EUROPEAN JOURNAL OF CANCER 47 (2011) 1603–1605

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Short Communication

Under usage of zoledronic acid in non-small cell lung cancer patients with metastatic bone disease – a short communication

R. Calderone [a], *K. Nimako* [a], *A. Leary* [a], *S. Popat* [a,b], *M.E.R. O'Brien* [a,*]

[a] *The Royal Marsden Hospital, NHS Foundation Trust, Downs Road, Sutton, Surrey, UK*
[b] *Molecular Genetics and Genomics Group, Imperial College London, Dove House Street, London, UK*

ARTICLE INFO

Article history:
Received 4 May 2011
Accepted 6 May 2011
Available online 16 June 2011

Keywords:
Lung cancer
NSCLC
Bone metastases
Zoledronic acid
Survival
Chemotherapy

ABSTRACT

Background and aim: The use of zoledronic acid (ZA) is now recommended for patients with NSCLC and metastatic bone disease (MBD). We thus examined the rates of ZA administration in NSCLC looking specifically at the use of this drug with systemic chemotherapy (ZCt) and comparing overall survival between patients who had ZCt from diagnosis to those who had chemotherapy (Ct) alone.

Method: In this retrospective audit, we analysed the data of 114 consecutive patients with stage IV NSCLC and MBD at presentation. Forty-three of these patients had received zoledronic acid and chemotherapy (ZCt) and 71 had received chemotherapy alone (Ct).

Results: Forty-three (37.7%, 43/114) of NSCLC patients diagnosed with MBD received ZA with their first chemotherapy (ZCt). Patients on ZCt, after adjustment for the planned prognostic factors (sites of disease, histology and PS), had better overall survival (OS), with a median of 34 weeks, compared to those who received chemotherapy alone, who had a median of 19 weeks ($p = 0.03$), HR = 0.60 (95%CI: 0.38–0.96). After adjusting for prognostic factors (sex, age. single versus doublet chemotherapy), ZCt patients still maintained a trend to better OS ($p = 0.06$) HR 0.63 (95%CI: 0.39–1.02) 34 versus 21 weeks.

Conclusions: The percentage of patients with MBD treated with ZA at first chemotherapy (37.7%) is low. The addition of ZA increased OS in NSCLC patients with MBD in this audit. More formal policies and dedicated trials on the treatment of MBD in NSCLC patients need to be put in place.

1. Background

The study by Henry et al.[1] on the use of denosumab in metastatic bone disease (MBD) met its primary end-point of a decrease in skeletal related events (SRE). The results are encouraging as a subgroup of 352 patients with NSCLC (40% of the whole study group) not only appeared to derive benefit from denosumab but may also have a survival benefit.[1] Historically, 30–40% of patients with advanced NSCLC develop bone metastases.[2] The median survival for all comers with stage IV NSCLC is 6 months but more recent studies are reporting a higher median survival of the order of 10 months.[3]

* *Corresponding author:* Address: Lung Unit, The Royal Marsden Hospital, Downs Road, Sutton, Surrey, UK. Tel.: +44 02086613278; fax: +44 02086430373.
E-mail address: mary.obrien@rmh.nhs.uk (M.E.R. O'Brien).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.05.008

Advanced lung cancer is often symptomatic, and patients' quality of life (QOL) typically decreases with disease progression.[4] Despite the well documented activity of the bisphosphonates and the inclusion of lung cancer in the licensing indications of ZA,[5,6] this treatment is often overlooked when patients present with advanced lung cancer with a myriad of other symptoms outside bone. In general bone metastases are not sought unless there are bone symptoms or hypercalcaemia or MBD is found incidentally on a PET or CT scan. Recently, a literature-based decision model was used to compare the cost utility of ZA with that of placebo in patients with bone metastases secondary to lung cancer from the perspective of the NHS in the UK. In modelled analyses, in patients receiving ZA, skeletal related events (SRE) costs were £1562 lower per patient and total costs were £89 lower per patient than in those receiving placebo.[7]

2. Patients and methods

This was a retrospective audit of stage IV NSCLC patients with MBD at first presentation of metastatic disease. The audit was approved by the local audit committee. The main objectives were to describe the rate of use of ZA at presentation with known MBD and to compare overall survival (OS) between those patients who received ZA plus chemotherapy (ZCt) (symptomatic or not), to those with MBD who received chemotherapy alone (Ct). ZA use at a later point was not considered in this study. Bone investigations were not undertaken in these patients unless they had symptoms. However, MBD was occasionally diagnosed with other staging investigations e.g. PET/CT or CT scan.

Between July 2004 and July 2009 all patients with stage IV NSCLC seen and treated with chemotherapy at the Royal Marsden Hospital were eligible. Details of their sites of metastases and other parameters were available from the electronic database. Data were collected between 1.7.2009 and 1.10.2009. The plan for the audit was to compare 50 consecutive patients with stage IV disease with bone metastases who had received ZCt to 50 consecutive patients who had not included ZA in the initial prescription. For this exploratory audit, these numbers were considered adequate to show a large difference of hazard ration (HR) of two corresponding to a survival difference of 25–30%.

Comparison between the treatment groups was performed using a Cox regression analysis adjusting for pre-planned prognostic factor (sites of disease, performance status (PS), histology).

3. Results

We identified 398 stage IV NSCLC patients, 168 had bone metastases MBD (42%). In order to collect 50 ZCt consecutive patients, the records of 124 consecutive patients had to be collected. Therefore, 74 Ct consecutive patients were collected. Once the 50 ZCt patients were identified, the remaining patients with MBD were not analysed. Of the 124 patients (50 ZCt and 74 Ct) a further 10 were excluded. One patient had a wrong diagnosis (ZCt arm), and 6 and 3 patients did not have combination chemotherapy in ZCt and Ct arms, respectively. Therefore, 43 ZCt and 71 Ct patients were analysed.

The median age for the patients in the 2 groups was 61 years (28–82) and 63 years (39–86) for ZCt and Ct, respectively. There were 58% females in ZCt and 44% in Ct. Adenocarcinoma was the histology in 65% ZCt and 51% Ct. Patients were of performance status 0 or 1 in 65% of ZCt and 65% of Ct, respectively. A platinum combination: single agent was used in 63:37% of ZCt patients and 81:19% of Ct patients. Subsequent tyrosine kinase inhibitor (TKI) use occurred in 9% versus 7% of ZCt and Ct patients, respectively. For ZCt and Ct there were liver metastases present in 28% versus 23%, CNS 16% versus 16%, $\geqslant$2 sites 51% versus 49% and bone only 24% versus 23%, respectively (See Table 1).

Overall survival (OS) adjusted for planned prognostic factors histology, sites of disease and PS was significantly longer in the ZCt group (median OS = 34 weeks, versus 19 weeks in Ct alone), $p = 0.03$ (HR: 0.60 (85% CI: 0.38–0.96). As the numbers were small and there were imbalances in the baseline characteristics a further unplanned analysis was done adjusting also for age, gender and chemotherapy (single versus doublet) and at this point the significance was lost $p = 0.06$ (HR: 0.63 (85% CI: 0.39–1.02) but the trend was the same in favour of adding ZA to initial chemotherapy. (Fig. 1)

4. Discussion

Our audit shows that initial bisphosphonate administration with chemotherapy is only used in 37.7% of NSCLC patients with known bone disease despite the evidence that available and well tolerated bisphosphonates can significantly reduce the rate of SRE and time to first event. There are a number of possible reasons for this – first, lung doctors may be biased in ZA prescription i.e. those with good PS and life expectancy may have been preferentially selected for ZA treatment, whilst this treatment may have been withheld from those with poorer prognosis; however, in our study prognostic factors like performance status and sites of disease were balanced. The ZCt group had slightly more females and adenocarcinomas and this group may have had a better prognosis but subsequent TKI use was infrequent and balanced.

It is provocative that ZA may increase survival. Given the lack of prospective data we can still hypothesise about a drug effect and the chance of it changing the biology and behaviour of the cancer lesions to influence survival. There may never be any more data with ZA as we are now setting our sights on newer more powerful and user friendly treatments. Denosumab is a novel antibody directed against RANK ligand. The antibody is given subcutaneously every 4 weeks. Compared to ZA, it would appear that denosumab has the same or greater positive effects on SREs across a wide range of solid tumours.[1] As is suggested in the Henry et al. data, lung cancer patients may get a survival benefit from this treatment but a lung cancer specific study powered to show a survival advantage is needed. All trials to date including the Henry et al.[1] study with denosumab have included NSCLC as an underpowered subgroup. More attention needs to be given to the importance of bone metastases in NSCLC both as a site of burden of symptoms and the potential to influence survival with

Table 1 – Patient and disease characteristics.

Characteristic	ZOMETA (ZCt)	NO ZOMETA (Ct)
Number	43 (38%)	71 (62%)
Gender		
Male:female	18 (42%)/25 (58%)	40 (56%)/31 (44%)
Age		
Median (range)	61 (28–82)	63 (39–86)
Ethnicity		
Caucasian	37 (86%)[a]	62 (87%)
Black	0 (0%)	3 (4%)
Indian subcontinent	2 (5%)	1 (1%)
Other Asian	2 (5%)	0 (0%)
Other and not know	2 (5%)	6 (8%)
Histology		
Adenocarcinoma + BAC	28 (65%)	36 (51%)
Squamous	5 (12%)	15 (21%)
Other/not specified	10 (23%)	20 (28%)
Chemotherapy		
Platinum + Navelbine	18 (42%)	32 (45%)
Platinum + Gemcitabine	4 (9%)	19 (27%)
Platinum + Taxane	5 (12%)	3 (4%)
Other platinum comb	0 (0%)	3 (4%)
Single agent	16 (37%)	14 (20%)
Metastases		
Bone only	24%	23%
Liver + bone	28%	23%
CNS + bone	16%	16%
⩾2 sites	51%	49%

[a] Total of percentages does not equal 100 due to rounding.

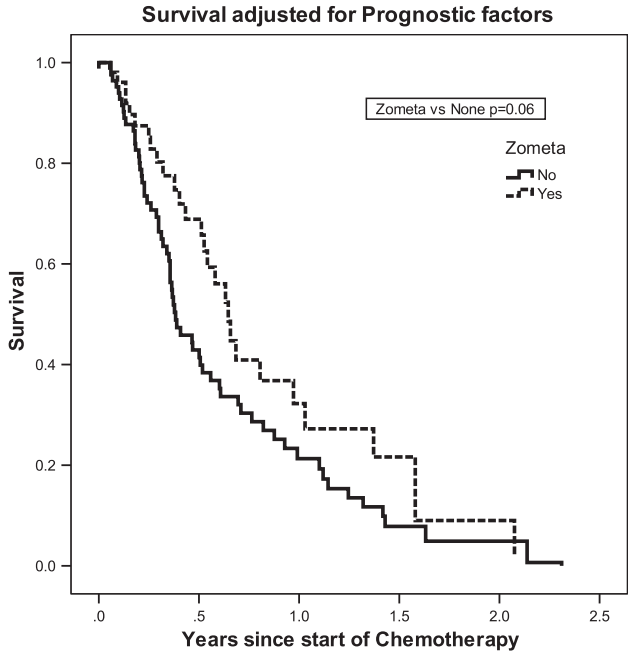

Fig. 1 – Survival adjusted for prognostic factors; planned (histology, site, PS) and unplanned (age, gender and chemotherapy).

new bone focussed treatments. A trial dedicated to this topic with appropriate sample collection and subgroup representation should raise awareness of the available treatments and the potential for improvement in stage IV NSCLC. This should convince doctors to give greater consideration to including a bone specific treatment as an automatic part of the first line prescription in patients with advanced lung cancer with bone metastases.

Funding source

None.

Conflict of interest statement

None declared.

Acknowledgements

There was no formal funding for the study. However, the authors would like to acknowledge NHS funding to the Royal Marsden Hospital/Institute of cancer Research NIHR Biomedical Research Centre. Dr. Popat is in receipt of a clinical senior lectureship award from the Higher Education Funding Council for England.

REFERENCES

1. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* 2011;**29**(9):1125–32.
2. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 2001;**27**(3):165–76.
3. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;**26**(21):3543–51.
4. Major PP, Cook RJ, Chen BL, Zheng M. Survival-adjusted multiple-event analysis for the evaluation of treatment effects of zoledronic acid in patients with bone metastases from solid tumors. *Support Cancer Ther* 2005;**2**(4):234–40.
5. Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with non-small cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. *Cancer* 2004;**100**(12):2613–21.
6. Zarogoulidis K, Boutsikou E, Zarogoulidis P, et al. The impact of zoledronic acid therapy in survival of lung cancer patients with bone metastasis. *Int J Cancer* 2009;**125**(7):1705–9.
7. Botteman MF, Foley I, Marfatia AA, Brandman J, Langer CJ. Economic value of zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer: The case of the United Kingdom (UK). *J Clin Oncol* 2007;**25**(18S):6617.