DRUG DELIVERY SYSTEMS AND METHODS FOR TREATMENT OF BLADDER CANCER

Cross-Reference to Related Applications

This application claims priority to U.S. Provisional Patent Application No. 61/696,027, filed August 31, 2012, which is incorporated herein by reference.

Background

This disclosure is generally in the field of pharmaceutical agents for use in treating the bladder, and more particularly to drug delivery systems, methods, and drug formulations for targeted treatment of urinary bladder cancer.

Delivery of therapeutic agents to the urinary bladder is difficult. Current practice requires systemic administration using doses which result in significant exposure to healthy tissues and relatively low exposure within the bladder. Frequently the systemic exposure leads to unwanted or harmful side effects which limit the usefulness of the agent in treating bladder disease.

To avoid systemic effects, drugs may be delivered locally onto tissues at or near the target tissue. However, such local administration may not be well tolerated by the tissue at the delivery site and/or may not be sufficiently permeable to the particular drug being delivered. Accordingly, there is a need to provide a therapeutic agent that is well tolerated by the bladder when the agent is applied at concentrations effective to achieve sufficient therapeutic (i.e., cytotoxic) concentrations within the target tissues.

Accordingly, there remains a need for improved drug delivery methods and systems for treating the bladder, such as in the treatment of bladder cancer, whether as neoadjuvant therapy, adjuvant therapy, or palliative therapy.

Summary

In one example, a medicament is disclosed that includes oxaliplatin for use in the treatment of bladder cancer by locally administering oxaliplatin into the bladder of a patient to achieve a sustained concentration of oxaliplatin in urine in the bladder sufficient to produce a therapeutic concentration of oxaliplatin in bladder tissue. The locally administering into the patient's bladder may be continuous or intermittent. In one

example, the oxaliplatin is delivered into the bladder from an intravesical drug delivery device inserted into the bladder, and the device continuously releases the oxaliplatin into the urine in the bladder over a sustained period. In an alternative example, the oxaliplatin is delivered into the bladder from a coating substance applied to the bladder, which coating substance continuously releases the oxaliplatin into the urine in the bladder over a sustained period. The coating substance may include a mucoadhesive formulation. In a further alternative example, a liquid form of the oxaliplatin is pumped into the bladder through a urethral catheter inserted into the bladder. In various examples, the oxaliplatin is released into the patient's bladder continuously over a period of at least 2 hours, such as from 1 day to 14 days. In an example, the oxaliplatin is released into the patient's bladder at a mean average amount of from 1 mg to about 100 mg oxaliplatin per day for 1 day to 14 days. In an example, the oxaliplatin is released into the patient's bladder at a mean average amount of from 1 mg to about 100 mg oxaliplatin per day for up to 7 days.

In another example, a medical device is disclosed for intravesical administration of oxaliplatin. In an example, the device includes a housing configured for intravesical insertion, and a dosage form comprising oxaliplatin, wherein the housing holds the dosage form and is configured to controllably release the oxaliplatin into the bladder in amount therapeutically effective for the treatment of bladder cancer. In an example, the device comprises 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. In an example, the device is configured to release from 1 mg/day to 100 mg/day of oxaliplatin for up to 7 days.

In still another example, a method is disclosed for administering oxaliplatin to a patient in need of treatment of bladder cancer. The method includes locally administering oxaliplatin into the bladder of a patient to achieve a sustained concentration of oxaliplatin in urine in the bladder sufficient to produce a therapeutic concentration of oxaliplatin in bladder tissue. The method may further include administering at least a second therapeutic agent to the patient. Non-limiting examples of second therapeutic agents include gemcitabine or another cytotoxic agent; an analgesic agent; an anti-inflammatory agent; or a combination thereof. The second therapeutic agent may be administered intravesically and/or by other routes of administration.

In one example, there is disclosed the use of oxaliplatin in the manufacture of a medicament for the treatment of bladder cancer, wherein the medicament is to be locally administered into the bladder of a patient to achieve a sustained concentration of oxaliplatin in urine in the bladder for at least 24 hours sufficient to produce a therapeutic concentration of oxaliplatin in bladder tissue. In another aspect, the present invention refers to a drug delivery device comprising a medicament according to any one of the preceding claims, configured to release oxaliplatin to achieve a sustained concentration of oxaliplatin in urine in the bladder for at least 24 hours when the drug delivery device is inserted into the bladder. In yet another aspect, the present invention refers to a medical device comprising a housing configured for intravesical insertion; and a dosage form comprising oxaliplatin, wherein the housing holds the dosage form and is configured to release the oxaliplatin to achieve a sustained concentration of oxaliplatin in urine in the bladder for at least 24 hours into the bladder in amount therapeutically effective for the treatment of bladder cancer.

Claims

1. Use of oxaliplatin in the manufacture of a medicament for the treatment of bladder cancer, wherein the medicament is to be locally administered into the bladder of a patient to achieve a sustained concentration of oxaliplatin in urine in the bladder for at least 24 hours sufficient to produce a therapeutic concentration of oxaliplatin in bladder tissue.

2. The use of claim 1, wherein the medicament is to be locally administered into the patient's bladder continuously.

3. The use of claim 1, wherein the medicament is to be locally administered into the patient's bladder at a mean average amount of from 1 mg to about 100 mg oxaliplatin per day for 1 day to 14 days.

4. The use of claim 1, wherein the medicament is to be locally administered into the patient's bladder at a mean average amount of from 1 mg to about 100 mg oxaliplatin per day for up to 7 days.

5. The use of claim 1, wherein the medicament is to be administered into the bladder from an intravesical drug delivery device which continuously releases the medicament into the urine in the bladder over a sustained period.

6. The use of claim 5, wherein the intravesical drug delivery device continuously releases the medicament into the urine in the bladder over a period of 1 day to 14 days.

7. The use of any one of claims 5 to 6, wherein the intravesical drug delivery device comprises a housing which contains and controllably releases the medicament 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.

8. The use of claim 7, wherein the medicament is in a non-liquid form.

9. The use of claim 8, wherein the non-liquid form is selected from the group consisting of tablets, granules, semisolids, capsules, and combinations thereof.

10. The use of claim 1, wherein the medicament is to be delivered into the bladder from a coating substance to be applied to the bladder, which coating substance continuously releases the medicament into the urine in the bladder over a sustained period.

11. The use of claim 10, wherein the coating substance comprises a mucoadhesive formulation.

12. The use of claim 1, wherein the locally administered comprises pumping a liquid form of the medicament into the bladder through a urethral catheter which is deployed into the bladder.

13. A drug delivery device comprising a medicament according to any one of the preceding claims, configured to release oxaliplatin to achieve a sustained concentration of oxaliplatin in urine in the bladder for at least 24 hours when the drug delivery device is inserted into the bladder.

14. The use of claim 1, wherein at least a second therapeutic agent is to be administered to the patient.

15. The use of claim 14, wherein the second therapeutic agent is to be administered intravesically.

16. The use of claim 14 or 15, wherein the second therapeutic agent comprises gemcitabine or another cytotoxic agent; an analgesic agent; an anti-inflammatory agent; or a combination thereof.

17. A medical device comprising:

a housing configured for intravesical insertion; and

a dosage form comprising oxaliplatin,

wherein the housing holds the dosage form and is configured to release the oxaliplatin to achieve a sustained concentration of oxaliplatin in urine in the bladder for at least 24 hours in amount therapeutically effective for the treatment of bladder cancer.

18. The device of claim 17, which is configured to release from 1 mg/day to 100 mg/day of oxaliplatin for up to 7 days.

19. The device of claim 17, wherein:

the dosage form is in a solid form, and

the housing comprises an elastomeric material and is configured to permit urine to enter the housing, contact the dosage form, solubilize the oxaliplatin, and thereafter to permit the solubilized oxaliplatin to diffuse through a wall of the housing, to diffuse through an aperture in a wall of the housing, or to flow by osmotic pressure through an aperture in a wall of the housing.