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Short Communication

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 guidelines 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].

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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 scheletal-related events	I	A
Efficacy of bisphosponates 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	N/A	N/A
c. Indication: lung cancer		
Efficacy of bisphosphonates in reducing scheletal-related events	III	B
d. Indication: renal cancer		
Efficacy of bisphosphonates in reducing scheletal-related events	III	B
e. Indication: other cancers		
Efficacy of bisphosphonates in reducing scheletal-related events	III	C
f. Lenght 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 metatases in absence of sintoms	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 therapeutical approach to patients affected by bone metastases	V	B
k. Vitamin D supplementation	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	II	A
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 ormonal 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
Selection of adequate bisphosphonate for cancer induced bone loss	I	A
Role of bisphosphonates in cancer patients bone health	I	A
Efficacy of bisphosphonates in cancer induced bone loss	I	A
c. Prevention and therapy of osteoporosis in breast cancer patients		
Selection of adequate bisphosphonate for prevention and therapy of osteoporosis	I	A
Bisphosphonates role in the prevention of osteoporosis	VI	B
Bisphosphonates role in the therapy of osteoporosis	I	A
Optimal length of therapy	VI	B
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
Other risk factors for osteoporosis in prostate cancer patients under androgen blockade	VI	B
Bisphosphonates role in the therapy of osteoporosis in prostate cancer patients under androgen blockade	VI	B
Optimal length of therapy	VI	B
Bisphosphonates role in the prevention of osteoporosis in prostate cancer patients under androgen blockade	I	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
Prevention	III	A
Oral surgery during endovenous bisphosphonate treatment	V	C
c. Rare adverse events		
Ocular adverse events	II	B