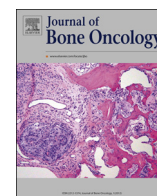




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Review Article

The Italian cross-sectional survey of the management of bone metastasis: ZeTa study

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ABSTRACT

Background: Several studies have emphasized the importance of the maintenance of bone health in a comprehensive cancer care. However, no survey about approach to bone metastasis care is currently available. The ZeTa study provides a picture of the Italian oncologists' therapeutics habits in this area, in a real clinical-practice scenario.

Design: This study was based on online questionnaire-based interviews to Italian oncologists that included 145 questions. The aim was to collect information on the treatment of bone metastasis, the current use of bisphosphonates, the awareness of guidelines and the concerns about ONJ, the use of vitamin D supplementation.

Results: 445 oncologists were contacted, 283 agreed to participate. The results show that the current management of bone metastasis is still sub-optimal, as the recommendations from current clinical guidelines are not completely followed by all specialists.

Conclusions: This survey highlights the urgent need to improve management of bone metastasis in cancer patients.

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1. Introduction

Several types of cancers, including those originating in the breast, prostate, and lung, have a propensity to metastasize to the bones [1,2]. Bone metastases severely impair skeletal metabolism, and result in important clinical sequelae, such as excruciating chronic bone pain and the so-called skeletal-related events (SREs), such as pathologic fracture, spinal-cord compression, surgery to bone, radiotherapy to bone, hypercalcemia with a dramatic reduction in quality of life and increased risk of death of the affected patients [2].

Moreover, different systemic oncologic treatments, including chemotherapy and endocrine therapy, further accelerate the natural process of bone loss, a phenomenon known as cancer treatment-induced bone loss (CITBL) [3,4]. This event, which is associated with an increased risk of fractures and worsening of prognosis, is observed for instance in breast cancer patients undergoing treatment with aromatase inhibitors, or in men with prostate cancer on androgen deprivation therapy [3,4].

Bone health, which includes the management of bone metastases and the treatment of CITBL, is a major concern in cancer patients. Several international guidelines/recommendations of major scientific societies (e.g. the American Society of Clinical Oncology [ASCO] and the National Comprehensive Cancer Network [NCCN]) have emphasized the importance of the maintenance of bone health, as an important component of comprehensive cancer care [5–10]. In particular, the use of bisphosphonates (BPs), potent inhibitors of bone resorption, to prevent, reduce, and delay cancer-related SREs and CITBL in cancer patients is supported by a general consensus [5–12], even if BP treatment is potentially associated with the onset of osteonecrosis of the jaw (ONJ) [5–10].

Although several guidelines for the treatment and management of cancer patients are now available, there is the perception of a wide gap between recommendations and actual clinical practice in Western Countries, including Italy [13–15]. However, to our knowledge, no survey of the oncologists' approach to bone metastasis care in cancer patients has been conducted to date, while it appears highly advocated. In addition, it has been suggested that further education of healthcare professionals is necessary to improve the awareness of the importance of bone health management in cancer patients, and to optimize specific medical therapy in this setting [16,17]. The introduction of new therapies, such as BP treatment, and the publication of new evidence in this field may result in

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measures to increase the level of education and training of oncologists and therefore improve the standard of care. This goal can be achieved, in our opinion, only if a clear picture of real clinical practice becomes available.

The aim of the ZeTa (ZomEta TAsk force) study is to provide a picture of the Italian oncologists' therapeutic habits in the care of bone metastasis, in real-life clinical practice.

2. Methods

This Italian study was based on online questionnaire-based interviews with Italian oncologists recruited via telephone.

The questionnaire was developed with the cooperation of a selected group of Italian oncologists, who are all experts in the field of bone health. The questionnaire included 145 questions (39 single-choice questions, 15 multiple-choice questions, 18 five-point ordinal scales, 34 ten-point ordinal scales, 35 numeric questions, and 4 open-ended), and was designed to collect information on the responding oncologist and his/her institution, the treatment of bone metastasis adopted in clinical practice, the current use of BPs in this setting, the awareness of guidelines and the concerns about ONJ, the use of vitamin D supplementation, and the foreseen developments of BPs treatment. The questionnaire was tested by the selected group of oncologists and some co-workers of theirs before the recruitment of participating clinicians.

The recruitment of the oncologists was conducted by GfK Eurisko, the leading market research organization operating in Italy (<http://www.gfk.com/gfk-eurisko/index.en.html>).

Four types of cancer were considered in this analysis (breast, lung, prostate and genito-urinary): therefore, it was decided to contact more than one oncologist per center, in order to collect the widest possible experience. Each oncologist was requested to reply to the questions regarding the type of cancer in which he or she had the highest level of experience; all participants were also free to address the questions regarding other types of cancer.

Respondents did not receive monetary compensation for completing the questionnaire.

2.1. Statistical analysis

Descriptive statistics were calculated on the total sample. The confidence level used in the calculation of significance tests for all data is 95%. The maximum sampling error of population parameters' estimates—at the 95% level of confidence—is 5.5%. Missing replies were not considered for this analysis.

3. Results

3.1. Participating oncologists and related institutions

In total, 170 centers were selected for inclusion in this survey, out of 350 Italian oncology centers (*Source*: Libro Bianco AIOM, 3rd edition; www.aiom.it). The centers were selected in order to be representative of all Italian regions; the centers were also stratified in terms of number of beds.

In total, 445 oncologists were contacted, and 283 agreed to participate (response rate: 63.6%; mean number of oncologists per center: 1.67).

The majority of participating oncologists belonged to non-university hospitals ($N=125$; 44%), followed by those affiliated to university hospitals ($N=59$; 21%), or those working in an ASL (Azienda Sanitaria Locale; a local service of healthcare) [$N=50$; 18%]. Most oncologists were males ($N=173$; 61%). No statistically significant difference in terms of oncologists' gender was observed,

Table 1

Proportion of patients receiving a treatment for bone metastasis, according to the oncologists participating to the survey ($N=283$).

Metastasis therapy	Breast cancer	Lung cancer	Prostate cancer	Genito-urinary cancer
Any treatment (%)	85	82	90	78
Radiotherapy (%)	37	43	40	42
Radio-metabolic therapy (%)	2	1	7	2
Surgery (%)	3	2	2	2
Chemo/hormonal therapy (%)	63	57	63	64
Interventional radiology (%)	6	5	3	4
Bisphosphonates (%)	70	62	69	70

either in relationship to the number of hospital beds or the Italian geographical macro-area. Their mean age was 46 ± 8 years, but about half of the sample was ≤ 45 years old ($N=136$; 48%). Despite the relatively young age of the participating oncologists, most of them had > 10 years' experience in oncology practice ($N=181$; 64%; mean 16 ± 8 years). Most oncologists ($N=184$, 65%) answered all sections of the questionnaire (breast, lung, prostate and genito-urinary cancer), 11% answered three sections, 9% two sections, and 15% one section, on the basis of their experience in different types of cancer.

3.2. Treatment of bone metastasis

Bone metastases are treated in the vast majority of patients, mostly with BPs; however, about 15–20% of subjects, depending upon the particular type of primary tumor, remain untreated for their entire history of bone metastasis (Table 1). About 70% of patients receive BP treatment, with the exception of subjects with lung cancer (62%). Overall, radiotherapy is used in about 40% of patients and chemo/hormonal therapy specifically designed for the treatment of bone metastases in about 60% of patients.

The decision to treat bone metastasis is made, in most cases, by consensus which includes other oncologists (32%) or other specialists in different fields (42%). The decision to treat bone metastasis is mainly made due to the presence of symptomatic disease (considered a very relevant factor by 232 oncologists; 82%), the metastatic site ($N=164$; 58%), and the potential risk of SREs ($N=156$; 55%). However, 232 oncologists (82%) stated that they sometimes decide not to treat bone metastasis, because of short life expectancy of the patient (62% of those declaring this decision), low performance status (55%) or asymptomatic metastasis (52%).

3.3. Risk of skeletal-related event (SRE) development

About 50% of Italian oncologists think that the median time to first SRE from the diagnosis of bone metastasis, independent of the type of primary tumor, is more than 1 year. The risk of the onset of SREs is mainly considered dependent upon the metastatic site and the nature of the metastases (osteolytic vs. osteoblastic vs. mixed) (Table 2). The majority of the clinicians stated that the occurrence of an SRE is an important predictor of the subsequent development of other SREs ($N=246$; 87%) and is associated with impairment of quality of life ($N=277$; 98%), while less consensus exists about the association between SREs and an increased risk of death ($N=204$; 72%). The rate of bone turnover (assessed with bone turnover markers) was considered a predictor of SRE by only 10% of oncologists. Furthermore, in clinical practice, only 8% of oncologists evaluate the markers of bone turnover in order to predict the risk of SRE.

3.4. Treatment with bisphosphonates (BPs)

In total, 170 oncologists (60%) prescribe BPs for the treatment of bone metastasis independent of the evaluation of the risk of SREs. This treatment is mainly intended to increase bone mass, reduce the risk of fractures and to prevent the onset of SREs (Fig. 1). About 60% believe that BPs may exert anticancer effects in

patients, and 28% think that this potential activity may result, in a metastatic setting, in a significant increase in survival. Zoledronic acid appears to be the BP of choice for the therapy of bone metastasis, as it is prescribed to about 80% of patients, regardless of the cancer type.

BP treatment is usually started at the first diagnosis of bone metastasis, independent of the presence of pain (N=212; 75%); however, some clinicians normally prescribe a BP only if the patient carries a high risk of SREs (N=48; 17%) or after the onset of pain (N=20; 7%).

BP treatment, is suspended within 24 months of its initiation according to 78% of oncologists (N=221), is continued until disease progression by 13% of the participants (N=37), and is continued for the entire natural history of disease by 9% (N=25). The reasons for treatment interruption before 24 months are, in most cases, because of progression of bone disease (40% of clinicians interrupt BP treatment before 24 months), occurrence of ONJ or SRE (19% each), or worsening of pain (18%) (Fig. 2). Reasons for prolonging BP treatment beyond this period are shown in Fig. 3. In total, 56% of oncologists who prolong BP treatment longer than 24 months reduce

Table 2
Factors contributing to the risk of skeletal-related events (SREs), according to the oncologists participating to the survey (N=283). Multiple choices were allowed.

Risk factor for SRE	Percentage of oncologists
Metastatic site	75
Nature of the metastasis	70
Previous SRE	54
Extension of bone metastasis	50
Number of bone metastases	19
Time to onset/diagnosis of metastasis	12
Bone turnover	7

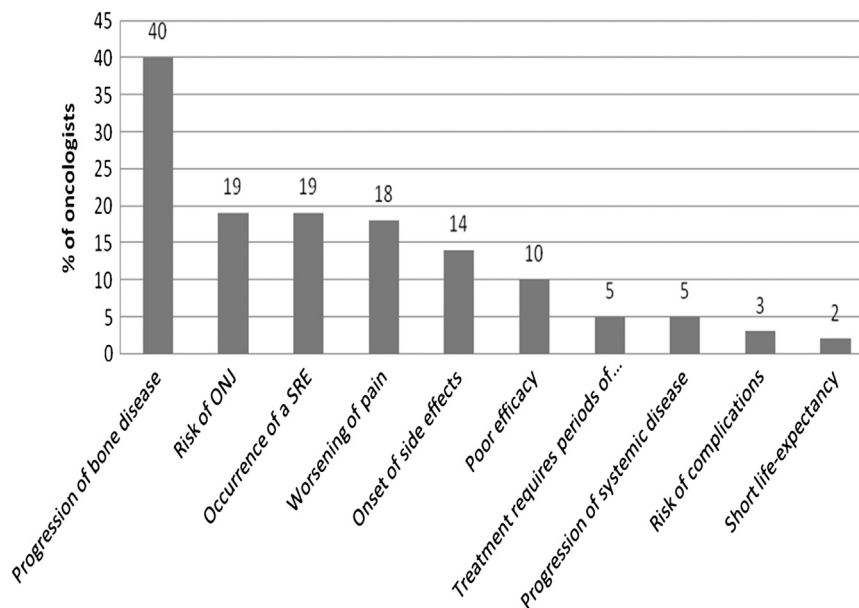


Fig. 1. Reasons for prescribing a treatment of bone metastasis with bisphosphonates, according to the oncologists participating to the survey (N=283). Multiple choices were allowed.

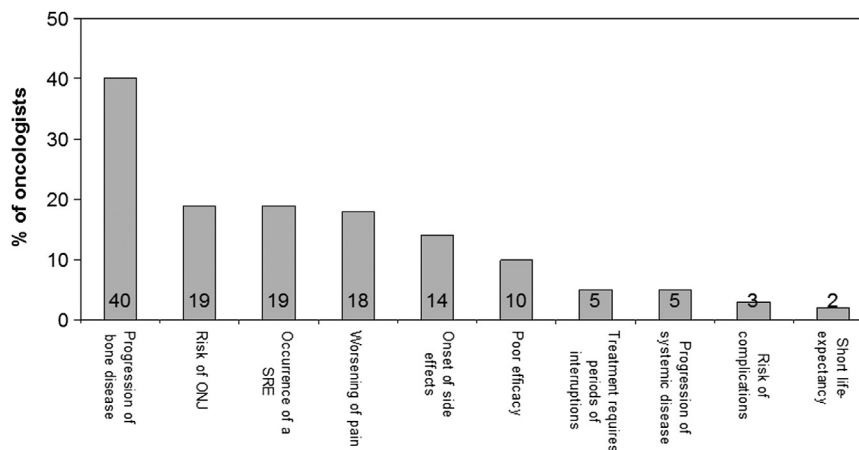


Fig. 2. Reasons for the interruption of bisphosphonate treatment before 24 months according to the oncologists participating to the survey (N=283). Multiple choices were allowed.

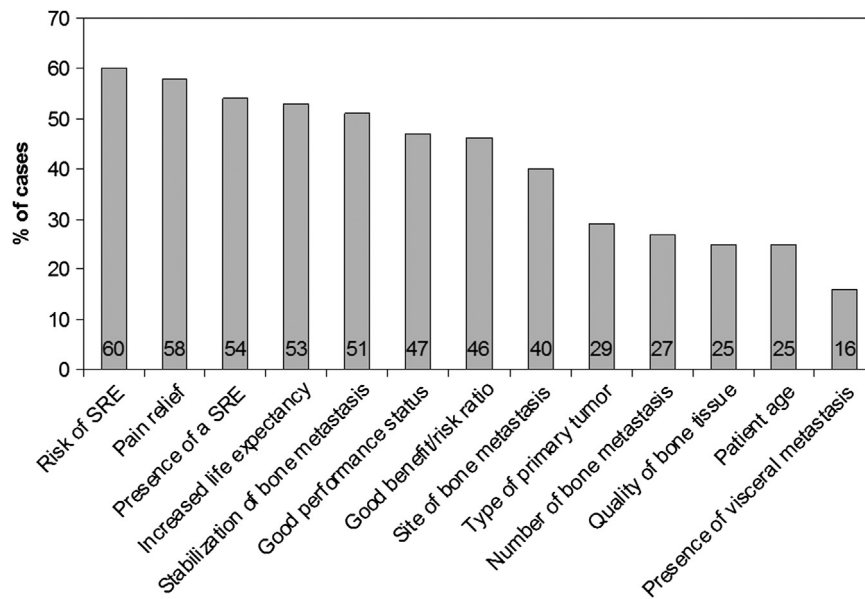


Fig. 3. Reasons for the decision to prolong the treatment of bone metastasis beyond a 2-year period.

the frequency of administration after 2 years, while 38% do not modify the therapeutic schedule (6% prescribe a switch to another BP). In most cases, the decision to prolong BP treatment beyond 2 years is taken in order to limit the risk of SRE (60%), to provide pain relief (58%), to treat an SRE already present (54%) or because the patient's life expectancy is long (53%). In total, 81% of the oncologists consider that the efficacy of BP treatment does not decrease if the schedule of administration is changed.

3.5. Safety perceptions and evaluation of the risk of osteonecrosis of the jaw

The reduction of ONJ incidence due to the implementation of dental hygiene protocols has contributed to less concern about this condition by the majority of oncologists ($N=170$; 60%); however, a minority of clinicians ($N=20$; 7%) stated that they are more worried by ONJ than in the past.

Preventive measures (clinical, radiographic or dental evaluation) are usually adopted before the initiation of BP treatment by the vast majority of oncologists ($N=269$ (95%); odontoiatric assessment 91%; orthopantomography 82%; clinical evaluation 36%; $N=14$, 5% of oncologists usually do not use preventive measures before the start of treatment with BP); however, these measures are applied in all patients by only 66% of clinicians ($N=187$), whereas 29% ($N=82$) prescribe these measures only in patients at risk of ONJ. The same measures (odontoiatric assessment, orthopantomography, clinical evaluation) are taken during BP treatment by the majority of oncologists (90%), but only by 43% routinely in all patients.

3.6. Awareness of guidelines

In total, 62 oncologists (22%) declared not to be aware of any guidelines, either national or international, for the specific treatment of bone metastasis. Among those who stated their awareness of one or more guideline, the AIOM (*Associazione Italiana di Oncologia Medica*, Italian Association for Medical Oncology) guidelines [8] were the most well-known (79%), followed by those issued by ASCO [9] (26%) and NCCN [5] (18%). In total, 86% of interviewed oncologists consider the available guidelines as very important for clinical practice.

4. Discussion

The results of this large survey, conducted in 170 oncology centers representative of all regions and clinical institutions in Italy, suggest that the current management of bone metastasis in cancer patients is still suboptimal. The recommendations from current clinical guidelines issued by Italian (AIOM) [8] and international (NCCN, ASCO, ESMO) [5,9,10] scientific societies are not completely followed by all specialists. It must be recognized that, like all observational surveys, the results of this study are likely to be an overestimation of actual clinical practice, and it cannot be ruled out that the understanding of each question may be different among participating clinicians. However, the questionnaire was tested by a group of experts before initiating the study, in order to limit this potential bias. In addition, the number of participating oncologists was high (approximately 10–15% of all Italian oncologists) and the participating clinicians had several years of experience in oncology practice; in our opinion, these factors could strengthen the validity of the results in reflecting current clinical practice.

To our knowledge, this is the first survey to specifically assess, in daily clinical practice, the management of bone metastasis and, in general, the perception of bone healthcare in Italy. However, the findings of this analysis are in overall agreement with those of previous studies, some referring to the Italian situation, in other fields of cancer treatment, which have highlighted the wide gap between guideline recommendations and clinical practice in the oncology and bone health setting [13–17]. In all of these studies, the level of care was suboptimal, and it was generally concluded that, although the education of oncologists and healthcare providers is improving, further procedures and implementation of educational programs to optimize their level of attention and awareness are required [17].

A detailed summary of the current recommendations for the management of bone metastasis in cancer patients is beyond the scope of the present publication. However, we believe some critical points deserve mentioning. For instance, while BPs, and in particular zoledronic acid, are prescribed by the majority of oncologists, it must be recognized that the main objectives of this therapy are, in the participants' opinion, of a palliative nature (e.g. pain relief) rather than curative (e.g. reduction of risk of death related to SRE). Moreover, about half of the participating oncologists may decide not

to treat asymptomatic bone metastases: current consensus recommends that BP treatment should be initiated regardless of the presence of symptomatic metastases and the development of SRE [6,8,18]. About 30% of participants do not support the association between SREs and the increase in the risk of death, despite it being well-documented in the medical literature [19,20]. Moreover, only a minor proportion of specialists consider bone turnover (measured with bone turnover markers such as urinary NTX or serum CTX) as a predictive factor for the appearance of SRE, despite different suggestions published in literature [1].

Some gaps between the actual prescribing attitudes of oncology specialists and current guidelines about BP treatment in oncology patients have also been highlighted by the present survey. About one out of four of the involved oncologists does not start BP treatment at the diagnosis of bone metastasis, contrary to current international recommendations [5–10]. Additionally, about 40% of oncologists interrupt zoledronic acid therapy when skeletal disease progresses, pain develops, or an SRE occurs, rather than continuing the same bisphosphonate as suggested by guidelines [6,8].

Interestingly, for about 40% of oncologists, ONJ still represents a concern in patients during BP treatment, despite current guidelines agreeing on the high efficacy of preventive measures, which should be implemented in all patients assigned to BP therapy [5–10]. Finally, the most alarming result was that about 20% of oncologists appear not to be aware of or follow any guidelines for the maintenance of bone health in their clinical practice.

Taken together, we believe that the results of this survey highlight an urgent need for further education of Italian oncologists in order to improve their awareness of the importance of bone health and the management of skeletal problems in cancer patients; for example, improving the educational programs on bone metastasis management in cancer patient during medical degree courses or during post-degree training, in cooperation with national and international scientific societies.

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Conflict of interest statement

The authors have no conflict of interest to declare.

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Appendix

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