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Chemoprevention and Novel Treatments of Non-Muscle Invasive Bladder Cancer

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1. Introduction

The Cancer Journal for Clinicians reports there will be 69,250 newly diagnosed cases of bladder cancer in 2011, with 52,020 being men and 17,230 being women with an increase by 50% of annual cases since 1985. Approximately 1 in 5 of those who develop bladder cancer will die due to the disease (relative mortality 20.8%, [Siegel et al., 2011, Golijanin et al., 2006]). Bladder cancer has become the second most prevalent cancer after cancer of the prostate in middle-aged to elderly male individuals. Many patients do not die from their disease, but typically have multiple recurrences (Pelucchi et al., 2006). This lends to a five-year cost to Medicare attributed to bladder cancer of over one billion dollars (Yabroff et al., 2008). Tobacco use and exposure to aromatic amines are well established etiologic contributors to bladder cancer and by eliminating or reducing contact with these substances has been shown to reduce such risk.

BCG (bacillus Calmette-Guerin) has become the standard of care in the treatment of carcinoma in situ as well as high grade T1 (invasion into the lamina propria) and when not appropriate, Mitomycin-C, has been proven to be an acceptable, albeit, less effective alternate. The goal of this chapter will be to describe novel agents that may show promise in the treatment of bladder cancer. This will include descriptions of the agents, their respective mechanism of action (e.g. molecular/biochemical pathways, cell cycle interaction, necrosis), clinical data, combinations of combinations of regimens and mode of delivery. and mode of delivery. A second goal of this chapter will be to consider whether any of these novel agents may have a role in the prevention of bladder cancer.

2. Chemoprevention

Kamat in his review of superficial bladder cancer stated that chemoprevention is needed for a multitude of reasons: high recurrence rates, increased morbidity from repeat resections, a tedious course of disease to see treatment outcomes, ability of agents to be concentrated in the urine, and the ability to monitor recurrence with cytology/cystoscopy (Kamat, 2003). Table 1 lists potential agents that may be considered for chemoprevention of bladder cancer.

POTENTIAL CHEMOPREVENTION AGENTS
• Vitamin A
• Vitamin E
• Vitamin C
• Selenium
• Cactus Pear
• Isoflavones
• Garlic
• Green Tea
• Difluoromethylornithine (DFMO)
• Non-Steroidal Anti-Inflammatory Drugs
• Statins

Table 1. Potential Chemoprevention agents for Bladder Cancer

2.1 Vitamin A

Vitamin A is necessary for light absorption in the retina and is also known to have a role in epithelial growth. Additionally, vitamin A has been researched as a chemotherapeutic and chemopreventive agent for a variety of malignancies. Currently, it is utilized to treat acute promyelocytic leukemia (Zusi et al., 2002). The mechanism of vitamin A's inhibition of tumor growth is thought to work through modulation of gene expression in cell growth, differentiation, and apoptosis (Zanardi et al., 2006). Evidence suggests that it does this through a variety of molecular pathways including binding to nuclear retinoic acid receptors (RAR) and ligand activating transcription factors such as retinoid X receptors (RXR) (Simeone & Tari, 2004). Additionally, vitamin A's anti-tumor activity may involve, among others, interactions with growth factors and cytokines, neoplastic stem cell pathways such as WNT, cAMP pathways, mitogen activated protein kinases (MAPKs), PI3K/AKT, cyclin-dependent kinases (CDKs), protein kinase C, and epigenetic modulation of gene expression (Garattini et al., 2007). Other studies indicate that some synthetic retinoids may even reduce VEGF expression, which is an important angiogenic factor in bladder cancer growth (Hameed & el-Metwally, 2008).

Several studies have examined vitamin A and its derivatives for chemoprevention of bladder cancer. The first clinical trial was performed in 1978 (Gunby, 1978) and was followed by several other prospective and controlled trials. Results for these trials were mixed, with some showing significant preventative effects (Alfthan et al., 1983; Studer et al., 1995; Yoshida et al., 1986) and others showing less promising results (Decensi et al., 2000; Prout & Barton, 1992). Mild to severe toxicities were also noted in many of these studies and may potentially limit vitamin A's use as a chemopreventive agent (Hameed & el-Metwally, 2008). More recently, to enable lower doses of retinoic acids and decrease unwanted side effects, combinations of retinoic acid and inhibitors of the CYP26A enzyme (involved in degradation of vitamin A) have been explored with some success (Hameed & el-Metwally, 2008). Although a recent cohort study showed no significant association of several vitamins including retinoids with urothelial carcinoma risk (Hotaling et al., 2011), other past studies provide some compelling evidence for vitamin A's efficacy. Thus further research into vitamin A's use in preventing bladder cancer is warranted.

2.2 Vitamin E

Vitamin E is a lipid soluble anti-oxidant and is known to be important in a variety of biological processes. It is also thought to possibly lower the risk of many malignancies through free radical scavenging, inhibition of N-nitroso compound formation (Mirvish, 1995), immunological stimulation (Beisel et al., 1981), and potent induction of apoptosis (Kline et al., 2004; Sigounas et al., 1997).

The clinical evidence for vitamin E in bladder cancer prevention has mixed results. A large Cohort study with Vitamin E and C and risk of bladder cancer mortality showed a reduced risk of mortality with regular intake of vitamin E (Jacobs et al., 2002). A phase III clinical trial using megadoses of several vitamins including E, when compared to patients who just received the recommended daily allowance (RDA) of the same vitamins, had a 40% reduction in bladder tumor recurrence after the first 10 months of the study (Lamm et al., 1994). However, in this same study, patients also received BCG therapy, which is known to promote immune response to tumors and may have confounded the results (Coulter et al., 2006). Further support comes from a prospective study, which showed an inverse relationship between vitamin E supplement consumption and the risk of bladder malignancy in men (Michaud et al., 2000).

In contrast to studies supporting vitamin E, a recent cohort study suggested no association of vitamin E intake and risk of urothelial carcinoma (Roswall et al., 2009). In addition, a meta-analysis for vitamin E and C intake and prevention of cancer indicated overall poor evidence for vitamin E in reduction of bladder cancer recurrence (Coulter et al., 2006). Additionally, a recently published cohort study indicated that the use of a variety of vitamins and supplements including vitamin E had no significant association with urothelial carcinoma risk in age-adjusted or multi-variate models (Hotaling et al., 2011). It should be noted that several studies have indicated that high doses of vitamin E may actually increase the risk for bladder cancer (The New England Journal of Medicine [NEJM], 1994; Miller et al., 2005). Since the evidence for vitamin E as a chemopreventive agent is conflicting, further studies should be performed to assess its true value.

2.3 Vitamin C

Vitamin C is an important vitamin found abundantly in fruits and vegetables. Proven to be a powerful antioxidant and necessary for a variety of metabolic activities, vitamin C consumption has also been researched as a method to reduce the risk of bladder cancer. It is hypothesized that vitamin C's anti-tumor activity is derived from inhibition of p53-induced replicative senescence, by suppressing both reactive oxygen species production and p38 MAPK activity (Kim et al., 2008), and sparing vitamin E to jointly reduce reactive α -tocopheroxy radicals (Park et al., 2010). Malignant transformation may also be decreased by vitamin C through reduction of N-nitroso compounds, which are known to be carcinogenic (Wu et al., 2000).

Despite these mechanisms proposed, data to support vitamin C as a chemopreventive agent is conflicting. A cohort study using data from 1981-1989 showed a significant reduction in relative risk for bladder cancer in patients taking vitamin C (Shibata et al., 1992). A more recent prospective study found a strong inverse relationship between vitamin C intake and bladder cancer risk in ex-smokers and non-smokers, but did not show the same results with current smokers (Michaud et al., 2000). High doses of vitamin C in combination with megadoses of vitamins A, B6, E and zinc were also found to be beneficial, in combination

with BCG therapy, in a phase III trial of Bladder cancer (Lamm et al., 1994). However, as mentioned earlier with Vitamin E, the results in this study may in part be confounded by BCG therapy (Coulter et al., 2006).

Other studies suggest less promising evidence. In a large cohort study of U.S. men and women, no associations were found between vitamin C use and bladder cancer death (Jacobs et al., 2002). This data is consistent with a cohort study by Hotaling et al. indicating the same relationship (Hotaling et al., 2011). A recent prospective study showed no significant effect of vitamin C, E or folate on prevention of urothelial carcinoma (Roswall et al., 2009) and there is evidence that doses of vitamin C beyond the RDA may contribute to oxalate stone formation (Taylor et al., 2004) and may even induce bladder carcinogenic activity (Mirvish, 1986). These studies indicating poor support for vitamin C's use, along with other studies supporting vitamin C as a bladder cancer chemopreventive agent, indicate that further investigation into vitamin C and bladder cancer prevention is required.

2.4 Selenium

An essential micronutrient that is primarily known for its function as a co-factor for reduction of antioxidant enzymes, selenium is also being researched for its potential in reducing the risk of several malignancies including bladder cancer (Silberstein & Parsons, 2010). A variety of mechanisms have been proposed for selenium's anti-tumor activity: free radical scavenging (Murawaki et al., 2008), modifying thiols, mimicking methionine methionine which leads to higher methylating efficiency of RNA and thiols (Jackson & Combs, 2008), enhancement of p53 activity towards DNA repair or apoptosis (Smith et al., 2004) and anti-androgenic activity, which is especially relevant in prostate cancer (Husbeck et al., 2006; Gazi et al., 2007).

The clinical evidence for selenium's anti bladder cancer activity is somewhat controversial. A recent meta-analysis from seven epidemiological studies showed that the overall risk of bladder cancer was inversely associated with elevated levels of selenium in serum and toenail samples, with the greatest effect seen in women (Amaral et al., 2010). Additionally, Wallace et al. showed no association of selenium levels in toenail samples with bladder cancer, it did find a significant association with moderate smokers and p53 positive cancers, suggesting selenium may affect the risk of bladder malignancies with specific p53 immunophenotypes (Wallace et al., 2009). This was further demonstrated in a case control study performed in Belgium that showed an inverse association between serum selenium concentrations and bladder cancer risk (Kellen et al., 2006).

In contrast to studies supporting selenium, a recent cohort study mentioned earlier, showed no significant association with selenium and urothelial carcinoma risk in an age-adjusted or multi-variate models (Hotaling et al., 2011). Current literature reviewed, there is a lack of interventional studies examining selenium and bladder cancer risk (Silberstein & Parsons, 2010).

2.5 Cactus pear

Cactus fruit, or prickly pear, is a fruit generally used as a dietary supplement and has been widely researched for its anti-oxidant effects (Fernández-López et al., 2010; Tesoriere et al., 2004; Zou et al., 2005). These fruits have a variety of ingredients shown to have health benefits including phenolics, flavonoids, and betalains. Recently, cactus pear has also been

studied for a possible application in cancer prevention. Although the mechanism is not completely understood, a recent study suggests it might be through increasing expression of annexin IV, a Ca²⁺ dependent membrane-binding protein important in apoptosis (Zou et al., 2005). Additionally, cactus pear extracts have been proposed to promote immune response and to decrease expression of VEGF (Liang et al., 2008), an important angiogenic factor in bladder and other malignancies (Zou et al., 2005).

Despite the proposed mechanisms, data supporting cactus pear for prevention of bladder cancer is limited, although some data exists to support use in other types of cancer. In a 2005 study, Arizona prickly cactus pear solution inhibited tumor growth in several different cancer cell cultures including ovarian and cervical (Zou et al., 2005). In another study, polysaccharides extracted from cactus pear fruit limited growth of S180 (sarcoma model) tumor cells in mice and induced features of apoptosis (Liang et al., 2008). In a 2010 study, cactus pear extracts induced reactive oxygen species production and apoptosis in ovarian cancer cells (Feugang et al., 2010). A specific species of cactus pear, *Opuntia humifusa*, was found to inhibit human glioblastoma cell lines (Hahm et al., 2010). Another study examining nine cactus pear species against prostate, colon, hepatic and mammary cancer cell lines showed some cytotoxic activity with certain species (Chavez-Santoscoy et al., 2009). However, normal fibroblast controls were also affected in this study with some of the pear species, thus the conclusions of this study are limited. More research, especially studies utilizing bladder cancer models, are necessary to determine the true potential of cactus pear as a chemopreventative agent for bladder cancer.

2.6 Isoflavones

Isoflavones are naturally occurring compounds found in soy and other products. They are primarily known for their phytoestrogen and anti-oxidant properties, although recent research has suggested they may also help in cancer prevention. Currently, isoflavones have shown at least some promise in preventing several types of cancers including but not limited to bladder, prostate (Yan & Spitznagel, 2005), breast (Bondesson & Gustafsson, 2010), lung (Hess & Igal, 2011), and liver (Ma et al., 2010).

Multiple mechanisms for this anti-tumor activity have been proposed. Several in vitro studies suggest that isoflavones may induce G2-M cycle arrest, apoptosis, and angiogenesis (Su et al., 2000; Zhou et al., 1998). Another study found that a possible mitochondrial mediated apoptosis pathway through regulation of AKT and MAPK pathways (Lin et al., 2010). Much of the research has focused on the specific isoflavone genistein, which has been shown to inhibit cancer through a variety of pathways. One study showed genistein inhibited EGF-R and EGF, of which the quantity and distribution are associated with urothelial abnormalities (Theodorescu et al., 1998). Another study on genistein showed that it might down regulate COX-2 (Hwang et al., 2009), which has been shown to play a role in tumorigenesis. A 2006 study indicated genistein down regulates nuclear factor kappa-B in bladder tumor tissue and reduces circulating insulin-like growth factor-1 levels, both important in tumor metastasis (Singh et al., 2006). Another more recent study showed that genistein modulates chromatin configuration and DNA methylation, thus activating tumor-suppressing genes (Zhang & Chen, 2011).

The clinical data for isoflavones as chemopreventive agents in bladder cancer has mixed results. In a 2000 study using seven human cancer cell lines, the isoflavone genistein significantly decreased bladder cancer cell growth and two other isoflavones directly

induced apoptosis (Su et al., 2000). Another study examining the effect of soy phytochemicals on poorly differentiated and highly metastatic human bladder cancer cell lines in vitro showed significant inhibition by cell cycle arrest in G2-M phases in addition to significant apoptosis (Singh et al., 2006). This same study also showed significant inhibition of clinically relevant orthotopic bladder tumor models by induction of tumor cell apoptosis and reduction of tumor angiogenesis. A study examining the effects of 13-Methyltetradecanoic acid (13-MTD), a soy fermentation product, on human bladder cancer cells found that 13-MTD induced apoptosis (Lin et al., 2010). In contrast to evidence supporting use, epidemiological studies have suggested an increased risk for bladder cancer with consumption of soy (Brinkman & Zeegers, 2008). Since the evidence is contradictory, more research needs to be performed into the potential of soy and soy products to act as chemopreventive agents.

2.7 Garlic

Garlic is considered both a food and supplement with medicinal properties. Extensive research has been performed into the health benefits of garlic and more recently garlic has been examined for cancer prevention. Studies suggest it may induce or prevent suppression of the immune response (Miroddi et al., 2011), induce cytokine production (Lamm & Riggs, 2000), scavenge free radicals (Butt et al., 2009), and bind thiol compounds important in crucial regulatory functions (Cerella et al., 2011). Numerous other mechanisms have also been proposed for specific components of garlic supported by in vitro studies (Shukla & Kaira, 2007).

Although many studies provide evidence of the anti-tumor activity of garlic on other types of cancer (Shukla & Kaira, 2007), research into garlic's anti-tumorigenic properties for prevention of bladder cancer is relatively sparse. A 1986 study using urothelial cancer lines in transplanted into the hind legs of mice, found a therapeutic effect of garlic when intraperitoneally injected (Lau et al., 1986). Another later study found a significant anti-tumor efficacy of garlic when given orally and subcutaneously in mice with injected urothelial carcinoma (Riggs et al., 1997).

Although some studies support the use of garlic, others fail to support garlic or garlic derivatives for chemoprevention of bladder cancer. In a 1993 study, diallyl sulfide, a primary component of garlic, failed to prevent the formation of urinary bladder papillomas in a rat model (Hadjiolov et al., 1993). A recently published cohort study indicated that the use of a variety of vitamins and supplements, including garlic, had no significant association with risk of urothelial carcinoma when adjusted for age and in multi-variate models (Hotaling et al., 2011). Due to these mixed results and lack of clinical studies, further research is needed into garlic and its potential as a chemopreventive agent for bladder cancer.

2.8 Green tea

Green tea is a widely consumed supplement worldwide with a variety of ingredients that have been researched for their health benefits. One application may be for cancer chemoprevention. Green tea has shown inhibitory activity on a variety of tumors in animal models including skin, lung, oral cavity, esophagus, stomach, intestine, colon, liver, pancreas, mammary gland, prostate, and bladder cancers (Lubet et al., 2007; Yang et al., 2011). Several mechanisms have been proposed. For example, one ingredient, polyphenols, has been shown to have antioxidant properties and may prevent cancer

through neutralization of free radicals (Forester & Lambert, 2011). Polyphenols also block ornithine decarboxylase (Messing et al., 1987), which is a key enzyme in polyamine synthesis and plays a major role in cell division and proliferation (Pegg, 2006). Another ingredient, catechins, may exhibit anti-tumor activity through inhibition of nitrosamine formations and decreased chromosomal damage (Kamori et al., 1993). Additional research on green tea suggests other possible mechanisms for a variety of its ingredients including caspase mediation (Oz & Ebersole, 2010), inhibition of angiogenesis (Tsao et al., 2009), and others.

Evidence for green tea in prevention of bladder cancer is variable. In rat models, green tea reduced bladder tumor incidence in several studies (Lubet et al., 2007; Sato, 1999; Sato & Matsushima, 2003). Additionally, green tea mixture modulated actin remodeling (through Rho activity) in an *in vitro* human bladder cancer model of non-transformed urothelial cell lines as well as reducing tumor growth (Lu et al., 2005). Since malignant cells require actin remodeling in a variety of malignant behaviors (altering morphology, loss of cohesion, invasiveness), this study may point out an additional mechanism for green tea's potential to inhibit bladder cancer (Lu et al., 2005). However, a recent review of the literature suggests caution promoting green tea as a chemopreventative agent for bladder cancer due to conflicting evidence (Boehm et al., 2009), citing two studies that either showed no association (Chyou et al., 1993) or an increased risk of developing bladder cancer (Wakai et al., 2004).

2.9 Difluoromethylornithine (DFMO)

Although originally tested for prevention of bladder and renal cancers (Dunzendorfer, 1981), Difluoromethylornithine (DFMO) is a drug primarily used for the treatment of hirsutism and trypanosomiasis (African sleeping sickness). Recently, there has been renewed interest in using DFMO to prevent a variety of malignancies, including bladder cancer. Although DFMO's mechanism of cancer prevention is not completely understood, it is well established as an irreversible inhibitor of ornithine decarboxylase, which plays a role in cell division and proliferation (Kelloff et al., 1994). A recent study showed that DFMO, when combined with sulindac (an NSAID), significantly reduced the risk of recurring colorectal polyps (Meyskens et al., 2008). Another controlled phase III clinical trial showed that DFMO might reduce the recurrence of basal cell carcinoma (Balley et al., 2010). In addition, DFMO is currently being researched in prevention of esophageal cancer (Sinicrope et al., 2011) and breast cancer (Izbicka et al., 2010). However, past studies assessing DFMO's possible efficacy in reducing recurring bladder cancer have mixed results. Initial studies using DFMO to suppress malignant urothelial cells from human cell lines (Messing et al., 1988) as well as suppressing BBN-induced urothelial carcinoma in mice (Boon et al., 1990) demonstrated selective inhibition of malignant cells. However, a recent controlled phase III clinical trial showed no difference in bladder tumor recurrence rates between placebo and DFMO treated patients (Messing et al., 2006). Due to the variable results, further research into DFMO as a chemopreventative agent in bladder cancer is recommended.

2.10 Non-steroidal anti-inflammatory drugs

NSAIDs, well known for their anti-inflammatory abilities, have also been recently proposed as chemopreventative agents. Studies suggest that cyclooxygenase enzymes may have a key

role in carcinogenesis, thus inhibitors have the potential for cancer prevention (Axelsson et al., 2010; Flossmann et al., 2007; Khan & Lee, 2011). Recent studies suggest an important role of COX-2 inhibitors in bladder cancer therapy. Several studies support increased COX-2 expression in bladder tumor stage and/or grade (Wadhwa et al., 2005; Yildirim et al., 2010; Yu et al., 2008). The primary mechanisms in which NSAIDs are thought to inhibit bladder cancer are through stimulation of apoptosis and reduction of angiogenesis (Thun et al., 2002). Another recent study suggested that COX-2 dependent and independent activation of downstream signals, such as CK2 α -Akt/uPA, may play a critical role in urothelial carcinoma cell survival and is neutralized by selective COX-2 inhibitors (Shimada et al., 2011).

Clinical data has mixed results for support of NSAID use in bladder and other cancer chemoprevention. A recent pooled analysis of three prospective cohort studies indicated a reduced risk in bladder cancer, particularly in non-smokers, with increased use of non-aspirin NSAIDs, but found no associated decrease in risk of bladder cancer with aspirin use (Daugherty et al., 2011). An *in vivo* bladder cancer model recently showed some efficacy of naproxen (Lubet et al., 2010). In a bladder tumor mouse model, rofecoxib, a selective COX-2 inhibitor, provided a significant reduction in incidence of neoplastic bladder lesions (D'Arca et al., 2010). Another study that examined multiple randomized trials using daily aspirin versus no aspirin on risk of gastrointestinal and other types of cancer death revealed increased survival, although bladder cancer was not specifically included in the analysis (Rothwell et al., 2011). Further research is needed into the possibility that NSAID's may prevent bladder cancer.

2.11 Statins

Statins are a class of drugs used to lower cholesterol levels through inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. However, there is some evidence suggesting that statins may have other properties in addition to their effect on lowering cholesterol. It is hypothesized that statins may inhibit tumor growth by neutralization of protein prenylation of GTPases, affecting downstream isoprenoids (Demierre et al., 2005), which in turn affect immune response, apoptosis, and cell maturation (Issat et al., 2011).

Currently statins are being researched for their efficacy in preventing a variety of cancers, including bladder malignancies. In a study examining atorvastatin and human bladder cancer cell lines, a significant anti-proliferative effect was observed when compared to controls (Kamat & Nelkin, 2005). In another study using mouse cells transfected with H-ras oncogene from human bladder carcinoma, researchers observed a significant *in vivo* inhibition of ras-oncogene transformed cells (Sebti et al., 1991). Other studies also point out additional reasons to use statins, since use may also improve local control in patients undergoing concurrent therapy for muscle invasive bladder cancer (Tsai et al., 2006).

However, not all studies support statin efficacy in preventing bladder and other types of cancers. A recent cohort study looking at statins and the occurrence of 10 types of cancer including bladder, showed no significant association with statin use (Jacobs et al., 2011). Using a female rat model, another recent study showed no significant difference in mammary carcinogenesis with simvastatin use (Kubatka et al., 2011). Additionally, a phase II clinical trial using atorvastatin with sulindac (NSAID) and probiotic dietary fiber failed to provide convincing evidence of decreased recurrence of colorectal carcinoma (Limburg et

al., 2011). Adding to the controversy, some data suggest that concurrent statin therapy with BCG may reduce clinical efficacy of the BCG therapy (Hoffmann et al., 2006), although this has not been consistent in all studies (Burglund et al., 2008) and not all literature supports discontinuation of the statin (Kamat & Wu, 2007). These results, in contrast with previous studies supporting anti-tumor growth, warrant further investigation into statin use in bladder cancer chemoprevention.

• Vitamin A	Alters cell growth, differentiation, and apoptosis through growth factors, cytokines, and neoplastic stem cell pathways
• Vitamin E	A free radical scavenger, inhibits N-nitroso compound formation as well as inducing apoptosis (some reports state may be a carcinogen)
• Vitamin C	Anti-oxidant, inhibits p-53 and p38 MAPK pathways
• Selenium	Works through methylation of RNA, anti-androgen, and promotes DNA repair
• Cactus Pear	Increases expression of Annexin IV, decreases VEGF, and promotes immune response
• Isoflavones	Induction of G2-M cell cycle arrest, apoptosis, and angiogenesis
• Garlic	Free radical scavenger, increases cytokines production, a thiol binder along with preventing suppression of the immune response
• Green Tea	Caspase mediator, angiogenesis inhibitor, and decreases chromosomal damage
• DFMO	Inhibits malignant urothelial cells through mostly unknown mechanisms, possibly inhibition of ornithine decarboxylase
• NSAIDS	Stimulates apoptosis and inhibits angiogenesis
• Statins	A neutralizer of protein prenylation of GTPases

Table 2. Key features of potential chemopreventative agents for bladder cancer.

3. Inheritance/biomarkers of bladder cancer

In a review article of the epidemiology of bladder cancer by Peluchhi et al., the risk of bladder cancer is increased by 50-100% in first-degree relatives in those that have the disease. Similar to cardiac disease, the risk for first-degree relatives is increased if the patient is diagnosed earlier than the age of 60 (Peluchhi et al., 2006; Goldgar et al., 1994). Current literature suggests a possible X-linked inheritance due to the increased incidence in siblings that are brothers (Pina & Hemminki, 2001).

It is well known of the increased risk that cigarette/tobacco consumption has on bladder cancer, Okkels and associates demonstrated the increased risk through the accumulation of slow acetylators with the Arylamine N-acetyltransferase 2 (NAT 2) genotype (Okkels et al., 1997). The relationship between NAT 1 and NAT 2 leads to the formation of DNA-binding metabolites for aromatic amines (carcinogens) in the bladder (Badawi et al., 1995).

Tobacco smoke also contains 4-aminobiphenyl (4-ABP), an aromatic amine, and for individuals with the NAT 2 phenotype, there is a stronger association, again with the slower acetylators (Yu et al., 1994).

Patients with inherited deletions of the gene, *GSTN1*, which encodes glutathione S-transferase M1, is associated with bladder cancer. This is in part due to the role of the gene, detoxification of carcinogens, being absent (Brockmoler et al., 1994). Although the aforementioned markers have shown an association with bladder cancer, the question that has still yet to be answered, is to what degree do *GSTN1*, NAT 1 and NAT 2, among others have on a patient and their risk of bladder cancer, especially with the exposure to carcinogens such as tobacco smoke and aromatic amines.

4. Gene therapy/ $\gamma\delta$ T-CELLS

The immunotherapy action of BCG works through binding and availability to major histocompatibility complex (MHC) class I expression on cancer cells (Kitamura et al., 2006). In a murine model, Yuasa et al. investigated, using $\gamma\delta$ T-cells (subset of human peripheral T cells), to augment immunotherapy in MHC-diminished superficial bladder cancer, which has been shown to be more aggressive than MHC-conservative bladder cancer. They demonstrated, by examining 123 patients undergoing either TUR or radical cystectomy, that not only was MHC class I expression diminished in lymph node and invasive bladder cancer, but they also experienced a shorter disease free and overall survival.

In their murine model (BALB/c SCID mice), using Luc-labeled bladder cancer cells and ex-vivo $\gamma\delta$ T-cells from peripheral blood from healthy patients, mice were treated with $\gamma\delta$ T-cells alone or in combination with zoledronic acid. Bladders were examined histologically with hematoxylin-eosin staining and immunohistochemically by with anti-human CD3. Using zoledronic acid to alter the cytotoxic effect, $\gamma\delta$ T-cells showed dose-dependent cytotoxicity (Kitamura et al., 2009). This shows potential for using $\gamma\delta$ T-cells to augment other intravesical treatments to accentuate their benefits.

5. Novel treatments

5.1 Silibinin

Silibinin, a flavonoid phytochemical found in milk thistle, has been shown in vitro, with TCC-SUP (high-grade invasive) and T-24 (high grade), to cause cell cycle arrest along with apoptosis. An induction of G₁ arrest along with cell growth inhibition was determined by various methods including: flow cytometry, cell growth assays (24, 48, and 72 hours of treatments), cell cultures, immunoprecipitation and immunoblotting. Cyclin-dependent kinase activity when uncontrolled, will lead to continuous cell progression. Cyclins are also a determining factor in G₁/S and G₂/M transition (Singh et al., 2002). Both cyclins and cyclin-dependent kinases are reduced with Silibinin as determined by antibodies against CDK2 or CDK4 and kinase assays. Cell death through apoptosis, which was only seen with high-grade invasive cancer, was determined by Annexin V and Propidium Iodide. For the previous experiments, doses of Silibinin varied from 50 to 200 micromolars (Tyagi et al., 2004). Later, the same investigators, with bladder transitional-cell papilloma RT4 cells, induced apoptosis with Silibinin through p53-caspase activation (Tyagi et al., 2006). Through further understanding of the biochemical/cell cycle pathways of bladder cancer, the effects of Silibinin will be better understood.

5.2 Keyhole Limpet Hemocyanin (KLH)

KLH is a copper-containing, extracellular, respiratory protein that was first investigated by Curtis et al., to have immunostimulatory properties (Curtis et al., 1970). Its potential role in the treatment of bladder cancer may be in a cytolytic reduction of tumor growth through a humoral response and an increase in natural killer cells. There have been reports when treating non-muscle invasive bladder cancer to have recurrence rates as low as 31% with less side effects (sepsis, cystitis) than BCG (Harris & Markl, 1999; Nseyo & Lamm, 1997).

Jurincic-Winkler et al. treated thirteen patients with CIS with intravesical KLH (20 mg) on a weekly schedule for 6 weeks, then monthly for one year, and bimonthly for a total of 3 years. Overall, only two patients were free of disease at 66 and 82 months of follow up with the majority requiring BCG or cystectomy (Jurincic-Winkler et al., 2000).

When reviewed, KLH could also be beneficial for carbohydrate-based immunotherapy in the appropriate adenocarcinoma when there are mucin-like epitopes as well as a potential treatment for melanomas (Harris & Markl, 1999). Overall, the evidence is lacking for KLH to be a major treatment for non-muscle invasive bladder cancer.

5.3 Apaziquone

Apaziquone, also referred commonly as EO9, is an indolequinone compound. Through an activation mechanism with NAD(P)H: Quinone oxidoreductase-1 (NQO1), Apaziquone, in an aerobic environment, has been shown to impact DNA-damaging species (Phillips et al., 2004). Increase in cell kill is also achieved through alkylating byproducts through redox cycling leading to single-strand breaks and DNA cross-linking (Comer & Murphy, 2003). In vivo, it has demonstrated activity against colon, non-small cell lung, renal, melanoma and central nervous system tumor models (Hendricks et al., 1993). With early promising results, it has failed to show favorable phase II outcomes with Phillips et al. citing its rapid pharmacokinetic elimination and poor penetration in avascular tissues (Phillips et al., 1998). In humans, Apaziquone's half-life is less than 10 minutes, via extra-hepatic metabolism by red blood cells, with its metabolites, EO5a, having decreased cytotoxicity (Schelens et al., 1994; Vainchtein et al., 2007).

Current research is aimed at finding adjunct compounds to improve its pharmacokinetic properties. A quinone-based bioreductive drug, 2,3-bis(aziridinyl)-5-hydroxy-1,4-naphthoquinone, through its selectivity for NQO1-rich cells under hypoxic conditions, has shown such potential (Phillips et al., 2004).

5.4 Mycobacterium phlei

This agent, has shown anti-tumor activity, is a cell wall extract, composed of carbohydrates, peptides, and lipids that is commonly found on the outer capsule of *Mycobacterium phlei*, a gram-positive microorganism that is located in soil, plants, and drinking water (Chin et al., 1996; & Mallick et al., 1985). Commonly prepared as a mineral oil emulsion, it has demonstrated inhibitory effects on bladder cancer cell lines through inhibition of cellular proliferation via apoptosis, as well as by an increase in the production of interleukin-12 through stimulation of cancer-infiltrating monocytes and macrophages. Bladder cancer cell lines, in a study by Filion et al., that have been tested include: HT-1197 along with HT-1376 (which are derived from anaplastic transitional cell carcinomas of the bladder from humans, both grade IV and grade III respectively). Cytokine analysis and cellular apoptosis were detected using ELISA and cell death was determined by dimethylthiazoldiphenyltetrazolium bromide

(MTT), (Filion et al., 1999). When tested in a murine model, mycobacterium phlei induced similar effects that are seen with BCG, namely a CD4+ T cell infiltrate when compared to control. Although the antitumor effect wasn't as significant as that seen with BCG, treatment was better tolerated overall (Chin et al., 1996).

5.5 Docetaxel

Docetaxel, a member of the taxane family, works through microtubule depolymerization inhibition and is commonly used in treatment of prostate and breast cancer, among others. Barlow et al., originally showed a 56% response rate in 18 patients who initially failed BCG therapy and refused to undergo cystectomy. The treatment regimen consisted of 6 weekly bladder instillations on a dose-escalation protocol (McKiernan et al., 2006). They continued their protocol, with the addition of 15 patients, for a median follow up of 29 months and had a 1 and 2 year recurrence-free survival rates of 45 and 32%. Adverse reactions to docetaxel included: dysuria, hematuria, facial flushing, frequency, rash, urinary tract infection, and premature voiding during instillation of the medication. Overall, they concluded that the data is very promising and offers an alternative treatment to those that have failed BCG and do not undergo cystectomy, however, large, multi-institutional, prospective trials are needed to concur effectiveness (Barlow et al., 2009).

Gefitinib, a selective epidermal growth factor receptor tyrosine kinase inhibitor, was studied by Kassouf et al., to determine its effect, in vitro, on enhancing the role of docetaxel on bladder cancer. Four bladder cancer cell lines were studied: 253J B-V, UM-UC-3, KU-7, and UM-UC-13. Through the use of flow cytometry and propidium iodide to determine cell cycle Analysis, along with Western Blot to establish EGFR downstream signaling, it was shown that when combined, gefitinib enhanced both the antiproliferative and apoptotic properties of docetaxel, but only when administered after the docetaxel (Kassouf et al., 2006).

5.6 Hyperthermia

A novel approach of combining local microwave hyperthermia along with Mitomycin C after undergoing transurethral resection was reported by Colombo et al., with 83 patients who were followed for 24 months. They take into account the detrimental effect that heat has on malignant cells (which are more sensitive to thermal changes in the environment than that of normal cells) such as inhibition of DNA synthesis, RNA, cellular protein, and DNA duplication in the cell cycle. In their study, 83 patients were randomly assigned (after undergoing transurethral resection of primary or recurrent noninvasive bladder cancer) to either receiving Mitomycin C alone or in conjunction with local microwave-induced hyperthermia. Hyperthermia was administered using the Synergo SB-TS:101-1, which consists of a 915 MHz intravesical microwave applicator, to reach a temperature of $42^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and maintained for 40 minutes.

The patients were all followed with urine cytology as well as cystoscopy every 3 months for 2 years, with biopsies taken if suspicious lesions were noted. Abdominal and pelvic ultrasound was also obtained on a bi-annual basis. Overall, 75 patients completed the protocol and those receiving the hyperthermia experienced more severe side effects: cystitis, suprapubic pain, and thermal reaction. Only six patients (17.1%) had recurrence with the combination therapy as compared to 23 patients (57.5%) receiving only Mitomycin C (P value = 0.0002). There was one patient with disease progression in the chemotherapy only

treatment group. Overall, the idea of combining intravesical chemotherapy along with hyperthermia is an attractive option for enhancing the effectiveness of chemotherapeutic agents especially for those that are not surgical candidates for radical cystectomy (Colombo et al., 2003).

A more recent study was carried out by Nativ et al., to examine those patients that experience recurrence of papillary non-muscle invasive bladder cancer after undergoing BCG treatment. They looked at 111 patients and followed them for 2 years with urine cytology and cystoscopy every 3 months. All patients were treated with hyperthermia, $42^{\circ}\text{C} \pm 2^{\circ}\text{C}$, for two cycles of 30 minute instillations of 20mg of Mitomycin C, for 6 weekly treatments followed by 6 maintenance sessions at 4 to 6 week intervals.

Adverse reactions were similar as compared to the earlier study with pain and bladder spasms being the most common (transient to mild at worse). Recurrence-free rates at one and two years were 85% and 56% respectively. There were 3 patients (3%) that progressed to muscle invasive bladder cancer during the follow up. Interestingly, those patients that received fewer than 10 maintenance treatments, had a tumor recurrence rate of 61% compared to 39% that completed the two year regimen (p value = 0.01) (Nativ et al., 2009). The combination of hyperthermia with intravesical treatment is very promising and should be considered very strongly for future trials in those patients that are considered BCG failures.

5.7 Inositol Hexaphosphate

Inositol Hexaphosphate (IP-6) is a naturally occurring polyphosphorylated carbohydrate that is found in foods that are high in fiber such as cereals, legumes, and grains (Fox & Eberl, 2002). It has already been shown to possess anti-tumor effects in numerous cancer cell lines: colon, hepatocellular, breast, lung, prostate, pancreas and melanoma among others while not being cytotoxic or cytostatic against normal cells (Shamsuddin et al., 1997). Zaslau et al., displayed its mechanism of action against bladder cancer cell lines (HTB9 [grade II], T24 [grade III], TCCSUP [grade IV]) via modulation of the cell cycle and induction of cellular apoptosis as well as necrosis (Zaslau et al., 2009).

Already demonstrating reduction in cellular proliferation, they tested IP-6's clinical efficacy with a 2-hour exposure time. All three cell lines (HTB9, T24, and TCCSUP) were plated and cultured with 2.5 and 4.5 mM of IP-6 for 2 hours and then had their supernatant incubated for an additional 24 and 48 hours. Cell viability was assessed through MTT colorimetric assay and cell cycle analysis through flow cytometry. All three cell lines, at all times tested, noted a significant reduction in cellular growth when treated with IP-6 with only a 2 hour incubation. Interestingly, when looking at cell cycle inhibition, IP-6 produced different results with the varying degrees of bladder cancer cell lines, which can be related to the different tumor grades replicating at different rates corresponding to diverse responses to the IP-6 treatments. There was an increase in cells in the G_0/G_1 phase, reduction in G_2/M , while no change in the S phase with the TCCSUP cell line. The T24 cell line was determined to be accelerating and not dividing through observances of cell reduction with 4.5 mM IP-6 in the G_0/G_1 phase and no change in both the S and G_2/M phases. Lastly, with the HTB9 cell line, as with the T24 cell line, no change was noted in G_2/M , however, there was an induction in the arrest at G_0/G_1 while a decrease in S phase (Zaslau et al., 2009).

IP-6 was later tested, with the same bladder cancer cell lines, using Annexin V-Fluorescein Isothiocyanate (FITC) and Propidium Iodine along with flow cytometry to determine method of cell kill. Using the same concentrations, 2.5 and 4.5 mM, at 2 hour incubations, HTB9 was effected by necrotic mechanisms, and T24 and TCCSUP went through an induction of apoptosis (Zaslau et al., 2010). The authors, with promising results thus far, state the Phase II clinical trials are needed to evaluate the safety and clinical utility of IP-6 for the intravesical use in bladder cancer.

5.8 HTI-286

HTI-286 is a synthetic analogue of the marine sponge product hemiasterlin. In a similar fashion to the taxanes, HTI-286 works through inhibition of tubulin polymerization with strong cytotoxic potential. In an in vitro study, HTI-286 was compared to MMC when tested in human bladder cancer cell lines RT4, MGH-U3, KU-7, as well as UM-UC3. In this study, it showed comparable cytotoxicity, inhibition of cell growth, and induction of apoptosis in all cell lines tested. An in vivo study using 8-week old nude mice demonstrated delayed cancer growth in a dose dependent manner (Hadaschik et al., 2008).

5.9 Suramin

Suramin, a polysulphonated naphthylurea, has anticancer functions that are comprised of growth factor antagonism and cellular DNA synthesis suppression (Walther et al., 1994; La Rocca et al., 1990).

Serious side effects including neurologic, renal, and metabolic Have been caused by systemic administration of suramin (La Rocca et al, 1990; Figg et al, 1994; Bowden et al, 1996) secondary to the compound having a 40-day plasma half-life in humans (Hawking, 1978). Suramin possesses several structural advantages for use intravesically in bladder cancer: its' high molecular mass (1429 Da) and negative ionic charge hamper systemic absorption (Ord et al, 2005); and its tendency to bind to protein favors growth factor antagonism in urine, which contains low protein levels (Ord et al, 2005). In particular, suramin inhibits the binding of epidermal growth factor (EGF) to its receptor, which are prevalent in high numbers in bladder cancer (Walther et al, 1996).

A phase I clinical trial found that intravesical treatment with suramin for cases of recurrent superficial bladder cancer was safe up to a 153mg/ml dose (Uchio et al, 2003). However, suramin's effects on bladder tumors has not yet been evaluated. Noted complications included bladder spasms and vesicoureteral reflux in a small percentage of the individual treatments, all of which completely abated within 48 hours (Uchio et al, 2003). Even at the highest dosages, plasma concentrations of suramin were minimal and further trials are warranted to decipher its usefulness.

5.10 Gemcitabine

Gemcitabine, as reported by Karak and Flechon, is a deoxycytidine analogue, a pyrimidine antimetabolite that is similar to cytarabine that works through inhibition of DNA synthesis (Karak & Flechon, 2007). Its effect on bladder cancer's cell cycle is via a blockage of cells progressing through the G1/S phase and a cytotoxic effect in S-phase (Guchelaar et al., 1996). It has already been approved through the Food and Drug Administration as a first line treatment for solid tumors of the pancreas as well as for inoperable, metastatic non-

small cell lung and breast cancer (Karak & Flechon, 2007). Gemcitabine has been known to cause myelosuppression (Aapro et al., 1998).

Gemcitabine has also been used as single agent for those patients that were considered BCG failures. In a phase II trial Dalbagni et al. examined 30 patients that were refractory to BCG treatment. Treatment was given twice weekly for 3 weeks and surveillance was conducted at 8 weeks and then every 3 months for one year. Although there was a complete response in 50% of patient at 3 months, this was reduced to only 10% at one year (Dalbagni et al., 2006).

5.11 Mitomycin-C & Gemcitabine

Gemcitabine, as described by Breyer et al., is 2',2'-difluoro-2'-deoxycytidine, that has shown broad spectrum anti-tumor activity. In their study, 10 patients that were either BCG refractory or BCG intolerant were treated with Gemcitabine (1000mg in 50cc sterile water) then MMC (40mg in 20cc sterile water) once a week for 6 weeks as their induction treatment. This was then followed by maintenance treatment (same dosage) once a month for 12 months. Median follow up for the patients (with median age of 67 years) was 26.5 months. Six out of ten patients were recurrence free at 14 months, with 4 patients having biopsy proven recurrence at a median of 6 months. Overall, the treatment was well tolerated with no major complications. Of note, 9 out of 10 patients had either high grade bladder cancer or carcinoma in situ before beginning treatment and had a median of five recurrences (Breyer et al, 2010). The same authors cited another study by Maymi and O'Donnell that compared Gemcitabine versus Gemcitabine in combination with MMC in 39 patients that have failed multiple, previous intravesical treatments. Alone, the median disease free survival was 6.5 months compared to 20 months for the combination of Gemcitabine and MMC (Maymi et al.). In a comparison study, Malmstrom et al. found only 4 out of 21 patients disease free that were treated with MMC for noninvasive bladder cancer at 3 years (Malmstrom et al., 1999). The literature that has been reviewed supports the use of MMC in combination with other intravesical agents to increase its effectiveness.

5.12 Mitomycin-C and BCG

The two leading intravesical treatments for non-muscle invasive bladder cancer are Mitomycin-C and BCG. There have been many studies that have looked to find an additive effect with the combination of the two agents (chemoimmunotherapy), but in whole, have not produced significant results. Witjes and colleagues examined 90 patients that underwent 4 weekly instillations of 40 mg of MMC followed by 6 weekly instillations of BCG (group 1) and compared them to 92 patients that just underwent 10 weekly instillations of MMC (group 2). Surprisingly, there was no significant difference seen between the two groups in regards to bacterial cystitis, chemical cystitis, and other local side effects. Eleven patients had fever (>38.5C) in group 1 compared to only 3 patients in group 2. Median follow up was 32 months. There were 35/90 patients with recurrence and 5/90 patients with progression in group 1 and 42/92 and 4/92 respectively, in group 2 (Witjes et al., 1998).

A prospective, randomized comparison of BCG alone with that of BCG and electromotive MMC was carried out by Di Stasi and colleagues. After being diagnosed with pT1 bladder cancer, 212 patients were randomly assigned to induction of either 81 mg of BCG for 2 hours once a week for 6 weeks or 81 mg of BCG over 2 hours once a week for 2 weeks, then 40 mg of electromotive MMC (intravesical electric current 20 mA for 30 min) once a week for three weeks. Exclusion criteria included previous treatment with either BCG or electromotive

MMC, any intravesical agent in the last 6 months, upper tract disease, and previous radiotherapy to the pelvis or chemotherapy among others. Maintenance for the BCG alone group consisted of 81 mg BCG once a month for 10 months compared to the group being treated with BCG and electromotive MMC which received the combination once a month for 2 months, then 81 mg of BCG once a month for three months. Of critical importance is that the authors defined the primary endpoint being disease-free survival with secondary endpoints being time to progression, overall survival and disease specific survival. Median follow-up was an impressive 88 months.

The patients that received the combination had a higher disease-free survival at 69 months compared to the patients that received only BCG, which was 21 months. Follow-up consisted of abdominal ultrasound, cystourethroscopy, and urine cytology every 3 months for the first three years and then every 6 months thereafter. If a patient was originally diagnosed with carcinoma in situ, the follow-up also included random bladder biopsies at 3 and 6 months. The combination group also has a lower rate of progression at 9.3% compared to 21.9% of BCG alone group, with 10 and 23 patients progressing to muscle-invasive bladder cancer respectively. Also, the BCG and electromotive MMC group only had 6 reported deaths due to bladder cancer compared to 23 in the BCG alone group. Adverse effects were similar between the two groups with each having 3 patients withdrawing from the trial. According to the authors, the benefit of the combination may be attributed to BCG-induced inflammation increasing the bladder mucosa permeability to the effects of the MMC, allowing it to reach the target tissue (Di Stasi et al., 2007).

• $\gamma\delta$ T-cells	Enhances immunotherapy by increasing MHC class I expression
• Silibinin	Induced G1 cell cycle arrest and reduces cyclin and cyclin-dependent kinases which decreases cell progression
• KLH	Possible mechanism of action could include an increase in humoral response in an association with an increase of natural killer cells
• Apaziquone	Needs to be combined with another agent or treatment modality to better its pharmacokinetics to lengthen its half-life and therapeutic effect
• Mycobacterium Phlei	Increases production of IL-12, induces apoptosis, as well as promoting a CD4+ T cell response
• Docetaxel	Inhibits microtubule depolymerization
• Hyperthermia	Environmental/thermal changes which malignant cells are more sensitive to and causes inhibition of DNA and RNA synthesis among other cellular pathways
• IP-6	Modulates cell cycle and induces cellular apoptosis and necrosis
• HTI-286	Similar mechanism of action as the taxanes (Docetaxel)

• Suramin	Growth factor antagonist and suppresses DNA synthesis
• Gemcitabine	Inhibits DNA synthesis and through a cytotoxic effect, inhibits malignant cells in G1/S and S-phase
• MMC and Gemcitabine	Overall, a well tolerated combination with beneficial results when compared to each agent alone.
• MMC and BCG	BCG may increase bladder mucosa permeability through an inflammatory response allowing MMC to reach its target at a more optimal level

Table 3. Mechanism of action of Novel Treatments for Bladder Cancer

6. Conclusion

Further advancement in the treatment of non-muscle invasive bladder cancer will come in the understanding of the disease's molecular/biochemical pathways and the effect on these pathways that chemopreventive and intravesical agents have on them. Certainly there are some areas that are more promising than others, especially with the combination of agents as well as the addition of hyperthermia to treatment regimens that are already producing significant positive results. As a review of the many agents discussed, table 2 provides the key features of potential chemopreventative agents for bladder cancer. Table 3 reviews the mechanism of action of Novel Treatments for Bladder Cancer. As always, it is not just the initial resection, or even the induction treatment that reduces recurrence and progression, but the role of maintenance therapy that is crucial for the patient to remain disease free. Again, with the new discoveries of cell signaling, cell cycle/death/apoptosis, interleukin, humoral and cell mediated responses, there will be more specific target treatments with the hopes of minimal side effects.

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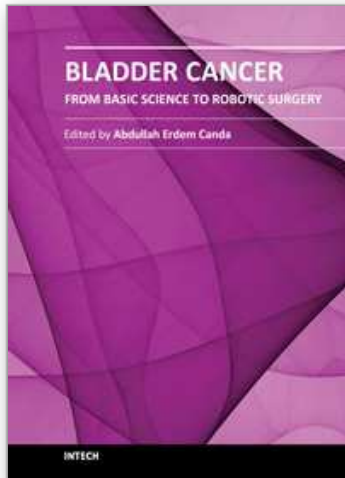
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This book is an invaluable source of knowledge on bladder cancer biology, epidemiology, biomarkers, prognostic factors, and clinical presentation and diagnosis. It is also rich with plenty of up-to-date information, in a well-organized and easy to use format, focusing on the treatment of bladder cancer including surgery, chemotherapy, radiation therapy, immunotherapy, and vaccine therapy. These chapters, written by the experts in their fields, include many interesting, demonstrative and colorful pictures, figures, illustrations and tables. Due to its practicality, this book is recommended reading to anyone interested in bladder cancer.

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