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Original Article

Bone Targeting Agents in Major Solid Tumours Metastases: Multinational Cohort Study.

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What was already known?

- Limited utilization of bone-targeting agents (BTAs) among bone metastasis patients in Asia.

What are the new findings?

- Underutilization of BTAs was observed across all sites and tumour types.
- The Sankey diagrams visualize the dynamic utilization patterns of BTAs, including treatment discontinuation, re-initiation, and switching.

What is their significance?

- Many bone metastasis patients may receive less-than-optimal care in Asia.

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Abstract

Objective: To describe the epidemiology, clinical characteristics and utilization patterns of bone-targeting agents (BTAs) in patients with bone metastases from breast, prostate, and lung cancer.

Methods: This is a multinational, retrospective cohort study including patients with 3 major solid tumours (breast-, prostate- and lung cancer) and newly receiving BTAs (i.e. denosumab, zoledronic acid, and pamidronate). Records were retrieved from nationwide health databases from Hong Kong, Taiwan (HK&TW: 2013-2017) and Korea (KR: 2012-2016). Descriptive analyses included the annual incidence rates of bone metastases and the cumulative incidence curves of BTA initiation. We used Sankey diagrams to visualize the dynamic BTA utilization patterns.

Results: The annual incidence rate of bone metastases ranged from 3.5%-4.5% in TW, 9.6%-10.3% in HK and 2.9%-3.8% in KR. We identified 14.1% (5,127), 9.3% (833), and 9.4% (4,800) of patients with bone metastases newly initiated on BTAs in TW, HK and KR, respectively. The most frequently used BTA in TW (67.1%) and HK (51.9%) was denosumab, while in KR (84.8%) it was zoledronic acid. Sankey diagrams indicated the proportion of patients remaining on denosumab was the highest in TW and HK, while it was zoledronic acid in KR. Specifically, in TW, patients who were on bisphosphonates or had discontinued treatment frequently switched to, or reinitiated denosumab.

Conclusions: We found the rate of BTA utilization remained low across all sites and tumour types in recent years. The dynamic utilization patterns of BTAs provide better understanding of the treatment landscape for future evaluation of associated outcomes of the patients.

Keywords: solid tumour, bone metastasis, bone targeting agents, multinational pharmacoepidemiologic study

BACKGROUND

Bone metastases are well-known complications in cancer patients, and they are most prevalent among patients with solid tumours, especially breast, prostate, and lung cancer.[1] Prompt management of bone metastases is clinically imperative as they disrupt bone homeostasis and increase the risk of bone complications, including pathologic fractures, spinal cord compression, bone surgery, and bone pain requiring palliative radiotherapy.[2] Randomized clinical trials has shown that the bone complications from bone metastases arising from breast cancer (BC) were most common with a 2-year cumulative incidence of 68%, followed by 49% for prostate cancer (PC), and 48% for lung cancer (LC) and other solid tumours.[3-5] Lower health-related quality of life and the economic burden imposed on patients and the health care system following bone complications highlight the need for optimal management of bone metastases from solid tumours.[6]

Bone targeting agents (BTAs) are indicated for prevention of bone complications among patients with bone metastases from solid tumours. Current clinical guidelines recommend the use of BTAs upon diagnosis of bone metastases to reduce and delay bone complications.[7 8] Real-world data on the utilization patterns of BTAs for the management of bone metastases have previously been presented in the US and Europe, which emphasized the issue of underutilization of BTAs.[9-12] Conversely, the treatment landscape for bone metastases in Asia still remains to be explored as the current real-world data are limited; most previous studies were based on an electronic health record (EHR) retrieved from a single tertiary centre, focused on highly specific patient populations, or limited by small sample size, limiting their generalizability.[13 14] Despite a general consensus across guidelines on the use of BTAs for the management of bone metastases from solid tumours, eligibility criteria for the reimbursement of BTAs vary widely by types of solid tumours and among different countries. These complicate direct comparison of BTA utilization across different regions.

Improved knowledge about current BTA utilization patterns, as well as epidemiology of bone metastases from solid tumours, would provide fundamental information for subsequent evaluations of clinical, economic and policy importance. Using population representative EHR from Hong Kong and medical claims data from Taiwan and Korea, this study aimed to evaluate the incidence rate, clinical characteristics and utilization patterns of BTA, including dosage, duration and switching patterns, in patients with bone metastases from BC, PC, and LC.

METHODS

Study Design Overview & Data Sources

This is a multinational retrospective cohort study using data from Taiwan (from 2013-2017), Hong Kong (from 2013-2017) and Korea (from 2012-2016). Taiwan's National Health Insurance Database (NHID) is a claims database that covers nearly 99.9% of Taiwan's population, approximately 25 million individuals.[15] Hong Kong's Clinical Data Analysis and Reporting System (CDARS) is a population representative EHR that covers about 7 million individuals, approximately 80% of all hospital admissions and more than 90% of cancer patients in Hong Kong.[16 17] Korea's NHID is a claims database that covers 97% of the Korean population, approximately 50 million individuals.[18] To maintain data confidentiality, we used a distributed network approach and executed the analysis independently from each site on the basis of common protocol. The coordinating centre, National Cheng Kung University, Taiwan, only collected summary results from each site without access to the individual data. The study was approved by the institutional review board of each site, National Cheng Kung University of Taiwan [A-ER-107-387], the University of Hong Kong/Hospital Authority Hong Kong West Cluster [UW18-691], and Sungkyunkwan University of Korea [SKKU 2019-06-008].

Study cohort assembly

We included patients with solid tumours (BC, PC and LC), aged 18+ years and newly diagnosed with bone metastases, as defined by International Classification of Diseases (ICD)-9 or ICD-10 codes listed in **Supplement 1**. Patients with no records of bone metastases within a two-year washout period before the first diagnosis of bone metastasis were considered as new cases. We only included 120mg denosumab (ATC code: M05BX04), 4mg zoledronic acid (ATC code: M05BA08) and any formulation of pamidronate (ATC code: M05BA03) to ensure the drugs were specifically classified as BTAs for the prevention of bone complications, and not for osteoporosis or other indications. New users of BTAs were identified from those with incident diagnosis of bone metastasis, and defined as patients with no BTA record within a one-year washout period before the first record of BTA prescription (index date). There were no denosumab users in Korea as it was not available during the study period. We excluded patients with incomplete age or sex data. We excluded patients who received a single BTA administration or with the interval between BTAs less than 14 days because the most likely indication was for hypercalcaemia. Patients were censored at the time of loss to follow-up, death, or the last day of the database (31st December 2017 for Taiwan and Hong Kong; 31st December 2016 for Korea).

Covariates and Statistical analysis

We investigated patients' age, sex, year of BTA initiation, types of BTA, primary cancer, comorbidities (mainly cardiovascular, psychiatric, neurological and endocrine diseases) and related medications. Details of the covariates are listed in **Supplements 2 & 3**.

We calculated the annual incidence rate of bone metastases as number of patients with bone metastases divided by number of patients with solid tumours. We also calculated the annual incidence rate of BTA use as number of patients who received BTAs divided by number of patients with bone metastases from solid tumours. We performed the Cochran Armitage test to evaluate the trend of incidence rates for bone metastases as well as for BTA use. Cumulative incidence curves were used to evaluate the rates of time to BTA initiation following diagnosis of bone metastases. We investigated the doses and intervals of BTA prescriptions. Moreover, we used Sankey diagrams to visualize BTA utilization patterns over 90-day intervals. Discontinuation was defined as no-refill exceeding 90 days after the last BTA prescription. Switching was defined as patients being exposed to BTAs differing from a previous one. We used numbers and percentages for categorical variables, and means with standard deviations (SD) and medians with interquartile range (IQR) for continuous variables. Sankey diagrams were drawn using the online open source tool (http://sankeymatic.com/). We used SAS version 9.4 for all statistical analyses.

RESULTS

Incidence Rate of Bone Metastasis

In total, we identified 36,347, 9,497 and 51,211 patients newly diagnosed with bone metastases from BC, PC, or LC in Taiwan, Hong Kong and Korea, respectively. The annual incidence rate of bone metastases ranged from 3.5% - 4.5% in Taiwan, 9.6% - 10.3% in Hong Kong and 2.9% - 3.8% in Korea during the study period. The incidence rates of bone metastases slightly decreased during the study period across all sites and tumour types, except for PC in Hong Kong. We found a higher proportion of LC patients with bone metastases, followed by PC and BC across all sites **(Figure 1)**.

The Trends of BTA Use

There were 5,127 [denosumab (D): 3,440, zoledronic acid (Z): 1,210 and pamidronate (P): 477], 883 (D: 458, Z: 357 and P: 68) and 4,800 (Z: 4,068 and P: 732) patients who initiated BTAs following diagnosis of bone metastases in Taiwan, Hong Kong and Korea, respectively **(Table 1).** We observed different trends of BTA use among the 3 sites. In Taiwan, the rate of denosumab increased from 0.9% to 6.7% during the study period, but the rates of zoledronic acid and pamidronate decreased from 2.5% to 0.7% and from 0.8% to 0.2%, respectively. In Hong Kong, the rate of denosumab increased from 0.7% to 2.8% from 2013 to 2015 but slightly decreased in 2016. In Korea, the rate of zoledronic acid and pamidronate did not change (zoledronic acid: between 4.0% and 4.3%; pamidronate: between 0.7% and 1.0%) during the study period **(Figure 2).**

Table 1: Characteristics of patients with solid tumours and bone metastases receiving different BTAs

	Taiwan	Hong Kong	Korea
Patients, *N*	5,127	883	4,800
Age at index date, years, mean (SD)	62.5 (13.3)	61.6 (12.2)	57.0 (12.6)
Age group at index date, years, *N* (%)			
<54	1,451 (28.3)	252 (28.5)	2,155 (44.9)
55–64	1,480 (28.8)	295 (33.4)	1,264 (26.3)
65–74	1,103 (21.5)	205 (23.2)	893 (18.6)
75–84	826 (16.1)	103 (11.7)	442 (9.2)
≥85	267 (5.2)	28 (3.2)	46 (1.0)
Sex, *N* (%)			
Male	2,047 (39.9)	318 (36.0)	1,197 (24.9)
Calendar year at index date, *N* (%)			
2012	N/A	N/A	811 (16.9)
2013	613 (11.9)	78 (8.8)	968 (20.2)
2014	797 (15.5)	150 (17.0)	967 (20.1)
2015	939 (18.3)	193 (21.9)	1,052 (21.9)
2016	1,350 (26.3)	245 (27.7)	1,002 (20.9)
2017	1,428 (27.9)	217 (24.6)	N/A

Original cancer type, *N* (%)			
Breast cancer	2,173 (42.4)	379 (42.9)	3,493 (72.8)
Prostate cancer	1,155 (22.5)	160 (18.1)	914 (19.0)
Lung cancer	1,799 (35.1)	344 (39.0)	393 (8.2)
BTAs type, *N* (%)			
Denosumab	3,440 (67.1)	458 (51.9)	N/A
Zoledronic acid	1,210 (23.6)	357 (40.4)	4,068 (84.8)
Pamidronate	477 (9.3)	68 (7.7)	732 (15.3)
Comorbidities, *N* (%)			
Cataract	644 (12.6)	5 (0.6)	373 (7.8)
Cerebrovascular disease	179 (3.5)	2 (0.2)	177 (3.7)
COPD	625 (12.2)	0 (0.0)	1,280 (26.7)
Congestive heart failure	220 (4.3)	6 (0.7)	202 (4.2)
Dementia	85 (1.7)	0 (0.0)	77 (1.6)
Depression	201 (3.9)	5 (0.6)	618 (12.9)
Diabetes mellitus	962 (18.8)	38 (4.3)	1,051 (21.9)
Dyslipidaemia	946 (18.4)	26 (2.9)	1,735 (36.1)
Glaucoma	118 (2.3)	2 (0.2)	461 (9.6)
Hypertension	1,970 (38.4)	52 (5.9)	1,565 (32.6)
Ischaemic heart disease	515 (10.0)	12 (1.4)	134 (2.8)
Liver disease	551 (10.7)	12 (1.4)	1,327 (27.6)
Macular degeneration	90 (1.8)	3 (0.3)	20 (0.4)
Osteoarthritis	1,281 (25.0)	6 (0.7)	1,323 (27.6)
Osteoporosis	318 (6.2)	0 (0.0)	1,248 (26.0)
Parkinson disease	70 (1.4)	1 (0.1)	29 (0.6)
Pneumonia	842 (16.4)	45 (5.1)	559 (11.6)
Renal failure	347 (6.8)	7 (0.8)	76 (1.6)
Comedications, *N* (%)			
Anti-dementia drugs	149 (2.9)	2 (0.2)	48 (1.0)
Anti-depressants	1,001 (19.5)	77 (8.7)	871 (18.1)
Anti-Parkinson drugs	168 (3.3)	10 (1.1)	373 (7.8)
Anti-psychotics	1,638 (31.9)	57 (6.5)	1,176 (24.5)
Hypnotics and anxiolytics	3,521 (68.6)	231 (26.2)	2,194 (45.7)
Alpha blockers	292 (5.7)	15 (1.7)	782 (16.3)
Anti-platelet drugs	935 (18.2)	91 (10.3)	766 (16.0)
Anti-coagulants	1,345 (26.2)	22 (2.5)	1,209 (25.2)
Beta blockers	1,234 (24.1)	121 (13.7)	680 (14.2)
Calcium channel blockers	1,656 (32.3)	247 (28.0)	999 (20.8)
Diuretics	1,804 (35.2)	104 (11.8)	1,530 (31.9)
RAS inhibitors	1,377 (26.8)	142 (16.1)	960 (20.0)
Hypoglycaemic agents	914 (17.8)	110 (12.5)	641 (13.4)
Lipid-lowering agents	870 (17.0)	152 (17.2)	869 (18.1)
NSAIDs	4,550 (88.7)	394 (44.6)	3,860 (80.4)
Opioids	4,004 (78.1)	600 (68.0)	3,847 (80.1)
Bronchodilators	2,445 (47.7)	92 (10.4)	1,448 (30.2)

BTA: bone-targeting agent; N/A: not applicable; NSAID: non-steroidal anti-inflammatory drug; RAS: renin-angiotensin system; COPD: chronic obstructive pulmonary disease

Patient Characteristics of BTAs users

The mean ages of the patients receiving BTAs were 62.5 (SD, 13.3), 61.6 (SD, 12.2) and 57.0 yrs (SD, 12.6) in Taiwan, Hong Kong and Korea, respectively. The rates of male patients were 39.9% in

Taiwan, 36.0% in Hong Kong and 24.9% in Korea. The proportions of BC, PC and LC were 42.4%, 22.5% and 35.1% in Taiwan, 42.9%, 18.1% and 39.0% in Hong Kong, and 72.8%, 19.0% and 8.2% in Korea, respectively. Denosumab was the most frequently used BTA in Taiwan (67.1%) and Hong Kong (51.9%), while in Korea (84.8%) it was zoledronic acid. The detailed baseline characteristics of BTA users and their comorbidities and comedications are shown in **Table 1.** The results for the baseline chemotherapy and molecularly targeted therapy are presented in **Supplement 4**.

BTAs Utilization Pattern

We found the dosages and frequencies of BTA use were similar among all sites, largely consistent with the recommendations of the clinical guidelines.[7 8 19] **Figure 3** presents the cumulative incidence curves of BTA initiation for patients diagnosed with bone metastases by different BTAs and sites. **Supplement 5** presents the details of BTA utilization patterns, including dosages, frequencies of BTAs and timing of initiation relative to bone metastases.

Figure 4 uses Sankey diagrams to present the utilization patterns of BTAs across the three sites, assessed in 90-day intervals. In both Hong Kong and Taiwan, the proportion of denosumab users remaining on their original treatment was higher than zoledronic acid and pamidronate users, within the 2 year follow-up period. For example, the proportions for denosumab at 90 days were 71% and 64.8% in Hong Kong and Taiwan, respectively, but they were around 50% for zoledronic acid users (Hong Kong: 50.7%, Taiwan: 55.1%) and even below 40% for pamidronate users (Hong Kong: 23.5%, Taiwan: 33.5%). Specifically, in Taiwan, the switching rates from denosumab to bisphosphonates ranged from 0.1 to 1.9 %, which was lower than for those switching from each bisphosphonate to denosumab (zoledronic acid: 7.9 - 15%, pamidronate: 4.4 – 9.7%) **(Figure 4a and Supplement 6)**. Unlike Taiwan, in Hong Kong the switching rates of denosumab users to the other BTAs were comparable to those switching from zoledronic acid to denosumab **(Figure 4b and Supplement 6)**. In Korea, more zoledronic acid users remained on their original treatment than did pamidronate users during the observation period. The switching rates from zoledronic acid to pamidronate ranged from 0.6 - 1.0%, which was lower than the switching rate from pamidronate to zoledronic acid (4.5 - 11.6%) **(Figure 4c and Supplement 6)**. The Sankey diagrams for the different cancer types are presented in **Supplements 7-9.**

DISCUSSION

This is the first multinational retrospective cohort study that look at the treatment landscape for bone metastases in Asia, using real-world data from patients with bone metastases from solid tumours (BC, PC and LC) diagnosed in Taiwan, Hong Kong and Korea. Our findings indicate that BTAs are significantly underutilized in Asia, with the treatment initiation rates across all sites lower than the rates reported previously in the US and Europe. We observed that the study subjects were receiving optimal treatment once initiated on BTAs; the dosages and dosing intervals were largely consistent with the recommendations of clinical guidelines. Our study utilized Sankey diagrams to visualize the longitudinal patterns of BTA use, from which we observed that a higher proportion of denosumab users remained on treatment, BTA users frequently experienced gaps in treatment, and the switching rates between the BTAs varied across the participating sites.

Across all sites and tumour types, we found a declining trend in the annual incidence of bone metastases, except for PC in Hong Kong. This observed trend could be attributable to several factors, such as improved oncology care and early cancer detection, which in turn could lead to better prognosis and improved survival. However, a study using the US Oncology Service Comprehensive Electronic Records demonstrated that the 1-year cumulative incidence of bone metastases increased from 0.5% (95% CI: 0.4-0.5) at stage I to 18.0% (95% CI: 17.7-18.4) at stage IV across all tumour types.[20] Although we did not have information on the cancer stages in our study, we considered the majority of patients with bone metastases secondary to solid tumours to be in the late stage. Therefore, the decreasing trends in annual incidence of bone metastases observed in our study may have been due to increasing numbers of patients being diagnosed with solid tumours at an earlier stage with relatively lower risk of developing metastases.

One study using US Medicare and commercial insurance claims reported that 43% to 47% of patients received BTAs in 2012, while another study using EHR from oncology practices in the US reported the 2-year cumulative BTA initiation rate to be 88%.[10 21] The rates of BTA initiation in our study (only 14.1%, 9.3% and 9.4% in Taiwan, Hong Kong and Korea, respectively) were substantially lower than those studies,[10 21] indicating that BTAs are highly underutilized in Asia. Previous studies have indicated that the use of BTAs prevents the occurrence of skeletal-related events and improves quality of life. Therefore, the underutilization of BTAs highlights the fact that treatment to prevent bone complications remains suboptimal. Indeed, not all patients are eligible to receive BTAs as the patients' unique clinical situations, such as poor dental health (a risk factor for osteonecrosis of the jaw), renal impairment (which is a relative contraindication for bisphosphonates), and hypocalcaemia,

may hamper the decision to treat.[10] Although our study did not explore the extent of these clinical restrictions, it would be highly unlikely to explain the underutilization of BTAs observed in our study. Additional studies are needed to explore the reasons for the underutilization of BTAs in Asia.

As expected, BC was the predominant type of solid tumour across all sites, which is consistent with previous reports.[9 11] However, among those who initiated BTAs, we found a relatively higher proportion of LC in Taiwan and Hong Kong, compared to studies from Western countries.[9 11] These findings represent heterogeneity in treatment landscape for bone metastases among different regions and are partly attributable to the variations in eligibility criteria for BTA reimbursement across different regions. While denosumab is approved for use by BC, PC and LC patients, zoledronic acid is only reimbursed for patients with BC and PC in Taiwan. This may have resulted in patients with LC in Taiwan preferentially initiating denosumab and could explain the higher proportion of denosumab users than in Hong Kong. Similarly, the proportion of LC patients was substantially lower in Korea than in Taiwan and Hong Kong as BTAs are not reimbursed for LC patients with bone metastases in Korea.[22] We observed a substantial discordance between the reimbursement criteria and recommendations of the clinical guidelines on the indications for BTAs. We speculate that this disparity arises because current data on the use of BTAs in LC are more limited than for BC and PC. In fact, efficacy data of BTAs in LC patients were mostly derived from studies that included all other solid tumours rather than focusing solely on bone metastases from LC.[5 23] Nevertheless, the consensus across guidelines is to initiate BTAs for management of bone metastases regardless of type of solid tumours, and that this needs to be incorporated into the eligibility criteria for BTA reimbursement to provide optimal care in preventing bone complications regardless of the type of solid tumour.

More than half of the study subjects in Taiwan (67.1%) and Hong Kong (51.9%) received denosumab, whereas in Korea (84.8%), zoledronic acid was the major treatment of choice, due to the unavailability of denosumab during the study period. Denosumab was approved in Korea in 2014 but was not reimbursed until 2018. We speculate that patients in Korea may have paid out-of-pocket to receive denosumab, which would not have been captured in the medical claims data. However, unlike in Taiwan and Hong Kong, the annual incidence rate of BTA initiation in Korea appears to have remained unchanged throughout the study period, so we consider the influence of this uncaptured denosumab initiation to be small. Furthermore, denosumab was found to be non-inferior and subsequently even superior to bisphosphonates in delaying bone complications in patients with bone metastases.[24-26] In addition, real-world data from recent observational studies have indicated that patients on denosumab had better compliance and lower treatment interruption rates than those on

bisphosphonates.[9 11 27] Gradual dissemination of this evidence during the study period may explain the growing preference for prescribing denosumab as the initial BTA treatment.

Treatment dynamics among the BTAs have already been assessed in the US population, with denosumab demonstrating better compliance and persistence than bisphosphonates.[9 11] Using the proportion of patients remaining on the treatment as a proxy for compliance,[28] similar trends were observed in our study; the proportions of those remaining on denosumab were the highest in Taiwan and Hong Kong. Specifically, patients who were on bisphosphonates or who discontinued treatment frequently switched to or re-initiated denosumab in Taiwan, which further contributed to a higher proportion remaining on denosumab throughout the follow-up period. The routine schedules for the use of bisphosphonate and denosumab were every 3-4 weeks in all countries. Interestingly, we observed a unique pattern whereby re-initiation of zoledronic acid following treatment discontinuation was evident in both Hong Kong and Korea. This pattern may have arisen as a result of the 12-week interval dosing regimen for zoledronic acid combined with the operational definition of treatment discontinuation. Some recent evidence indicates that zoledronic acid every 12 weeks, compared to every 4 weeks, is non-inferior and cost-effective in preventing bone complications in patients with bone metastases.[29 30] Hence the 12-week interval dosing schedule may have been classified as a re-initiation of zoledronic acid because our study used a treatment gap greater than 90 days to define treatment discontinuation, which is in line with the definition commonly used.[10 11] However, it should be noted that Sankey diagrams are not suitable to assess an individual's compliance to a treatment, and are used in our study solely to visualize the dynamic utilization patterns of BTA; future study is needed to build on the findings of our study and to present real-world data on compliance with BTA treatment in Asia.

The main strength of our study is that we have provided a first look at epidemiology of bone metastases from solid tumours and utilization patterns of BTAs in Asia by incorporating a large population sample representative of each participating site. The findings from previous studies on the utilization patterns of BTAs lacked generalizability as they were either based on the data from tertiary care centres or focused on certain types of solid tumour, mostly BC. In contrast, we used nationwide databases to present treatment landscapes for bone metastases across different regions, improving the generalizability of our results. However, the study also has some limitations. Our study was descriptive and was not designed to demonstrate significant differences in outcomes between different BTAs, solid tumour types, or participating sites. As with all medical claims-based research, there may be inaccuracies in the diagnosis code and incomplete records that may undermine the

validity of our study findings. The validity of ICD code-based identification of bone metastases in medical claims databases has previously been explored, with the sensitivity ranging from 0.54 (95% CI: 0.39-0.69) in the Danish national registry of patients to 0.78 (95% CI: 0.74-0.81) in the US medical claims database.[31 32] Given this modest sensitivity, ICD code-based identification of bone metastases in our study may have led to underestimation of incidence rates of bone metastases. Subsequently, we may have missed those who were receiving BTAs off-label or for the prevention of bone complications without documented diagnosis of bone metastases, especially in Korea where it was not possible to capture patients who were receiving denosumab. Dental health may have affected the decision to use BTAs or to withdraw. For example, some dentists may advise patients to stop using the drugs if they need dental surgery. However, our databases did not include information of dental conditions or the reasons for drug discontinuation. Additionally, financial issues may have influenced the selection of treatment, especially for patients of low socioeconomic status, which our databases has no information on. However, since all use of BTAs is reimbursed by the national health insurance programs or subsidized by the public health service of the countries, we considered the impact of financial issues on the treatment selection to be insubstantial. Finally, the short delay before BTA treatment following bone metastases may be underestimated due to (1) a gap between the actual diagnosis date for bone metastases and the date recorded in the medical claims database, and (2) bone metastases being recorded in response to the occurrence of bone complications or BTA initiation.

CONCLUSION

This multinational retrospective cohort study is the first to describe the treatment landscape for bone metastases in Asia. Underutilization of BTAs was observed across all sites and tumour types, indicating that many patients with bone metastases may receive less than optimal care to prevent bone complications. Our study employed Sankey diagrams to visualize the dynamic utilization patterns of BTA, through which we observed that treatment discontinuation, re-initiation, and switching among the BTAs during the study period were prominent across all sites. Further research is warranted to build on the findings of our study to better understand the treatment landscape and the associated patient outcomes.

STATEMENTS

Authorship

Conceptualization, Methodology and Writing - Review & editing: all authors. Data curation: EC-C Lai (Taiwan NHID), C-L Cheung (Hong Kong's CDARS), and J-Y Shin (Korea's NHID). Funding acquisition: EC-C Lai. Investigation: EC-C Lai, C-L Cheung and J-Y Shin. Project administration: C-Y Shen. Software, resources, formal analysis, validation and visualization: JH Kim, C-Y Shen, PC-M Au, Y-H Baek, T-C Liao, and C-W Sing;. Supervision: EC-C Lai, C-L Cheung and J-Y Shin. Writing - original draft: JH Kim, C-Y Shen.

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Competing Interests

CL Cheung reports receipt of funding from Amgen and Abbott outside the submitted work. J-Y Shin reports receipt of research funding from the Ministry of Food and Drug Safety, Ministry of Health and Welfare, and the National Research Foundation of the Republic of Korea; furthermore grants from pharmaceutical companies including Amgen, Pfizer, Hoffmann-La Roche, Dong-A ST, and Yungjin outside the submitted work. EC-C Lai reports receipt of research funding from the Ministry of Science and Technology and Ministry of Health and Welfare of Taiwan; furthermore grants from pharmaceutical companies including Amgen and Takeda outside the submitted work. The remaining authors declare no conflicts of interest. The sponsors had no role in the design, execution, interpretation, or writing of this study.

Research ethics and patient consent

The authors complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. The study was approved by the institutional review board of each site—the Institutional

Review Board National Cheng Kung University of Taiwan [A-ER-107-387; 18 Jan 2019], the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster [UW18-691; 10 Jan 2019], and the Institutional Review Board of Sungkyunkwan University of Korea [SKKU 2019-06-008; 1 July 2019].

Data management and sharing

We used a distributed network approach and executed the analysis independently from each site on the basis of a common protocol. The coordinating centre, National Cheng Kung University, Taiwan, only collected summary results from each site without access to individual data. The datasets analysed in the current study will not be available to the public due to data privacy regulations in each participating country. Qualified researchers may request data from the corresponding author.

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FIGURE LEGENDS

Figure 1: Incidence rate of patients with bone metastases by different solid tumours. (**A**) Taiwan, (**B**) Hong Kong, and (**C**) Korea. Results of the Cochran-Armitage trend test in Taiwan: BC < 0.0001, PC < 0.0001, LC < 0.0001, Total < 0.0001; Hong Kong: BC = 0.2357, PC < 0.0001, LC = 0.0041, Total = 0.1326; Korea: BC < 0.0001, PC < 0.0001, LC < 0.0001, Total < 0.0001. BC: breast cancer; IR: incidence rate; LC: lung cancer; PC: prostate cancer

Figure 2: Incidence rate of different BTAs used in patients with solid tumours and bone metastases (**A**) Taiwan, (**B**) Hong Kong and (**C**) Korea. Results of Cochran-Armitage trend test in Taiwan: D < 0.0001, Z < 0.0001, P < 0.0001, Total < 0.0001; Hong Kong: D = 0.0001, Z < 0.0001, P = 0.9114, Total = <0.0001; Korea: Z = 0.2364, P = 0.6860, Total = 0.3508. BTA: bone-targeting agent; IR: incidence rate; D: denosumab; Z: zoledronic acid; P: pamidronate; N/A: not applicable

Figure 3: Time from diagnosis of bone metastases to initiation of BTA use. (**A**) Taiwan, (**B**) Hong Kong and (**C**) Korea

Figure 4: Utilization pattern of BTAs in patients with solid tumours and bone metastases (by Sankey diagram). (**A**) Taiwan, (**B**) Hong Kong and (**C**) Korea