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Safety of zoledronic acid and incidence of osteonecrosis of the jaw (ONJ) during adjuvant therapy in a randomised phase III trial (AZURE – BIG 01-04) for women with stage II/III breast cancer

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ABSTRACT

Purpose. The AZURE trial is an ongoing phase III, academic, multi-centre, randomised trial designed to evaluate the role of zoledronic acid (ZOL) in the adjuvant therapy of women with stage II/III breast cancer. Here we report the safety and tolerability profile of ZOL in this setting.

Patients and methods. Eligible patients received (neo)adjuvant chemotherapy and/or endocrine therapy and were randomised to receive either no additional treatment or intravenous ZOL 4mg. ZOL was administered after each chemotherapy cycle to exploit potential sequence dependent synergy. ZOL was continued for 60 months post-randomisation (6 doses in the first 6 months, 8 doses in the following 24 months and 5 doses in the final 30 months). Serious (SAE) and non-serious adverse event (AE) data generated during the first 36 months on study were analysed for the safety population.

Results. 3360 patients were recruited to the AZURE trial. The safety population comprised 3340 patients (ZOL 1665; control 1675). The addition of ZOL to standard treatment did not significantly impact on chemotherapy delivery. SAE were similar in both treatment arms. No significant safety differences were seen apart from the occurrence of osteonecrosis of the jaw (ONJ) in the ZOL group (11 confirmed cases; 0.7%; 95% confidence interval 0.3% to 1.1%).

Conclusions. ZOL in the adjuvant setting is well tolerated, and can be safely administered in addition to adjuvant therapy including chemotherapy. The adverse events were consistent with the known safety profile of ZOL, with a low incidence of ONJ.

Key words: Breast cancer; zoledronic acid; adjuvant therapy; safety; osteonecrosis of the jaw.

BACKGROUND

Despite significant advances in the adjuvant treatment of early breast cancer, the disease still results in approximately 410,000 global deaths each year [1,2]. The "AZURE" phase III trial is investigating whether addition of the bisphosphonate zoledronic acid (ZOL) to standard adjuvant treatments further improves the disease-free survival (DFS) of stage II/III breast cancer patients.

Widely used in benign and malignant bone diseases, the bisphosphonates have become familiar agents in routine clinical practice. ZOL is a bisphosphonate that efficiently inhibits osteoclast function, resulting in profound inhibition of bone resorption. Additionally a body of evidence is emerging that describes anti-tumour activity of bisphosphonates, including evidence of synergy with cytotoxic agents[3,4]. In the clinical setting, a phase III study in 1,800 pre-menopausal women with oestrogen receptor positive disease, demonstrated a 36% reduction in the risk of developing recurrent disease from the addition of ZOL to endocrine therapy [5].

Bisphosphonates are generally well tolerated, with renal dysfunction [6] and osteonecrosis of the jaw (ONJ) the only clinically important toxicities associated with their use [7,8]. However, combining ZOL with chemotherapy has the potential for enhanced toxicity, especially if there is a synergistic interaction with chemotherapy on normal tissues. Safety evaluation within the AZURE trial is the ideal opportunity to assess this. Here we report the largest dataset evaluating safety of ZOL outside the metastatic setting and the first analysis at this intensive dosing schedule addressing specific adverse events of note including renal

and cardiovascular effects, outcomes of pregnancies and ONJ as well as potential effects on chemotherapy related side-effects such as neutropaenic fever and mucositis.

PATIENTS AND METHODS

AZURE is a multi-centre, international, open label, randomised parallel group trial (ISRCTN79831382). Figure 1 shows the trial schema. Eligible patients were women with stage II/III breast cancer scheduled to receive (neo)adjuvant chemotherapy and/or endocrine therapy, of ECOG performance status 0-1 and aged ≥18 years. Patients with abnormalities of bone metabolism, prior treatment with bisphosphonates within 1 year, or evidence of renal impairment (serum creatinine >1.5 times upper limit of normal) were excluded. All patients gave written informed consent before study entry.

ZOL was administered at a dose of 4mg intravenous (i.v.) over 15 minutes. Dose reductions and interuptions for renal impairment (calculated creatinine clearance <60ml/minute) were as specified by the current prescribing information. Chemotherapy- or endocrine-related toxicities were handled according to local protocols.

Baseline and safety assessments

Safety assessments consisted of recording and immediate reporting of all serious adverse events (SAEs), recording of adverse events (AEs) potentially related to either treatment or the disease process using Common Toxicity Criteria (CTC) [9], regular monitoring of blood chemistry and physical examinations. AEs considered unrelated to the study drug, cancer treatment(s) or the disease process were not routinely collected. SAEs were described according to duration, seriousness, relationship to study drug or underlying cancer and any

action taken. Serum creatinine was measured at baseline and every treatment visit for patients receiving ZOL. In the control arm, renal monitoring was required at baseline, three and six months and then at the same frequency as the ZOL arm.

SAEs were sent to the Clinical Trials Research Unit (CTRU), Leeds, whilst non-serious AE data were sent to the local participating clinical trials units. All safety data were overseen by an independent Data Monitoring and Ethics Committee. Additionally, a Trial Steering Committee (TSC) was established to provide overall supervision of the trial including patient safety.

In February 2004, following the emergence of a potential link between ONJ and bisphosphonates [10], the patient information sheet was revised to address this possible risk and consent was re-obtained for those patients already enrolled. The protocol was amended in July 2005 to exclude patients with significant active dental problems or recent jaw surgery. In May 2006, dental hygiene advice was distributed to all patients, and guidance on the diagnosis, prevention and treatment of ONJ based on emerging clinical guidelines provided to all investigators. Investigators were requested to report all possible cases of ONJ as serious adverse events for central review. This triggered a request for additional detailed information on clinical features, prior dental interventions, imaging and biopsy results for central review. A diagnosis of ONJ was “confirmed” if the description conformed to the definition stipulated in the guidance documents from the American Association of Oro-Maxillary Surgeons (AAOMS)[11] and the American Association for Bone and Mineral Research (ASBMR) [8]. All other cases reported by investigators were classified as “possible ONJ”.

Statistical methods

Patients were stratified by participating centre and randomised using minimisation to ensure lymph node involvement, tumour stage, ER status, type of adjuvant systemic therapy, use of statins and menopausal status were similar in both arms.

Two time periods have been evaluated: i) randomisation to 6 months to capture safety information during (neo)adjuvant chemotherapy and ii) 6 months to 3 years to represent the follow-up period when ZOL was given alone in the treatment arm (+/- endocrine treatments according to ER status or trastuzumab for HER2 positive patients recruited during 2005/6).

ONJ rates were calculated using cumulative incidence functions, where deaths without diagnosis of ONJ were considered competing-risk events, and compared using the log-rank test. Patients without evidence of ONJ were censored at date of death or the last date they were known to be alive. Hypothesis testing was at the 5% significance level (2-sided) and performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Safety population

This safety analysis includes data from the first 3 years of follow up from randomisation for which we have complete data in approximately 95% of patients. Patients are included in the treatment group to which they were randomised. In the treatment arm, patients who did not receive any ZOL have been excluded from the safety population. Control patients who received ZOL at a later visit (regardless of the reason) have been censored at the time of

first administration. Patients who developed distant metastasis have been censored at the time this was confirmed.

RESULTS

Patient population

The AZURE trial recruited 3360 patients between September 2003 and February 2006 from 174 centres. The safety population comprises 3340 patients, 1675 patients in the control arm (CONTROL) and 1665 patients in the zoledronic acid arm (ZOL). 1600 CONTROL and 1590 ZOL patients received chemotherapy. The treatment groups were well balanced in terms of baseline characteristics (table 1).

Chemotherapy phase (randomisation – 6 months)

Overall safety profile

The addition of 3-4 weekly ZOL to standard treatment did not affect tolerability or safety of systemic treatment. The most frequent AEs occurring in >10% of patients are listed in table 2. The proportions of patients reporting one or more AEs were similar (CONTROL 91.4% versus (vs) ZOL 93.1%). The median number of AEs per patient was equal in both groups (n=14, range 1-75). 45031 AEs were reported in total (CONTROL 22255 vs ZOL 22776); grade 3 or 4 AEs reported were of similar frequency (CONTROL 1035 [4.7%] vs. ZOL 1116 [4.9%]). Myalgia/arthralgia was the only AE to show a significant difference in frequency (CONTROL 374 [23.4%] vs ZOL 456 [28.7%]; p=<.05), probably reflecting the well characterised acute phase response to zoledronic acid.

SAEs were reported among 22.0% (352/1600) and 24.5% (389/1590) of patients in the CONTROL and ZOL groups respectively (Table 3). 1007 SAEs were reported in total (CONTROL 480 vs. ZOL 527). Amongst patients receiving ZOL, the SAE was suspected to be related to ZOL in 14 (2.7%): pyrexia (n=7), anaphylactic reaction (n=2), ONJ (n=1), pain (n=1), vomiting (n=1), iritis (n=1) and elevated creatinine (n=1). The most common SAE was neutropenic sepsis (CONTROL 9.3% vs. ZOL 9.4%). All other SAEs occurred in less than 3% of patients.

Chemotherapy duration and dose reductions

The median duration of chemotherapy delivery was similar in both groups (CONTROL 4.0 months vs. ZOL 3.9 months). Chemotherapy dose reductions were required in 230/1600 [14.4%] CONTROL and 209/1590 (13.1%) ZOL patients. The duration of chemotherapy and number of dose reductions were similar in both the neoadjuvant and post-operative settings (data not shown).

Renal toxicity

Serum creatinine data were available for 3278 (98%) patients (CONTROL 1648 vs. ZOL 1630). Mean baseline serum creatinine levels were similar (CONTROL 73.6mmol/l [S.D. 13.87] vs. ZOL 73.7mmol/l [S.D. 13.64]), and remained similar to baseline levels in both groups. During the adjuvant chemotherapy phase, renal failure was reported as an SAE in 3 cases (CONTROL 1 vs. ZOL 2). The 2 cases in the ZOL group were reported as not suspected to be related to the bisphosphonate. Additionally, increases in serum creatinine of any CTC grade were uncommon (CONTROL 0.5% vs. ZOL 0.4%). ZOL was delayed in accordance with the

product characteristics in 7 patients and/or the dose reduced at the clinician's discretion in 6 patients due to a decline in calculated creatinine clearance.

Dental adverse events

Dental problems were reported as an AE in 62 patients (1.9%) (CONTROL 27 [1.7%] vs. ZOL 35 [2.2%]). Jaw pain was reported more frequently in the ZOL arm (CONTROL 7 [0.4%] vs. ZOL 29 [1.8%]). One confirmed case of ONJ was reported during adjuvant chemotherapy (see below).

Early deaths on treatment

13 patients died within 6 months of randomisation, (CONTROL 8 [0.5%] vs. ZOL 5 [0.3%]. Primary causes of death within the control arm were recorded as: "chemotherapy toxicity" (n=4), pneumonia (n=1), septicaemia (n=1), thrombo-embolic disease (n=1) and suicide (n=1). Primary causes of death within the ZOL arm were recorded as: "breast cancer related" (n=1), "chemotherapy toxicity" (n=1), pulmonary embolus (n=1), cardiac failure (n=1) and unknown (n=1).

<u>Post chemotherapy phase (6 months-3 years)</u>

During this period ZOL continued to be administered every 3 months from month 9 until 30 months on study and then every 6 months until 60 months. During this phase no patient received chemotherapy. Trastuzumab and/or endocrine therapy were given as per local guidelines.

Overall safety profile

Overall the administration of ZOL was well-tolerated and without significant additional toxicity. SAE were reported in 289 (8.7%) patients (CONTROL 137/1675 [8.2%] vs. ZOL 152/1665 [9.1%]). 335 SAEs were reported in total (CONTROL 155 vs. ZOL 180). The most frequent SAEs occuring in >0.2% of patients are displayed in table 4. No single SAE occurred in >1% of patients.

Effects on renal function

2 cases (<0.1%) of renal failure were described as SAEs, 1 case in each arm. The case of renal failure in the patient receiving ZOL occurred in a 44 year old patient following 12 doses of ZOL, 1065 days from randomisation. She had acute renal failure and hypercalcaemia, not suspected to be related to ZOL.

Other adverse events of interest

Osteonecrosis of the jaw

11 patients with confirmed ONJ (0.7%, 95% confidence interval (CI) 0.3% to 1.2%) have been reported in the ZOL arm (1 during chemotherapy, 10 in follow-up period) whilst no cases have been reported in the control arm (log-rank test = 10.9808, degrees of freedom = 1, p = 0.0009). Cases were confirmed according to published definitions [8,11]. In 5 patients ONJ affected more than one site. All were suspected to be related to treatment with ZOL (Table 5). An additional four cases in the ZOL arm were reported by the investigator as possible ONJ did not meet the diagnostic criteria for a definitive diagnosis.

The case during adjuvant chemotherapy followed a dental abscess requiring extraction after the 1st ZOL infusion. Affecting both the mandible and maxilla, the condition was confirmed

after the 6th infusion when ZOL was discontinued. Following resolution of ONJ a year later, ZOL was reintroduced without any subsequent recurrence of ONJ.

The median number of ZOL 4mg infusions prior to confirmation of ONJ was 10 (range 6-14). The median age of patients at time of confirmation of ONJ was 54 years (range 39-72). 9 cases underwent a dental extraction prior to the diagnosis of ONJ. The median time from randomisation to confirmation of ONJ was 746 days (range 238-1029). Outcomes of cases to date are as follows: "completely recovered" n=4; "recovered with sequelae" n=2; "improving" n=2; "condition present and unchanged" n=3.

In addition, two patients in the ZOL group developed avascular necrosis (AVN) of the femoral head (one bilateral). Both AVN patients had received chemotherapy and corticosteroids in the preceding three months. In both cases ZOL was discontinued, although a causal association could not be established.

Cardiovascular events

During chemotherapy, a cardiovascular SAE was reported in 71 (2.2%) patients (CONTROL 29 [1.8%] vs. ZOL 42 [2.6%]). Between 6 and 36 months, 29 cardiovascular SAE were reported (CONTROL 11 [0.7%] vs. ZOL 18 [1.1%]. These events were (CONTROL vs. ZOL arm): pulmonary embolus (12 vs. 22); deep vein thrombosis (15 vs. 11); loss of consciousness (2 vs. 7); atrial fibrillation/flutter (2 vs. 3); cerebrovascular accident (3 vs. 5); transient ischaemic attacks (2 vs. 2); dizziness (1 vs. 2); ventricular tachycardia (1 vs. 0); myocardial infarction (1 vs. 3); left ventricular failure (0 vs. 2); palpitations (1 vs. 2);

cardiomyopathy (0 vs. 1). None of the events were suspected to be related to ZOL, and differences between groups do not reach statistical significance.

Pregnancies whilst on study

15 patients from the defined safety population became pregnant (CONTROL 6 vs. ZOL 9). Two patients (1 from each arm) became pregnant twice, resulting in a total of 17 pregnancies. 9 of these pregnancies were aborted (6 planned terminations, 3 spontaneous abortions), 7 resulted in live births (CONTROL 3, ZOL 4), while in the remaining case the outcome of the pregancy is not known. Of the 4 ZOL treated patients who had a live birth, the first had 12 doses and stopped treatment 11 months prior to delivery, the second had 11 doses, stopping 18 months prior to delivery, the third had 11 doses, stopping 15 months prior to delivery, while the fourth received 10 doses but the time between her last zoledronic acid treatment cannot be determined. No overt abnormalities were seen at delivery or have been subsequently reported in any of the live births.

New primary cancers

From randomisation to 3 years follow up, 55 (1.6%) patients have developed a second malignancy (CONTROL 30 [1.8%] vs. ZOL 25 [1.5%]). Sites of second cancer were (CONTROL vs. ZOL): contralateral breast (8 vs. 10), haematological (3 vs. 3), unknown primary site (6 vs. 2), skin (2 vs. 3), lung (2 vs. 1), endometrium (0 vs. 3), colon (2 vs. 1), brain (2 vs. 1), bladder (2 vs. 0), tongue (1 vs. 1), cervix (1 vs. 0) ovary (1 vs. 0).

DISCUSSION

We report the largest safety analysis of zoledronic acid given on an intensive schedule in the non-metastatic cancer setting. This extensive body of data from a randomised trial confirms that ZOL can be given safely in combination with chemotherapy, without significant impact on toxicity of chemotherapy. Although not formally calculated, the similar duration of chemotherapy and frequency of dose reductions indicate that ZOL had no clinically relevant impact on the dose intensity of chemotherapy.

This is the first study to report on the use of ZOL in the adjuvant setting combined with chemotherapy. The ABCSG-12, ZOFAST, Z-FAST, EZO-FAST studies all evaluated ZOL alongside hormonal therapy in the adjuvant setting, and with a less intensive 6-monthly schedule [5,12,13,14]. As in these trials, with the usual advice given to patients on minimising the effects of the acute phase reaction and renal monitoring [15], the toxicity impact of ZOL was minimal with the exception of a low frequency of ONJ. At the time of data lock, all patients had completed at least 3 years of treatment and we were in receipt of >95% of data related to these treatment. With the possible exception of ONJ, for which patients remain at risk throughout years 4 and 5 on treatment (and potentially beyond completion of treatment), further additional safety signals of note are unlikely to emerge now that treatment administration is on a 6 monthly frequency. However, this will be fully evaluated in future reports as the study matures.

The association between bisphosphonate use and ONJ was first described in 2003 [10]. Causation has been difficult to prove and the pathogenesis of the condition uncertain and probably multifactorial. ONJ is also associated with the use of denosumab [16], suggesting

that the suppression of osteoclast numbers and function has a central role in the pathophysiology of this condition. However, ONJ has also been reported in association with angiogenesis inhibitors such as bevacizumab [17], supporting the notion of mulitple aetiological factors. The incidence of ONJ amongst patients receiving oral bisphosphonate for osteoporosis is very low (<1 in 10,000), and substantially less than is seen with intravenous bisphosphonates for advanced malignancy [11]. In the metastatic setting, it has been concluded that dental interventions, disease and treatment related immune suppression, duration of exposure and number of bisphosphonate infusions are the most significant risk factors for development of the condition [8,11]. The incidence of ONJ in metastatic cancer has been estimated at 0.8-12% (2.9-5.3% in breast cancer) [8,11,18,19], with an average of approximately 1% per year on treatment [20].

In AZURE, the low frequency of ONJ (0.7%, 95% CI 0.3% to 1.1%)) is likely to reflect less immune suppression than occurs in the metastatic setting, limited exposure to chemotherapy, careful monitoring, and conservative dental intervention whenever possible, plus the less intensive schedule used once the initial 6 month chemotherapy phase was completed. However, the frequency of ONJ appears more than has been reported with 6 monthly ZOL in the ABCSG-12, ZOFAST, Z-FAST and EZO-FAST studies. Here only two possible cases of ONJ have been reported out of >4000 patients [5, 12, 13, 14].

In advanced cancer, renal effects related to dose, infusion duration and total number of infusions of ZOL may be seen [6]. It is likely that in the advanced setting, nephrotoxicity is multifactorial, compounded by advancing cancer, co-morbidities and other drugs [21].

However, our results indicate that ZOL given in the adjuvant setting for patients with early breast cancer has no significant impact on renal function.

The initial reports of atrial fibrillation (AF) in relation to ZOL use came from outside the cancer setting. In the HORIZON study of postmenopausal women with osteoporosis, serious AF (new or recurrent) was seen in 1.3% of patients receiving ZOL compared to 0.5% in the control arm [22]. No clear association between bisphosphonates and AF could be identified in subsequent safety reviews [23,24]. However, a recent claims based analysis of 6857 cancer patients aged >65 and receiving bisphosphonates identified an approximate 30% increased risk for both AF and supraventricular tachycardias (SVT) when compared with matched cancer controls [25]. In our study, it is possible that some non serious episodes of AF or other supraventricular tachycardias were not reported as these were not adverse events of interest until the initial reports in 2007. However, our findings do not suggest any clinically relevant excess risk for AF with use of zoledronic acid in the adjuvant setting. A numerical excess of cardiovascular SAE was reported but there was no significant excess of any individual cardiovascular event in the ZOL arm, and very similar numbers of arhhythmias.

Bisphosphonates have been shown to cross the placenta in pre-clinical studies, raising concern for birth defects [26,27]. The few case reports of bisphosphonate administration during pregnancy are, however, reassuring [28,29]. Of the pregnancies which went to term in the ZOL arm of AZURE, all were planned and therefore ZOL was stopped before conception. Despite this, there remains concern that, due to the long retention time of bisphosphonates in bone, foetal exposure may occur even if the drug is stopped long before

conception [29]. A recent study of pre-pregnancy or early pregnancy exposure to alendronate (n=20) reported no major malformations and 5 spontaneous abortions [30]. In another series who received bisphosphonates (not ZOL) within 12 months of conception or during the first trimester of pregnancy (n=21), no increased risk of birth defects was seen [29]. There were no published reports found of exposure to ZOL and pregnancy outcome, but concerns regarding foetal development remain due to the potency and long offset duration of ZOL [31].

CONCLUSION

This safety analysis expands our understanding of the tolerability and risks of ZOL in the adjuvant setting and shows that it can be administered safely without compromising chemotherapy delivery. A low incidence of ONJ was observed. If the efficacy of adjuvant ZOL is confirmed and does become part of standard adjuvant treatment, this report is reassuring and predicts for a favourable risk-benefit ratio.

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Legend to Figures:

Figure 1: Trial schema. “Standard therapy” refers to any locally approved cytotoxic chemotherapeutic or endocrine agents

Figure 2: CONSORT diagram of patient disposition in trial

Figure 1:

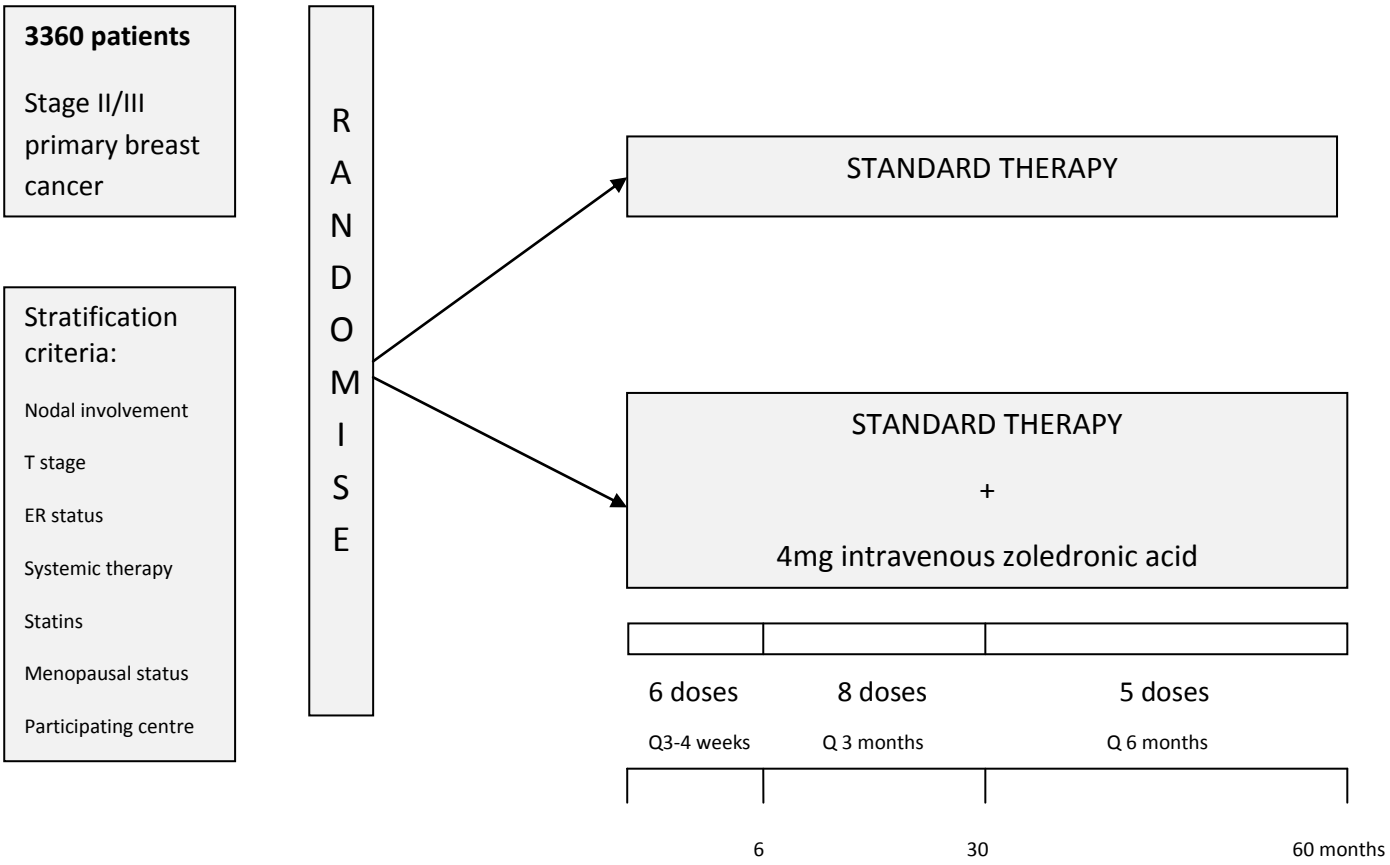
3360 patients
Stage II/III primary breast cancer
Stratification criteria:
Nodal involvement
T stage
ER status
Systemic therapy
Statins
Menopausal status
Participating centre
RANDOMISE
STANDARD THERAPY
STANDARD THERAPY
+
4mg intravenous zoledronic acid
6 doses
Q3-4 weeks
8 doses
Q 3 months
5 doses
Q 6 months
6
30
60 months

Figure 2:

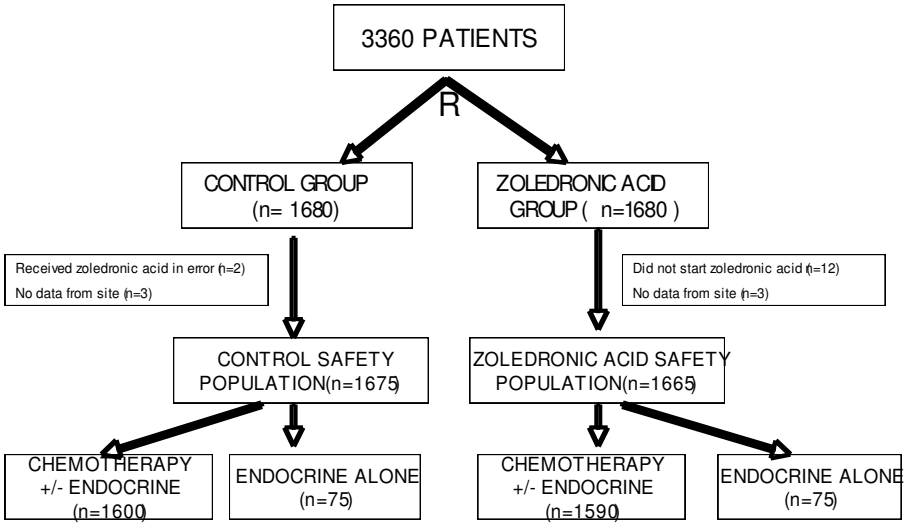

Table 1: Table of baseline characteristics and (neo)adjuvant treatments

	CONTROL GROUP		ZOL GROUP	
	Number	**Percent**	**Number**	**Percent**
Lymph node involvement				
1 to 3 nodes involved	1007	60.1	1010	60.7
≥4 nodes involved	565	33.7	556	33.4
Unknown (neoadjuvant)	100	6.0	96	5.8
Sentinel node +ve - Ax. RT	3	0.2	3	0.2
Tumour stage				
T1	522	31.2	535	32.1
T2	867	51.8	845	50.8
T3	226	13.5	225	13.5
T4	59	3.5	57	3.4
TX	1	0.1	3	0.2
ER status				
ER positive	1285	76.7	1281	76.9
ER negative	345	20.6	345	20.7
ER unknown	45	2.7	39	2.3
Neoadjuvant therapy				
Yes	108	6.4	105	6.3
No	1567	93.6	1560	93.7

Systemic therapy				
Endocrine therapy alone	75	4.5	75	4.5
Chemotherapy alone	360	21.5	361	21.7
Endocrine + chemotherapy	1240	74.0	1229	73.8
Anthracyclines				
Yes	1561	93.2	1553	93.3
No	114	6.8	112	6.7
Taxanes				
Yes	383	22.9	385	23.1
No	1292	77.1	1280	76.9
Use of statins				
Yes	100	6.0	94	5.6
No	1575	94.0	1571	94.4
Menopausal status				
Pre-menopausal	749	44.7	744	44.7
≤ 5 years since menopause	243	14.5	245	14.7
> 5 years since menopause	524	31.3	513	30.8
Status unknown	159	9.5	163	9.8

Abbreviations: ZOL=zoledronic acid; ER=oestrogen receptor; Ax. RT=axillary radiotherapy

Table 2: Number and percentage of AEs (all grades and occuring in >10% of patients) during adjuvant chemotherapy period (randomisation to 6 months).

	Control group	ZOL group
	Number (%)	Number (%)
Alopecia	1116 (69.8%)	1113 (70.0%)
Nausea	1034 (64.6%)	1064 (66.9%)
Fatigue/lethergy	962 (60.1%)	957 (60.2%)
Constipation	672 (42.0%)	699 (44.0%)
Vomiting	555 (34.7%)	529 (33.3%)
Mucositis/stomatitis	525 (32.8%)	514 (32.3%)
Myalgia/arthralgia*	374 (23.4%)	456 (28.7%)
Diarrhoea	360 (22.5%)	344 (21.6%)
Infection	339 (21.2%)	329 (20.7%)
Stomatitis	275 (17.2%)	283 (17.8%)
Indigestion	272 (17.0%)	274 (17.2%)
Skin	286 (17.9%)	254 (16.0%)
Neutropenia	253 (15.8%)	247 (15.5%)
Neurosensory	199 (12.4%)	206 (13.0%)
Hot flushes	172 (10.8%)	173 (10.9%)
Phlebitis	164 (10.3%)	163 (10.3%)
Taste disturbance	158 (9.9%)	167 (10.5%)
Headache	154 (9.6%)	165 (10.4%)

* significant difference noted between treatment groups p = <.05

Table 3: SAEs occurring in >1% patients in either treatment group during the adjuvant chemotherapy period (randomisation to 6 months); % represents percentage patients reporting the SAE

	Control Group		ZOL Group	
	Number of patients	**Percent**	**Number of patients**	**Percent**
Neutropenic sepsis	148	9.3	149	9.4
Neutropenia	46	2.9	38	2.4
Pyrexia	20	1.3	35	2.2
Vomiting	21	1.3	33	2.1
Lower Respiratory Tract Infection	25	1.6	16	1.0
Central line infection	15	0.9	20	1.3
Pulmonary Embolus	11	0.7	17	1.1

Table 4: Most frequent SAEs occurring in >0.2% of patients overall from 6 months post-randomisation to 3 years follow up

	Control Group		ZOL Group	
	Number	**Percent**	**Number**	**Percent**
Cellulitis	8	0.5	10	0.6
Neutropenic sepsis	10	0.6	8	0.5
New primary breast Cancer	8	0.5	9	0.5
Chest pain	6	0.4	6	0.4
Osteonecrosis of Jaw	0	0.0	14*	0.8
Central line infection	5	0.3	5	0.3
Wound infection	6	0.4	4	0.2
Chest infection	5	0.3	4	0.2
Pyrexia	4	0.2	3	0.2
Breast infection	2	0.1	5	0.3

* only 10 confirmed

Table 5: Details of the 11 confirmed ONJ cases.

ONJ case no.	Age at diagnosis of ONJ (years)	No. Doses ZOL prior to confirmed diagnosis of ONJ	Description of event	Outcome of event
1	53	6	Elective admission for tooth extraction 18 days after ZOL dose. Tooth extraction site left mandible did not heal. Admission for debridement and pain control. ONJ confirmed left mandible and right maxilla	Recovered. ZOL restarted without sequelae
2	61	9	Referred to Oral surgery with concerns for ONJ, planned debridement and exploration under general anaesthetic. ONJ confirmed right and left mandible	Condition present and unchanged
3	67	12	Presented with dental sepsis 6 weeks after 12th dose ZOL. Underwent dental clearance revealing pus exuding from necrotic maxillary bone. Histopathology of bone confirmed necrotic and inflammatory change. ONJ confirmed right maxilla and mandible	Recovered with sequelae
4	54	10	Presented with possible gum abscess 3 months after 7th ZOL dose, required tooth extraction and dental follow up. ONJ confirmed left maxilla.	Completely recovered
5	39	9	Patient underwent tooth extraction 3 months after 8th ZOL dose. Failure to heal and referred to maxillofacial surgery. ONJ right mandible	Condition present and unchanged
6	72	12	Simple tooth extraction, unconfirmed timing relating to ZOL dose. Ongoing problems with swelling around site of extraction. Several courses of antibiotics but exposed bone remains in upper mandible. ONJ confirmed mandible. Ongoing assessment by maxillofacial surgeons..	Condition present and unchanged
7	63	13	Simple tooth extraction while on treatment. 2 months after 13 dose ZOL. Patient presented with painful jaw and possible infection. Underwent debridement revealing a piece of bone, continues on antibiotics. ONJ confirmed left maxilla	Completely healed
8	54	8	Jaw pain since simple dental extraction 5 months after 8th dose ZOL. 9th dose omitted. At next follow up exposed bone of lower mandible. Confirmed ONJ left mandible	Recovered with sequelae
9	43	14	Tooth extraction whilst on treatment with delayed healing of extraction site. Exposed bone confirmed in clinic. Treated with antibiotics and mouthwashes.	Condition improving
10	53	8	Presented with purulent discharge left canine tooth. Referred to maxillofacial surgeons. Granulation tissue and infection within defect around previously extracted tooth with radiographic changes. Confirmed ONJ left mandible and maxilla	Completely recovered
11	67	14	Underwent 3 dental extractions 3 months after 14th ZOL dose. Persistent soreness of mouth. Exposed bone confirmed by dental hospital. Confirmed ONJ left mandible and right maxilla.	Condition improving