Research Article

Personalized (tailored) treatment with antiresorptive drugs (bisphosphonates, denosumab) in patients with bone metastases from solid tumors – A "Pico" document by Rete Oncologica Piemonte-Valle D'Aosta Bone Metastatic Disease Study Group

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Background. The optimal use of antiresorptive agents (bisphosphonates; denosumab) in patients with bone metastases from solid tumors is uncertain in several aspects, including the initial drug choice and the planned treatment duration, till the long-term therapy. Drug costs, logistics and facilities, patients' preferences, renal toxicity, and expected risk of Medication-Related Osteonecrosis of the Jaw (MRONJ), as well as other side effects, may conditionate the oncologists' choice.

Material and Methods. Italian oncologists from a study group on bone metastatic disease within the "Rete Oncologica Piemonte-Valle d'Aosta" (a cancer network in North-Western Italy) evaluated scientific literature and current guidelines and recommendations, to answer a PICO (Patient/population; Intervention; Comparison; Outcome) question. The question was: in patients

with bone metastases from solid tumors, is treatment with antiresorptive drugs (bisphosphonates or denosumab) amenable to personalized use (for choice of drug and duration of treatment) based on the type of disease, the expected risk of side effects, and patient compliance, as an alternative to "one-fit-for-all" therapy (monthly zoledronic acid or denosumab, indefinitely), in order to: reduce the commitment to the patient and to the oncological structure; reduce economic costs; reduce the risk of medium/long-term side effects (e.g., MRONJ)?

Results. The study group analysed the cost of drugs; the engagement of the oncology unit; the patient commitment/compliance; the risk of side effects (renal toxicity, hypocalcaemia, MRONJ); the options of the planned initial duration of treatment; the timing of administration (monthly versus quarterly). Early antiresorptive treatment was recommended (at the diagnosis of bone metastases, after pre-therapy dental evaluation). Four types of tailored treatment options were recommended, in four main different metastatic cancer scenarios.

Conclusion. A tailored antiresorptive treatment might reduce the number of accesses to oncological structures by the patient, the costs for the structure and for the healthcare system (both in terms of work and cost of drugs), and the risk of medium/long-term side effects (renal failure; MRONJ), potentially without reducing the expected benefits of the treatment.

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Introduction

The Italian Guidelines "Bone Metastases" [1] periodically released by the Italian Association of Medical Oncology, AIOM as well as the European ESMO Clinical Practice Guidelines 2020 [2] and other recommendations (ASCO-Cancer Care Ontario) [3][4] indicate several medical treatment options with antiresorptive agents for bone metastases from solid tumors, with a preference for prolonged (indefinite) treatment with monthly zoledronic acid or monthly denosumab.

However, many indications are based on low levels of evidence and are weak recommendations, for various reasons.

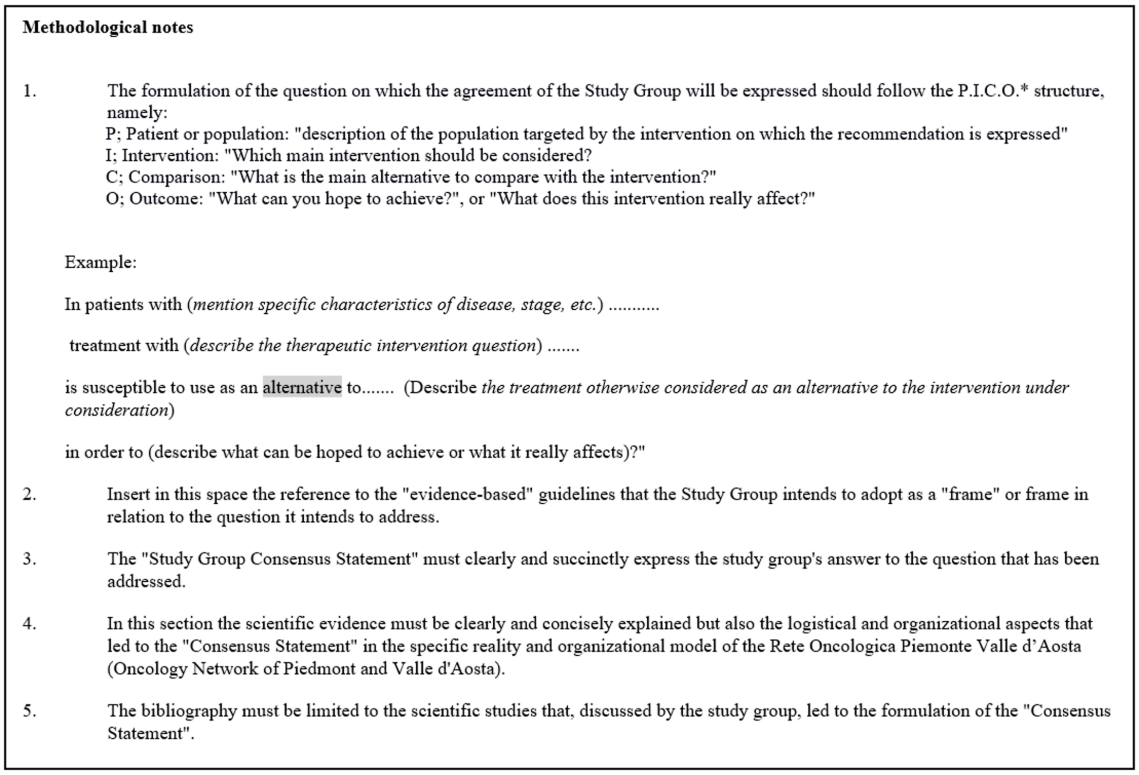
a. The pivotal and comparative studies present several methodological critical aspects (short duration; variable endpoints; superiority/non-inferiority studies; absence of long-term follow-up, especially for late side effect analysis).

b. There are no comparative studies clarifying the optimal pre-defined duration (annual, biennial, indefinite).
c. Studies comparing "monthly" (every 3-4 weeks) versus "quarterly" (every 12 weeks) administration are limited and related only to zoledronic acid.
d. The risk of side effects is noticeably different [5][6] between different treatments.
e. The commitment to the patient (in terms of access to oncological facilities) is different between "monthly" (every 4 weeks) versus "quarterly" (every 12 weeks) versus continuous administration with oral administration (ibandronate, which still requires active medical surveillance).
f. The cost of individual drugs is very variable (in Piedmont, Italy: from less than 2 euros to more than 200 euros, for 4 weeks of therapy).
g. The commitment (cost) for the oncological structures (especially in terms of nursing commitment and engagement of place/chair for administration) is different between the different drugs (intravenous infusion for 2 hours or 15-30 minutes, versus subcutaneous injection, versus delivery of drug for oral administration at home)

In 2020, the "Rete Oncologica di Piemonte e Valle d'Aosta" (a cancer network in North-Western Italy) committed to a Study Group about Cancer Bone Metastases (involving oncologists, nurses, and other specialists) one document about the best options for medical treatment including antiresorptive drugs, also named Bone Modifying Agents (BMAs) or Bone Targeted Agents (BTAs): bisphosphonates and denosumab. The document had to answer a PICO (Patient/population; Intervention; Comparison; Outcome) question and a pre-defined form (see Methods section). Notably, the works of the group were conducted in 2020, during the Covid epidemic. Herein, we present a translation in English of the document, released in January 2021, with minor changes, a discussion section, and further references.

Methods

The document requested by the oncology network had to follow some methodological notes (see Figure 1), and results had to be collected in a pre-defined form (see Figure 1), according to the oncology network commitment.



Methodological notes

1. The formulation of the question on which the agreement of the Study Group will be expressed should follow the P.I.C.O.* structure, namely:
   P; Patient or population: "description of the population targeted by the intervention on which the recommendation is expressed"
   I; Intervention: "Which main intervention should be considered?
   C; Comparison: "What is the main alternative to compare with the intervention?"
   O; Outcome: "What can you hope to achieve?", or "What does this intervention really affect?"

   Example:

   In patients with (*mention specific characteristics of disease, stage, etc.*) .....

   treatment with (*describe the therapeutic intervention question*) .....

   is susceptible to use as an alternative to..... (Describe *the treatment otherwise considered as an alternative to the intervention under consideration*)

   in order to (describe what can be hoped to achieve or what it really affects)?"

2. Insert in this space the reference to the "evidence-based" guidelines that the Study Group intends to adopt as a "frame" or frame in relation to the question it intends to address.

3. The "Study Group Consensus Statement" must clearly and succinctly express the study group's answer to the question that has been addressed.

4. In this section the scientific evidence must be clearly and concisely explained but also the logistical and organizational aspects that led to the "Consensus Statement" in the specific reality and organizational model of the Rete Oncologica Piemonte Valle d'Aosta (Oncology Network of Piedmont and Valle d'Aosta).

5. The bibliography must be limited to the scientific studies that, discussed by the study group, led to the formulation of the "Consensus Statement".

Figure 1. Methodological notes for consensus statement

Members of the Study Group worked online between April 2020 and December 2020. One member (VF) collected a short selection of the main recent literature [1][2][3][4][5][6][7][8][9][10][11][12][13][14][15] and wrote a first draft. After some comments and revisions, the final document was approved by all the members of the group and published in the Italian language on the website of the oncology network (www.reteoncologica.it).

Results

The PICO question formulated by the members of the Stud Group was as follows.

In patients with bone metastases from solid tumours,

is treatment with antiresorptive drugs (bisphosphonates or denosumab) amenable to personalized use (for choice of drug and duration of treatment) based on the type of disease, the risk of side effects, patient compliance,

as an alternative to "one-fit-for-all" therapy (monthly zoledronic acid or denosumab, indefinitely),

in order to: reduce the commitment to the patient and to the oncological structure; reduce economic costs; reduce the risk of medium/long-term side effects (e.g., MRONJ)?

The following factors were analysed.

COST OF THE DRUG. The cost of drugs is very variable (in Piedmont: from less than 2 Euros to more than 200 Euros, for 4 weeks of therapy) (See Figure 2).

Treatment option	Cost of the drug (per "month")	Notes
Pamidronate intravenous	Generic drug 60mg vials = € **8,50**. ➔ if dose 90 mg = **€ 12.75**	
Zoledronic intravenous	Generic drug 4mg vials = € **1,689**	
Ibandronate intravenous	Bondronat 6mg vials = **€ 103,5**	Only for breast cancer
Ibandronate oral	Bondronat 50mg,28 cpr = **€ 219,24**	Only for breast cancer
Denosumab subcutaneous	Xgeva 120mg vials = **€ 153,97**	

Figure 2. Cost of the drug in Piedmont (in November 2020) for the Regional Healthcare System

COMMITMENT OF THE STRUCTURE. The commitment (and cost, not fully quantifiable) for the oncological structure must be considered for:

- *blood sampling and examination* (creatinine level and calcium level, for all drugs);
- *pharmacy commitment* (preparation of infusion bottles of intravenous pamidronate, zoledronate, ibandronate; distribution only for subcutaneous denosumab and oral ibandronate);
- *nursing commitment* (intravenous infusion of pamidronate, ibandronate, zoledronate; possible subcutaneous injection only for denosumab);
- *chair commitment for intravenous administration* (different between different drugs: 2-hour intravenous infusion for pamidronate, or 15-30 minutes for intravenous zoledronate and ibandronate; none for denosumab and oral ibandronate).

PATIENT COMMITMENT/COMPLIANCE. The commitment to the patient (in terms of access to oncological facilities) is clearly different between intravenous or subcutaneous "monthly"

administration (denosumab, ibandronate and zoledronate every 4 weeks; rarely every 3 weeks, together with chemotherapy) versus intravenous "quarterly" administration (zoledronate every 12 weeks) versus oral administration (ibandronate, which however requires active medical surveillance).

RENAL TOXICITY. Pamidronate and zoledronic acid are associated with a risk of acute renal failure. Therefore, in patients with renal impairment already present, it is necessary to reduce the doses of zoledronate and prolong the infusion of pamidronate. In these cases, denosumab is preferred.

HYPOCALCAEMIA. More frequent with denosumab than with zoledronic acid (particularly in patients treated with denosumab who have renal impairment).

MEDICATION-RELATED OSTEONECROSIS OF THE JAW BONES (MRONJ). Data from comparing studies, part of meta-analyses and especially "real life" observational data show that the MRONJ risk is greater in patients treated with denosumab (especially if administered for prolonged times), zoledronic acid (idem) or undergoing a shift from zoledronic acid to denosumab, compared to patients treated with pamidronate. The duration of treatment, the cumulative dose of the drug administered, and the observation time would seem fundamental for the MRONJ risk. Quarterly administration of zoledronic acid appears to reduce the incidence of MRONJ compared to monthly administration.

OPTIMAL DURATION (PLANNED) OF TREATMENT. There are no comparative studies clarifying the planned optimal duration (annual, biennial, indefinite). Most pivotal studies were based on data from patients on a median treatment time between one and two years. Despite the absence of specific control studies, many guidelines recommend "indefinite" therapy (until the patient's general condition decays) or arbitrary treatments for two years (followed by "tailoring" therapy, at the discretion of the caregiver).

TIMING OF ADMINISTRATION (MONTHLY VERSUS QUARTERLY). The comparative studies between quarterly and monthly administration, referred so far to zoledronic acid alone, have highlighted possible advantages (albeit with some critical issues) of the quarterly administration of zoledronate (after an initial period of 3-6-12 months of monthly administration; or "upfront", already from the beginning of therapy) and this practice is rapidly gaining share among clinicians (at least in North America).

OTHER SIDE EFFECTS. Less important in the choice of the drug: symptoms (fever, widespread pain) from acute phase reaction (more frequent with pamidronate and zoledronate); femoral atypical fractures, (rare, observed both after zoledronate and denosumab); ocular side effects.

Members of the Study Group designed a summary table with the analysis carried out on the main therapeutic options, valid for most solid tumors (and for multiple myeloma), illustrating the pros and cons of different drugs and schedules, in a semi-quantitative manner (Figure 3).

	Pamidronate 90 mg monthly	**Zoledronic acid 4 mg monthly**	**Zoledronic acid 4 mg quarterly**	**Denosumab 120 mg monthly**
Lower cost	++++	++	+++	+
Favourable logistics	+	++	+++	++++
Less MRONJ	++++	++	+++	+
Lower nephrotoxicity	+++	+	++	++++
Lower hypocalcaemia	++	+++	++++	+

Figure 3. Legend: mg = milligrams; monthly = every 3-4 weeks; quarterly = every 12 weeks.

Consequently, the Study Groups expressed the following statements.

TREATMENTS with ANTIRESORPTIVE DRUGS for BONE METASTASES FROM SOLID TUMORS can be INDIVIDUALIZED based on different parameters:

1. Known activity data (SRE reduction/delay)
2. Duration of treatment reported in studies (annual vs biennial vs indefinite)
3. Commitment to the oncological structure (monthly vs quarterly; intravenous versus subcutaneous versus oral)
4. Economic cost of the drug (pamidronate vs zoledronic acid vs ibandronate vs denosumab)
5. Commitment to the patient (number of accesses to hospital facilities)
6. Risk of medium- and long-term side effects (mainly: nephrotoxicity, MRONJ)

The indications of the main Guidelines and Recommendations to start treatment with anti-resorptive drugs as soon as possible [1][2][3][4], at the diagnosis of bone metastases (regardless of tumor burden and symptomatic status), after pre-therapy dental control (according to the Italian SIPMO-SICMF

Recommendations, endorsed by several Italian Scientific Societies, including AIOM) [15] are confirmed.

Based on these parameters, the Study Group generally recommends these individualized treatment options:

1. Treatment with *monthly denosumab or zoledronic acid, for at least 12 months*, in case of aggressive and/or symptomatic disease, and/or in case of pain or high risk of fracture (defined by specialist or – where possible – multidisciplinary evaluation). In case of excellent response to medical treatments, another 12 months can be evaluated with the same treatment (or shift to zoledronic acid quarterly).
2. Treatment with *zoledronic acid for 12 months and then quarterly for another 12 months*, in case of indolent bone disease, oligometastatic and/or low risk of short-term fracture (defined by specialist or – where possible – multidisciplinary evaluation). Consider resumption of treatment in case of clinical or symptomatic progression, as well as in case of Skeletal Related Event (SRE).
3. Treatment with *monthly denosumab* in case of renal failure, for 12-24 months.
4. Treatment with *quarterly zoledronic acid "upfront"* in case of frail elderly patient, in the absence of pain and in the absence of high risk of short-term fracture (defined by specialist or – where possible – multidisciplinary evaluation).

More detailed documents, referring to patients with metastatic breast cancer and patients with castration-resistant metastatic prostate cancer, will be the subject of separate recommendations, which will be proposed to the Study Groups of single cancer type.

The following note was added: please note there are alerts on a "rebound" effect on discontinuation of denosumab (increase in markers of bone turnover), but there are no conclusive data. As a precautionary measure, treatment with zoledronic acid (monthly or quarterly) is recommended in case of discontinuation of denosumab.

As requested by methodological notes, reasons and possible comments on the toxicity/benefit ratio were summarized, as follows.

The purpose of these treatment indications is to reduce (where possible):

1. the number of accesses to oncological structures by the patient;

2. the costs for the structure and for the Italian National Health System (both in terms of work and cost of drugs);
3. the risk of medium/long-term side effects (renal failure; MRONJ)

without reducing the potential benefits of treatment.

Discussion

Antiresorptive drugs have a relevant part in the management of cancer patients with bone metastases, even if with a supportive care role (no impact on survival was demonstrated) [1][2]. In randomized trials, antiresorptive drugs showed to reduce the risk of SREs and are consequently largely recommended in this setting, starting as early as possible after the diagnosis of bone metastases to prevent or delay SREs.

Recent randomized trials did not clarify all the aspects of the pros and cons of prolonged treatment, and optimal use of antiresorptive drugs in bone metastatic patients remains still uncertain in clinical practice [16].

The choice of the antiresorptive drug can depend on many criteria. The drug cost (for individuals or healthcare systems) and several indirect costs (e.g., hospital facilities; staff for intravenous versus subcutaneous drug administration; costs for blood calcium and creatinine monitoring; dental check-ups; etc) are important and present large differences linked to regional-country specificity and type of healthcare system.

In the reported document, a Study Group about Cancer Bone Metastases (involving oncologists, nurses, and other specialists) answered a request by the Head Office of the "Rete Oncologica di Piemonte e Valle d'Aosta" (a cancer network in North-Western Italy) about best options of medical treatment including antiresorptive drugs. The requested document had to answer a PICO (Patient/population; Intervention; Comparison; Outcome) question and a pre-defined form. The document (elaborated in 2020, during the Covid pandemic peak) tried to help oncologists choose the antiresorptive drug with a positive cost-benefit analysis for main different patient subpopulations.

One strength of the document is that it is based on the clinical practice of the Study Group members and the knowledge of the regional real-life problems and issues, besides the literature results. The main weakness of the document is the lack of literature data about antiresorptive effects in the four

specific patient subpopulations described in the report, supporting the suggestions of the Study Group.

Conclusion

A tailored antiresorptive treatment might reduce the number of accesses to cancer care units by the patient, the costs for the structure and for the healthcare system (both in terms of work and cost of drugs), and the risk of medium/long-term side effects (renal failure; MRONJ). Further studies are needed to confirm that personalized schemes (as the four schemes proposed by the Study Group) are worthy, without reducing the benefit of antiresorptive drugs.

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Declarations

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