

trials to treat 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.

[0009] It is known that such liquid formulations are voided from the bladder after short dwell times of 1 to 2 hours thus limiting their 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 with limited dwell time. However, in addition to local tolerability issues, intravesical delivery of high doses of gemcitabine can lead to significant systemic absorption and cause gastrointestinal, bladder and bone marrow toxicity further limiting its utility.

[0010] Systemic gemcitabine is often used in combination with systemic cisplatin both neoadjuvantly and adjuvantly to radical cystectomy to treat muscle invasive bladder cancer and to treat metastatic disease. However, many patients are ineligible or refuse treatment with these agents due to their side effects which include bone marrow suppression.

[0011] Accordingly, there remains a need for methods for treating tumors at distant sites in an individual with a tumor in the bladder.

[0012] The disclosures of all publications, patents, patent applications and published patent applications referred to herein are hereby incorporated herein by reference in their entirety.

BRIEF DESCRIPTION SUMMARY

[0013] The present ~~invention~~disclosure in various ~~aspect~~examples provides methods of treating tumor metastasis, reducing (such as eradicating) preexisting tumor metastasis, reducing incidence or burden of preexisting tumor metastasis, suppressing or delaying tumor metastasis, inhibiting tumor cells at a second site distinct from a first tumor site in the bladder of an individual comprising locally delivering to the bladder an effective amount of a chemotherapeutic agent, wherein the chemotherapeutic agent is delivered continuously to the bladder for period of time.

[0013a] In one aspect, the present disclosure refers to use of gemcitabine in the manufacture of a medicament for inducing an immune response against a tumor cell at a second tumor site distinct from a first tumor site in the bladder of an individual, wherein an effective amount of gemcitabine is to be locally delivered to the bladder, wherein gemcitabine is to be delivered continuously to the bladder for at least about 24 hours.

[0014] In some ~~embodiment~~examples, there is provided a method of inhibiting tumor cell growth at a second tumor site distinct from a first tumor site in the bladder of an individual, comprising locally delivering to the bladder an effective amount of a chemotherapeutic agent,

wherein the chemotherapeutic agent is delivered continuously to the bladder for at least about 24 hours. In some [embodimentexamples](#), the tumor cells at the second tumor site are located at a pelvic node. In some [embodimentexamples](#), the tumor cells at the second tumor site are located at a distant node. In some [embodimentexamples](#), the tumor cells at the second tumor site are circulating tumor cells. In some [embodimentexamples](#), the tumor cells at the first tumor site result from metastasis of a primary tumor at the second tumor site. In some [embodimentexamples](#), the tumor cells at the second site are selected from the group consisting of liver, lung, bone, brain, lymph node, pelvic node, peritoneum, skin, prostate, breast, colon, rectum, and cervix. In some [embodimentexamples](#), the individual has a urothelial carcinoma of lower tract.

[0015] In some [embodimentexamples](#), also provided herein is a method of treating or suppressing tumor metastasis at a site distinct from the bladder in an individual having a urothelial carcinoma of lower tract, comprising locally delivering to the bladder an effective amount of a chemotherapeutic agent, wherein the chemotherapeutic agent is delivered continuously to the bladder for at least about 24 hours. In some [embodimentexamples](#), the tumor metastatic site is at one or more of: liver, lung, bone, brain, lymph node, pelvic node, peritoneum, skin, prostate, breast, colon, rectum, and cervix. In some [embodimentexamples](#), the tumor metastasis is at two or more different sites.

[0016] In some [embodimentexamples](#) according to any of the methods described above, the individual has bladder cancer. In some [embodimentexamples](#), the individual has muscle invasive bladder cancer or carcinoma in situ (CIS). In some [embodimentexamples](#), the individual is unfit for or refuses cystectomy.

[0017] In some [embodimentexamples](#) according to any of the methods described above, the individual has not undergone transurethral resection of bladder tumors (TURBT).

[0018] In other [embodimentexamples](#), the individual has undergone transurethral resection of bladder tumors (TURBT). In some of these [embodimentexamples](#), the individual has undergone transurethral resection of bladder tumors (TURBT) and has residual tumor at the site of resection.

[0019] In some [embodimentexamples](#) according to any of the methods described above, the chemotherapeutic agent is delivered at a dose of from about 1 mg/day to about 300 mg/day. In some [embodimentexamples](#), the concentration of the chemotherapeutic agent in the urine is from about 0.1 µg/mL to about 200 µg/mL during the delivery period.

[0020] In some [embodimentexamples](#) according to any of the methods described above, the chemotherapeutic agent is delivered continuously to the bladder of the individual for a period of about 7 days to about three weeks. In some [embodimentexamples](#), the method comprises an induction delivery period followed by a maintenance delivery period. In some [embodimentexamples](#), the induction delivery period and the maintenance delivery period are separated by a rest period of about 7 to about 14 days. In some [embodimentexamples](#), the chemotherapeutic agent is delivered at a first release rate during the induction delivery period followed and a second release rate during the maintenance delivery period.

[0021] In some [embodimentexamples](#) according to any of the methods described above, the method comprises a) an induction delivery period, wherein the concentration of chemotherapeutic agent in the urine of the individual is at least about 0.1 µg/mL; b) a rest period; and c) a maintenance delivery period, wherein the concentration of the chemotherapeutic agent in the urine of the individual is greater than about 0.1 µg/mL.

[0022] In some [embodimentexamples](#) according to any of the methods described above, the individual does not receive a radiation therapy. In other [embodimentexamples](#), the method further comprises a radiation therapy.

[0023] In some [embodimentexamples](#) according to any of the methods described above, the chemotherapeutic agent is delivered by an intravesical delivery device. In some [embodimentexamples](#), the intravesical device contains 100 mg to 500 mg of the chemotherapeutic agent. In some [embodimentexamples](#), the intravesical device comprises a housing configured for intravesical insertion; and a dosage form comprising chemotherapeutic agent, wherein the housing holds the dosage form and is configured to release chemotherapeutic agent. In some [embodimentexamples](#), the intravesical drug delivery device comprises: a housing defining a reservoir; a first unit contained within the reservoir, the first unit comprising an chemotherapeutic agent; and a second unit contained within the reservoir in a position distinct from the first unit, wherein the second unit comprises a functional agent that facilitates in vivo release of the chemotherapeutic agent from the housing. In some [embodimentexamples](#), the intravesical drug delivery device comprises a housing which contains and controllably releases the chemotherapeutic agent and is elastically deformable between a retention shape configured to retain the device in the individual's bladder and a deployment shape for passage of the device through the individual's urethra. In some [embodimentexamples](#), the device comprises a drug reservoir lumen bounded by a first wall and a second wall, wherein the first wall is impermeable to the

drug and the second wall is permeable to the chemotherapeutic agent. In some [embodimentexample](#), the chemotherapeutic agent is released from the device by osmotic pressure. In some [embodimentexamples](#), the chemotherapeutic agent is released from the device by diffusion. In some [embodimentexample](#), the chemotherapeutic agent contained in the housing is in a non-liquid form. In some [embodimentexamples](#), the non-liquid form is selected from the group consisting of tablets, granules, powders, semisolids, capsules, and combinations thereof.

[0024] In some [embodimentexamples](#) according to any of the methods described above, the chemotherapeutic agent is selected from the group consisting of a nucleoside analog, a taxane, a platinum-based agent, and an anthracycline analogue. In some [embodimentexamples](#), the chemotherapeutic agent is a nucleoside analog. In some of these [embodimentexamples](#), the nucleoside analog is gemcitabine.

[0025] In some [embodimentexamples](#) according to any of the methods described above, the individual is human. In some [embodimentexamples](#), the individual is unsuitable for systemic chemotherapy. In some [embodimentexamples](#), the individual has a compromised immune system. In some [embodimentexamples](#), the individual has a high tumor burden.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] FIG. 1 shows a modified bladder perfusion system to introduce tumors into bladder and subcutaneous tissue.

[0027] FIG. 2 shows the treatment and dosing schedule for four groups of rats: 1) untreated rats inoculated with subcutaneous tumor only; 2) untreated rats inoculated with bladder tumor and then subcutaneous tumor; 3) rats inoculated with bladder tumor, perfused with 180 µg/mL gemcitabine, and then inoculated with subcutaneous tumor and again perfused with 180µg/mL gemcitabine; and 4) rats inoculated with bladder tumor and subcutaneous tumor simultaneously and perfused with 180 µg/mL gemcitabine twice.

[0028] FIG. 3 shows the average volume of subcutaneous tumors in four groups of rats after introducing tumors into bladder and/or subcutaneous tissue and during the course of the treatment.

[0029] FIG. 4 shows the volume of subcutaneous tumors in each individual rat in the four groups after introducing tumors into bladder and/or subcutaneous tissue and during the course of the treatment.

CLAIMS

- ~~1. A method of treating or suppressing tumor metastasis at a site distinct from the bladder in an individual having a urothelial carcinoma of lower tract, comprising locally delivering to the bladder an effective amount of a chemotherapeutic agent, wherein the chemotherapeutic agent is delivered continuously to the bladder for at least about 24 hours.~~
- ~~2. The method of claim 1, wherein the tumor metastatic site is at one or more of: liver, lung, bone, brain, lymph node, pelvic node, peritoneum, skin, prostate, breast, colon, rectum, and cervix.~~
- ~~3. The method of any one of claims 1-2, wherein the tumor metastasis is at two or more different sites.~~
- ~~4. A method of inhibiting tumor cell growth at a second tumor site distinct from a first tumor site in the bladder of an individual, comprising locally delivering to the bladder an effective amount of a chemotherapeutic agent, wherein the chemotherapeutic agent is delivered continuously to the bladder for at least about 24 hours.~~
- ~~5. The method of claim 4, wherein the tumor cells at the second tumor site are located at a pelvic node.~~
- ~~6. The method of claim 4, wherein the tumor cells at the second tumor site are located at a distant node.~~
- ~~7. The method of claim 4, wherein the tumor cells at the second tumor site are circulating tumor cells.~~
- ~~8. The method claim 4, wherein the tumor cells at the first tumor site result from metastasis of a primary tumor at the second tumor site.~~

~~9. The method of claim 8, wherein the tumor cells at the second site are selected from the group consisting of liver, lung, bone, brain, lymph node, pelvic node, peritoneum, skin, prostate, breast, colon, rectum, and cervix.~~

~~10. The method of any one of claims 4-9, wherein the individual has a urothelial carcinoma of lower tract.~~

1. Use of gemcitabine in the manufacture of a medicament for inducing an immune response against a tumor cell at a second tumor site distinct from a first tumor site in the bladder of an individual, wherein an effective amount of gemcitabine is to be locally delivered to the bladder, wherein gemcitabine is to be delivered continuously to the bladder for at least about 24 hours.

2. The use of claim 1, wherein the immune response comprises an increase in the level of one or more pro-inflammatory cytokines.

3. The use of claim 1 or 2, wherein the one or more pro-inflammatory cytokine is TNF- α or IFN- γ .

4. The use of any one of claims 1-3, wherein the immune response comprises a decrease in the level of one or more anti-inflammatory cytokines.

5. The use of claim 4, wherein the anti-inflammatory cytokine is TGF- β .

6. The use of any one of claims 1-5, wherein the immune response comprises a decrease in the level or activity of regulatory T cells.

7. The use of claim 6, wherein the decrease in the level of regulatory T cells is a decrease in the level or percentage of the regulatory T cells relative to CD4+CD25- T cells.

8. The use of any one of claims 1-7, wherein the immune response comprises an increase in the level or the activity of one or more cells selected from the group consisting of effector T cells, helper T cells, memory cells, and plasmablasts.

~~11.9.~~ The ~~method-use~~ of any one of claims 1-~~810~~, wherein the individual has bladder cancer.

~~12.10.~~ The ~~method-use~~ of any one of claims 1-9~~claim 11~~, wherein the individual has muscle invasive bladder cancer or carcinoma in situ (CIS).

~~13.11.~~ The ~~method-use~~ of any one of claims 1-10~~claim 11 or 12~~, wherein the individual is unfit for or refuses cystectomy.

~~14.12.~~ The ~~method-use~~ of any one of claims 1-~~113~~, wherein the individual has not undergone transurethral resection of bladder tumors (TURBT) prior to intravesical administration of gemcitabine.

~~15.13.~~ The ~~method-use~~ of any one of claims 1-~~113~~, wherein the individual has undergone transurethral resection of bladder tumors (TURBT).

~~16.14.~~ The ~~method-use~~ of claim 1~~35~~, wherein the individual has residual tumor at the site of resection.

15. The use of any one of claims 1-14, wherein the individual is unsuitable for systemic chemotherapy.

~~17.16.~~ The ~~method-use~~ of any one of claims 1-1~~56~~, wherein the ~~gemcitabinechemotherapeutic agent~~ is to be delivered continuously to the bladder of the individual for a period of about ~~seven~~ 7-days to about three weeks.

17. The use of claim 16, wherein the gemcitabine is to be delivered continuously to the bladder of the individual for a period of about seven days to about three weeks at least two times.

18. The use of claim 16, wherein the gemcitabine is to be delivered continuously to the bladder of the individual for about three weeks.

19. The use of any one of claims 1-18, wherein the gemcitabine is to be delivered at a dose of from about 10 mg/day to about 50 mg/day.

~~18. The method of any one of claims 1-17, wherein the method comprises an induction delivery period followed by a maintenance delivery period.~~

~~19. The method of claim 18, wherein the induction delivery period and the maintenance delivery period are separated by a rest period of about 7 to about 14 days.~~

~~20. The method of claim 18, wherein the chemotherapeutic agent is delivered at a first release rate during the induction delivery period followed and a second release rate during the maintenance delivery period.~~

~~21. The method of any of claims 1-20, wherein the chemotherapeutic agent is delivered at a dose of from about 1 mg/day to about 300 mg/day.~~

~~22.20. The method-use of any one of claims 1-1921, wherein the concentration of the gemcitabinechemotherapeutic agent in the urine is from about 0.1 µg/mL to about 200 µg/mL during the delivery period.~~

~~23. The method any one of claims 1-22, comprising~~

~~a) an induction delivery period, wherein the concentration of chemotherapeutic agent in the urine of the individual is at least about 0.1 µg/mL;~~

~~b) a rest period; and~~

~~c) a maintenance delivery period, wherein the concentration of the chemotherapeutic agent in the urine of the individual is greater than about 0.1 µg/mL.~~

~~24. The method of any of claims 1-23, wherein the individual does not receive a radiation therapy.~~

25. ~~The method of any one of claims 1-24, wherein the method further comprises a radiation therapy.~~
- 26.21. ~~The method-use of any one of claims 1-205, wherein the gemcitabine chemotherapeutic agent is to be delivered by an intravesical delivery device.~~
- 27.22. ~~The method-use of claim 216, wherein the intravesical device contains 225100 mg to 500 mg of gemcitabine the chemotherapeutic agent.~~
23. The use of claim 21, wherein a gemcitabine releasing intravesical device is to be placed in the bladder of the individual, wherein the device remains in the bladder for about 21 days.
24. The use of claim 23, wherein the device releases gemcitabine for about 1 to about 21 days.
25. The use of claim 24, wherein the device releases gemcitabine for about 7 to about 21 days.
26. The use of any one of claims 1-25, wherein the second tumor site distinct from the bladder is selected from the group consisting of liver, lung, bone, brain, lymph node, pelvic node, peritoneum, skin, prostate, breast, colon, rectum, and cervix.
28. ~~The method of any of claims 26-27, wherein the intravesical device comprises a housing configured for intravesical insertion; and a dosage form comprising chemotherapeutic agent, wherein the housing holds the dosage form and is configured to release chemotherapeutic agent.~~
29. ~~The method of any one of claims 26-28, wherein the intravesical drug delivery device comprises:~~
- ~~a housing defining a reservoir;~~
 - ~~a first unit contained within the reservoir, the first unit comprising an chemotherapeutic agent; and~~

a second unit contained within the reservoir in a position distinct from the first unit, wherein the second unit comprises a functional agent that facilitates in-vivo release of the chemotherapeutic agent from the housing.

30. The method of any one of claims 26-29, wherein the intravesical drug delivery device comprises a housing which contains and controllably releases the chemotherapeutic agent and is elastically deformable between a retention shape configured to retain the device in the individual's bladder and a deployment shape for passage of the device through the individual's urethra.

31. The method of any one of claims 26-30, wherein the device comprises a drug reservoir lumen bounded by a first wall and a second wall, wherein the first wall is impermeable to the drug and the second wall is permeable to the chemotherapeutic agent.

32. The method of any one of claims 26-31 wherein the chemotherapeutic agent is released from the device by osmotic pressure.

33. The method of any one of claims 26-31, wherein the chemotherapeutic agent is released from the device by diffusion.

34. The method of any of claims 22-29, wherein the chemotherapeutic agent contained in the housing is in a non-liquid form.

35. The method of claim 34, wherein the non-liquid form is selected from the group consisting of tablets, granules, powders, semisolids, capsules, and combinations thereof.

36. The method of any one of claims 1-35, wherein the chemotherapeutic agent is selected from the group consisting of a nucleoside analog, a taxane, a platinum-based agent, and an anthracycline analogue.

- ~~37. The method of any one of claims 1-36, wherein the chemotherapeutic agent is a nucleoside analog.~~
- ~~38. The method of claim 37, wherein the nucleoside analog is gemcitabine.~~
- ~~39. The method of any one of claims 1-38, wherein the individual is human.~~
- ~~40. The method of any one of claims 1-39, wherein the individual is unsuitable for systemic chemotherapy.~~
- ~~41. The method of any one of claims 1-40, wherein the individual has a compromised immune system.~~
- ~~42. The method of any one of claims 1-41, wherein the individual has a high tumor burden.~~