Bone Effects of Anti-Cancer Treatments in 2024

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Abstract

Considerable progress has been made in the management of cancer patients in the last decade with the arrival of anti-cancer immunotherapies (immune checkpoint inhibitors) and targeted therapies. As a result, a broad spectrum of cancers, not just hormone-sensitive ones, have seen several patients achieve profound and prolonged remissions, or even cures. The management of medium- and long-term side-effects of treatment and quality of life of patients are essential considerations. This is especially true for bone, as bone fragility can lead to increased fractures and loss of autonomy, ultimately reducing the possibility of resuming physical activity. Physical activity is essential for lasting oncological remission and prevention of fatigue. While the issue of hormone therapies and their association with breast cancer has been recognized for some time, the situation is relatively new with regards to targeted therapies and immunotherapies. This is particularly challenging given the wide range of available targeted therapies and their application to numerous cancer types. This article provides a comprehensive review of the bone effects of the main anti-cancer therapies currently in use. The review goes beyond glucocorticoids and hormone therapies and discusses for each drug category what is known regarding cellular effects, BMD effects, and fracture incidence.

Keywords Cancer treatment induced bone loss (CTIBL) · Bone mineral densitometry · Side effects · Fracture risk · Osteoblast · Osteoclast

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Introduction

In the last decade, oncology and hematology fields underwent drastic improvements in cancer care with the onset of novel non-chemotherapy drugs. This has contributed to the transformation of cancer into a chronic disease in an increasing number of patients across all tumor types even in metastatic stages. Beyond survival itself, issues of long-term quality of life in cancer patients becomes increasingly important. In particular, the issue of long-term bone health was a quite common parameter in breast and prostate cancers patients on hormonal therapy. Nowadays this question may be expanded to many other cancer types including pediatric cancers [1–3].

Mobility is one of the major items involved in autonomy and quality of life in patients. This mobility relies on bone strength, muscle strength, healthy joints and movement coordination.

Bone strength comprises two components, bone mass and bone quality that may be impaired during cancer treatment. The paradigm of cancer treatment-induced bone loss (CTIBL) is the one observed during hormonal deprivation. Most upcoming drugs in oncology and hematology are not chemotherapy drugs but signaling pathway modulators in cancer cells. Most of bone effects of these long-term treatments remain unknown and to our knowledge, there is no recent review dealing with bone effects of these new drugs used in cancer management. Thus, there is a need to review in adults, the beneficial and adverse bone effects of newer drugs used in cancer management. In childhood cancer patients, the drugs used are associated with particular adverse effects due to their effects on growth and bone development of children, with subsequent consequences as they grow into adults [1, 2]. This manuscript will not consider bone fragility encountered in metastatic bone disease nor associated measures for bone health prevention [3].

Materials and Methods

We performed a systematic literature research. The search criteria were in vitro, in vivo and human studies of the effects of anti-cancer drugs on bone mineral density (BMD), fracture risk and bone cells (osteoblasts and osteoclasts) mainly in adults. Drugs included in the research were corticosteroids, hormone therapy drugs, proteasome inhibitors, tyrosine kinase inhibitors, anti-VEGF antibodies, immune checkpoint inhibitors, mTor inhibitors, anti-angiogenics and cytostatics. The keywords used on Pubmed/Medline were: ("Bone and Bones/drug effects" [Mesh] OR "Bone and Bones/pathology" [Mesh]

OR "Bone Remodeling/drug effects" [Mesh] OR "Osteoblasts" [Mesh]) AND ("Antineoplastic Agents/adverse effects" [Mesh] OR "Antineoplastic Agents/drug effects" [Mesh] OR "Antineoplastic Agents/drug therapy" [Mesh] OR "Antineoplastic Agent" [TiAb] OR "Anticancer Agent" [OR "Chemotherapy Agent" [TiAb] OR "Antitumor Agent" [TiAb] OR "Protein Kinase Inhibitors" [Mesh] OR "Protein Kinase Inhibitors" [TiAb] OR "Proteasome Inhibitors" [Mesh] OR "Proteasome Inhibitor*" [TiAb]). One article, not referenced on Pubmed/Medline but in Google Scholar, has also been selected. The last literature search has been performed on August 2023. Anti-resorptive agents and odanacatib have been excluded from the search since they have direct bone effects but they are not considered as anti-cancer drugs themselves. The bibliographic search identified cases, studies, reviews and meta-analyses without limitation. All non-English references were excluded. Figure 1.

Results

Glucocorticoid Therapy

In oncology, glucocorticoids (dexamethasone, prednisone, prednisolone) are used in high doses and as background, support or adjuvant treatment to chemotherapy either to potentiate the effects of anticancer drugs or to prevent adverse effects. Glucocorticoids are also known to induce effects on bone cells. Most BMD and fracture risk data have been obtained in non-cancer inflammatory chronic diseases. The use of glucocorticoids is different between oncology and inflammatory chronic diseases. Inflammatory chronic diseases require usually long term use with the search of the minimum effective dose and slow reduction in stages. By contrast, in oncology and hematology, glucocorticoids are prescribed on a high dose intermittent basis with various objectives during chemotherapy: anti-nausea, anti-allergic, anti-oedematous and anti-tumoral. Bone effects are more severe when glucocorticoid is prolonged and the daily dose is high, leading to a high cumulative dose. Thus, a dose of more than 7.5 mg/day – and for some even 5 mg/day- of oral prednisone or equivalent daily, exceeding 3 months of treatment is the commonly agreed upon threshold for considering glucocorticoids as risk factor for osteoporosis [4]. Nevertheless, it is a continuum and there may be individual variations but there is no trivial glucocorticoid dose for bone. Regular intermittent high dose regimens in oncology have been less studied. The worst case-scenario would probably be the long term weekly regimen of high dose dexamethasone in elderly with multiple myeloma that already have a severe bone fragilization. Another frequent side-effect is glucocorticoid-induced epiphyseal bone osteonecrosis [5].
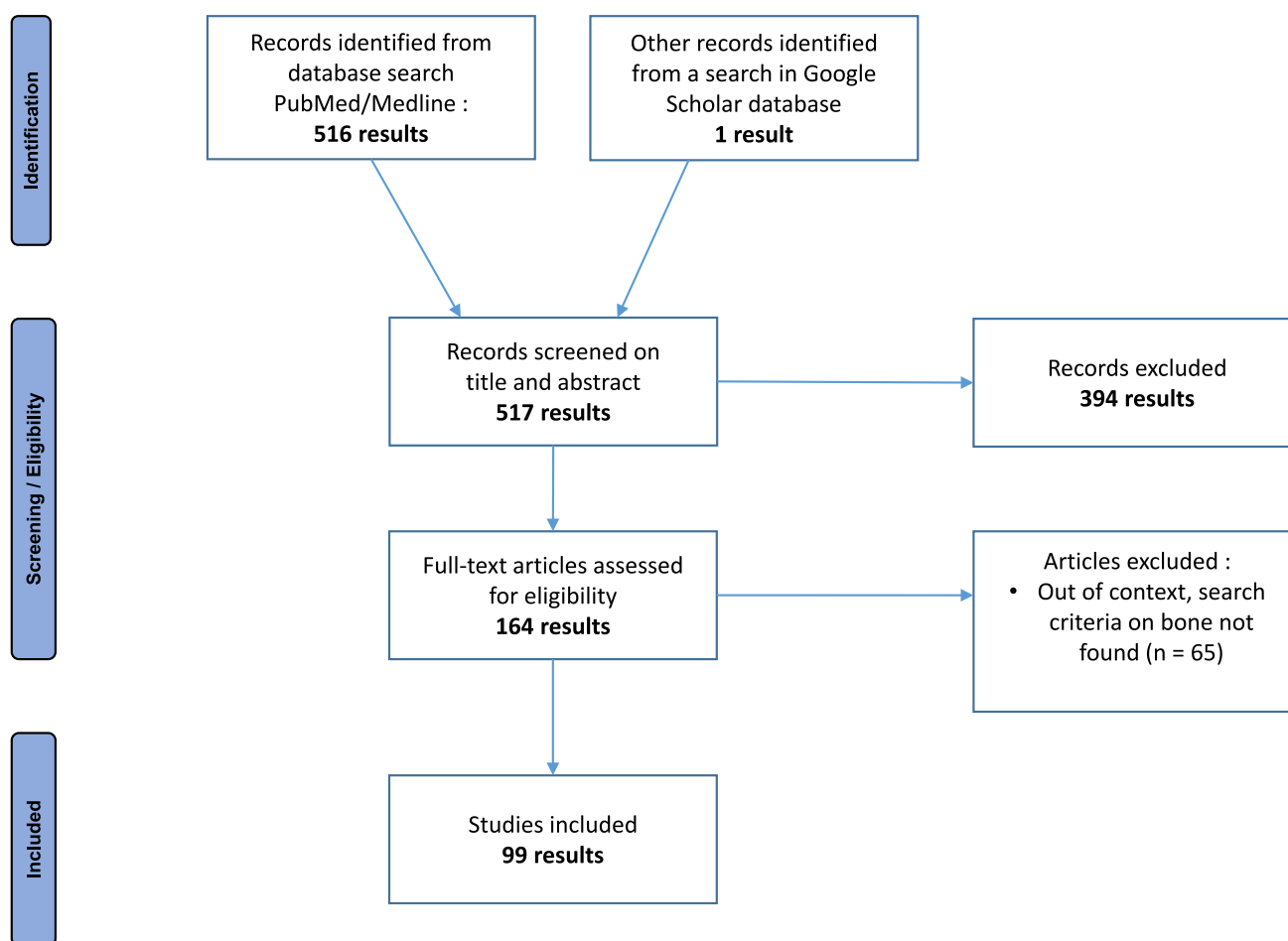
Fig. 1 PRISMA flow diagram for identification, screening/eligibility, and inclusion of the studies

Moreover, in cancer setting, glucocorticoids have also been involved as an additional risk factors of osteonecrosis of the jaw in bone metastatic patients treated with high dose intensity of antiresorptive agents. Altogether, there is interaction between underlying bone health, co-treatments and the glucocorticoids. Bone toxicity of glucocorticoids has been largely reviewed elsewhere [4, 6]. Key points are summarized below.

Risk of Fracture

Fracture risk increases early, as soon as 3–6 months after initiation [7]. Notably, the vertebral fracture risk is particularly increased [8]. Although fracture risk is related to the glucocorticoids dose, lower doses also have an effect (+20% at 5 mg/day compared to +60% at 20 mg/day) [7, 8].

For a similar BMD value, the relative risk of any fracture in patient on glucocorticoids ranged from 1.98 at the age of 50 years to 1.66 at the age of 85 years in comparison with untreated patients. For hip fracture, the risk is 4.42 and 2.48, respectively [9].

Fracture risk may be high, even if BMD loss is not severe. Physicians should be aware of this discrepancy and consider the cumulative doses, duration of exposure and the persisting drug exposure [1]. Cumulative doses are correlated with an increased risk of vertebral and non-vertebral fractures, particularly at the hip and forearm [7]. These effects appear to be reversible within one year of cessation of treatment, regardless of underlying pathology, age, or gender [4].

Effect on BMD

In adults, glucocorticoid therapy is associated with increased bone loss from the first few months and in a dose-dependent manner. Return to normal values upon glucocorticoid withdrawal is not universal, and usually, there is only a partial recovery. Nevertheless, with glucocorticoid therapy there is a discrepancy between the magnitude of BMD changes and the severity of bone strength impairment.

Adolescents may be subject to very high doses, ≥ 900 mg/m^2 prednisone equivalent. Compared with adults, adolescents are more likely not to achieve peak bone mass and to

develop bone loss due to the effect of glucocorticoids on bone formation and bone growth [10]. Nevertheless, some data from nephrology studies with such high doses are reassuring in showing that despite their shorter stature, children have no deficit in bone mineral content of the spine or whole body after adjustment for age, bone size, sex, and degree of maturation [11].

Of note, different types of glucocorticoids differ in potency and side effects. In particular dexamethasone, one of the most powerful glucocorticoid regularly used in multiple myeloma, is associated with a much higher risk of bone loss compared with other glucocorticoids throughout the duration of treatment [10, 12].

Effect on Bone Cells and Metabolism

Glucocorticoid has negative effects on osteoblast physiology. Indeed, on osteoblasts, the bone forming cells, dexamethasone inactivates the transcription factors Osterix and Runx2, involved in osteoblastic differentiation. At high doses, dexamethasone decreases regulatory pathways involved in proliferation and differentiation such as Wnt/β-catenin, BMP and Notch [10]. An indirect pathway has also been described through the stimulation of sclerostin that is secreted by osteocytes and which is one of the main physiological inhibitors of Wnt/β-catenin osteoblast anabolic pathway. Indeed, dexamethasone acts on sclerostin promotor that has several glucocorticoid response elements [13]. Thus, dexamethasone administration enhances sclerostin expression that inhibits Wnt pathway and mineralization. Interestingly, *sclerostin* deletion was associated with a marked loss of dexamethasone inhibition effect on bone formation suggesting that sclerostin was a key player in steroid-induced osteoporosis [13]. Furthermore, dexamethasone activates the TAK1 signaling pathway, which is involved in apoptotic events in both osteocytes and osteoblastic cells [14].

In addition, high doses of glucocorticoids increase the number and activity of osteoclasts, the bone resorbing cells, by increasing RANKL synthesis and suppressing osteoprotegerin (OPG) levels shifting the ratio in favor of osteoclastogenesis [10].

Glucocorticoid therapy impacts markers of bone turnover by markedly reducing bone formation markers (bone alkaline phosphatase (ALP), osteocalcin, P1NP) and enhancing bone resorption markers such as serum CTX. For example, dexamethasone suppresses ALP during the intensification period of treatment of acute lymphocytic leukemia. Next, ALP partially normalizes after discontinuation. In addition, the use of high-dose glucocorticoids during the induction and intensification phases is associated with an altered longitudinal bone growth. This growth impairment is significantly more severe with dexamethasone [10].

Hormone Therapy

Estradiol and, to a lesser extend, testosterone, are sex steroid hormones essential for bone development, growth and maintenance. These hormones naturally synthesized by the body, have numerous effects on various tissues. Some tumors expressing steroid hormone receptors are called hormone-sensitive since their growth is related to these hormones. In breast cancers, estrogen is a key factor for cancer cells. Estrogen is not only produced by ovaries but also in adipose tissue by peripheral conversion of androgens into estrogens (aromatization). This peripheral conversion persists after menopause. In addition, breast cancer cells are also able to synthesize estradiol, independent of circulating serum estradiol levels [15].

In men, testosterone and dihydrotestosterone are two major androgens, essential for normal prostate development and maintenance of physiological functions. Testicles, ovaries and adrenal glands are the organs that produce most of these androgens. Just like breast cancer, prostate tumor cells can synthesize the enzymes involved in androgen synthesis, allowing them to survive, grow and resist to hormones deprivation therapies.

Therefore, in hormonal sensitive breast and prostate cancers, the treatment goal is to fully block this synthesis by either surgical means, radiotherapy or pharmacological castration. Pharmacological drugs act either through a central or peripheral blockade. In central blockade, the hypothalamo-hypophyseal GnRH/LH-FSH axis is blocked. This can be achieved by GnRH antagonists or continuous GnRH agonists to induce a decrease in the production of pituitary FSH/LH resulting in a decrease in circulating estradiol/testosterone concentrations. Onset of action is rapid, within the first week (Table 1). GnRH agonists are used in premenopausal breast cancer and allow ovarian conservation, although the use of GnRH agonists sequentially or concurrently with chemotherapy shows no significant difference in all-cause survival [16, 17].

In men with prostate cancer, all-cause survival is improved by GnRH agonist therapy in locally advanced forms of prostate cancer [18]. In a meta-analysis, compared with agonists, GnRH antagonists are associated with improved all-cause mortality (RR: 0.48, 95% CI: 0.26–0.90, $p = 0.02$) but there is no difference on prostate-specific antigen (PSA) progression over a short follow-up period [19]. Peripheral blockade may be achieved by antagonizing androgen/estrogen receptors; or by blocking peripheral conversion (aromatase inhibitors).

GnRH Analogs

Risk of Fracture Between 1 and 5 years after cancer diagnosis, the risk of fracture is 19.4% under GnRH agonist

Table 1 Treatments used as hormonotherapy in cancer

Mechanism of action	Physiological consequences	Indication	Class		Molecule	Administration	Brand name	Comment
GnRH agonist	Indosable E and T	Breast and prostate			triptorelin	injection	Decapeptyl®Gonapeptyl®	T flair up effect at initiation
					leuprorelin	injection	Enantone®, Eligard®	T flair up effect at initiation
					goserelin	injection	Zoladex®	T flair up effect at initiation
GnRH antagonist	Indosable T	Prostate			degarelyx	injection	Firmagon®	
Estrogen inhibitor - Selective Estrogen Receptor Modulator (SERM)	E favorable actions on bone, cardiovascular system, brain and lipids	Breast			tamoxifen	oral	Nolvadex®	
	Inhibition of action of E on mammary gland, endometer, breast cancer				toremifen		Fareston®	
Estrogen inhibitor - Selective Estrogen Receptor Degrader (SERD)	Indosable E	Breast			elacestran	oral	Orserdu®	Indicated in case of ESR1 mutation
					fulvestrant	oral	Fazlodex®	
Aromatase inhibitor (AI)	Indosable E	Breast	steroidal		aromasine	oral	Exemestane®	
			non steroidal		letrozole	oral	Femara®	
					anastrozole	oral	Arimidex®	
Anti-androgen receptor	Indosable T	Prostate	1st generation	steroidal	cyproteron acetate	oral	Androcur®	in association with GnRH agonist
				non steroidal	bicalutamide	oral	Cazodex®	in association with GnRH agonist
					flutamide	oral	Prostadirex®	in association with GnRH agonist
					nulutamide	oral	Anandron®	in association with GnRH agonist
			2nd generation		enzalutamide	oral	Xtandi®	in association with GnRH agonist
					apalutamide	oral	Erleada®	in association with GnRH agonist
					darolutamide	oral	Nubeqa®	in association with GnRH agonist
Androgen synthesis inhibitor (CyP17) in adrenal gland	Indosable T	Prostate			abiraterone acetate	oral	Zytiga®	in association with prednisone 5mg

treatment and 12.6% without treatment and increases with length of treatment. This excess risk of fracture (RR = 1.21) is associated with increased mortality [20, 21]. In 218 men on GnRH agonists, the mean age of onset of fractures was 78 years with a mean time to onset of 28 months and consistently associated with a decrease in BMD [22]. The rate of musculoskeletal events including fracture risk is significantly higher with GnRH antagonists. One treatment strategy is to offer a GnRH antagonist for a short period of time

followed by a GnRH agonist to avoid a large increase in testosterone and the use of anti-androgens [19].

Effect on BMD Available data on BMD are more extensive in women with breast cancer than in men with prostate cancer. At low or high doses, GnRH antagonists are associated with a decrease in BMD as early as week 12 of treatment [23]. Figure 2.
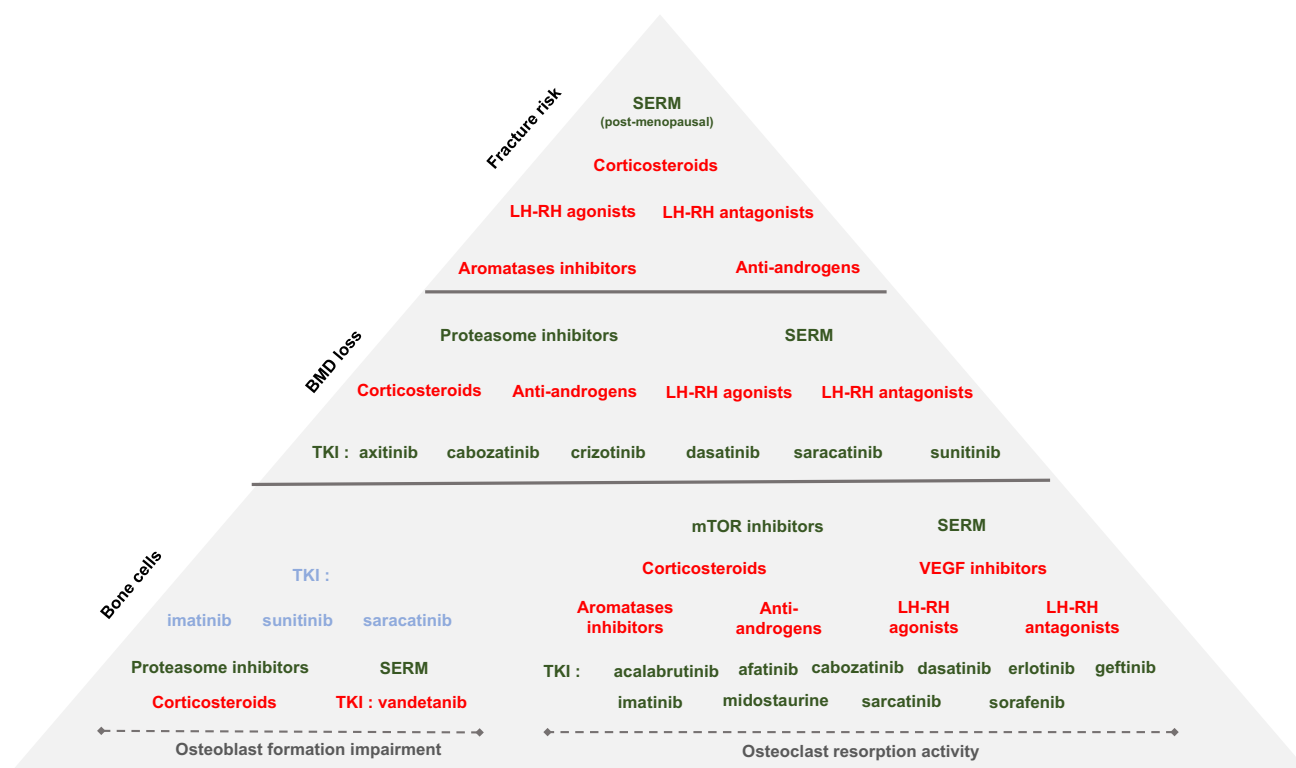
Fig. 2 Schematic representation of bone effects of anti-cancer drugs according to three levels of evidence: osteoblast and osteoclast, bone mineral density and fracture. BMD: Bone Mineral Density, SERM: Selective Estrogen Receptor Modulator, TKI:Tyrosine Kinase Inhibitor 5-FU: 5-fluorouracil and AI: aromatase inhibitor. In red: increase, in green: decrease and in blue: neutral

In premenopausal women on GnRH analogues monotherapy, a decrease in BMD of 8.2%/year of the lumbar spine is observed and 9.3%/year when combined with aromatase inhibitors (AIs) [24]. In men, bone loss is significant, especially during the first year of treatment. This trend is observed as long as the subject is on treatment but is even more severe in the first year of treatment when castration is complete and sudden. Upon discontinuation, an improvement in bone loss is observed but this is usually only partial [20, 25, 26]. The therapeutic strategy of intermittent administration reduces the risk of progressive bone loss [27]. In children, GnRH agonists induce bone loss in the trabecular and cortical bone as early as 6 months of age. Upon discontinuation, reversibility is only partial [1].

Effect on Bone Remodeling The hormonal deficit caused by GnRH analogues has an impact on bone remodeling [23]. This is more pronounced with GnRH agonists than with anti-androgens and involves an acceleration of bone remodeling as shown by urinary NTX or osteocalcin [27, 28]. With GnRH antagonists, a dose-dependent increase in serum CTX is observed within the first 6 months. GnRH agonists and antagonists also increase bone resorption and accelerate loss of bone strength [23].

Anti-Androgens

Blocking the hypothalamo-hypophyseal axis alone is generally not sufficient to completely block androgen production and induce complete castration in men. This is why a combination of anti-androgens is frequently used. There are steroidal anti-androgens (cyproterone acetate and abiraterone) and non-steroidal anti-androgens (enzalutamide, bicalutamide, apalutamide, flutamide, nilutamide and darolutamide). Abiraterone is a selective inhibitor of P450 C17, a key enzyme in the synthesis of testosterone, allowing the blockage of its production. It is indicated in hormone-sensitive and castration-resistant metastatic forms. Cyproterone is a competitive inhibitor of 5-dihydrotestosterone binding to its receptor. The other non-steroidal anti-androgens are androgen receptor inhibitors. Compared with bicalutamide, the other molecules have a higher affinity for their target without exerting an agonist effect. They are indicated in prostate cancer metastatic or non-metastatic forms, hormone-sensitive or not, depending on the molecule.

Risk of Fracture Incidence of fractures in patients on anti-androgens is 7.3% at 24 months (vs. 1.1% in control group) corresponding to a sevenfold higher incidence. The difference was already significant after 12 months of follow-up [18]. At 5 years, epidemiologic and retrospective studies indicate that approximately 20% of men receiving anti-androgens will have an osteoporotic fracture [29]. With new generation (or non-steroidal) anti-androgens, the occurrence of fractures is 6.3% (vs. 4.6% with placebo) with apalutamide [30], 6.5% (vs 4.2% with placebo) with enzalutamide [31] and 4.2% (vs. 3.6% with placebo, ns) with darolutamide [32, 33]. Fracture risk has been computed in a meta-analysis of 519,168 men (16 studies) by Wu et al. They report that androgen deprivation use is associated with an increased fracture risk of nearly 40% (OR, 1.39; 95% CI, 1.26–1.52). OR for fracture requiring hospitalization is also increased (OR, 1.55; 95% CI, 1.29–1.88) [34].

Effect on BMD The extent of bone loss depends on the duration of treatment and whether the anti-androgens are administered continuously or discontinuously. Decrease in BMD is rapid, usually observed as early as 9 to 12 months of treatment [35, 36]. For example, at 1 year, a decrease in BMD on the spine between 2% and 8% and on the femoral neck between 1.8% and 6.5% is observed. Beyond 2 years of treatment, BMD continues to decrease under treatment [29]. The incidence of osteoporosis (T-score ≤ -2.5) is highest in the distal forearm and femoral neck [37]. Recovery is dependent on testosterone levels at cessation of treatment. Other studies, on the other hand, have shown the protective role of bicalutamide on BMD [38]. Compared with untreated men, postmenopausal women and women treated with aromatase inhibitors, bone loss is greater in men treated with anti-androgens.

Effect on Bone Cells and Remodeling Urinary markers of bone turnover are significantly increased by anti-androgens [37]. In vitro, inhibition of osteoclastogenesis with down-regulation of osteoclastic markers (TRAP, κ-cathepsin, metalloproteinase-9) and up-regulation of osteoblastic markers (ALP, osteocalcin) are observed. In vitro and in vivo, enzalutamide decreases the expression of TGFBR2 on the osteoblast, which is responsible for the development of bone lesions [39]. The effects on bone of apalutamide, darolutamide, flutamide and nilutamide have not yet been studied.

Anti-Estrogens

Anti-estrogens bind to estrogen receptors, blocking the binding of natural estrogen to its receptor. There are 2 types of anti-estrogens: "Selective Estrogen Receptor Modulators" (SERM) that are competitive inhibitors of estradiol binding to the receptor (tamoxifen, toremifene and raloxifene) and "Selective Estrogen Receptor Degraders" (SERD) that bind to the ER and cause the ER to be degraded and thus down-regulated (fulvestrant).

Risk of Fracture Over a long-term period, a 32% reduction in the risk of fracture over 7 years was observed with tamoxifen (RR = 0.68; 95%CI 0.51–0.92) and 50% over 2 years with

toremifene. This effect is observed at low doses at 20 mg/day [40–42]. Interestingly, a differential effect seems to exist between premenopausal and postmenopausal breast cancer women. In a case control study ($n = 5520$ per group), there is an increased fracture risk in tamoxifen treated premenopausal women vs. untreated women (6.3% vs 3.6%; $p < 0.001$). This is not observed in the postmenopausal women (10.1% vs 9.3%; ns) [43]. Indeed this is due to a differential effect of SERM according to estrogen impregnation. In low estrogen impregnation (post-menopausal), SERM have an agonist effect on bone while in regular estrogen impregnation (pre-menopausal), SERM have a competitive action with estrogen that decreases bone mass [43]. Fracture risk on fulvestrant has not been studied.

Effect on BMD Tamoxifen and toremifene preserve or even increase BMD of the lumbar spine, hip, and femoral neck at 2 years in postmenopausal women with breast cancer [42]. In 140 postmenopausal women, tamoxifen increased BMD by 0.6% vs. placebo group (1% loss) [44]. In premenopausal women, a decrease in BMD of 1.4% was observed at 3 years vs. a gain of 0.2% in the placebo group. This was also reported by Powles et al. with a mean annual loss over 3 years of 1.4%/year at lumbar spine vs. a gain of 0.3%/year in placebo in premenopausal women whereas a significant gain was observed in postmenopausal women (1.2%/year) on tamoxifen [45]. As for fracture risk, the discrepancy between pre- and post-menopausal women is explained by the SERM mechanism of action in presence (premenopausal) or in absence (postmenopausal) of estradiol. In absence of estradiol, SERM acts as an agonist on bone and thus prevents bone loss. By contrast in premenopausal situation, since SERM is less potent than estradiol, it acts as a partial antagonist competitor of estradiol leading to bone loss [24, 46]. In combination with gosereline, the decrease at 2 years in total BMD is lower compared with goseroline alone (-5% goseroline alone vs. -1.4% goseroline + tamoxifen) [47]. The effect of BMD on fulvestrant has not been studied.

Effect on Bone Remodeling Alone or in combination with AIs, tamoxifen decreases bone turnover [42, 48]. Urinary NTX decreases rapidly in the first few months and then gradually over the course of treatment. Bone turnover markers are significantly lower at 1 and 2 years of treatment compared to AIs. Bone ALPs are significantly lower at 2 years of treatment vs. on AI [49].

Aromatase Inhibitors

Aromatase is an enzyme involved in the conversion of androgens to estrogens in postmenopausal women. Aromatase inhibitors block the activity of this enzyme, preventing the binding of estrogens to the receptors of tumor cells and consequently their growth. The most commonly used are exemestane (steroidal), anastrozole and letrozole (non-steroidal).

Risk of Fracture Third generation AIs are associated with an increased risk of osteoporosis and fractures in breast cancer studies in comparison with SERMs or placebo [50–55]. For example, in the BIG 1–98, fracture incidence on letrozole was significantly higher on AI than tamoxifen (8.6% vs 5.8%, respectively; $p = < 0.001$) [56]. This was the same with the ABCSG study [54, 57]. The difference is significant even if the protocol starts with tamoxifene for 2 or 3 years before introducing the exemestane [58]. In RCT, the gap with AI seems to be higher with tamoxifen, that has a small protective bone effect, than with placebo [59]. In real life, based on Swedish National registers, Colzani et al. also highlighted a trend of excess risk of fractures under AI in comparison with tamoxifen (HR = 1.48; 95%CI 0.98–2.22) [60].

Interestingly, long term follow-up at 100 months of the ATAC study confirms this higher fracture rate with anastrozole compared with tamoxifen (2.93% vs. 1.9%; p < 0.0001) during the time on therapy [61]. Nevertheless, upon treatment discontinuation, the increased fracture risk is not persistent over the long term suggesting bone loss remains partially reversible [61–63].

A meta-analysis has been performed by Goldvaser et al. including 16,349 postmenopausal women from 7 trials [64]. The odds ratio for bone fractures is OR = 1.34; 95%CI 1.16–1.55. There is no association between relative OR and median age at random assignment, median duration of follow-up, or the proportion of women previously treated with tamoxifen or chemotherapy. Absolute fracture risk is increased on AI (6.3%) with an absolute difference of + 1.39%.

Effect on BMD Bone loss is evidenced in the spine and hip higher on AI compared with SERMs [42, 52, 65, 66]. AI bone loss is related to the collapsed residual estradiol levels [67]. Therefore, these effects are also most pronounced in the 10 years after the onset of menopause [26, 42, 63, 67, 68]. All AIs cause a comparable, rather constant decrease of BMD at all sites; likewise, fracture risk is equivalently increased as shown in MA 27 study [69]. Direct comparisons of BMD loss between AIs are scarce but there is no significant difference between anastrozole and exemestane on BMD at 2 years [49, 63]. Nevertheless, in animals, some studies report a difference between AI class with non-steroidal AIs inducing less bone loss in comparison with steroidal AIs due to the mechanism of action [70]. Interestingly, in the long-term bone loss analysis of anastrozole vs. tamoxifen, a partial regression was observed upon treatment discontinuation [26].

In addition to aBMD, the MAP.3 study has performed high-resolution peripheral quantitative CT at the distal radius and tibia in non-osteoporotic post-menopausal women receiving exemestane vs. placebo. After 2 years on exemestane, total volumetric BMD declines (-6.1% vs. -1.8% and -5.0% vs. -1.3% at the radius and the tibia, respectively). Cortical thickness is also altered (-7.9% vs -1.1% and -7.6% vs -0.7% at the radius and the tibia, respectively) [71].

Effects on Bone Remodeling AIs are associated with elevated markers of bone resorption and increased bone turnover [42, 49]. These markers (urinary NTX, bone ALP) increase early in treatment and then levels stabilize [49]. Upon discontinuation and concomitant with improved BMD, bone remodeling decreases, mineralization and matrix volume increase [26].

Preventing Hormonal Therapy Induced Bone Loss

Several studies have demonstrated the efficacy of oral bisphosphonates to prevent hormonal therapy induced bone loss particularly with aromatase inhibitors in breast cancer as summarized by Rizzoli et al. in a systematic review [72] and the meta-analysis of Su [73]. Zoledronic acid (ZA), an intravenous bisphosphonate, has also demonstrated its efficacy versus placebo to prevent bone loss in premenopausal women with studies like ProBONE II (ZA 4 mg/3 months regimen) and ABCSG 12 (ZA 4 mg/6 months regimen) [74, 75]. In postmenopausal women, strategy studies testing immediate versus delayed ZA also demonstrated the impact of an early ZA treatment to prevent induced bone loss, particularly in recently post-menopausal women (ZO-FAST, Z-FAST) [76, 77]. Denosumab (60 mg/6 months) has been also evaluated and demonstrated a significant gain of BMD in post-menopausal women treated by aromatase inhibitors [78–80]. Moreover, a significant fracture risk reduction has been observed in ABCSG 18 [80]. In addition, a significant antitumor benefit (recurrence, distant recurrence, bone recurrence and breast cancer mortality) has been demonstrated with adjuvant bisphosphonates in postmenopausal women with breast cancer [81]. Prevention of castration induced bone loss in men suffering from hormone sensitive prostate cancer has also been demonstrated for ZA [82–85] and oral bisphosphonates [86–88]. Altogether these results contributed to the current ESMO guidelines to prevent hormonal therapy induced bone loss [89].

Proteasome Inhibitors (PIs)

Ubiquitin–proteasome system has an essential role in controlling cell division, signal transduction, apoptosis and protein quality enhancement. The targets of proteasome-dependent proteolysis may be various oncogenes/antioncogenes such as p21 and p27 proteins, tumor suppressor proteins p53, RB (retinoblastoma protein), BCL-2, MYC, FOS and JUN family of oncogenes, E2A, E2F, STAT transcription factors and NF-kB transcription factor inhibitors. The ultimate goal of PIs (carfilzomib, bortezomib and ixazomib) is to induce tumor cell death and improve survival in myeloma [90], mantle cell lymphoma [91]. In terms of efficacy, PIs are comparable [92].

Risk of Fracture

Fracture risk of PIs has not been studied in humans. In mice, bortezomib promotes fracture healing in young mice and the combination with bisphosphonates promotes fracture healing in old mice [93].

Effect on BMD

A significant increase in BMD is detected at axial sites under bortezomib and with an increase in trabecular bone volume under ixazomib [94, 95].

Effect on Bone Cells

On the osteoblast, PIs stimulate osteoblastic differentiation without impacting the number of osteoblastic progenitors and the viability of mature osteoblasts [94–96]. This activation is enabled by positive modulation of proteolytic degradation of Runx2/Cbfa1 transcription factors, through inhibition of *Dkk-1* gene expression but without impacting the canonical signaling pathway. Bortezomib also significantly increases the expression of *DLX-5*, a transcription factor involved in osteoblast development [94]. Finally, ixazomib stimulates osteoblastogenesis from mesenchymal stem cells as it increases the expression level of BMP-2 mRNA [96].

PIs promote bone formation through activation of β-catenin signaling pathways and induction of TCF transcriptional activity on osteoblastic and stromal cells [94]. The level of bone formation markers correlates with treatment response [95]. In vitro, bortezomib induces a moderate though not significant increase in ALP after 4, 7 and 14 days [94].

On osteoclasts, PIs are potent osteoclastogenesis inhibitors by intervening at the early and late stages of osteoclast differentiation without affecting precursor viability. This inhibition is dose-dependent and enabled by modulation of the signaling pathway involving p38, RANK-induced NF-κB signaling pathways, and transcriptional factor AP-1 [94–96]. MIP-1α is a key component of osteoclastogenesis, expressed by osteoclasts and myeloma cells. Their concentration correlates with the presence of osteolytic lesions. Bortezomib also inhibits MIP-1α, a key component of osteoclastogenesis [94].

Tyrosine Kinase Inhibitors (TKIs)

Membrane receptors with tyrosine kinase activity and cytoplasmic tyrosine kinases are important therapeutic targets in cancer treatment, due to their involvement in cell proliferation and survival [97–99]. TKI can inhibit one or several tyrosine kinases leading to different inhibition profiles and have become essential tools for eligible tumors and allow to introduce personalize medicine for patients (Supplemental Table 1).

Effect on BMD and Fracture

Available data on the bone effect of TKIs on BMD and bone cells are limited and summarized in Table 2. There are no data in humans either on BMD or on fragility fracture risk. In mice, data are very scarce. A group of reported TKIs increase BMD: axitinib, cabozantinib, crizotinib, dasatinib, saracatinib, nilotinib. This was not the case for sunitinib, which decreases BMD [100, 101].

Globally, TKI treatments are well tolerated. The most frequent adverse events are digestive or hematological. Some bone adverse effects have been also described: periosteal reaction under pazopanib, osteonecrosis under sorafenib and sunitinib, secondary hyperparathyroidism under nilotinib, sunitinib and imatinib [102–108]. These adverse effects indicate that TKIs exert an effect on bone metabolism probably depending on their molecular target.

Effect on Bone Cells

Most TKIs inhibit osteoclastogenesis [100, 105, 109, 110]. This is not the case for afatinib [111]. Bosutinib, as a specific Src kinase inhibitor, has an action on osteoclast and osteoblast function. Interestingly, the c-kit inhibitory effect of bosutinib, is weak, making it a good alternative in children [112]. Bone resorption markers are also affected but differently in adults and children [100]. A decrease in markers in adults up to more than 50% in men has been noticed. Conversely, an increase in CTX in children on imatinib has been reported [113]. This inhibition is reversible or partially reversible upon discontinuation [100].

On the osteoblast, platelet-derived growth factor receptor (PDGFR) inhibition contributes to block osteoblast differentiation, proliferation, and mitogenesis in vitro [100, 101]. But in vivo, a large variability in results has been observed depending on the TKI. Saracatinib and bosutinib have no effect on bone formation markers [100, 112]. Even though a transient increase in Runx2 and osteocalcin at 3 months is observed on imatinib followed by a non-significant decrease at 18 months, this is dependent on the stage of osteoblast maturation [100, 105]. With nilotinib, the effect on osteoblasts may be neutral and accounts for the

Table 2 Available data on bone tyrosine kinase inhibitory effects on bone mineral density and bone cells

| Drugs	BMD	Bone cells
Abemaciclib	uk	uk
Acalabrutinib	uk	OC: inh
Afatinib	uk	OC: inh
Alectinib	uk	uk
Alpelisib	uk	uk
Axitinib	+ (mice)	uk
Bosutinib	uk	0
Brigatinib	uk	uk
Cabozantinib	+	OC: inh
Ceritinib	uk	uk
Cobimetinib	uk	uk
Crizotinib	+	uk
Dabrafenib	uk	uk
Dasatinib	+ (mice)	OC: inh
Entrectinib	uk	uk
Erdafitinib	uk	uk
Erlotinib	uk	OC: inh
Gefitinib	uk	OC: inh
Ibrutinib	uk	uk
Imatinib	±	OB: 0 OC: inh
Lapatinib	uk	OC: inh
Larotrectinib	uk	uk
Lenvatinib	uk	uk
Lorlatinib	uk	uk
Midostaurine	uk	OC: inh (mice)
Nilotinib	uk	OB: inh OC: inh
Osimertinib	uk	uk
Palbociclib	uk	uk
Pazopanib	uk	uk
Ponatinib	uk	uk
Pralsetinib	uk	uk
Regorafenib	uk	uk
Ribociclib	uk	uk
Ripretinib	uk	uk
Saracatinib	+	OB: 0 OC: inh
Sorafenib	uk	OC: inh
Sunitinib	- (mice)	OB: 0 OC: inh
Trametinib	uk	uk
Vandetanib	uk	OB: inh
Vemurafenib	uk	uk

BMD Bone mineral density, *OC* Osteoclastogenesis, *OB* osteoblast formation activity, *uk* Unknown, *inh* Inhibition, + indicates an increase of BMD,—indicates a decrease of BMD and 0 indicates an absence of effect

balance between c-abl and PDGFR activity [101]. Lastly, osteocalcin was shown decreased on vandetanib treatment [100]. These effects on bone remodeling can cause disproportionate effect or even destruction of cortical bone, bone demineralization, ischemia or increased trabecular volume or even growth retardation in children [100, 113–115]. The effects of each TKI on osteoclastogenesis and osteoblastogenesis are summarized in Table 2 and Fig. 3 and 4.

Immune Checkpoint Inhibitors

Immune check point inhibitors aim at blocking the negative signal that prevents immune T-cells to activate and kill tumor cells. The use of this strategy started in the melanoma and lung cancer fields and is now widely proposed in adjuvant or in metastatic setting.

In a recent study, following the report of Moseley [116], Ye et al. reported a 20% increase of fracture incidence in patients on immune checkpoint inhibitors [117]. A possible
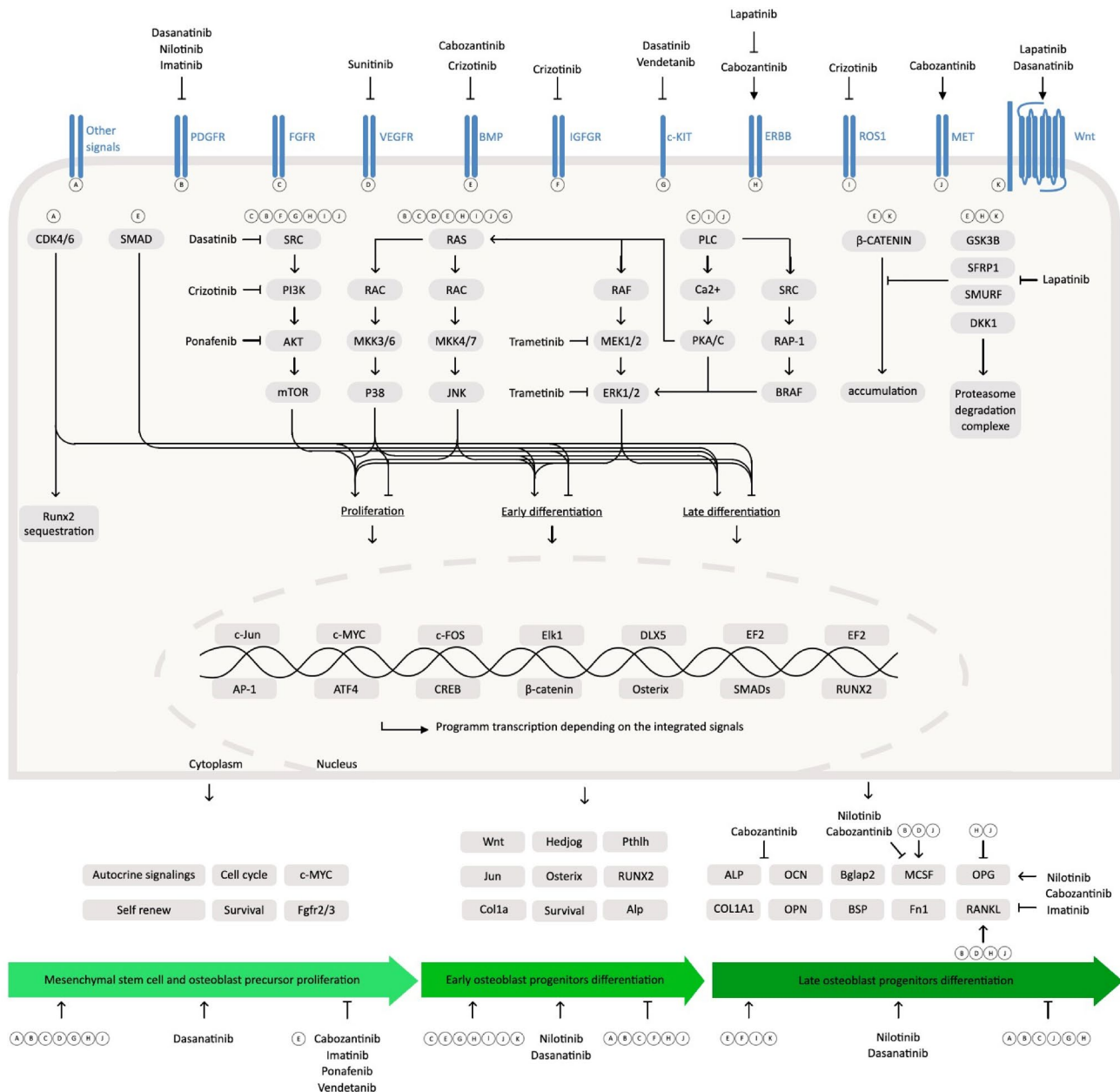
Fig. 3 Integration of tyrosine kinase inhibitor (TKI) pathways in osteoblast signaling. Each membrane receptor may act on one or several intracellular pathway(s) resulting on biological effect(s) on osteoblast (OB) precursor proliferation, early and/or late OB differentiation. Intracellularly, TKI act mainly on PI3K/AKT/mTOR and MEK/ERK pathways
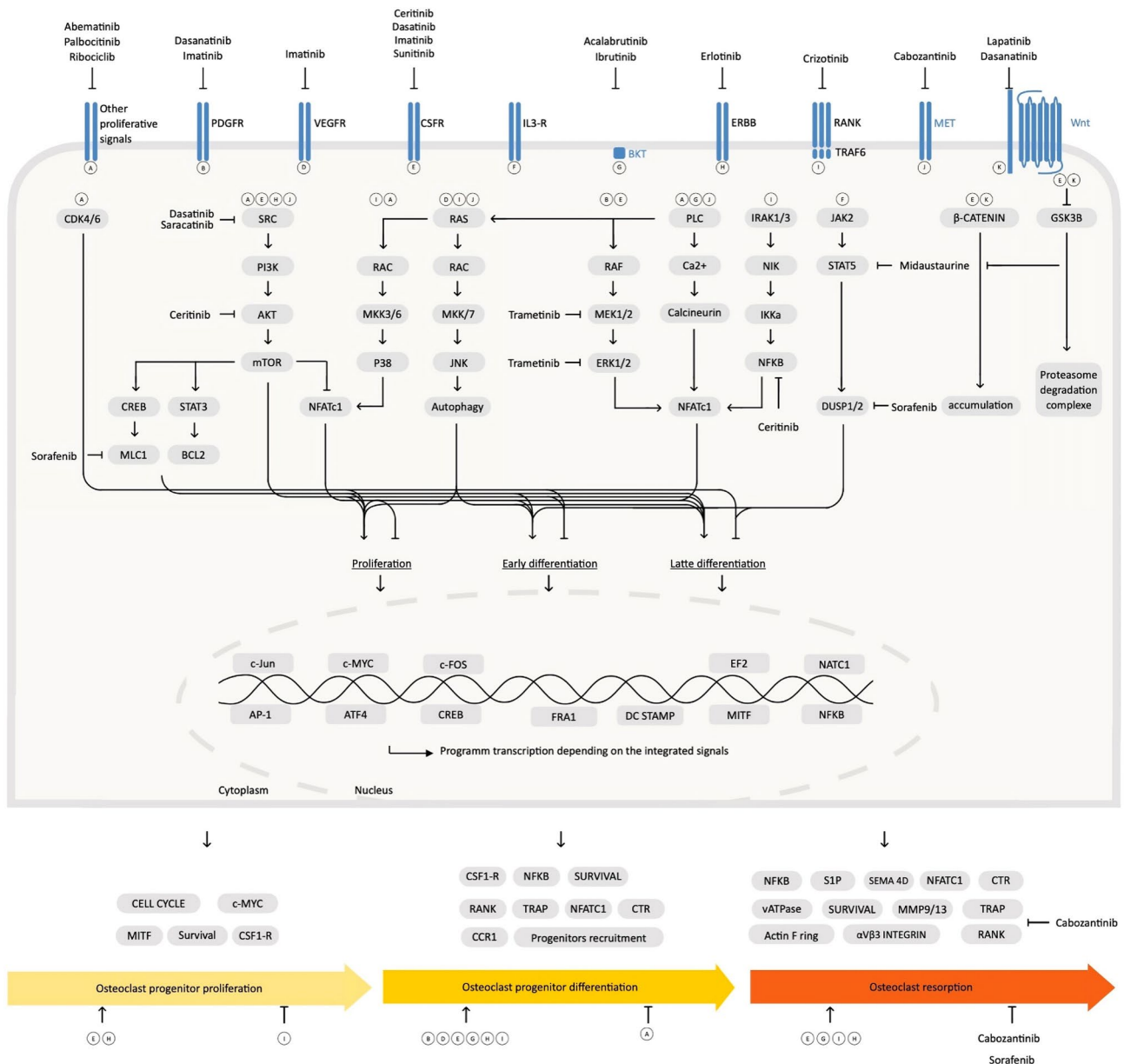
Fig. 4 Integration of tyrosine kinase inhibitor (TKI) pathways in osteoclast signaling. Each membrane receptor may act on one or several intracellular pathway(s) resulting on biological effect(s) on osteoclast (OC) progenitor proliferation, OC progenitor differentiation and/or OC resorption activity

explanation may come from the immune activation that would increase osteoclastogenesis and osteoclast activity and thus decrease bone mass.

In mice, the group of Johnson analyzed the bone phenotype of *PD-L1* knock out mice. They observed a decreased bone volume, an impaired bone micro-architecture and a decreased bone strength [118]. The same results have been observed during pharmacological blockade of PD1. Preliminary results support the immune hypothesis stating that an increase in T cells number and increased osteoclast activity alter PD1 blockade.

mTor Inhibitors

mTor are kinases that regulate cell growth, angiogenesis and survival. Everolimus and temsirolimus are 2 mTor inhibitors. Everolimus is indicated, in combination, for the management of hormone receptor positive advanced breast cancer. Temsirolimus is indicated for the treatment of renal cell carcinoma and mantle cell lymphoma. The addition of everolimus to exemestane doubles the time to progression-free survival compared with exemestane alone in postmenopausal women with HER2 + breast cancer [119].

Effect on Fractures and BMD

Effects of mTor inhibitors on BMD in humans have not been studied. In mice, after 4 weeks of treatment, BMD improves and the bone volume/total volume ratio is 37% higher than in the control group [120]. There are no available fracture data.

Effect on Bone Cells

In vitro and on intervertebral disc cells, mTor inhibitors showed their anti-senescence and anti-apoptotic properties through anti-IL1β activity inhibition. They also exert an anti-catabolic effect (MMP-2,9,13 and TIMP-1, 2) on the bone matrix through the activation of signaling pathways involving the Akt family [121].

Bone marrow edema associated with fracture has been reported 6 months after initiation of everolimus. Resolution of the adverse effect was observed 2 weeks after discontinuation and appears to be correlated with a decrease in intraosseous perfusion. This event seems to be related to its action on bone metabolism since everolimus exerts a potential inhibitory effect on osteoclast formation and activity and on osteoblast differentiation by inhibiting osteoblast gene expression [122]. Browne et al. also show in vitro and in mice, that osteoclastic precursor viability and osteoclast differentiation markers decreased significantly under everolimus regardless of its concentration. At higher concentrations, markers of osteoblast activity (ALP, OCN, OPG and Runx2) were also decreased, but without affecting the viability of pre-osteoblasts. Interestingly, everolimus prevents the significant increase of bone turnover and bone loss induced by ovariectomy [120].

Anti-Angiogenic Drugs

Anti-VEGF Antibodies

Vascular endothelial growth factor (VEGF) plays an essential role in vasculogenesis and angiogenesis. Levels of VEGF are increased in the serum of patients with primary malignant bone tumors [123, 124]. Bevacizumab binds to VEGF, inhibiting the binding of VEGF to its receptors on the surface of endothelial cells. At the tumor level, bevacizumab inhibits the formation of new tumor vessels and tumor growth.

No data are available on the risk of fracture and BMD with bevacizumab. However, the combination of a VEGF inhibitor and a VEGF receptor inhibitor is superior to VEGF inhibitor therapy alone on the progression of bone metastases in animals [125]. Moreover, anti-angiogenic drugs are known to induce osteonecrosis, particularly when combined with bisphosphonates (> 10%). However, osteonecrosis of the jaw has been observed without associated risk factors [126, 127]. These events are dose- and time-dependent and can be explained by their mechanism of action. In rabbits, VEGF regulates osteoclast differentiation and stimulates bone resorption [128].

Thalidomide and its Derivatives

Thalidomide, lenalidomide and pomalidomide are immunomodulators (IMIDs) used in the treatment of myeloma or lymphoma. These drugs inhibit angiogenesis and belong to the class of anti-angiogenics. However, there are no studies describing the effects of anti-angiogenics on BMD and fracture risk.

Thalidomide and lenalidomide have a significant inhibitory effect on osteoblast differentiation, even at the lowest doses [129]. This inhibition is observed at the late stages of differentiation, accompanied by a reduction in matrix mineralization and a decrease in ALP. In addition, the expression of the bone-forming transcription factors *Runx2* and *DLX-5* is decreased while the expression of the inhibitory proteins DKK-1 and inhibin βA is increased. In *vitro*, pomalidomide totally inhibits RANKL-induced osteoclast formation over a 21-day test period. This inhibition is observed early in the differentiation stages of hematopoietic progenitor cells, also resulting from a negative regulation of the transcription factor PU.1. These data are confirmed by a significant decrease in CFU-GM precursors without any toxic effect [130].

These in vitro data were confirmed in vivo [130]. Lenalidomide and pomalidomide directly inhibit osteoclasts through the inhibition of αVβ3-integrin and cathepsin K expression and indirectly by decreasing in myeloma cells, protein expression levels of RANKL (but not OPG) conducting to a decrease in RANKL/OPG ratio and by limiting APRIL, BAFF and MIP-1α [131, 132]. Immunomodulating drugs thus exert a direct and indirect inhibitory effect on osteoclasts.

Intravenous Chemotherapy

Anti-cancer management also relies on cytostatics, which are not targeted therapies. For some of them, the effects on bone or BMD are described. Most of the anti-cancer drugs listed are used in neoadjuvant chemotherapy of primary malignant bone tumors (methotrexate, cyclophosphamide, doxorubicin, ifosfamide and 5-fluorouracil), such as primary malignant osteosarcoma and Ewing´s family of tumors [133, 134]. These tumors predominantly affect children or adolescents during accrual of peak bone mass which may be disrupted by the treatment. Animal studies show that chemotherapy has a profound negative effect on all measures of bone mass and cortical and cancellous bone architecture [135]. While some drugs appear to significantly reduce BMD, it has not

yet been conclusively established that this reduced BMD is correlated with an increased fracture risk [136, 137].

5-Fluorouracil (5-FU)

In vitro, both aspects of osteoclast physiology decrease under 5-FU: differentiation in a dose-dependent manner, and activation as assessed by MCP-1, IL-1β, and VEGF production. In mice, the expression of genes involved in osteoclastogenesis is inhibited via the NF-κB signaling pathway [138].

Cyclophosphamide, Methotrexate, Doxorubicin, Ifosfamide

Effect on BMD. In the treatment of breast cancer in premenopausal women, after 1 year of amenorrhea, the decrease in BMD is about 6% in the spine and 5% in the femur under cyclophosphamide and methotrexate [25]. In children, the cumulative dose of methotrexate > 40,000 mg/m^2 is associated with a reduction in BMD with a decrease in bone volume and an increased risk of osteopenia [1, 136, 137]. In the long term, ifosfamide causes a decrease in BMD in children [1, 136, 137].

Effect on bone. Methotrexate exerts a cytotoxic effect on the proliferation of pre-osteoblasts and on the osteoblasts with an alteration of bone formation and in parallel to a stimulation of osteoclast activity [1]. These same effects are found in vitro under doxorubicin [1, 12].

Conclusion

Beyond glucocorticoid and hormone therapies, the bone effects of anticancer drugs are only partially evaluated. Since overall survival and recurrence-free survival have been drastically improved in many cancers, the impact of these drugs on bone cells, bone density and fracture risk is a major issue to investigate in order to improve patients' long-term quality of life during the "post-cancer time". Figure 2.

In addition, to the bone effects of these drugs, physicians should be aware that these drugs may also have distinct effects on muscle which may contribute to an increased risk of falls. Furthermore, tumor-related osteosarcopenia and cachexia may have a further negative impact on bone health in these patients.

Therefore altogether the oncologist, the bone metabolism specialist, and the general practitioners need to be aware of the effects of oncology treatments on the skeleton. In the future, clinical trials documenting efficacy of osteoporosis therapies in protecting from adverse skeletal outcomes need to be performed. This is one of the numerous upcoming challenges for cancer and bone physicians alike.

Declarations

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