Can patients with a history of radiation therapy use FORTEO® (teriparatide injection)?

Please refer to the citations provided at the end of the document for a more in-depth review of radiation and the risk of osteosarcoma.

INTRODUCTION

Radiation-induced osteosarcoma is a rare but well-recognized complication in human radiotherapy patients that was first reported in patients after treatment with ionizing radiation in the 1920s.[1]

The skeletal effects from irradiation depend on a number of variables, including the

- character of the radiation
- dose rate and accumulated dose
- time of exposure
- radiation exposure (acute or continuous), and
- character of the irradiated tissues.[1]

In most radiotherapy protocols, high doses of therapeutic radiation are directed at the tumor tissue. Other tissues, including the skeleton and likely the entire body, can be exposed to comparatively low doses of unwanted radiation via scattering of radiation within the body and low level leakage from the treatment apparatus.[2]

Development of second malignant neoplasms (SMNs), including osteosarcoma, in tissues that are located in-field (in the path of the therapeutic beam) and out-of-field (outside the path of the therapeutic beam but affected by scatter) can occur years or decades after initial treatment.[1,2]

While advances in radiobiology have led to the availability of high-energy beams of photons, protons, and carbon ions that may better spare normal tissues from acute radiation toxicity, these more recent therapies have also resulted in reports of SMNs, including osteosarcoma.[2-5]

According to the US prescribing information, use of teriparatide should be avoided in patients with increased risk of osteosarcoma, including those who have had prior external beam or implant radiation therapy involving the skeleton.[6]

Eli Lilly and Company (Lilly) provides the following information to clarify “prior radiation therapy involving the skeleton” and relevant citations are included for reference.

PRIOR RADIATION THERAPY WHERE TERIPARATIDE SHOULD NOT BE USED

Teriparatide should not be used if patient had exposure to

- therapeutic external beam radiation, including
  - radiation therapy for a soft tissue malignancy, such as breast cancer (such patients likely have experienced radiation affecting the skeleton around the breast [the sternum or ribs])[7,8]
- any type of radiation implanted into the body, including

    - brachytherapy
    - interstitial radiation
    - intracavitary radiation,[7,9] or
- stereotactic radiation to the brain or other areas of the body, including
    - stereotactic radiosurgery
    - fractionated stereotactic radiotherapy
    - stereotactic body radiation therapy
    - Gamma Knife®
    - X-Knife®
    - CyberKnife®
    - Clinac®.[7,10]

Case reports of SMNs, including osteosarcoma, have been reported in patients receiving these therapies.[3-5]

PRIOR RADIATION THERAPY WHERE TERIPARATIDE MAY BE CONSIDERED

Teriparatide use may be considered in patients who had

- radioactive iodine therapy
- low doses of nonpenetrative radiation (Grenz radiation) used for treatment of skin conditions
- diagnostic radiation, including
    - radiographs
    - computed tomography (CT) scans
    - radionuclide scans, or
- non-radioactive forms of radiation, including
    - ultraviolet radiation
    - phototherapy.[7]

INFORMATION ON THE USE OF RADIATION DURING OR AFTER TERIPARATIDE THERAPY

If a patient is receiving teriparatide and develops a need for radiation therapy, Lilly advises that the teriparatide treatment be discontinued immediately or prior to radiation therapy.

There are no studies to describe the effect of teriparatide exposure on subsequent risk of osteosarcoma in patients that have radiation therapy after teriparatide exposure.

Case Series on Teriparatide Use in Patients With a History of Radiation Therapy

Cheung et al identified patients treated with teriparatide at their institution between January 2010 and 2021 despite having a history of radiotherapy. Patients who had received radiation

therapy after completion of teriparatide treatment were excluded. The aim of the analysis was to explore the practice regarding radiotherapy and teriparatide use at the institution.[11]

Among the 6 patients (4 female, 2 male) included in the final case series,

- mean age at the time of starting teriparatide was 65 (range 38-84) years
- all had severe and complex osteoporosis (risk factors for osteoporosis: former smokers, 2; history of glucocorticoid use, 4; family history of osteoporosis, 3; premature menopause, 2; high fall risk, 3)
- 5 had a history of multiple fragility fractures (≥2), and
- 4 had tried one or more types of bisphosphonates, while 2 were treatment-naïve.[11]

The radiotherapy regimens and indications for the same included

- 3060 cGy at the lumbar spine for B-cell lymphoma
- 750 cGy at the right hip as prophylaxis for hip heterotopic ossification surgery
- whole-body irradiation of unknown dose for acute lymphoid leukemia (ALL) allogeneic transplant
- 7920 cGy at the prostate bed and pelvis for prostate cancer
- 4990 cGy at the left breast for ductal carcinoma in situ of the breast, and
- 5500 cGy at the right shin for squamous cell carcinoma of the skin.[11]

Among the 3 patients who had received radiotherapy prior to teriparatide commencement,

- in 2 cases, teriparatide had been commenced and was administered for 2 years as its potential benefits were believed to outweigh the potential osteosarcoma risk, and
- in 1 case, it was not known whether the osteosarcoma risk had been discussed between the endocrinologist and patient before starting treatment, but teriparatide was stopped after 3 months because of concerns regarding the patient's prior radiation history.[11]

The time duration between completion of radiotherapy and commencement of teriparatide was 5 and 15 months in the first 2 cases and 12 years in the third case.[11]

The remaining 3 patients started radiotherapy during the course of teriparatide treatment. Two of them received teriparatide throughout their radiotherapy as their endocrinologist was not aware of the radiotherapy, whereas in 1 case, teriparatide was stopped early upon the endocrinologist's recommendation because of the increased risk of osteosarcoma.[11]

The median duration of follow-up was

- 3.8 (range, 2.6-4.7) years after commencement of teriparatide, and
- 3.6 (range, 1.8-4.9) years after the last radiotherapy treatment.[11]

No significant adverse events or cases of osteosarcoma were reported during the follow-up period. Patients completing 2 years of teriparatide experienced increases in bone mineral density and did not incur any further fragility fractures during the follow-up.[11]

The findings of this study must be interpreted with caution. Although the incidence of second cancers after radiotherapy alone tends to increase with time, it is unclear how long it typically takes for osteosarcoma to develop after combination radiotherapy/teriparatide. Hence, no definitive conclusions can be derived regarding the safety of teriparatide use during/after radiotherapy from this study. In addition, the follow-up duration was too short to derive any meaningful estimates of fracture incidence in this small cohort. Finally, patients with bone metastases and bone marrow malignancies are a unique population, and this study did not investigate the risks and considerations associated with this subset of patients.[11]

Last Reviewed: 16-August-2022

ENCLOSED PRESCRIBING INFORMATION

FORTEO® (teriparatide injection), Lilly

REFERENCES

The published references below are available by contacting 1-800-LillyRx (1-800-545-5979).

1. Kalra S, Grimer RJ, Spooner D, et al. Radiation-induced sarcomas of bone: factors that affect outcome. *J Bone Joint Surg Br.* 2007;89-B(6):808-813. http://dx.doi.org/10.1302/0301-620X.89B6.18729

2. Newhauser WD, Durante M. Assessing the risk of second malignancies after modern radiotherapy. *Nat Rev Cancer*. 2011;11(6):438-448. http://dx.doi.org/10.1038/nrc3069

3. Sanno N, Hayashi S, Shimura T, et al. Intracranial osteosarcoma after radiosurgery. *Neurol Med Chir (Tokyo)*. 2004;44(1):29-32. http://dx.doi.org/10.2176/nmc.44.29

4. Abedalthagafi M, Bakhshwin A. Radiation-induced glioma following CyberKnife® treatment of metastatic renal cell carcinoma: a case report. *J Med Case Rep*. 2012;6:271. http://dx.doi.org/10.1186/1752-1947-6-271

5. Balasubramaniam A, Shannon P, Hodaie M, et al. Glioblastoma multiforme after stereotactic radiotherapy for acoustic neuroma: case report and review of the literature. *Neuro Oncology*. 2007;9(4):447-453. http://dx.doi.org/10.1215/15228517-2007-027

6. Forteo [package insert]. Indianapolis, IN: Eli Lilly and Company; 2021.

7. Data on file, Eli Lilly and Company and/or one of its subsidiaries.

8. Benveniste MF, Gomez D, Carter BW, et al. Recognizing radiation therapy-related complications in the chest. *Radiographics* 2019;39(2):344-366. https://doi.org/10.1148/rg.2019180061

9. Getting internal radiation therapy (brachytherapy). American Cancer Society. Accessed August 16, 2022. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/radiation/internal-radiation-therapy-brachytherapy.html

10. Getting external beam radiation therapy. American Cancer Society. Accessed August 16, 2022. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/radiation/external-beam-radiation-therapy.html

11. Cheung YM, Hamnvik OR. Teriparatide in individuals with a prior history of radiation therapy-a case series. *Arch Osteoporos*. 2021;16(1):149. https://doi.org/10.1007/s11657-021-01007-3

PUBLICATIONS DISCUSSING THE USE OF TERIPARATIDE AFTER RADIATION THERAPY

Porcelli T, Sessa F, Caputo A, et al. Teriparatide replacement therapy for hypoparathyroidism during treatment with lenvatinib for advanced thyroid cancer: a case report. *Endocrinol.* 2018;9(244). http://dx.doi.org/10.3389/fendo.2018.00244

THE FOLLOWING CITATIONS ARE PROVIDED FOR A MORE IN-DEPTH REVIEW OF RADIATION AND THE RISK OF OSTEOSARCOMA

Bartlett H, Elghobashy M, Deshmukh N, et al. Radiation-associated primary osteosarcoma of the breast. *Pathobiology*. 2020;87(5):322-326. https://doi.org/10.1159/000509580

Brady MS, Gaynor JJ, Brennan MF. Radiation-associated sarcoma of bone and soft tissue. *Arch Surg*. 1992;127(12):1379-1385. https://doi.org/10.1001/archsurg.1992.01420120013002

Chabchoub I, Gharbi O, Remadi S, et al. Postirradiation osteosarcoma of the maxilla: a case report and current review of literature. *J Oncol.* 2009. http://dx.doi.org/10.1155/2009/876138

de Souza LL, Pontes HAR, Santos-Silva AR, et al. Oral radiation-induced sarcomas: systematic review. *Head Neck*. 2020;42(9):2660-2668. https://doi.org/10.1002/hed.26176

Dray MS, Miller MV. Paget's osteosarcoma and post-radiation osteosarcoma: secondary osteosarcoma at Middlemore Hospital, New Zealand. *Pathology*. 2008;40(6):604-610. http://dx.doi.org/https://doi.org/10.1080/00313020802320663

Fang Z, Matsumoto S, Ae K, et al. Postradiation soft tissue sarcoma: a multiinstitutional analysis of 14 cases in Japan. *J Orthop Sci*. 2004;9(3):242-246. https://doi.org/10.1007/s00776-004-0768-5

Franco Gutierrez V, Llorente Pendas JL, Coca Pelaz A, et al. Radiation-induced sarcomas of the head and neck. *J Craniofac Surg*. 2008;19(5):1287-1291. https://doi.org/10.1097/SCS.0b013e3181869df1

Gössner W. Pathology of radiation-induced bone tumors. *Leuk Res*. 1986;10(7):897-901. https://doi.org/10.1016/0145-2126(86)90321-8

Huvos AG, Woodard HQ, Cahan WG, et al. Postradiation osteogenic sarcoma of bone and soft tissues: a clinicopathologic study of 66 patients. *Cancer.* 1985;55(6):1244-1255. http://dx.doi.org/10.1002/1097-0142(19850315)55:6<1244::Aid-cncr2820550617>3.0.Co;2-1

Janowski M, Cox R, Strauss PG. The molecular biology of radiation-induced carcinogenesis: thymic lymphoma, myeloid leukaemia and osteosarcoma. *Int J Radiat Biol*. 1990;57(4):677-691. http://dx.doi.org/10.1080/09553009014550851

Kappel AD, Bernstock JD, Ditoro DF, Lu Y. Radiation-induced intracranial osteosarcoma of the anterior skull base after treatment of esthesioneuroblastoma. *BMJ Case Rep*. 2021;14(1):e238928. https://doi.org/10.1136/bcr-2020-238928

Koshurnikova NA, Gilbert ES, Sokolnikov M, et al. Bone cancers in Mayak workers. *Radiat Res*. 2000;154(3):237-245. https://doi.org/10.1667/0033-7587(2000)154[0237:BCIMW]2.0.CO;2

Longhi A, Barbieri E, Fabbri N, et al. Radiation-induced osteosarcoma arising 20 years after the treatment of Ewing's sarcoma. *Tumori*. 2003;89(5):569-572. http://www.ncbi.nlm.nih.gov/pubmed/14870790

Lorigan JG, Libshitz HI, Peuchot M. Radiation-induced sarcoma of bone: CT findings in 19 cases. *Am J Roentgenol*. 1989;153(4):791-794. http://www.ajronline.org/doi/pdf/10.2214/ajr.153.4.791

Maruyama A, Yasuoka S, Katoh N, Asai J. Radiation-induced osteosarcoma of the skull mimicking cutaneous tumor after treatment for frontal glioma. *J Dermatol*. 2020;47(1):69-71. https://doi.org/10.1111/1346-8138.15125

Morris B, Williams W, Shuttleworth GN. Osteosarcoma after external beam radiation therapy for recurrent choroidal melanoma. *Ophthal Plast Reconstr Surg*. 2006;22(4):301-302. http://dx.doi.org/10.1097/01.iop.0000225423.00759.26

Noh JM, Huh SJ. Two cases of post-radiation osteosarcoma of the sacrum after pelvic irradiation for uterine cervical cancer. *Eur J Gynaecol Oncol.* 2007;28(6):497-500. http://www.ncbi.nlm.nih.gov/pubmed/18179145

Ozisik YY, Meloni AM, Zalupski MM, et al. Deletion of chromosome 13 in osteosarcoma secondary to irradiation. *Cancer Genet Cytogenet.* 1993;69(1):35-37. http://dx.doi.org/10.1016/0165-4608(93)90109-Y

Palm A, Johansson KA. A review of the impact of photon and proton external beam radiotherapy treatment modalities on the dose distribution in field and out-of-field; implications for the long-term morbidity of cancer survivors. *Acta Oncologica*. 2007;46(4):462-473. http://dx.doi.org/10.1080/02841860701218626

Palmerini E, Ferrari S, Bertoni F, Bacci G. Prognosis of radiation-induced sarcoma is similar to primary osteosarcoma [letter to the editor]. *Clin Orthop Relat Res.* 2007;462:255-256. http://dx.doi.org/10.1097/BLO.0b013e31813c1015

Powers BE, Gillette EL, McChesney SL, et al. Bone necrosis and tumor induction following experimental intraoperative irradiation. *Int J Radiat Oncol Biol Phys.* 1989;17(3):559-567. http://dx.doi.org/10.1016/0360-3016(89)90107-7

Pritchard DJ, Finkel MP, Reilly CA Jr. The etiology of osteosarcoma. a review of current considerations. *Clin Orthop Relat Res.* 1975;111:14-22. http://dx.doi.org/10.1097/00003086-197509000-00003

Rupp B, Lorenz U, Schmidt J, Werenskiold AK. Discordant effects of activator protein-1 transcription factor on gene regulation, invasion, and metastasis in spontaneous, radiation-

induced, and fos-induced osteosarcomas. *Mol Carcinog*. 1998;23(2):69-75. http://dx.doi.org/10.1002/(SICI)1098-2744(199810)23:2%3C69::AID-MC3%3E3.0.CO;2-E

Scheuermann A, Phelan R, Browning M. Development of secondary osteosarcoma after TBI and allogeneic bone marrow transplant: a case series of 3 patients. *J Pediatr Hematol Oncol*. 2020;42(2):e100-e103. https://doi.org/10.1097/MPH.0000000000001442

Schneider U, Lomax A, Hauser B, Kaser-Hotz B. Is the risk for secondary cancers after proton therapy enhanced distal to the planning target volume? A two-case report with possible explanations. *Radiat Environ Biophys*. 2006;45(1):39-43. http://dx.doi.org/10.1007/s00411-006-0034-7

Sheppard DG, Libshitz HI. Post-radiation sarcomas: a review of the clinical and imaging features in 63 cases. *Clin Radiol.* 2001;56(1):22-29. http://dx.doi.org/10.1053/crad.2000.0599

Stather JW. Effects of alpha-particle irradiation on carcinogenesis. *Int J Radiat Biol.* 1990;58(5):871-874. https://www.ncbi.nlm.nih.gov/pubmed/1977832

Subbiah V, Madsen VS, Raymond AK, et al. Of mice and men: divergent risks of teriparatide-induced osteosarcoma. *Osteoporos Int.* 2010;21(6):1041-1045. http://dx.doi.org/10.1007/s00198-009-1004-0

Taghian A, de Vathaire F, Terrier P, et al. Long-term risk of sarcoma following radiation treatment for breast cancer. *Int J Radiat Oncol Biol Phys.* 1991;21(2):361-367. http://dx.doi.org/10.1016/0360-3016(91)90783-Z

Thompson MA. Maintaining a proper perspective of risk associated with radiation exposure. *J Nucl Med Technol.* 2001;29(3):137-142. http://tech.snmjournals.org/cgi/content/full/29/3/137

Verma RK, Ahlawat S, Patir R, Gupta RK. Radiation-induced osteosarcoma of the calvarium in a patient of left frontal oligodendroglioma following surgery and radiotherapy. *Neurol India*. 2019;67(3):869-870. https://pubmed.ncbi.nlm.nih.gov/31347570/

Virtanen A, Pukkala E, Auvinen A. Incidence of bone and soft tissue sarcoma after radiotherapy: a cohort study of 295,712 Finnish cancer patients. *Int J Cancer.* 2006;118(4):1017-1021. http://dx.doi.org/10.1002/ijc.21456

Watanabe T, Fuse T, Umezu M, et al. Radiation-induced osteosarcoma 16 years after surgery and radiation for glioma--case report. *Neurol Med Chir (Tokyo).* 2006;46(1):51-54. http://dx.doi.org/10.2176/nmc.46.51

Yalow R. Editorial: The contributions of 131I to the understanding of radiation carcinogenesis. *Endocrinology.* 1990;126(4):1787-1789. http://dx.doi.org/10.1210/endo-126-4-1787