mg. Compared with docetaxel alone, the addition of von- detanib did not improve median progression-free survival (6.9 weeks versus 11.1 weeks: P = .92) or median overall survival (30.6 weeks versus 25.4 weeks; P = .35).

An ongoing phase II trial is evaluating second-line docetaxel in combination with ramucirumab or IMC-18FI in patients with bladder, urethra, ureter, or renal pelvis carcinoma [56]. The multicenter trial will enroll approximately 138 patients in 30 study locations. Patients who had disease progression on first-line platinum- based chemotherapy will be randomly assigned to treatment with docetaxel, docetaxel plus ramucirumab, or docetaxel plus IMC-18FI. The primary endpoint is progression-free survival.

**SUMMARY**

Outcomes in bladder cancer rely on early tumor detection and ablation with traditional endoscopic surgical tech- niques. New optical imaging modalities improve the diagnostic accuracy of standard WLC, enhance the quality of surgical resection, and reduce the risk of local tumor recurrence. Advances in intravesical therapy, particularly elec- tromotive MMC, may play a role in prolonging disease-free survival. Several clinical trials are evaluating new sys- temic approaches to eradicate bladder cancer, including targeted therapies and novel chemotherapy-based combination regimens for patients with high-risk disease and those who fail more conserva- tive frontline measures. Findings from these ongoing trials may redefine the standards of care for the detection and treatment of bladder cancer.
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1. Which of the following endoscopic imaging methods requires the intravesical instillation of photoactive porphyrins to visualize bladder lesions?
   A. Confocal laser endomicroscopy
   B. Fluorescence-guided cystoscopy
   C. Narrow-band imaging
   D. Optical coherence tomography

2. Which of the following endoscopic imaging methods provides real-time dynamic images with micron-level resolution that rivals standard histology?
   A. Confocal laser endomicroscopy
   B. Fluorescence-guided cystoscopy
   C. Narrow-band imaging
   D. Optical coherence tomography

3. Which of the following intravesical adjuvant therapies significantly reduced the risk of tumor recurrence and prolonged disease-free survival compared with transurethral resection of the bladder tumor (TURBT) alone?
   A. Pre-TURBT passive-diffusion mitomycin-C (MMC)
   B. Post-TURBT passive-diffusion MMC
   C. Pre-TURBT electromotive MMC
   D. Post-TURBT electromotive MMC

4. In a phase III trial of patients with advanced or metastatic transitional-cell carcinoma of the urothelium (TCCU), gemcitabine/cisplatin (GC) reduced the risk of which grade 4 adverse event(s) compared with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC)?
   A. Neutropenia
   B. Neutropenic infection
   C. Thrombocytopenia
   D. Both A and B

5. In a phase III trial, second-line vinflunine significantly improved overall survival compared with best supportive care alone in which group of patients with advanced TCCU?
   A. Patients in the intent-to-treat population
   B. Patients in the per-protocol population
   C. Patients who failed ≥ 2 prior platinum-based chemotherapy regimens
   D. Patients aged ≤ 65 years
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Discuss the emerging role and economics of new therapies in the treatment of bladder cancer 5 4 3 2 1

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2. A  B  C  D
3. A  B  C  D
4. A  B  C  D
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