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

In an 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 human patient, comprising inserting an intravesical drug delivery device into the patient's bladder, wherein the intravesical drug delivery device is configured to release gemcitabine at a mean average amount from 5 mg/day to 100 mg/day of gemcitabine (FBE) continuously to the bladder of the patient over a period of 1 day to 30 days; and wherein the gemcitabine is well tolerated by urothelium in the patient's bladder.

In one example, a medicament is provided 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 examples, 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 examples, 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 example, 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 example, 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 example, 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.

In another example, a drug delivery device is provided 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 example, 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 example, the housing releases the gemcitabine without a predefined release aperture. In a particular version of this preferred example, 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.

In still another example, 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 examples, 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 example, the method further includes administering at least a second therapeutic agent to the patient. The second therapeutic agent may be administered intravesically. In another example, 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 examples, 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

We claim:

1. Use of gemcitabine in the manufacture of a medicament for the treatment of bladder cancer in a human patient, comprising inserting an intravesical drug delivery device into the patient's bladder,

wherein the intravesical drug delivery device is configured to release gemcitabine at a mean average amount from 5 mg/day to 100 mg/day of gemcitabine (FBE) continuously to the bladder of the patient over a period of 1 day to 30 days; and

wherein the gemcitabine is well tolerated by urothelium in the patient's bladder.

2. The use of claim 1, wherein the intravesical drug delivery device continuously releases gemcitabine to the patient's bladder over a period from 1 day to 14 days.

3. The use of claim 1 or claim 2, wherein the intravesical drug delivery device continuously releases gemcitabine to the patient's bladder over a period from 1 day to 7 days.

4. The use of any one of claims 1-3, wherein the intravesical drug delivery device releases about 140 mg of gemcitabine over 7 days.

5. The use of any one of claims 1-4, wherein the intravesical drug delivery device is configured to release gemcitabine at a mean average amount from 10 mg/day to 50 mg/day of gemcitabine (FBE).

6. The use of any one of claims 1-5, wherein the intravesical drug delivery device is configured to release gemcitabine at a mean average amount from 15 mg/day to 25 mg/day of gemcitabine (FBE).

7. The use of any one of claims 1-6, wherein the intravesical drug delivery device is elastically deformable between a retention shape configured to retain the device in the bladder and a deployment shape for passage of the device through the urethra.

8. The use of any one of claims 1-7, wherein the intravesical drug delivery device comprises a housing which contains and controllably releases the gemcitabine.

9. The use of claim 8, wherein the gemcitabine contained in the housing is in a non-liquid form.

10. The use of claim 9, wherein the non-liquid form is selected from the group consisting of tablets, granules, semisolids, capsules, and combinations thereof.

11. The use of any one of claims 8-10, wherein the housing is configured to release the gemcitabine by osmotic pressure through a predefined release aperture that is in communication with a drug reservoir.

12. The use of claim 11, wherein the predefined release aperture is a 150-micron laser-drilled release aperture.

13. The use of claim 11 or claim 12, wherein the drug reservoir further comprises an osmotic agent.

14. The use of claim 13, wherein the drug reservoir further comprises a viscosity enhancing agent.

15. The use of claim 13 or claim 14, wherein the osmotic agent is urea.

16. The use of claim 15, wherein the gemcitabine is provided in a first region of the intravesical drug delivery device comprising one or more minitablets and the urea is provided in a second region of the intravesical drug delivery device comprising one or more minitablets, wherein the first and second regions are discrete spaces within the drug reservoir.

17. The use of any one of claims 1 to 16, wherein the bladder cancer is non-muscle invasive bladder cancer (NMIBC).

18. The use of any one of claims 1 to 17, wherein the bladder cancer is BCG refractory NMIBC.