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New developments in the management of non-muscle invasive bladder cancer

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Abstract

Purpose of review—In this review, we summarize the core principles in the management of NMIBC with an emphasis on new developments that have emerged over the last year.

Recent findings—Non-muscle invasive bladder cancer (NMIBC) has a propensity to recur and progress. Risk stratification has facilitated appropriate patient selection for treatment but improved tools, including biomarkers, are still needed. Enhanced cystoscopy with photodynamic imaging and narrow band imaging show promise for diagnosis, risk stratification, and disease monitoring and has been formally recommended this year by the American Urological Association. Attempts at better treatment, especially in refractory high-risk cases, include the addition of intravesical hyperthermia, combination and sequential therapy with existing agents, and the use of novel agents such as mycobacterial cell wall extract. New data are emerging regarding the potential role of early cystectomy in BCG-refractory NMIBC patients.

Summary—NMIBC represents an assortment of disease states and continues to pose management challenges. Continued research is needed to bolster the evidence needed for patients and providers to make data-driven treatment decisions.

Keywords

non-muscle invasive bladder cancer; intravesical therapy; cystectomy; cystoscopy

Introduction

In 2016, an estimated 77,000 Americans will be diagnosed with urothelial carcinoma of the bladder which represents almost 5% of all incident cancers in the United States.(1) While over 70% of these tumors are non-muscle invasive,(2) many patients will experience one or more tumor recurrences over the course of their lifetime and some will progress to muscle invasion.(3*) Because progression to muscle invasive disease is potentially life threatening and because recurrences are costly and inconvenient for patients, efforts to reduce the risk of bladder tumor recurrences and progression constitute the primary focus of the non-muscle invasive bladder cancer (NMIBC) research agenda.

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In this review, we summarize the core principles in the management of NMIBC with an emphasis on new developments that have emerged over the last year. Building on our previous work,(4) we review the latest data regarding enhanced cystoscopic techniques, the role of re-resection, the use of perioperative intravesical chemotherapy, the role of induction and maintenance Bacillus Calmette-Guerin (BCG), novel approaches to BCG refractory disease, and the role of radical cystectomy and urinary diversion.

Enhanced Cystoscopic Techniques

The mainstay of initial management for a new bladder tumor is the complete surgical resection of all visible disease. Recognizing that not all disease may be visible to the naked eye, the American Urological Association (AUA) has now formally recommended the use of enhanced cystoscopic techniques (specifically blue light cystoscopy [BLC]) in the latest guidelines on the management of NMIBC.(5**) BLC is a proprietary photodynamic platform that uses hexaminolevulinate, a heme precursor, to identify tumors before they are readily visible under white light conditions.(6) The decision to include BLC in the AUA guidelines was mostly predicated on the findings from a recent meta-analysis commissioned by the Agency for Healthcare Research and Quality (AHRQ) which found that BLC not only improved the detection of bladder cancer but that it also decreased recurrences.(7**) However, enthusiasm for this technology needs to be tempered by several practical considerations. First, the FDA has not approved BLC for repeated use.(8) Second, BLC requires the use of specific endoscopic platforms which may not be used in some hospitals, and switching to these platforms may be cost prohibitive and impractical. Lastly, research has suggested that many factors can decrease the specificity of BLC such as a recent TURBT, intravesical therapy, concomitant urinary tract infection (UTI), and/or the presence of inflammation – though admittedly specificity may improve with increasing experience.(9)

Another enhanced cystoscopic technique included in the guidelines, though with less enthusiasm, is narrow band imaging (NBI). Unlike BLC, NBI does not require the intravesical instillation of an agent but rather relies on the blue and green wavelengths of light to enhance the detail of mucosal lesions.(10) A recently reported clinical trial from the Clinical Research Office of the Endourological Society randomized 481 patients to white light TURBT and 484 patients to NBI-TURBT, and found that NBI reduced the 12-month risk of recurrence in low-risk patients (27.3% vs. 5.6%).(11*) However, because the trial was largely negative and because the risk groups were not well defined, the AUA guideline panel interpreted the results of this trial with caution.(5**)

The Role of Repeat TURBT

There are 3 scenarios where a clinician should consider a repeat TURBT after an initial resection: 1) when the initial TURBT was incomplete; 2) in patients with high-risk high grade noninvasive tumors; and 3) in patients with T1 tumors, especially when muscle was not present in the initial specimen. With respect to the first scenario, a repeat resection should be performed in an effort to render the patient disease free. Certainly there are extenuating circumstances whereby re-resection is not indicated, such as large unresectable tumors that will necessitate a cystectomy anyhow or for patients with tumors in a

diverticulum where a partial or radical cystectomy is planned. However, when feasible, a repeat TURBT should be performed in most patients with residual disease.(12)

With respect to the second scenario, patients with high risk high grade noninvasive tumors have a significant risk of residual disease. Up to 50% will have residual tumor in the bladder and 15% will be upstaged.(13*) As a result, the AUA guidelines recommend that a repeat TURBT should be performed within 6 weeks of the original diagnosis, though the guidelines do allow for exceptions where small high grade noninvasive tumors are clearly resected. (5**) In patients with T1 tumors, a repeat TURBT may not only offer diagnostic and prognostic benefit but also therapeutic benefit. While it is well known that disease understaging can occur in up to 30% of all T1 tumors, and in up to 50% of T1 tumors without muscularis propria in the specimen, (13*) a repeat resection in the setting of T1 disease is also associated with better BCG response rates.(14)

Intravesical Therapy for Low Risk Disease (Low grade [LG], solitary, Ta tumor <3cm)

A single postoperative dose of intravesical chemotherapy, particularly Mitomycin C, for one to two hours after a TURBT for cystoscopically appearing LG bladder tumors has been shown to decrease tumor recurrence by 10–15% with no effect on progression or long-term survival.(15–17) The number needed to treat to prevent on recurrence in this setting is 8.5. (15) The biologic rationale of this approach is grounded in the theory that tumor cells disperse within the bladder after the TURBT and may implant and become incorporated within the extracellular matrix within a few hours after surgery.(18) It should be noted that emerging evidence suggests that patients with a prior recurrence rate of more than one recurrence per year, or in patients with a European Organization for Research and Treatment of Cancer (EORTC) recurrence score of ≥5, may not benefit from a single postoperative course of intravesical chemotherapy.(19) Furthermore, postoperative intravesical chemotherapy should be avoided when bladder perforation is expected or when the tumor is high grade or invasive appearing. While Epirubicin and Thiotepa have both been used as single dose intravesical chemotherapeutics for low risk disease, Mitomycin C is the preferred agent in this setting.(5**)

Intravesical Therapy for Intermediate Risk Disease (Recurrent LG tumors within one year, solitary LG tumors >3cm, multifocal LG tumors, HG Ta tumors <3cm, and LG T1)

Intermediate risk tumors do not fit nicely within the intravesical therapy treatment paradigm. These tumors are heterogeneous and are more similar to low risk tumors in that they are more susceptible to tumor recurrence rather than progression. An induction course of BCG, Mitomycin C, Doxorubicin, and Epirubicin have all been shown to decrease tumor recurrences in patients with intermediate risk tumors with no effect on the risk of progression.(7) Because BCG is associated with a greater risk of toxicity, Mitomycin C may be a better choice in this setting, especially since the main effect is primarily limited to preventing recurrence and not progression.

Intravesical Therapy for High Risk Disease (HG T1, CIS, Recurrent HG Ta, Variant Histology)

Patients with high risk NMIBC have manifestly high recurrence and progression rates. Up to 70% of patients will recur and up to 45% of patients will progress within 5 years of diagnosis.(3*) A 6-week induction course of BCG has been shown to decrease the risk of recurrence by 44% and progression by 61% compared to no intravesical therapy.(7) With respect to which strain of BCG is most effective, the data are mixed. There are at least 8 strains in use worldwide,(20) but comparative data exist for only two of them. BCG Connaught resulted in significantly better 5-year recurrence free survival rates (74%) compared to BCG Tice (48%) but there were no differences in rates of progression.(21) Similarly, because BCG is associated with toxicity (cystitis, febrile illness, pain, and rarely scarring of the bladder), some investigators have studied whether dose reduction can result in similar efficacy with reduced adverse effects. While most trials have found no significant differences between standard dose BCG and reduced dose BCG in terms of recurrences or progression, a relatively recent meta-analysis did suggest a slight improvement in the recurrence free survival rates with standard dose compared to reduced dose BCG.(22) However, the point estimate was modest (HR 1.162) and the lower limit of the 95% confidence interval includes very small effects (1.051, 1.285). Furthermore, in a well-publicized analysis of full dose and 1/3 dose BCG in the maintenance setting, toxicities were not different between groups.(23)

Combination Therapy

Many investigators have explored combining BCG with other intravesical therapies in an effort to improve the efficacy of BCG in preventing recurrences and progression in high risk populations. The most notable development has been publication of CUETO 93009, a randomized comparison of Mitomycin C plus BCG versus BCG alone which demonstrated that the 5-year recurrence free survival rates favored the combination therapy group (HR 0.57, 95% CI: 0.39,0.83), though no differences were noted in progression rates.(24*) However, given the significantly increased local toxicity experienced by the combination group, the authors suggest that only patients with recurrent T1 disease should be offered this therapy given that they have the highest likelihood of recurrence. Another strategy has explored the ability to enhance the immune response by adding cytokines such as interferon alpha2B to BCG with minimal evidence of improved efficacy.(25)

Regional Hyperthermia

The synergistic effect of combining hyperthermia with chemotherapy or radiation has been exploited for the treatment of invasive cancers for years.(26) In recent years, investigators have used intravesical conductive and intracavitary hyperthermia for NMIBC.(27,28) There are 3 techniques for regional hyperthermia in bladder cancer, including using 70 to 120 MHz antennas, intracavitary radiofrequency hyperthermia using a 916 MHz antenna, and intravesical conductive therapy using a heated perfusate.(29) Geijsen et al. reported their prospective experience with regional 70 MHz hyperthermia in patients with NMIBC.(27) Twenty patients with intermediate to high-risk disease were treated with intravesical

Mitomycin C (40 mg) combined with regional hyperthermia in 6 weekly sessions followed by a maintenance period of 1 year. Fourteen patients completed the induction period and 4 dropped out due to toxicity. The 24-month recurrence free survival rate was robust at 78%.

Maintenance BCG

In intermediate and high risk patients with good responses, consideration should be given to maintenance BCG (3 week courses at 3, 6, 12, 18, 24, and 36 months). In a subgroup analysis of EORTC 30962, 1-year full dose maintenance BCG was equivalent to 3-year full dose maintenance BCG for patients with intermediate risk NMIBC.(23) However, among high-risk NMIBC patients, the full dose 3-year maintenance schedule is supported by findings from both EORTC 20962 and SWOG 8507.(23,30*)

Emerging Data for BCG Refractory Disease

Many patients with recurrent, BCG-refractory high-risk disease may consider radical cystectomy, yet many others either refuse or are not medically fit. In these instances, further intravesical therapy should be considered. Emerging data has suggested that Gemcitabine alone may be effective in the setting of BCG failure.(31,32) In a recent retrospective analysis of 27 patients, Cockerill et al. report a favorable and durable recurrence-free survival of 15.2 months.(33) A multi-institutional analysis for sequential intravesical Gemcitabine with Mitomycin C found that patients with high-grade NMIBC or BCG refractory disease had a 2 year recurrence free survival of nearly 40%.(34) These studies lend further evidence that salvage protocols utilizing Gemcitabine in this setting show promise.

Systemically administered Docetaxel has some efficacy in metastatic bladder cancer, leading investigators to posit whether locally administered Docetaxel might prevent recurrence or progression. Several studies have evaluated the utility of intravesical Docetaxel for the treatment of BCG-refractory NMIBC. A recent phase I clinical trial by Barlow et al. studied 54 patients with 6 weekly instillations of intravesical Docetaxel.(35) An impressive 59% of patients achieved a complete response, with 18 going on to receive further maintenance therapy. The 5-year disease-specific and overall survival rates were 85% and 71%, respectively.

Because BCG is a live attenuated mycobacterium, it can be associated with systemic side effects, which on occasion can be quite severe. Mycobacterial cell wall extract (MCWE) from *Mycobacterium phlei* is comparable in composition to BCG but does not contain any live bacterial elements, and thus may lessen the risk of systemic toxicity. A multi-institutional clinical trial evaluating the use of mycobacterial cell wall-DNA complex (MCC) – which is essentially MCWE without a mercury-based preservative called thiomersal – in BCG-naïve and -refractory patients with CIS, showed a 46% complete response rate at 12 weeks.(36*) After 18 months, almost a third of these participants remained disease free. A phase III trial testing MCC among BCG-refractory CIS or recurrent high grade NMIBC is currently underway (ClinicalTrial.gov; no. NCT00406068).

Role of Cystectomy in NMIBC

There are several instances where a patient with NMIBC should be considered for a cystectomy. Medically fit patients with HG T1 recurrences after an induction course of BCG should be offered a cystectomy. Emerging data suggests delaying a cystectomy in this setting is associated with poorer cancer-specific survival.(37) High risk patients with persistent T1 disease despite re-resection with associated CIS, lymphovascular invasion (LVI) or variant histologies should also be offered a cystectomy. Myriad studies have demonstrated poorer oncologic outcomes with intravesical therapy in patients with the adverse pathologic features.(38–40) Finally, patients with recurrent high risk bladder cancer within one year following two induction courses of BCG or BCG maintenance should likewise be considered for radical cystectomy. Patients who underwent a cystectomy in this setting had improved five-year cancer-specific survival compared to patients managed with further intravesical therapy.(41)

Conclusion

While management strategies continue to evolve, timely detection, appropriate risk stratification, and individualized treatment remain paramount in the care of the patient with NMIBC. Recent advances in endoscopic tumor detection, coupled with improved intravesical therapies, have helped tailor treatment. Further, well-designed clinical trials are needed to enhance risk stratification and treatment options for those patients refractory to current lines of therapy. Continued research is needed to facilitate data-driven decision making for patients and providers alike.

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Key Points

Blue light cystoscopy is a proprietary photodynamic platform that uses hexaminolevulinate, a heme precursor, to identify tumors before they are readily visible under white light conditions.

With respect to the second scenario, patients with high risk high grade noninvasive tumors have a significant risk of residual disease. Up to 50% will have residual tumor in the bladder and 15% will be upstaged.

Medically fit patients with high grade T1 recurrences after an induction course of BCG should be offered a cystectomy. Emerging data suggests delaying a cystectomy in this setting is associated with poorer cancer-specific survival.