Welcome!

FLS Bone Health ECHO® TeleECHO Clinic

We will be recording this TeleECHO Clinic for educational and quality improvement purposes.

By participating in this clinic you are consenting to be recorded.

If you do not wish to be recorded, please email andrea.medeiros@nof.org at least one week prior to the TeleECHO Clinic you wish to attend.

Please type in your name, location, and email address in the chat.

Clinic will start in less than 15 minutes

Some helpful tips:

Please mute your microphone when not speaking

Position webcam effectively

Communicate clearly during clinic:

- Speak clearly
- Use chat function

Project ECHO's goal is to protect patient privacy

To help Project ECHO accomplish that goal, please only display or say information that doesn't identify a patient or that cannot be linked to a patient.

References:

For a complete list of protected information under HIPAA, please visit www.hipaa.com

Common HIPAA Identifier Slip-Ups and Easy Ways to Protect Patient Privacy

1st – **Names:** Please do not refer to a patient's *first/middle/last name* or use any *initials*, etc. Instead please use the *ECHO ID*.

2nd – **Locations:** Please do not identify a patient's *county, city or town*. Instead please use only the patient's *state* if you must or the *ECHO ID*.

3rd – **Dates:** Please do not use any dates (like *birthdates*, etc.) that are linked to a patient. Instead please use only the patient's *age* (unless > 89)

4th – **Employment:** Please do not identify a patient's *employer*, work *location* or *occupation*. Instead please use the *ECHO ID*.

5th – **Other Common Identifiers:** Do not identify patient's *family* members, *friends, co-workers, numbers, e-mails*, etc.

NOF Staff Disclosures

Andrea P. Medeiros, Director, Programs, Policy & Membership: Nothing to Disclose

Ami Patel, Director, Professional Education and Medical Affairs: Nothing to Disclose

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Wake Forest™
Baptist Medical Center

Post Radiation and Use of Anabolic Therapy for Treatment of Osteoporosis

Doris Brown, MD, PhD

Wake Forest Baptist Health

Disclosures

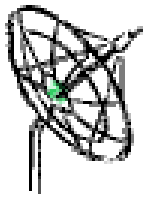
- I have no financial relationships to disclose
- I will be discussing a therapy for an indication for which there is a black box warning

Objectives

- List the types of radiation used in clinical treatment
- Recognize the important factors in late effects of cancer treatment
- Recall the effects of radiation on bone health
- Discuss risks and benefits of therapy for treatment of Osteoporosis in the patient that has undergone radiation treatment

What is Radiation?

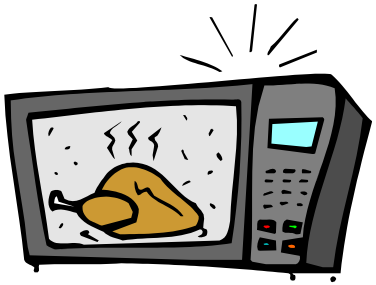
- **Energetic waves or particles traveling through air, water, space, tissue, etc.**
- **Heat and visible light are the only forms of radiation that humans sense**
- **We are all familiar with these everyday examples of non-ionizing radiation:**



Radar

TV

Radio



Microwave

Sun

What is Radiation Therapy?

- Use of ***IONIZING*** radiation in waves (photon) or particles (electrons, neutrons or protons) to kill cancer cells
- Target is the nuclear DNA—with the goal to cause double stranded DNA breaks
- Radiation injury is not specific to cancer cells, leading to acute and chronic effects on surrounding normal tissues

Types of Radiation

- Alpha & Beta Emission (Nuclear Medicine)
- Photons
  - Orthovoltage
  - Natural gamma rays
  - High energy x-rays (Clinical Accelerators)
- Particles
  - Electrons
  - Protons, Neutrons, Carbon Ions

Methods of Radiation Delivery

- Radiation dose is reported in Gray (Gy)
- Photon Radiation can be delivered two main ways:

Teletherapy

At A Large Distance

Given Outside → In

- Conformal (3D)
- IMRT

Brachytherapy

At a Short Distance

Given Inside → Out

- LDR (seeds)
- HDR (single source)

Late Effects

- A good resource for late effects of cancer treatment can be found here:

  http://www.cancer.gov/cancertopics/pdq/treatment/lateeffects/HealthProfessional/page1

Important Factors for Late Effects

- Tumor-Related Factors
- Treatment Related Factors
- Patient Related Factors

Important Factors for Late Effects

- Tumor-Related Factors
  - Type of Cancer
  - Where the tumor is in body
  - How the tumor affects the organ function
- Treatment Related Factors
- Patient Related Factors

Important Factors for Late Effects

- Tumor-Related Factors
- Treatment Related Factors
  - Type of surgery
  - Chemotherapy
  - RT location & dose
  - Transplant
  - Transfusion
- Patient Related Factors

Important Factors for Late Effects

- Tumor-Related Factors
- Treatment Related Factors
- Patient Related Factors:
  - Gender, age at diagnosis & treatment
  - Genetics (predispositions)
  - Environmental exposures
  - Family history
  - Health problems

Radiation and Bone Health

- High doses of radiation (>70 Gy) can directly result in osteoradiation necrosis (ORN)
- Microvascular Occlusion in bone can lead to avascular necrosis
- Lower doses of radiation can result in insufficiency fractures, the mechanism is unknown
- Up to 30% of patients treated in the pelvis can develop fracture by 5 years post treatment

Radiation and Bone Health

- Radiation increases the number and activity of osteoclasts resulting in bone loss during and shortly after treatment
- Radiation causes persistent damage to osteoblasts decreasing new bone formation
- Use of anti-reabsorptive therapies during treatment has not been demonstrated yet to prevent or delay radiation bone loss

Treatment options for Radiation Associated Bone Loss

- Calcium and Vitamin D
- Anti-Reabsorptive Agents
  - Bisphosphonates
  - RANK-ligand inhibitor
  - Calcitonin
  - Selective estrogen receptor modulators

Treatment options for Radiation Associated Bone Loss

- Anabolic Agents
  - Parathyroid Hormone Analog
  - Parathyroid Hormone-Related Protein Analog
  - Humanized monoclonal antibody against Sclerostin

Anabolic Agents and Risk of Osteosarcoma: Teriparatide and Abaloparatide

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe Forteo® only for patients for whom the potential benefits are considered to outweigh the potential risk. Forteo should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton) *[see Warnings and Precautions (5.1), Adverse Reactions (6.2), and Nonclinical Toxicology (13.1)]*.

Anabolic Agents and Risk of Osteosarcoma: Teriparatide and Abaloparatide

WARNING: RISK OF OSTEOSARCOMA

See full prescribing information for complete boxed warning.

- **Abaloparatide caused a dose-dependent increase in the incidence of osteosarcoma, a malignant bone tumor, in male and female rats. It is unknown whether TYMLOS will cause osteosarcoma in humans. (5 1, 13.1)**
- **Use of TYMLOS is not recommended in patients at increased risk for osteosarcoma. (5.1)**
- **Cumulative use of TYMLOS and parathyroid hormone analogs (e.g., teriparatide) for more than 2 years during a patient's lifetime is not recommended. (5.1)**

Anabolic Agents for Cancer Patients

- Are not indicated for patients with known bone metastases or known osteosarcoma (denosumab or Zolendronic Acid are preferred)
- Are useful for patients with therapy associated bone loss (e.g., anti-hormonal therapy)
- *Should be used with caution in patients that have previously received radiation?*

Anabolic Agent Use for Bone Loss

- Stimulates new bone formation and increases bone mass and strength
- For patients with severe osteoporosis or treatment related ORN or fracture, it is often the final option when other modalities have failed
- The effects of anabolic agents in radiation associated bone loss are under studied, but the mechanism of action should be beneficial

Anabolic Agents and Sarcoma Risk

- What is the level of data?
  - Rat studies have shown that near-lifetime use of doses >3-58 times therapeutic is associated with increased risk of osteosarcoma for teriparatide and abaloparatide but not for romosozumab
  - Monkey and post-marketing studies have not shown an increase in incidence

Anabolic Agents and Sarcoma Risk

- Unlike humans and nonhuman primates, rats respond to PTH primarily in new bone formation which continues into adult life
- Humans will likely receive teriparatide in their adult life for limited duration of time
- The FDA issued a black box warning due to the severity of this potential adverse effect

Real World Data and Sarcoma Risk

Results From a Fifteen-Year Postmarketing Drug Safety Surveillance Study of Adult Osteosarcoma and Teriparatide in the US

Alicia Gilsenan, PhD[1]; Kirk Midkiff, MPH[1]; David Harris, MPH[1]; Nicole Kellier-Steele, PhD[2]; Elizabeth B. Andrews, PhD[1]
[1]RTI Health Solutions, Research Triangle Park, NC, United States; [2]Eli Lilly & Co., Indianapolis, IN, United States

- 3,809 incident cases of osteosarcoma reported in 30 cancer registries were identified
- 1,165 patients (46%) were interviewed

DISCUSSION AND CONCLUSIONS

- Of those interviewed, 3 patients reported use of teriparatide prior to diagnosis of osteosarcoma, which is within the expected range assuming no increased risk with treatment.
- Drug safety surveillance studies that involve both a rare drug exposure and a rare cancer outcome require participation by many cancer registries.
- Results from this study indicate that, while resource intensive, patient contact studies with multiple cancer registries are feasible.

Presented at the 2019 North American Association of Central Cancer Registries Annual Conference; June 11-13, 2019; Vancouver, British Columbia, Canada

Why only limit with RT use?

- In 2006 the first report of probable teriparatide-associated osteosarcoma occurred
- A second case in 2009 and a third in 2010 raised concern that a patient had a history of radiation therapy and subsequent development of osteosarcoma (within 2 months of treatment)
- The incidence of osteosarcoma reported thus far is below the incidence in the general population

Who really is at risk?

MOLECULAR AND CLINICAL ONCOLOGY 12: 144-147, 2020

Teriparatide may accelerate the growth of a pre-existing malignant tumor in an elderly patient with osteoporosis: A case report

TETSUYA OGAWA[1], SHUSA OHSHIKA[1], MICHIRO YANAGISAWA[1], AKIRA KUROSE[2] and YASUYUKI ISHIBASHI[1]

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DOI: 10.3892/mco.2019.1966

Why only limit with RT use?

- Radiation therapy associated second cancers can occur years after treatment
- Increased risk of second cancers may be genetically predisposed in cancer survivors
- Therapy associated sarcomas occur with the use of other treatment modalities in the absence of radiation…what about those risks?

Second Malignancies and Radiation

- Radiation therapy associated second cancers must:
  - Be of a different type than initial cancer
  - Occur within the treatment field
  - Occur after an interval of time
- There is not a clear dose-response relationship with development of second cancers

Risk of second bone sarcoma and RT

- Data from childhood cancer survivors found an absolute excess risk of bone sarcoma of 35.1 per 100,000 person-years
- The risk increases slowly up to a dose of 15 Gy and then strongly increases for higher radiation doses >30 Gy
- This increased risk is not the same for adults treated with radiation, 3.2 per 1000 at 15 years

Schwartz, et al. Radiat Environ Biophys. 2014: 53(2): 381-390.

Is the Warning Appropriate?

Journal of Clinical Epidemiology 68 (2015) 698–702

Acting on black box warnings requires a GRADE evidence table and an implementation guide: the case of teriparatide

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Accepted 31 January 2015; Published online 11 February 2015

Conclusions Regarding the Warning

- The quality of evidence supporting the development of osteosarcoma is very low
- Teriparatide has clear benefit with a meta-analysis demonstrating 70% reduction in the risk of fractures
- The Black Box warning likely results in over-translation and exclusion of use in patients that may be benefited from therapy

Black Box Warnings for One and All

WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION, STROKE AND CARDIOVASCULAR DEATH

See full prescribing information for complete boxed warning.

- **EVENITY may increase the risk of myocardial infarction, stroke and cardiovascular death. (5.1)**
- **EVENITY should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors. (5.1)**
- **If a patient experiences a myocardial infarction or stroke during therapy, EVENITY should be discontinued. (5.1)**

Reported use of Teriparatide and RT

Osteoporos Int. 2018 Apr;29(4):987-992. doi: 10.1007/s00198-017-4343-2. Epub 2017 Dec 16.

Teriparatide therapy for severe, refractory osteoradionecrosis of the jaw.

Cha YH[1], Hong N[2], Rhee Y[2], Cha IH[3].

Author information

Abstract

Although osteoradionecrosis (ORN) is a serious complication of craniofacial radiotherapy, the current management methods remain suboptimal. Teriparatide (TPTD), a recombinant human parathyroid hormone (1-34), has shown beneficial effects on osseous regeneration in medication-related osteonecrosis of the jaw or periodontitis. However, TPTD therapy in irradiated bones has not been indicated yet because of the theoretical risk of osteosarcoma seen in rat models. Hence, we first report here two patients with tongue cancer with late-emerging ORN who were successfully treated with TPTD for 4-6 months with serum calcium and vitamin D supplementation. In contrast to the usual progress of ORN, the bone defect regenerated well and bone turnover markers including serum C-terminal telopeptide of type 1 collagen and osteocalcin were restored with TPTD therapy. Our experience might suggest that TPTD therapy with careful monitoring can provide an effective treatment option for patients with ORN in select refractory cases, with the benefits outweighing the potential risks.

KEYWORDS: Osteoradionecrosis; Radiation therapy; Recombinant human parathyroid hormone (1–34)

PMID: 29249017 DOI: 10.1007/s00198-017-4343-2

Where do we go from here?

- Patients with a history of radiation treatment should be discussed with a radiation oncologist to determine dose to skeletal bones
- Patients that have received ablative I-131 treatment should be counseled on the risk, but are not necessarily within the warning criteria
- Patients that have failed other therapies should be considered for anabolic agent use

Counseling Patients on Risk/Benefit

- Tamoxifen, a widely used SERM for preventing breast cancer recurrence, carries a black box warning about the risk of uterine sarcoma
- Every chemotherapy drug carries a risk of second cancers
- Radiation risk of bone sarcomas increases with dose to bone and possible age of treatment (inverse risk)
- In the absence of a genetic predisposition the risk is very low

Counseling Patients on Risk/Benefit

- The risk of death from insufficiency fractures can be as high as 25% at one year in older patients
- Severe morbidity in terms of pain, immobility and complications impacts quality of life
- For patients that have severe osteoporosis, ORN or avascular necrosis the risks of osteosarcoma likely are less than the benefits of treatment

Counseling Patients on Risk/Benefit

- In the absence of cardiovascular risk factors, consider the use of romosozumab over teriparatide and abaloparatide for cancer survivors (both radiation and chemotherapy treatment) as there is not a currently known increased risk of sarcoma
- Consider obtaining imaging prior to initiation on high risk individuals (those with prior RT or those with low impact fractures where tissue was not obtained at time of reduction)

Carcinogenesis — Two carcinogenicity bioassays were conducted in Fischer 344 rats. In the first study, male and female rats were given daily subcutaneous teriparatide injections of 5, 30, or 75 mcg/kg/day for 24 months from 2 months of age. These doses resulted in systemic exposures that were, respectively, 3, 20, and 60 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 mcg (based on AUC comparison). Teriparatide treatment resulted in a marked dose-related increase in the incidence of osteosarcoma, a rare malignant bone tumor, in both male and female rats. Osteosarcomas were observed at all doses and the incidence reached 40% to 50% in the high-dose groups. Teriparatide also caused a dose-related increase in osteoblastoma and osteoma in both sexes. No osteosarcomas, osteoblastomas or osteomas were observed in untreated control rats. The bone tumors in rats occurred in association with a large increase in bone mass and focal osteoblast hyperplasia.

Source: https://www.drugs.com/pro/forteo.html#s73

The second 2-year study was carried out in order to determine the effect of treatment duration and animal age on the development of bone tumors. Female rats were treated for different periods between 2 and 26 months of age with subcutaneous doses of 5 and 30 mcg/kg (equivalent to 3 and 20 times the human exposure at the 20-mcg dose, based on AUC comparison). The study showed that the occurrence of osteosarcoma, osteoblastoma and osteoma was dependent upon dose and duration of exposure. Bone tumors were observed when immature 2-month old rats were treated with 30 mcg/kg/day for 24 months or with 5 or 30 mcg/kg/day for 6 months. Bone tumors were also observed when mature 6-month old rats were treated with 30 mcg/kg/day for 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with 5 mcg/kg/day for 6 or 20 months. The results did not demonstrate a difference in susceptibility to bone tumor formation, associated with teriparatide treatment, between mature and immature rats.

The relevance of these animal findings to humans is uncertain.

Source: https://www.drugs.com/pro/forteo.html#s73