RTOG 0518: Randomized Phase III Trial to Evaluate Zoledronic Acid for Prevention of Osteoporosis and Associated Fractures in Prostate Cancer Patients

Published in final edited form as:
Prostate Cancer Prostatic Dis. 2013 December ; 16(4): . doi:10.1038/pcan.2013.35.

RTOG 0518: Randomized Phase III Trial to Evaluate Zoledronic Acid for Prevention of Osteoporosis and Associated Fractures in Prostate Cancer Patients

Lisa A. Kachnic, M.D.[1], **Stephanie L Pugh, Ph.D.**[2], **Patricia Tai, M.D.**[3], **Matthew Smith, M.D**[4], **Elizabeth Gore, M.D.**[5], **Amit B. Shah, M.D.**[6], **Andre-Guy Martin, M.D.**[7], **Harold E. Kim, M.D.**[8], **Abdenour Nabid, M.D.**[9], and **Colleen AF Lawton, M.D.**[3,10]

[1]Boston University, Boston, USA

[2]RTOG Statistical Center, Philadelphia, USA

[3]University of Sasktachewan, Canada

[4]Harvard Medical School, Boston, USA

[5]Medical College of Wisconsin, Milwaukee, USA

[6]York Cancer Center, York, USA

[7]Laval University, Quebec, Canada

[8]Wayne State University Medical School, USA

[9]Universitaire de Sherbrooke

[10]Medical College of Wisconsin, Milwaukee, USA

Abstract

Background—RTOG 0518 evaluated the potential benefit of zoledronic acid therapy in preventing bone fractures for patients with high grade and/or locally advanced, non-metastatic prostate adenocarcinoma receiving luteinizing hormone-releasing hormone (LHRH) agonist and radiotherapy (RT).

Methods—Eligible patients with T-scores of the hip (< −1.0, but > −2.5 vs. > −1.0) and negative bone scans were prospectively randomized to either zoledronic acid, 4 mg, concurrently with the start of RT and then every six months for a total of 6 infusions (Arm 1) or observation (Arm 2). Vitamin D and calcium supplements were given to all patients. Secondary objectives included quality of life (QOL) and bone mineral density (BMD) changes over a period of three years.

Results—Of 109 patients accrued before early closure, 96 were eligible. Median follow-up was 36.3 months for Arm I and 34.8 months for Arm 2. Only two patients experienced a bone fracture (1 in each arm) resulting in no difference in freedom from any bone fracture (p=0.95), nor in QOL. BMD percent changes from baseline to 36 months were statistically improved with the use of zoledronic acid compared to observation for the lumbar spine (6% vs. −5%, p<0.0001), left total hip (1% vs. −8%, p=0.0002), and left femoral neck (3% vs. −8%, p=0.0007).

Correspondence: Lisa A. Kachnic, M.D., Department of Radiation Oncology, Boston University Medical Center, 830 Harrison Avenue, LL, Boston, MA 02118, Tel:617-638-7070, Fax: 617-638-7037, lisa.kachnic@bmc.org.

CONFLICT OF INTEREST: No conflicts of interest to report.

SUPPEMENTARY INFORMATION: Supplementary information is available at Prostate Cancer and Prostatic Diseases website.

Conclusions—For patients with advanced, non-metastatic prostate cancer receiving LHRH agonist and RT, the use of zoledronic acid was associated with statistically improved BMD percent changes. The small number of accrued patients resulted in decreased statistical power to detect any differences in the incidence of bone fractures or QOL.

Keywords

radiation therapy; androgen deprivation therapy; osteoporosis; prostate cancer; bone fractures

INTRODUCTION

The Radiation Therapy Oncology Group (RTOG) study 8531 demonstrated that the use of androgen deprivation therapy (ADT) in conjunction with radiotherapy (RT) for locally advanced and/or high-grade adenocarcinoma of the prostate increases disease-free and overall survival[1]. However, patients who have utilized luteinizing hormone-releasing hormone (LHRH) agonists have an increase in the incidence of osteoporosis, with a prevalence rate of 27%, as well as associated osteoporotic bone fractures[2,3]. Direct medical care costs of osteoporotic fractures were estimated in 2004 to be $12.2 to $17.9 billion per year in 2002 U.S. dollars, not including indirect costs associated with lost productivity of patients and caregivers[4]. Decreasing this fracture rate, therefore, may have important implications in this population of prostate cancer patients.

Prostate cancer patients with locally advanced non-metastatic disease who received RT and long term LHRH therapy (i.e., >1 year) are a unique population in that they are at risk of osteoporosis of their pelvic bones from ADT and the effects of RT. Whether zoledronic acid therapy is needed beyond vitamin D and calcium is still not known. Because of the lack of data, the current standard of care for prostate cancer patients receiving long term LHRH therapy does not include bisphosphonate therapy. In a randomized, double-blind, placebo-controlled trial of zoledronic acid in men with non-metastatic prostate cancer who were just beginning ADT, Smith *et al.* observed significant increases in BMD of the spine and hip after one year[4].

Therefore, RTOG 0518 was designed with the primary objective to evaluate the potential benefit of zoledronic acid in the prevention of bone fracture (defined as any bone fracture, ABF) in patients receiving LHRH and RT for locally advanced adenocarcinoma of the prostate. Secondary objectives were to evaluate the potential benefit in quality of life and BMD over a period of three years. The study focused on patients without any osteoporosis at baseline.

MATERIALS AND METHODS

This study was coordinated by the RTOG and performed with the approval of the institutional review board for human research at each institution. Eligible patients had pathologically confirmed adenocarcinoma of the prostate, with ≥ T3 disease or < T3 with Gleason's score (GS) > 8, or < T3 with GS 7 and PSA ≥ 15, or < T3 with GS < 7 and PSA ≥ 20, any N stage, and a negative bone scan; Zubrod performance status 0–1; age ≥ 18 years; and normal calcium levels. Patients were stratified prior to randomization by dual-emission x-ray absorptiometry (DXA) scans with T scores of the hip (<−1.0 but > −2.5 vs. ≥ −1.0) and planned duration of LHRH therapy (≥ 1 year and ≤ 2.5 years vs. >2.5 years). The treatment allocation scheme described by Zelen[5] was used to balance patient factors. Patients receiving concurrent RT and LHRH therapy were randomized by permuted block to either zoledronic acid (Arm 1) or observation (Arm 2). Vitamin D and calcium supplements were given to all patients.

Patients on Arm 1 received the first dose of zoledronic acid concurrently with the start of RT and then every six months for a total of 3 years (6 infusions). The dosage for zoledronic acid was 4 mg, given by infusion. Dosage adjustment was required for those with renal impairment. Vitamin D dose was 400 IU and calcium dose was 500 mg, both taken orally every day for 3 years. DXA scans were to be performed prior to treatment and at 18 and 36 months. Adverse events were reported according to the Common Terminology Criteria for Adverse Events version 3.0.

The primary endpoint of this study was freedom from any bone fracture (FABF), measured from the date of randomization to the date of documented bone fracture(s), defined as ABF. It was hypothesized that Arm 1 would have reduced probability of ABF at 36 months compared to Arm 2. It was assumed that the control arm (arm 2) would have a 3-year ABF rate of 12% (FABF 88%), translating to a yearly ABF hazard rate of 0.0426. The study was designed to show a 40% relative reduction in the yearly ABF hazard rate, from 0.0426 to 0.0256, resulting in a 3-year ABF rate of 7.4% (FABF 92.6%). Using a one-sided log-rank test with α=0.05 and 1 interim analysis for efficacy, 101 bone fractures were required with a total of 1030 patients to provide 80% statistical power. Guarding against an ineligible rate of 10% and a drop-out rate of 10%, the target accrual was 1272 patients. Of note, follow-up ceased at 3 years from the start of treatment.

All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and were intent-to-treat but excluding patients that did not meet inclusion criteria. The FABF function was estimated by the Kaplan-Meier method and the log-rank test was used to test the primary hypothesis at a significance level of 0.0496 (adjusting for the interim efficacy analysis) once all patients were potentially followed for at least 3 years. Patients were censored at their last known follow-up. The percent change in BMD from baseline to 36 months between treatment arms was compared using a two-sample t-test with a significance level of 0.05.

Quality of life (QOL), measured by the Functional Assessment of Cancer Therapy-General (FACT-G)[6] and EuroQoL (EQ-5D), was collected pretreatment and every six months for a total of 36 months. The FACT-G consists of 4 subscales: physical well-being, social/family well-being, emotion well-being, and functional well-being. Two-sample t-tests were used to compare the change of total FACT-G score as well as the 4 subscale scores from baseline to 36 months between treatment arms. A Bonferroni-adjusted significance level of 0.01 was used to maintain the overall type I error 0.05 for the QOL analyses.

RESULTS

The trial opened on March 28, 2006 but it did not meet its annual accrual goals and was closed early on January 30, 2009 with 109 patients (Fig. 1). Of these 109 patients, 96 were eligible. Table 1 shows the pretreatment characteristics. Median age was 70 years old. The majority of men enrolled were white (93%), not Hispanic or Latino (99%), had a Zubrod performance status of 0 (94%), a Gleason score between 8–10 (69%), N0 stage (89%), and T2 stage (48%). Median follow-up was 36.3 months for Arm 1 and 34.8 months for Arm 2. Due to the early closure, the planned interim analysis was not conducted.

There was one patient death (grade 5 myocardial ischemia) in Arm 1 that was reported as possibly related to treatment, but no autopsy was performed and one death in Arm 2 (grade 5 cardiac) not related to treatment. There was one patient with grade 3 myocardial ischemia in Arm 2 that was reported as unlikely related to treatment. No patients in either arm developed osteonecrosis of the jaw. There were no Grade 4 adverse events definitely, probably or possibly related to treatment (Supplemental Table 1). Zoledronic acid was discontinued

early by 19 patients (Figure 1) and a mean of 5.5 doses per patient was administered. Given the early trial closure, zoledronic acid treatment delivery was not centrally reviewed.

Only two patients experienced a bone fracture (1 in each arm) resulting in no difference in FABF (p=0.95), with a 3-year rate of 98% (95% confidence interval: 94%, 100%) in Arm 1 and 97.4% (92.3%, 100%) in Arm 2. However, BMD percent changes from baseline to 36 months were statistically improved with the use of zoledronic acid compared to observation for the lumbar spine (6% [6%, 6%] vs. −5% [−6%, −4%] respectively, p=<0.0001), left total hip (1% [1%, 1%] vs. −8% [−9%, −7%] respectively, p=0.0002), and left femoral neck (3% [3%, 3%] vs. −8% [−10%, −6%] respectively, p=0.0007). Although not statistically significant, there was also improvement in the BMD percent changes for the right hip (−2% [−4%, 0%] vs. −5% [−7%, −3%], respectively, p=0.4772) and right femoral neck (1% [−1%, 3%] vs. −6% [−8%, −4%], respectively, p=0.0762). Results for BMD are shown in Table 2. Fig. 2 shows the BMD data at 18 and 36 months follow-up.

Out of the 91 men (95% of eligible patients) who consented to QOL data collection, patient compliance for completing the FACT-G was 96% at baseline, 82% at 12 months, 71% at 24 months, and 58% at 36 months. No difference was seen in QOL with the use of zoledronic acid in these patients. The small number of accrued patients resulted in decreased statistical power to detect any differences in QOL or the incidence of bone fractures.

DISCUSSION

The results of RTOG 0518 are in line with other reported studies[7]. Although not meeting the primary endpoint, zoledronic acid effectively prevents bone loss and significantly increases BMD in men treated with ADT and pelvic RT for advanced, non-metastatic prostate cancer. Similarly, other investigators have shown that the rapid bone loss within the first 6 months of ADT is prevented by weekly risedronate as well as weekly alendronate treatment[8,9].

Currently, zoledronic acid is used only to prevent skeletal-related events related to castration-resistant prostate cancer in men with bone metastases. This trial found zoledronic acid also to be useful in the prevention of BMD deterioration associated with ADT among patients without osteoporosis at baseline.

Diamond *et al.* found that the rate of bone loss was 2–8% in the spine and from 1.8–6.5% in the hip in the first year of commencing ADT, and increased with time[10]. His published treatment algorithm has been widely used: if the DEXA scan reveals osteoporosis (T-score < −2.5), then bisphosphonate therapy should be initiated. If the DEXA scan reveals osteopenia (T-score −1 to −2.5) then the DEXA should be repeated in 1 year. If the T-score is >−1, repeat the DEXA scan in 2 years.

The National Osteoporosis Foundation (NOF) of the United States recommends BMD testing for all men aged 70 years or older and for those aged 50 to 69 years if there is concern about osteoporosis on the basis of their risk factor profile[11]. Similarly, the American College of Physicians recommends that clinicians assess older men for osteoporosis risk factors and use DXA scans to screen men at increased risk who are candidates for drug therapy for osteoporosis[12]. The United Kingdom National Osteoporosis Guideline Group uses the absolute 10-year risk of fracture to guide interventions and recommends an age-dependent intervention threshold, which ranges from 7.5% risk of major osteoporotic fracture at age 50 to 30% at age 80[13].

There has been a paradigm shift in the prevention and treatment of osteoporosis and fractures[14,15]. The focus now is on preventing fragility fractures and their negative consequences, rather than on treating low bone mineral density, which is viewed as only one

of several risk factors for fracture[16]. The WHO Fracture Risk Assessment Tool (FRAX)[17] calibrated for use in a specific country, is the most commonly used instrument presently to estimate the 10-year probabilities of a major osteoporosis-related fracture. Treatment is recommended if the risk of major osteoporotic fracture over 10 years exceeds 20%. The FRAX algorithm is utilized by the National Osteoporosis Foundation guideline in the United States[18]. In Canada, patients with a 10-year fracture rate of 10–20% are classified as moderate risk, and factors that warrant consideration for pharmacological therapy include men receiving ADT for prostatic cancer[19].

Denosumab is approved for osteoporosis/fracture in a variety of settings, and is currently the only therapy specifically approved to prevent these bone complications during ADT for prostate cancer. Annual zoledronic acid is also approved for the prevention of osteoporosis/fractures in a variety of patient populations including men with osteoporosis, although it is not specifically approved in men receiving ADT for prostate cancer.

Compared to retrospective studies, RTOG 0518 had undertaken vigorous data collection and analysis. Patients were encouraged to be compliant with vitamin D and calcium supplements and this may account for the very low fracture rate in both arms of this investigation as compared to other studies. Eligible patients for RTOG 0518 do not have T-scores in the osteoporosis range (i.e. worse than −2.5) and as such, would be expected to benefit less from zoledronic acid. It is noteworthy that a recent randomized study on 1199 men with primary or hypogonadism-associated osteoporosis found a significant benefit in the prevention of bone-related events with zoledronic acid use[20]. The rate of any new morphometric vertebral fracture was 1.6% in the zoledronic acid group (5 mg for 2 annual doses) and 4.9% in the placebo group, over a 24-month period, representing a 67% risk reduction with zoledronic acid (relative risk, 0.33; 95% CI: 0.16 to 0.70; P = 0.002).

Although RTOG 0518 also has longer follow-up duration compared to most studies, more fractures would likely be observed with even further duration. Krupski *et al.* found a fracture rate of 25.9% in 3 years of follow-up for men on ADT[3]. At 5 years, this fracture rate increased to 32.9%, and those with longer ADT duration (≥ 697 days) had an even higher proportion of fractures. By the end of the 7-year follow-up period, fracture rates were 46% and 41% for the ADT groups with the longer and shorter durations, respectively. Subjects with a longer duration of ADT experienced a higher proportion of pathologic fractures, osteoporosis/osteopenia, and non-pathologic fractures.

The regimen of zoledronic acid in RTOG 0518 of 4 mg every 6 months for a total of 6 doses was well tolerated. There was 1/50 patients reported to have myocardial infarct in arm 1, compared to 18/588 in the study of Boonen *et al.* which used zoledronic acid 5 mg annually for 2 doses[20]. No patients in the both studies developed osteonecrosis of the jaw.

There is one notable limitation of RTOG 0518 that should be discussed. Due to the early closure, the trial results are limited by small patient numbers. This likely resulted in decreased statistical power to detect any differences in the incidence of bone fractures or QOL.

CONCLUSIONS

Men with prostate cancer are at increased risk for adverse bone effects from both their disease as well as the treatment. In patients with advanced, non-metastatic prostate cancer receiving LHRH agonist and RT, RTOG 0518 showed that the BMD was statistically improved with the use of zoledronic acid in combination with vitamin D and calcium for those with T-score above −2.5. Vitamin D and calcium, by themselves, were insufficient to protect against osteoporosis. The zoledronic acid regimen, 4 mg every 6 months for 6

infusions, is safe and well tolerated. Physicians should assess individual fracture risk with FRAX and decide if medication for prevention of osteoporosis is warranted for patients on ADT for at least one year.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This trial was conducted by the Radiation Therapy Oncology Group (RTOG), and was supported by RTOG grant U10 CA21661 and CCOP grant U10 CA37422 from the National Cancer Institute (NCI). This manuscript's contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute. Zometa® was manufactured and packaged by Novartis and provided to patients on study.

REFERENCES

1. Lawton CA, Winter K, Murray K, Machtay M, Mesic JB, Hanks GE, et al. Updated results of the phase III Radiation Therapy Oncology Group (RTOG) trial 85–31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavorable prognosis carcinoma of the prostate. Int J Radiat Oncol Biol Phys. 2001; 49(4):937–946. [PubMed: 11240234]
2. Bruder JM, Ma JZ, Basler JW, Welch MD. Prevalence of osteopenia and osteoporosis by central and peripheral bone mineral density in men with prostate cancer during androgen-deprivation therapy. Urology. 2006; 67(1):152–155. [PubMed: 16413352]
3. Krupski TL, Smith MR, Lee WC, Pashos CL, Brandman J, Wang Q, et al. Natural history of bone complications in men with prostate carcinoma initiating androgen deprivation therapy. Cancer. 2004; 101(3):541–549. [PubMed: 15274067]
4. Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol. 2003; 169(6):2008–2012. [PubMed: 12771706]
5. Zelen M. The randomization and stratification of patients to clinical trials. J Chronic Dis. 1974; 27(7–8):365–375. [PubMed: 4612056]
6. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993; 11(3):570–579. [PubMed: 8445433]
7. Serpa Neto A, Tobias-Machado M, Esteves MA, Senra MD, Wroclawski ML, Fonseca FL, et al. Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2012; 15(1):36–44. [PubMed: 21894175]
8. Taxel P, Dowsett R, Richter L, Fall P, Klepinger A, Albertsen P. Risedronate prevents early bone loss and increased bone turnover in the first 6 months of luteinizing hormone-releasing hormone-agonist therapy for prostate cancer. BJU Int. 2010; 106(10):1473–1476. [PubMed: 20456336]
9. Greenspan SL, Nelson JB, Trump DL, Resnick NM. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. Ann Intern Med. 2007; 146(6):416–424. [PubMed: 17371886]
10. Diamond TH, Higano CS, Smith MR, Guise TA, Singer FR. Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: recommendations for diagnosis and therapies. Cancer. 2004; 100(5):892–899. [PubMed: 14983482]
11. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation; 2008.
12. Qaseem A, Snow V, Shekelle P, Hopkins R Jr, Forciea MA, Owens DK. Screening for osteoporosis in men: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008; 148(9):680–684. [PubMed: 18458281]

13. Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A. Case finding for the management of osteoporosis with FRAX--assessment and intervention thresholds for the UK. Osteoporos Int. 2008; 19(10):1395–1408. [PubMed: 18751937]

14. Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ. 2002; 167(10 Suppl):S1–S34. [PubMed: 12427685]

15. Cheung AM, Detsky AS. Osteoporosis and fractures: missing the bridge? JAMA. 2008; 299(12): 1468–1470. [PubMed: 18364489]

16. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ. 2010; 182(17):1864–1873. [PubMed: 20940232]

17. World Health Organization. FRAX WHO Fracture Risk Assessment Tool. World Health Organization; 2012. Available at www.shef.ac.uk/FRAX/. [Accessed 6/10/2013]

18. Saylor PJ, Kaufman DS, Michaelson MD, Lee RJ, Smith MR. Application of a fracture risk algorithm to men treated with androgen deprivation therapy for prostate cancer. J Urol. 2010; 183(6):2200–2205. [PubMed: 20399451]

19. [last accessed September 2012] Osteoporosis Canada. Available at www.osteoporosis.ca

20. Boonen S, Reginster JY, Kaufman JM, Lippuner K, Zanchetta J, Langdahl B, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. N Engl J Med. 2012; 367(18):1714–1723. [PubMed: 23113482]

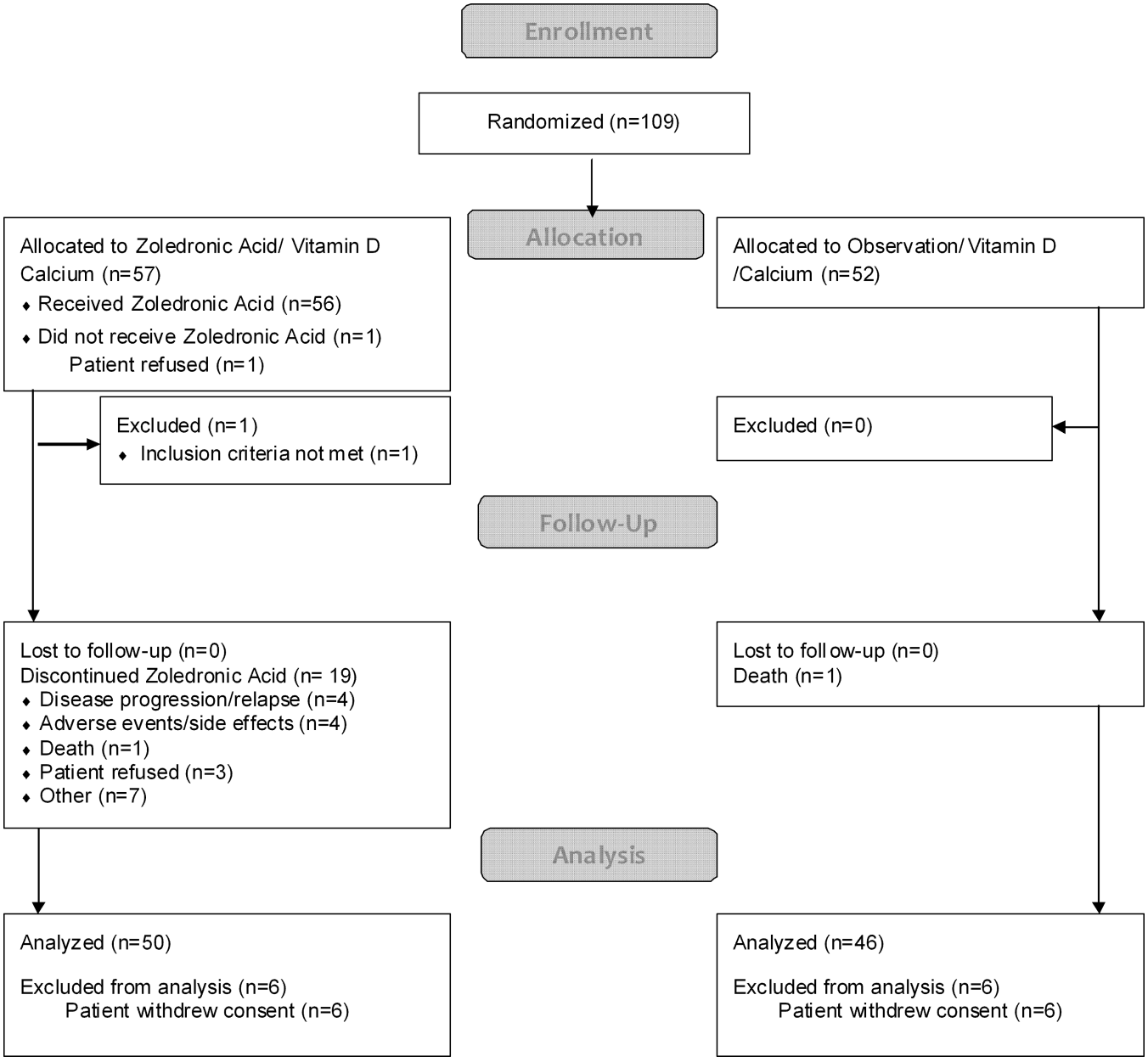

Figure 1.
Consort diagram of RTOG 0518

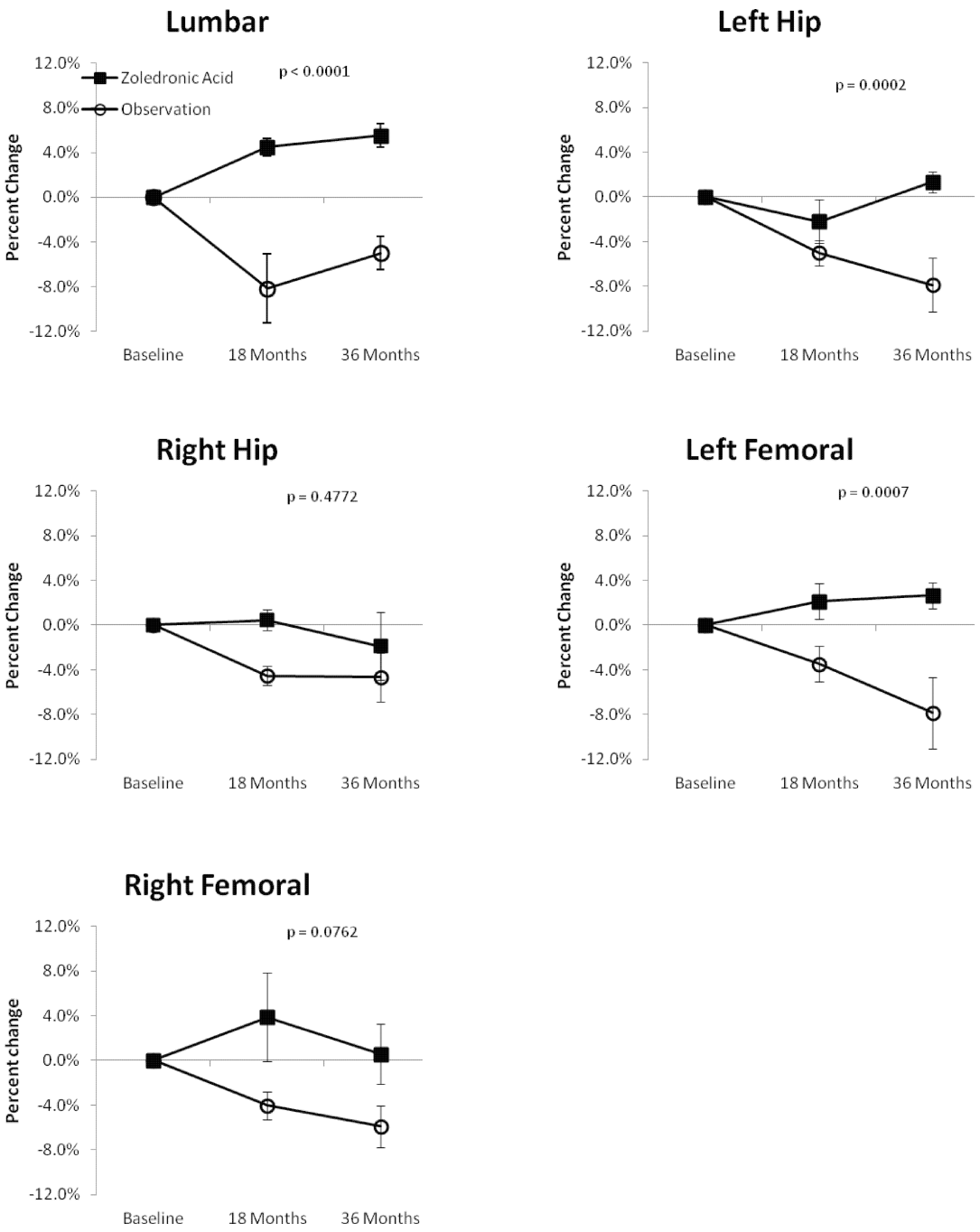

Figure 2.

Mean (± SE) percent change from baseline in bone mineral density (BMD) 18 and 36 months follow-up. P-values are for between-arm comparisons of the percent change from baseline to 36 months.

Table 1

Pretreatment characteristics

	Vitamin D/Calcium/ Zoledronic Acid (n=50)	Vitamin D/Calcium (n=46)
Age (years)		
Median	70	71
Min - Max	51 – 87	56 – 84
Q1 – Q3 (Q1 = first quartile; Q3 = third quartile)	62 – 75	66 – 75
Race		
Black or African American	4 (8.0%)	3 (6.5%)
White	46 (92.0%)	43 (93.5%)
Ethnicity		
Not Hispanic or Latino	50 (100.0%)	45 (97.8%)
Unknown	0 (0.0%)	1 (2.2%)
Zubrod Performance Status		
0	49 (98.0%)	41 (89.1%)
1	1 (2.0%)	5 (10.9%)
Gleason		
6	1 (2.0%)	3 (6.5%)
7	15 (30.0%)	11 (23.9%)
8–10	34 (68.0%)	32 (69.6%)
T Stage		
T1	9 (18.0%)	16 (34.8%)
T2	27 (54.0%)	19 (41.3%)
T3	14 (28.0%)	11 (23.9%)
N Stage		
N0	44 (88.0%)	41 (89.1%)
N1	2 (4.0%)	1 (2.2%)
NX	4 (8.0%)	4 (8.7%)
LHRH Therapy, Planned Duration (Stratification factor)		
≤ 2.5 years (at least 1 year)	36 (72.0%)	31 (67.4%)
> 2.5 years	14 (28.0%)	15 (32.6%)
DXA Scan T Score (Hip) (Stratification factor)		
< −1.0 (greater than −2.5)	23 (46.0%)	21 (45.7%)
≥ −1.0	27 (54.0%)	25 (54.3%)

Prostate Cancer Prostatic Dis. Author manuscript; available in PMC 2014 June 01.

Table 2

Bone mineral density (BMD) results

Location	Time point	Descriptive statistics	Vitamin D/Calcium/ Zoledronic Acid	Vitamin D/ Calcium	Total	p-value*
Lumbar	Baseline		(n=49)	(n=43)	(n=92)	
		Mean (SD)	1.22 (0.03)	1.44 (0.21)	1.32 (0.10)	0.2879
		Median (range)	1.18 (0.90 – 2.00)	1.24 (0.86 – 10.15)	1.21 (0.86 – 10.15)	
	% change at 36 months		(n=26)	(n=14)	(n=40)	
		Mean (SD)	6% (0.01)	−5% (0.01)	2% (0.01)	<0.0001†
		Median (range)	5% (−0.05 – 0.15)	−3% (−0.19 – 0.01)	1% (−0.19 – 0.15)	
Right hip	Baseline		(n=15)	(n=14)	(n=29)	
		Mean (SD)	1.00 (0.03)	1.01 (0.03)	1.01 (0.02)	0.9643
		Median (range)	1.01 (0.75 – 1.25)	1.00 (0.85 – 1.19)	1.01 (0.75 – 1.25)	
	% change at 36 months		(n=6)	(n=6)	(n=12)	
		Mean (SD)	−2% (0.03)	−5% (0.02)	−3% (0.02)	0.4772
		Median (range)	1% (−0.17 – 0.03)	−3% (−0.13 – 0.01)	−1% (−0.17 – 0.03)	
Left hip	Baseline		(n=40)	(n=37)	(n=77)	
		Mean (SD)	1.02 (0.02)	1.00 (0.02)	1.01 (0.01)	0.3430
		Median (range)	1.02 (0.77 – 1.52)	0.99 (0.80 – 1.27)	1.00 (0.77 – 1.52)	
	% change at 36 months		(n=19)	(n=9)	(n=28)	
		Mean (SD)	1% (0.01)	−8% (0.02)	−2% (0.01)	0.0002†
		Median (range)	1% (−0.06 – 0.13)	−9% (−0.18 – 0.03)	0% (−0.18 – 0.13)	
Right femoral neck	Baseline		(n=15)	(n=11)	(n=26)	
		Mean (SD)	0.89 (0.03)	0.86 (0.04)	0.88 (0.03)	0.6404
		Median (range)	0.90 (0.70 – 1.17)	0.89 (0.55 – 1.05)	0.89 (0.55 – 1.17)	
	% change at 36 months		(n=6)	(n=6)	(n=12)	
		Mean (SD)	1% (0.03)	−6% (0.02)	−3% (0.02)	0.0762
		Median (range)	3% (−0.13 – 0.04)	−9% (−0.09 – 0.00)	0% (−0.13 – 0.04)	
Left femoral neck	Baseline		(n=42)	(n=34)	(n=76)	
		Mean (SD)	0.87 (0.03)	0.87 (0.02)	0.87 (0.02)	0.9059
		Median (range)	0.85 (0.59 – 1.52)	0.86 (0.62 – 1.22)	0.86 (0.59 – 1.52)	
	% change at 36 months		(n=20)	(n=10)	(n=30)	

Location	Time point	Descriptive statistics	Vitamin D/Calcium/ Zoledronic Acid	Vitamin D/ Calcium	Total	p-value*
		Mean (SD)	3% (0.01)	−8% (0.03)	−1% (0.02)	0.0007†
		Median (range)	3% (−0.08 – 0.12)	−4% (−0.26 – 0.03)	2% (−0.26 – 0.12)	

*p-value comes from t test statistic;

†statistically significant at 0.05 level; n, number of patients; SD, standard deviation.