Toremifene to Reduce Fracture Risk in Men Receiving Androgen Deprivation Therapy for Prostate Cancer

BACKGROUND:

- Treatment of prostate cancer often involves **androgen deprivation therapy**, either with bilateral orchectomy or administration of a GnRH agonist. Androgen deprivation therapy decreases levels of serum testosterone *and* serum estradiol, causing adverse effects such as **decreased bone mineral density**, increased cholesterol, and increased triglycerides.

OBJECTIVE:

- The objective of this study was to determine if toremifene is safe and effective in preventing fractures associated with androgen deprivation therapy in prostate cancer.

METHODS:

- Randomized, placebo-controlled, double-blind, parallel multicenter trial
- Patients were enrolled over a two-year period and followed for 24 months each
- Inclusion Criteria:
  - Age > 50
  - Male
  - Histologic diagnosis of prostate cancer
  - Receiving androgen deprivation therapy for at least 6 months continuously or at least 1 year intermittently
  - Increased risk of fracture (Age > 70 or osteopenic)
  - Baseline PSA ≤ 4 ng/mL
  - Adequate bone marrow, liver, and renal function
  - Zubrod performance status 0-1
- Exclusion Criteria:
  - Received a bisphosphonate, a selective estrogen receptor modulator (SERM), PTH, teriparatide, calcitonin, oral glucocorticoids, a 5-α reductase inhibitor, Prostate Cancer-SPES (PC-SPES), or saw palmetto in the previous 45 days
  - Prior treatment with toremifene
  - Less than 8 evaluable vertebrae from T4 to L4
  - Weight > 300 lbs
  - Chronic hepatitis/cirrhosis
  - History of thromboembolic disease
- 1389 patients were randomized to receive either toremifene 80 mg PO once daily (699 patients) or matching placebo PO once daily (690 patients)
- **Primary Outcome Measure**: Incidence of new vertebral fractures
- **Secondary Outcome Measures**: Incidence of fragility fractures and changes in bone mineral density (hip, spine, & femoral neck), changes in bone turnover markers (bone specific alkaline phosphatase, C-telopeptide, osteocalcin), and changes in serum lipids (total cholesterol, LDL, HDL, triglycerides)
- Power for incidence of new vertebral fractures was calculated to be 80% with an alpha level of 0.05 to detect a 40% reduction in fracture incidence at 24 months with 1200 patients, assuming 75% completion rate
- Data handling method was modified intent-to-treat: all patients who received a dose were included in the safety analysis; only patients who had a baseline and ≥ 1 follow-up x-ray were included in the primary efficacy analysis; only complete records, without imputation, were included in the analysis of the secondary endpoints

RESULTS:

- 320 patients (45.8%) in the toremifene group and 316 patients (45.8%) in the placebo group completed the study
- **Primary outcome measure**: Statistically significant decrease in vertebral fracture incidence in the toremifene group (ARR = 2.4%, RRR = 50%, 95% CI = 1.5% to 75.0%, $p < 0.05$)
- **Secondary outcome measures**: There were statistically significant differences in the mean change from baseline vs placebo in BMD, bone turnover markers, and lipids:

BMD	Bone Turnover Markers	Serum Lipids
Lumbar Spine: +2.3% (p < 0.0001)	BS Alk Phos: -18.3% (p < 0.0001)	Total Cholesterol: -4.7% (p < 0.001)
Hip: +1.9% (p < 0.0001)	Osteocalcin: -23.9% (p < 0.0001)	LDL: -7.0% (p < 0.001)
Femoral Neck: +1.9% (p < 0.0001)	C-telopeptide: -14.5% (p = 0.031)	HDL: +7.2% (p < 0.0001)
		Triglycerides: -17.6% (p < 0.001)

Incidence of fragility fractures was not reported

Incidence of all fractures showed a statistically significant reduction (ARR = 3.8%, RRR = 38%, 95% CI = 2.2% to 60.2%, p = 0.036)

There were no statistically significant differences in the number of patients who had > 7% decrease in BMD (p = 0.129) or in levels of testosterone, estradiol, or LH

FSH significantly decreased 65% vs placebo (95% CI = 54.5% to 75.5%, p < 0.001)

- Adverse events rates were mostly similar in both groups. Incidence of venous thromboembolism was increased in the toremifene group (2.6% vs 1.1%). No p-values were reported for AE incidence.
- **Authors' conclusion**: Toremifene reduces fracture risk, increases BMD, and has a beneficial effect on bone turnover markers and serum lipids. For this reason, toremifene may find clinical utility in preventing fractures in men receiving androgen deprivation therapy for prostate cancer.

STRENGTHS:

- Randomized, controlled double-blind study design
- Primary endpoint is a clinical endpoint, not a surrogate endpoint

WEAKNESSES:

- High dropout rate
- Lack of compliance monitoring
- Poor statistical reporting of baseline characteristics, outcome measures, and adverse event rates
- No data reported for prostate cancer progression
- Need to treat 84 patients to prevent one vertebral fracture per year (NNT- number needed to treat)
- Lack of long-term risk/benefit data

CONCLUSIONS:

- Due to study weaknesses including high dropout rate and poor reporting of adverse events, ruther studies evaluating toremifene for fracture prophylaxis in patients receiving androgen deprivation therapy for prostate cancer are needed.
- Prostate cancer patients usually receive a bisphosphonate as a standard of care, and bisphosphonates appear to have an antitumor effect, are significantly less expensive, and dosed less frequently.
- Toremifene presents a useful alternative for fracture prevention in patients who cannot tolerate bisphosphonates and have low risk for thromboembolic complications.
- Future research should focus on:
    - Long-term risk/benefit
        - Thromboembolism risk
        - Tumor progression risk
        - Clinical benefit of increased serum lipid panel
    - Correcting study weaknesses of high dropout, poor compliance monitoring and poor data reporting/analysis
    - Comparing toremifene to other treatment options, including bisphosphonates, denosumab, raloxifene, parathyroid hormone, teriparatide, and/or calcium + vitamin D

Reference: Smith MR, Morton RA, Barnette KG, et al. Toremifene to Reduce Fracture Risk in Men Receiving Androgen Deprivation Therapy for Prostate Cancer. J Urol. Oct 2010; 184(4): 1316-21.

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