DRUG DELIVERY SYSTEMS AND METHODS FOR TREATMENT OF BLADDER CANCER WITH GEMCITABINE

Cross-Reference to Related Applications

This application claims the benefit of U.S. Provisional Patent Application No. 61/949,215, filed March 6, 2014, which are incorporated herein by reference.

Field of Invention

The present invention relates generation to the treatment of cancer, and more particularly relates to compositions, devices, and methods for the treatment of urinary bladder cancers.

Background

Bladder cancer is a significant medical problem, and currently available treatment options are unsatisfactory for a number of reasons.

In general, bladder cancers are classified as muscle invasive bladder cancer (MIBC) or non-muscle invasive bladder cancer (NMIBC). The pathological classification and staging of bladder cancer is as follows: pTa (urothelial involvement); pTis (high risk urothelial confined); pT1 (lamina propria invasion); pT2 (muscularis invasion); pT3 (perivesical fat invasion); and pT4 (pelvic organ extension). Bladder cancers can also be classified by grade as Grade 1/3 (well differentiated); Grade 2/3 (moderately differentiated); Grade 3/3 (poorly differentiated). In addition, bladder cancers can be classified by stage as Stages 0-IV. Most bladder cancers are transitional cell carcinomas of epithelial origin and classified as non-muscle invasive cancer (NMIBC) confined to the inner lining of the bladder. At initial presentation, most bladder cancers are superficial NMIBCs and include stages pTa, pTis and pT1 disease. MIBC include stages pT2, pT3 and pT4.

The typical clinical protocol of early stage bladder cancer is cystoscopy visualization followed by surgical removal of the tumor(s), known as transurethral resection (TUR). However, there is a high rate of recurrence after surgery and the cancer may progress to muscle-invasive disease. Therefore, surgery is often combined with adjuvant intravesicular installation (direct administration of the chemotherapeutic agent into the bladder through a catheter) of chemotherapeutic or immunotherapeutic agents to help prevent or delay the incidence and severity of recurrence. Bacile Calmette-Guerin (BCG) is such an immunotherapeutic and is typically instilled into the bladder following surgery. However, many patients do not respond to BCG, and BCG treatment can also induce a range of

adverse effects leading to discontinuation of treatment. Chemotherapeutic agents are usually reserved for patients who have failed BCG therapy. Chemotherapy is typically applied intravesically to concentrate the chemotherapeutic agent at the tumor sites and eliminate any residual tumor after resection while avoiding systemic exposure of the drug.

One such chemotherapeutic agent used in clinical trials for treating bladder cancer is gemcitabine**.** Gemcitabine (2',2'-difluorodeoxycytidine) is a pyrimidine analogue with activity against metastatic bladder cancer. Gemcitabine has also been used in clinical trials to treat superficial bladder cancers and NMIBC by instillation in the bladder with various weekly schedules. Gemcitabine is typically instilled over 1 to 2 hours once or twice a week for several weeks at doses typically ranging from 500 to 2000 mg in up to 100 ml of saline.

It is known that such formulations are voided from the bladder before full efficacy is achieved. The short dwell times of 1 to 2 hours limit therapeutic benefit. In addition, high concentrations (40 mg/ml) and high doses (up to 2 grams per instillation) are used in an attempt to achieve therapeutic tissue levels in order to try to overcome the dwell time limitations. However, intravesical administration of high doses of gemcitabine can lead to significant systemic absorption and cause gastrointestinal, bladder and bone marrow toxicity further limiting the clinical utility in addition to local tolerability issues.

The literature also reports that intravenous systemic administration of gemcitabine by bolus injection, e.g., over 1 to 2 minutes, is better tolerated by patients than slow intravenous infusion, e.g., over 90 minutes. This suggests that prolonged exposure to gemcitabine increases toxicity and should be avoided.

Accordingly, there remains a need for improved drug delivery methods and systems for treating bladder cancer. For example, there remains a need to administer therapeutic levels of gemcitabine to patient over sustained periods while avoiding or mitigating toxicity and tolerability issues that have been observed to limit the clinical utility of gemcitabine.

Brief Summary

The present disclosure provides a medicament which comprises gemcitabine for use in the treatment of bladder cancer by locally administering the gemcitabine into the bladder of a patient to achieve a sustained concentration of the gemcitabine in the urine in the bladder sufficient to produce a therapeutic concentration of the gemcitabine in the bladder tissues, wherein the local administration into the patient's bladder is at a mean average amount of from 1 mg/day to about 300 mg/day of the gemcitabine free base equivalent (FBE).

In one aspect of the present disclosure, there is provided a use of gemcitabine in the manufacture of a medicament for the treatment of bladder cancer in a patient, wherein the medicament is to be locally administered into the bladder of the patient, before and/or after transurethral resection of bladder tumor (TURBT), to achieve a sustained concentration of the gemcitabine in the urine in the bladder sufficient to produce a therapeutic concentration of the gemcitabine in the bladder tissues, wherein the locally administering into the patient's bladder at a mean average amount of from 1 mg/day to 300 mg/day of the gemcitabine free base equivalent (FBE) continuously over a period of from 1 day to 30 days,
wherein the gemcitabine is to be delivered into the bladder from an intravesical drug delivery device which releases the gemcitabine into the urine in the bladder over the period.

In embodiments, the local administer into the patient's bladder is at a mean average amount of from 1 mg/day to 200 mg/day of the gemcitabine (FBE), from 5 mg/day to 100 mg/day of

the gemcitabine (FBE), from 10 mg/day to 50 mg/day of the gemcitabine (FBE), or from 15 mg/day to 25 mg/day of the gemcitabine (FBE). In one case, the locally administering into the patient's bladder is at a mean average amount of about 20 mg/day of the gemcitabine (FBE). The local administer into the patient's bladder may be continuous or intermittent. In embodiments, the continuous or intermittent administration is over a period from 1 day to 30 days, from 1 day to 14 days, or from 1 day to 7 days.

In a preferred embodiment, the gemcitabine is delivered into the bladder from an intravesical drug delivery device which continuously releases the gemcitabine into the urine in the bladder over a sustained period. In another embodiment, the gemcitabine is delivered into the bladder from a coating substance applied to the bladder, which coating substance (e.g., a mucoadhesive formulation) releases the gemcitabine into the urine in the bladder over a sustained period. In still another embodiment, a liquid form of the gemcitabine is pumped into the bladder over a sustained period through a urethral or suprapubic catheter which is deployed into the bladder.

The present disclosure also provides a drug delivery device for administering gemcitabine to a patient in need of treatment of bladder cancer by intravesically administering gemcitabine into the bladder of the patient to achieve a sustained concentration of the gemcitabine in urine in the bladder sufficient to produce a therapeutically effective concentration of the gemcitabine in the tissues of the bladder.

In a particular embodiment, the drug delivery device includes a housing configured for intravesical insertion, and a dosage form comprising gemcitabine, wherein the housing holds the dosage form and is configured to release the gemcitabine into the bladder in an amount therapeutically effective for the treatment of the prostate, wherein the device is configured to release gemcitabine into the bladder at a mean average amount of from 1 mg/day to about 300 mg/day of the gemcitabine. In a preferred embodiment, the housing releases the gemcitabine without a predefined release aperture. In a particular version of this preferred embodiment, the housing releases the gemcitabine by diffusion through a drug permeable polymeric wall. The housing which contains and controllably releases the gemcitabine may be elastically deformable between a retention shape configured to retain the device in a patient's bladder and a deployment shape for passage of the device through the patient's urethra.

The present disclosure also provides methods of treating bladder cancer are provide by locally administering the gemcitabine into the bladder of a patient to achieve a sustained concentration of the gemcitabine in the urine in the bladder sufficient to produce a therapeutic concentration of the gemcitabine in the bladder tissues. In embodiments, the

local administration into the patient's bladder is at a mean average amount of from 1 mg/day to about 300 mg/day of the gemcitabine (FBE). In one embodiment, the method further includes administering at least a second therapeutic agent to the patient. The second therapeutic agent may be administered intravesically. In another embodiment, the method further includes administering urea or another solubility altering agent into the bladder in an amount effective to enhance or otherwise alter solubilization of the gemcitabine. In embodiments, the second therapeutic agent and/or the solubility altering agent is released from an intravesical device which releases the gemcitabine.

Brief Description of the Drawings

FIGS. 1A-1B illustrate one embodiment of an intravesical drug delivery device that may be used for administering gemcitabine as described herein.

FIGS. 2A-2B illustrate another embodiment of an intravesical drug delivery device that may be used for administering gemcitabine as described herein.

FIGS. 3A-3C illustrate still another embodiment of an intravesical drug delivery device that may be used for administering gemcitabine as described herein.

FIGS. 4A-4B illustrate a method of inserting an intravesical drug delivery device into the bladder of a patient for local administration of gemcitabine as described herein.

FIG. 5A illustrates a material applied to the inner surface of the bladder wall for local administration of gemcitabine as described herein.

FIG. 5B illustrates a method of applying a coating material onto to the inner surface of the bladder wall for local administration of gemcitabine as described herein.

FIG. 6 illustrates a method of applying a liquid drug or drug formulation into the bladder.

FIG. 7 illustrates the concentration of gemcitabine in the prostate after bladder perfusion and intravenous administration.

FIG. 8 illustrates the plasma levels of gemcitabine after bladder perfusion and intravenous administration.

FIG. 9 illustrates ^{14}C gemcitabine concentration in the bladder after bladder perfusion and intravenous administration.

FIGS. 10A-C illustrate one embodiment of an intravesical drug delivery device for releasing gemcitabine via permeation disks. **FIG. 10A** is a plan view of the device. **FIG. 10B** is a cross-sectional view of one of the four drug reservoir modules of the device shown in **FIG. 10A**, showing the drug tablets and permeation disks of each module. **FIG. 10C** is a

perspective view of a portion of the housing/body portion of the device shown in **FIG. 10A** before assembly with the other components of the device.

FIGS. 11-12 are graphs showing in cumulative amounts of gemcitabine released in vitro from the devices shown in **FIGS. 10A-C**.

FIGS. 13-14 are graphs showing in urine concentrations of gemcitabine, dFdU, and the combination thereof, respectively, from an animal study.

Detailed Description

It has been discovered that continuous delivery of gemcitabine by intravesical administration yielded unexpected drug distribution across the bladder wall and achieved drug levels at or above the projected therapeutic threshold in all layers of the bladder—without significant plasma/systemic exposure. Accordingly, the compositions, systems, and methods described herein can be used to achieve therapeutically effective amounts of gemcitabine in the tissues of the bladder where needed, while also being well tolerated by the normal bladder tissue and minimizing systemic exposure.

As used herein, the term "gemcitabine" includes the compound gemcitabine as well as its pharmaceutically acceptable salts, esters, amides, solvates and prodrugs. In particular, the hydrochloride salt of gemcitabine is included. The gemcitabine may be formulated with one or more suitable pharmaceutically acceptable excipients.

In certain embodiments, a controlled amount of gemcitabine is dissolved in urine in the patient's bladder in a concentration and over a time sufficient to produce and maintain therapeutic concentrations of the drug in tissues of the bladder. However, because the bladder limits the absorption of urine components into the general circulation, systemic exposure to the drug is advantageously minimized.

A variety of methods can be used to achieve the required urine concentrations of the gemcitabine. In one embodiment, the drug can be provided by direct instillation of a simple solution into the bladder. For example, a solution of the drug may be pumped into the bladder through a urethral or suprapubic catheter in a continuous or pulsatile manner over the treatment period. In another embodiment, the drug is released from a device or composition deployed in the bladder, wherein the device or composition releases the drug (continuously or intermittently) at a rate effective to produce the desired concentration of drug in the urine over a specified treatment period. For example, the drug may be released from an intravesically-inserted device into the bladder and then the drug diffuses into the bladder. At the end of the treatment period, the device may be retrieved from the bladder, or it may be eliminated by being resorbed, dissolved, excreted, or a combination thereof.

In a preferred embodiment, the gemcitabine is administered to the bladder from an intravesical device. Examples of intravesical drug delivery devices, which can be tailored to achieve the dosage regimens described herein, and methods of deploying those devices into the bladder are described in the following U.S. Patent Application Publications: US 2012/0203203 (Lee et al.); US 2012/0089122 (Lee et al.); US 2012/0089121 (Lee et al.); US 2011/0218488 (Boyko et al.); US 2011/0202036 (Boyko et al.); US 2011/0152839 (Cima et al.); US 2011/0060309 (Lee et al.); US 2010/0331770 (Lee et al.); US 2010/0330149 (Daniel et al.); US 2010/0003297 (Tobias et al.); US 2009/0149833 (Cima et al.); US 2007/0202151 (Lee et al.); WO 2014/144066 (Lee et al.); U.S. 2014/0276636 (Lee et al.); and WO 2015/026813 (Lee et al.).

In embodiments in which the gemcitabine is delivered from an intravesical drug delivery device, the drug may be housed in the device in various forms, which may depend on the particular mechanism by which the device controllably releases the drug into fluid (e.g., urine) in the bladder. In some embodiments, the drug is provided in a solid, semi-solid, or other non-liquid form, which advantageously may facilitate stable storage of the drug before the device is used and advantageously may enable the drug payload of the device to be stored in smaller volume than would be possible if the drug were housed in the form of a liquid solution. In an embodiment, the non-liquid form is selected from tablets, granules, semisolids (e.g., an ointment, cream, paste, or gel), capsules, and combinations thereof. In one embodiment, the drug is in the form of a plurality of tablets, such as mini-tablets described in U.S. Patent No. 8,343,516. In other embodiments, the drug may be housed in a liquid form, such as in a solution with one or more pharmaceutically acceptable excipients.

An embodiment of a drug delivery device **100** is illustrated in **FIG. 1A**. The device **100** includes a device body having a drug reservoir portion **102** and a retention frame portion **104**. In **FIG. 1**, the device **100** is shown in a relatively expanded shape suited for retention in the body. Following deployment into the body, the device **100** may assume the relatively expanded shape to retain the drug delivery device in the body cavity or lumen.

For the purposes of this disclosure, terms such as "relatively expanded shape," "relatively higher-profile shape," or "retention shape" generally denote any shape suited for retaining the device in the intended implantation location, including but not limited to the pretzel shape shown in **FIG. 1** that is suited for retaining the device in the bladder. Similarly, terms such as "relatively lower-profile shape" or "deployment shape" generally denote any shape suited for deploying the drug delivery device into the body, including a

linear or elongated shape that is suited for deploying the device through the working channel of catheter, cystoscope, or other deployment instrument positioned in the urethra. In embodiments, the drug delivery device may naturally assume the relatively expanded shape and may be deformed, either manually or with the aid of an external apparatus, into the relatively lower-profile shape for insertion into the body. Once deployed the device may spontaneously or naturally return to the initial, relatively expanded shape for retention in the body.

In the illustrated embodiment, the drug reservoir and retention frame portions **102, 104** of the drug delivery device **100** are longitudinally aligned and are coupled to each other along their length, although other configurations are possible. The drug delivery device **100** includes an elastic or flexible device body **106** that defines a drug reservoir lumen **108** (i.e., the drug housing) and a retention frame lumen **110**. The drug reservoir lumen **108** is designed to house a drug formulation that comprises the drug. In the illustrated embodiment, the drug formulation comprising gemcitabine is in the form of a number of solid drug units **112**, which may be tablets. The retention frame lumen **110** is designed to house a retention frame **114** to form the retention frame portion **104**. The illustrated lumens **108, 110** are discrete from each other, although other configurations are possible.

As shown in the cross-sectional view of **FIG. 1B**, the device body **106** includes a tube or wall **122** that defines the drug reservoir lumen **108** and a tube or wall **124** that defines the retention frame lumen **110**. The tubes **122, 124** and lumens **108, 110** can be substantially cylindrical, with the drug reservoir lumen **108** having a relatively larger diameter than the retention frame lumen **110**, although other configurations can be selected based on, for example, the amount of drug to be delivered, the diameter of the retention frame, and deployment considerations such as the inner diameter of the deployment instrument. The wall **124** that defines the retention frame lumen **110** may extend along the entire length of the wall **122** that defines the drug reservoir lumen **108**, so that the retention frame lumen **110** has the same length as the drug reservoir lumen **108** as shown, although one wall may be shorter than the other wall in other embodiments. The two walls **122, 124** are attached along the entire length of the device in the illustrated embodiment, although intermittent attachment can be employed.

As shown in **FIG. 1A**, the drug reservoir lumen **108** is loaded with a number of drug units **112** (comprising gemcitabine) in a serial arrangement. Essentially any number of drug units may be used, for example, depending upon the sizes of the reservoir and the drug units. The drug reservoir lumen **108** includes a first end opening **130** and an opposed

second end opening **132**. Once the drug units **112** are loaded, restraining plugs **120** are disposed in the openings **130** and **132**. The restraining plugs **120**, in this embodiment, are cylindrical plugs secured into the openings **130, 132**. In other embodiments, the openings **130** and **132** are closed off with other structures or materials, which may, depending on the particular embodiments, include an aperture or a water- or drug-permeable wall to facilitate ingress or egress of water or drug during use.

In other embodiments, the drug reservoir lumen may be loaded with gemcitabine forms other than as solid drug units. For example, gemcitabine, may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredients may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

In one embodiment, the gemcitabine is formulated with one or more excipients that include a viscosity enhancing agent to control release of solubilized gemcitabine from a release aperture in the device housing. In another embodiment, the device reservoir includes both gemcitabine and a viscosity enhancing agent, but they are not co-formulated and instead are provide in discrete regions within the reservoir, e.g., as separate tablets. Suitable viscosity enhancing agents, including but not limited to polyethylene oxide (PEO), are known in the pharmaceutical arts. In some variations of the embodiment, the viscosity enhancing agent may be provided, e.g., formulated, with urea or another osmotic agent.

In one embodiment, the gemcitabine is administered to the patient with a solubility enhancing agent. In an embodiment, the solubility enhancing agent is urea. In one embodiment, the urea is provided in a tablet or other solid form and loaded with the gemcitabine in the drug reservoir of an intravesical drug delivery device. The urea may also function, depending on the device, as an osmotic agent to facilitate generation of an osmotic pressure in a drug reservoir. In a particular embodiment, the gemcitabine and the osmotic agent are configured as separate tablets (or other solid forms) positioned within different regions of the drug reservoir as described in PCT WO 2015/026813 (Lee et al.) which is incorporated by reference herein.

The retention frame lumen **110** is loaded with the retention frame **114,** which may be an elastic wire, e.g., a superelastic alloy such as nitinol. The retention frame **110** may be configured to return spontaneously to a retention shape, such as the illustrated example "pretzel" shape or another coiled shape, such as those disclosed in the applications

previously incorporated. In particular, the retention frame **114** may retain the device **100** in the body, such as in the bladder. For example, the retention frame **114** may have an elastic limit and modulus that allows the device **100** to be introduced into the body in a relatively lower-profile shape, permits the device **100** to return to the relatively expanded shape once inside the body, and impedes the device from assuming the relatively lower-profile shape within the body in response to expected forces, such as the hydrodynamic forces associated with contraction of the detrusor muscle and urination. Thus, the device **100** may be retained in the body once implanted, limiting or prevent accidental expulsion.

The material used to form the device body **106**, at least in part, may be elastic or flexible to permit moving the device **100** between deployment and retention shapes. When the device is in the retention shape, the retention frame portion **104** may tend to lie inside the drug reservoir portion **102** as shown, although the retention frame portion **104** can be positioned inside, outside, above, or below the drug reservoir portion **102** in other cases.

The material used to form the device body **106** may be water permeable so that solubilizing fluid (*e.g.*, urine) can enter the drug reservoir portion **102** to solubilize the drug units **112** once the device is implanted. For example, silicone or another biocompatible elastomeric material may be used. In other embodiments, the device body may be formed, at least in part, of a water-impermeable material.

FIG. 2A illustrates another embodiment of an intravesical drug delivery device **200**, which includes a drug reservoir **202** loaded with drug **212** and a retention structure that includes two filaments **220**, **222** associated with a fastener **230**. As shown, the drug reservoir **202** is an elongated tube that can be deformed between a relatively linear deployment shape, such as the shape shown in **FIG. 2A**, and a relatively circular retention shape, such as the shape shown in **FIG. 2B.** The drug **212** may be loaded in the tube in a flexible form, so that the drug reservoir **202** can be moved between the two shapes. For example, the drug **212** may be a number of solid drug tablets, a liquid, or a gel. The filaments **220**, **222** may be attached to opposite ends of the drug reservoir **202** and joined by the fastener **230**. The fastener **230** can be adjusted to adjust the position of one filament **220** with reference to the other **222**, thereby adjusting the position of one end of the drug reservoir **202** with reference to the other end. The device **200** can assume the retention shape by adjusting the filaments **220**, **222** to draw the ends of the drug reservoir **202** closer together, and thereafter the device **200** can be retained in the retention shape by preventing adjustment of the filaments **220**, **222** with the fastener **230**. In such an embodiment, the

device **200** is manually adjusted into the retention shape by manually adjusting the filaments **220**, **222** after the device **200** is inserted into the bladder.

In the illustrated embodiment, the fastener **230** is a cinch nut that permits shortening the portion of the filaments **220**, **222** between the drug reservoir ends and the cinch nut, but prevents lengthening of these portions of the filaments **220**, **222**. Thus, the ends of the drug reservoir **202** can be drawn closer together by pulling one or both of the filaments **220**, **222** through the cinch nut, causing the device **200** to assume the retention shape. Once the filaments **220**, **222** have been so adjusted, the cinch nut prevents lengthening of the filaments **220**, **222**, retaining the device in the retention shape. Thus, manually adjusting the device **200** into the retention shape once implanted merely requires pulling one or both of the filaments **220**, **222**, although other fasteners **230** that require separate manipulation can be employed. Other fasteners may also be used.

Another embodiment of an intravesical drug delivery device is illustrated in **FIGS. 3A-3C**. In this embodiment, the device includes a housing **300** having a single, continuous structure with multiple, discrete drug reservoir lumens **320** and optionally having at least one retention frame lumen **330** in which a retention frame **360** is disposed. Each drug reservoir lumen **320** has two defined openings, as shown a cross-sectional view in **FIG. 3B**, and is dimensioned to hold at least one solid drug unit **340**. For example, solid drug unit **340** may be a drug tablet or capsule. In another embodiment, not shown, each drug reservoir lumen has a single defined opening. The housing may be formed of a flexible polymer, such as silicone. **FIG. 3B** is a cross-sectional view of the plane that bisects one of the drug reservoir lumens **320** of the housing shown in **FIG. 3A** along line 3B-3B. As shown in **FIG. 3B**, the monolithic housing **300** has two defined openings (**350a**, **350b**) in its drug reservoir lumen **320** that expose both ends of the solid drug unit **340**. The retention frame lumen **330**, in this embodiment, is aligned parallel to the longitudinal axis of the housing and perpendicular to the drug reservoir lumen **320**. **FIG. 3C** is a perspective view of a portion of the embodiment of the device **300** shown in **FIG. 3A** when the device is in its retention shape, which is taken when the retention frame **360** is disposed in the retention frame lumen **330**. The drug reservoir lumens **320** and the retention frame **360** in the housing of this embodiment are oriented so that the drug reservoir lumens **320** are outside the arc of the retention frame **360**. Alternatively, the housing in **FIG. 3C** can be rotated 180 degrees about the retention frame **360** to yield a configuration in which the drug reservoir lumens **320** are arranged within the retention frame's **360** arc. With this embodiment, the devices provide sufficient direct contact between solid drug units and with urine

surrounding the device when deployed and retained in the bladder. In embodiments, release of the drug from the device is controlled by erosion of an exposed portion of the surface of a solid drug unit, such that the rate of drug release from the drug delivery device may be directly proportional to and limited by the total exposed surface area of the solid drug units.

The release of gemcitabine from the intravesical devices described herein may be driven and controlled by different mechanisms of action. In various embodiments, the drug may be released from the intravesical drug delivery device by diffusion to through a wall of the drug housing, by diffusion to through one or more defined apertures in a wall of the drug housing, by osmotic pressure through an aperture in the drug housing, by osmotic pressure through one or more transiently formed microchannels, by erosion of a drug formulation in contact with urine in the bladder, or by a combination thereof. In a preferred embodiment, drug release is controlled by drug diffusion through a drug-permeable polymer or matrix component defining part of the device housing. In one embodiment, the device includes a drug-permeable polymer component.

In a particular embodiment, the drug delivery device includes a housing having a closed drug reservoir lumen bounded by a first wall structure and a hydrophilic second wall structure; and a drug formulation comprising gemcitabine contained in the drug reservoir lumen, wherein the first wall structure is permeable or impermeable to water and impermeable to the drug, and the second wall structure is permeable to the gemcitabine. The walls bounding and defining the drug reservoir of the device are made of a first material that serves as the first wall structure and a second material that serves as the second wall structure, such that drug release occurs essentially only through the second material. In one embodiment, the device does not include an aperture; drug release is only by diffusion through the second wall structure. As used herein, the terms “impermeable to the drug” and “impermeable to water” refer to the wall structure being substantially impermeable to the drug or to water, such that essentially no drug or water is released via the wall structure over the therapeutic release period. For use in the bladder, it is desirable that the device be compliant (i.e., easily flexed, soft feeling) during detrusor muscle contraction in order to avoid or mitigate discomfort and irritation to the patient. Thus, the durometer of the first and second materials of construction are a design consideration, and the proportion of a high durometer material may be limited in constructing a device housing of a given size while keeping it suitably compliant in the bladder. For example, Tecophilic™ thermoplastic polyurethane (Lubrizol Corp.) may have a Shore hardness greater than 70A, such as from 80A to 65D, while silicone tubing which may have a Shore hardness of from 50A to 70A.

Accordingly, it can be advantageous to utilize the combination of these two different polymeric materials, rather than making the device entirely of the water-swelling hydrophilic, drug-permeable second material.

Continuing with this particular embodiment, the first wall structure may be formed of a silicone. For example, the housing may include a silicone tube, the wall of the silicone tube serving as the first wall structure. In other embodiments, the first wall structure may be formed of other water permeable materials. The drug preferably is in a solid form (e.g., a tablet or plurality of tablets) and the first wall structure is water permeable to permit *in vivo* solubilization of the drug while in the drug reservoir lumen. For example, the first wall structure may be formed of silicone having a Shore durometer value from about 50A to about 70A. The second wall structure may be a hydrophilic polymer, which is designed to absorb water. For example, the second wall structure may be a hydrophilic elastomeric material, which is at least partially made of hydrophilic polyurethane, hydrophilic polyesters, or hydrophilic polyamides. In a preferred embodiment, the second wall structure includes a thermoplastic polyurethane, such as Tecophilic™ thermoplastic polyurethane, HydroThane™ thermoplastic polyurethane (AdvanSource Biomaterials Corp.), Quadraphilic™ thermoplastic polyurethane (Biomerics, LLC) (ALC grades are aliphatic polycarbonate-based and ALE grades are aliphatic polyether-based hydrophilic polyurethanes), HydroMed™ (AdvanSource Biomaterials Corp.), or Dryflex® (HEXPOL TPE). Another hydrophilic polymer is polyether block amide Pebax® MV 1074 SA 01 MED (Arkema), which is a thermoplastic elastomer made of flexible and hydrophilic polyether and rigid polyamide. For example, the hydrophilic material of the second wall structure may have a Shore durometer value from about 70A to about 65D. The particular material and its thickness and wall area can be selected to control the water and drug permeation rates and thereby achieve a particular release profile of the gemcitabine.

The arrangement of the first and second wall structures can take a variety of forms. In certain embodiments, the first wall structure is a cylindrical tube and the second wall structure is an end wall disposed at least one end of the cylindrical tube, or the first wall structure and the second wall structure are adjacent one another and together form a cylindrical tube. That is, drug release is controlled by drug diffusion through a drug-permeable component defining a portion of the closed device housing. The drug-permeable wall structure may be located, dimensioned, and have material properties to provide the desired rate of controlled drug diffusion from the device. In one embodiment, as described

in Example 4 below, the first wall structure is a cylindrical tube and the second wall structure is an end wall disposed at least one end of the cylindrical tube.

One embodiment of inserting an intravesical device **400** for subsequent controlled release of the drug into the bladder is shown in **FIGS. 4A** and **4B**. Here, the device **400** is shown assuming a retention shape as the device exits a deployment instrument **402**. The deployment instrument **402** may be any suitable device. It may be a lumenal device, such as a catheter, urethral catheter, or cystoscope. The deployment instrument **402** may be a commercially available device or a device specially adapted for the present drug delivery devices. **FIG. 4B** illustrates the insertion of the device **400** into the bladder, wherein the adult male anatomy is shown by way of example. The deployment instrument **402** is inserted through the urethra to the bladder, and the device **400** may be passed from/through the deployment instrument **402**, driven by a stylet or a flow of lubricant or a combination thereof until the device **400** exits into the bladder, and as shown is in a retention shape.

From the studies described in the Examples below, it has surprisingly been discovered that device embodiments with extremely small release apertures, or orifices, are preferable, and that device embodiments that release drug without a predefined orifice are more preferable. This is because it was observed that these embodiments can be effective to eliminate, or at least substantially reduce the incidences of urothelial lesions, as compared to device embodiments utilizing relative larger release orifices. Without being bound by any theory, it is believed that the larger orifice devices enable the formation of local high drug concentrations of gemcitabine at the urothelial tissue surface in the area adjacent to the release apertures of the device, and that these local tissue areas can be damaged as a result. In contrast, such local high drug concentrations are less likely to occur with device systems utilizing release mechanisms having no predefined orifice or having very small release orifices. Examples of such suitable "no-orifice" release systems are described in PCT Patent Application Publication No. WO 2014/144066 (TB 130) and U.S. Patent Application Publication No. 2014/0276636 (TB 134), which are incorporated herein by reference.

In some embodiments in which the device comprises a drug in a solid form, elution of drug from the device occurs following dissolution of the drug within the device. Bodily fluid enters the device, contacts the drug and solubilizes the drug, and thereafter the dissolved drug diffuses from the device or flows from the device under osmotic pressure or via diffusion. For example, the drug may be solubilized upon contact with urine in cases in which the device is implanted in the bladder.

In various embodiments, the intravesical device may release the drug continuously or intermittently to achieve a concentration of the drug in the bladder that produces a sustained, therapeutically effective concentration of the drug in the prostate over a period from 1 hour to 1 month, for example from 2 hours to 2 weeks, from 6 hours to 1 week, from 24 hours to 72 hours, etc. In certain embodiments, the intravesical device may release the gemcitabine in an amount of from 1 mg/day to 1000 mg/day, for example from 20 mg/day to 300 mg/day or from 25 mg/day to 300 mg/day. In certain embodiments, these release rates are provided over a treatment period from 14 days to 21 days.

In another embodiment, a coating substance may be intravesically applied to the bladder wall (e.g., to an area of the urothelium inside the urinary bladder), wherein the coating substance includes the gemcitabine or other drug and one or more excipient materials that promote adherance of the coating substance to the bladder wall and provides continuous controlled release of the drug over the treatment period. The coating substance may be a mucoadhesive formulation, such as gels, ointments, creams, pastes, films, emulsion gels, tablets, polymers, or a combination thereof. Mucoadhesive formulation polymers may include hydrogels or hydrophilic polymers, polycarbophil (i.e. Carbopols, etc.), chitosan, polyvinylpyrrolidone (PVP), lectin, polyethyleneglycolated polymers, celluloses, or a combination thereof. Suitable celluloses include methyl cellulose (MC), carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), or combinations thereof. The coating substance may include a permeation enhancer. Non-limiting examples of permeation enhancers include dimethyl sulfoxide (DMSO), sodium carboxymethyl cellulose (NaCMC), lipids, surfactants, or combinations thereof. As shown in **FIG. 5A**, a coating substance **500** may be deployed in the bladder **550** so that the coating substance **500** engages the bladder wall **552**.

The coating substance may be deployed in the bladder using a deployment instrument. **FIG. 5B** is a sagittal view of a male genitourinary system, illustrating a coating substance **500** being deployed through a deployment instrument **502** into an implantation site. By way of example, the male anatomy is shown and the implantation site is shown as the bladder **550**. The coating substance **500** may be an embodiment of one of the coating substances described herein. The deployment instrument **502** may be any device designed to navigate natural lumens of the body to reach the intended implantation site. For deployment in the bladder **550**, the deployment instrument **502** is sized and shaped for passing through a urethra **560** of a patient to a bladder **550** as shown. The deployment instrument **502** may be a known device, such as a catheter or cystoscope, or a specially

designed device. The deployment instrument **502** is used to deploy the coating substance **500** into the body and is subsequently removed from the body, leaving the coating substance **500** wholly implanted in the body. Once so implanted, the coating substance **500** may release drug into the body for an extended period. A comparable procedure can be used to deploy any of the devices or drugs described herein into other parts of the body through other natural lumens. For example, as shown in **FIG. 6**, a deployment instrument **602** can be used to deploy a liquid drug or drug formulation **600** into the bladder **650** by passing the deployment instrument **602** through a urethra **660**.

In one embodiment, a second therapeutic agent is administered to the patient. The second agent may be administered simultaneously, sequentially, or in an overlapping manner, with respect to the administration of the gemcitabine. The second therapeutic agent may be administered intravesically. The methods and systems described herein may be used to administer the second therapeutic agent intravesically. The second therapeutic agent may include a cytotoxic agent, an analgesic agent, an anti-inflammatory agent, or a combination thereof. The second agent may function by a mechanism of action different from the gemcitabine, and/or may function synergistically with the gemcitabine. In one embodiment, the second therapeutic agent prevents, treats, or ameliorates cystitis of the bladder. In still another embodiment, the gemcitabine is used as a chemoimmunotherapeutic first (e.g., during a first week following TURBT) with bacillus Calmette-Guérin (BCG) being administered periodically for a follow-on period thereafter. See, e.g., Cho et al., *J. Int'l Med. Res.* 37:1823-30 (2009).

In various embodiments, the intravesical administration of gemcitabine to the patient can be conducted before TURBT, after TURBT, both before and after TURBT, or without TURBT.

In one embodiment, the intravesical gemcitabine is used in non-muscular invasive bladder cancer (NMIBC) treatment. In another embodiment the intravesical gemcitabine is used in BCG refractory NMIBC. In still another embodiment, it is used in a repeat dose fashion with an induction period followed by a series of maintenance doses, e.g., one-week treatments once a month for three months, followed by a one-week maintenance dose once every three months as appropriate.

The terms "patient" or "subject" as used herein refers to humans or other mammals, such as in veterinary, livestock, and clinic study applications. In a particular embodiment, the patient or subject is an adult human. In other embodiments, the patient or subject includes cows, dogs, cats, goats, sheep, and pigs.

The present invention may be further understood with reference to the following non-limiting examples.

Example 1: Gemcitabine Prostate Uptake from Bladder

A study was conducted on male Sprague Dawley rats administering ^{14}C gemcitabine by intra-urinary bladder cannula, over a 6- or 24-hour continuous perfusion, or by a single IV bolus. The 6- and 24-hour continuous perfusions perfused 6.9 and 26.6 mg, respectively, of gemcitabine into the bladder. The single IV bolus included 5.0 mg of gemcitabine.

Blood (**FIG. 8**), urine, and tissue samples (e.g., bladder, prostate)(**FIGS. 7** and **9**) were collected and analyzed for gemcitabine content. The results are illustrated in **FIGS. 7-9**. The results show that sustained gemcitabine urine concentrations have been found to produce significant gemcitabine levels in bladder tissue, which are at or exceed therapeutic concentrations based on *in vitro* bladder cancer cell experiments. The gemcitabine levels in the bladder are shown in **FIG. 9**, which also depicts a significantly lower concentration of gemcitabine in the bladder 24 hours after a clinically relevant IV dose. The gemcitabine levels observed for each of the bladder epithelium, lamina propria, muscularis, and adventitia are shown in **FIG. 14**, which also illustrates a target effective range for the gemcitabine tissue concentration.

Example 2: Gemcitabine Study in Large Mixed Breed Hounds

Two gemcitabine release systems (devices as shown in **FIGS. 1A-1B**) designed to release therapeutic levels (4 mg/day and 40 mg/day) into the urine were screened. The devices used either laser-drilled orifices or punched orifices for release of the gemcitabine. The systems tested were compared to intravesical instillations which were designed to mimic the standard intravesical doses used clinically. The test animals were large mixed breed hounds, with N=3 for each group.

Each system *in vitro* exhibited different release rates of gemcitabine. *In vivo*, one system yielded very low urine and tissue concentrations but was well tolerated by the test animal. The other system produced target urine concentration levels but was poorly tolerated by the test animal. Urine profiles were also variable and the duration of drug release was unacceptably short. It was also observed that intravesical administration produced significant urothelial lesions consistent with the symptoms reported in the literature.

In sum, this study demonstrated that the device/tablet formulation design impacts both gemcitabine urine concentrations over time and bladder tolerability.

Example 3: Gemcitabine Bladder Perfusion Study in Minipigs

Varying concentrations of gemcitabine were perfused into pigs for 7 days, N=5 (2 males and 3 females per treatment group). The perfusion animals were dosed at concentrations selected to bracket the target doses for bladder cancer in humans. For comparison, a gemcitabine releasing device (as shown in FIGS. 1A-1B) with large bore end caps (restraining plugs with a large aperture therethrough for drug release) with an intermediate *in vitro* release rate was deployed in a separate group of animals. All perfusion groups tolerated gemcitabine well, including the highest perfusion dose. In contrast, the gemcitabine-releasing devices produced intermediate urine concentrations but were not well tolerated.

Example 4: Modular Device Releasing Gemcitabine by Permeation System

Gemcitabine HCl was tested in a four-module device **1000**, which is illustrated in **FIGS. 10A-C**. **FIG. 10A** shows that device **1000** includes four drug reservoir modules **1010A**, **1010B**, **1010C**, and **1010D**. For clarity, **FIG. 10C** shows only the housing portion of the device (with other components omitted) and only for drug reservoir modules **1010A** and **1010D**. **FIG. 10C** illustrates how the reservoir sidewalls **1040A** and **1040D** of drug reservoir modules **1010A** and **1010D**, respectively are integrally connected by wall segment **1012** and retention frame lumen **1014**. The reservoir sidewalls **1040A** and **1040D**, as well as wall segment **1012**, and retention frame lumen **1014** were formed by cutting a segment out of a dual-lumen silicone tube. (The four-module device was made by cutting three, spaced segments out of the dual lumen silicone tube.) Each drug reservoir module was comprised of silicone tube made of MED-4750 (Nusil) with the dimensions of 2.64 mm ID and 0.20 mm wall thickness. The silicone tube included a retention frame lumen having a 0.51 mm ID and 0.20 mm wall thickness. A nitinol retention frame was inserted into the retention frame lumen **1014**. **FIG. 10B** illustrates the structure of drug reservoir module **1010A**, including the disks **1060** through which solubilized drug was released by diffusion. (The other three drug reservoir modules were identical in construction to module **1010A**.) Disk **1060** is stabilized within the lumen of the cylindrical tube sidewalls **1040A** by sandwiching the disk **1060** between **o**uter washer **1100** and inner washer **1120**. Each disk **1060** was made of HP-93A-100 (Tecophilic® Thermoplastic Polyurethanes), and the dimensions of each disk **1060** were approximately 0.5 mm thickness and 3.0 mm OD. The OD (3.0 mm) of the disk was larger than the silicone tube ID (2.64 mm), and so the disk was frictionally fit in the silicone tube. The inner and outer silicone washers **1120**, **1100**

were made of MED-4780 (Nusil), and located next to disks **1060** with silicone adhesive applied around the washers **1120**, **1100** to fix the washers in the silicone tube **1040A**. The silicone outer washer **1100** had the dimensions of ID, OD, and the length of approximately 2.5 mm, 3.2 mm, and 2 mm, respectively, and the silicone inner washer **1120** had the dimensions of ID, OD, and the length of approximately 1.58 mm, 2.77 mm, and 2 mm, respectively.

Multiple drug tablets **1080** with 2.6 mm OD were loaded into the silicone tube **1040A** before closing off both ends of the reservoir with disk **1060** and inner and outer washers **1120** and **1100**. The tablet formulation was 90% gemcitabine HCl, 5% PVP, 2.5% Neusilin, and 2.5% magnesium stearate. The total mass of the tablets loaded in each four-module device was approximately 800 mg.

In vitro release experiment with three units (R204-4 to 6) was performed at 37 °C. The release medium was deionized water, and time point samples were collected. Gemcitabine release was controlled by diffusion through the Tecophilic disks. The cumulative amount and release rate in free base equivalent (FBE) are shown in **FIG. 11** and **FIG. 12**, respectively. Each error bar is standard deviation around the mean (n=3). Some error bars are smaller than symbols.

The devices with the same design were tested *in vivo* with three Göttingen minipigs. Each device was inserted into the bladder of each animal through the urethra non-surgically by cystoscope. The urine concentration of gemcitabine and 2',2'-difluoro-2'-deoxyuridine (dFdU) was measured over an 8-day period. After the 8-day study, each device was removed through the urethra non-surgically by cystoscope and forceps. The urine concentration of the combined gemcitabine and dFdU is shown in **FIG. 13**.

Example 5: Gemcitabine Delivery Device Screen Studies in Minipigs

A series of prototype screening studies were undertaken to refine the drug delivery system design based on the intrinsic tolerability of gemcitabine discovered in the mini pig perfusion study described above. In this study, three prototype devices were designed to release therapeutic levels of gemcitabine into the urine. Two devices were of the **FIGS. 1A-1B** design (with large bore end caps or laser-drilled orifices for drug release) and one device was of the **FIGS. 10A-10C** design (drug permeable disks for drug release). Three studies were completed, each study tested a single prototype design in three minipigs in which blood and urine samples were intensively collected over a 7-day period.

The devices of the **FIGS. 1A-1B** design having large bore end caps for drug release were found to consistently produce urothelial lesions in the animal. However, devices of the **FIGS. 1A-1B** design having a laser-drilled orifice in which a viscosity enhancing agent was included with the gemcitabine were found to reduce the incidences of urothelial lesions. The no-orifice devices of the **FIGS. 10A-10C** design were found to completely eliminate the incidences of urothelial lesions. Such a design is believed to prevent transient high local concentrations of the gemcitabine (at the tissue surfaces adjacent to the device's drug release apertures) which are believed to contribute to the incidences of urothelial lesions.

Example 6: Gemcitabine Delivery Device Screen Studies in Minipigs

In this study, osmotic prototype devices were designed to release therapeutic levels of gemcitabine into the urine. The devices were configured to use tablets of gemcitabine and tablets of osmotic agent positioned in separate positions within the drug reservoir, as described generally in PCT WO 2015/026813, which is incorporated in pertinent part herein. A first subset of the devices each included a silicone tube having a 75-micron laser-drilled orifice in a region centrally located between the ends of the tube for drug release. The lumen of the tube was loaded with tablets of a mixture of gemcitabine and urea in the central region about the release orifice and with tablets of urea/Lubritab in the end regions of the lumen. A second subset of the devices each included a silicone tube having a 150-micron laser-drilled orifice in a region centrally located between the ends of the tube for drug release. The lumen of the tube was loaded with tablets of a mixture of gemcitabine and urea in the central region about the release orifice and with tablets of urea/PEO in the end regions of the lumen. The devices were tested *in vivo* in minipigs and *in vitro*, measuring cumulative and average gemcitabine released over 7 days. Gemcitabine release rates were approximately 120 mg over 7 days from the 75 micron orifice device and approximately 140 mg over 7 days from the 150 micron orifice device. Variations in urine concentration with time were observed to be modestly less using the urea/PEO formulation when compared with the urea/Lubritab formulation. The viscosity of solubilized drug solution in the device lumen therefore may be a factor in controlling drug release.

Conclusions from the Examples

Literature studies providing target concentrations –in vitro concentrations across tumor cell lines—typically have IC50 values ranging between 0.5 and 3.0 µg/g (microgram per gram) for responsive cell lines (*see* Jeon et al., *J. Urol.* 186(5):2084-93 (2011)). The literature also suggests that high urine concentrations (e.g., 2000 mg in up to 50 mL) are

required for efficacy, but that intravesical instillations to achieve such concentrations are associated with issues of safety and tolerability, systemic toxicity, and lower urinary tract symptoms (LUTS) (*see* Cattel et al., *Annals Oncol.* 17(Supp 5): v142-47 (2006)).

However, from the studies described in the foregoing Examples, concentrations of gemcitabine in urine needed to achieve these therapeutic tissue concentrations have been determined, and found to be tolerated by the urothelium. That is, high intravesical urine concentrations are not required. In particular, it has been discovered that an intravesical system delivering $1/100^{th}$ of those levels (e.g., 20 mg in up to 50 mL) can be effective.

Also, it has been discovered by that prolonged intravesical delivery of gemcitabine can be carried out without damage to the urothelium, in contrast to what the literature taught regarding intravenous perfusion of gemcitabine.

Publications cited herein and the materials for which they are cited are specifically incorporated by reference. Modifications and variations of the methods and devices described herein will be obvious to those skilled in the art from the foregoing detailed description. Such modifications and variations are intended to come within the scope of the appended claims.

We claim:

1. Use of gemcitabine in the manufacture of a medicament for the treatment of bladder cancer in a patient, wherein the medicament is to be locally administered into the bladder of the patient, before and/or after transurethral resection of bladder tumor (TURBT), to achieve a sustained concentration of the gemcitabine in the urine in the bladder sufficient to produce a therapeutic concentration of the gemcitabine in the bladder tissues, wherein the locally administering into the patient's bladder is at a mean average amount of from 1 mg/day to 300 mg/day of the gemcitabine free base equivalent (FBE) continuously over a period of from 1 day to 30 days,
wherein the gemcitabine is to be delivered into the bladder from an intravesical drug delivery device which releases the gemcitabine into the urine in the bladder over the period.

2. The use of claim 1, wherein the locally administering into the patient's bladder is at a mean average amount of from 1 mg/day to 200 mg/day of the gemcitabine (FBE).

3. The use of claim 1, wherein the locally administering into the patient's bladder is at a mean average amount of from 5 mg/day to 100 mg/day of the gemcitabine (FBE).

4. The use of claim 1, wherein the locally administering into the patient's bladder is at a mean average amount of from 10 mg/day to 50 mg/day of the gemcitabine (FBE).

5. The use of claim 1, wherein the locally administering into the patient's bladder is at a mean average amount of from 15 mg/day to 25 mg/day of the gemcitabine (FBE).

6. The use of claim 1, wherein the locally administering into the patient's bladder is at a mean average amount of 20 mg/day of the gemcitabine (FBE).

7. The use of any one of claims 1 to 6, wherein the locally administering into the patient's bladder is continuous over a period from 1 day to 14 days.

8. The use of any one of claims 1 to 6, wherein the locally administering into the patient's bladder is continuous over a period from 1 day to 7 days.

9. The use of claim 1, wherein the intravesical drug delivery device comprises a housing which contains and controllably releases the gemcitabine and is elastically deformable between a retention shape configured to retain the device in a patient's

bladder and a deployment shape for passage of the device through the patient's urethra.

10. The use of claim 9, wherein the gemcitabine contained in the housing is in a non-liquid form.

11. The use of claim 10, wherein the non-liquid form is selected from the group consisting of tablets, granules, semisolids, capsules, and combinations thereof.

12. The use of claim 1, wherein the intravesical drug delivery device comprises a housing which comprises a drug reservoir and a release orifice in communication with the drug reservoir, wherein the gemcitabine is contained in the drug reservoir with (i) a viscosity enhancing agent, (ii) an osmotic agent, or (iii) a combination of a viscosity enhancing agent and an osmotic agent.

13. The use of any one of claims 1 to 12, wherein the bladder cancer is non-muscular invasive bladder cancer (NMIBC).

14. The use of claim 13, wherein the bladder cancer is BCG refractory NMIBC.