PROFESSOR MONICA PENTENERO (Orcid ID: 0000-0003-3972-1203)

DR STEFANO FEDELE (Orcid ID: 0000-0001-9006-9412)

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Time to onset of bisphosphonate-related osteonecrosis of the jaws: a multicentre retrospective cohort study

Fung PPL, ¹ Bedogni G, ² Bedogni A, ^{3, 4} Petrie A, ¹ Porter S, ¹ Campisi G, ⁵ Bagan J, ⁶ Fusco V, ⁷ Saia G, ⁴ Acham S, ⁸ Musto P, ⁹ Petrucci MT, ¹⁰ Diz P, ¹¹ Colella G, ¹² Mignogna MD, ¹³ Pentenero M, ¹⁴ Arduino P, ¹⁵ Lodi G, ¹⁶ Maiorana C, ¹⁷ Manfredi M, ¹⁸, Hallberg P, ¹⁹ Wadelius M, ¹⁹ Takaoka K, ²⁰ Leung YY, ²¹ Bonacina R, ²² Schiødt M, ²³ Lakatos P, ²⁴ Taylor T, ²⁵ De Riu G, ²⁶ Favini G, ²⁷ Rogers SN, ²⁸ Pirmohamed M, ²⁹ Nicoletti, P, ³⁰ GENVABO Consortium, ³¹ Fedele S. ^{1,32}

- 1. University College London / University College London Hospital Eastman Dental Institute and Hospital, London UK
- 2. Liver Research Centre, Clinical Epidemiology Unit, Basovizza, Trieste, Italy
- 3. University of Verona, Department of Maxillofacial Surgery, Verona, Italy
- 4. University of Padua, Department of Maxillofacial Surgery, Padua, Italy
- 5. University of Palermo, Dip. Discipline Chirurgiche, Oncologiche e Stomatologiche, Palermo, Italy
- 6. Valencia University, Oral Medicine, University General Hospital, Department of Oral and Maxillofacial Surgery, Valencia, Spain.
- 7. Ospedale SS Antonio e Biagio e C Arrigo, Department of Oncology and Haematology, Medical Oncology Unit, Alessandria, Italy
- 8. Medical University of Graz, University Clinic of Dental Health and Oral Medicine, Department of Oral Surgery and Orthodontics, Graz, Austria
- 9. IRCCS, Referral Cancer Center of Basilicata, Scientific Direction, Rionero in Vulture (Potenza), Italy
- 10. "Sapienza" University, Department of Cellular Biotechnologies and Haematology, Rome, Italy
- 11. Santiago de Compostela University, School of Medicine and Dentistry, Santiago de Compostela, Spain

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- 13. 15. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33.
- 12. Second University of Naples, Department of Medical, Surgical and Dental Specialties, Naples, Italy
 - Federico II University, Department of Neurosciences, Reproductive and Odontostomatological Sciences, Head & Neck Clinical Section, Naples, Italy
 - 14. University of Torino, Department of Oncology, Oral Medicine and Oral Oncology Unit, Turin, Italy
 - L5. University of Turin, CIR Dental School, Turin, Italy
 - 16. Università degli Studi di Milano, Dipartimento di Scienze Biomediche, Chirurgiche e Odontoiatriche, Milan, Italy.
 - Fondazione IRCCS Policlinico Cà Granda, Ospedale Maggiore Policlinico, and University of Milan, Dipartimento di Scienze Biomediche, Chirurgiche ed Odontoiatriche, Italy
 - 18. Parma University, Dipartimento di Scienze Biomediche, Biotecnologiche e Traslazionali S.Bi.Bi.T., Unità di Odontostomatologia, Parma, Italy
 - 19. Uppsala University, Department of Medical Sciences, Clinical Pharmacology and Science for Life Laboratory, Uppsala, Sweden
 - 20. Hyogo College of Medicine, Department of Oral and Maxillofacial Surgery, Japan
 - 21. Oral and Maxillofacial Surgery, Faculty of Dentistry, The University of Hong Kong
 - 22. Department of Dentistry, Ospedale Papa Giovanni XXIII, Bergamo, Italy
 - 23. Department of Oral and Maxillofacial Surgery, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
 - 24. First Department of Medicine, Semmelweis University Medical School, Budapest, Hungary
 - 25. Department of Oral Surgery, King's College Hospital, London, UK
 - 26. Department of Maxillofacial Surgery, University Hospital of Sassari, Italy
 - 27. Department of Dentistry, San Francesco Hospital, Nuoro, Italy
 - 28. University Hospital Aintree, Liverpool, UK
 - 29. Institute of Translational Medicine, University of Liverpool, Liverpool, UK
 - 30. Department of Systems Biology, Columbia University, New York, US
 - 31. GENVABO Consortium: a list of contributing members is provided below *
 - 32. University College London Hospitals Biomedical Research Centre, London UK

Corresponding author email id: s.fedele@ucl.ac.uk

* Collaborating investigators and sites of GENVABO Consortium (in alphabetical order by site):

Jose L López-Cedrún (*Complexo Hospitalario Universitario da Coruña, Spain*); Sanne Madsen (*Copenhagen University Hospital, Denmark*); Gennaro Sadile, Stefania Leuci (*Federico II University, Italy*); Cristina Mirelli, Giulio Conti, Rita Maiavacca (*Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Italy*); Masahiro Urade, Hiromitsu Kishimoto, Shin Okui, Yusuke Zushi, Michiyo Yamamura, Kyohei Yoshikawa (*Hyogo College of Medicine, Japan*); Giovanna Mansueto (*IRCCS, Referral Cancer Center of Basilicata, Italy*); Patrik KE Magnusson (*Karolinska*

Institutet, Sweden); Shina Popat (King's College Hospital, UK); Barbara Kirnbauer, Barbara Obermayer-Pietsch, Norbert Jakse (Medical University Graz, Austria); Umberto Mariani, Valeria Martini (Ospedale Papa Giovanni XXIII, Italy); Antonella Fasciolo, Iolanda De Martino, Manuela Alessio (Ospedale SS Antonio e Biagio e C Arrigo, Italy); Jacinto F Sanromán (Policlinico Vigo SA, Spain); Sara Grammatico (Sapienza University, Italy); Giovanni Siniscalchi, Angelo Itro (Second University of Naples, Italy); Bernadett Balla, Janos P. Kosa, Mihaly Vaszilko (Semmelweis *University Medical School, Hungary*); John Lo (*The University of Hong Kong, Hong Kong*); Eleni Besi, Francesco D'Aiuto, Kwee Yong, Nikos Donos, Valeria Mercadante (University College London, UK); Robert Stein, Shirley D'Sa, (University College London Hospital, UK); Elena Varoni (Università degli Studi di Milano, Italy); Damiano Soma, Silvio Meloni (University Hospital of Sassari, Italy); Jane Evely, Anita Hanson (University of Liverpool, UK); Francesco Giancola, Olga Di Fede, Vera Panzarella (*University of Palermo, Italy*); Giordana Bettini (*University of Padua, Italy*); Elisabetta Merigo, Giovanni Mergoni, Paolo Vescovi (University of Parma, Italy); Sergio Gandolfo, Roberto Marino, Mattia Berrone (University of Turin, Italy); Alessio Gambino, Elisa Menegatti, Roberto Broccoletti (University of Turin, CIR Dental School, Italy); Elena Hens, Leticia Bagan (*University of Valencia, Spain*).

Running title: Time to onset of bisphosphonate-related osteonecrosis of the jaws

Correspondence to: Dr Stefano Fedele, University College London/University College London Hospital Eastman Dental Institute and Hospital, 256 Gray's Inn Road, WC1X 8LD London UK.

ABSTRACT

Objectives: Osteonecrosis of the jaw (ONJ) is a potentially severe adverse effect of bisphosphonates (BP). Although the risk of ONJ increases with increasing duration of BP treatment, there are currently no reliable estimates of the ONJ time to onset (TTO). The objective of this study was to estimate the TTO and associated risk factors in BP-treated patients.

Subjects and methods: Retrospective analysis of data from 22 secondary care centres in 7 countries relevant to 349 patients who developed BP-related ONJ between 2004 and 2012.

Results: The median (95%CI) TTO was 6.0 years in patients treated with alendronate (n = 88) and 2.2 years in those treated with zoledronate (n = 218). Multivariable Cox regression showed that dentoalveolar surgery was inversely associated, and the use of antiangiogenics directly associated, with the TTO in cancer patients treated with zoledronate.

Conclusions: The incidence of ONJ increases with the duration of BP therapy, with notable differences observed with respect to BP type and potency, route of administration and underlying disease. When data are stratified by BP type, a time of 6.0 and 2.2 years of oral alendronate of intravenous zoledronate therapy, respectively, is required for 50% of patients to develop ONJ. After stratification by disease, a time of 5.3 and 2.2 years of BP therapy is required for 50% of patients with osteoporosis and cancer, respectively, to develop ONJ. These findings have significant implications for the design of future clinical studies and the development of risk reduction strategies aimed at either assessing or modulating the risk of ONJ associated with BP.

INTRODUCTION

Osteonecrosis of the jaw (ONJ) is a serious adverse effect of therapy with bisphosphonates (BP) and other anti-resorptive agents (Ruggiero *et al*, 2009; Sivolella *et al*, 2013). Affected individuals often present with areas of necrotic ischemic jawbone exposed through fenestration of the oral mucosa or facial skin (Filleul *et al*, 2010), while approximately one in four patients present with necrotic jawbone covered by intact mucosa (non-exposed variant) (Fedele *et al*, 2010). Other manifestations include pain, secondary infection, tooth loss, fistula formation, pathological fractures, sinusitis, and oro-antral communication (Filleul *et al*, 2010). It has been estimated that ONJ develops in up to 7% of cancer patients using intravenous BP and in approximately 0.12% of osteoporosis patients taking oral BP (Kühl *et al*, 2012).

The pathogenic mechanisms of, and the risk factors for, ONJ are still controversial (Landesberg et al, 2011). For instance, several studies have reported that the risk of ONJ is greater in patients who have undergone surgical procedures to the jaw bones (e.g. dental extraction) (Campisi et al, 2014). However, it is also known that many ONJ cases, possibly up to 30-40%, are not triggered by surgical interventions (Filleul et al, 2010). Less controversial is the association between the incidence of ONJ and the cumulative dose and duration of BP treatment (Thumbigere-Math et al, 2012; Fleisher et al, 2013), in keeping with type C adverse drug reactions (Edwards and Aronson, 2000). Indeed, the incidence of ONJ is low during the first few years of BP treatment and increases substantially thereafter (Barasch et al, 2011). However, it is important to note that there is a great variability and inconsistency in the time to ONJ (TTO) reported in the literature, possibly because of different study designs and diagnostic criteria, and generally low sample sizes (Bamias et al, 2005; Pozzi et al, 2007; Mavrokokki et al, 2007; Boonyapakorn et al, 2008; Vahtsevanos et al, 2009; Saia et al, 2010; Hasegawa et al, 2012; Watters et al, 2013).

A precise estimate of TTO is important for the design of clinical trials. Trials where follow-up is too short would in fact miss most incident cases and provide flawed estimates of ONJ incidence and its risk factors. A precise estimate of TTO is also important for developing risk reduction strategies (e.g. BP dosage reduction or cessation) and surveillance programs (Fedele *et al*, 2009). In order to obtain a more precise estimate of TTO, we have studied the clinical data collected in GENVABO, a multicentre cross-sectional study aimed at identifying genetic variants predisposing to BP-related ONJ.

METHODS

Study design

We performed a retrospective secondary analysis of data belonging to a cohort of ONJ patients enrolled into the GENVABO (GENetic VAriants as Biomarkers of jaw Osteonecrosis associated with bisphosphonates) study, a genome-wide association study with the primary aim of identifying genetic variants that predispose to ONJ. The present report follows the STROBE recommendations (von Elm et al, 2008).

Setting and inclusion criteria

GENVABO study was designed by Investigators at the University College London and included a total of twenty-two international clinical centres with an interest in the diagnosis and management of ONJ. The Ethics Committees of the coordinating centre (Central London REC 4, reference 08/H0715/69) and participating sites approved the study and all patients gave their written informed consent to participate. Patients referred to the participating centres between January 2004 and June 2012 were eligible for GENVABO if they had: 1) ONJ diagnosed as per AAOMS criteria (Ruggiero *et al*, 2009) (Ruggiero *et al*, 2014); and 2) non-exposed ONJ defined as reported by Fedele *et al*. and other authors (Junquera and Gallego, 2008; Fedele *et al*, 2010; Patel *et al*, 2011). ONJ was diagnosed and adjudicated in all cases by local multidisciplinary teams of specialists in Oral Medicine, Oral and Maxillofacial Surgery, Oncology, Haematology, Rheumatology and Radiology.

Data collection

Clinical charts of consecutive ONJ patients recruited into the GENVABO study between January 2004 and June 2012 were reviewed and the data of interest were collected between October 2008 and June 2012. Such data were extracted by local investigators and entered into a standardized case report form. All data were inputted into a definitive database using a double entry process performed by two different investigators. The data extracted for the present analysis included: 1) age, gender and race; 2) details of BP therapy including BP type, date of start and length of therapy, and indication for BP use; 3) details of ONJ including date of diagnosis, site and type; 4) dental history including history of dentoalveolar surgery and use of dentures preceding ONJ diagnosis; 5) medical history including type 2 diabetes mellitus (T2DM) and use of corticosteroids and antiangiogenics; 6) smoking history; and 7) recruiting centre and relevant country. For patients who had been treated with more than one type of BP, the BP used for the longest time was used for the present analysis. The dataset was reviewed by a central study panel and underwent data cleaning and verification according to standard procedures. Stata 14.1 (Stata Corp., College Station, TX, US) programs were written to ensure the reproducibility of data management and data cleaning.

Study objectives

The main aim of GENVABO is to identify genetic variants associated with the risk of developing ONJ. The primary objective of the present secondary analysis was to estimate TTO in patients with BP-related ONJ. TTO was defined as the number of years elapsed between the initiation of BP therapy and the diagnosis of ONJ as outlined above. We did not attempt to differentiate the time to diagnosis from the time to development/onset, as the early symptoms of ONJ can be non-specific and they are difficult to assess retrospectively. We also calculated the cumulative incidence of ONJ and evaluated the association of TTO with potential risk factors (Thumbigere-Math *et al*, 2012; Hasegawa *et al*, 2012; Fleisher *et al*, 2013).

Statistical analysis

The point estimates and the 95% confidence interval of TTO were calculated using the Kaplan-Meier estimator (Hosmer *et al*, 2011). Kaplan-Meier curves for TTO were stratified by disease (metastatic breast cancer *vs.* multiple myeloma *vs.* metastatic prostate cancer *vs.* other cancers *vs.* osteoporosis), cancer (yes *vs.* no) and BP (alendronate *vs.* ibandronate *vs.* pamidronate *vs.* zoledronate). Multivariable Cox regression was used to test whether TTO was associated with gender (discrete, male *vs.* female), age (continuous, decade), dentoalveolar surgery (discrete, yes *vs.* no), T2DM (discrete, yes *vs.* no), use of steroids (discrete, yes *vs.* no) and use of antiangiogenics (discrete, yes *vs.* no) in cancer patients (Model 1) and in non-cancer patients (Model 2) (Hosmer *et al*, 2011). Cluster confidence intervals were calculated using the study country as cluster. The proportional hazard assumption made by Cox regression was checked using Schoenfeld residuals (Hosmer *et al*, 2011). Multivariable fractional polynomials were used to test whether the multivariable relationship of TTO with age was linear (Royston and Sauerbrei, 2008). Statistical analysis was performed using Stata version 14.1.

RESULTS

Details of the cohort

Clinical notes of 384 consecutive patients with BP-related ONJ recruited into GENVABO study were available for analysis. Missing or conflicting data were identified for 35 (9%) patients, who were excluded from further analysis. The majority of the 349 analysed patients (**Table 1**) were of Caucasian origin (93%); 85% were aged \geq 60 years and 71% were females. The majority (n = 318; 91%) of the participants had exposed ONJ. The most common indications for ONJ treatment were osteoporosis (OP, 32%), multiple myeloma (MM, 27%), metastatic breast cancer (MBC, 24%), and metastatic prostate cancer (MPC, 10%). Zoledronate (ZOL, 63%) and alendronate (ALE, 25%) were the two most commonly employed BP, followed by pamidronate (PAM, 5%), ibandronate (IBA, 4%) and risedronate (RIS, 3%). Concomitant corticosteroids and antiangiogenics (bevacizumab, sunitinib, thalidomide, lenalidomide, bortezomib) were used in 22% and 14% of patients respectively. Dentoalveolar surgery preceding ONJ development was reported by 53% of patients, tobacco smoking by 21% and T2DM by 10%.

Time to ONJ onset

In the whole cohort (n = 349), the 50th (95%CI) percentile of TTO was 3.2 (2.8 to 3.7) years, the 25th percentile 1.7 (1.4 to 1.9) years, and the 75th percentile 5.8 (5.2 to 6.2) years. The minimum and maximum TTO were 0.1 and 19.9 years, respectively.

Table 1 shows the median TTO after stratification on several variables including disease and BP type. In brief, when stratified by BP type, the median (50th percentile) TTO was 6.0 (5.3 to 6.4) years for ALE and 2.2 (2.1 to 2.6) for ZOL. When stratified by disease, the median TTO was 5.3 (4.4 to 6.1) years for OP, 3.1 (2.2 to 3.6) for MBC and 2.3 (2.1 to 3.0) for MM. The median TTO was 2.2 (2.1 to 2.8) years for all cancer patients (n = 237).

Figures 1A, 1B and 1C present the Kaplan-Meier plots of the cumulative incidence of ONJ in patients stratified by disease, cancer and BP type. **Figure 1A** shows that ONJ developed faster in patients with cancer than in those with osteoporosis. Among patients with different cancer types, development was most rapid in those with MPC, followed by OC, MM and MBC (**Figure 1C**). **Figure 1B** shows that ONJ developed faster in patients treated with ZOL, RIS and IBA than in those treated with PAM and ALE.

Table 2 shows the multivariable Cox regression models used to evaluate the association between TTO and potential predictors in cancer and non-cancer patients. Model 1 refers to cancer patients taking ZOL (212 out of 237 patients with cancer, 89%) while Model 2 refers to non-cancer patients taking ALE (84 out of 112 patients, 75%). A history of dentoalveolar surgery was inversely associated (hazard ratio, HR = 0.71, 95%CI 0.56 to 0.91) and the use of antiangiogenics (HR = 1.10, 95%CI 1.01 to 1.19) directly associated with TTO in the subgroup of cancer patients taking ZOL (Model 1).

DISCUSSION

Cumulative dosage and duration of anti-resorptive therapy are two of the most consistently reported risk factors for ONJ development (Thumbigere-Math *et al*, 2012; Fleisher *et al*, 2013) and there remains little doubt that ONJ is a time- and dose-related adverse effect. However, data regarding TTO are controversial as they vary significantly among studies (Palaska *et al*, 2009). Fleisher *et al*. (Fleisher *et al*, 2013) reported a median time of 3 and 5 years for ONJ to develop in individuals using intravenous and oral BP respectively, whereas a 2009 review reported a mean time of 1.8 and 4.6 years after ZOL and ALE therapy, respectively (Palaska *et al*, 2009). Other authors reported that ONJ developed after only 4 months of ZOL therapy, which they suggest was possibly triggered by invasive dental surgical procedures (Saussez *et al*, 2009). Moreover, a recent study of 191 ONJ cases recruited in a primary care setting (dental practice-based research network) reported a 10-fold increase in risk of ONJ associated with <2 years of BP therapy, which increased to 40-fold among individuals treated with BP for more than 2 years (Barasch *et al*, 2011).

Such inconsistency in the data on TTO has negative clinical consequences as it can hinder the delivery of potential risk-reduction strategies such as prophylactic dental measures and BP

dosage reduction or discontinuation. It can also affect the delivery of clinical surveillance programs (Kyle et al, 2007; Kyrgidis et al, 2013) and cause confusion in the interpretation of clinical studies. For example, clinical trials with a short observation time, e.g. shorter than the median TTO, would miss a significant number of incident cases and therefore provide flawed estimates of ONJ incidence and its risk factors. The most likely reasons accounting for the inconsistency and variability of current TTO estimates are different study designs, generally low sample sizes, ambiguous definitions of TTO, short follow-up times, and diagnostic criteria limited to exposed ONJ (Palaska et al, 2009). The present study was undertaken with the aim of overcoming these limitations. A significant strength of our study is the large sample size (n =349), making it the largest study performed so far to investigate TTO. Another strength of our study is the use of a strict definition of TTO as the time elapsed between the commencement of BP therapy and ONJ diagnosis, as determined by a multidisciplinary team. Previous studies have interchangeably used TTO as per clinicians' diagnosis and TTO as based on symptoms reported by patients (Bamias et al, 2005; Pozzi et al, 2007; Mavrokokki et al, 2007; Boonyapakorn et al, 2008; Vahtsevanos et al, 2009; Saia et al, 2010; Hasegawa et al, 2012; Watters et al, 2013) and other studies have used unclear diagnostic criteria (Palaska et al, 2009). On the contrary, our study defined TTO precisely and consistently among centres and avoided the bias associated with the mixing of the diagnoses made by physicians and those made by patients (Lazarovici et al, 2009). The use of strict diagnostic criteria in multicentre cross-sectional cohort studies reduces the risk of selection bias (Hudson et al, 2005).

We estimated a median TTO of 3.2 years in the whole cohort. When stratified by BP type, the median TTO was 6.0 years for ALE and 2.2 for ZOL. The corresponding figures were 2.1 years for IBA, 2.4 years for RIS and 6.2 years for PAM. With respect to the cumulative incidence (numbers and percentages) of individuals being diagnosed with ONJ at different time points after commencement of BP therapy (Figure 1), our analysis shows that it took 4.1 years for 75% of ZOL-exposed ONJ patients and 8.5 years for 75% of ALE-exposed ONJ patients to develop their disease. Also, 50% of ZOL-exposed and ALE-exposed ONJ individuals developed their disease in 2.2 and 6 years.

Our results are not notably different from those of previous studies, which were mostly single-centre and had much smaller cohorts. The three largest single-centre studies performed so far include the 60 ZOL ONJ cases reported by Watters *et al.* (Marx *et al*, 2007; Watters *et al*, 2013), the 27 ALE ONJ cases described by Marx *et al.* (Marx *et al*, 2007; Watters *et al*, 2013), and the 31 ZOL- and 16 ALE-related ONJ cases reported by Lazarovici *et al.* (Lazarovici *et al*, 2009), which grouped together make up a smaller sample than the one we recruited and studied. These studies reported a median time to onset of 1.75 years for ZOL-related ONJ (Marx *et al*, 2007; Watters *et al*, 2013), 5.7 years for ALE-related ONJ (Marx *et al*, 2007; Watters *et al*, 2013), and median times of 2 and 5 years the ZOL-related and ALE-related ONJ, respectively (Lazarovici *et al*, 2009). Our study confirms that ZOL is associated with a shorter TTO with respect to ALE (Bamias *et al*, 2005; Pozzi *et al*, 2007; Mavrokokki *et al*, 2007; Boonyapakorn *et al*, 2008; Vahtsevanos *et al*, 2009; Thumbigere-Math *et al*, 2012; Watters *et al*, 2013), which is consistent with the greater potency and better bioavailability of intravenous ZOL. However, in the present study, the median TTO was slightly longer than in previous studies for both ZOL and ALE.

Another strength of this study is the use of multivariable analysis to investigate the joint association of potential risk factors with TTO. Previous studies suggested that a number of risk factors may have an "additive" impact on ONJ pathogenesis, therefore leading to shorter TTO (Bamias et al, 2005; Pozzi et al, 2007; Mavrokokki et al, 2007; Thumbigere-Math et al, 2012; Boonyapakorn et al, 2008; Palaska et al, 2009; Vahtsevanos et al, 2009; Saia et al, 2010; Hasegawa et al, 2012; Fleisher et al, 2013; Watters et al, 2013). These factors included corticosteroid use, smoking, alcohol, T2DM, dental extraction and use of dentures (Bamias et al, 2005; Pozzi et al, 2007; Mavrokokki et al, 2007; Boonyapakorn et al, 2008; Palaska et al, 2009; Vahtsevanos et al, 2009; Saia et al, 2010; Hasegawa et al, 2012; Watters et al, 2013). Our study considered up to 7 risk factors in a multivariable regression model (Harrell et al, 1996) and shows that none of the previously suggested variables is associated with shorter TTO, including dental risk factors (alveolar surgery and use of dentures). In the subgroup of cancer patients taking ZOL, the only factor associated with shorter TTO in the present study was the use of antiangiogenic agents (Table 2). This was not unexpected, as antiangiogenic medications are known to cause ONJ per se. Quite surprisingly, a history of dento-alveolar surgery to the jawbones was associated with a lower hazard for ONJ in the same subgroup of cancer patients taking ZOL. It is not clear why ONJ developed faster in individuals who had not received dento-alveolar surgery. Of note, despite the relatively large number of subjects compared to the predictors (7 for Model 1 and 6 for Model 2), the estimated hazard ratios have wide 95%CI suggesting that larger samples are needed to estimate these effects more precisely.

A limitation of the present study lies in its retrospective nature. However, provided that the outcome can be thoroughly assessed, retrospective cohort designs offer a number of advantages over prospective cohort designs if the time to outcome is long (Hudson *et al*, 2005). For example, based on the present study, one can estimate that a hypothetical prospective study observing cancer patients for 2 years after the start of ZOL therapy would identify less than 50% of incident ONJ cases. This would not only decrease the confidence with such incidence estimate can be accepted, but also may identify different risk factors from those identifiable with a longer follow-up.

Conclusions

This is the largest study performed to date to investigate TTO and its risk factors. It has been conducted in a large well-phenotyped multicentre cohort, with a strict definition of the outcomes, clear diagnostic criteria, and the use of multivariable regression modelling. We believe that its findings can be promptly translated into clinical application to inform the design of clinical trials, epidemiological studies and surveillance programs. For example, a follow-up of at least 2.2 and 6.0 years is needed to capture at least 50% of the incident cases of ONJ in ZOL and ALE users respectively. Corresponding figures of 4.1 and 8.5 years are needed to capture instead 75% of ZOL-exposed and ALE-exposed ONJ incident cases. Clinicians should expect that

ZOL-treated cancer patients who also receive anti-angiogenic therapy may develop ONJ earlier than other patients.

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Transparency declaration: The lead author (Stefano Fedele) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Tables and figures

Table 1: Details of the study cohort and time to event stratified by potential risk factors.

| Potential risk factor | | N | % | Median Time to event (years) |
|-----------------------|-----------|-----|------|------------------------------|
| 7 | | | | (95%CI) |
| | | | | |
| Age (decade) | 30-39 | 2 | 0.6 | 2.2 (2.2 to NA) |
| | 40-49 | 8 | 2.3 | 3.7 (0.4 to 7.5) |
| | 50-59 | 41 | 11.7 | 2.4 (1.6 to 3.5) |
| | 60-69 | 125 | 35.8 | 3.3 (2.8 to 4.3) |
| | 70-79 | 134 | 38.4 | 2.8 (2.2 to 3.7) |
| | 80-89 | 39 | 11.2 | 4.2 (2.9 to 5.8) |
| | Total | 349 | 100 | 3.2 (2.8 to 3.7) |
| Gender | Female | 247 | 70.8 | 3.9 (3.2 to 4.3) |
| | Male | 102 | 29.2 | 2.1 (1.8 to 2.6) |
| Race | Caucasian | 323 | 92.6 | 3.2 (2.8 to 3.7) |
| | Other | 26 | 7.4 | 2.9 (2.4 to 5.4) |

| Underlying disease | Metastatic Breast Cancer (MBC) | 84 | 24.1 | 3.1 (2.2 to 3.6) |
|--------------------|----------------------------------|-----|------|------------------|
| | Multiple Myeloma (MM) | 93 | 26.6 | 2.3 (2.1 to 3.0) |
| | Metastatic Prostate Cancer (MPC) | 33 | 9.5 | 1.8 (1.6 to 2.1) |
| | Other Cancers (OC) | 27 | 7.7 | 2.1 (1.0 to 2.8) |
| | Osteoporosis (OP) | 112 | 32.1 | 5.3 (4.4 to 6.1) |
| BP type | Alendronate (ALE) | 88 | 25.2 | 6.0 (5.3 to 6.4) |
| | Ibandronate (IBA) | 15 | 4.3 | 2.1 (0.6 to 3.2) |
| | Pamidronate (PAM) | 17 | 4.9 | 6.2 (4.6 to 7.2) |
| | Risedronate (RIS) | 11 | 3.2 | 2.4 (0.3 to 4.7) |
| | Zoledronate (ZOL) | 218 | 62.5 | 2.2 (2.1 to 2.6) |
| Medical History | Corticosteroids | 76 | 21.8 | 3.2 (2.6 to 4.1) |
| | Antiangiogenics* | 49 | 14.0 | 2.3 (1.8 to 3.2) |
| | Type 2 diabetes mellitus | 34 | 9.7 | 2.9 (2.3 to 4.6) |
| | Smoking | 74 | 21.1 | 3.4 (2.6 to 4.5) |
| Dental History | Dento-alveolar surgery | 186 | 53.3 | 3.9 (3.2 to 4.5) |
| | Denture use | 73 | 20.9 | 4.2 (2.7 to 5.3) |
| ONJ features | Non-exposed type | 31 | 8.9 | 3.3 (1.7 to 5.8) |
| | Exposed type | 318 | 91.1 | 3.2 (2.8 to 3.7) |
| | Maxilla | 88 | 25.2 | 3.3 (2.7 to 3.9) |
| | Mandible | 227 | 65.0 | 2.9 (2.4 to 3.6) |
| | Both maxilla and mandible | 34 | 9.7 | 4.2 (3.0 to 5.1) |
| | | | | |

N = number of patients; NA = not available; * bevacizumab, sunitinib, thalidomide, lenalidomide, bortezomib

Table 2: Multivariable Cox regression of factors potentially associated with TTO of ONJ in cancer patients taking ZOL (Model 1) and in non-cancer patients taking ALE (Model 2). Cluster confidence intervals were calculated using the study country as cluster.

| | MODEL 1 | MODEL 2 | | |
|--|----------------------------|-----------------------------------|--|--|
| | Cancer patients taking ZOL | Non-cancer patients
taking ALE | | |
| Male sex (1= yes; 0 =no) | 1.25 [0.92, 1.68] | 1.12 [0.50, 2.53] | | |
| | | | | |
| Age/10 (years) | 0.97 [0.92, 1.03] | 1.06 [0.83, 1.34] | | |
| Dentoalveolar surgery (1= yes; 0 =no) | 0.71 ** [0.92, 1.03] | 1.03 [0.68, 1.23] | | |
| Type 2 Diabetes Mellitus (1= yes; 0 =no) | 1.00 [0.92, 1.09] | 0.94 [0.59, 1.51] | | |
| Smoking (1= yes; 0 =no) | 1.00 [0.74, 1.36] | 1.05 [0.70, 1.58] | | |
| Corticosteroids (1= yes; 0 =no) | 1.18 [0.92, 1.50] | 1.06 [0.90, 1.25] | | |
| Antiangiogenics (1= yes; 0 =no) | 1.10 * [1.01, 1.19] | | | |
| N | 212 | 84 | | |

Values of hazard rates from multivariable Cox regression with 95% confidence intervals in brackets

^{*} *p* < 0.05, ** *p* < 0.01

Figure Captions

Figure 1: Kaplan-Meier curves of number and percentage of patients developing ONJ over time. The data are obtained from a retrospective cohort study including only patients who developed ONJ (see text for details). Stratification by [A] underlying disease (cancer *vs.* non-cancer), [B] bisphosphonate type, and [C] underlying disease (all). MBC: metastatic breast cancer; MPC: metastatic prostate cancer; MM: multiple myeloma; OC: other cancers; OP: osteoporosis; ALE: alendronate; PAM: pamidronate, ZOL: zoledronate; IBA: ibandronate; RIS: risedronate.

