

Bone metastases: an overview

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Abstract

Bone is a frequent site of metastases and typically indicates a short-term prognosis in cancer patients. Once cancer has spread to the bones it can rarely be cured, but often it can still be treated to slow its growth. The majority of skeletal metastases are due to breast and prostate cancer. Bone metastasis is actually much more common than primary bone cancers, especially in adults. The diagnosis is based on signs, symptoms and imaging. New classes of drugs and new interventions are given a better quality of life to these patients and improved the expectancy of life. It is necessary a multidisciplinary approach to treat patients with bone metastasis. In this paper we review the types, clinical approach and treatment of bone metastases.

Introduction

Metastasize is a process that involves loss of intercellular cohesion, cell migration, angiogenesis, access to systemic circulation, survival in circulation, evasion of local immune responses, and growth at distant organs.^{1,2}

Bone is the third most frequent site of metastasis, behind lung and liver.³ Prostate and breast cancer (BC) are responsible for the majority of the skeletal metastases (up to 70%).⁴ This reflects both the high incidence and relatively long clinical course of these

tumors. The overall incidence of bone metastasis is not known.³ The relative incidence of bone metastasis by type of tumor, in patients with advanced metastatic disease, is: 65-75% in BC; 65-75% in prostate; 60% in thyroid; 30-40% in lung; 40% in bladder; 20-25% in renal cell carcinoma and 14-45% in melanoma. The median-survival from diagnosis of bone metastasis is: 6months in melanoma; 6-7 months in lung; 6-9 months in bladder; 12 months in renal cells carcinoma; 12-53 months in prostate; 19-25 months in BC and 48 months in thyroid.⁵

Bone metastases are a major cause for morbidity, characterized by severe pain, impaired mobility, pathologic fractures, spinal cord compression, bone marrow aplasia and hypercalcemia.⁴

Types of bone metastasis

Bone metastasis are classified as osteolytic, osteoblastic or mixed, according to the primary mechanism of interference with normal bone remodeling:

- *Osteolytic*, characterized by destruction of normal bone, present in multiple myeloma (MM), renal cell carcinoma, melanoma, non-small cell lung cancer, non-hodgkin lymphoma, thyroid cancer or langerhans-cell histiocytosis. The great majority of BC produces osteolytic metastases. This bone destruction is primarily mediated by osteoclasts and not a direct effect of tumor cells.^{5,6} Other way, with lesser importance, is the compression of vasculature and consequent ischaemia in the late stages of cancer.³ Parathyroid hormone-related peptide (PTHrP) has a major role in the development of osteolytic lesions.⁷ It is unclear if bone microenvironment induces cancer cells to express PTHrP or if cells that metastasize to bone have an intrinsic higher PTHrP expression.⁸ The receptor activator of NF-kappaB ligand (RANKL) play a critical role in the formation of osteoclasts by stimulating precursor cells when binds to receptor activator of NF-kappaB (RANK) on the cell membrane of osteoclast precursors.⁹
- *Osteoblastic* (or sclerotic), characterized by deposition of new bone, present in prostate cancer, carcinoid, small cell lung cancer, Hodgkin lymphoma or medulloblastoma. The mechanisms of osteoblastic metastases are still poorly understood. In some instances the new bone formation is not necessarily preceded by bone resorption.³ Transforming growth factor, bone morphogenic proteins (BMP) and endothelin-1 are associated with osteoblast generation.¹⁰ Prostate-specific antigen (PSA), can cleave PTHrP, allowing the osteoblastic reaction predominate by decreasing bone reabsorption.¹¹ Core binding factor alpha1 (Cbfa1), also known as Runx-2, is linked to osteoblast differentiation.¹²
- *Mixed*, if a patient has both osteolytic and osteoblastic lesions, or if an individual metastasis has both osteolytic and osteoblastic components, present in BC, gastrointestinal can-

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cers and squamous cancers. Although BC gives origin predominantly to osteolytic lesions, 15-20% of women have osteoblastic lesions, or both type of lesions.¹³

Mechanisms of metastases to bone

Bone metastasis are almost always multiple and involve axial skeleton.⁴ It has been suggested that this distribution might be in relation to the hematopoietically active red bone marrow.¹³ There exists a paravertebral network that may play a role in the development of bone metastasis.¹⁴ This theory is supported by the high incidence of bone metastases without corresponding lesions in the lung (suggest an alternative pathway of spread). In addition, the microenvironment must be favorable for tumor cell survival.⁴

Once the tumor cell is in circulation, it needs:

- *Vascular adhesion and extravasation:* the cell interacts with endothelium in order to extravasate and stay in a specific tissue.¹⁵ Chemoattractive and adhesion molecules play a fundamental role in this selective retention of cancer cells in bone marrow vasculature. Cancer cells use equivalent molecules to vascular cell adhesion molecules (VCAM) and E-selectin to adhere to endothelium.^{16,17} We also know that chemokines, integrins, osteopontin, bone sialoprotein and type I collagen are critical for organ colonization by cancer cells.^{18,19} Examples of such interactions are: expression of CXCR4 by neuroblastoma tumors that mediates the attachment to stromal-cell derived factor 1 in bone (SDF-1 or CXCL12);²⁰ expression of RANK by BC that mediates the attachment to RANKL in bone;²¹ expression of sialoprotein by non-small cell lung cancer that facilitate binding to collagen type I in bone.²²
- *Micro-environmental support:* The *seed-and-soil* hypothesis tells us that the microenvironment provides a fertile ground (*the soil*), for the survival and growth of metastatic cancer cells (*the seed*).²³ The bone formation and reabsorption release and activate survival and growth promoting factors that may contribute to bone metastases development.²⁴
- *Epithelial - Mesenchymal transition:* Normal cell can lose their epithelial features and acquire mesenchymal characteristics. This process is called Epithelial-Mesenchymal Transition, and enables epithelial cells to migrate to a new environment. This occurs mainly during embryogenesis, but in cancer cells this process confers the invasive phenotype.⁴

Clinical aspects

The median survival of patients after first bone metastasis by BC is 20 months. This is in marked contrast to those with metastases of BC in the liver, 3 months, or with bone metastases from non-small cell lung cancer, 6 months.^{25,26}

In prostate cancer, men with a good performance status and bone only disease, affecting predominantly the axial skeleton, have a median duration of disease control after androgen blockade of 4 years and a median survival of 53 months. This is in marked contrast to those with visceral disease with a median survival of 30 months and 12 months with visceral disease and poor performance status.²⁷

Bone metastases are a major cause for morbidity, characterized by severe pain, impaired mobility, pathologic fractures, spinal cord compression, bone marrow aplasia and hypercalcemia.⁴

Hypercalcaemia is the most common metabolic complication of malignant disease.²⁸ It is frequent in squamous-cell carcinomas

of the lung, BC and kidney, MM and lymphoma. The four main contributors are: focal osteolysis by tumor cells, generalized osteolysis by humoral factors secreted by the tumor, increased renal tubular reabsorption of calcium and impaired renal glomerular function. BC secretes PTHrP; MM leads to impaired renal function due to deposition of Bence-Jones proteins; some lymphomas produce active metabolites of vitamin-D, which increases both bone resorption and intestinal absorption of calcium.²⁸

Moderate to severe hypercalcaemia, if left untreated, causes a number of unpleasant symptoms related to dysfunction of the gastrointestinal tract, kidneys and central nervous systems such as constipation, polyuria, polydipsia and fatigue. In final stages, hypercalcemia can lead to cardiac arrhythmias and acute renal failure.³ With hypercalcaemia, parathyroid hormone levels are suppressed, and PTHrP may be elevated. This leads to increased osteoclastic bone resorption. Hypercalcaemia carries a poor prognosis with a median survival of 10-12 weeks.⁵

Pathologic fractures occur in 10-30% of all cancer patients, with proximal parts of the long bones being the most frequent fracture site, and the femur accounting for over half of all cases.⁵ Rib fractures and vertebral collapses are also very common, which can lead to kyphoscoliosis and a degree of restrictive lung disease.²⁹ BC accounts for 60% of the pathologic fractures and lung cancer for only 10% of cases.^{30,31}

The most disability is caused by a long bone fracture or epidural extension of tumor into the spine.³ The probability of developing a pathological fracture increases with the duration of metastatic involvement. Although the intensity of bone pain is not directly associated with fracture risk, pain that is exacerbated by movement does appear to be an important factor in predicting impending fracture. Primary internal stabilization followed by radiotherapy is usually the treatment of choice.³

Bone pain is the most common type of pain from cancer, is poorly localized, worse at night, not necessarily relieve with sleep or lying down.³² In cancer patients, development of bone pain usually is considered to be highly suggestive of bone metastases.⁵ The pain associated with bone metastasis could be either of inflammatory or mechanical origin. Inflammatory pain is related to the local release of cytokines and chemical mediators by the tumor cells, periosteal irritation, stimulation of intraosseous nerves. Mechanical pain is related to the pressure or mass effect of the tumor tissue within the bone, with loss of bone strength thus turning into activity-related pain.⁵ The inhibition of osteoclastic bone reabsorption reduces bone pain.³² The use of osteoclast inhibitors, such bisphosphonates and denosumab, reduce bone pain.

The development of back pain in a patient with cancer, associated with an abnormal spinal radiograph should warn the physician for possible spinal cord compression. It is more commonly seen in BC (20-30%) and lung cancer (15%).⁵ For a successful rehabilitation the diagnosis must be fast, high-dose corticosteroids treatment, rapid assessment and urgent referral for both decompression and spinal stabilization. If compression is not relieved within 24-48 h, neurologic recovery is unlikely.^{3,28}

A basic screening must be performed when one of the signs and symptoms described above are present: a complete blood-cell count to evaluate for anemia and myelosuppression; serum calcium, phosphorus, 25-hydroxyvitamin D, alkaline phosphatase, creatinine, thyroid-stimulating hormone, protein electrophoresis and parathyroid hormone level to identify bone turnover and evaluate hypercalcemia.^{5,33} This study must be complemented with imaging data.⁵

Bone scintigraphy is highly sensitive but usually has a low specificity. Sensitivity of ⁹⁹Tc scintigraphy has been reported to range from 62 to 89%, with a false-positive rate as high as 40%. It

is more sensitive and more specific than plain films and computed tomography (CT) scans, while magnetic resonance imaging (MRI) is superior in evaluating vertebral metastases.³⁴ It provides information on osteoblastic activity and skeletal vascularity, with preferential uptake of tracer at sites of active bone formation that reflects the metabolic reaction of bone to the disease process, whether neoplastic, traumatic or inflammatory.³³

Radiographs are a fast, cheap, and readily available technique for evaluating bone metastases. Plain radiography should be the first test in the evaluation of bone pain. A plain radiography is very specific but sensitivity is low (44-50%) because metastatic lesions may not appear on X-ray at initial stages. Lesions up to 1cm might go undetected, while more than 50% of trabecular bone must be destroyed before it will be evident on film. Medullary lesions are more difficult to detect than lesions in cortical bone because of the limited contrast in trabecular bone.³⁵ Osteolytic lesions appear as a darker hole in the gray-white bone image; osteoblastic lesions appear as spots that are whiter than the bone around them.

The sensitivity of *CT* for the diagnosis of bone metastases ranges from 71-100%.³⁶ *CT* produces images with excellent soft tissue and contrast resolution. Bone destruction and sclerotic deposits are usually clearly shown and any soft tissue extension of bone metastases is easily visualized. *CT* is particularly useful to localize lesions for biopsy.³³

MRI is required to diagnose spinal cord compression and is useful in imaging bone marrow to assess involvement by the tumor. The sensitivity ranges from 82-100% and its specificity ranges from 73-100%.³⁷

Positron emission tomography (*PET*) detects the presence of tumor directly by quantifying metabolic activity. It is superior to bone scintigraphy in the detection of bone metastases from lung cancer (sensitivity 92%, specificity 99%),³⁸ and from BC (sensitivity 95%, specificity 94%).³⁹ It has lower accuracy in renal and prostate cancer bone metastasis because they are slow growing (so, the uptake of 18-fluorodeoxyglucose is low).⁴⁰ *PET* permits earlier diagnosis of bone metastases in MM, showing bone resorption sites undetected with conventional diagnostic methods. In addition, it can reveal metastatic spread to sites other than bone.⁴¹

Treatment

Treatment decisions depend on several parameters, for example, if bone disease is localized or widespread, if there is evidence of extraskelatal metastases, the kind of cancer and his features (like estrogen-receptors in BC), prior treatment history and disease response, the symptoms and the general state of health.²⁸ Treatments can often shrink or slow the growth of bone metastases and can help with the symptoms they are causing but, they are not curative.

Bisphosphonates are analogues of pyrophosphate, a natural inhibitor of bone demineralization.²⁸ Bisphosphonates bind avidly to exposed bone mineral around resorbing osteoclast and this leads to very high local concentrations of product in the resorption lacunae. Then, bisphosphonates are internalized by the osteoclast causing disruption of the chemical process involved in bone resorption.^{5,42} Bisphosphonates also cause osteoclast apoptosis and some studies suggest that they may also have direct apoptotic effects on tumour cells.^{5,43} In oncology, bisphosphonates are the standard treatment for tumour-induced hypercalcaemia and a new form of therapy for bone metastasis.⁴⁴

With intravenous bisphosphonates and rehydration, 70-90% of patients will achieve normocalcaemia. The effect on pain in bone metastases is independent of the nature of the underlying tumour

and the sclerotic lesions respond similarly to lytic metastases.⁴⁵ The studies are mainly done in BC and MM; lung, kidney and prostatic cancer have few studies.

They are well tolerated. The most common adverse events include flu-like symptoms (fever, arthralgia, myalgia and weakness), anemia, nausea, dyspnea and peripheral edema. These events are mostly limited and mild to moderate.⁵ A rare but very serious side effect is osteonecrosis of the jaw. All bisphosphonates undergo renal clearance so, patients with renal impairment (serum creatinine level >3.0 mg/dL) should not receive the treatment.⁴⁶

There are three generations of bisphosphonates: 1st generation, etidronate, clodronate, tiludronate; 2nd generation, pamidronate, alendronate, ibandronate; 3rd generation, risedronate, zoledronic acid. The approved ones are: oral clodronate at a daily dose of 1600 mg and oral ibandronate 50 mg; intravenous (IV) pamidronate 90 mg (infusion of 2 h), ibandronate 6 mg (infusion of 1 h), zoledronic acid 4 mg (infusion of 15 min). Zoledronic acid is the newer bisphosphonate approved for MM, lung, prostate and BC with bone metastasis. It is 100-times more effective than pamidronate.⁴⁷ Patients doing these treatments should take a supplement containing calcium and vitamin D.

Bisphosphonates, besides the beneficial effects on pain and reduction of fractures, also display antimyeloma and antitumor activity with prolonged overall survival reported for various malignancies.⁴⁸⁻⁵¹ Bisphosphonates exert their antitumor effects by interrupting the vicious cycle of increased osteolysis coupled with increased tumor growth. With this action, bisphosphonates may preserve bone health and delay bone lesion progression. Direct effects of bisphosphonates on cancer cells may contribute to the antitumor effect. For example, zoledronic acid inhibits growth, migration, and matrix-associated invasion of BC cells. In vitro, BC cells treated with ibandronate showed attenuated proliferation.⁵² Bisphosphonates may induce apoptosis in neoplastic cells via modulation of the activity of small GTPases (GTPases downregulate the expression of proapoptotic genes in malignant cells, and bisphosphonates inhibit the activity of small GTPases).⁵³ At last, bisphosphonates may stimulate innate antitumor immune mechanisms. In patients with prostate cancer, zoledronate therapy elicited a long-term shift of peripheral T cells towards an activated effector memory-like state associated with improved immune surveillance against malignant cells.⁵⁴

A meta-analysis that included 17 trials with 1520 patients analyzed in bisphosphonates groups, and 1490 analyzed in control groups, found no significant effect of bisphosphonates on overall survival and progression-free survival.⁵⁵ On the other hand, zoledronic acid demonstrated disease-free survival benefits and a 15% improvement in overall survival in a metaanalysis including 9518 BC patients.⁵⁶ We conclude that information is very contradictory but beneficial seems to be obvious.

Denosumab is a human monoclonal antibody that inhibits the RANKL, preventing the development of osteoclasts. It can help prevent or delay problems like fractures in patients with bone metastases at least as well as zoledronate, and is safe to give to patients with impaired renal function. It also can be helpful when zoledronate is no longer working.⁵⁷ It is injected subcutaneously. Dosing ranges from 60 mg every 6 months in order to preserve bone density in postmenopausal women to 120 mg every 4 weeks for malignant disease metastatic to the bone. Denosumab does not accumulate in the bone as bisphosphonates, and its effect is reversible after treatment discontinuation.⁵⁸ Side effects are similar to bisphosphonates, including nausea, diarrhea, weakness and can cause osteonecrosis of the jaw too.⁵⁷

Osteonecrosis of the jaw is more common when IV bisphosphonates or denosumab are administered on a monthly basis for

control of metastases and is much less frequent with less intensive use of bisphosphonates or denosumab for preservation of bone mass. Osteonecrosis of the jaw management is mostly conservative, and healing occurred in more than one-third of patients. Most of the patients with confirmed osteonecrosis of the jaw had a history of tooth extraction (62%), poor oral hygiene and/or use of a dental appliance.⁵⁹

Radiotherapy is the treatment of choice for localized bone pain, but in presence of poorly localized bone pain or recurrence of pain in previously irradiated skeletal sites, the bisphosphonates are an alternative treatment approach.²⁸

The main benefits of denosumab are the possibility to be used in renal failure (denosumab clearance is independent of renal function, in contrast to bisphosphonates clearance, since denosumab is cleared by reticuloendothelial system);⁶⁰ the reversibility of its effect after treatment discontinuation; acute-phase reactions occur rarely after denosumab (but are frequent after zoledronic acid); in prostate and BC patients, suppression of bone turnover markers is greater than by bisphosphonates.^{61,62} The weaknesses of denosumab are the increased infection rate in patients with osteoporosis or early BC;⁶³ the post-market period of denosumab is still comparably short and yet unknown side effects may emerge; in lung and MM cancer patients it is equipotent to bisphosphonates in preventing skeletal-related events;⁶⁴ it was showed a worse survival in patients with MM treated with denosumab compared to zoledronate;⁶⁴ and the economic burden.

External radiotherapy provides excellent palliation for localized metastatic bone pain however,⁶⁵ the mechanism of pain relief after radiation therapy is poorly understood.²⁸ Pain relief usually occurs rapidly, with more than 50% of responders showing benefit within 1-2 weeks. If improvement in pain has not occurred by 6 weeks or more after treatment, it is unlikely to be achieved.³³ Indications for radiotherapy for bone metastases include pain, risk for pathologic fracture and neurological complications arising from spinal cord compression.⁵

Radiation therapy can be delivered using three forms of treatment: local-field radiation therapy, wide-field radiation therapy and radionuclide therapy.²⁸ The local-field radiation therapy is considered the conventional treatment of bone metastases. It treats the involved bone and yields a pain relief rate of 80-90%.⁶⁶ Several randomized trials have indicated that a single fraction of 8Gy is adequate for pain relief.⁶⁵ Wide field (half-body, hemibody) radiation therapy can be used as primary palliative therapy for widespread symptomatic bone metastases or as an adjuvant to local-field radiation to reduce the later expression of occult metastases and to reduce the frequency of re-treatment.^{67,68} It is possible to distinguish: upper wide-field treatments (from skull or C1 to L2-3) - optimal single-dose is 6Gy; mid-body wide-field treatments (from L1 to upper third of the femurs) - optimal single-dose is 8Gy; lower wide-field treatments (from L3-4 to above the knees) - optimal single-dose is 8Gy.⁶⁶ Wide-field radiation provides pain relief for 64-100% of patients and approximately 50-66% of patients maintain pain relief for the remainder of their lives. The radiation fields must be shaped to reduce exposure of sensitive structures such as lung, gut, kidney and liver.

Radionuclide therapy is the systemic use of radioisotopes for bone pain.²⁸ Radiopharmaceuticals like strontium-89, rhenium-186 or samarium-153, have been shown to be effective in palliation of metastatic bone pain. They are preferentially taken up at sites for bone formation, so they probably are most effective for osteoblastic metastases.⁶⁹ The principal side effects are myelosuppression and pain flare.

Recently we have the radium-223, calcium mimetic and alpha emitter that selectively binds to areas of increased bone turnover in

bone metastases. It bounds into newly formed bone stroma and the radiation induces mainly double-stranded DNA breaks that result in a potent and highly localized cytotoxic effect. Toxic effects on adjacent tissues and particularly the bone marrow are minimal due to the short path of the alpha particles. Radium-223 significantly prolonged overall survival in patients who had castration-resistant prostate cancer and bone metastases, with a 30% reduction in the risk of death.⁷⁰

Ablation is the procedure where a needle or probe is introduced into a tumor and using heat, cold or a chemical, the tumor is destroyed. It may be used if only 1 or 2 bone tumors are causing symptoms. The most common types of ablation are radiofrequency ablation (RFA), where an electric current delivered through the needle heats the tumor to destroy it; and cryoablation, where a very cold probe is put into the tumor to freeze the cancer cells.⁷¹ Although effective at reducing a patient's pain, RFA has a critical limitation, which is the nonvisualization of the ablation margin with CT monitoring. In contrast to RFA, the ablation zone of cryoablation is readily identified with CT imaging as a low-attenuation ice ball beyond which tissues are safe from thermal injury.⁷² Another advantage of cryoablation relative to RFA is that patients treated with cryoablation do not experience increased pain during the procedure or in the immediate posttreatment period.⁷³ Although the complication rate using RFA and cryoablation for treatment of painful metastases is low, it was reported neurologic injuries, neuropathic pain and infection in the treatment area.⁷⁴ For *systemic antitumor* treatment selection, the pathological type of the tumor is most important. In lymphoma and germ cell tumors involving bone chemotherapy can be curative, while in renal cell carcinoma or melanoma it has little effect.³

Recently, there are cabozantinib (XL184), an oral tyrosine kinase inhibitor whose targets include VEGFR2, MET, KIT, and mutationally activated RET. It was associated with high rates of bone scan improvement, but the side effects required dose reduction or treatment discontinuation. In addition, statistically significant improvement in progression-free survival was seen with cabozantinib compared with placebo, in metastatic prostate cancer.⁷⁵

Surgery is only indicated for fractures of long bones and hip joints, in spinal cord involvement, or peripheral nerve compression.⁵

Stereotactic radiosurgery has emerged as a new treatment option for the multidisciplinary management of metastases located within or adjacent to vertebral bodies and the spinal cord. The goals of stereotactic radiosurgery are to improve local control over conventional fractionated radiation therapy and to be effective for the treatment of previously irradiated lesions with an acceptable safety profile. Stereotactic radiosurgery offers several theoretical advantages as a treatment modality for spinal tumors: early treatment of these lesions before a patient becomes symptomatic and the stability of the spine, it avoids the need to irradiate large segments of the spinal cord, the early treatment of spinal lesions may obviate the need for extensive spinal surgery for decompression and fixation in these already debilitated patients and may also avoid the need to irradiate large segments of the spinal column, which is known to have a deleterious effect on bone marrow reserve in these patients. The avoidance of open surgery and the preservation of bone-marrow function facilitate continuous chemotherapy in this patient population. Other advantage is that treatment can be completed in a single day rather than over the course of several weeks. The limitations of stereotactic radiosurgery for spinal metastasis are: the quality of literature is poor; no randomized controlled study has been conducted; stereotactic radiosurgery is more expensive than conventional RT.^{76,77}

Assessing the response of bone metastases to therapy is difficult; the events in the healing process are slow to evolve and quite subtle, with sclerosis of lytic lesions only beginning to appear 3-6 months after the start of therapy and taking more than a year to mature. It is generally accepted that sclerosis of lytic metastases with no radiological evidence of new lesions constitutes tumor regression (a partial response). Confounding factors include the appearance of sclerosis in an area that was previously normal. After successful therapy for metastatic disease, the healing processes of new bone formation cause an initial increase in tracer uptake and scans carried out during this phase are likely to show increased production of new bone and isotope uptake gradually falls.³³

Conclusions

The presence of bone metastases is a sign of disseminated disease and foretells a short-term prognosis in cancer patients. The bone metastases have an important impact on patient's quality of life so, new strategies are necessary to prevent skeletal disease and palliate established skeletal events. A multidisciplinary approach should include medical oncologist, radiotherapist, pain control team, intervention radiologist, endocrinologist, orthopedic surgeon and psychologist.

More studies are necessary to elucidate the interaction between tumor cell and bone microenvironment to reach new therapeutic interventions.

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