Farmaci bone-targeted: basi biologiche e razionale d'uso

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DICHIARAZIONE

Relatore: Giovanni Pavanato

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **: NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario **:NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board: **NIENTE DA DICHIARARE**
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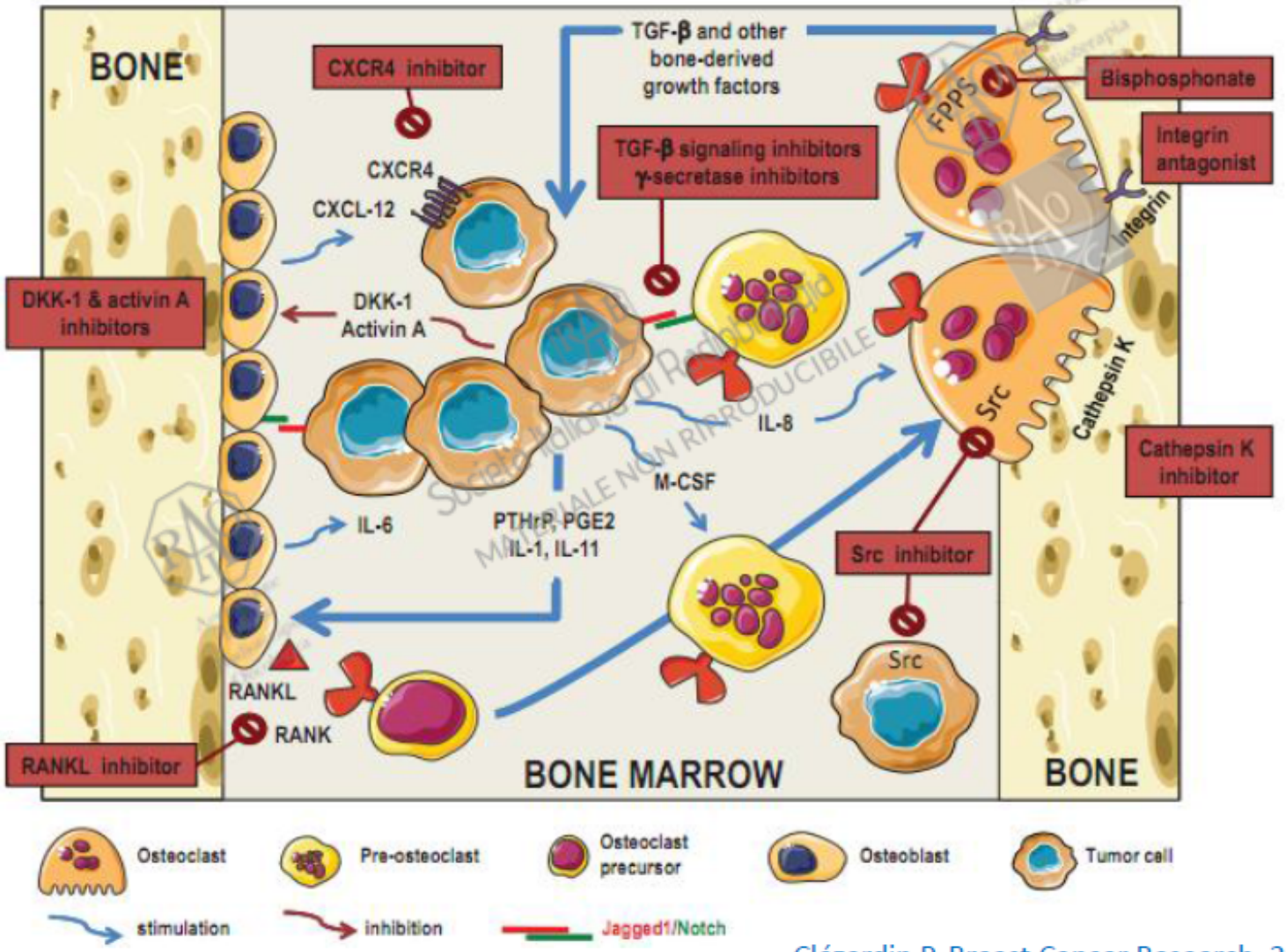
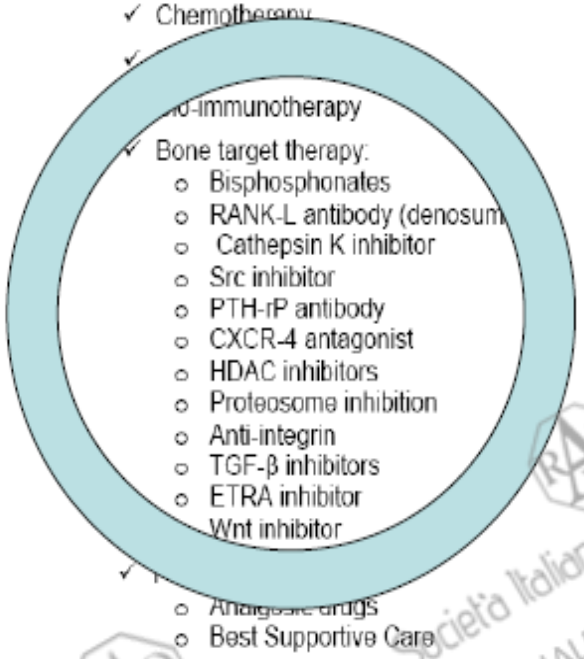
Bone Targeted Therapy



Clézardin P, Breast Cancer Research, 2011

Treatment of Bone Metastases

Medical treatment



Radiotherapy

Radiometabolic treatment

Orthopedic surgery

Interventional radiology

Rehabilitation

RANK-L, receptor activator of nuclear factor-kb ligand; PTH-rP, parathyroid hormone-related peptide; CXCR-4, chemokine receptor type 4; HDAC, histone deacetylase;TGF-β, tumor growth factor β; ETRA, endothelin receptor A

Schedules

Medical treatment of bone metastases has become progressively complex and currently includes:

✓ well known antitumor agents

✓ **bone targeted molecules**

Ibrahim T, Tumori 2013

Overview:
bone health and (new) target molecules

- **Bisphosphonates (B)**
- **Denosumab (D)**

- *Abiraterone*
- *Enzalutamide*
- *Radium-233*
- *Cabozantinid*
- *Dasatinib*
- *Anti-endothelin drugs*
- *Cathepsin K inhibitors*

BTT: primary sites

- **Breast**
- **Prostate**

- Lung
- Kidney
- Others

Primary Site of Malignancy	Incidence of Skeletal Metastasis	Median Survival After Bone Metastasis (months)
Lung	20%[2]	9.7[3]
Kidney	20–35%[4,5]	12[4]
Thyroid	47%[6]	29 (all types)[7] 46 (DTC)[8]
Melanoma	18%[9]	3[9]
Breast	65–75%[43]	50 (sol)[44] 25 (mult)[44] 24–32 (BM first)[45,46]
Prostate	90%[27]	40[47]

BM first=bone metastases before other solid organ metastases; DTC=differentiated thyroid carcinoma; mult=multiple bone metastases; sol=solitary bone metastasis.

Goals of BTT

Reduction of incidence and delay in occurence of skeletal-related events
(SREs: pathologic fracture, radiation therapy, surgery, spinal cord compression)

Improvement in quality of life, pain control and (in some cases) increased survival

BTT: when?

Initiation and treatment duration

to maximize their benefit they should be initiated as soon as bone metastases are diagnosed, even if asymptomatic

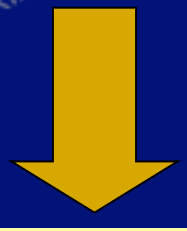
BTT: how long?

Since the risk of SREs is going to continue, BTT should be prolonged (2 yrs)

and it should not be discontinued once SREs occur
(in case of good tolerability)

Bisphosphonates

- Accumulate in the mineralized bone matrix and are released during bone resorption
- Nitrogen-containing B (pamidronate,alendronate, ibandronate and zoledronic acid) affect osteoclast activity and survival, inhibiting a key enzyme (farnesylpyrophosphate synthetase)



prevention of prenylation and activation of small signaling proteins
(Ras)

Bisphosphonates: other functions (in vitro and preclinical studies)

- Act on tumor cells and endothelial cells
- Induce apoptosis of osteoclasts and tumor cells
- Inhibit adhesion of tumor cells to extracellular matrix
- Slow the progression of bone lesions and prevent bone metastasis
- Prevention of visceral metastasis (only Zoledronic Acid)

Bisphosphonates: meta-analytic data

- Cochrane Database Sist Rev 2(2012) – NH Wong et al: Bisphosphonates and other bone agents for breast cancer

- 2806 BC pts with BM; B reduce risk of SREs of 15% compared to placebo, with significant delays in the median time to SREs
- Mild toxicity; jaw's osteonecrosis potential problem

Bisphosphonates: recent data

- Lancet Oncol, 14 (7) 2013 – D Amadori et al: Efficacy and safety of 12-weekly vs 4-weekly zoledronic acid for prolomged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open label, randomised, non- inferiority trial.

- SREs per pts/year was 0,26 in 12-weeks group and 0,22 in 4-weeks group (non inferiority)

Bisphosphonates: recent data

- J Clin Oncol 32(2014) – GN Hortobagyi et al: Efficacy and safety of continued zoledronic acid every 4 weeks versus every 12 weeks in women with bone metastases from breast cancer: result of the OPTIMIZE 2 trial.

- SREs rate was 22% in q4w and 23,2% in q12w (non inferiority), but trend towards a higher incidence of SREs in q12w arm

Bisphosphonates: recent data

- J Clin Oncol 33(2015) – AL Himelstein et al: CALGB 70604: a randomised phase III study of standard dosing vs longer interval dosing of zoledronic acid in metastatic cancer.

- Same conclusions

in clinical practice the two schedules can be considered equivalent

Ongoing study: BISMARK trial: It will help clinicians in defining the optimal timing of B administration and effective utility of biomarkers monitoring.

Denosumab

- Fully human monoclonal antibody with high affinity and specificity for RANKL (Receptor Activator of Nuclear factor Kb Ligand)
- It can neutralize the activity of RANKL (acting as *osteoprotegerina* OPG/OCIF – osteoclastogenesis inhibitory factor)
- RANKL has a significant role in cell migration and tissue-specific metastatic behavior of cancer cells

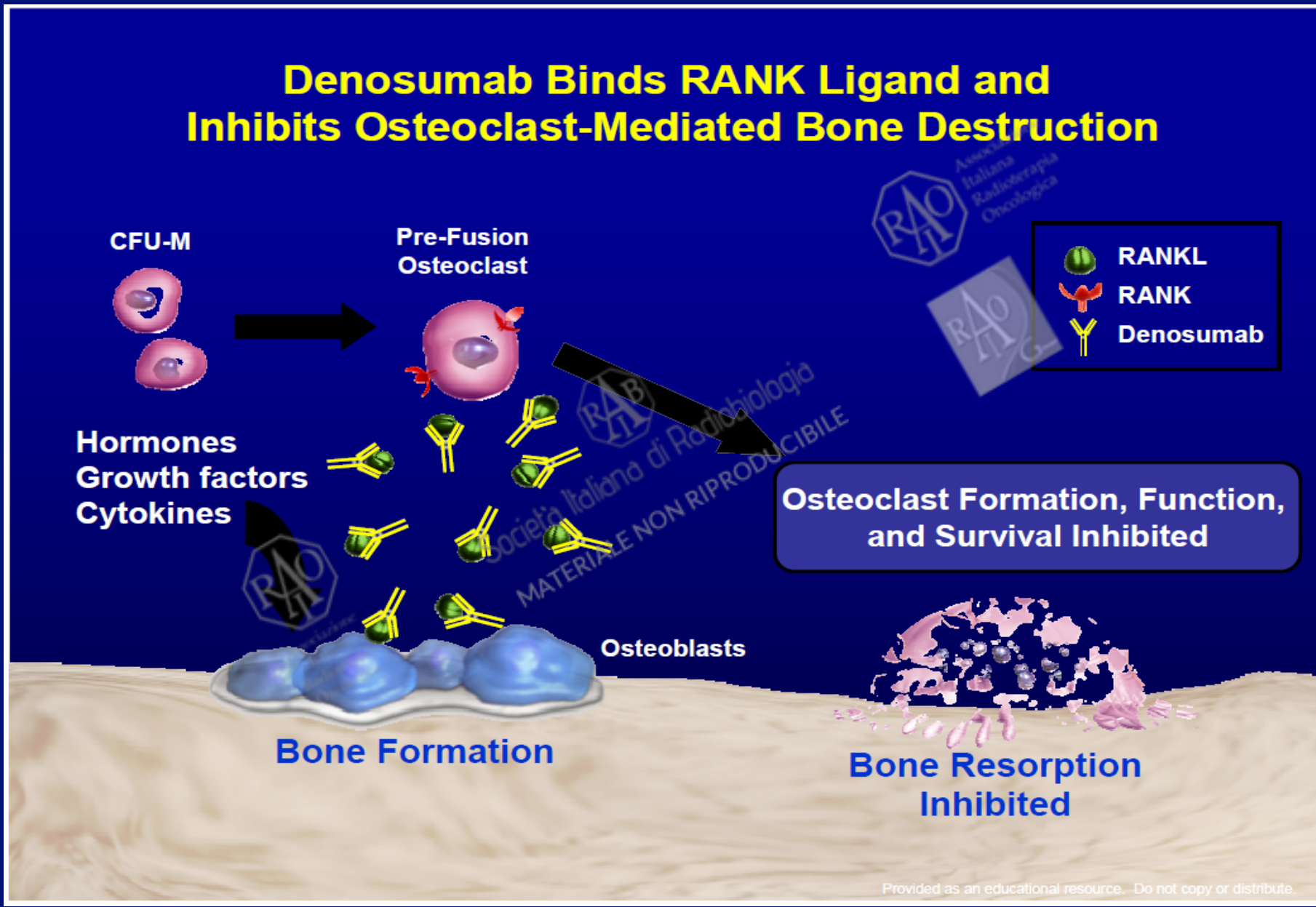
→ D may delay the development of metastases

Denosumab

- RANKL is expressed on subsets of T and B cells, with a theoretical possibility that D may be immunosuppressive (not observed in clinical trials)

Biol Targets Ther 6(2012) – U Brown-Glaberman et al: Role of denosumab in the management of skeletal complications in pts with bone metastases from solid tumors.

Denosumab Binds RANK Ligand and Inhibits Osteoclast-Mediated Bone Destruction



Denosumab - Xgeva®

- Commercial formulation of D used in the prevention of SREs in adults with BM from solid tumors

recomended dose of Xgeva® is 120 mg sc as single administration every 4 weeks

Denosumab

- J Clin Oncol 28(35) 2010 – AT Stopeck et al: Denosumab compared with zoledronic acid for the treatment of bone metastases in pts with advanced BC: a randomized double-blind study.

- D reduced the risk of developing multiple SREs by 23%
- D reduced the mean skeletal morbidity rate by 22%
- Rates of adverse events (AEs) were similar between groups (included ONJ)

Overall survival and desease progression were similar

Denosumab

- Cancer 119(4) 2013 – CS Cleeland et al: Pain outcomes in pts with advanced BC and BM: results from a randomized double-blind study of D and ZA.

- D demonstradted improved pain prevention and comparable pain palliation
- Fewer D treated pts shifted to strong opioid drugs

Denosumab

- Clin Oral Implants Res 27(3) 2016 – A Boquete-Castro et al: Denosumab and osteonecrosis of the jaw (ONJ). A systematic analysis of events reported in clinical trials.

- 8963 pts different solid tumors/7 RCT
- Overall incidence of ONJ was 1,7% (95% CI 0,9-3,1)
- Significant increased risk of ONJ compared to B (p 0.078) or placebo (p 0.017)

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Review Article

Bone targeted therapy for preventing skeletal-related events in metastatic breast cancer

Azzurra Irelli [a,b,*], Valentina Cocciolone [a,b], Katia Cannita [a], Luigi Zugaro [c], Mario Di Staso [d], Paola Lanfiuti Baldi [a], Stefania Paradisi [a,b], Tina Sidoni [a], Enrico Ricevuto [a,b], Corrado Ficorella [a,b]

In conclusion, although any difference in survival was not found in patients with mBC treated with denosumab compared to zoledronic acid, randomized clinical trials have shown that the inhibitor of RANKL is superior to zoledronic acid in preventing or delaying the SREs and improving the quality of life also thanks to the subcutaneous administration and to its good toxicity profile.

INTERNATIONAL JOURNAL OF ONCOLOGY 40: 1313-1320, 2012

Novel strategies in the treatment of castration-resistant prostate cancer (Review)

ILARIA MARECH[1], ANGELO VACCA[1], GIROLAMO RANIERI[2], ANTONIO GNONI[3] and FRANCO DAMMACCO[1]

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- Chemotherapy
- Hormonotherapy
- Immunotherapy
- Targeted therapy
- **BONE-TARGETED AGENTS**

Table I. Selected agents under development for castration-resistant prostate cancer.

Drug	Mechanism of action	Study design	FDA approval
Hormonal therapy			
Abiraterone	Inhibitor of cytochrome p17	Phase III	Yes (US FDA)
Other chemotherapy agents			
Cabazitaxel	Microtubule inhibitor	Phase III	Yes (US FDA)
Satraplatin	Binds to the DNA's cancer cells	Phase III	No
Vaccines			
Sipileucel	Elicit an immune response against cancer cells carrying the PAP antigen	Phase III	Yes (US FDA)
GVAX	Activate dendritic cells expressing GM-CSF	Phase II	-
PROSTVAC-VF	Stimulate T-cell responses expressing PSA sequence which alteration in HLA-A2 epitope	Phase III	No
Anti-apoptotic agents			
Oblimersen	bcl-2 antisense oligonucleotide	Phase II	-
Angiogenesis inhibitors			
Bevacizumab	Anti-VEGF inhibitor	Phase III	No
Aflibercept	Anti-VEGF inhibitor	Phase III	No
Tyrosine kinase inhibitors			
Dasatinib	Src-inhibitor	Phase III	No
Sorafenib	Inhibitor of Raf kinase, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-B, c-Kit, FLT-3, RET	Phase II	-
Sunitinib	Inhibitor of VEGFR 1-3, PDGFR α-β, c-Kit, FLT3, RET	Phase II	-
Vitamin D analogues			
Calcitriol	Inhibits proliferation and stimulates apoptosis activating VDR-RXR complex	Phase III	No
Endothelin receptor antagonists			
Atrasentan	Anti-ETA and ETB receptors	Phase III	No
Zibotentan	Anti-ETA receptors	Phase III	No

PDGFR, platelet-derived growth factor receptor; VDR, vitamin D receptor; RXR, retinoic acid X receptor.

BTT: NOVEL DRUG TARGETS (currently in clinical testing)

- Inhibitors of endothelin A receptor 1 (expressed by osteoclasts and osteoblasts)
- Inihibitors of cathepsin K (produced by osteoclasts and also by tumor cells)
- Drugs iterfering with the Wnt pathway/DKK1 (regulating also osteoblast function)
- Inhibitors of Src activity (Dasatinib)

Qualità Globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Nelle pazienti affetta da carcinoma mammario con metastasi ossee alla prima diagnosi il trattamento con denosumab può essere utilizzato **La valutazione complessiva della qualità delle evidenze ad oggi disponibili circa "l'efficacia di denosumab in pazienti affetta da carcinoma mammario con metastasi ossee alla prima diagnosi", la valutazione del rapporto tra i benefici ed i danni correlati e la formulazione della raccomandazione relativa al quesito posto, sono state analizzate secondo metodologia GRADE (vedere capitolo 12).*	**Positiva debole**

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
B	Il Denosumab come i Bisfosofnati può trovare impiego per il controllo del dolore in pazienti con metastasi ossee da carcinoma delle mammella e pare più efficace dell'acido zoledronico nel ritardare la progressione del dolore. Come per i BP non può sostituire i farmaci analgesici.	**Positiva debole**

Take home message: I bisfosfonati sono efficaci nel ridurre le complicanze scheletriche, nel ritardare il tempo di comparsa delle complicanze scheletriche e nel ridurre il dolore osseo in pazienti con metastasi ossee secondarie a carcinoma mammario. Il Denosumab è una valida alternativa all'uso dei bisfosfonati per quanto riguarda la prevenzione delle complicanze scheletriche. **Il Denosumab è superiore all'acido zoledronico in termini di ritardo della comparsa del primo e dei successivi SRE.**

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	L'uso dei bisfosfonati e di Denosumab è raccomandato in pazienti con metastasi ossee da carcinoma prostatico resistente alla castrazione, in quanto in grado di ritardare la comparsa di eventi scheletrici.	Positiva forte

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
B	Bisfosfonati e Denosumab possono trovare impiego per il controllo del dolore in pazienti con metastasi ossee da carcinoma prostatico resistente alla castrazione, ma non possono sostituire i farmaci analgesici.	Positiva debole

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
B	Il denosumab potrebbe essere impiegato nel paziente con metastasi ossee da carcinoma prostatico ormono-sensibile.	Positiva debole

Take home message: I bisfosfonati (ac. zoledronico) sono efficaci nel ridurre e ritardare le complicanze scheletriche di pazienti con metastasi ossee da carcinoma prostatico refrattario alla castrazione e possono essere efficaci nel controllare parzialmente il dolore osseo. Il Denosumab è una valida alternativa all'uso dei bisfosfonati per quanto riguarda la prevenzione delle complicanze scheletriche nel paziente con malattia refrattaria alla castrazione

Radiotherapy and Oncology 119 (2016) 194–201

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

The effect of radiotherapy, and radiotherapy combined with bisphosphonates or RANK ligand inhibitors on bone quality in bone metastases. A systematic review

Karlijn H.J. Groenen [a,*], Martin H. Pouw [b], Gerjon Hannink [a], Allard J.F. Hosman [b], Yvette M. van der Linden [c], Nico Verdonschot [a,d], Esther Tanck [a]

[a] Radboud university medical center, Radboud Institute for Health Sciences, Orthopaedic Research Laboratory, Nijmegen; [b] Radboud university medical center, Department of Orthopaedics, Nijmegen; [c] Leiden University Medical Center, Department of Radiotherapy, Leiden; and [d] University of Twente, Laboratory for Biomechanical Engineering, Enschede, The Netherlands

A B S T R A C T

Purpose: The role of radiotherapy in stabilizing metastatic bones is unclear. This systematic review assessed the effects of (1) radiotherapy, (2) radiotherapy combined with bisphosphonates, and (3) radiotherapy combined with RANK ligand (RANKL) inhibitors on bone quality and bone strength in bone metastases originating from solid tumors.

Methods: Pubmed, EMBASE and the Cochrane Library were searched. Any type of study design and type and dose of radiotherapy, bisphosphonates and RANKL inhibitors were allowed.

Results: 39 articles were identified. Animal studies showed that radiotherapy had similar effects on bone quality and strength as receiving no treatment, whereas adding bisphosphonates to radiotherapy restored bone quality and strength. In patient studies, bone density increased after radiotherapy and radiotherapy combined with bisphosphonates. However, due to the often non-optimal study design and study quality, it was unclear whether this increase could be attributed to these treatments. There was insufficient evidence to assess the additional effect of bisphosphonates or RANKL inhibitors.

Conclusion: Despite the clinical experience that radiotherapy is an effective treatment for bone metastases, there was no sufficient evidence for a positive effect on bone quality and fracture risk. Animal studies showed that adding bisphosphonates to radiotherapy restored bone quality and strength, whereas this was not proven in patients. There were no studies addressing the adjunct effect of RANKL inhibitors to radiotherapy. Although associated with several methodological, practical and ethical challenges, randomized controlled trials are needed.

Conclusion

Based on this systematic review, it can be concluded there was no sufficient evidence that radiotherapy had a positive effect on bone quality and fracture risk. In addition, animal studies showed that the addition of BPs to radiotherapy restored bone quality and bone strength to that of healthy bone, whereas this is not yet proven in patients. Furthermore, there were neither animal nor patient studies addressing the effect of RANKL inhibitors as an adjunct to radiotherapy on bone quality and bone strength.