European Journal of Cancer 94 (2018) 70–78

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Adjuvant zoledronic acid reduces fractures in breast cancer patients; an AZURE (BIG 01/04) study

C. Wilson [a,*], R. Bell [b], S. Hinsley [c], H. Marshall [c], J. Brown [a], D. Cameron [d], D. Dodwell [e], R. Coleman [a]

[a] *Academic Unit of Clinical Oncology, Weston Park Hospital, University of Sheffield, Sheffield, UK*
[b] *Deakin University, Geelong, Australia*
[c] *Clinical Trials Research Unit, Leeds, UK*
[d] *Cancer Research UK Edinburgh Centre, Western General Hospital, University of Edinburgh, UK*
[e] *Institute of Oncology, Bexley Wing, St James Hospital, Leeds, UK*

Received 27 November 2017; received in revised form 5 February 2018; accepted 7 February 2018

KEYWORDS
Adjuvant;
Zoledronic acid;
Fractures;
Breast cancer

Abstract The fracture impact of adjuvant bisphosphonates in breast cancer is not defined with most trials reporting changes in bone mineral density as a surrogate. The AZURE trial (ISRCTN79831382) evaluated the impact of adjuvant zoledronic acid (ZOL) on fractures.

The AZURE trial is an academic, multi-centre, randomised phase III study evaluating the addition of ZOL 4 mg to standard therapy (neo/adjuvant chemotherapy and/or endocrine therapy) for 5 years (administered by intravenous (iv) infusion every 3–4 weeks for 6 doses, then 3 monthly × 8 and 6 monthly × 5) in patients with stage II/III early breast cancer. Fracture data collected as part of skeletal-related adverse event reporting were analysed after a median of 84.2 months of follow-up and 966 disease-free survival (DFS) events. We assessed number of fractures, time-to-first fracture and the incidence of fractures before and after disease recurrence.

Two hundred forty-four patients reported ≥1 fracture, 140 (8.3%) in the control arm (171 fractures) and 104 (6.2%) in the ZOL arm (120 fractures). Of the 291 fractures reported, 207 fractures occurred in the absence of recurrence (control 111, ZOL 96), 80 after recurrence (control 59, ZOL 21). The 5-year fracture rate was reduced from 5.9% (95%CI 4.8, 7.1%; control) to 3.8% (95%CI 2.9, 4.7%) with ZOL. ZOL significantly increased time-to-first fracture (HR 0.69, 95%CI 0.53–0.90; $P = 0.0053$) but the majority of fracture prevention benefit

* *Corresponding author*:
E-mail address: c.wilson@sheffield.ac.uk (C. Wilson).

https://doi.org/10.1016/j.ejca.2018.02.004

occurred after a DFS event (HR 0.3; 95%CI 0.17, 0.53; $P < 0.001$). Fracture benefits from ZOL were similar across menopausal sub-groups.

In conclusion, adjuvant ZOL reduced the risk of clinical fractures, the majority of this protection occurred after disease recurrence.

1. Introduction

Adjuvant chemotherapy and endocrine treatments are an integral part of the multi-modality management of early breast cancer used to reduce the risk of disease recurrence and mortality. However, these therapies result in bone loss, either due to the direct effect on the balance of bone formation by osteoblasts and bone resorption by osteoclasts or due to indirect effects of lowering systemic oestrogen (ovarian failure/suppression in premenopausal patients and aromatase inhibitors (AIs) in postmenopausal women) [1,2]. A breast cancer diagnosis *per se* is associated with an increased risk of fracture in the absence of metastatic disease [3,4] and standard risk estimation scores (i.e. FRAX) underestimate fracture risk [5]. Fractures impair quality of life, increase health care costs and decrease survival [6].

Because of the adverse impact of treatments on bone health, breast cancer patients may require intensive bone protective management. Postmenopausal women have a natural yearly loss in bone mineral density (BMD) at the lumbar spine of 1%/year; rising to 2%/year in breast cancer patients receiving AIs and up to 7%/year in premenopausal patients with treatment-induced ovarian failure [6]. Bisphosphonates can prevent treatment-related bone loss, with most data available for zoledronic acid (ZOL) which prevents both the bone loss associated with AIs and with ovarian failure/suppression [7,8]. The majority of adjuvant bisphosphonate studies, as bone protective agents, have focused on changes in BMD as the primary end-point and were not designed to reliably assess treatment effects on fracture incidence [9–14].

The AZURE study is an academic, multi-centre, international phase III trial that randomised patients with early breast cancer to standard adjuvant therapy (chemotherapy and/or endocrine therapy) alone or with the addition of an intravenous infusion of ZOL 4 mg for 5 years (administered every 3–4 weeks for 6 doses, then 3 monthly × 8 and 6 monthly × 5). The efficacy data have been published previously [15,16] with disease-free survival (DFS) events showing that, despite a reduction in the risk of developing bone metastases, there was no effect on overall breast cancer recurrence. However, pre-planned sub-group analyses identified benefit in women who were in established menopause at the time of study entry (N = 1041, adjusted HR 0.77; 95%CI 0.63, 0.96), an observation which has been confirmed by the Early Breast Cancer Clinical Trials Collaborative Group (EBCTCG) meta-analysis of >18,000 women included in randomised trials of adjuvant bisphosphonates [17].

The AZURE study also collected data on fractures as part of skeletal-related event reporting by treating clinicians and represents one of the largest data sets for evaluation of fracture incidence in patients treated ± ZOL during adjuvant therapy. In this study, we present the data on fractures, as a pre-planned secondary end-point analysis, to assess the effects of ZOL on fractures pre- and post-disease recurrence and the differential effect according to menopausal status at baseline.

2. Patients and methods

Eligibility criteria have been reported previously [15]. To summarise, eligible patients had; histologically confirmed invasive breast cancer, pathologically involved axillary lymph node metastasis or a T3/T4 primary tumour, complete resection of the primary tumour or planned resection if receiving neoadjuvant chemotherapy, aged ≥18 years, Karnofsky performance status index ≥80, not pregnant or breast feeding. Patients were ineligible if there was clinical/imaging evidence of distant metastases before study entry, current, recent (previous year) or intended use of bisphosphonates for pre-existing bone disease.

Between September 2003 and February 2006, 3360 patients were randomised 1:1 using a computer-generated system which included the following minimisation criteria; number of involved lymph nodes, clinical tumour stage, oestrogen receptor status, clinical menopausal status, type and timing of systemic therapy, study centre and statin use.

Patients received standard adjuvant therapy and locoregional treatments according to institutional protocols ± intravenous ZOL, 4 mg every 3–4 weeks for 6 cycles and then every 3 months for 8 doses, followed by 5 cycles on a 6-month schedule for a total of 5 years [15]. Once distant recurrence was identified, trial medication was stopped and patients were treated as per local site protocol. Ethical approval was obtained for all participating centres, and all patients gave written informed consent before enrolment.

2.1. Patient evaluation

Fractures were reported as part of trial follow-up visits, occurring 3–4 weekly for the first 6 months, 3 monthly