Published in final edited form as:

Breast. 2009 April ; 18(2): 84–88. doi:10.1016/j.breast.2009.01.003.

Bone Quality Test (BQT) scores of fingernails in postmenopausal patients treated with adjuvant letrozole or tamoxifen for early breast cancer

Zhuoxin Sun, PhD¹, Aron Goldhirsch, MD², Karen N. Price, BS³, Marco Colleoni, MD⁴, Alberto Ravaoli, MD⁵, Edda Simoncini, MD⁶, Ian Campbell, MD⁷, Richard D. Gelber, PhD⁸, and Mark Towler, PhD⁹

¹IBCSG Statistical Center, Dana-Farber Cancer Institute and Harvard School of Public Health, Boston, MA. zhuoxin@jimmy.harvard.edu

²Department of Medicine. European Institute of Oncology, Milan, Italy, and Oncology Institute of Southern Switzerland, Bellinzona, Switzerland. aron.goldhirsch@ibcs.org

³IBCSG Statistical Center and Frontier Science and Technology Research Foundation, Boston, MA. price@jimmy.harvard.edu

⁴Research Unit in Medical Senology, Department of Medicine, European Institute of Oncology, Milan, Italy. marco.colleoni@ieo.it

⁵Department of Oncology Ospedale Infermi Rimini and Istituto Scientifico Romagnolo per lo studio e la cura dei tumori, Meldola (FC), Italy. aravaoli@auslrm.net

⁶Oncologia Medica-Spedali Civili, Brescia, Italy. bscivile@ns.numerica.it

⁷Waikato Hospital, New Zealand. campbeli@waikatodhb.govt.nz

⁸IBCSG Statistical Center, Dana-Farber Cancer Institute, Harvard School of Public Health and Harvard Medical School, Boston, MA. gelber@jimmy.harvard.edu

⁹Materials & Surface Science Institute, University of Limerick, Limerick, Ireland Mark.Towler@ul.ie

SUMMARY

Background—The relationship between nail and bone may be measurable, thus making the fingernail a potentially valuable tool for assessing bone health for women receiving treatment for breast cancer. In the BIG 1-98 Fingernail Pilot Substudy, Bone Quality Test (BQT) scores of fingernails were measured at two assessment timepoints.

Methods—Thirteen eligible patients were enrolled into the substudy during their treatment with tamoxifen (4 patients) or letrozole (9 patients). Two fingernails were tested and BQT scores averaged for two assessments six months apart.

Results—BQT scores collected six months later (second assessment) significantly decreased compared with those at first collection ($p = 0.007$) regardless of treatment and prior fracture.

Corresponding author before publication: Karen N. Price, Mailing address: Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, tel: 617-632-2459; fax: 617-632-5444, price@jimmy.harvard.edu. Corresponding author after publication: Aron Goldhirsch, MD, European Institute of Oncology, Via Ripamonti 435 20141 Milano, Italia; Phone: +39 02 57489 439, Fax: + 39 02 94379 224; aron.goldhirsch@ibcs.org.

Conflict of Interest Statement: None of the authors have any conflicts of interest.

Conclusion—The reduction of BQT scores observed in the patients of our small exploratory study during exposure to bone-altering breast cancer treatments is an incentive for larger studies using this technique.

Keywords

fingernail; bone quality test; breast cancer; hormonal therapy; letrozole

INTRODUCTION

The microarchitecture of the fingernail is an excellent analogue for bone quality due to the similarity of keratin in the fingernail and type I collagen in bone, both used for structural strength (1). The relationship between nail and bone may be measurable, thus making the fingernail a potentially valuable tool for assessing bone health, in addition to dual x-ray absorptiometry (DXA) and/or as a means of following patients on treatments for osteoporosis. Patients receiving treatment for osteoporosis have anecdotally reported a hardening of their fingernails, as collagen formation and keratin synthesis may undergo similar alterations, leading to distinct damage of bone or fingernail structure. Pathological changes of the bone may theoretically be reflected in altered fingernail structure or composition (2).

Bone Quality Test (BQT) is a new biomarker being developed by Crescent Diagnostics (1) that tests fingernail structure to evaluate bone health. It uses a fingernail sample and a Raman laser system to detect a surrogate marker for bone microarchitecture status present in the fingernail. Disulphide bonds between certain amino acids are required for the strength and flexibility of both nails and bones. BQT allows the identification of sulfur, component of the disulphide bonds, thus providing information on bone quality. Importantly, BQT provides information on the state of trabecular bone (bone structure) rather than cortical bone (bone mass). Raman spectroscopy allows the analysis of human fingernail for BQT by means of a laser beam which hits the fingernail for a few seconds. Reflected light provides information on the chemical structure of the disulphide bonds in the fingernail. By analyzing the wavelengths of the reflected light, information on the level and types of chemical bonds present can be obtained.

BQT is still a new technology under early investigation for clinical applicability with limited data available. Some preliminary studies have shown significantly lower disulphide content in nails obtained from patients with a history of fracture (3) and in patients with osteoporosis (4). A weak association was observed between Raman measurement of disulphide content and bone mineral density as measured by DXA (2).

Adjuvant systemic treatment for postmenopausal women with endocrine-responsive early breast cancer, which represents 23% of all new breast cancer diagnoses (5), most often includes either a selective estrogen receptor modulator (SERM) agent, usually tamoxifen, an aromatase inhibitor (letrozole, exemestane, anastrozole), or SERM followed by aromatase inhibitor, all over a period of at least five years.

Treatment with aromatase inhibitors, both steroidal, anastrozole and letrozole, and non-steroidal, predispose postmenopausal women to bone loss and an increase fracture rate. Letrozole, a non-steroidal aromatase inhibitor, lowers circulating estrogen levels to almost unrecordable levels in postmenopausal women, predisposing them to bone loss and an increase in fracture risk (6). This observation has been described for other non steroidal (6) and steroidal (7) aromatase inhibitors. On the other hand, tamoxifen has a protective effect on bone loss for postmenopausal women (8), while it has been reported to cause, if given without ovarian function suppression, bone loss in premenopausal women (9). The

relationship between aromatase inhibitors or tamoxifen and changes of fingernails are not described in the medical literature. Anecdotal reports on flaking of fingernails after tamoxifen, presumably taken during premenopause, are reported. The BIG 1-98 trial, as well as other reports of aromatase inhibitor trials, showed an excess of fractures reported in the aromatase inhibitor group compared to tamoxifen in postmenopausal breast cancer patients. As all of these aromatase inhibitor trials also showed an efficacy advantage for the aromatase inhibitor studied over tamoxifen, for example, letrozole was superior to tamoxifen in the BIG 1-98 trial (10, 11), aromatase inhibitors have become more widely used. Patients who receive aromatase inhibitors, more so than those treated with tamoxifen, must be routinely followed for bone health. A simple test using fingernails is therefore worth investigating as a measure of bone health for patients who receive adjuvant aromatase inhibitors.

In the BIG 1-98 Fingernail Pilot Substudy, BQT scores of fingernails were measured to determine whether nail structure can be used to evaluate bone fragility. The patients enrolled in the substudy had received three to nearly five years of letrozole or tamoxifen as adjuvant therapy for endocrine-responsive early breast cancer through participation in the BIG 1-98 trial.

The BIG 1-98 trial has been described elsewhere (11). Briefly, BIG 1-98 is a randomized, phase 3, double-blind trial comparing four treatment groups: monotherapy with letrozole or with tamoxifen for five years, and sequential administration of tamoxifen for two years followed by letrozole for three years, or letrozole for two years followed by tamoxifen for three years. The trial was conducted in postmenopausal women with estrogen receptor (ER) and/or progesterone receptor (PgR) positive operable invasive breast cancer. From March 1998 to March 2000, patients were randomized to two arms: monotherapy with letrozole (2.5 mg daily) or tamoxifen (20 mg daily). From April 1999 to May 2003, patients were randomized to one of 4 treatment groups: tamoxifen alone for 5 years, letrozole alone for 5 years, tamoxifen for 2 years followed by letrozole for 3 years, or letrozole for 2 years followed by tamoxifen for 3 years.

METHODS

Study Design

The Fingernail Pilot Substudy was launched in April 2005 and closed in July 2007. Postmenopausal women with operated breast cancer, randomized and receiving adjuvant endocrine treatment within BIG 1-98 with either letrozole or tamoxifen (assigned for 5 years) who were still receiving trial treatment (prior to completion of five years trial treatment) and who had not relapsed or had a second primary cancer were eligible for this substudy. The objectives of the substudy are to compare the effects of tamoxifen and letrozole on the fingernails, to compare fingernail assessments for patients who have had a bone fracture and those who have not, and to evaluate the effect of further drug treatment (after 6 months) on the properties of fingernails.

The original sample size target was 60 evaluable patients, 15 in each of the four cohorts defined by treatment group and prior occurrence of a bone fracture: patients receiving tamoxifen who had not had a bone fracture; patients receiving letrozole who had not had a bone fracture; patients receiving tamoxifen who had had a bone fracture; patients receiving letrozole who had had a bone fracture. As the BQT techniques are new, there have not been any large-scale studies from which to establish reliable statistics that can be used in power calculations. As a pilot study, 30 in each treatment group and 30 in each bone fracture group (with and without) were considered to be enough to establish reasonably reliable statistics for use in further study sample size calculation. Sixteen patients were eventually enrolled

and informed consent was obtained from all. In many participating centers the substudy was either not activated or activated late, and after all of the patients on the BIG 1-98 trial had completed their five year treatment program the Fingernail Pilot Substudy closed.

Two fingernail clippings were obtained at the first collection and six months later (i.e. the second collection) for each patient. The BQT scores of the fingernail clippings were obtained by Crescent Diagnostics, which evaluated different potentially relevant features in the Raman spectra collected from the fingernails. The average of BQT scores of the two fingernail clippings obtained at the same time were used for the analysis. Therefore, for each patient, there are two BQT scores, one at the first collection and the other six months later (i.e. the second collection). All fingernail samples (first and second collections) were analyzed blinded and at the same time.

Statistical Methods

Wilcoxon rank sum tests were used to compare the BQT scores for tamoxifen vs. letrozole and for fracture vs. non-fracture at each assessment. Wilcoxon signed rank tests were used to assess the statistical significance of changes in BQT scores between the two assessments. Wilcoxon sum rank tests were used to compare the change of BQT scores (BQT at second assessment – BQT at first assessment) between the tamoxifen and letrozole groups, and between the fracture and non-fracture groups.

RESULTS

Eligible Patients

Of the 16 patients enrolled, three patients were ineligible, all on the tamoxifen arm. Two of these patients had the first sample obtained after treatment completion, and one patient was taking bisphosphonates. The remaining 13 eligible patients were included in this analysis. Figure 1 shows the timing of the two assessments with the five-year treatment period for the 13 eligible patients. The first collection of fingernails ranged from 3.0 to 4.7 years after patients were randomized to BIG 1-98. All 13 patients had the first assessment, and 12 patients had the second assessment.

Characteristics at the substudy entry for the 13 eligible patients are shown in Table 1. The average age was 63.8 years. Nine patients received letrozole and 4 patients received tamoxifen. Eight patients had a prior bone fracture. Among these, 3 had bone fractures prior to receiving treatment and 5 had bone fractures while on BIG 1-98 treatment. For the 3 patients who had fracture prior to treatment, the sites of fractures were radius right, ribs, tibia; and the occurrences of the fractures ranged from 0.2 year to 3.4 years before the patients were randomized to BIG 1-98. For the 5 patients who had bone fractures while on BIG 1-98 treatment, the sites of fractures were metacarpal, wrist, pelvis, humerus/wrist, and ankle; and the most recent occurrences of the fractures were 0.2, 4.3, 1.1, 2.6, 1.2 years respectively after the patients were randomized to BIG 1-98. All the fractures occurring while on treatment were due to trauma.

BQT Scores at First and Second Collections

Figure 2 gives scatter plots of the BQT scores at the first collection and second collection, and also the differences of BQT scores between the two collections. Table 2 provides the descriptive summary data of the BQT scores and the percentage change of the BQT scores overall, by treatment arms, and by fracture/non-fracture groups. We observed no treatment effect on BQT scores at the first and the second assessments. Also no differences were observed in BQT scores at the first and the second assessments in patients with or without prior fracture. However, clearly there was a consistent decrease of BQT scores from the first

collection to the second collection. The BQT scores collected six months later significantly decreased compared with those at first collection ($p=0.007$; based on signed rank test). This reduction was similar in both treatment groups and fracture/non-fracture groups. There were no treatment or bone fracture effects on the changes of BQT scores between the two time points (Tables 2).

DISCUSSION

From this pilot substudy, with only 13 eligible patients, no differences were detected in BQT scores between treatment and between patients with or without fractures. However, even with this small sample size, we observed a significant reduction in BQT scores after 6 months during treatment. Endocrine therapies, either tamoxifen (anecdotal reporting (12)), or aromatase inhibitors may change the structure of hair (13), skin and nails. For the latter information is based on observations (14) rather than on systemic reporting from clinical trials. The opportunity to test bone health in relationship to the structure of fingernails is obviously appealing, but requires systematic prospective sample obtainment. Our pilot substudy was not successful in providing a sufficient degree of information on differential changes in the nails in the four cohorts of interest, because of several reasons: late planning during the conduct of the trial, shortage of funding, and especially, impossibility to guarantee available fingernails for many of the patients. Reasons for difficulties of retrieving suitable nails for testing included: nail biting, onychomycosis, nails not recovered from changes during adjuvant chemotherapy, and the increasing use of nail gel for artificial enhancement of nails. The average nail growth is reported at 0.1mm per day, meaning that a nail takes around six months to completely regenerate (15). In this substudy, patients had already been receiving endocrine therapies for 3 or more years before the first assessment, therefore, our study could not capture the effects of endocrine therapy on the BQT in the first 2.5 years.

The current method for identification of osteoporosis is related to the measurement of bone mineral density (BMD) obtained by exposing of parts of the skeleton (usually lumbar spine, part of the hip inclusive the femur head and neck), to low level x-ray (DXA) scans. BMD does not directly provide information on risk for fractures because it is unable to detect bone fragility (related to structural deficiencies).

The BQT method provides information on the chemical structure of the disulphide bonds in the fingernail allowing for the theoretical identification of fragility of nails and bone. The reduction of BQT observed in the patients of our small exploratory study during exposure to endocrine therapy, be it letrozole or tamoxifen is an important incentive for further investigation, which should include the collection of BMD measurements in order to compare the BQT and BMD.

Current information on the use of adjuvant bisphosphonates to prevent osteoporosis-related bone events (16), and other types of breast cancer events (17) might require innovative approaches for testing bone strength and flexibility to allow tailoring bisphosphonates therapies for those patients who will benefit from them the most.

A special effort for obtaining finger or toe nails from patients exposed to adjuvant therapies might allow a better choice of therapies aimed at the skeletal microenvironment, which currently includes not only bisphosphonates but also RANKL inhibitors (18). A simple, reproducible method for testing flexibility and strength of bone structure will be of major therapeutic relevance for planning treatment strategies for patients with breast cancer.

CONCLUSION

The reduction of BQT scores observed in the patients of our small exploratory study during exposure to endocrine therapy is an important incentive for further investigation. We hope that the intriguing results from our small study will encourage investigators to conduct larger studies using this technique for women receiving bone-altering breast cancer treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of support: The International Breast Cancer Study Group is supported by the Swedish Cancer Society, The Cancer Council Australia, Australian New Zealand Breast Cancer Trials Group, Frontier Science and Technology Research Foundation, Swiss Group for Clinical Cancer Research (SAKK), National Cancer Institute Grant CA-75362, Cancer Research Switzerland/Oncosuisse, and the Foundation for Clinical Cancer Research of Eastern Switzerland (OSKK). These groups had no role in writing this paper.

References

1. [October 28, 2008] Crescent Diagnostics. Available from URL: <http://www.crescentds.com>
2. Pillay D, Lyons MJ, German NS, Lawson HM, et al. The use of fingernails as a means of assessing bone health: a pilot study. *J of Women's Health*. 2006; 14:339–344.
3. Towler MR, Wren A, Rushe N, Saunders J, Cummins NM, Jakeman PM. Raman spectroscopy of the human nail: A potential tool for evaluating bone health? *J Mater Sci: Mater Med*. 2007; 18:759–763. [PubMed: 17136606]
4. Moran P, Towler M, Chowdhury S, Saunders J, German M, Lawson N, Pollock H, Pillay I, Lyons D. Preliminary work on the development of a novel detection method for osteoporosis. *J Mater Sci: Mater Med*. 2007; 18:969–974. [PubMed: 17221317]
5. CANCERmondial. [October 29 2008] Available from URL: <http://www-dep.iarc.fr/>
6. Eastell R, Hannon RA, Cuzick J, et al. ATACTrialists' Group. Effect of an aromatase inhibitor on BMD and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial (18233230). *J Bone Miner Res*. 2006; 21:1215–1223. [PubMed: 16869719]
7. Geisler J, Lønning PE, Krag LE, et al. Changes in bone and lipid metabolism in postmenopausal women with early breast cancer after terminating 2-year treatment with exemestane: A randomised, placebo-controlled study. *Eur J Cancer*. 2006; 42:2968–2975. [PubMed: 16963261]
8. Ding H, Field TS. Bone health in postmenopausal women with early breast cancer: how protective is tamoxifen? *Cancer Treat Rev*. 2007; 33:506–513. [PubMed: 17573199]
9. Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. *J Clin Oncol*. 1996; 14:78–84. [PubMed: 8558225]
10. Coates AS, Keshaviah A, Thürlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: Update of study BIG 1–98. *J Clin Oncol*. 2007; 25:486–492. [PubMed: 17200148]
11. BIG 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med*. 2005; 353:2747–2757. [PubMed: 16382061]
12. Breastcancer.org. [October 28, 2008] Available from URL: http://www.breastcancer.org/treatment/hormonal/side_effects/tamoxifen.jsp
13. Buzdar A, Douma J, Davidson N, Elledge R, Morgan M, et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *J Clin Oncol*. 2001; 19:3357–3366. [PubMed: 11454883]
14. [October 28,2008] Womens-wellness.com. Available from URL: <http://www.womenswellness.com/wellness/200208/msg00016.html>

15. BEAN WB. Nail growth. Thirty-five years of observation. Archives of Internal Medicine. 1980; 140:73–76. [PubMed: 7352807]
16. Brufsky A, Bundred N, Coleman R, Lambert-Falls R, et al. Z-FAST and ZO-FAST Study Groups. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. Oncologist. 2008; 13:503–514. [PubMed: 18515735]
17. Gnant M, Mlineritsch B, Schippinger W, et al. Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with hormone-response, stage I and II breast cancer: first efficacy results from ABCSG-12. Journal of Clinical Oncology. 2008; 26:15S. Abstract LBA4.
18. Lipton A, Steger GG, Figueroa J, Alvarado C, et al. Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. J Clin Oncol. 2007; 25:4431–4437. [PubMed: 17785705]

Figure 1.

Timing of first and second assessments within the 5-year treatment period of tamoxifen or letrozole for 13 eligible patients enrolled in the Fingernail Pilot Substudy

* Patients who had a bone fracture prior to the first collection

Figure 2. Scatter plots of the BQT scores at the first collection and second collection, and differences in BQT scores between the two collections according to treatment and according to whether the patient had a prior bone fracture or not.

Table 1

Age and Bone Fractures History at the Substudy Entry

	TREATMENT		
	Tamoxifen (n=4) Mean (SD)	Letrozole (n=9) Mean (SD)	TOTAL (n=13) Mean (SD)
Age (years)	64.8(8.1)	63.3(7.6)	63.8(7.4)
	N (%)	N (%)	N (%)
Bone fracture prior to receiving treatment			
No	4(100.0)	6(66.7)	10(76.9)
Yes	0(0)	3(33.3)	3(23.1)
Bone fracture while on treatment			
No	2(50.0)	6(66.7)	8(61.5)
Yes	2(50.0)	3(33.3)	5(38.5)
Patients who have had a bone fracture			
No	2(50.0)	3(33.3)	5(38.5)
Yes	2(50.0)	6(66.7)	8(61.5)

*
standard deviation

Table 2

BQT Assessments

	All patients				P-value [*]		
	N	Mean (SD)	Median (Range)				
1st assessment	13	1.22 (0.06)	1.20 (1.16,1.32)				
2nd assessment	12	1.15 (0.05)	1.15 (1.07,1.25)				
% change of the two assessments	12	-0.06 (0.06)	-0.06 (-0.19,0.04)		0.007		
	Treatment						P-value ^{**}
	Tamoxifen			Letrozole			
	N	Mean (SD)	Median (Range)	N	Mean (SD)	Median (Range)	
1st assessment	4	1.22(0.06)	1.22(1.16,1.30)	9	1.22(0.06)	1.20(1.16,1.32)	0.91
2nd assessment	4	1.14(0.04)	1.13(1.10,1.20)	8	1.15(0.05)	1.15(1.07,1.25)	0.81
% change of the two assessments	4	-0.06(0.08)	-0.07(-0.16,0.04)	8	-0.05(0.06)	-0.05(-0.19,0.01)	0.46
	Patients who have had a bone fracture						P-value ^{**}
	No			Yes			
	N	Mean (SD)	Median (Range)	N	Mean (SD)	Median (Range)	
1st assessment	5	1.22(0.05)	1.22(1.16,1.30)	8	1.22(0.07)	1.20(1.16,1.32)	0.75
2nd assessment	5	1.14(0.03)	1.15(1.10,1.17)	7	1.15(0.06)	1.14(1.07,1.25)	1.00
% change of the two assessments	5	-0.06(0.06)	-0.06(-0.16,0.01)	7	-0.05(0.07)	-0.06(-0.19,0.04)	0.88

^{*} based on Wilcoxon signed rank test

^{**} based on Wilcoxon sum rank test