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An Italian survey on the use of denosumab for the management of skeletal-related events in patients with bone metastases

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Abstract. – OBJECTIVE: The Italian Association for Medical Oncology (AIOM) recommends preventive treatment of skeletal-related events in order to improve survival and the quality of life of patients with advanced malignancies. The aim of the study was to evaluate whether routine clinical practice is in agreement with recommendations about the use of denosumab.

PATIENTS AND METHODS: A survey was carried out in Italy in the oncological setting.

RESULTS: The answers to the survey showed that a large proportion of patients with metastases from solid tumors receive treatment; almost all oncologists administered denosumab every 4 weeks but for a shorter period of time than recommended.

CONCLUSIONS: This survey showed that Italian oncologists favor the use of bone-targeted therapy to prevent skeletal-related events in patients affected by metastatic breast, prostate or lung cancer, in agreement with current recommendations.

Key Words:
Skeletal-related events, Bone metastases, Bisphosphonate, Denosumab, Survey.

Introduction

Bone is the most common site for metastatic disease in several tumors and is of particular clinical importance in advanced lung, breast and prostate cancers because of the high prevalence of these malignancies[1,2]. Bone lesions represent approximately 90% of metastases in multiple myeloma, 70% in breast cancer, 85% in prostate cancer, and 40% in renal and lung cancers, respectively[3].

Tumor cells escaped from the primary site can colonize the bone microenvironment, assume a state of dormancy, remain quiescent for years, and resume proliferation causing overt metastasis, years later. Tumor cell proliferation within the bone causes activation of osteoclast-mediated osteolysis, which is clinically evidenced by elevated levels of bone turnover markers, including calcium, and is associated with a poor prognosis[3,4]. The assessment of bone turnover markers in patients with bone metastases revealed a complex metabolic scenario: the values of bone formation markers were found to progressively increase in patients with lytic, mixed and blastic lesions, but bone resorption marker levels did not show any differences according to the types of bone appearances. These data underlined that there are no differences in terms of osteoclastic activity activation in blastic bone lesions as opposed to lytic ones[5]. This means that all patients with bone metastases, regardless of the type of bone lesions, are at risk of adverse skeletal-related events (SREs). The increase in osteoblastic activity typical of blastic bone lesions can lead to calcium entrapment in bone, leading to increased serum parathyroid hormone PTH levels. This phenomenon, known as "bone hunger syndrome", leads to increased osteolysis and greater fragility in non-metastatic bone[6].

Bone structural damage can lead to considerable morbidities, resulting in pain, fractures, spinal cord compression and hypercalcemia. These SREs greatly impair the patient quality of life[7].

In most clinical trials, SREs have been identified as an endpoint for assessing complications in patients with bone metastases[8]. SREs are a

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composite of radiation to the bone, pathological fracture, surgery on the bone, and spinal cord compression[1,9-11], and have been associated with a significant decrease in patient function and health-related quality of life[12]. Their incidence may be related to risk factors, as in subjects with bone metastatic prostate cancer with a history of SREs, Gleason ≥7, and elevated serum alkaline phosphatase[13].

Management of SRE is rarely curative, but disease control is often possible for many years by using systemic anticancer treatments on a background of multidisciplinary supportive care. This care should include bone-targeted agents to inhibit tumor-associated osteolysis and prevent skeletal morbidity[7]. Some bone-targeted agents, including pamidronate, zoledronic acid, and denosumab, reduce the incidence of SREs and delay the occurrence of first and further SREs[14-19].

In concomitance with antineoplastic treatment, the bisphosphonate zolendronate has been used to prevent and manage SREs in patients with bone metastases from solid tumors. As zolendronate was associated with osteonecrosis of the jaw and impairment of renal function while not improving survival, additional bone-directed treatments were needed[3,15]. Denosumab is a human monoclonal antibody against the ligand of the receptor activator of NF-κB (RANKL), an osteoclastogenic cytokine, preventing excessive bone turnover and its complications[20]. Renal dysfunction has no impact on its pharmacokinetics[21]. A phase III trial in patients with breast cancer with bone metastases showed that denosumab was superior to zoledronic acid in delaying the time to first SRE during the study (hazard ratio, 0.82; 95% CI: 0.71-0.95; p=0.01 superiority) and time to first and subsequent (multiple) SREs during the study (rate ratio, 0.77; 95% CI: 0.66-0.89; p=0.001)[22]. Another phase III trial in patients with castration-resistant prostate cancer demonstrated that denosumab was superior to zoledronic acid in delaying the time to first SREs (median time, 20.7 months for denosumab versus 17.1 months for zoledronic acid; p=0.008 for superiority)[23]. In addition, denosumab was found to be effective on symptomatic SREs[24]. Denosumab was investigated in combination with several anticancer agents, including checkpoint inhibitors and androgen deprivation. The combinations were feasible, and no unexpected safety issues were recorded[25,26].

The Italian Association for Medical Oncology (AIOM) recommends preventive treatment of skeletal-related events (SREs) in order to improve the survival and quality of life of patients with metastatic solid cancers. To provide data on whether the Italian oncologists follow these guidelines in routine clinical practice, a survey was carried out in Italy to explore the current use of bone directed drugs for the prevention of SREs in the oncological setting, focusing on the last introduced one, denosumab, and to identify possible issues in the current clinical practice. This article presents a short revision of the literature on the denosumab for managing SREs and the survey results.

Patients and Methods

The survey was developed with the assistance of an independent third party with broad experience in market research in the pharmaceutical setting (Doxa Pharma, Milan, Italy). Between June and October 2019, the survey was proposed to oncology centers all over Italy and could be answered by one oncologist per center; the participants were chosen because they cared for patients with solid cancer and bone metastases. The oncology centers included in the AIOM White Book 2018, the database of Sportello Cancro (Corriere della Sera, Milan, Italy), and the oncology database of Doxa Pharma was asked to take part in the project.

The questionnaire was developed by Doxa Pharma, and then, shared with the authors for discussions *via* several online meetings until a final agreement was reached. The questionnaire was then delivered online *via* a computer-assisted web interview. The questionnaire contained 25 questions. Open and closed (multiple-choice, with either single or multiple permitted answers) questions were included. Interviews were anonymous. Data were analyzed by descriptive statistics and presented as absolute numbers or percentages.

The English version of the survey questionnaire is presented in the **Supplementary Material**.

Results

Between June and October 2019, the survey was proposed to 707 oncology centers, and 357 of them participated in the study, while 350 declined to participate or could not be reached.

Among the participating centers, only 10 were located within cancer centers, while the

remaining were within university centers or hospitals.

Physicians' eligibility criteria to fulfill the survey included Board Certification in Medical Oncology. Nevertheless, some participants had additional specializations (i.e., 12 in hematology, six in general medicine, and four in pneumology). The main area of clinical activity had been oncology for at least 10 years for 248 respondents.

The care setting of participating centers included an outpatient clinic in 98% of cases, a day hospital in 97%, and inpatient services in 63% of them. In total, 66% of centers were specially dedicated to one tumor type (among these centers, 78 were reserved for breast cancer, 65 for lung cancer, 63 for colon rectum cancer, 58 for prostate cancer, and 45 for kidney cancer).

A multidisciplinary team for managing patients with bone metastases was present in 31% of centers. These teams included oncologists (100% of cases), radiologists (91%), pain therapists (76%), orthopedists (69%) and, occasionally, surgeons, urologists, physiatrists, neurosurgeons and psychologists.

Management of Bone Metastases

In the last 12 months, 251,164 patients with solid tumors were observed in the participating centers. The most frequently observed solid tumor was reported to be breast cancer (n=82,303, 33% of all solid tumors), followed by colorectal cancer (n=44,555, 18%), lung cancer (n=32,029, 13%) and prostate cancer (n=24,367, 10%). Kidney, uterus and bladder cancers, melanoma and neuroendocrine tumors were less frequently observed.

Participants reported that 61,064 out of 251,164 (24.3%) patients observed in the last 12 months had bone metastases. Table I reports the distribution of bone metastases in each tumor type. No relevant differences could be observed in the therapeutic approach to bone metastases in different types of tumors. Overall, 7,872 (13%) patients were reported to receive no treatment for their bone metastases, while 27,731 (45%) received zoledronic acid, 22,169 (36%) denosumab, 1,463 (2%) bisphosphonates other than zoledronic acid, and the remaining 3% received other pharmacologic treatments.

Table I. Patients (n = 61064) with bone metastases and different solid tumors.

	N	Tumor type (%)
Breast cancer	19,537	32
Prostate cancer	11,518	56
Colon rectum cancer	4,685	13
Lung cancer	11,272	39
Kidney cancer	2,859	37
Malignant melanoma	1,410	21
Cervical cancer	963	12
Bladder cancer	2,101	28
Neuroendocrine tumors	665	13
Other	6,054	21

Table II presents the frequency of different treatments for bone metastases in each tumor type, as reported by participants.

A mean number per center of 171 patients with solid tumor and bone metastases was present. Among these, 62 (36%; range, 0-500) patients received denosumab, while 78 (45%; range, 0-350) patients received zoledronic acid. Denosumab 75% of cases, and at home in 25% of cases; 124 centers provided homely administration of denosumab.

Denosumab was administered every 4 weeks to patients with breast cancer in 155/160 (97%) centers, and to patients with prostate or lung cancer in 149/160 (93%) centers. It was administered every 2 months to patients with breast cancer by 3/160 (2%) centers and patients with prostate or lung cancer by 11/160 (7%) centers. Only one center administered denosumab every 4 months to patients with breast cancer, while administration every 4 months was never used for patients with prostate or lung cancer.

Respondents estimated the mean duration of treatment with denosumab to range from 2 to 48 months in patients with breast cancer (mean: 20 months), between 1 and 36 months in patients with prostate cancer (mean: 20 months), and from 1 to 24 months in subjects with lung cancer (mean: 12 months).

Discussion

This article reports information about the use of bone-targeted agents in oncological patients with bone metastases, in Italy. Information was obtained through a survey directed to oncologists; participants were asked to report the incidence of their clinical choices in the last 12 months before the survey. Our results express the clinical attitude of clinicians, as promoted by their everyday practice. This approach was chosen to explore whether the usual clinical behavior in Italy was in agreement with current Italian recommendations for the management of bone metastases.

As a result of several prospective randomized clinical trials, zoledronic acid and denosumab have

Table II. Absolute number and (mean number per center) of patients receiving different treatments for bone metastases, according to their tumor type, in the last 12 months, as reported by the 367 respondents.

	Breast	Prostate	Colon rectum	Lung	Kidney	Melanoma	Cervix	Bladder	NET	Other	Total
No treatment	1290 (4)	1794 (5)	929 (3)	1388 (4)	413 (1)	299 (1)	184 (1)	310 (1)	179 (1)	1086 (3)	7872 (22)
Denosumab	9738 (27)	3847 (11)	1074 (3)	3452 (10)	1032 (3)	429 (1)	291 (1)	622 (2)	157 (0)	1527 (4)	22,169 (62)
Zoledronic acid	7907 (22)	5192 (14)	2418 (7)	5732 (16)	1306 (4)	618 (2)	432 (1)	1027 (3)	281 (1)	2818 (8)	27,731 (78)
Other bisphosphonate	287 (1)	251 (1)	90 (0)	232 (1)	52 (0)	18 (0)	31 (0)	36 (0)	13 (0)	453 (1)	1463 (4)
Other treatment	315 (1)	434 (1)	174 (0)	468 (1)	56 (0)	46 (0)	25 (0)	106 (0)	35 (0)	170 (0)	1829 (5)

NET = neuroendocrine tumor

been registered and are currently recommended in patients with bone metastases to prevent adverse SREs[15,16,27]. Meta-analyses of these trials failed to demonstrate a survival advantage of bone resorption inhibitors. However, the occurrence of SREs was associated not only with quality-of-life impairment but also with the reduction of survival expectancy[18,28-30]. Randomized clinical trials evaluating bone resorption inhibitors were conducted several years ago when many modern efficacious therapies – that is, targeted therapies and immunotherapy – were not available. Recently, hormonal therapies currently available for the management of prostate cancer have been demonstrated to provide both a survival advantage and a reduction in SREs. It is not clear whether bone resorption inhibitors are effective in association with these drugs; nonetheless, current and emerging evidence from clinical studies suggest that the addition of bisphosphonates or denosumab to new therapies may provide further clinical benefits for patients with prostate cancer and bone metastases as they may delay the occurrence of SREs, which place a burden on patients and healthcare systems[31]. Noteworthy, modern anticancer therapies are not always associated with preventive effects on SREs. Metastatic NSCLC patients with *EGFR*-mutated disease treated with EGFR tyrosine kinase inhibitors have a relatively long survival expectancy. A recently published Italian study[32] showed that patients with bone metastases are at high risk of developing SREs. These adverse events occur early – that is, when the tumors are still sensitive to EGFR targeting agents[32]. These findings provide the rationale to administer this treatment in patients with bone metastases in an early stage.

Overall, answers to our survey reported that only 13% of participants' patients with metastases did not receive pharmacological bone-targeted treatment, without any difference among tumor types; 45% received zoledronic aid, 36% denosumab, 2% other bisphosphonates and 2% other therapies. These figures suggest that many patients are treated more than previously found in retrospective published case series[33-36]. The difference between previous observations and data from this survey may be related to the origin of data (clinical charts for observational studies and memory for the survey). The difference could suggest that oncologists recall a wider use of denosumab than real, maybe because they are willing to prescribe denosumab and bisphosphonates more than they actually do in practice.

The schedule of denosumab administration is mainly adherent to AIOM recommendations and Italian health authority (Agenzia Italiana del Farmaco) approval, as up to 97% of patients are treated every 4 weeks[27]. On the contrary, the mean duration of denosumab treatment was shorter than recommended (12 months for lung cancer and 20 months for breast and prostate cancer). The duration of therapy is recommended to be at least 2 years, provided that good health status is preserved[18,37], although clinical studies were designed with very variable treatment periods, from 12 weeks to 34 months[22,23,27,38]. This discrepancy could be due to the high frequency of poor health conditions. Both bisphosphonates and denosumab were associated with an increased, similar risk of osteonecrosis of the jaw[31]. Although this adverse event is not frequent and may be managed conservatively, it may be speculated that the shorter than the recommended duration of therapy with denosumab is partly due to this potential problem and its possible suboptimal management[18,39].

Conclusions

This survey showed that Italian oncologists favor the use of bone-targeted therapy to prevent SREs in patients affected by metastatic breast, prostate or lung cancer, in agreement with current recommendations. Denosumab is administered with the recommended schedule but for a shorter period of time than suggested based on evidence.

Conflict of Interest

RB received funding supporting research projects or grants for advisory boards from: Astra Zeneca, Boehringer Ingelheim, Novartis, MSD, Otsuka, Lilly, Roche, Amgen, GSK, EISAI, BMS in the last 2 years. PAZ reports outside the submitted work personal fees for advisory role, speaker engagements and travel and accommodation expenses from Merck Sharp and Dohme, Astellas, Janssen, Sanofi, Ipsen, Pfizer, Novartis, Bristol Meyer Squibb, Amgen, AstraZeneca, Roche, and Bayer. AB and LB declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' Contribution

LB developed the manuscript. All authors analyzed and interpreted data, revised and approved the manuscript.

Data Availability Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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