Evidence-based guidelines: Improving AGREEment on consistence evaluation

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Abstract

Modern clinical practice relies on evidence-based medicine (EBM) and evidence-based guidelines (EBGs). The critical evaluation of EBGs value is therefore an essential step to further improve clinical practice. In our opinion, correlating levels of evidence and grades of recommendation can be an easy tool to quickly display internal consistence of EBGs.

1. Introduction

Evidence-based medicine (EBM) has been defined as the "integration of best research evidence with clinical expertise and patient values". The first historical descriptions of EBM date back to the beginning of 1990s, when the work of Gordon Guyatt, David Sackett and others established the emerging methodologies of EBM [8,20]. The main products of EBM are evidence-based guidelines (EBGs), "systematically developed statements to assist practitioner and patient decision about appropriate health care for specific clinical circumstances" [21]. EBGs indeed substantially improve clinical care [29].

Costs, ethical concerns in placebo-controlled trials, publication bias and a real risk of reductionism are the most emphasized limitations of EBM. In order to overcome these limitations and improve EBGs quality standards, different societies (among which the World Health Organization, WHO) produced guidelines for guideline developers.

Preliminary steps for guideline development are evaluation of priority settings [14], composition of an expert panel [9], management of conflicts of interests [3], determination of appropriate group processes [10], of important outcomes [22] and of which evidences have to be included [15].

Then developers have to produce synthesis and presentation of evidences [16], exposing criteria for grading evidence and recommendations [23], integrating when possible values (e.g. ethical considerations) and consumer involvement [24]. Next, considerations of cost-effectiveness, affordability and resource implications [7], of equity [17], applicability, transferability and adaptation [25] should be included.

The final steps are the report of guidelines recommendations [18], the dissemination and implementation of guidelines [11] and their evaluation [19].

Since EBGs frequently vary widely in quality [26,27], their evaluation is very important. Updating a first systematic review [12,28] found 24 different EBGs appraisal tools. The Appraisal of Guidelines for Research and Evaluation (AGREE) instrument was a validated, easy-to-use, and transparent tool, which was internationally developed and widely accepted. It was developed through a process of item generation, selection and scaling, field-testing and refinement. The final version of the instrument contained 23 items grouped into six domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence [2].

Despite the good review of the AGREE instruments, two important limitations are present: although it can be used to compare clinical practice guidelines, AGREE instrument does not set a threshold to classify them as good or bad, and it does not assess the quality of the evidence supporting the recommendations [29].
### Table 1
Levels of evidence and respective grades of recommendation in the guidelines for the treatment of bone metastases by the Italian Society for Medical Oncology.

| Topic | Level of evidence | Grade of recommendation |
|-------|-------------------|-------------------------|
| **1. Bisphosphonates in metastatic cancers**  |
| a. **Indication: breast cancer** |
| Efficacy of bisphosphonates in reducing skeletal-related events | I | A |
| Efficacy of bisphosphonates in reducing pain levels and improving quality of life | I | A |
| Route of administration of bisphosphonates: endovenous vs oral | I | A |
| Efficacy of zoledronic acid vs other bisphosphonates | II | A |
| b. **Indication: prostate cancer** |
| Efficacy of bisphosphonates in reducing skeletal-related events | N/A | N/A |
| c. **Indication: lung cancer** |
| Efficacy of bisphosphonates in reducing skeletal-related events | III | B |
| d. **Indication: renal cancer** |
| Efficacy of bisphosphonates in reducing skeletal-related events | III | B |
| e. **Indication: other cancers** |
| Efficacy of bisphosphonates in reducing skeletal-related events | III | C |
| f. **Length of the therapy** |
| Extension of treatment after the first two years | V | B |
| Switch from oral bisphosphonate to zoledronic acid | V | B |
| g. **Timing of therapy start** |
| Therapy after radiological evidence of bone metastases in absence of symptoms | V | B |
| h. **Dosage and schedule** |
| Standard dosage and schedules suggested in clinical trials and by FDA and EMEA | I | A |
| i. **Route of administration** |
| Endovenous or oral administration, according to criteria exposed in the guideline | I | A |
| j. **Multidisciplinary approach** |
| Team-based therapeutic approach to patients affected by bone metastases | V | B |
| k. **Vitamin D supplementation** |
| Role of bisphosphonates in preventing bone loss | N/A | N/A |
| l. **Markers of bisphosphonate efficacy** |
| Role of N-terminal telopeptide | III | C |
| m. **Quality of life** |
| Control of bone pain | I | A |
| Co-analgesic effect in combination with major analgesic drugs | I | A |
| Selection of adequate bisphosphonate for quality of life and pain management | I | A |
| High-dose bisphosphonates in opioid-resistant bone pain | V | D |
| High-dose ibandronate in severe bone pain | V | D |
| Zoledronic acid role in incident pain | V | D |
| Overall effects of bisphosphonates in improving quality of life | V | D |
| **2. Bisphosphonate in cancer induced bone loss**  |
| a. **Diagnosis of osteoporosis in cancer patients** |
| DEXA in the diagnosis of osteoporosis in cancer patients | I | A |
| b. **Fracture risk in breast cancer patients** |
| Evaluation of fracture risk in breast cancer patients with preserved ovarian function or in postmenopause under tamoxifen or no hormonal treatment | I | A |
| Evaluation of fracture risk in breast cancer patients with premature menopause due to medical/surgical therapies or in postmenopause under aromatase inhibitor treatment | I | A |
| Global decision algorithm, in consideration of bone mass density, age and other factors | VI | B |
| c. **Prevention and therapy of osteoporosis in breast cancer patients** |
| Selection of adequate bisphosphonate for cancer induced bone loss | I | A |
| Role of bisphosphonates in cancer patients bone health | V | B |
| Bisphosphonates role in the therapy of osteoporosis | I | A |
| Efficacy of bisphosphonates in cancer induced bone loss | I | A |
| d. **Fracture risk and osteoporosis in prostate cancer patients under androgen blockade** |
| Fracture risk in prostate cancer patients under androgen blockade | I | A |
| Selection of adequate bisphosphonate | VI | B |
| Decision algorithm for prostate cancer patients under androgen blockade | VI | B |
| Bisphosphonates role in the prevention of osteoporosis in prostate cancer patients under androgen blockade | VI | B |
| Optimal length of therapy | VI | B |
| **3. Bisphosphonate safety**  |
| a. **Renal safety** |
| Role of bisphosphonates dosage and infusion speed on renal function | II | A |
| Bisphosphonate dosage reduction in patients with impaired renal function | II | A |
| Risk of hypocalcemia and hypomagnesemia after bisphosphonate endovenous administration | II | A |
| Endovenous ibandronate and renal safety | II | A |
| Oral ibandronate and renal safety | II | A |
| b. **Osteonecrosis of the jaw** |
| Diagnosis and treatment | V | C |
| c. **Rare adverse events** |
| Ocular adverse events | II | B |
Level of evidences and grade of recommendations in fact do not necessarily correlate, since the first is a measure of scientific strength and the latter of clinical utility.

Recently, an improved version of the AGREE, i.e. the AGREE II instrument, has been released [4,5], partly overcoming the previous limitations. Indeed, the introduction of the new item assessing the description of strengths and limitation of the body of evidences can be considered as a precursor for clinical validity or appropriateness of the recommendations. The authors recognize the value of this point, in fact they state that the AGREE consortium is targeting this area as its next priority for further study in the AGREE A3 initiative [6].

In our opinion, correlating level with grade could be a valid way to integrate the AGREE II instrument and quickly display the internal consistence of EBGs.

### 2. Material and methods

The guidelines for the treatment of bone metastases by the Italian Society for Medical Oncology (AIOM) are based on: European Society for Medical Oncology (ESMO) guidance on the use of bisphosphonates in solid tumors [1] and on the management of aromatase inhibitor-associated bone loss [13]; Cochrane network reviews; critical review of the literature updated to June 2009.

The topics covered by the AIOM guidelines are use of bisphosphonates in metastatic cancers; use of bisphosphonates in the prevention and treatment of cancer treatment induced bone loss; safety of bisphosphonates use; treatment of bone metastases pain; role of bisphosphonates in specific settings; role of orthopedic surgery in bone metastases; role of radiotherapy in bone metastases.

| Topic | Level of evidence | Grade of recommendation |
|-------|------------------|-------------------------|
| 4. Treatment of bone metastases pain | | |
| a. Pharmacological treatments | | |
| Usage of non-opiate, opiate and adjuvant drugs for pain control | I | A |
| Tramadol vs other opiate drugs in mild-moderate pain | VI | B |
| Adverse events related to analgesic treatments | III | C |
| Selection of drugs for moderate–severe pain | I | A |
| Efficacy of analgesic therapy | I | A |
| 5. Role of bisphosphonates in specific settings | | |
| a. Old patients and/or patients with comorbidity | | |
| Efficacy of bisphosphonates in reducing skeletal-related events in old patients | VI | B |
| Role of renal function and hydration status monitoring in old patients | VI | B |
| Criteria for oral bisphosphonate selection in old patients | VI | B |
| Criteria for endovenous bisphosphonate selection in old patients | VI | B |
| Adverse gastrointestinal effects and compliance in old patients | VI | B |
| Risk of osteonecrosis of jaw in old patients | VI | B |
| b. Bisphosphonate with specific oncological treatments | | |
| Synergistic effects between chemotherapy drugs and bisphosphonates | V | D |
| 6. Role of orthopedic surgery in bone metastases | | |
| a. Lesions to appendicular skeleton or pelvic and shoulder girdles | | |
| Class 1 patients: asportation of bone metastases | IV | B |
| Class 2 and 3 patients: external fixation | IV | B |
| Class 4 patients: surgery only after mechanical failure or progressive pain | IV | B |
| Fracture risk of pelvic lesions | IV | B |
| Surgical treatment of pelvic lesions | IV | B |
| Bone curettage | IV | B |
| Prosthetic surgery | IV | B |
| b. Spinal metastases | | |
| Role of surgery in spinal metastases | IV | B |
| c. Spinal compression | | |
| Role of surgery in spinal compression | IV | B |
| d. Type of surgery | | |
| Complete removal of metastatic lesions | IV | B |
| Vertebroplasty/kypheoplasty in painful metastatic lesions | IV | B |
| 7. Role of radiotherapy in bone metastases | | |
| a. External beams in bone metastases | | |
| Pain control in hypofractionated short vs long radiation therapy | I | A |
| Timing of radiation therapy | II | B |
| Pain control in monofractionated vs multifractionated radiation therapy | I | A |
| Monofractionated treatment of painful metastatic lesion | I | A |
| Hypofractionated treatment of painful metastatic lesion | I | A |
| Antalgic effects and complete response | II | B |
| Reirradiation feasibility | III | B |
| Reirradiation dosage | III | B |
| b. Radiotherapy in medullary compression | | |
| Therapy for good prognosis patients | III | C |
| Therapy for bad prognosis patients | I | A |
| Reirradiation in medullary compression | VI | C |
| c. Radiomethabolic therapy | | |
| Efficacy of radiomethabolic therapy | I | A |
| Synergisms vs side effects of combining chemotherapy and radiomethabolic therapy | I | B |
| Inefficacy of combining of external beam radiotherapy and radiomethabolic therapy | I | B |

N/A: not applicable.
Level of evidences (I–VI) and grade of recommendations (A–E) were provided according to the recommendations of the Italian Centre for the Evaluation of the Efficacy of Health Assistance coordinated by the Italian National Health Institute (Istituto Superiore di Sanità) and are presented in Table 1.

We performed an analysis of levels of evidence and respective grades of recommendations of the guidelines for treatment of bone metastases by AIOM.

Spearman’s rank correlation coefficient was calculated per each topic of the guidelines, a p value < 0.05 was considered statistically significant. The final correlation was performed using a linear regression model (GraphPad Prims version 5.04, La Jolla California USA); linear r² value was reported to weight the results and a p value < 0.05 was considered statistically significant.

3. Results

The results of our analysis showed a statistically significant correlation between the levels of evidence and the grades of recommendation in the following topics: use of bisphosphonates in metastatic cancers (p < 0.01); use of bisphosphonates in the prevention and treatment of cancer treatment induced bone loss (p < 0.01); safety of bisphosphonates use (p < 0.05); role of bisphosphonates in specific settings (p < 0.01); role of orthopedic surgery in bone metastases (p < 0.0001); role of radiotherapy in bone metastases (p < 0.01).

Finally, a statistically significant correlation was also found considering all the levels of evidence and grades of recommendations together regardless of the division in topics (r² = 0.4454, p < 0.0001; Fig. 1).

4. Discussion

EBGs represent a milestone for modern evidence-based clinical practice; they indeed substantially improve clinical care [29]. Nevertheless, EBGs frequently vary widely in quality [26,27], thus their evaluation is of critical importance. Among several evaluation tools, the AGREE instrument is the most widely used, even though it has known limitations, i.e. the impossibility to classify EBGs as good or bad and to assess the quality of the evidences supporting the recommendations.

In order to overcome these limitations, we performed an analysis of levels of evidence and respective grades of recommendations of the guidelines for treatment of bone metastases by AIOM. In six out of seven topics, levels of evidence and respective grades of recommendations significantly correlated. Moreover, a statistically significant correlation was also found considering all the levels of evidence and grades of recommendation together regardless of the division in topics. These results indicate that the authors of the guidelines worked scientifically with a correct approach and that these guidelines are likely to be adherent with modern medical literature.

However, we cannot exclude that a significant correlation for some topics could be due to low levels of evidences from medical literature and consequent low grades of recommendations.

Moreover, the lack of concordance in specific items could also derive from the impossibility for the physicians to prescribe a specific drug in a specific setting (i.e. low grade of recommendation) due to the delayed approval by regulatory agencies (e.g. FDA, EMA) even in presence of adequate scientific literature (i.e. high level of evidence).

The critical evaluation of EBGs is an underestimated issue in current clinical practice. Moreover, specific methodological aspects for the evaluation of EBGs are of increasing interest in the medical oncology community. Here we provide clinicians with a quick tool to evaluate the internal consistence of EBGs. Further analysis should confirm the reliability of this method, which could be easily implemented in future EBGs.

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