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Review Article

Anti-RANKL therapy for bone tumours: Basic, pre-clinical and clinical evidences

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ABSTRACT

Bone remodelling is related to coordinated phases of bone resorption and bone apposition allowing the maintenance of bone integrity, the phosphocalcic homoeostasis all along the life and consequently the bone adaptation to mechanical constraints or/and to endocrine fluctuations. Unfortunately, bone is a frequent site of tumour development originated from bone cell lineages (primary bone tumours: bone sarcomas) or from nonosseous origins (bone metastases: carcinomas). These tumour cells disrupt the balance between osteoblast and osteoclast activities resulting in a disturbed bone remodelling weakening the bone tissue, in a strongly altered bone microenvironment and consequently facilitating the tumour growth. At the early stage of tumour development, osteoclast differentiation and recruitment of mature osteoclasts are strongly activated resulting in a strong bone matrix degradation and release of numerous growth factors initially stored into this organic/calcified matrix. In turn these soluble factors stimulate the proliferation of tumour cells and exacerbate their migration and their ability to initiate metastases. Because Receptor Activator of NFκB Ligand (RANKL) is absolutely required for in vivo osteoclastogenesis, its role in the bone tumour growth has been immediately pointed out and has consequently allowed the development of new targeted therapies of these malignant diseases. The present review summarises the role of RANKL in the bone tumour microenvironment, the most recent pre-clinical and clinical evidences of its targeting in bone metastases and bone sarcomas. The following sections position RANKL targeted therapy among the other anti-resorptive therapies available and underline the future directions which are currently under investigations.

1. Introduction

Bone is a very dynamic tissue resulting from coordinated phases of formation and resorption called bone remodelling. Additional to its role in phosphocalcic homoeostasis, bone remodelling process is necessary for bone growth, for renewal of cellular and extracellular matrix components to adapt bone organisation to the various biological and mechanical constraints [1–3]. Bone remodelling then leads to the renewal of around 10% of total bone mass each year in human. This metabolic process is based on a molecular crosstalk occurring between osteoblasts involved in bone apposition and osteoclasts specialized in bone resorption. Osteoclasts are multi-nucleated cells that originated from hematopoietic stem cells [4–6] whereas osteoblasts are derived from bone marrow mesenchymal stem cells [3,7,8]. Osteoblasts control osteoclast differentiation and activation through a very complex network of soluble factors which act in combination with various hormones produced by endocrine system even if contacts between both cell types also strongly contribute to full activation of osteoclasts [9,10]. Reciprocity between osteoblasts and osteoclasts can be observed as shown by bidirectional signalling limiting osteoclast activities and stimulating osteoblast differentiation [11].

Bone remodelling can be dysregulated by oncologic events originated from bone cells (primary bone tumours: osteosarcoma, chondrosarcoma, Ewing's sarcoma, etc.) or from nonosseous origins (bone metastases). Large series revealed that around 0.2% of all neoplasms are bone sarcomas and two new primary bone tumours arise per 100,000 persons a year [12]. Bone tissue is then the most frequent site of their first relapse and consequently, the incidence of bone metastases is relatively high and is dependent on the cancer cell types (i.e. in 70–80% of patients with breast or prostate cancer, in 40% of patients with lung metastases or with kidney cancer). Bone

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metastases are frequently associated with numerous clinical complications named skeletal-related events (SREs) and have a strong deleterious impact on the quality of life. SREs include pathological fractures or spinal cord compression and exacerbated bone pains. All bone tumours disrupt the equilibrium between bone apposition and bone resorption leading to the first stop of the tumour development to an osteolytic process followed or not by bone forming lesions. Soluble mediators stored initially into the bone matrix contribute in turn to stimulate the tumour growth and to maintain the vicious cycle between bone and tumour cells [13]. The loss of equilibrium between bone formation and degradation combined with an osteomimetism behaviour of cancer cells (cancer cells acquire bone-like properties) explains the diversity of histological features (osteolytic or bone forming tumours) of bone metastases [14]. Additionally, the modulation of bone micro-environment ("niche" concept) by cancer cells is beneficial for their proliferation and also contributes to the drug resistance patterns [15].

In the late 1990s, two research groups in Japan and in USA have identified a truncated TNF receptor-like molecule (named OPG for osteoprotegerin, TNFRSF11B) inducing marked osteopetrosis phenotype when overexpressed in transgenic mice [16,17]. One year later, RANKL (Receptor Activator of Nuclear Factor kB Ligand or TNFSF11) has been identified as a ligand for OPG [18,19]. In a few years, OPG/RANKL couple became the principal system regulating osteoclastogenesis and bone resorption and has impressively stimulated the development of OPG/RANKL targeting agents for the treatment of osteolytic disorders in oncologic contexts or not competing with bisphosphonates, a well admitted drug class for the treatment of bone loss [13,19–23].

In all bone cancers, a strong relationship between tumour cells and bone micro-environment has been then clearly established, facilitating the tumour development and/or the metastatic process. These specific communication pathways have strongly stimulated the research and development programs to design new drugs to treat oncologic bone diseases and have led specifically to the development of therapies targeting RANKL. The present review summarises the most recent progresses in the treatment of bone cancers based on RANKL targeting and underlines the future directions which are currently under pre-clinical investigations.

2. OPG, RANK and RANKL are key protagonists controlling osteoclast biology and bone remodelling

The critical function of OPG in osteoclastogenesis has been initially revealed by the osteopetrotic phenotype of mice overexpressing it [18,19]. In contrast, OPG deficient mice exhibit osteoporotic phenotype which is totally reversed by administration of recombinant OPG [24]. RANKL has been identified as the main ligand of OPG known to bind RANK (TNFRSF11A), a transmembrane receptor of the TNFR

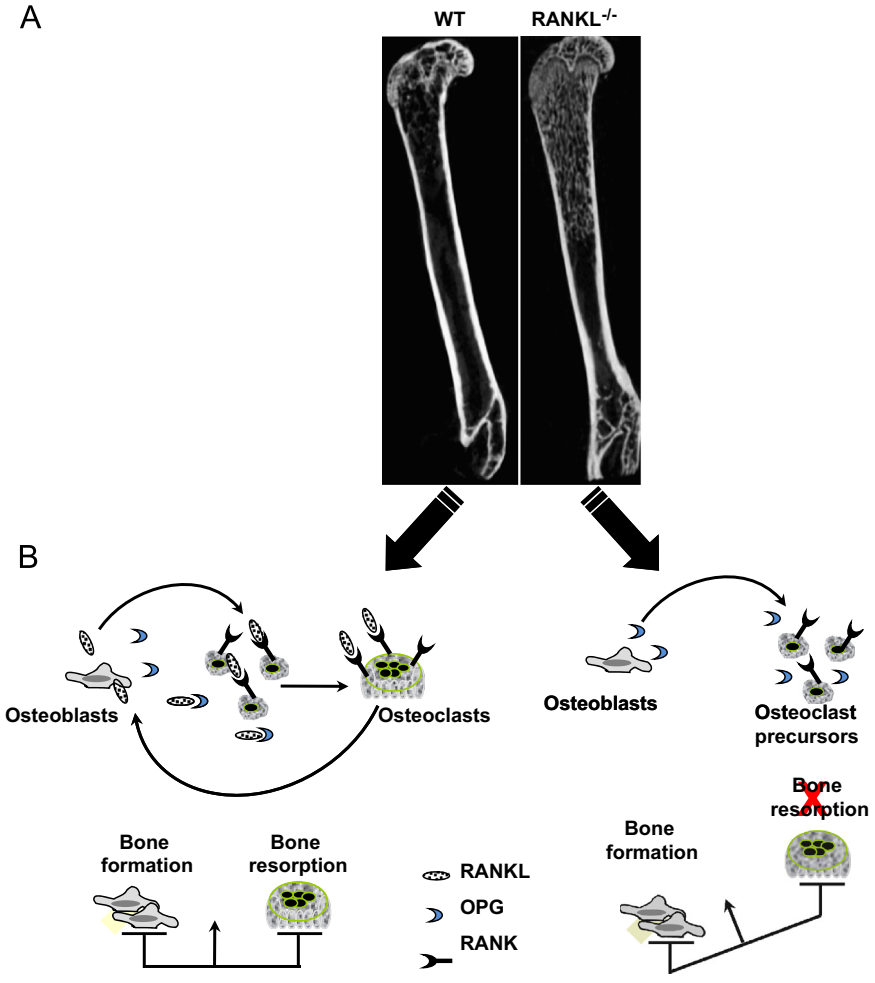


Fig. 1. *RANKL is absolutely required for osteoclast differentiation in vivo as revealed by the bone phenotype exhibited by RANKL knockout mice.* (A) Osteopetrotic phenotype exhibited by RANKL knockout ($RANKL^{-/-}$) compared to wild type (WT) C57BL6 mice analysed by μCT (skyscan 1076). (B) Osteoblasts produced RANKL (membrane and soluble forms) which binds to membrane RANK expressed by osteoclast precursors, OPG synthesised by osteoblasts acts as a decoy receptor, blocks the RANKL/RANK interactions and then inhibits bone resorption. The lack of RANKL results in a disturbed bone remodelling characterised by an excessive bone formation and a reduced bone resorption compared to the control mice.

superfamily [25]. RANKL transgenic mice and RANKL knockout mice are respectively osteoporotic and osteopetrotic (Fig. 1). In fact, membrane and soluble RANKL produced by osteoblasts interact with RANK expressed on monocyte lineage and osteoclast precursors, induces osteoclast differentiation and consequently activates bone resorption [23, Fig. 1]. Discovery of the RANK/RANKL signalling pathway through NFkB in the osteoclast has clearly provided new insights into the mechanisms of osteoclastogenesis and how hormonal networks impact bone remodelling [23–26]. OPG is the third protagonists and acts as a decoy receptor, binds to RANKL, inhibits RANK–RANKL interactions and in fine is a strong anti-resorptive agent. The balance between bone resorption and bone apposition consequently depends on the ratio OPG/RANKL (Fig. 1). For instance, the relative equilibrium between OPG and RANKL levels results in a stable bone mass, and in contrast for instance to RANKL knockout where bone remodelling is in favour of excessive bone formation due a marked reduction of osteoclastogenesis (Fig. 1). Similarly, a clear relationship has been established between RANKL/OPG ratio and the severity of osteolysis in oncologic diseases as in benign diseases [27]. It is now admitted that RANKL is absolutely required for osteoclastogenesis in vivo even if RANKL can be substituted in vitro by other ligands such as TNFα [28]. As the other TNF members, OPG, RANK and RANKL exhibit very complex stoichiometric characteristics. Indeed, OPG is a dimeric molecule, but it can even act as a monomer and RANL and RANK are homotrimeric complexes [20,28–30]. Additionally, OPG biology is more complex than those initially described and possesses numerous ligands such as other TNF Related Apoptosis Inducing Ligand (TRAIL) [31], proteoglycans [32] and glycosaminoglycans [33,34], von Willebrand factor [35], complex VIII [36] which modulate its own activity.

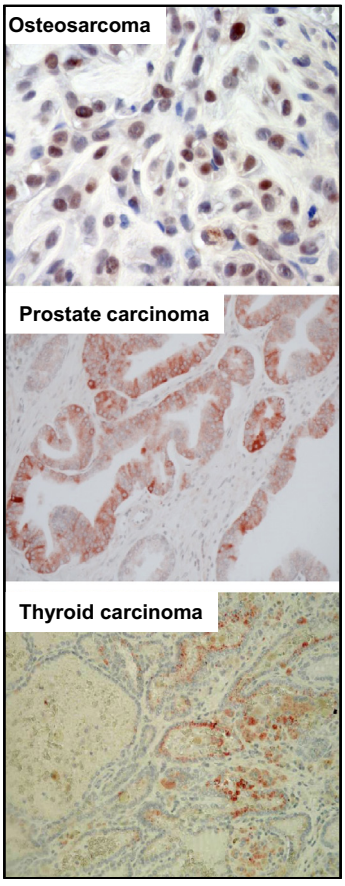
3. OPG, RANK and RANKL contribute to the vicious cycle established between tumour cells and bone microenvironment: evidences for sarcomas and carcinomas

In bone microenvironment, OPG/RANK/RANKL molecular triad is not solely expressed by bone cells. Whether OPG is considered as a ubiquitary receptor [20], membrane RANK is expressed by various tumour cells that originate from primary bone tumours or bone metastases, from mesenchymal and epithelial origin (Fig. 2A and B). A recent study showed that more than 80% of bone metastases from solid tumours are RANK positive as revealed by immunohistochemistry [42,43]. RANK is also expressed in more than 50% of human osteosarcoma specimens, with preferential expression in osteosarcomas that develop in pathological bone and are bad responders to chemotherapy [39]. These observations then identify tumour cells as potential RANKL targets. In addition to its expression by osteoblasts and bone marrow stromal cells, RANKL is produced similarly as RANK by numerous cancer cell types from various origins (Fig. 2C). RANKL expression is modulated by a lot of cytokines, hormones [20] and by hypoxia dysregulating bone remodelling, a common feature of malignant tumours [77]. Indeed, the invasion of bone tissue by a primary or metastatic tumour cell precociously affects the balance between bone resorption and bone formation. According to the tumour entities, tumour-derived factors (IGF, BMP, etc.) can stimulate osteoblast differentiation and activation and lead to tumour associated osteoblastic lesions (Fig. 3) or in contrast, RANKL released by tumour cells can activate osteoclastogenesis and the recruitment of mature osteoclasts resulting in osteolytic lesions. The co-existence of both phenomena leads to the formation of mixed osteoblastic/osteoclastic lesions. In

A

RANK-positive Tumors	References
Giant cell tumor	37
Osteosarcoma	38-40
Chondrosarcoma	41
Breast	42-45
Prostate	42, 45-48
Oral squamous	42, 49, 50
Thyroid	42, 51
Thymic	42
Eosophageal	42
Lung	42
Hepatic	42
Colorectal	42, 46
Bladder	42
Cervical	42
Endometrial	42
Renal	53
Melanoma	46, 54, 55
Hodgkin	56

B



C

RANKL-positive Tumors	References
Giant cell tumor	27
Osteosarcoma	27, 57
Chondrosarcoma	27
Breast	58-60
Prostate	46, 61-63
Oral squamous	64
Thyroid	51, 65
Lung	66
Hepatic	67
Renal	53
Lymphoma	68-70
Myeloma	71-75
Neuroblastoma	76

Fig. 2. *RANK is expressed by numerous tumour cell type.* (A) Main tumour cell types expressing RANK [37,41,49,55,56]; (B) RANK immunostaining on osteosarcoma [39], prostate carcinoma and thyroid carcinoma [51]. (C) RANKL is also expressed by cancer cells [27,46,53,58–79].

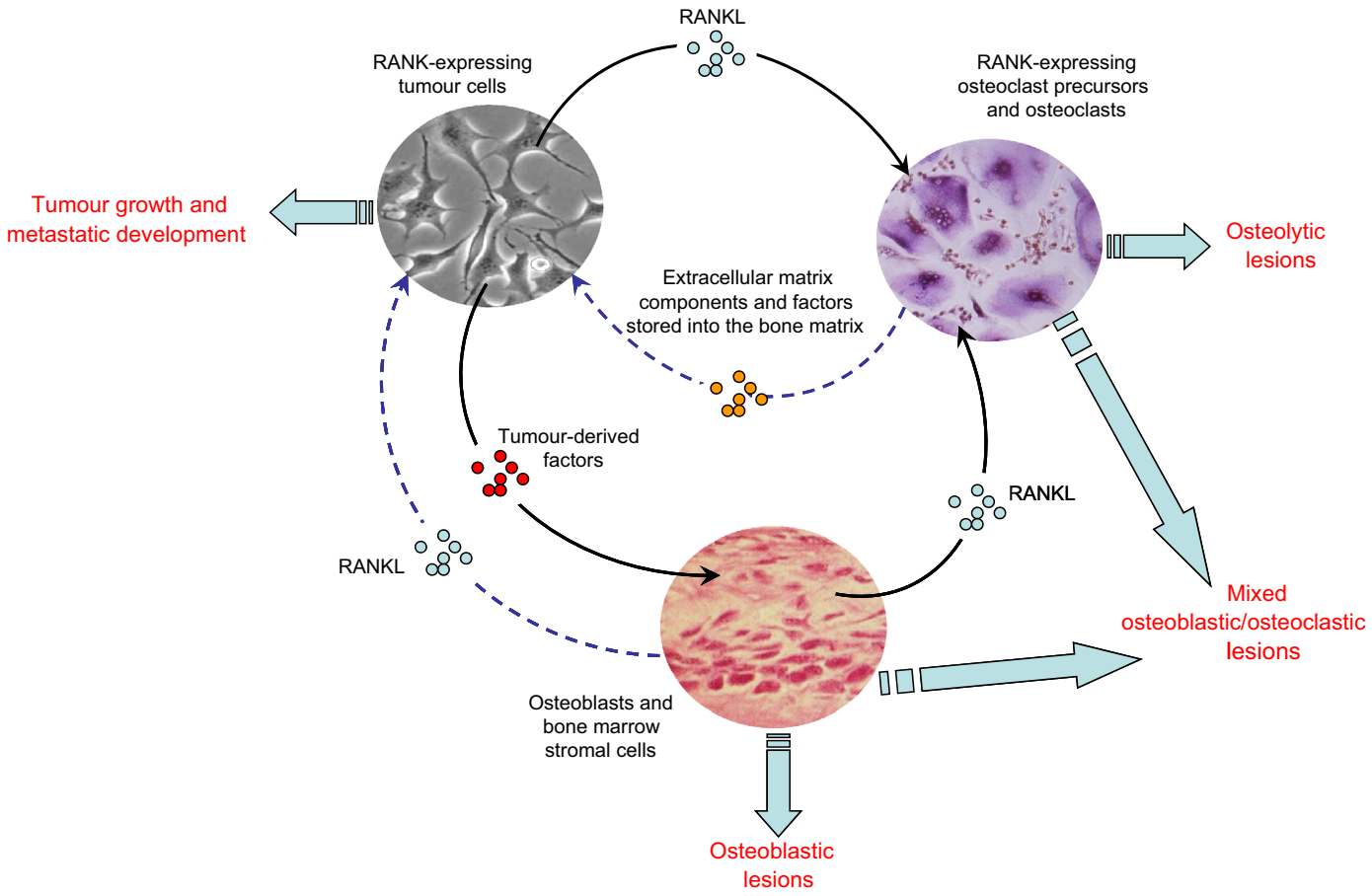


Fig. 3. *Direct and indirect role of RANKL in bone tumour development*. RANKL contributes to the development of bone tumours via the activation of osteoclastogenesis and bone resorption defining an osteoclast-dependent pathway. RANKL also can bind directly RANK-expressing tumour cells, stimulating epithelial mesenchymal transition, cell migration and then identifying an independent osteoclast. Tumour cells dysregulate the balance between osteoblasts and osteoclasts, resulting in osteolytic, osteoblastic or osteoblastic–osteoclastic mixed lesions according the tumour cell type.

turn, dysregulated bone cells-released extracellular matrix components and soluble mediators (TGFβ, etc.) are initially trapped in the bone matrix and stimulate proliferation of tumour cells and then the growth of tumour mass (Fig. 3). This mechanism is defined as the osteoclast-dependent role of RANK/RANKL axis in tumorigenesis. However, RANK/RANKL axis influences tumorigenesis through osteoclast-independent pathway (Fig. 3). RANKL produced by bone microenvironment constitutes a fertile soil for RANK-positive tumour cells. Initially proposed by Paget at the end of 1900 the concept of the seed and soil for primary and secondary bone tumours has been strengthened by the discovery of RANKL and RANKL partly explains why various tumours preferentially metastasise to bone. RANKL released by osteoblasts and bone marrow stromal cells creates a cytokine gradient between bone site and extraosseous sites and triggers the migration of RANK-positive tumours cells. Interestingly, numerous tumour cells expressed functional RANK as shown by the signal transduction (P-ERK1/2, P-P38, P-IkB, etc.) induced by RANKL [39,47,50]. The first evidence of this mechanism has been established by Jones et al. [45] and has been now described as prostate carcinoma [45,47,48], breast carcinoma [45], oral squamous carcinoma [50], lung cancer cells [52] and melanoma [45]. The implication of RANK/RANKL axis in tumour cell migration has been confirmed by exploration in human samples. Indeed, the levels of RANK expressed by primary tumour cells are directly related to the occurrence of bone metastases in solid tumours and more specifically in breast, prostate and melanoma [42–44]. Furthermore, RANK expression could be considered as an independent predictor of poor prognosis in breast cancer patients with bone metastasis in contrast with visceral metastasis for which no correlation has been shown [77]. Similarly, increased RANKL expression is related to the migration of renal carcinoma [53]. Whether the role of functional RANK expression has been clarified for carcinomas, its role in the pathogenesis of sarcomas is not fully understood. Indeed, it has been shown that osteosarcoma cells express the RANK protein [39]. RANK signalling, under the action of RANKL, results in the modulation of a panel of more than 70 specific genes demonstrating that osteosarcoma cells are therefore RANKL targets [40]. Wittrant et al. [38] showed that RANKL directly induces BMP-2 expression in RANK positive osteosarcoma cells and may contribute by this way to the osteoblastic lesions characteristic of osteosarcomas. More recently, Lee et al. observed that RANKL expression is correlated to clinical behaviour of patients suffering from high-grade osteosarcoma [57].

4. RANK/RANKL axis is involved in the tumorigenic process

RANK/RANKL axis is associated with the bone metastastic process, and as several arguments point out it is also involved in the tumorigenicity process itself. RANK/RANKL may participate in the initial oncogenic program as shown by high expression of RANK in melanoma-initiating cells compared to the other melanoma cells [54]. Epithelial mesenchymal transition (EMT) is the first step allowing the extravasation and migration of carcinoma cells and RANKL appears clearly involved in this process. Indeed, Yamada et al. show that RANKL promotes EMT and induces angiogenesis

independent of VEGF in a human head and neck squamous carinoma [78]. RANKL has also a strong impact on normal epithelial cells as shown by its effect on mammary gland development evidenced by a lactation defect in RANKL knockout mice [79,80]. In fact, RANKL promotes the proliferation and survival of mammary epithelial cells [79–82] and RANK expression increases during the gestation more specifically at ductal branch points [82]. More interestingly, whether RANKL or RANK overexpression in the mammary epithelial cells results in aberrant proliferation and hyperplasia of mammary glands, it directly correlates with preneoplasias and the development of spontaneous mammary tumours [83,84]. Several authors hypothesised that RANKL may act as a paracrine factor for mammary stem cells [85,86]. Consequently, blockade of RANKL significantly reduces the occurrence of mammary tumours [84]. Overall, these data give clear evidences that the RANK/RANKL axis contributes to the initial steps of tumorigenesis at least for mammary glands, to the dissemination process of carcinoma cells and to the establishment of bone metastases.

5. Therapies targeting RANK/RANKL axis for patients suffering from bone tumours: pre-clinical and clinical arguments

Given this context, targeting of RANKL signalling with its decoy receptor OPG or with a soluble form of its membranous receptor RANK (RANK-Fc) inhibits tumour associated osteolysis in several experimental bone tumour models, including rat and mouse primary bone tumours and bone metastases. Indeed, OPG and RANK-Fc administered by nonviral gene transfer or as recombinant molecules are effective in preventing the formation of osteolytic lesions associated with osteosarcoma development and in reducing the tumour incidence leading to a significant increase of animal survival [87,88]. Moreover, recent experiments demonstrated that RNA interference strategy targeting RANKL improved the tumour response to chemotherapy in a murine model of osteosarcoma [89]. Similarly, administration of recombinant OPG-Fc or RANK-Fc has been investigated in numerous murine models of bone metastases [20,23,79] and confirms that blockade of the RANK/RANKL axis is extremely efficient in pre-clinical assessment to prevent tumour-induced osteolysis, to reduce tumour growth and to improve the survival rate. According these pre-clinical proofs of concept, recombinant OPG (OPG-Fc) has been evaluated in postmenopausal [90] and in patients suffering from myeloma and osteolytic bone metastases (Table 1). Results demonstrated that OPG was well tolerated and demonstrated the efficacy of a single injection of OPG, which strongly reduced bone turnover for a sustained period and suppressed bone resorption as indicated by the decrease of bone resorption markers (urinary NTX/creatinine); these effects were comparable to those obtained with pamidronate. However, due to the risk of immune modulation of OPG through its binding to TRAIL [31] and other ligands [32–36], a fully human monoclonal antibody (IgG2) specifically targeting soluble and membrane RANKL has been developed [92,93]. Clinical data in osteoporotic patients revealed that denosumab was well tolerated with no related serious adverse events occurred and that a single-dose (0.01–3.0 mg/kg)

Table 1
Summary of the main clinical trials in oncology assessing anti-RANKL therapies.

Clinical trials drug assessed	Cancer	Number of patients included	Doses	References
Phase I OPG recombinant	Bone metastases (Breast) Myeloma	26 28	s.c. 0.1–3 mg/kg	[91]
Phase I, Denosumab	Bone metastases (Breast)	29	Denosumab s.c. 0.1–3 mg/Kg Pamidronate 90m g i.v.	[95]
	Myeloma	25		
Randomized, double blind	Bone metastases (excluding breast, prostate and myeloma)	886	Denosumab s.c. 120 mg monthly Zoledronate i.v. 4 mg monthly	[96]
Denosumab versus zoledronate		890		
Randomized, double blind	Bone metastases (Breast)	1026	Denosumab s.c. 120 mg monthly Zoledronate i.v. 4 mg monthly	[97]
Denosumab versus zoledronate		1020		
Phase II, Denosumab with and without bisphosphonate exposure	Bone metastases	366	Denosumab s.c. 60 or 180 mg every 12 weeks Denosumab s.c. 30, 120, or 180 mg every 4 weeks	[98–100]
Denosumab vs placebo and adjuvant aromatase inhibitors	Non-metastatic breast cancer	127 (treated) 125 (placebo)	Denosumab s.c. 60 mg every 6 weeks	[101, 102]
Phase II, randomized trial Denosumab after i.v. bisphosphonates	Bone metastases (prostate, breast cancers and other neoplasms)	111	Denosumab s.c. 180 mg every 4 or 12 weeks	[103]
Phase II Denosumab	Myeloma	96	Denosumab s.c.120 mg on days 1, 8, and 15 (loading doses) of cycle 1 (28 day), and then on study day 29 (day 1 of cycle 2) and on day 1 of every cycle (28 day) thereafter	[104]
Phase II, Randomized Denosumad after i.v. bisphosphonates	Bone metastases (Prostate)	111	Denosumab s.c. 180 mg every 4 or 12 weeks	[105]
Double-blind study Denosumad and androgen-deprivation	Prostate cancer	734 per group	Denosumab s.c. 60 mg every 6 months	[106]
Double-blind study Denosumab and androgen-deprivation	Prostate cancer	734 per group	Denosumab s.c. 60 mg every 6 months	[107]
Phase III Denosumab in castration-resistant patients	Prostate cancer	716 per group	Denosumab s.c. 120 mg every 4 weeks	[108]
Phase III, Denosumab versus zoledronate in castration-resistant patients	Prostate cancer	950 per group	Denosumab s.c. 120 mg or zoledronate 4 mg i.v. every 4 weeks	[109]
Phase II Denosumab	Giant cell tumours of bone	37	Denosumab s.c. 120 mg monthly	[110]

resulted in a dose-dependent sustained decrease from baseline in bone turnover [92,93]. This antibody, named denosumab, only recognises the human protein and its nonhuman-primate homologue and its administration in chimeric mice expressing murine/human leads to a strong inhibition of bone resorption concomitantly to an increase of the bone mineral density [94].

Numerous clinical trials (phase II and phase III) have been then designed to evaluate the efficacy of denosumab in oncology mainly in breast and prostate bone metastases (Table 1). These studies revealed that denosumab reduced significantly bone turnover markers similarly to osteoporotic patients. More specifically, it reduced levels of uNTX/Cr as well as serum TRAP5b thus showing a marked inhibition of osteoclastogenesis. According to the results obtained, the recommendations for the use of denosumab are 120 mg s.c. every 4 months in oncology. Using this dose, bone resorption markers are suppressed around 90% in most patients independent of the tumour types [103]. Various studies have been set up to compare denosumab versus bisphosphonate treatment mainly zoledronic acid [95–97,103,109]. Single dose of pamidronate for instance (90 mg i.v.) reduced in a similar intensity the levels of bone resorption markers but the effects of denosumab were more sustained [95]. Phase III study demonstrated that denosumab significantly delayed the time of first SRE (Skeletal Related Event) but also the risk of multiple SRE and whether zoledronic acid showed similar effects, statistical analyses are in favour of superiority for denosumab (Table 1). The time of disease progression and the overall survival rate were similar between anti-RANKL treatment and bisphosphonate. Zoledronic acid treatment requires a strict monitoring of kidney function due to its toxicity in contrast to denosumab even if a greater hypocalcemia requiring specific monitoring has been classically observed after denosumab treatment [111]. In addition to the phase acute phase reaction observed in patients after the first administration of zoledronic acid, osteonecrosis of the jaw occurred infrequently after long-term treatment by nitrogen-bisphosphonates, in around 2% of patients [97,108,109,112–115]. This incidence appears similar in bisphosphonate- and denosumab-treated patients. Consequently, the establishment of meticulous oral hygiene and surgical procedures prior to the administration of bisphosphonates and denosumab is the best method for preventing osteonecrosis of the jaw; prevention being better than treatment. In all studies, denosumab was well tolerated with the convenience of a subcutaneous administration and no requirement for renal monitoring. Overall, these clinical trials demonstrated that denosumab represents a potential treatment option economically viable for patients with bone metastases [116]. Very recently, a novel anti-RANKL antibodies derived from camelidae has been assessed in postmenopausal patients [117]. The results from this Phase I trial, including the one year follow-up information, indicate that ALX-0141 is well tolerated and can be administered safely over a wide range of doses. ALX-0141 exhibited a strong and sustained inhibitory effect on bone resorption markers.

6. The other anti-resorptive in therapies of bone cancer

Bisphosphonates have been used successfully for many years to treat the skeletal complications associated with the benign and malignant bone diseases [118–121]. Bisphosphonates became progressively a standard treatment for cancer-associated with hypercalcemia and to control metastatic bone pain. Bisphosphonates are chemical compounds based on a phosphorus–carbon–phosphorus template and are characterised by their strong affinity for bone hydroxyapatite crystals and their anti-resorptive potency. Three families of bisphosphonate have been produced: the first possesses simple substituents attached to the central carbon and inhibits weakly the bone resorption; the second family possesses an aliphatic side chain containing a single nitrogen atom and exerts a more potent anti-resorptive activity; the third generation contains a heterocyclic substituent with one or two nitrogen atoms and are powerful bone resorption inhibitors and anti-tumour agents [118,119]. The members of the first family which do not contain nitrogen atom are metabolised in cytotoxic analogues of ATP leading to cell death. Nitrogen-containing bisphosphonates inhibit the activity of two enzymes involved in the mevalonate pathway: farnesyl diphosphate synthase (FPP) and geranylgeranyl diphosphate synthase (GGPP). This inhibition results in osteoclast apoptosis by the strong reduction of the prenylation process, the loss of osteoclastic ruffled border and modifications of cell cytoplasmic actin ring

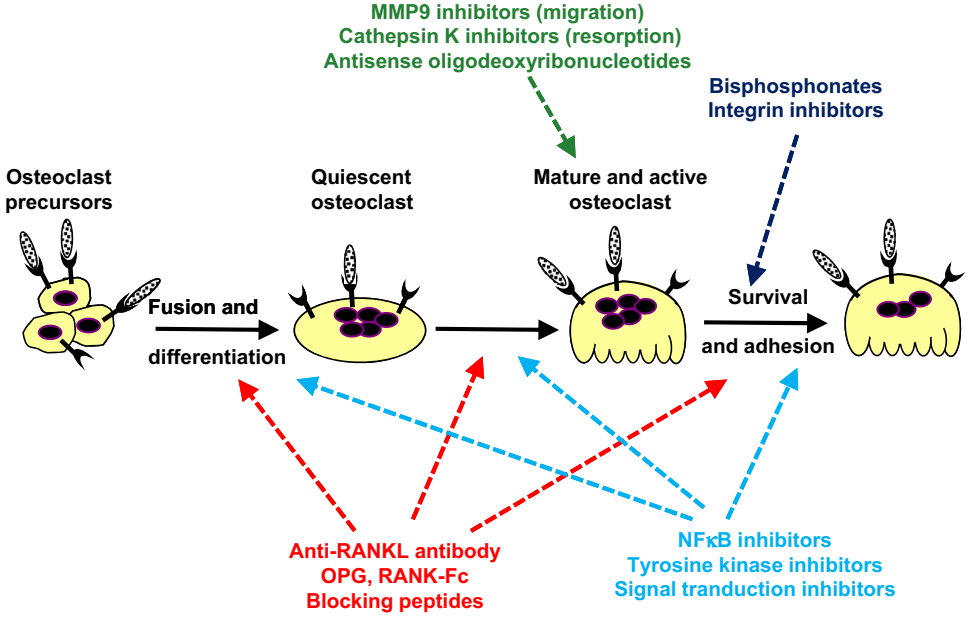


Fig. 4. *Therapeutic arsenals currently used or in development targeting osteoclast lineage to treat bone tumours.* These therapeutic approaches target osteoclasts, their differentiation and/or their activation by blocking RANKL binding to RANK, by signal transduction, cell adhesion and migration or enzymatic activities.

[118,119]. Additionally, nitrogen-containing bisphosphonates exert direct activities on tumour cells (breast, prostate, lung renal carcinoma, osteosarcoma, chondrosarcoma, etc.) through the inhibition of prenylation mechanim which induces tumour-cell apoptosis, inhibits cell proliferation, modulates tumour-cell adhesion and inhibits tumour-cell dissemination [118–124]. Thus, bisphosphonates inhibit the development of bone tumours through direct activity on tumour cells and indirect activity on osteoclasts. Pre-clinical studies revealed the therapeutic benefits of bisphosphonates for the treatments of primary bone tumours and bone metastases alone and in combination with chemotherapy or signalling pathway inhibitors [125–133]. Clinical trials have clearly confirmed their therapeutic interests (Table 1).

Since many decades, bone tumours have stimulated imagination of researchers and numerous therapeutic alternatives have been proposed [134,135, Fig. 4]. The better knowledge of OPG/RANK/RANKL system leads to the development of peptides mimicking OPG and blocking RANK–RANKL interactions [136–139]. Inhibitors of NF-KB signalling showed interesting anti-resorptive activities [140–143]. The targeting of integrins more specifically $\alpha v\beta 3$ strongly reduced the osteolytic process and the development of bone tumours [144–150]. Specific blockade of enzymatic activities has been envisaged with a great success. MMP9 involved in osteoclast migration and its targeting blocked by antisense oligodeoxyribonucleotide strongly affects osteoclast migration and resorption [151]. Cathepsin K, a key cysteine-proteinase related to osteolytic process [152,153], stimulates a huge enthusiasm in the world of bone research. Several companies have then developed chemical inhibitors of cathepsin K to treat malignant and non-malignant bone loss with interesting results [154–157]. Thus, forty-three women suffering from breast metastatic disease have been recently randomized in a double-blind study to evaluate the impact of oral cathepsin K inhibitors [odanacatib 5 mg daily for 4 weeks or 4 mg zoledronic acid i.v] on bone resorption markers [157]. Odanacatib appeared generally safe and well tolerated and has suppressed osteolytic markers similar to zoledronic acid after 4 weeks of treatment. These results strengthen the therapeutic interest of cathepsin K for oncologic bone loss.

7. Conclusions

Bone tissue massively attracts tumour cells where they find a favourable environment to maintain the stem cell dormancy and where they find a fertile ground for their development. This “fatal attraction” linked to the specific bone niche has boosted therapeutic innovations targeting the tumour cells and/or their microenvironment [158]. During the last past decade, RANK/RANKL axis emerged in bone biology as predominant protagonists of bone remodelling and as therapeutic targets of bone loss diseases. Better knowledge of RANK/RANKL biology will better define their relevance as biomarkers in bone oncology, and a complete cartography of RANK expression will be very useful to predict good responders to anti-RANKL therapies. Although anti-RANKL therapy progressively competes with approaches by bisphosphonates, a lot of prospect including signal transduction inhibitors, peptides or enzymatic inhibitors has been already identified and pre-clinical data as well as clinical trials allow personalised therapies in bone oncology.

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