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REVIEW

Emerging intravesical therapies for management of nonmuscle invasive bladder cancer

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Jeffrey J Tomaszewski
Marc C Smaldone

Department of Urology, University of Pittsburgh School of Medicine, Pennsylvania, USA

Abstract: Transitional cell carcinoma (TCC) is the second most common urologic malignancy, and 70% of patients present with superficial or nonmuscle invasive bladder cancer (NMIBC). Intravesical bacillus Calmette-Guerin (BCG) is the most effective agent for preventing disease recurrence, and the only therapy able to inhibit disease progression. However, recurrence rates as high as 30% and significant local and systemic toxicity have led to increased interest in alternative intravesical therapies. In patients refractory or intolerant to BCG, BCG-interferon α2b, gemcitabine, and anthracyclines (doxorubicin, epirubicin, valrubicin) have demonstrated durable clinical responses. Phase I trials investigating alternative cytotoxic agents, such as apaziquone, taxanes (docetaxel, paclitaxel), and suramin are reporting promising data. Novel immunomodulating agents have demonstrated promise as efficacious alternatives in patients refractory to BCG. Optimization of existing chemotherapeutic regimens using hyperthermia, photodynamic therapy, magnetically-targeted carriers, and liposomes remains an area of active investigation. Despite enthusiasm for new intravesical agents, radical cystectomy remains the treatment of choice for patients with NMIBC who have failed intravesical therapy and selected patients with naïve T1 tumors and aggressive features. This report provides a comprehensive review of contemporary intravesical therapy for NMIBC and refractory NMIBC, with an emphasis on emerging agents and novel treatment modalities.

Keywords: transitional cell carcinoma, nonmuscle, invasive, intravesical therapy, BCG

Introduction

Bladder cancer is the fourth most common malignancy among men in the Western world.[1] More than 90% of bladder cancer diagnoses are made in patients older than 55 years of age, with a three-to-one male to female predominance.[2] Transitional cell carcinomas (TCC) predominate, with superficial or nonmuscle invasive bladder cancers (NMIBC) found at diagnosis in more than 70%.[3]

Transurethral resection (TUR) facilitates accurate tumor grading and staging, provides local disease control, and is typically performed for the management of newly diagnosed TCC. Following TUR alone, TCC recurs or progresses in 50%–80% and 14%, respectively, despite adequate resection.[4] The risk of disease recurrence and progression is highly variable, and risk-stratification based on pathologic and clinical variables is commonly utilized for more accurate prediction.[5]

The perioperative instillation of chemotherapy immediately following TUR has been advocated to destroy residual microscopic tumor cells and to prevent re-implantation.[6] Intravesical therapy has also been employed in an induction and/or maintenance fashion to provide long-term immuno-stimulation of chemotoxicity in

Correspondence: Marc C Smaldone
Department of Urology, University of Pittsburgh School of Medicine, Suite 700, 3471 Fifth Avenue, Pittsburgh, PA 15213, USA
Tel +1 412 692 4100
Fax +1 412 692 4101
Email smaldonemc@upmc.edu

an effort to prevent disease recurrence.[7] The high rate of tumor recurrence in patients with NMIBC mandates lifetime surveillance and leads to high health care related costs despite the use of adjuvant intravesical therapy.[8] We review intravesical treatment strategies, discuss modes of efficacy enhancement, and explore the role of novel agents in the management of NMIBC.

Immunomodulators

Immunotherapeutic strategies produce antitumor effects via either passive or active immunity.[9] Enhancing active immunity, ie, recruitment and imprinting of the host immune system to recognize and effectively destroy tumor cells, is the focus of most of the current work in bladder cancer immunotherapy. Interleukins (ILs), which contribute to the host immune response by stimulating T-cell and natural killer (NK) cell proliferation and cytokine production, have been shown to have antitumor activity in animal models,[10] and investigators were hopeful that adjunctive IL therapy would improve the efficacy of traditional intravesical agents.[9] However, initial trials utilizing IL-2,[11] IL-12,[12] tumor necrosis factor (TNF),[13] and granulocyte macrophage colony stimulating factor (GM-CSF)[14] demonstrated poor evidence of tumor response, local and systemic side effects, and early disease recurrence.

Bacillus Calmette-Guerin

BCG, an attenuated mycobacterium developed as a vaccine for tuberculosis, has been shown to have significant antitumor activity against many different malignancies.[6] First described by Morales for the treatment of superficial bladder cancer nearly 20 years ago,[13] its use in the treatment of NMIBC has gained widespread acceptance in the urologic community. The action of BCG is based on inducing cytokine release in the urine and bladder wall, resulting in the chemoattraction of granulocytes and mononuclear cells. Although the exact mechanism of action is debatable, the initial step appears to be the binding of fibronectin, facilitating attachment to the urothelium and subsequent incorporation of glycoproteins into the bladder wall. The resulting nonspecific immune stimulation leads to release of macrophages, T-lymphocytes, B-lymphocytes, NK cells, and various cytokines. Cytokine release (interferon-γ, IL-2, and TNF) induces a TH_1-mediated response and antitumor activity.[6,15]

Intravesical administration of BCG as induction therapy for NMIBC has been shown to delay the time to first recurrence compared with TUR alone.[6] Shelley et al reviewed six randomized trials comparing TUR alone versus TUR-BCG in patients with Ta and T1 bladder cancer. Using tumor recurrence as their outcome of interest, their analysis revealed a significant advantage in patients treated with BCG following TUR over TUR alone.[16] A recent meta-analysis of 24 randomized clinical trials including nearly 5000 patients with carcinoma in situ (CIS), Ta, or T1 TCC reported that BCG reduced the odds of disease progression by 27% compared with TUR alone or resection and another treatment other than BCG. Of importance, these benefits were only seen in patients receiving maintenance therapy and there was no effect on overall or disease-specific survival.[6,17]

Induction treatment regimens of BCG typically begin two to four weeks following resection and are most commonly administered weekly for six weeks. However, there is debate as to the optimal dosing schedule, and controversy persists regarding the role of maintenance therapy and its long-term effect on recurrence and progression.[18] In a randomized, prospective trial, 550 patients with NMIBC or CIS were randomized to a maintenance therapy arm or no maintenance therapy following a six-week induction course of BCG. Findings demonstrated a significant difference in median recurrence-free survival in the maintenance therapy arm (76.9 versus 35.7 months, $P < 0.0001$) and a 5% improvement in five-year overall survival ($P = 0.08$) with a median follow-up of 120 months.[19] Initial reports from large meta-analyses suggest that maintenance therapy should be administered, but the optimal schedule and duration of therapy remains undetermined.[6,7,17,20]

The use of BCG can be limited by its side effect profile and subsequent intolerance that occurs in approximately 20% of patients during maintenance therapy.[21] BCG toxicity includes local and systemic reactions, ranging from cystitis, hematuria, bladder contracture, and mild flu-like symptoms, to life-threatening sepsis.[22] However, findings of recent large meta-analyses suggest that while the toxicity with BCG is higher than with intravesical chemotherapy, systemic effects do not predict efficacy,[23] and there is no difference in toxicity between induction and maintenance regimens.[24,25] Some recent trials have demonstrated that a reduced regimen (one-third dose) may be as effective as standard dosing with fewer side effects.[26,27]

Concern regarding BCG-related toxicity and disease progression has led to the study of other intravesical chemotherapeutic agents (Table 1) in the treatment of NMIBC, most notably mitomycin C (MMC).[9] However, large meta-analyses examining patients with Ta and T1 TCC have concluded that BCG is superior to intravesical chemotherapy in preventing tumor recurrence in patients at high risk[28,29]

Table 1 Emerging immunomodulating and cytotoxic intravesical agents currently under investigation

Agent	Mechanism	Advantages	Disadvantages	Toxicity
Immunomodulating agents				
IFN (+ BCG)	T-Helper Type I cell and NK cell stimulation, MHC I antigen expression	a) increased efficacy b) salvage therapy c) efficacy not affected by prior BCG exposure	a) costly b) loss of prognostic information provided by response to BCG monotherapy	mild to moderate local adverse effects
Bropirimine	Aryl pyrimidine that augments endogenous IFN production	a) powerful antitumor properties	a) significant hematologic and systemic toxicity	cardiac effects*
Keyhole-Limpet hemocyanin	Nonspecific immune stimulator	a) lacks toxicity b) greater efficacy than MMC c) minimal side effects	a) unclear protection against disease progression b) optimal dosing not defined	safe and well tolerated
Mycobacterial cell wall complexes	Nonspecific immune stimulator Induction of apoptosis	a) eplicates efficacy of BCG without the side effects	a) side effects ill-defined	mild to moderate local adverse effects
Mistletoe lectin	Induces cytokine release, increases lymphocyte activation marker expression	a) safe	a) clinical efficacy not yet defined	safe and well tolerated
Chemotherapeutic agents				
Gemcitabine	Pyrimidine analog that inhibits cell growth and induces apoptosis	a) salvage therapy b) minimal systemic absorption and toxicity c) prophylactic efficacy	a) myelosuppression b) anemia	mild to moderate local adverse effects
Anthracyclines	Topoisomerase II inhibitor	a) increased efficacy b) inexpensive c) safe	Efficacy of maintenance therapy unknown	mild to moderate local adverse effects†
Apaziquone	Alkylating agent	a) not cell-cycle specific	a) frequent side effects (leukopenia, irritative voiding symptoms)	mild to moderate local adverse effects
Taxanes	Microtubule polymerization inhibitor	a) no systemic absorption b) limited toxicity	a) poor aqueous solubility b) limited clinical experience	mild to moderate local adverse effects
Suramin	VEGF antagonist	a) limited local and systemic toxicity	a) limited clinical experience	metabolic, hematologic, renal and neurologic sequelae (systemic administration); minimal effects with intravesical adminstration

Abbreviations: Ab, antibody; NK, natural killer; MHC, major histocompatability complex; VEGF, vascular endothelial growth factor.
*Discontinued by manufacturer in 1996 due to cardiac toxicity; †Synthetic derivatives epirubicin and valrubicin show improved local toxicity profiles.

and when maintenance therapy is utilized.[17,30] Sylvester et al reviewed nine randomized trials including 700 patients with CIS treated with either BCG or intravesical chemotherapy (MMC, epirubicin, adriamycin, or combination therapy). With a median follow-up of 3.6 years, the researchers concluded that intravesical BCG significantly reduces the risk of short- and long-term treatment failure compared with intravesical chemotherapy and that BCG is first-line therapy for treatment of CIS.[31] Further review of these analyses has led to the current American Urological Association (AUA) consensus that an induction course of BCG followed by maintenance therapy is recommended for the treatment of high-grade Ta or T1 TCC and CIS.[6,7,9]

Although currently first-line therapy for high-risk NMIBC, five-year recurrence rates are estimated to be 34% in patients receiving BCG maintenance therapy.[7] The efficacy of BCG is also hampered by side effects and treatment intolerance, as well as the risks of understaging or progression to muscle-invasive disease. Radical cystoprostatectomy and urinary diversion is currently the standard of care for muscle-invasive TCC,[32] and there is growing consensus that relative indications for early cystectomy include recurrent NMIBC

refractory to intravesical therapy and naïve T1 disease with high-risk features for tumor progression.[33] However, the risk of perioperative complications and morbidity associated with cystectomy has spawned further interest in the utility of novel intravesical agents for BCG refractory disease.[6]

Interferon

Interferon (IFN) α2b has been utilized as both monotherapy and adjunct therapy in BCG-refractory patients.[6,9] IFNs are glycoproteins that mediate the host immune response in a dose-dependent manner by increasing antibody responsiveness, stimulating NK cells, and inducing expression of Class I major histocompatibility complex antigens.[9,34] The results of early investigations of IFN as monotherapy to prevent disease recurrence have been disappointing, demonstrating no benefit or inferior recurrence rates when compared with placebo controls[35] or other intravesical agents (BCG, MMC, MMC-IFN).[6,36]

In contrast, results from initial trials investigating the combination of IFN-BCG have been more promising.[6] O'Donnell et al reviewed their experience utilizing BCG plus 50 million units of IFN in 40 patients who had relapsed following induction BCG therapy.[9] With a mean follow-up of 30 months, 63% and 53% recurred at one and two years, respectively.[37] In a multicenter Phase II trial, BCG-IFN was administered to 536 BCG-naïve patients and 467 BCG-refractory patients with NMIBC. With a median follow-up of 24 months, recurrence-free rates were 59% and 45% in the BCG-naïve and BCG-refractory groups, respectively.[6] Factors associated with tumor recurrence were tumor size $>$ 5 cm, prior BCG failure, and tumor multifocality.[38] In a recent subanalysis of the same cohort, Gallagher et al reported that BCG-refractory patients who relapsed more than one year following induction therapy had similar response rates to those of BCG-naïve patients.[6] However, recurrence rates were higher in those with recurrent disease less than one year following induction therapy.[39] The use of BCG-IFN as initial therapy is limited and currently there is no consensus regarding the benefit of the addition of IFN in BCG-naïve patients.[40] Based on the available data, BCG-IFN appears to be a well-tolerated alternative to salvage therapy in selected patients with BCG-refractory NMIBC, but radical treatment options should be pursued for early failures and true BCG-refractory disease.[9]

Emerging agents under investigation

Bropirimine is a broad-spectrum immunostimulatory compound with oral absorption and urinary excretion.[6] Although not currently available in the US, the findings of a recent clinical trial demonstrated equivalent response rates to BCG in 55 BCG-naïve patients with CIS.[41] The results of a Phase II trial examining the utility of bropirimine in 86 BCG-refractory patients reported a complete response in 24% of patients, with a 6% rate of progression to muscle-invasive disease or metastasis.[42] However, a recent Southwest Oncology Group Phase II trial investigating combination bropirimine-BCG therapy in 51 BCG-naïve patients with CIS reported discouraging five-year progression-free (53%) and overall survival (80%) rates, and recommended that no further evaluation of this combination be conducted.[43] Bropirimine was discontinued by the manufacturer in 1996 due to significant concerns regarding cardiac toxicity and is currently not under clinical investigation in NMIBC.[9]

Keyhole limpet hemocyanin (KLH) is a highly antigenic respiratory pigment of the mollusk *Megathura cranulata* that results in nonspecific immune stimulation.[44] Attractive as an alternative to BCG due to its limited side effect profile, there have been several small Phase I and II clinical trials investigating its use as an intravesical agent.[9] Jurincic-Winkler et al treated 13 Tis patients with six weeks of KLH induction monotherapy, monthly treatments for one year, and bimonthly treatments for the two following years, reporting two complete responses at 66 and 82 months.[9,45] However, patients not responding to two KLH treatments were managed with BCG, and most patients exhibited disease progression regardless of therapy. In a multicenter study, Lamm et al reported a durable response in 64 patients with Tis (50%) and residual Ta-T1 disease (20%) treated with escalating doses of KLH for six weeks.[46] Despite promising results, comparative studies with BCG and chemotherapeutic agents (MMC, ethoglucid) have not demonstrated a benefit with KLH in patients with refractory NMIBC,[47,48] and further investigation is necessary before KLH can be recommended in patients refractory or intolerant to BCG.[9]

As a live bacterium, BCG carries the potential for significant adverse effects of varying clinical severity. In an effort to minimize these reactions, researchers have investigated using reduced dosages, adjunctive antibiotics, or heat/radiation-inactivated bacteria, with minimal success.[9,49] However, recent work investigating the use of *Mycobacterium phlei* mycobacterial cell wall complexes (MCC) containing mycobacterial DNA has generated significant interest.[9] A dual mechanism of action has been postulated, with both immunomodulatory (similar to BCG) as well as chemotherapeutic apoptotic features.[50] Early clinical work utilizing an MCC emulsion in 61 patients

with Tis over a 48-week duration demonstrated a partial or complete response rate in 52% of BCG-refractory patients and 69% of BCG-naïve patients with acceptable side effects.[51] Subsequent work has resulted in a new product formulation which still contains mycobacterial DNA but without the toxic preservative thimerosal.[49] This formulation is currently being investigated in 55 patients with CIS (30% had additional papillary tumors), 25 of whom received 4 mg MCC per treatment, and 30 received 8 mg MCC per treatment on similar schedules. Early results demonstrate an encouraging initial complete response rate (27%–46%) at weeks 12 and 26 in both treatment groups, whereas response rates were more marginal at 18 months follow-up (23%–32%) and were comparable between BCG-refractory and BCG-naïve patients.[52] Based on these early promising results, patients are currently being enrolled for clinical trials examining the efficacy of MCC in high-grade nonmuscle invasive lesions refractory to BCG as well as in BCG-naïve patients at high risk for recurrence or progression.[49]

A recombinant form of mistletoe lectin, another potential immunotherapeutic agent, is currently under development. By stimulating the release of cytokines and expression of lymphocyte activation markers, mistletoe lectin has been shown to inhibit urothelial carcinogenesis in rat models.[53] In the first clinical application, Goebell et al randomized 45 patients with pTa G1–2 TCC to a single adjuvant mistletoe lectin treatment two weeks following TUR versus no adjuvant therapy. At 18 months' follow-up, there were no significant differences with respect to recurrence-free interval or the number of recurrences between groups.[54] However, in a subsequent Phase II study examining use of mistletoe lectin induction therapy in 30 patients with NMIBC, Elsasser-Beile et al reported no local or systemic side effects and a 33% recurrence rate at 12 months, which was comparable with findings in an historical control group of patients undergoing BCG induction therapy. While further investigation is warranted to determine the optimal dose and timing of treatment, mistletoe lectin may ultimately prove to be a better tolerated alternative to BCG in selected patients.[55]

Gene therapy

Gene therapy has several theoretical advantages over conventional intravesical therapies, including a high selectivity for tumor cells with mutated genes, potential to restore normal cell growth by correcting genetic defects, and potential to reduce chemoresistance.[6,56] Gene delivery systems include both viral (adenovirus, vaccinia) and nonviral vectors (lipoplexes, Table 2). While the relative advantages/disadvantages of each method of gene delivery is beyond the scope of this review, the inadvertent systemic absorption of viral vectors resulting in an excessive immune response is a significant concern that may be avoidable with the utilization of intravesical or nonviral vectors.[6,57] Viral receptor expression and physical composition of urothelial surface cells are formidable barriers to the delivery of intravesical gene therapy. Current research efforts have been directed at modulating coxsackie-adenovirus receptor expression,[58] as well as coadministration of the polyamide syn3 to disrupt the urothelial barrier,[59] thereby increasing viral uptake and improving adenoviral therapy efficacy. Use of replication-competent viral systems is also being explored in animal models, but concerns include infection of non-targeted cells and the potential for carcinogenic insertional mutagenesis.[56]

Early *in vivo* and *in vitro* studies have shown promising results. Using a rat model, Conner et al demonstrated the efficacy of adenoviral-mediated gene-delivered IFN therapy to inhibit bladder cancer growth, with increased drug concentrations and retention times compared with standard intravesical instillation.[60] Utilizing a replication-competent oncolytic adenovirus (CG0070) encoding GM-CSF, Ramesh et al demonstrated selective replication, cytotoxicity, GM-CSF production, and antitumor efficacy in both *in vitro* and *in vivo* bladder TCC models compared with normal human cells.[61] Recombinant vaccinia virus delivery of a p53 gene in an orthotopic mouse bladder tumor model provided a survival advantage compared with phosphate buffer or empty vector control groups.[62] In a murine bladder tumor model, Lee et al examined the efficacy of recombinant BCG and murine IL-12 DNA vaccines using eukaryotic expression vectors.[6] The cumulative survival of mice treated with both the BCG vaccine and the IL-12 vaccine was significantly higher compared with that of controls or those treated with either vaccine alone.[63] Horinaga et al administered intravesical IL-12 gene therapy delivered in cationic liposome vector in a mouse model with orthotopic bladder tumors.[6] When compared with a high-dose BCG-treated group and negative controls, IL-12 therapy was equivalent to BCG, and both treatments were superior to the reporter gene-negative controls.[6] Interestingly, surviving IL-12-treated mice rechallenged with additional tumor cell implantation after 60 days survived significantly longer than BCG-treated mice, suggesting a more durable tumoricidal effect.[64]

Early Phase I clinical trials have demonstrated that intravesical gene therapy can be safely administered in bladder cancer patients with minimal toxicity. In four patients with muscle invasive bladder cancer, Gomella et al administered

Table 2 Investigational genetic therapies for the management of NMIBC

Agent	Mechanism	Advantages	Disadvantages
Gene therapy			
Vectors			
Adenovirus	Cell entry via the coxsackie/adenovirus membrane receptor	a) DNA does not integrate into host chromosomes b) ease of obtaining recombinant proteins and producing vectors in high titers c) high viability of host cells post-infection	a) poor viral uptake b) inadvertent systemic absorption may elicit excessive immune response or insertional mutagenesis in host cells
Vaccinia	Recombinant double-stranded DNA virus	a) broad applicability b) rapid infection c) efficient transgene expression	a) vaccination against small pox may inhibit gene transfer
Nonviral (lipoplexes)	Ionic cellular uptake	a) simple preparation b) inexpensive c) low immunogenicity d) carry larger genes	a) poor cell uptake and transfer
Monoclonal antibodies (Thrombospondin-1, EGF receptor)	Reduce tumor angiogenesis and induce apoptosis	a) simple preparation b) highly specific c) low immunogenicity	a) Lack of adequate delivery vehicle
Hemagglutinating virus of Japan envelope factor (HVJ-E)	Induces extensive immunologic antitumor activity	a) no need for concurrent chemotherapy administration	a) investigational b) poor specificity
siRNA	Silences targeted gene expression on the mRNA level	a) specificity b) high efficiency	a) insertional mutagenesis b) iatrogenic leukemia c) inefficient cellular uptake and local delivery
Therapeutic targets			
p53	Dysregulation of apoptosis; direct lytic effect		
IFN-α	Inhibits tumor proliferation; induces differentiation		
IL-10	Suppresses APC capacity		
CG0070	Preferential GM-CSF production activates host immune response		

Abbreviations: NMIBC, nonmuscle invasive bladder cancer; INFα, interferon alpha; APC, antigen presenting cell; IL, interleukin; GM-CSF, granulocyte macrophage colony stimulating factor; EGF, epidermal growth factor.

three increasing doses of intravesical DryVax (Wyeth-Ayerst Laboratories, Philadelphia, PA), a DNA poxvirus, prior to cystectomy.[65] Histologic examination of the bladders 24 hours following the last dosing revealed evidence of viral infection in both tumor and normal cells, and a significant mucosal and submucosal inflammatory reaction in both tumor and normal tissue.[6] There were no clinical or laboratory manifestations of vaccinia-related toxicity with the exception of mild dysuria. In patients with histologically confirmed TCC, Kuball et al administered an intratumoral injection or intravesical instillation of an adenoviral vector containing wild-type p53 with a gene transfer enhancer (SCH 58500) in 11 patients prior to cystectomy. Specific transgene expression was detected in tumors and normal bladder samples in 7/8 patients treated intravesically, but was not seen in patients receiving intratumoral injection. No cases of dose-limiting toxicity were observed and side effects were transient.[6,66] In a feasibility study, Pagliaro et al administered repeated doses of adenoviral vector-mediated p53 (Ad5CMV-p53) to 13 patients with locally advanced TCC who were not candidates for cystectomy. The treatment was well tolerated by all patients and specific transgene expression was found in 2/7 patients.[67] Emerging therapies currently being investigated include gene therapy using viral and nonviral vectors for transfer, monoclonal antibodies, and direct tumoricidal viruses. While there is currently little evidence demonstrating a clinical benefit in human studies, gene therapy remains an exciting field for future investigation, and the further development of alternative vector systems will help define a therapeutic role in the management of NMIBC.

Chemotherapeutic agents

The use of intravesical chemotherapeutic agents for NMIBC has been met with variable success.[68] Traditionally reserved for use in patients with BCG-refractory disease, multiple agents, most commonly MMC, epirubicin, and valrubicin, are currently being investigated as primary and secondary therapy for NMIBC.[6] Early data suggested that the addition of intravesical chemotherapy to TUR yields a 14% reduction of tumor recurrence but has limited benefit with respect to disease progression.[69] However, in two recent meta-analyses examining the impact of multiple intravesical chemotherapeutic agents on recurrence prevention, Huncharek reported that recurrence rates may be reduced by as much as 70% when compared with TUR alone.[6] Variations in dosage and treatment schedules were postulated to account for the large differences in recurrence rates observed across studies.[70,71] Current efforts are focused on defining the ideal treatment schedule, optimizing the efficacy of traditionally utilized therapies, and investigating novel chemotherapeutic agents.

Mitomycin C

MMC is a cross-linking agent that inhibits DNA synthesis.[72] Due to its high molecular weight (329 kDa), there is reduced risk of transurothelial absorption and side effects are minimal even in the immediate postoperative period.[9,73] Currently, the dosage varies from 20 to 60 mg per instillation.[6] The most commonly used dose is 40 mg in 40 mL of saline or sterile water administered weekly for eight weeks followed by monthly instillations for one year.[7] Initial studies investigating the use of MMC as monotherapy for NMIBC following TUR showed promising results.[74,75] In a small prospective trial, Huland et al randomized 58 patients with NMIBC following TUR to either no further therapy or MMC at 20 mg/20 mL instilled every two weeks for the first year and every four weeks for the second year. Although patients with superficial low-grade tumors were probably included, recurrence rates with MMC (7%) were significantly lower compared with the control group (50%).[76] Tolley et al randomized 502 patients following TUR to no adjuvant treatment, one perioperative instillation of MMC, and up to five MMC instillations at three-month intervals following resection. With a median follow-up of five years, the authors reported decreased recurrence rates and an increased recurrence-free interval in patients undergoing MMC therapy, with evidence to suggest a slight advantage of multiple instillations over one perioperative instillation.[6,77]

Significant attention is currently being directed towards defining the optimal MMC treatment schedule, and identifying which patients will benefit from a single perioperative treatment compared with chronic maintenance therapy.[6] Chemotherapeutic agents are preferred to BCG in the immediate perioperative period due to reduced risks of systemic absorption following TUR. Tolley et al reported a significant decrease in tumor-recurrence risk in patients with NMIBC treated with a perioperative (less than 24 hours following TUR) 40 mg MMC treatment compared with TUR alone.[77] Benefits of a single immediate instillation on the risk of tumor recurrence have been reported with epirubicin[78] and doxorubicin[79] as well, although optimal timing post-TUR has not been determined. In a meta-analysis of seven randomized trials comparing TUR alone with TUR plus one immediate instillation of chemotherapy, Sylvester et al reported a 39% reduction in risk of recurrence (odds ratio [OR] 0.61, $P < 0.0001$). Benefits were seen in patients with a single tumor or with multiple tumors. However, recurrence was higher in patients with multiple tumors compared with solitary tumors (65.2% versus 35.8%).[80] Based on these data, the current AUA superficial bladder cancer guidelines recommend that a single dose of intravesical chemotherapy be administered immediately postoperatively (less than six hours) in patients with small volume solitary tumors when there is no evidence of bladder perforation.[7] Currently consensus is lacking regarding effectiveness of perioperative MMC on decreasing recurrence rates compared with other chemotherapeutic agents.[6]

In patients with intermediate- and high-risk NMIBC, induction therapy is recommended to prevent disease recurrence.[7] The literature currently supports the superiority of BCG in limiting disease recurrence and progression compared with chemotherapeutic agents.[31] However, BCG toxicity limits its use in a significant number of patients, resulting in an increasing need for alternative therapies. In a meta-analysis of six trials comparing BCG and MMC in 1527 patients, Shelley et al reported a reduced incidence of local (30% versus 44%) and systemic toxicities (12% versus 19%) with MMC, with no significant difference in recurrence, progression, or survival. While the overall analysis, which included low-risk patients, failed to show a difference in risk of recurrence, a subgroup analysis of three trials including only patients with high-risk NMIBC revealed a 31% reduced risk of tumor recurrence with BCG compared with MMC.[6,28,29] Additional meta-analyses have demonstrated that maintenance BCG is required to see the greatest benefit in reducing tumor recurrence and progression when compared with MMC.[6,24,30]

Until recently, there was general consensus that chemotherapy was effective in reducing short-term risk for recurrence but its efficacy was only marginal in the long term.[79,81,82] However, in a recent prospective trial, Friedrich et al randomized 495 patients with intermediate- to high-risk NMIBC following TUR to a six-week course of BCG, a six-week course of MMC, or a six-week course of MMC followed by monthly instillations for three years. Three-year recurrence-free rates were 65.5% for short-term BCG, 68.6% for short-term MMC, and 86.1% for patients undergoing long-term MMC therapy,[83] supporting the potential use of MMC maintenance therapy as an alternative to BCG in high-risk populations. Current efforts are being directed towards optimizing the efficacy of chemotherapeutic agents and will be discussed later in this review.[9]

Thiotepa

Thiotepa, an alkylating agent that inhibits nucleic acid synthesis by inducing the cross-linkage of DNA, RNA, and proteins,[84] is currently the only chemotherapeutic agent approved by the Food and Drug Administration for papillary TCC.[6] Dosing ranges from 30 mg in 30 mL to 60 mg in 60 mL sterile water or saline, with six- to eight-weekly instillations followed by administration monthly for one year.[6] Risks of local toxicity such as irritating voiding symptoms are prevalent, and there is a significant risk of systemic myelosuppresion requiring frequent leukocyte and platelet count monitoring due to the low molecular weight of thiotepa (189 kDa).[85]

Initial trials demonstrated the efficacy of thiotepa in preventing recurrence when compared with controls.[84,86] However, subsequent trials have demonstrated inferior results when thiotepa is compared with MMC[85] or BCG. Martinez-Pineiro et al reported the results of a prospective trial in which patients with NMIBC were randomized to 15 courses of intravesical doxorubicin 50 mg, thiotepa 50 mg, or BCG 150 mg following TUR.[87] With three years of follow-up, patients randomized to BCG demonstrated a significant reduction in risk of recurrence (13.7%) when compared with thiotepa (35.7%) or doxorubicin (43.4%).[6] A similar trend was seen when patients were stratified by stage of disease. Review of these initial studies identified nine controlled trials including 1130 patients. Reviewing five of the trials that achieved statistical significance,[84,88–91] the mean rate of recurrence in the control populations was 61% versus 49% in the treated groups, resulting in a modest 12% benefit with thiotepa therapy.[69] Currently, due to its marginal efficacy and risk of systemic toxicity, use of thiotepa is limited to patients who cannot tolerate BCG or selected BCG-refractory cases not medically fit for cystectomy.[6]

Gemcitabine

Gemcitabine is a pyrimidine analog that exhibits antitumor activity by inhibiting cell growth and triggering apoptosis, and is currently a staple in the systemic chemotherapeutic regimens utilized in metastatic and locally advanced TCC.[6,9,92] Phase I trials have reported that the high molecular weight of gemcitabine (299.66 kDa) prevents systemic toxicity with an intact bladder,[93] and the ablative efficacy of gemcitabine has also been demonstrated in early tumor marker studies.[94]

Phase II clinical trials are currently underway investigating the efficacy of intravesical gemcitabine following TUR for NMIBC.[9] In 116 patients undergoing weekly dosing for six weeks following TUR, Bartoletti et al reported recurrence rates of 25.9% and 77.1% in patients with intermediate-and-high risk disease, respectively.[95] With a novel pre- and post-TUR dosing scheme in nine patients with persistent or recurrent Ta-1, Grade 1–2 TCC following previous intravesical therapy, Mattioli et al reported recurrence in 77.7% of patients.[96] Dalbagni et al recently reported their observations in 30 patients who were either refractory or intolerant to BCG and treated with twice-weekly gemcitabine for three weeks. With a median follow-up of 19 months, 50% achieved a complete response, 40% relapsed with a median recurrence-free survival of 3.6 months, and 37% progressed to cystectomy.[97] A randomized Phase III clinical trial of gemcitabine versus MMC in recurrent bladder cancer revealed 72% and 61% disease-free recurrence rates in the gemcitabine and MMC arms, respectively, at a median follow-up of 36 months.[98] A recent single-arm prospective trial utilizing gemcitabine in 20 patients with BCG-refractory NMIBC revealed 55% disease recurrence at a median follow-up of 15.2 months. In this series, the authors reported a mean time to first recurrence of 3.5 months, and 45% of patients with recurrent disease exhibited disease progression.[99] While promising as both a primary and adjuvant therapy, further prospective comparisons with contemporary agents are warranted, and at this time gemcitabine is limited to conservative use in selected cases of intravesical treatment failure.[6,9]

Anthracyclines

Doxorubicin, epirubicin, and valrubicin are anthracycline antibiotics that prevent protein synthesis by binding DNA base pairs and inhibiting topoisomerase II.[9,100] While side effects including chemical cystitis, decreased bladder capacity, hematuria, and post-instillation fever have hampered the

use of doxorubicin, the synthetic derivatives epirubicin and valrubicin show similar therapeutic efficacy with better local toxicity profiles.[9,101] Five early trials randomizing patients to intravesical doxorubicin or TUR alone reported an average recurrence rate of 38% with doxorubicin compared with 53% for TUR, with no benefit shown for disease progression.[6,9,69] Studies comparing epirubicin and valrubicin with TUR alone have reported disease recurrence rates comparable with doxorubicin.[78,101] Randomized controlled trials have demonstrated that recurrence rates following administration of doxorubicin and epirubicin are inferior to BCG,[102,103] which has limited anthracycline use in most early studies to immediate postoperative instillation, BCG-refractory disease, and CIS.[9]

Small trials have indicated that a single perioperative dose of epirubicin reduces disease recurrence compared with IFN or TUR alone.[104] In a small series of patients with NMIBC randomized to perioperative epirubicin, induction epirubicin, or induction MMC with five years of follow-up, Liu et al reported similar recurrence rates and minimal toxicity in the perioperative epirubicin arm, suggesting that a single perioperative dose of epirubicin may be the most efficacious means of preventing TCC recurrence in the short term with minimal adverse effects.[9,105] However, the superiority of BCG was demonstrated in a recent randomized prospective trial comparing BCG with the combination of epirubicin and IFN α2b for the adjuvant treatment of high-grade T1 tumors. Sixty-two percent were disease-free in the combination arm as opposed to 73% in the BCG arm at 24 months' follow-up, although there were no differences regarding progression and adverse events between groups, and the subgroup analysis showed that the superiority of BCG was mainly in those with concomitant CIS.[106] Sequential instillation therapy with doxorubicin in combination with MMC has been investigated in a small series.[6,9] Sekine et al randomized 42 patients with NMIBC to either BCG or doxorubicin with MMC. Initial response rates (86% versus 81%) were equal between groups and, with a mean follow-up of 47 months, only five patients developed disease progression.[107] A recent multi-institutional study investigated the use of valrubicin in 90 patients with refractory CIS, 60% of whom had failed three or more intravesical agents. The findings of this study demonstrated that 21% of patients had a complete response, 10% remained disease-free over a follow-up of 10 years, and 56% progressed to cystectomy.[108] Based on these data, use of anthracyclines has been widely accepted overseas, demonstrating the most utility in patients with NMIBC and CIS who have failed or are intolerant to BCG therapy.[6]

Apaziquone

Apaziquone is an indoloquinone bioreductive alkylating agent that results in cell death via the redox cycle and alkylation of DNA.[109] The relative stability of the compound and rapid pharmacokinetic elimination of the drug make it an intriguing agent for use in NMIBC, and Phase I/II trials have confirmed minimal local and systemic toxicity.[9,110,111] In a recent update of their Phase I study, Jain et al reported that of the eight patients who achieved a complete response, 50% relapsed over a median follow-up of 31 months. Of note, the recurrence-free interval significantly increased following apaziquone administration compared with historic recurrence intervals pretreatment.[112] In the largest clinical experience to date, Van der Heijden et al administered six weekly instillations of 4 mg/40 mL apaziquone to 46 patients with Ta-1, G1–2 NMIBC following TUR.[6] Two-thirds of subjects demonstrated a complete histologic response rate at 2–4 weeks, with local side effects comparable with those of other chemotherapy instillations.[9,113] With longer follow-up, of the 31 patients who achieved a complete response, observed recurrence-free rates at one and two years were 56.5% and 49.5%, respectively.[114] These initial data support apaziquone's promise as an intravesical agent, and Phase III trials investigating its use during immediate postoperative instillation and post-TUR induction therapy are underway.[6]

Taxanes

Docetaxel and its close relative, paclitaxel, are from a class of cytotoxic agents (taxoids) that inhibit the polymerization of microtubules by promoting intracellular bundling, resulting in M-phase cell cycle arrest and cell death.[9,100] The systemic administration of taxanes have resulted in antitumor activity in metastatic bladder cancer,[115] and recent *in vitro* studies have demonstrated their efficacy in TCC cytotoxicity assays as well.[9,116] In a Phase I trial of six weekly docetaxel treatments in 18 patients with recurrent NMIBC who had failed at least one intravesical therapy, McKiernan et al reported a complete response rate of 56% at post-treatment cystoscopy and biopsy, with minimal local toxicity.[6,9,117] Long-term clinical outcomes in this cohort revealed 22% and 17% complete and partial response rates, respectively, while 61% failed treatment at a median follow-up of 48.3 months.[118] In a recent update of their series of 33 patients with refractory NMIBC, Barlow et al reported a 61% complete response rate after six weeks of induction therapy, and one- and two-year recurrence-free survival rates were 45% and 32%, respectively.[119] Taxoids are attractive candidates for intravesical therapy due to their potency, high molecular

weight (853.9–861.9 kDa), and lipophilicity.[6] However, poor aqueous solubility has previously limited their practicality for intravesical administration. Current studies investigating the feasibility of bioadhesive polymicropheres to optimize paclitaxel release and adhesion to the urothelium in murine models are in progress and will be discussed later in this review.[9,120]

Suramin

Suramin is a polysulfonated naphthylurea and a potent antagonist of vascular endothelial growth factor (VEGF).[109] Previous studies have demonstrated that increased VEGF levels in primary superficial tumors or in urine are associated with early recurrence or stage progression,[121] and identified VEGF as a possible candidate for targeted therapy in NMIBC.[9] Suramin was shown to inhibit the activity of several angiogenic factors produced by bladder cancer cell lines, as well as cell proliferation, during *in vitro* studies.[122] Inhibition of invasion of bladder cancer cell lines with suramin was also demonstrated in a bladder tissue explant model.[123] Although serious metabolic, hematologic, renal, and neurologic sequelae have been reported following systemic administration of suramin, its high molecular weight (1429 kDa) should prevent systemic absorption during intravesical administration.[109] In an open-labeled, nonrandomized dose escalation Phase I trial, Ord et al administered six weekly intravesical doses of Suramin (10–150 mg/mL in 60 mL saline) to 12 patients with a history of recurrent NMIBC.[9,124] Findings demonstrate minimal evidence of local or systemic toxicity, and Phase II trials are currently in the preparatory phase.[6]

Optimizing efficacy of current agents

The unique properties of the bladder render it an ideal organ for regional therapy (Table 3). Access per urethra is non-invasive, and the urothelium provides a barrier preventing the systemic absorption of most small-molecule drugs.[6,9] However, with topical therapies, cell kill is proportional to the duration of exposure and drug concentration rather than dosage.[6,125] Current goals for improving the efficacy of intravesical therapy are maximizing tumor exposure to the therapeutic agent and limiting systemic exposure and host toxicity.[6,9] Intravesical drug disposition is variable, and is affected by drug properties (molecular weight, and hydrophilicity, lipophilicity), urine volume and pH, patient hydration status, and urothelial integrity.[9,57]

Drug concentration in the bladder is dependent on dose, volume of dosing solution, urine production, and the residual urine volume during instillation.[6] Response rates with differing chemotherapeutic agents are variable, and several techniques have been employed to increase drug concentration and to enhance drug delivery. Completely emptying the bladder prior to drug administration, repositioning the catheter, or frequently changing patient position can help to avoid excessive residual urine volumes.[9,126] In addition, patients should be encouraged to retain the instilled agent for as long as possible, with a two-hour urothelial contact time as an optimal goal.[57]

Decreasing urine production and urine alkalinization

Optimization regimens have been established to maximize the effectiveness of MMC. A six-hour fasting period prior to instillation, reported to decrease urine volume and prevent 20% of drug dilution, is currently recommended in the European Association of Urology guidelines for NMIBC.[9,127] Cliff et al reported a 38% increase in intravesical MMC concentration following the administration of 0.2 mg of oral desmopressin one hour prior to instillation;[128] however, care must be taken in patients with cardiac failure or hyponatremia, and widespread use has not gained acceptance.[6,9] Alkalinizing the urine with oral bicarbonate has also been shown to improve MMC drug stability, cellular uptake, and muscle penetration.[57]

Based on results from pharmacokinetic modeling that described drug disposition in urine and bladder tissues, the International Mitomycin C Consortium synthesized an optimized MMC treatment protocol that was tested in a multicenter, two-arm Phase III clinical trial.[6] Patients in the optimized arm received a 40 mg dose of MMC with pharmacologic manipulations to maximize drug delivery (ultrasound-guided bladder emptying, voluntary dehydration, and urine alkalinization with sodium bicarbonate) and patients in the standard arm received a 20 mg dose in a 20 mL dosing volume without manipulations.[6] Using a primary endpoint of time to recurrence and a secondary end point of recurrence-free rate, those in the optimized arm demonstrated a significantly increased median time to recurrence (29.1 versus 11.8 months, $P < 0.001$) and a 19.1% increase in five-year recurrence-free rates.[9,126]

Increasing bladder wall penetration

A number of novel chemical and physical approaches have been utilized in an effort to increase bladder wall penetration and enhance chemotherapeutic efficacy.[6,9] It is important to note that while these techniques are promising, their efficacy in humans remains to be determined, and the findings presented need to be interpreted with caution.[6,9]

Table 3 Optimization of intravesical therapy for NMIBC

Method	Mechanism	Side effects
Permeation enhancers		
DMSO	Promotes urothelial penetration of water soluble and lipophilic drugs	Promotes systemic drug absorption and urine production
Chitosan	Cationic polysaccharide rearranges cellular junction and enhances paracellular drug transport	Promotes systemic absorption
Polycarbophil	Mucoadhesive polyacrylic acid cross-linked with divinyl glycol chelates extracellular calcium ions and opens cellular tight junctions	Promotes systemic absorption
Hyaluronidase	Hydrolyzes hyaluronan in bladder mucosa extracellular matrix; direct tumor suppression	High concentrations may promote tumor growth
Electromotive therapy	Temporarily breaches bladder urothelium	Increased plasma absorption
Hyperthermia	Enhances DNA damage and inhibition of DNA synthesis, alters intracellular drug trafficking and distribution	Increased local irritation
Photodynamic therapy	Accumulation of a photosensitizing agent facilitates selective tumor destruction following exposure to light	Skin hypersensitivity, detrusor scarring and contracture
Prolonging residence time		
Bio-adhesive microspheres	Sustained-retention delivery depots extend drug exposure in the bladder cavity	Not yet evaluated in humans
Magnetic targeting	External magnets localize drug-containing magnetic micro- and nano-particles in tumors	Unknown; nonspecific localization of magnetic particles
Oral bicarbonate	Urine alkalinization improves drug stability and cellular uptake	Few

Chemical methods of increasing bladder wall permeability include use of dimethyl sulfoxide (DMSO), chitosan, polycarbophil, and hyaluronidase.[57] Initially utilized in the treatment of patients with interstitial cystitis, DMSO has been shown to induce and alter inflammatory tissue responses and neurotransmission. DMSO is a bipolar molecule that is highly miscible with water, lipids, and organic agents.[6,9] Its ability to cross cellular membranes led to increased interest in the coadministration of DMSO with intravesical agents to promote the penetration of water- and lipid-soluble drugs. Initial efforts with cisplatin, doxorubicin, and paclitaxel showed promise.[129] However, DMSO also resulted in increased urine production, as well as promoting systemic absorption of paclitaxel,[129] which has dampened initial enthusiasm. Permeability enhancers that enhance drug transport by rearrangement of cellular tight junctions (chitosan, polycarbophil) or hydrolyzation of the bladder mucosal hyaluronan network (hyaluronidase) have also been investigated.[9] In a porcine study, chitosan and polycarbophil were shown to increase bladder wall tissue penetration of pipemidic acid.[130] Coadministration with hyaluronidase has been shown to reduce recurrence significantly in patients with NMIBC treated with MMC, without increasing systemic absorption.[131]

Physical methods to enhance permeability by urothelial disruption include hyperthermia, electromotive therapy, and photodynamic therapy.[6,9] Hyperthermia has been shown to enhance the efficacy of chemotherapeutic agents on inhibition of DNA synthesis and repair, increasing cell membrane permeability, and altering intracellular drug transport.[109] Colombo et al evaluated the effectiveness of neoadjuvant local bladder hyperthermia in combination with MMC in 29 patients compared with 23 patients receiving MMC alone.[6] All patients underwent TUR one week following therapy, and a pathologic complete response was observed in 66% versus 22% of patients, respectively ($P < 0.01$).[132] This study was followed by a prospective, multicenter, randomized trial in which 42 patients with intermediate- and high-risk NMIBC received MMC in combination with local microwave-induced hyperthermia and 41 patients received MMC alone following TUR.[9] With a minimum follow-up of 24 months, recurrence rates were significantly reduced in the combination therapy arm compared with the MMC alone arm (17.1% versus 57.5%, $P = 0.002$) respectively.[133] The efficacy of local bladder hyperthermia in conjunction with intravesical chemotherapy has been confirmed in an additional single-arm series of patients with NMIBC.[134] While these early results show exciting promise, trials comparing

adjuvant microwave hyperthermia and MMC with single postoperative MMC instillation or adjuvant BCG are needed to define a true disease-recurrence benefit before it can be accepted as first-line therapy.[6,9]

Electromotive drug administration (EMDA), utilizing iontophoresis to create a potential difference across the bladder wall, has been shown to increase drug transport through biologic membranes and to enhance the effectiveness of intravesical agents when compared with passive administration alone.[6,9] In a pilot study of 28 patients with high-risk NMIBC treated with EMDA-MMC versus MMC alone, complete response rates were equivalent, but a lower recurrence rate and disease-free interval were observed in the combination therapy arm.[9,135] Di Stasi et al prospectively randomized 108 patients with high-risk NMIBC following TUR to EMDA-MMC, MMC alone, or BCG alone. Compared with MMC alone, the EMDA-MMC-treated arm showed a significant improvement in six-month recurrence-free rate (58% versus 31%, $P = 0.01$) and median time to recurrence (35 versus 19.5 months, $P = 0.01$), and equivalent rates compared with the BCG treatment arm.[9,136] A subsequent trial randomized 212 patients with T1 TCC to BCG alone versus BCG followed by three cycles of EMDA/MMC.[6] With a median follow-up of 88 months, patients treated with BCG followed by EMDA/MMC had lower recurrence rates (41.9% versus 57.9%, $P = 0.001$), and an increased disease-free interval (69 versus 21 months, $P = 0.001$) when compared with BCG alone.[137] Di Stasi et al recently presented data describing a new concept of preoperative recurrence prophylaxis with one single intravesical EMDA/MMC instillation immediately prior to TUR. In this prospective study, 167 patients with pTa G1-G2 bladder tumors were randomized to TUR alone, TUR + one single postoperative MMC instillation, or intravesical EMDA/MMC prior to TUR. With a median follow-up of 84.7 months, recurrence rates following preoperative EMDA/MMC (37%) were superior to TUR alone (67%), and MMC post-TUR (54%, $P = 0.007$) which indicates that new therapeutic strategies may result in improved remission rates.[9,138]

Photodynamic therapy (PDT) is emerging as an intriguing alternative treatment option.[6] Based on the premise that accumulation of a photosensitizing agent in tumor cells may facilitate more selective destruction of malignant cells following exposure to light, early studies focused on porphyrin mixtures (Photofrin®) and hematoporphyrin derivatives.[9] Although response rates were encouraging, undesirable side effects including prolonged skin hypersensitivity and detrusor scarring and contracture discouraged its use.[139] Subsequent trials of 5-aminolaevulinic acid (ALA), a precursor of the photosensitizer protoporphyrin IX, have shown that local and systemic (hypotension, tachycardia) toxicity could be avoided with intravesical administration.[140] Berger et al administered 5-ALA (50 mL) in a 3% concentration intravesically in 31 patients with recurrent NMIBC (32% BCG-refractory). With a mean follow-up of 23.7 months, treatment was well tolerated, and 48% of patients developed tumor recurrence. Due to the favorable side effect profile, the authors concluded that PDT could be applied safely in patients with recurrent bladder cancer who had failed BCG therapy or had comorbidities precluding more invasive surgical therapy.[6,9,141] Current work to determine optimal ALA concentration and light energy required for effective ALA-PDT eradication is ongoing.[140]

Prolonging residence time and site-directed targeting

Prolonging bladder mucosal exposure to intravesically administered chemotherapy is a major challenge, due to agent insolubility in the aqueous form and immediate evacuation with voiding.[6] Sustained-retention delivery platforms offer the promise of extending drug exposure in the bladder cavity beyond the voiding of urine.[57] Bioadhesive microspheres and hydrogel systems have been tested in experimental models and have been shown to prolong bladder retention of agents, including paclitaxel[120] and adriamycin,[142] to promote urothelial absorption.[9] Liposomes, positively-charged multilamellar lipid vesicles, have been utilized in animal models to enhance the intravesical delivery of hydrophobic agents such as capsaicin,[143] currently being investigated in animal studies to facilitate intravesical drug delivery.[6] Further studies are necessary prior to human trials, but sustained-retention delivery platforms show exciting potential in improving intravesical drug delivery.[9]

Magnetically-targeted carrier therapy utilizes a magnet placed externally on the skin covering a predetermined bladder site to localize drug containing magnetic particles in tumors and provide prolonged exposure to higher drug concentrations.[6,9] Magnetically-targeted carriers are microparticles containing metallic iron to increase magnetic susceptibility and activated carbon to facilitate binding of the chemotherapeutic agent. In a porcine model, Leakakos et al demonstrated the feasibility of the intravesical administration of doxorubicin utilizing 300–800 mg magnetic particles.[6] Plasma doxorubicin concentrations were below the level of detection, and histologic studies confirmed targeted

microparticle localization in superficial and deep bladder tissue.[144] While still in the initial investigatory period, this technology shows promise, particularly for bladder preserving protocols, and warrants further study.[6,9]

Early radical cystectomy

There is increasing evidence that intravesical chemotherapy, while effectively reducing recurrence rates, does not show a disease-progression or survival benefit in patients with NMIBC.[6] In addition, recent data has shown a disturbing trend towards decreasing disease-free survival rates in patients with T1 disease undergoing radical cystectomy following intravesical therapy.[145] Of significant concern in these patients is the high prevalence of clinical understaging,[7] which supports the consensus that the timing of radical cystectomy for high-grade NMIBC is critical to prognosis and long-term survival.[6,9] Early cystectomy has been shown to result in better outcomes in patients with BCG-refractory T1 disease as well as CIS.[33] Restaging TUR in patients with T1 disease is mandatory,[7] especially in patients with evidence of disease recurrence.[6] Furthermore, the case for performing early cystectomy in appropriate surgical candidates is strengthened by recent reports demonstrating improved perioperative morbidity and mortality rates,[32] as well as improved patient satisfaction following orthotopic urinary diversions.[6,9,146] While intravesical therapy is an important component of the oncologist's armamentarium in the treatment of superficial bladder cancer, a radical cystectomy should be considered in all patients who have failed conservative management or who have T1 high-grade disease and tumor characteristics with high prognostic risk for recurrence.[6,9]

Conclusion

Bladder cancer is a prevalent disease with significant associated health care costs and social implications. The high rates of disease recurrence and progression and the need for lifetime surveillance impart a large financial and emotional burden on the health care system and patients diagnosed with bladder cancer. Following diagnosis, prompt repeat TUR represents the current standard of care to accurately stage patients and to identify patients who may benefit from early extirpative surgery. For patients with low volume Ta tumors, a single perioperative dose of intravesical chemotherapy is recommended by the AUA, and may provide a durable cure in many patients. The use of induction and maintenance BCG is recommended in patients with intermediate and high risk noninvasive disease, and may prevent disease recurrence and progression. For patients with muscle invasive disease, radical cystectomy remains the gold standard. Early radical cystectomy with continent diversion remains the gold standard for the treatment of muscle invasive disease, but may also improve quality of life and oncologic efficacy in patients with high grade T1 tumors with aggressive prognostic features, and should be considered as definitive first line thearpy.

For patients with NMIBC refractory to intravesical chemotherapy, radical cystectomy should be performed in appropriate surgical candidates. Unsuitable surgical candidates and BCG intolerant patients present a management dilemma. Reduction in BCG dosing limits local and systemic side effects and improves tolerability, but may compromise cancer control. Large meta-analyses have demonstrated the efficacy of chemotherapeutic agents including MMC, thiotepa, and doxorubicin as alternatives to BCG in preventing disease recurrence compared with TUR alone.[6] Urine alkalinization, dehydration, and bladder emptying may improve the efficacy of currently available agents. Alternatively, photodynamic, gene, and electromotive therapies are emerging device-assisted technologies that may further optimize current treatments. Cytotoxic agents including gemcitabine, valrubicin, and BCG plus IFN as salvage therapy are currently under investigation, and have exhibited promising early efficacy. Apaziquone, taxoids, and suramin are the newest agents under investigation, but it will take several more years to compare their efficacy and superiority, if any, to current treatments. The ideal agent for the treatment of NMIBC remains unidentified, however a number of novel therapies appear promising, and we anticipate further significant advances concomitant with forthcoming discoveries.

Disclosures

The authors report no conflicts of interest in this work.

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