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

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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 seven 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 patients with cancer 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 and 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.

Keywords: jaw osteonecrosis; bisphosphonates; breast cancer; multiple myeloma; prostate cancer; osteoporosis

Introduction

Osteonecrosis of the jaw (ONJ) is a serious adverse effect of therapy with bisphosphonates (BP) and other antiresorptive 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 oroantral communication (Filleul et al, 2010). It has been estimated that ONJ develops in up to 7% of patients with cancer using intravenous BP and in approximately 0.12% of osteoporosis patients taking oral BP (K€uhl 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; Mavrokokki et al, 2007; Pozzi 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 programmes (Fedele et al, 2009). 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 BPrelated ONJ.

Methods

Study Design

We performed a retrospective secondary analysis of data belonging to a cohort of patients with ONJ enrolled into the GENVABO (GENetic VAriants as Biomarkers of jaw Osteonecrosis associated with bisphosphonates) study, a genomewide 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 (i) ONJ diagnosed as per AAOMS criteria (Ruggiero et al, 2009) (Ruggiero et al, 2014) and (ii) 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 patients with ONJ 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 the following: (i) age, gender and race; (ii) details of BP therapy including BP type, date of start and length of therapy, and indication for BP use; (iii) details of ONJ including date of diagnosis, site and type; (iv) dental history including history of dentoalveolar surgery and use of dentures preceding ONJ diagnosis; (v) medical history including type 2 diabetes mellitus (T2DM) and use of corticosteroids and antiangiogenics; (vi) smoking history; and (vii) 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 data set 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, USA) 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 (Hasegawa et al, 2012; Thumbigere-Math 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 patients with cancer (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 BPrelated 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 ≥ 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 (2.8–3.7) years, the 25th percentile 1.7 (1.4–1.9) years and the 75th percentile 5.8 (5.2–6.2) 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 (5.3–6.4) years for ALE and 2.2 (2.1–2.6) for ZOL. When stratified by disease, the median TTO was 5.3 (4.4–6.1) years for OP, 3.1 (2.2–3.6) for MBC and 2.3 (2.1–3.0) for MM. The median TTO was 2.2 (2.1–2.8) years for all patients with cancer (n = 237). Figure 1a–c presents 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 patients with cancer taking ZOL (212 of 237 patients with cancer, 89%), while Model 2 refers to noncancer patients taking ALE (84 of 112 patients, 75%). A history of dentoalveolar surgery was inversely associated (hazard ratio, HR = 0.71, 95% CI: 0.56–0.91) and the use of antiangiogenics (HR = 1.10, 95% CI: 1.01–1.19) directly associated with TTO in the subgroup of patients with cancer 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 programmes (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, for example 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; Mavrokokki et al, 2007; Pozzi 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 patients with ONJ and 8.5 years for 75% of ALE-exposed patients with ONJ to develop their disease. Also, 50% of ZOLexposed 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 ALErelated 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; Mavrokokki et al, 2007; Pozzi 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; Mavrokokki et al, 2007; Pozzi et al, 2007; Boonyapakorn et al, 2008; Palaska et al, 2009; Vahtsevanos et al, 2009; Saia et al, 2010; Hasegawa et al, 2012; Thumbigere-Math 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; Mavrokokki et al, 2007; Pozzi 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 seven 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 patients with cancer 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 dentoalveolar surgery to the jawbones was associated with a lower hazard for ONJ in the same subgroup of patients with cancer taking ZOL. It is not clear why ONJ developed faster in individuals who had not received dentoalveolar surgery. Of note, despite the relatively large number of subjects compared to the predictors (seven for Model 1 and six 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 patients with cancer 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 programmes. 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 ZOLexposed and ALE-exposed ONJ incident cases. Clinicians should expect that ZOL-treated patients with cancer who also receive antiangiogenic therapy may develop ONJ earlier than other patients.

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Conflict of interest

All authors declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Author contributions

All authors named in the article byline meet the ICMJE requirements for authorship as they contributed to the conception or design of the work, or the acquisition, analysis or interpretation of data for the work; drafted the work or revised it critically for important intellectual content; approved the final the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of

the work are appropriately investigated and resolved. The other non-author contributors listed under the group 'GENVABO Consortium' collected data and provided and cared for study patients.

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.

Appendix

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

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TABLE

Table 1. Details of the study cohort and time to event stratified by potential risk factors
N, number of patients; NA, not available.

Potential risk factor		N	%	Median Time to event (years) (95%CI)
Age (decade)	30–39	2	0.6	2.2 (2.2–NA)
	40–49	8	2.3	3.7 (0.4–7.5)
	50–59	41	11.7	2.4 (1.6–3.5)
	60–69	125	35.8	3.3 (2.8–4.3)
	70–79	134	38.4	2.8 (2.2–3.7)
	80–89	39	11.2	4.2 (2.9–5.8)
	Total	349	100	3.2 (2.8–3.7)
Gender	Female	247	70.8	3.9 (3.2–4.3)
	Male	102	29.2	2.1 (1.8–2.6)
Race	Caucasian	323	92.6	3.2 (2.8–3.7)
	Other	26	7.4	2.9 (2.4–5.4)
Underlying disease	Metastatic Breast Cancer (MBC)	84	24.1	3.1 (2.2–3.6)
	Multiple Myeloma (MM)	93	26.6	2.3 (2.1–3.0)
	Metastatic Prostate Cancer (MPC)	33	9.5	1.8 (1.6–2.1)
	Other Cancers (OC)	27	7.7	2.1 (1.0–2.8)
	Osteoporosis (OP)	112	32.1	5.3 (4.4–6.1)
BP type	Alendronate (ALE)	88	25.2	6.0 (5.3–6.4)
	Ibandronate (IBA)	15	4.3	2.1 (0.6–3.2)
	Pamidronate (PAM)	17	4.9	6.2 (4.6–7.2)
	Risedronate (RIS)	11	3.2	2.4 (0.3–4.7)
	Zoledronate (ZOL)	218	62.5	2.2 (2.1–2.6)
Medical History	Corticosteroids	76	21.8	3.2 (2.6–4.1)
	Antiangiogenics [a]	49	14	2.3 (1.8–3.2)
	Type 2 diabetes mellitus	34	9.7	2.9 (2.3–4.6)
	Smoking	74	21.1	3.4 (2.6–4.5)
Dental History	Dentoalveolar surgery	186	53.3	3.9 (3.2–4.5)
	Denture use	73	20.9	4.2 (2.7–5.3)
ONJ features	Non-exposed type	31	8.9	3.3 (1.7–5.8)
	Exposed type	318	91.1	3.2 (2.8–3.7)
	Maxilla	88	25.2	3.3 (2.7–3.9)
	Mandible	227	65	2.9 (2.4–3.6)
	Both maxilla and mandible	34	9.7	4.2 (3.0–5.1)

N, number of patients; NA, not available.

a Bevacizumab, sunitinib, thalidomide, lenalidomide, bortezomib.

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 patients with cancer taking ZOL (212 of 237 patients with cancer, 89%), while Model 2 refers to non-cancer patients taking ALE (84 of 112 patients, 75%). A history of dentoalveolar surgery was inversely associated (hazard ratio, HR = 0.71, 95% CI: 0.56–0.91) and the use of antiangiogenics (HR = 1.10, 95% CI: 1.01–1.19) directly associated with TTO in the subgroup of patients with cancer taking ZOL (Model 1).

Table 2. Multivariable Cox regression of factors potentially associated with TTO of ONJ in patients with cancer 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
	Patients with cancer 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

Figure 1a–c presents 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.

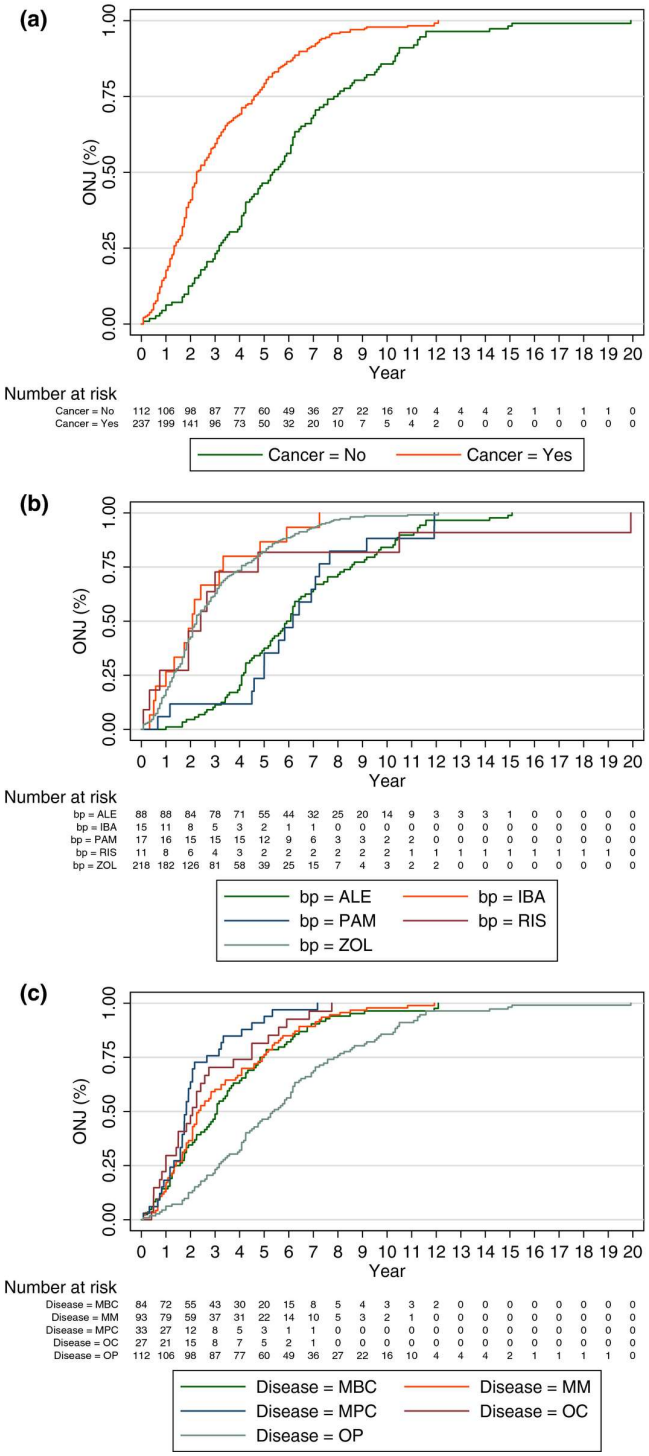

Figure 1.

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