ACTA
STOMATOLOGICA
CROATICA
www.ascro.hr

Acta Stomatol Croat. 2009;43(4):271-278.

IZVORNI ZNANSTVENI RAD
ORIGINAL SCIENTIFIC PAPER

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Prevalencija osteonekroze čeljusti povezane s bisfosfonatima kod pacijenata s rakom dojke

Prevalence of Bisphosphonate Associated Osteonecrosis of the Jaws in Breast Cancer Patients

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Sažetak

Svrha rada: Zadatak je bio ocijeniti tijekom sistematičnih oralnih pregleda prevalenciju nekroze kostiju povezanu s bisfosfanatima (BP-ONJ) i zaštitnim čimbenicima od razvoja BP-ONJ-a kod pacijentica s rakom dojke i koštanim metastazama pod terapijom bisfosfanatima. **Ispitanici i metode**: Na Odjelu ginekologije klinike u Mainzu (Njemačka) bila je provedena retrospektivna studija. Sudjelovale su sve pacijentice s rakom dojke (n=51) pod terapijom bisfosfanatima u razdoblju od srpnja 2006. do rujna 2007. Primarni kriterij bio je razvoj BP-ONJ-a i traženje mogućih dodatnih "okidača" za njegov razvoj te eventualni čimbenici za izbjegavanje. **Rezultati**: Samo kod jedne od 51 pacijentice razvio se BP-ONJ (2,0%). Pretpostavlja se da bi se kao dodatni "okidač" mogla identificirati ekstrakcija zuba. Stupanj oralne higijene tih pacijentica bio je iznad prosjeka. **Zaključak**: U usporedbi s ostalim malignim bolestima, BP-ONJ se kod pacijentica s rakom dojke ne javlja često. Primarna bolest mogla bi utjecati na njegov razvoj. Vjeruje se da bi dobra oralna higijena mogla biti zaštitni čimbenik.

Zaprimljen: 15. srpanj 2009.
Prihvaćen: 20. listopad 2009.

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Ključne riječi
bisfosfonati; osteonekroza; čeljust, bolesti; rak dojke; oralna higijena

Uvod

Rak dojke jedan je od glavnih uzroka smrti žena oboljelih od karcinoma diljem svijeta (1), s incidencijom između 84,6 i 99,4 na sto tisuća žena u zapadnoj Europi i sjevernoj Americi (1). Kod takvih bolesnica kost je jedno od najčešće metastazama pogođenih mjesta (2). Doista, incidencija koštanih metastaza kod oboljelih od raka dojke iznosi između 65 i 75 posto (3). Metastaze su osteolitičke (48%), osteoblastičke (13%) ili miješane (38%),(2). Maligne stanice otpuštaju osteoklastno stimulirajuće stanice, prema tome većina skeletalnih oštećenja uzrokovana je osteoklastima (3). Tipične skeletalne komplikacije su bolovi, smanjena pokretljivost, hiperkalcijemija, patološke frakture te kompresije leđne moždine i spinalnih živaca. U terapiji koštanih metastaza nekoliko je pristupa: hormonalna terapija, operacija, kemoterapija, radioterapija te bisfosfanati. Glavni učinak bisfosfanata je inhibicija funkcije osteoklasta. Bisfosfanati s dušikom inhibiraju farnesil-difosfatsku sintazu (4), a oni bez dušika ugrađuju se u molekule ATP-a (5), što zajedno djeluje na apoptozu osteoklasta te smanjuje poteškoće sa skeletom. Negativne popratne pojave mogu se svrstati u tri glavne skupine: reakcije akutne faze, poteškoće u gornjem probavnom i dišnom sustavu te učinci vezani za funkciju bubrega. Godine 2003. prvi je put bila opisana osteonekroza kostiju čeljusti povezana s bisfosfanatima (BP-ONJ-om) (6), a nakon toga se sustavno sve češće dijagnosticirala (7). Na početku je uzročno-posljedična veza bila upitna, pa se osteonekroza tumačila djelovanjem drugih čimbenika: malignih bolesti, mogućih anemija, zračenja, kemoterapije, lijekova poput steroida, infekcija podrijetlom iz zuba ili paranazalnih sinusa, prijašnjih stomatoloških zahvata i korištenja lokalnog anestetika s vazokonstriktorom (8). U međuvremenu je mogući nastanak BP-ONJ-a dodan na karakteristike produkta. Prema definiciji *udruge American Association of Oral and Maxillofacial Surgeons,* BP-ONJ je eksponirana nekrotična kost u maksilofacijalnom području koja traje dulje od osam tjedana kod pacijenata trenutačno pod terapijom bisfosfanatima ili su je tek završili, te u anamnezi nemaju zračenje (9). Raspravljalo se o različitim teorijama u vezi s patogenezom. Kao dodatni utjecaj uz djelovanje bisfosfanata na osteoklaste, pogođeni su i osteoblasti, što sve rezultira smanjenom remodelacijom kosti (10). Budući da bisfosfanati djeluju antiangiogenetski, i to djelomice može biti razlog za razvoj avaskularne koštane nekroze (11). Postoje dokazi da učinak bisfosfanata može potaknuti pro-

Introduction

Breast cancer is the leading cause of cancer death in women worldwide, with an incidence between 84.6 and 99.4 per 100.000 for western Europe and North America (1). Bone is the most often affected site of metastases in breast cancer patients (2). Indeed, the incidence of bone metastases for breast cancer patients at the time of autopsy is described as 65-75% (3). These metastases are either osteolytic (48%), osteoblastic (13%) or mixed (38%) (2). Malignant cells release factors stimulating osteoclasts; therefore most of the skeletal destruction is done by osteoclasts (3). Typical skeletal complications are pain, impaired mobility, hypercalcaemia, pathological fractures, spinal cord and nerve compression.

In the treatment of bone metastases, several approaches such as hormonal therapy, surgery, chemotherapy, radiotherapy and bisphosphonates are used. The main effect of bisphosphonates is the inhibition of the osteoclasts' function. Nitrogen-containing bisphosphonates inhibit the farnesyl diphosphate synthase, whereas non nitrogen containing bisphosphonates are integrated into the ATP molecule (4,5); both result in apoptosis of the osteoclast and thereby decrease skeletal related events.

Negative side effects can be separated into 3 main groups: acute-phase-reactions, upper aerodigestive tract issues, and effects concerning renal function. In 2003, a new adverse effect, bisphosphonate associated osteonecrosis of the jaw (BP-ONJ), was described for the first time and has been subsequently diagnosed with increasing frequency (6,7).

A causal relationship was questioned at first, and the appearance of osteonecrosis was explained by the existence of other risk factors: malignant disease, possible anemia, radiation, chemotherapy, medications such as steroids, infections of dental or sinus origin, preceding dental procedures and the use of local anesthetics with vasoconstrictors, all of which are all related to the development of an osteonecrosis (8). Meanwhile, the development of BP-ONJ has been added to the summary of product characteristics.

According to the American Association of Oral and Maxillofacial Surgeons, BP-ONJ is defined as exposed, necrotic bone in the maxillofacial region that has persisted for more than 8 weeks in patients who are currently receiving or have received bisphosphonate treatment and have no radiation anamnesis (9). Several theories about the pathogenesis are being discussed.

In addition to the bisphosphonate's impact on osteoclasts, osteoblasts are also influenced, resulting

padanje sluznice te kao posljedicu razvoj BP-ONJ-a (12, 13). Uz neposrednu ulogu bisfosfanata, pacijenti s BP-ONJ-om gube zube, imaju zubobolje ili parodontnu bolest, a to su sve potencijalni "okidači" za razvoj BP-ONJ-a (7). Na radiogramu se mogu vidjeti prijašnje ekstrakcije zuba kod nezacijeljenih alveola (14). Pacijenti s nekoliko rizičnih čimbenika za razvoj osteonekroze čeljusti, kao što je dodatno zračenje glave i vrata, u većoj su opasnosti (15). Pacijenti s BP-ONJ-om mogu osjećati bol u kostima i mukoznim membranama u blizini enoralno izložene inficirane kosti. Takvi bolesnici često imaju zadah iz usta, a daljnji simptomi uključuju zahvaćanje maksilarnog sinusa te, ako je zahvaćen mandibularni kanal, mogu imati peresteziju. Između istraživanja kojima je zadatak bio ocijeniti prevalenciju ili incidenciju BP-ONJ-a kod pacijentica s karcinomom dojke, samo dvije prospektivne studije uključivale su sustavni pregled oralne šupljine svih oboljelih (16, 17). Svrha ove studije bila je ocijeniti prevalenciju BP-ONJ-a kod pacijentica s karcinomom dojke, uz naglasak na preventivne čimbenike kao što su oralna higijena te one rizične poput oralnokirurških zahvata, zubobolje ili parodontne bolesti.

Ispitanici i postupci

U provedbi presječne studije na Odjelu za opstetriciju i ginekologiju Sveučilišta Johannesa Gutenberga u Njemačkoj, bile su od srpnja 2006. do rujna 2007. pregledane *sve pacijentice* pod terapijom bisfosfanatima zbog raka dojke. Bile su (n=51) na kontroli kod ginekologa i maksilofacijalnog kirurga. Primarno se tražio nastanak BP-ONJ-a, a mogući "okidač" (ekstrakcije zuba, zubna bol, oralno-kirurški zahvati) za njegov nastanak također je bio u području interesa studije.

Prikupljeni su bili podaci o dobi, o godini kada je dijagnosticiran karcinom dojke, o primjeni bisfosfanata, o ostalim bolestima i lijekovima, o mogućem zračenju glave i vrata te koliko su često sudionice odlazile na stomatološke kontrole.

Svaka je pacijentica bila temeljito pregledana kako bi se ustanovio dentalni status: manjkaju li im

in reduced bone remodeling (10). Since bisphosphonates are characterized by an antiangiogenetic effect, this might be partially responsible for the development of the avascular bone necrosis as well (11). There is evidence that the effect of bisphosphonates might trigger mucosal breakdown, with subsequent development of BP-ONJ (12,13).

In addition to direct role of bisphosphonates, patients with BP-ONJ also had a previous loss of a tooth, denture pressure sores or periodontal disease, potentially triggering the BP-ONJ (7). In many cases the previous tooth extraction can be seen in the non healing alveolar socket in the x-ray (14). Patients with several risk factors for developing osteonecrosis of the jaws, such as additional radiation to the head and neck area, have an increased risk of developing osteonecrosis (15). Patients with BP-ONJ may experience pain if the bone and the mucous membrane in the vicinity of the enoral exposed bone have become infected. Patients often present with foetor ex ore; further symptoms might be the affection of the maxillary sinus and in case of affection of the mandibular canal patients might report paraesthesia.

Among studies aimed at evaluating prevalence or incidence of BP-ONJ in breast cancer patients, only two prospective studies have included systematic, oral cavity examinations of all study subjects (16,17). The aim of this cross sectional study was to evaluate the prevalence of BP-ONJ in breast cancer patients, with thought given to preventative factors of BP-BOJ such as dental hygiene, and risk factors of BP-ONJ such as dental surgical procedures, denture pressure sores or periodontal diseases.

Material and Methods

In a cross-sectional-study conducted in the Department for Obstetrics and Gynecology at the Johannes Gutenberg-University, Germany, *all patients* with bisphosphonate treatment due to breast cancer treated from 07/2006-09/2007 were comprised. All patients (n=51) were examined by a gynecologist and a maxillofacial surgeon. The primary outcome was the development of BP-ONJ; possible additional trigger factors (tooth extractions, dental pressure sores, and dental-surgical procedures) for the development of BP-ONJ were also of interest.

Collected data were age, age at diagnosis of breast cancer, applied bisphosphonates, further diseases and medication, possible radiation of the head and neck area, and dentist consultation frequency.

Each patient had a thorough oral examination to check dental status: missing teeth, caries (yes/no),

zubi i koji, imaju li karijes (da/ne), parodontnu bolest (da/ne), protetske nadomjeske (stupnjevi od 0 do 3) te enoralno izložene nekrotične kosti.

Sve pacijentice su potpisale suglasnost. Zbog malog uzorka, statistička je analiza bila ograničena samo na deskriptivnu.

Rezultati

U ispitivanju je sudjelovala 51 pacijentica, a prosječna dob im je bila 61,1 godina (±10,0 standardna devijacija). Za dvije se ne zna koliko su godina imale u razdoblju kada im je bila postavljena dijagnoza karcinoma dojke. Prosječna dob ostalih 49 pacijentica u razdoblju kada im je bila postavljena dijagnoza karcinoma iznosila je 53,1 (±10,4) godinu. Ostale njihove bolesti bile su: hipertenzija kod deset pacijentica te dijabetes melitus kod dviju. Jedna je dodatno bolovala od tumora na mozgu te još jedna od raka na debelom crijevu. Tijekom sudjelovanja u studiji propisivani su im bili samo bisfosfanati Zoledronat i Ibandronat. Petnaest pacijentica primilo je u prosjeku 13,5 (±9,9) doza Zoledronata (medijan 12 primjena), 26 je dobilo prosječno 18,1 (±16,0) dozu Ibandronata (medijan: 13 primjena; podatka o jednoj pacijentici nije bilo), a 10 je imalo određene doze u varijabilnom slijedu. U prosjeku su pacijentice primile Ibandronat 19,2 (±10,9) puta (medijan: 10) i Zoledronat 12,5 (±11,2) puta (medijan: 22). Bisfosfanate su sve bolesnice dobivale intravenski, osim triju – one su peroralno primale Ibandronat. Jedna je dobivala i Zoledronat i Ibandronat, te joj je istodobno obiteljski liječnik odredio dodatno Etidronat tijekom prve dvije i pol godine, nakon čega je zbog osteoporoze preporučio Risedronat u sljedeće dvije i pol godine. Steroide je dobivalo 14 pacijentica, 46 kemoterapiju, 30 edokrinu terapiju (18 bolesnica dobivalo je inhibitore aromataza, 7 antiestrogene i 5 inhibitore aromataza i antiestrogene zajedno) a sedam je bilo podvrgnuto radijacijskoj terapiji – zračen im je bio cervikalni dio kralježnice. Čeljusti nisu bile pogođene radijacijskom terapijom. Sve pacijentice, osim njih šest, redovito su odlazile stomatologu - tri više od dva puta na godinu, 29 dva puta na godinu i 13 jedanput na godinu. Trinaest pacijentica imalo je parodontnu bolest, dvadeset protetske nadomjeske i šest proteze. Deset pacijentica (19,6%) imalo je sve zube i bile su bez protetskih nadomjestaka. Dvije su imale karijes koji se trebao liječiti. Najčešće popratne pojave nakon primjene bisfosfanata bile su zamor kod sedam pacijentica te povraćanje kod četiriju. Jedna od 51 pacijentice imala je BP-ONJ u doba pregleda,

periodontal disease (yes/no), odontoseisis (grade:0-3) and the presence of enoral exposed necrotic bone.

Each patient gave informed consent. Due to the small sample size of patients, the statistical analysis was restricted to a descriptive analysis only.

Results

51 patients at an average age of 61.1 (±10.0 standard deviation) years at time of examination were comprised. In two patients, the age at time of breast cancer diagnose was missing. The average age for the rest of the 49 patients was 53.1 (±10.4) years.

Further diseases the patients suffered from were hypertension in 10 patients and diabetes mellitus in two patients. One patient suffered from an additional brain tumor and another one from colon cancer.

Only the bisphosphonates zoledronate and ibandronate had been applied. 15 patients had received an average of 13.5 (±9.9) zoledronate applications (median: 12 applications), 26 patients had received an average of 18.1 (±16.0) ibandronate applications (median: 13; information on one patient was missing) and 10 patients had received ibandronate and zoledronate in varying application sequences. On average, these patients received ibandronate 19.2 (±10.9) times (median: 10), and zoledronate 12.5 (±11.2) times (median: 22). The bisphosphonates were administered via IV in all patients except for three, who received ibandronate orally. One patient had received zoledronate and ibandronate, and in parallel her family physician had additionally prescribed first etidronate for 2.5 years, followed by risedronate for another 2.5 years due to osteoporosis.

14 patients had received steroids, 46 had chemotherapy, 30 patients had undergone endocrine therapy (18 patients with aromatase inhibitors, 7 with antiestrogens and 5 with aromatase inhibitors and antiestrogens) and seven patients had received radiation therapy, seven of which included cervical vertebra radiation. The jaws were not affected by radiation therapy.

All patients save six had visited the dentist regularly: 3 more than twice a year, 29 twice a year and 13 once a year. 13 patients had periodontal disease. 20 patients had odontoseisis and 6 patients had a denture. 10 patients (19.6%) did not have a single loss of a tooth and no odontoseisis. Two patients had caries that had to be treated.

The most frequently quoted negative side effects reported shortly after the bisphosphonate application was fatigue in seven and nausea in four patients.

što je rezultiralo prevalencijom od 2 posto. Bila je to 86-godišnja bolesnica koja je dobila Zoledronat (17 doza), zatim je slijedio Ibandronat (21 doza) te kao dodatak Etidronat i Risedronat u razdoblju kada se razvila osteonekroza. Bila je na kemoterapiji i dobivala je inhibitore aromataza. Nije bolovala od dodatnih bolesti, posjećivala je stomatologa češće od dva puta na godinu te osjećala bol u područ-

One out of 51 patients had BP-ONJ at the time of examination, resulting in a prevalence of 2%. She was 86 years old, had received zoledronate (17 applications), followed by ibandronate (21 applications), and additionally etidronate and risedronate by the time the osteonecrosis developed. She had received chemotherapy and aromatase inhibitors. She suffered from no additional diseases, visited the

Tablica 1. Usporedba između pacijentica bez osteonekroze čeljusti povezane s bisfosfanatima i pogođenih pacijentica
Table 1 Comparison between the patients without bisphosphonate associated osteonecrosis of the jaws and the affected patient.

	Svi pacijenti • All patients	**Pacijenti bez BP-ONJ-a • Patients without BP-ONJ**	**Pacijenti s BP-ONJ-em • BP-ONJ-patient**
Broj (postotak) • Number (percentage)	51 (100)	50 (98)	1 (2)
Dob: medijan (raspon) • Age at examination in years: median (range)	60 (42 - 87)	60 (42 – 82))	87
Dob tijekom postavljanja dijagnoze • Age at age of breast cancer diagnosis in years	52 (34 – 80)	52 (34 - 79)	80
Ibandronat posebno (br.doza ± SD) • Ibandronate only (applications ± SD)	26 (18±16)	26 (18±16)	0
Ibandronat i zoledronat u slijedu (br.doza ± SD) • Ibandronate and zoledronate sequently (applications ± SD)	10 (19±11 & 13±11)	9 (19±12 & 12±12)	1 (21 &17) and etidronate and risedronate
Zoledronate posebno (br.doza ± SD) • Zoledronate only (applications ± SD)	15 (13±10)	15 (13±10)	0
Samo *peroralno* • Oral application only	3	3	0
Steroidi • Steroids	14	14	0
Kemoterapija • Chemotherapy	46	45	1
Zračenja glave i vrata • Head and neck radiation	7	7	0
Posjeti stomatologu • Dentist appointments > 2 x na godinu • > 2 x / year 2 x na godinu • 2 x / year 1 x na godinu • 1 x / year rjeđe • less often	 3 29 13 3	 2 29 13 3	 1 0 0 0
Proteze • Denture	6	5	1

Tablica 2. Objavljena istraživanja koja se bave osteonekrozom čeljusti kod pacijentica s karcinomom dojke povezanom s bisfosfonatima
Table 2 Published studies dealing with Bisphosphonate associated osteonecrosis of the jaws in breast cancer patients.

Autor • Author	**Godina • Year**	**Nacrt istraživanja • Study design**	**Svi pacijenti pregledani oralno • All patients orally examined**	**Pacijenti • Patients (n)**	**BP-ONJ slučajevi • BP-ONJ cases**	**Incidencija • Incidence (%)**
Aguiar Bujanda [16]	2007.	css	da • yes	35	4	11,4
Bamias [18]	2005.	pros	ne • no	70	2	2,9
Durie [25]	2005.	web pregled • web survey	ne • no	299	13	4,3
Estilo [22]	2008.	retro	da • yes	134	18	13,4
Guarneri [26]	2005.	retro	ne • no	48	3	6,3
Hoff [21]	2008.	retro	ne • no	1338	16	1,2
Ibrahim [27]	2008.	retro	ne • no	220	5	2,3
Sanna [17]	2006.	pros	da • yes	81	5	6,2
Wang [28]	2007.	retro	ne • no	81	2	2,5

Legenda • Legend
CSS - presječna istraživanja • cross sectional study; pros - prospektivno istraživanje • prospective study

ju nedavne ekstrakcije zuba koju je obavio njezin stomatolog. Nakon inicijanog enoralnog apscesa, BP-ONJ je bio uspješno izliječen s trima lokalnim debridmanima. Pacijentici su nakon toga prepisane otopine za ispiranje usta i antibiotici.

Rasprava

Sve je više incidencija BP-ONJ-a opisano u literaturi nakon prvih retrospektivnih istraživanja i današnjih prospektivnih studija. U prvim objavljenim istraživanjima incidencija je iznosila 9,9 posto (11 od 111 pacijenata) za multipli mijelom (18). Nedavno tiskana prospektivna studija, u sklopu koje je svakog pacijenta pregledao stomatolog, a ne samo one koji su upozorili na problem, opisana je kod multiplog mijeloma incidencija od 17,2 posto (18) i 18,6 posto za rak prostate (20). Incidencija kod raka dojke u rasponu je od 1,2 posto (21) kod retrospektivnih studija bez stomatološkog pregleda pacijenata, do 11,4 posto (16) kod presječnih studija i 13,4 posto kod retrospektivnih (22) s oralnim pregledom svih pacijenata (Tablica 2.). U našem je istraživanju prevalencija dva posto, što je dosta slično već opisanim rezultatima. Zanimljivo je da rezultat nije viši s obzirom na to da je karakter našeg nacrta studije prospektivan, kao što je bio slučaj kod drugih bolesti tretiranih bisfosfanatima. U prospektivnom nacrtu studije neotkrivena, asimptomatična BP-ONJ te neobjavljene tegobe povezane s njime, trebale bi se bolje otkrivati. U ovom istraživanju prosjek dobi bio je nizak – 53,1 godina u razdoblju kada je bolesnicama bila postavljena dijagnoza karcinoma dojke, u usporedbi s prosječnim zabilježenim registrom u Saarskoj pokrajini koji u prosjeku iznosi 62 godine (23). U mlađoj dobi obično je bolja manualna sposobnost, pa se zbog toga može i bolje održavati oralna higijena. Pokretljivost ruku obično je smanjena kod starijih ljudi (24). Budući da pacijenti imaju bolju oralnu higijenu, više nisu toliko česte ni restauracije (ispuni, krunice), ni vađenje zuba, ni proteze. Zato se izbacuju neki "okidači" opisani u povijesti bolesti pacijenata s BP-ONJ-om (7). U skupini od 65 do 74 godine samo 2,6 posto ljudi ima svoje zube. U istoj dobnoj skupini 17,3 posto pacijenata ima barem jedan zub s karijesom (24). Pacijentice u našem istraživanju imale su znatno manje karijesa, vjerojatno zbog češćih posjeta stomatologu, a 19,6 posto imalo je još sve svoje zube zahvaljujući dobroj oralnoj higijeni. Uspoređujući druge objavljene rezultate pacijenata s rakom prostate

dentist more than twice a year and had a denture pressure sore at the site of a recent tooth extraction performed by her dentist.

After an initial enoral abscess, the BP-ONJ was finally successfully treated after three local debridements. In addition, the patient received mouth rinses and antibiotics.

Discussion

The reported incidences of BP-ONJ in the literature have increased from the first retrospective studies to more recent prospective ones. The first published study described an incidence of 9.9% (11 out of 111 patients) for multiple myeloma (18). A recently published prospective study, where every patient, rather than only the ones that had indicated a problem, was examined by a dentist, described an incidence of 17.2% for multiple myeloma (19) and 18.6% for prostate cancer (20). Incidences for breast cancer published to date range from 1.2% (21) in a retrospective study without a dental examination in all patients, to 11.4% (16) in a cross sectional study and 13.4 in a retrospective study (22) with oral examination of all patients, Table 2.

Our study shows a prevalence of 2% and is quite similar to the previously described results. Interestingly, the result is not higher in spite of the prospective nature of the study design, as has been the case for other diseases treated with bisphosphonates. In a prospective study design, undetected, asymptomatic BP-ONJ and unreported BP-ONJ problems are thought to be better detected.

This study's clientele had a low average age of 53.1 years at the diagnose of breast cancer compared to the average recorded at the cancer register of Saarland, Germany, which is an average age of 62 years (23). The younger age usually corresponds with better manual capabilities and therefore the possibility of better oral hygiene. Manual dexterity is usually reduced in older patients (24). Since the patients have better oral hygiene, the need for restorations (fillings, crowns), tooth extractions and, later on, dentures is reduced. This equates to a lack of trigger factors that are commonly described in the history of BP-ONJ patients (7). In the age group of 65-74 years, only about 2.6% of people still have all their teeth. In the same age group, 17.3% of the patients have at least one tooth with caries (24). The patients of our study had remarkably fewer caries, probably as a result of highly frequent dentist appointments, and 19.6% of these patients still had all their teeth due to a good oral hygiene. Compared to another previously pub-

(20) korištenjem identičnog nacrta studije, samo su četvorica od njih 43 imala sve zube, što iznosi 9,3 posto (podaci nisu objavljeni u članku). Prevalencija BP-ONJ-a u tom istraživanju raka prostate bila je 18,6 posto. Ti rezultati potvrđuju da je prije terapije bisfosfanatima i tijekom nje prijeko potrebno obavijestiti pacijente o održavanju oralne higijene i redovitim kontrolama te prema potrebi i o terapiji. Daljnji zaključak jest da je danas bolja oralna rehabilitacija, što je karakteristično za žene (24). To djelomice može objasniti nižu incidenciju BP-ONJ-a kod žena te tako i kod oboljelih od raka dojke u odnosu prema ostalim malignim bolestima. Bez obzira na oralnu higijenu, možda postoji neovisni rizik za nastanak BP-ONJ-a, ovisno o primarnoj bolesti koja je uvjetovala primjenu bisfosfanata. Pacijentice s rakom dojke možda su manje ugrožene od bolesnika s multiplim mijelomom i rakom prostate.

Zaključak

Na kraju možemo istaknuti da dobiveni podaci pokazuju kako je potrebno da se pacijenti kojima će se odrediti terapija bisfosfanatima pošalju stomatologu ili oralnom kirurgu zbog prijeterapijskog restauriranja zuba i opsežnih uputa o održavanju oralne higijene.

Sukobi interesa

Dr. Walter je primio sredstva za istraživanje od Novartisa;
Prof. Grötz je držao predavanja za Novartis i Roche, a Prof. Al-Nawas za Roche.

lished study conducted by the same research group on prostate cancer patients (20) using exactly the same study design, only 4 out of 43 patients had all their teeth, resulting in 9.3% (this data was not published in the article). The prevalence of BP-ONJ in the study with prostate cancer patients was 18.6%. These results support the idea of introducing patients before starting bisphosphonate therapy and recalls during bisphosphonate treatment for hygiene instructions and treatment if necessary.

A further aspect that should be pointed out is the better state of oral rehabilitation that is characteristic of women (24). This might partially explain a lower incidence of BP-ONJ in women, and therefore breast cancer patients, compared to other malignant diseases.

Independent from oral hygiene, there might be a different risk for BP-ONJ depending on the primary disease that caused bisphosphonates to be applied. Breast cancer patients might have a lower risk compared to patients with multiple myeloma and prostate cancer.

Conclusion

In conclusion, these data support the idea of introducing patients who are about to start bisphosphonate therapy to a dentist or oral and maxillofacial surgeon, the aim being to preemptively restore the teeth and provide detailed oral hygiene instructions.

Conflict of interest

Dr. Walter received research funding from Novartis.
Prof. Grötz gave speeches for Novartis and Roche.
Prof. Al-Nawas gave speeches for Roche

Abstract
Objective: To evaluate the prevalence of Bisphosphonate-associated-osteonecrosis-of-the-jaws (BP-ONJ) and protective factors of BP-ONJ-development in breast cancer patients with osseous metastasis and bisphosphonate therapy using systematical dental oral examinations. **Material and Methods:** A cross-sectional-study was conducted in the Department for Gynecology in Mainz, Germany. All breast cancer patients (n=51) treated with bisphosphonate in the time span from 07/2006 to 09/2007 were recruited. Primary outcome was the development of BP-ONJ and the detection of possible additional trigger factors for the development of BP-ONJ, as well as possible factors for avoiding BP-ONJ. **Results:** Only 1 out of 51 patients developed BP-ONJ (2.0%). A tooth extraction could be identified as an additional trigger factor. The overall dental hygiene of this patient clientele was above average. **Conclusion:** Compared to other malignant diseases, BP-ONJ in breast cancer patients does not appear as often. The underlying disease might be of importance in the development of BP-ONJ. A good dental hygiene might be a protective factor.

Received: July 15, 2009
Accepted: October 20, 2009

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Key words
Bisphosphonates; Osteonecrosis; Jaw diseases; Breast cancer; Oral hygiene

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