[0017] The present disclosure relates to 25-hydroxyvitamin D therapy as adjunctive therapy and/or to treat cancer in a patient. In one aspect, the present invention provides a composition comprising 25-hydroxyvitamin D for use in a method of treatment of a patient, the method being: (i) a method of treating or preventing iatrogenic hypocalcemia and secondary hyperparathyroidism in a patient treated with an agent that increases the risk of hypocalcemia, where the method comprises administering to the patient an effective amount of said 25-hydroxyvitamin D; or (ii) a method of increasing bone mineral density in a patient treated with an agent that increases the risk of hypocalcemia, where the method comprises administering to the patient an effective amount of said 25-hydroxyvitamin D; or (iii) a method of decreasing the blood level of a bone resorption marker in a patient treated with an agent that increases the risk of hypocalcemia, where the method comprises administering to the patient an effective amount of said 25-hydroxyvitamin D; or (iv) a method of treating bone pain in a patient treated with an agent that increases the risk of hypocalcemia, where the method comprises administering to the patient an effective amount of said 25-hydroxyvitamin D; or (v) a method of increasing the time to the first post-treatment skeletal-related event in a patient treated with an agent that increases the risk of hypocalcemia, where the method comprises administering to the patient an effective amount of said 25-hydroxyvitamin D; or (vi) a method of treating a patient treated with an agent that increases the risk of hypocalcemia, where the method comprises administering to the patient an effective amount of said 25-hydroxyvitamin D to effectively and safely restore blood 25-hydroxyvitamin D levels to at least 30 ng/mL and to maintain blood 25-hydroxyvitamin D levels at such optimal levels. In one example, a method of treating or preventing iatrogenic hypocalcemia and/or secondary hyperparathyroidism in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D. In another example, a method of increasing bone mineral density in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D.

[0018] In another example, a method of decreasing the blood level of a bone resorption marker in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D. In another example, a method of treating bone pain in a patient treated with an agent that

increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D.

[0019] In another example, a method of increasing the time to the first post-treatment skeletal-related event in a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D. In another example, a method of treating a patient treated with an agent that increases the risk of hypocalcemia comprises administering to the patient an effective amount of 25-hydroxyvitamin D to effectively and safely restore blood 25-hydroxyvitamin D levels to at least 30 ng/mL and to maintain blood 25-hydroxyvitamin D levels at such optimal levels.

[0020] In any of the methods disclosed herein, the agent that increases the risk of hypocalcemia is optionally selected from the group consisting of an antiresorptive agent, an anti-convulsant agent, a corticosteroid, an anti-hypercalcemia agent, an antimicrobial agent, and combinations thereof. In one example, the agent that increases the risk of hypocalcemia is an antiresorptive agent, optionally selected from the group consisting of bisphosphonates (e.g., zoledronic acid, alendronate, risedronate, ibandronate, etidronate, and pamidronate), selective estrogen receptor modulators (e.g., raloxifene), calcitonin, hormones (e.g., estrogen), and monoclonal antibodies (e.g., denosumab).

[0021] In another aspect, a composition comprising 25-hydroxyvitamin D for use in a method of treatment of a patient, the method being: (i) a method of lowering elevated serum parathyroid hormone levels in a patient having a bone metastasis and being treated with an antiresorptive agent, where the method comprises administering an effective amount of said 25-hydroxyvitamin D; or (ii) a method of stabilizing serum calcium levels in a patient having a bone metastasis and being treated with an antiresorptive agent. In one example, a method of lowering elevated serum parathyroid hormone levels in a patient having a bone metastasis and treated with an antiresorptive agent comprises administering an effective amount of 25-hydroxyvitamin D. In another example, a method of

stabilizing serum calcium levels in a patient having a bone metastasis and treated with an antiresorptive agent comprises administering an effective amount of 25-hydroxyvitamin D. In still another example, a method of treating hungry bone syndrome comprises administering an effective amount of 25-hydroxyvitamin D to a patient in need of thereof.

[0022] In any of the methods of the present disclosure, the patient optionally has osteoporosis and/or cancer. In another example, there is provided a composition comprising 25-hydroxyvitamin D for use in a method of treatment of a patient, the method being: (i) a method of managing iatrogenic hypocalcemia and secondary hyperparathyroidism in a patient with a bone metastasis receiving therapy with an antiresorptive agent, where the method comprises administering an effective amount of said 25-hydroxyvitamin D to prevent or reverse iatrogenic hypocalcemia and lower the patient's serum parathyroid hormone level; or (ii) a method of inhibiting the proliferation and migration of cancer cells, where the method comprises administering an effective amount of said 25-hydroxyvitamin D to a patient in need thereof; or (iii) a method of mitigating the progression of cancer in the bone, where the method comprises administering an effective amount of said 25-hydroxyvitamin D to a patient; or (iv) a method of treating a patient having cancer and a bone metastasis, where the method comprises the administration of (a) a prophylactic and continuing course of an effective amount of said 25-hydroxyvitamin D to stabilize serum 25-hydroxyvitamin D levels and calcium levels in said patient without causing or exacerbating hypercalcemia, followed by (b) treatment with an agent known to increase the risk of iatrogenic hypocalcemia, wherein the treatment in step (a) prevents and/or treats said iatrogenic hypocalcemia in said patient; or (v) a method of treating cancer in a patient, where the method comprises administering to the patient an effective amount of a combination of said 25-hydroxyvitamin D and an anticancer agent; or (vi) a method of mitigating cancer progression and/or a skeletal related event in a patient with a bone metastasis from a solid tumor, where the method comprises treating said patient with (a) an anticancer agent; (b) an antiresorptive agent and (c) said 25-hydroxyvitamin D compound, wherein the combination of (a), (b), and (c) is effective to slow tumor growth and/or metastasis and increase the time to the first post-treatment skeletal-related event. In one example, a method of managing iatrogenic hypocalcemia and secondary hyperparathyroidism in a patient with a bone metastasis treated with an antiresorptive agent comprises administering an effective amount of 25-hydroxyvitamin D to prevent or reverse the iatrogenic hypocalcemia and lower the patient's

serum parathyroid hormone level. In another example, a method of mitigating cancer progression and/or a skeletal related event in a patient with a bone tumor, optionally a bone metastasis from a solid tumor, comprises treating the patient with (a) an anticancer agent; (b) an antiresorptive agent; and (c) a 25-hydroxyvitamin D compound, wherein the combination of (a), (b), and (c) is effective to slow tumor growth and/or metastasis and/or increase the time to the first post-treatment skeletal-related event. In still another example, a method of treating a patient having cancer and a bone metastasis comprises the administration of (a) a prophylactic and continuing course of an effective amount of 25-hydroxyvitamin D to stabilize 25-hydroxyvitamin D levels and calcium levels in the patient without causing or exacerbating hypercalcemia; followed by (b) treatment with an agent known to increase the risk of iatrogenic hypocalcemia, wherein the treatment in step (a) prevents and/or treats the iatrogenic hypocalcemia in the patient.

[0023] In another example, a method of mitigating the progression of cancer in the bone in a patient comprises administering an effective amount of 25-hydroxyivtamin D. In another aspectexample, a method of inhibiting the proliferation and migration of cancer cells comprises administering an effective amount of 25-hydroxyvitamin D to a patient in need thereof. In another example, a method of treating cancer in a patient comprises administering to the patient an effective amount of a combination of 25-hydroxyvitamin D and an anticancer agent. In any of the foregoing methods, the patient optionally has a cancer selected from the group consisting of bone cancer, bladder cancer, breast cancer, colon cancer, endometrial cancer, kidney cancer, leukemia, lung cancer, lymphoma, pancreatic cancer, prostate cancer, skin cancer, thyroid cancer, and metastatic forms thereof.

[0024] The present disclosure also relates to the use of 25-hydroxyvitamin D, optionally in a modified release formulation, as adjunctive therapy to treat hypocalcemia in a patient in need thereof. In one example, the disclosure provides a pharmaceutical composition comprising (a) 25-hydroxyvitamin D and (b) an agent that increases the risk of hypocalcemia and/or an anticancer agent. In another aspect, the disclosure provides a kit comprising (a) 25-hydroxyvitamin D; (b) an agent that increases the risk of hypocalcemia and/or an anticancer agent; and (c) instructions for co-administering effective amounts of (a) and (b) to a patient in need thereof.

[0025] In another example, a method according to the present disclosure comprises administering 25-hydroxyvitamin D in a modified release formulation, optionally an oral modified release formulation. In yet another aspect, there is provided a composition comprising 25-hydroxyvitamin D, optionally in a modified release formulation, for use in a method of treatment of a patient, the method being an adjunctive therapy to treat or prevent hypocalcemia in a patient in need thereof. In another example, the 25-hydroxyvitamin D is administered in a sterile intravenous formulation. In various examples, the 25-hydroxyvitamin D can be selected from the group consisting of 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, 25-hydroxyvitamin D_4, 25-hydroxyvitamin D_5, 25-hydroxyvitamin D_7 and combinations thereof.

[0026] For the compositions and methods described herein, optional features, including but not limited to components, compositional ranges thereof, substituents, conditions, and steps, are contemplated to be selected from the various aspects, embodiments, and examples provided herein.

[0027] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description, taken in conjunction with the drawings. While the compositions and methods are susceptible of embodiments in various forms, the description hereafter includes specific embodiments with the understanding that the disclosure is illustrative and is not intended to limit the invention to the specific embodiments described herein.

DETAILED DESCRIPTION

[0028] The present disclosure relates to 25-hydroxyvitamin D therapy as adjunctive therapy and in the treatment of cancer. In various embodiments, the disclosure provides methods for dosing a subject receiving treatment with an agent that increases the risk of hypocalcemia and/or an anticancer agent with an effective amount of 25-hydroxyvitamin D, optionally as a modified release oral formulation or administered in intravenous form. The

What is claimed is:

1. A composition comprising 25-hydroxyvitamin D for use in a method of treatment of a patient, the method being:

i. a method of treating or preventing iatrogenic hypocalcemia and secondary hyperparathyroidism in a patient treated with an agent that increases the risk of hypocalcemia, where the method comprises administering to the patient an effective amount of said 25-hydroxyvitamin D; or

ii. a method of increasing bone mineral density in a patient treated with an agent that increases the risk of hypocalcemia, where the method comprises administering to the patient an effective amount of said 25-hydroxyvitamin D; or

iii. a method of decreasing the blood level of a bone resorption marker in a patient treated with an agent that increases the risk of hypocalcemia, where the method comprises administering to the patient an effective amount of said 25-hydroxyvitamin D; or

iv. a method of treating bone pain in a patient treated with an agent that increases the risk of hypocalcemia, where the method comprises administering to the patient an effective amount of said 25-hydroxyvitamin D; or

v. a method of increasing the time to the first post-treatment skeletal-related event in a patient treated with an agent that increases the risk of hypocalcemia, where the method comprises administering to the patient an effective amount of said 25-hydroxyvitamin D; or

vi. a method of treating a patient treated with an agent that increases the risk of hypocalcemia, where the method comprises administering to the patient an effective amount of said 25-hydroxyvitamin D to effectively and safely restore blood 25-hydroxyvitamin D levels to at least 30 ng/mL and to maintain blood 25-hydroxyvitamin D levels at such optimal levels.

2. The composition for use of any one of the preceding claims, wherein the patient treated with an agent that increases the risk of hypocalcemia is receiving or has previously received treatment with an agent that increases the risk of hypocalcemia.

3. The composition for use of any one of the preceding claims, wherein the agent that increases the risk of hypocalcemia is selected from the group consisting of antiresorptive agents, anticonvulsant agents, corticosteroids, antihypercalcemia agents, antimicrobial agents, and combinations thereof

4. The composition for use of any one of the preceding claims, wherein the agent that increases the risk of hypocalcemia is an antihypercalcemia agent, optionally the anti-hypercalcemia agent cinacalcet.

5. The composition for use of claim 9 or 10, wherein the 25-hydroxyvitamin D is administered following administration of the antihypercalcemia agent.

6. The composition for use of any one of claims 1-9, wherein the agent that increases the risk of hypocalcemia is an antiresorptive agent.

7. A composition comprising 25-hydroxyvitamin D for use in a method of treatment of a patient, the method being:

i. a method of lowering elevated serum parathyroid hormone levels in a patient having a bone metastasis and being treated with an antiresorptive agent, where the method comprises administering an effective amount of said 25-hydroxyvitamin D; or

ii. a method of stabilizing serum calcium levels in a patient having a bone metastasis and being treated with an antiresorptive agent.

8. The composition for use of claim 6 or 7 , wherein the antiresorptive agent is selected from the group consisting of bisphosphonates, selective estrogen receptor modulators, calcitonin, hormones, monoclonal antibodies, and combinations thereof

9. The composition for use of claim 6 or 7 or 8, wherein the antiresorptive agent comprises a RANKL inhibitor, optionally the RANKL inhibitor denosumab.

10. The composition for use of claim 6 or 7 or 8, wherein the antiresorptive agent comprises a bisphosphonate, optionally the bisphosphonate zoledronic acid.

11. A composition comprising 25-hydroxyvitamin D for use in a method of treatment of a patient, the method being a method of treating hungry bone syndrome, where

the method comprises administering an effective amount of said 25-hydroxyvitamin D to a patient in need of thereof.

12. The composition for use of any one of the preceding claims, wherein the patient has osteoporosis.

13. The composition for use of any one of the preceding claims, wherein the patient has cancer.

14. A composition comprising 25-hydroxyvitamin D for use in a method of treatment of a patient, the method being:

i. a method of managing iatrogenic hypocalcemia and secondary hyperparathyroidism in a patient with a bone metastasis receiving therapy with an antiresorptive agent, where the method comprises administering an effective amount of said 25-hydroxyvitamin D to prevent or reverse iatrogenic hypocalcemia and lower the patient's serum parathyroid hormone level; or

ii. a method of inhibiting the proliferation and migration of cancer cells, where the method comprises administering an effective amount of said 25-hydroxyvitamin D to a patient in need thereof; or

iii. a method of mitigating the progression of cancer in the bone, where the method comprises administering an effective amount of said 25-hydroxyvitamin D to a patient; or

iv. a method of treating a patient having cancer and a bone metastasis, where the method comprises the administration of (a) a prophylactic and continuing course of an effective amount of said 25-hydroxyvitamin D to stabilize serum 25-hydroxyvitamin D levels and calcium levels in said patient without causing or exacerbating hypercalcemia, followed by (b) treatment with an agent known to increase the risk of iatrogenic hypocalcemia, wherein the treatment in step (a) prevents and/or treats said iatrogenic hypocalcemia in said patient; or

v. a method of treating cancer in a patient, where the method comprises administering to the patient an effective amount of a combination of said 25-hydroxyvitamin D and an anticancer agent; or

vi. a method of mitigating cancer progression and/or a skeletal related event in a patient with a bone metastasis from a solid tumor, where the method comprises treating said patient with (a) an anticancer agent; (b) an antiresorptive agent and (c) said 25-hydroxyvitamin D compound, wherein the combination of (a), (b), and (c) is effective to slow tumor growth and/or metastasis and increase the time to the first post-treatment skeletal-related event.

15. The composition for use of claim 14, option v or vi, wherein the anticancer agent is selected from the group consisting of azacitidine, axathioprine, bevacizumab, bleomycin, capecitabine, carboplatin, chlorabucil, cisplatin, cyclophosphamide, cytarabine, daunorubicin, docetaxel, doxifluridine, doxorubicin, epirubicin, etoposide, fluorouracil, gemcitabine, herceptin, idarubicin, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, tafluposide, teniposide, tioguanine, retinoic acid, valrubicin, vinblastine, vincristine, vindesine, vinorelbine, receptor tyrosine kinase inhibitors, and combinations thereof.

16. The composition for use of claim 13 or 14, wherein the cancer is selected from the group consisting of bone cancer, bladder cancer, breast cancer, colon cancer, endometrial cancer, kidney cancer, leukemia, lung cancer, lymphoma, pancreatic cancer, prostate cancer, skin cancer, thyroid cancer, and metastatic forms thereof.

17. The composition for use of any one of the preceding claims, wherein the patient has a metastatic bone cancer, metastatic prostate cancer, metastatic lung cancer, and/or metastatic breast cancer.

18. The composition for use of any one of the preceding claims, wherein the patient has a bone tumor, optionally a bone metastasis from a solid tumor.

19. The composition for use of any one of the preceding claims, wherein the patient has impaired renal function, optionally associated with Chronic Kidney Disease Stage 1, 2, 3, 4, or 5.

20. The composition for use of any one of the preceding claims, wherein the effective amount of 25-hydroxyvitamin D is effective to restore or maintain the patient's serum calcium level to at least about 8.0 mg/dL, optionally in a range of about 8.3 mg/dL to about 11.6 mg/dL.

21. The composition for use of any one of the preceding claims, wherein the effective amount of 25-hydroxyvitamin D is effective to safely increase the patient's serum level of 25-hydroxyvitamin D to at least 30 ng/mL, optionally in a range of about 30 ng/mL to about 100 ng/mL.

22. The composition for use of any one of the preceding claims, wherein the effective amount of 25-hydroxyvitamin D is effective to decrease the patient's serum parathyroid hormone level, optionally by 30% or more.

23. The composition for use of any one of the preceding claims, wherein the effective amount of 25-hydroxyvitamin D is effective to decrease the patient's serum parathyroid hormone related peptide levels.

24. The composition for use of any one of the preceding claims, wherein the effective amount of 25-hydroxyvitamin D is effective to safely increase the patient's serum level of 1,25-dihydroxyvitamin D to above the normal range, optionally at least to 50 pg/mL.

25. The composition for use of any one of the preceding claims, wherein the effective amount of 25-hydroxyvitamin D is effective to achieve or maintain safe serum phosphorus levels and treat or prevent hypophosphatemia.

26. The composition for use of any one of the preceding claims, wherein the effective amount of 25-hydroxyvitamin D is effective to have a positive effect on the patient's serum level of a marker of bone formation by more than what is accomplished with treatment with the antiresorptive agent alone.

27. The composition for use of any one of the preceding claims, wherein the effective amount of 25-hydroxyvitamin D is effective to decrease the patient's serum level of a marker of bone resorption, optionally by at least 20%.

28. The composition for use of claim 27, wherein the marker of bone resorption is selected from the group consisting of PTHrP, FGF23, NTX, CTX, TRAC-5b, and combinations thereof.

29. The composition for use of any one of the preceding claims, wherein the effective amount of 25-hydroxyvitamin D is effective to maintain or decrease the patient's tumor burden.

30. The composition for use of claim 29, wherein the effective amount of 25-hydroxyvitamin D is effective to maintain or decrease the patient's serum level of a marker of tumor burden.

31. The composition for use of claim 30, wherein the marker of tumor burden is selected from the group consisting of CEA, CA 125, CA15-3, CA 27-29, prostate specific antigen (PSA), and combinations thereof.

32. The composition for use of any one of the preceding claims, wherein the effective amount of 25-hydroxyvitamin D is effective to inhibit the proliferation and/or migration of cancer cells.

33. The composition for use of any one of the preceding claims, wherein the 25-hydroxyvitamin D is administered in a modified release formulation.

34. The composition for use of claim 33, wherein the modified release formulation is selected from the group consisting of a sustained release formulation, a delayed release formulation, and a delayed, sustained release formulation.

35. The composition for use of claim 33 or 34, wherein the modified release formulation comprises a waxy formulation.

36. The composition for use of any one of claims 33-35 wherein the modified release formulation consists essentially of about 20 wt% paraffin, about 20 wt% to about 25 wt% glycerol monostearate, about 10 wt% a mixture of lauroyl macrogolglycerides and lauroyl polyoxylglycerides, about 30 wt% to about 35 wt% mineral oil, and about 10 wt% to about 15 wt% hydroxyl propyl methylcellulose.

37. The composition for use of any one of the preceding claims, wherein the effective amount of 25-hydroxyvitamin D is administered in an oral sustained release formulation.

38. The composition for use of any one of the preceding claims, wherein the 25-hydroxyvitamin D is administered in the form of a capsule.

39. The composition for use of any one of the preceding claims, wherein the effective amount of 25-hydroxyvitamin D is absorbed primarily in the ileum and/or colon of the patient.

40. The composition for use of any one of claims 1-32, wherein the 25-hydroxyvitamin D is administered in an oral immediate release formulation in multiple daily doses in order to produce a pharmacokinetic profile of serum 25-hydroxyvitamin D that is similar to that achieved by an oral modified or sustained release formulation.

41. The composition for use of any one of claims 1-34, wherein the 25-hydroxyvitamin D is administered in a sterile intravenous formulation.

42. The composition for use of claim 41, wherein the 25-hydroxyvitamin D is administered in an intravenous bolus.

43. The composition for use of claim 42, wherein the 25-hydroxyvitamin D is infused over a course of at least 1 hour.

44. The composition for use of any one of the preceding claims, wherein the 25-hydroxyvitamin D is selected from the group consisting of 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, 25-hydroxyvitamin D_4, 25-hydroxyvitamin D_5, 25-hydroxyvitamin D_7 and combinations thereof.

45. The composition for use of any one of the preceding claims, wherein the 25-hydroxyvitamin D comprises 25-hydroxyvitamin D_3 and/or 25-hydroxyvitamin D_2.

46. The composition for use of any one of the preceding claims, wherein the 25-hydroxyvitamin D comprises 25-hydroxyvitamin D_3.

47. The composition for use of any of the preceding claims, wherein the 25-hydroxyvitamin D is administered in a dosage of 30 μg to 300 μg per day.

48. A composition comprising 25-hydroxyvitamin D, optionally in a modified release formulation, for use in a method of treatment of a patient, the method being an adjunctive therapy to treat or prevent hypocalcemia in a patient in need thereof.

49. A pharmaceutical composition comprising (a) 25-hydroxyvitamin D and (b) an agent that increases the risk of hypocalcemia and/or an anticancer agent.

50. A kit comprising (a) 25-hydroxyvitamin D, (b) an agent that increases the risk of hypocalcemia and/or an anticancer agent, and (c) instructions for co-administering effective amounts of (a) and (b) to a patient in need thereof.