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Bone and brain metastasis in lung cancer: recent advances in therapeutic strategies

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***Abstract*:** Bone and brain metastases are a very common secondary localization of disease in patients with lung cancer. The prognosis of these patients is still poor with a median survival of less than 1 year. Current therapeutic approaches include palliative radiotherapy and systemic therapy with chemotherapy and targeted agents. For bone metastasis, zoledronic acid is the most commonly used bisphosphonate to prevent, reduce the incidence and delay the onset of skeletal-related events (SREs). Recently, denosumab, a fully human monoclonal antibody directed against the receptor activator of nuclear factor κB (RANK) ligand inhibiting the maturation of pre-osteoclasts into osteoclasts, showed increased time to SREs and overall survival compared with zoledronic acid. The treatment of brain metastasis is still controversial. Available standard therapeutic options, such as whole brain radiation therapy and systemic chemotherapy, provide a slight improvement in local control, overall survival and symptom relief. More recently, novel target agents such as the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib and afatinib have shown activity in patients with brain metastasis. *Inter alia*, in patients harboring EGFR mutations, the administration of EGFR TKIs is followed by a response rate of 70–80%, and a longer progression-free and overall survival than those obtained with standard chemotherapeutic regimens. This review is focused on the evidence for therapeutic strategies in bone and brain metastases due to lung cancer.

Keywords: afatinib, bone, brain, epidermal growth factor, erlotinib, gefitinib, lung cancer, metastases

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Bone metastasis in lung cancer

Lung cancer is the third most common form of cancer to spread to bone. About 30–40% of patients with lung cancer developed bone metastases during the course of their disease; the median survival time of patients with this secondary lesion is 7 months [Coleman, 2001]. These metastases are associated with significant morbidity, loss of functional independence and reduction in quality of life (QOL) [Berenson *et al.* 2006]. Bone metastasis accounts for 350,000 cancer patients deaths each year [Mundy, 2002] and in lung cancer is associated with increased social costs due to medical care, hospitalization days and cost of treatment [Botteman *et al.* 2007].

In a retrospective study of 259 nonsmall cell lung cancer (NSCLC) patients, the most common site of skeletal metastases was the spine in 50% of patients, followed by the ribs (27.1%), ilium (10%), sacrum (7.1%), femur (5.7%) and humerus, scapula and sternum (2.9%) [Tsuya *et al.* 2007]. The prognosis was worse in patients with metastasis to the appendicular bone than in patients with metastases only on an axial bone [Sugiura *et al.* 2008].

Pain is usually the first symptom of lung cancer with bone metastases in 80% of patients [Kosteva and Langer, 2008]. Patients with osseous metastases complain of pain at some point with wide variation in pattern and severity [Delaney *et al.* 2008]. Many factors are implicated in the pain of osseous metastases but a significant portion of the pain seems to be related to osteoclastic bone resorption.

European Society for Medical Oncology (ESMO) guidelines recommend a bone scan in lung cancer patients only when there is bone pain, hypercalcaemia or elevated alkaline phosphatase levels [D'Addario *et al.* 2010]. In a recent study, 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computerized tomography (CT) was superior with respect to bone scan in detecting bone lesions with a sensitivity and specificity of 94.3% *versus* 78.1% ($p = 0.001$) and 98.8% *versus* 97.4% ($p = 0.006$) respectively, which means a lower incidence of false positive and false negative results than with a bone scan [Song *et al.* 2009]. In the past, the main limitation of PET was its lack of accurate anatomical information, but the recent development of the combination of PET and CT has overcome the limitations of PET alone. A meta-analysis in lung cancer patients was performed to compare the capability for bone metastasis assessment of 18F-FDG-PET, 18F-FDG-PET-CT, magnetic resonance imaging (MRI) and bone scanning. The results showed that both 18F-FDG-PET-CT and 18F-FDG-PET were better imaging methods for diagnosing bone metastasis than MRI and bone scanning. 18F-FDG-PET-CT has higher diagnostic value (sensitivity, specificity) than any other imaging methods [Qu *et al.* 2012]. This might be due to its ability to detect the presence of tumors directly by metabolic activity rather than indirectly by increased bone mineral turnover.

Pathophysiology of bone metastasis

In the development of bone metastases, there is evidence of reciprocal signaling between the tumor and bone microenvironment. Bone resorption is increased in patients with bone metastases by secretion from malignant cells of many factors such as interleukin (IL1, IL6), receptor activator of NF-κB (RANK) ligand, parathyroid hormone-related protein (PTHrP) and macrophage inflammatory protein-1-α (MIP-1α) that stimulate osteoclast and osteoblast activity [Hirsh *et al.* 2008]. In turn, osteoclasts release growth factors such as transforming growth factor-β (TGFβ) and insulin-like growth factor-1 (IGF-1) from the bone matrix which stimulate PTHrP production and promote tumor growth.

This interaction between tumor cells and the bone microenvironment results in a vicious cycle of bone destruction and tumor growth. Release of PTHrP stimulates osteoclast activity, prevents osteoclast apoptosis and enhances renal tubular reabsorption of calcium causing malignant hypercalcemia [Delea *et al.* 2006]. Tumor cells achieve local bone resorption with the activation of osteoclast precursor cells (preosteoclasts) of the monocyte/macrophage cell line and stimulating their fusion and formation of mature osteoclasts. This osteoclastogenesis process is regulated by the nuclear factor κB (NFκB) ligand (RANKL)/RANK/osteoprotegerin (OPG) system. RANKL is mainly expressed on the surface of osteoblasts, whereas its specific receptor (RANK) is expressed on osteoclast precursors. Stimulation of RANK by its ligand induces osteoclast formation and activation [Lewis *et al.* 2011]. The soluble glycoprotein, OPG, is a receptor that binds to RANKL and thus inhibits the RANK–RANKL interaction that leads to preosteoclast recruitment, fusion into multinucleated osteoclasts, osteoclast activation and osteoclast survival. It is worth emphasizing that, in patients with bone metastases treated with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), it is possible to detect the presence of an osteoblastic reaction that is also associated with a significant response.

Sometimes bone condensation may increase or even appear within osteolytic lesions over time. This phenomenon, called osteoblastic flare, is a temporary increase in tracer uptake associated with therapy response of bone metastases that were previously undetected and is a healing response to effective cytostatic chemotherapy. These findings are very interesting and confirm that, in patients with NSCLC treated with a TKI, the initial presence or development of an osteoblastic reaction seems to be related to a more favorable outcome compared with patients with extraosseous metastasis. In patients with an osteoblastic reaction (before or during treatment), the tumors present with the clinical and biological characteristics of a response to TKI as well as better survival. Thus, the occurrence of an osteoblastic reaction during treatment with TKI, although extraosseous metastases are stable or in response, should not be considered as disease progression.

Skeletal-related events

'Skeletal-related events' (SREs) is a term used to describe a collection of adverse events associated with bone metastases. SREs include pathologic fractures, the requirement for surgery or radiotherapy, spinal cord compression and, less frequently, malignant hypercalcemia [Coleman, 2000].

Patients who developed a SRE have a prognosis worse than patients without SRE: this occurrence increases the risk of death by 20% to 40% [Saad *et al.* 2007]. The risk of developing a second SRE increases after the first event, and it has been shown that patients who developed a SRE had their survival reduced by half compared with patients who did not develop an SRE [Hirsh *et al.* 2008]. Also, Tsuya and colleagues showed that overall survival (OS) was 6.2 months for patients with any SRE *versus* 12.2 months in patients without a SRE [Tsuya *et al.* 2007]. Delea and colleagues reported that patients with SREs have 4 months of median survival time after their first SRE [Delea *et al.* 2004]. SREs caused a statistically significant decrease of physical and emotional functions of these patients [Weinfurt *et al.* 2005]. Prevention of SREs could have an important economic impact; the increased healthcare cost in patients with SREs was estimated at approximately US$ 27,982, costs of treatment of SREs were US$ 9480 [95% confidence interval (CI) US$7625–11,374] per patient [Delea *et al.* 2006]. Fractures are the most commonly reported SREs. Surgical intervention is used for the treatment of pathologic fractures and prevention of impending fractures that are common through lytic lesions.

Hypercalcemia will be experienced by up to a third of cancer patients at some point in their disease course. Humoral hypercalcemia occurs most often in patients with squamous cell malignancies of the lung. Very important for the treatment of malignant hypercalcemia is **adequate** hydration – diuretics, like furosemide 40 mg intravenous every 12 to 24 hours, also glucocorticoids, such as 60 mg of prednisone orally daily or 100 mg of hydrocortisone intravenously (IV) every 6 hours, can be used. Administration of IV bisphosphonate, coupled with **adequate** hydration, effectively normalizes serum calcium in the majority of cancer patients [Lewis *et al.* 2011]. Nonsystemic therapies, although important, are not discussed in this review.

Treatment of malignant bone pain

Bone pain may originate from the bone (direct invasion with microfractures, increased pressure of the endosteum, distortion of the periosteum), from nerve root compression (particularly in association with vertebral collapse) or from muscle spasms in the area of the bone lesions. As reported by Ripamonti and colleagues, unlike periosteum and blood vessels, cortex and bone marrow do not have any nerve endings; consequently, the pain derives from the stimulation of the periosteum and endosteum receptors [Ripamonti *et al.* 2000]. Distortion of the periosteum may be caused by an enlargement of the tumor mass or perilesional inflammatory edema [Ripamonti *et al.* 2000; Hanks *et al.* 1988]. The mechanism of metastatic bone pain is mainly somatic (nociceptive) although, in some cases, neuropathic and visceral stimulations may overlap. In addition to these kind of pain related to bone metastasis, there is a particular kind of bone pain that is called 'incident' or 'movement-related pain'. This is mainly variable in frequency and severity, and is often unpredictable. The pain is described as dull, constant and gradually increasing in intensity. Incident pain usually has a sudden onset, reaching a peak pain intensity within a few minutes.

Different kinds of bone pain require different kinds of drug to improve the relief. The conventional symptomatic treatment of metastatic bone pain requires the use of multidisciplinary therapies such as radiotherapy on the painful area or, at the time of risk of fracture, in association with systemic treatment with the support of analgesic therapy [Coleman, 1998; Bruera *t al.* 1999]. Nonopioid drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol are suggested to manage pain of mild intensity. Opioid analgesics are classified according to their ability to control mild-to-moderate pain (codeine, tramadol, dextropropoxyphene) and those used for moderate-to-severe pain (morphine, methadone, oxycodone, buprenorphine, hydromorphone, fentanyl). Corticosteroids are frequently used as co-analgesics in the treatment of bone metastatic pain, but their role in cancer-related pain has not been thoroughly investigated [McCormack, 1994; Watanabe *et al.* 1994]. Gabapentin and tricyclic antidepressants are used for neuropathic pain, generally as adjuvant therapy associated with opioids [Fallon *et al.* 2013].

Chemotherapy options

Combination chemotherapy is the standard of care for NSCLC. In selected patients, combination with cisplatin (CDDP) or carboplatin (CBCDA) or use of TKIs (erlotinib and gefitinib) or monoclonal antibodies (bevacizumab) has been performed. In small trials in patients affected by NSCLC and bone metastases, chemotherapy

may have beneficial effects on bone resorption – the combination of mitomycin C, CDDP and vinblastine in first-line treatment resulted in a significant reduction in bone resorption ($p < 0.05$) [Kolaczkowska *et al.* 1998].

A retrospective Japanese trial analyzed 642 patients with metastatic NSCLC treated with first-line platinum-based chemotherapy (73.1%) and gefitinib (18.2%). Only 6.6% of patients received the bisphosphonate zoledronic acid and the results showed that median survival was 15.4 months. In total, 118 (18.4%) patients experienced SREs, 40.7% of which were within 6 months of starting first-line antitumor therapy. The first SRE usually occurs within 12 months in the majority of patients, so that the prevention of these events represents the best therapeutic approach.

Risk factors for SREs in patients with NSCLC and bone metastases treated with chemotherapy are male sex, ECOG Performance Status (PS) >2–3 and multiple metastatic bone sites with hazard ratios (HRs) of 1.44 (0.98–2.11), 2.21 (0.97–5.03) and 4.43 (2.91–6.76) respectively [Sekine *et al.* 2009]. In a recent Korean study, analysis of risk factors for SREs suggested that long-term smoking, nonadenocarcinoma tumors, poor PS and no history of treatment with EGFR TKIs were predictors for SREs [Sun *et al.* 2011]. An important question is whether it is possible to translate these findings to the European population because this study published included Asian patients. We do know that some differences exist between Asian and European patients: the rate of EGFR mutations is definitely higher in Asians and sensitivity to both chemotherapy and anti-*EGFR* TKIs seems not to be the same. The mechanism behind the differences of EGFR mutation rates among different ethnicities is still unclear and is the subject of intense research. Chemotherapy and zoledronic acid ameliorated the QOL, reduced the pain and reduced SRE. A combination of zoledronic acid and chemotherapy seems to prolong the median time to the first radiation treatment and maintain QOL regarding pain and activity status, and significantly reduces pain scores and analgesic use [Hu *et al.* 2010].

Bisphosphonate

Bisphosphonates (BPs) are an important class of therapeutic agents. They are synthetic analogues of pyrophosphate, a natural regulator of bone metabolism found abundantly in bone matrix, which inhibits osteoclast-mediated bone resorption and prevents related skeletal complications. Biphosphonates can be distinguished as follows: clodronate, etidronate and tiludronate are incorporated into nonhydrolyzable adenosine triphosphate (ATP) analogues, interfering with cellular metabolism, whereas nitrogen-containing bisphophonates such as pamidronate, alendronate, risedronate, zoledronate and ibandronate prevent posttranslational prenylation of small guanosine triphosphate (GTP) binding proteins in osteoclasts [Rogers *et al.* 2000]. Zoledronic acid, pamidronate and ibandronate are more potent than simple bisphosphonates and thus represent the treatment of choice in patients with bone metastasis.

Among all these agents zoledronic acid is the only bisphosphonate that has broad efficacy in the treatment of bone metastases from all solid tumor types, including lung. Zoledronic acid has demonstrated superior efficacy compared with pamidronate disodium [Major *et al.* 2001]. Data regarding the use of bisphosphonates in NSCLC patients with bone metastasis are scarce and consensus regarding their use is lacking. Bisphosphonates in preclinical studies on human cancer cells lines derived also from small cell lung cancer (SCLC) and NSCLC seem to inhibit proliferation, induce apoptosis, and have an immunomodulatory effects and active antitumor immune response [Green, 2003; Matsumoto *et al.* 2005; Fournieri *et al.* 2006]. Patients treated with zoledronic acid at a dose of 4 mg experienced fewer skeletal complications, and had a significantly delayed onset of complications and a significantly reduced annual incidence of skeletal complications [Spizzo *et al.* 2009]. Zoledronic acid not only exhibited these effects from the time of the initiation of therapy, but maintained consistent, long-term benefits over the course of 21 months of treatment [Spizzo *et al.* 2009].

Preclinical evidence supports that at least part of the antitumor activity of bisphosphonates may be attributed to an anti-angiogenic effect; Santini and colleagues showed a significant decrease of circulating levels of vascular endothelial growth factor (VEGF) in bone metastatic cancer patients receiving a single dose of either zoledronic acid or pamidronate [Santini *et al.* 2002, 2003]. In another study it was demonstrated that a low-dose repeat and intermittent schedule of zoledronic acid (1 mg for 1 week) was able to induce

a significant decrease of VEGF serum levels in cancer patients. Only 7 days after the first 1 mg infusion of zoledronic acid, the median VEGF basal level showed an early and statistically significant decrease ($p = 0.038$). Clinically relevant doses of bisphosphonates administered at a low dosage on a daily or weekly dosing schedule produced meaningful antitumor effects reducing bone destruction as well as skeletal tumor burden, whereas monthly dosing did not show this [Daubine *et al.* 2007].

These studies represent the rational basis to consider the metronomic administration of bisphosphonates as a new potential therapy targeting endothelial–tumor–stroma behavior. The efficacy of metronomic therapy could be significantly increased when administered in combination with anti-angiogenic drugs, such as antibodies against VEGF or VEGF receptor 2 or small tyrosine kinase molecules that inhibit multiple angiogenic receptors – platelet-derived growth factor (PDGFR), vascular endothelial growth factor (VEGFR) and EGFR. The clinical implications and helpfulness of the bisphosphonates effect on VEGF levels should be investigated and should represent the objective of future clinical trials.

Zaragoulidis and colleagues published a study in lung cancer patients with evidence of metastasis bone scan and demonstrated a survival benefit of 6 months in patients who received zoledronic acid and a time-to-progression benefit of almost 4 months (8.8 *versus* 5 months) [Zaragoulidis *et al.* 2009]. Approval of zoledronic acid in lung cancer and other solid tumors arose from the phase III, randomized, placebo-controlled trial published by Rosen and colleagues in 2004 [Rosen *et al.* 2004], in which patients with bone metastases from solid tumors received zoledronic acid with a reduction of patients who experienced at least one SRE (39% *versus* 48% with placebo; $p = 0.039$) and each type of SRE. The annual incidence of SRE significantly decreased with zoledronic acid (2.71 for year in the placebo group *versus* 1.74 for year in the BPs group; $p = 0.012$) and increased the median time to first SRE compared with placebo (236 days *versus* 155 days; $p = 0.009$). In conclusion, zoledronic acid in this trial reduced the risk of SRE by 31% *versus* placebo (relative risk: 0.693; $p = 0.003$) [Rosen *et al.* 2004]. Also in patients who have experienced an SRE, zoledronic acid reduced the risk of developing a second SRE and reduced the skeletal morbidity rate (1.96 *versus* 2.81 for year events in placebo group $p = 0.030$) and prolonged the median time to first SRE by 4 months (215 *versus* 106 days in placebo group, $p = 0.011$) [Hirsh *et al.* 2004]. The beneficial effects of zoledronic acid in NSCLC with bone metastases may be limited to the subgroup of patients at high risk for SRE; in fact, in a phase III trial of zoledronic acid *versus* placebo the frequency of SREs was similar among the patients receiving zoledronic acid (42%) or placebo (45%), with a positive trend at time to the first SRE in the bisphosphonate group [Rosen *et al.* 2003].

No data are available on the use of pamidronate in NSCLC patients with bone metastasis. A retrospective study was conducted to determine the tolerability and the effect of pamidronate use in patients with NSCLC and bone metastases. Pamidronate appeared to be well tolerated and to be a safe and cost-effective alternative to zoledronic acid [Spizzo *et al.* 2009].

Denosumab

The RANK–RANKL system plays a fundamental role in the maturation and function of osteoclasts and thus in the development and progression of bone metastasis in multiple cancers. Inhibition of this system has been evaluated as a therapeutic target for the treatment of bone metastasis. Osteoclast bone-resorbing activity is dependent on the binding of the OPG ligand (OPGL), which is expressed on activated T cells and osteoblasts, to a receptor termed receptor activator of nuclear factor kβ (NF-kβ) called also RANK [Kong *et al.* 1999]. OPG is a soluble tumor necrosis factor receptor molecule that is secreted and binds to the RANK activating site of OPGL and preventing OPGL from binding and activating the osteoclast RANK receptor [Thompson and Tonge, 2000].

Denosumab is a fully human monoclonal antibody that binds and neutralizes RANKL, thereby inhibiting osteoclast function. It has several advantages over bisphosphonates and its elimination is mediated by the immunoglobulin clearance pathway *via* the reticuloendothelial system [Tabrizi *et al.* 2006]. The promising outcomes in the initial trials with denosumab led to exploration of its use for the prevention of SREs in patients with solid tumors and bone metastasis.

The US Food and Drug Administration (FDA) approved denosumab (Xgeva) in 2010 in patients

Table 1. Comparison of zoledronic acid and denosumab.

Zoledronic acid	Denosumab
Synthetic analogues of pyrophosphate	Fully human monoclonal antibody
Lower cost (but needs cost-effectiveness analyses)	Moderate cost (but needs cost-effectiveness analyses)
10 years of experience in clinical practice	Recent approval by FDA
4 mg intravenously every 3–4 weeks	120 mg subcutaneously every 4 weeks
Elimination through renal excretion	Elimination through reticuloendothelial system
No patients with renal insufficiency (CrCL <30 ml/min)	Safer in patients with renal insufficiency
No use in patients with nephrotoxicity by cht	Patients with nephrotoxic cht-like platinum
Lower risk ONJ	Moderate risk ONJ
Lower risk hypocalcemia	Moderate risk hypocalcemia
Major risk of acute phase reactions	Lower risk of acute phase reactions
Well tolerated in many patients	Use in patients with intolerance to bisphosphonates
Minor delay of SRE	Major delay of SRE
30–50% of patients develop SRE	Use in patients with SRE after bisphosphonates
Decrease in uNTx	Major decrease in uNTx
Patients with port-a-cath or IV access	Patients without IV access

FDA, US Food and Drug Administration; CrCL, creatinine clearance; cht, chemotherapy; IV, intravenous.ONJ, osteonecrosis of the jaw; SRE, skeletal-related events; uNTx, urine levels of *N*-telopeptide of type I collagen.

with bone metastases from solid tumors at a dose of 120 mg subcutaneously every 4 weeks to help prevent SREs in patients with cancer that has metastasized to the bone and caused SREs including bone fractures from cancer and bone pain requiring radiation. There have been three international phase III randomized, double-blind studies comparing denosumab with zoledronic acid for the prevention of SREs in patients with bone metastases which led to FDA approval of denosumab [Stopeck *et al.* 2010].

The phase III trial by Henry and colleagues comprised patients with multiple myeloma or solid tumors (40% of enrolled patients had NSCLC) other than breast or prostate cancer with bone metastasis [Henry *et al.* 2011]. The median time to first on-study SRE was 20.6 months for denosumab and 16.3 months for zoledronic acid. In this study, denosumab also failed to reduce time to first and subsequent SREs significantly but the reason for this discordant result may be the smaller number of patients randomized and shorter time on study. When stratified by tumor type, the hazard ratio (HR) for time to first on-study SRE for denosumab *versus* zoledronic acid was 0.84 (95% CI 0.64–1.10, $p = 0.20$) for NSCLC.

In all phase III trials, disease progression and OS were similar among denosumab or zoledronic acid groups, as was the incidence of adverse events (osteonecrosis of the jaw was similarly low in both treatment groups). However in a subgroup analysis from a randomized phase III study of Henry and colleagues, denosumab was associated with improved median OS *versus* zoledronic acid in 702 patients with NSCLC (9.5 *versus* 8.0 months; HR 0.78, $p = 0.01$) not significant on analysis of NSCLC by histological type in patients with squamous cell carcinoma [Henry *et al.* 2011]. Overall, denosumab may be more suitable for patients with NSCLC treated with nephrotoxic regimens such as platinum compounds and for elderly patients with a compromised creatinine clearance, who usually require an adjustment of the dosing of bisphosphonate. Table 1 provides a comparison of zoledronic acid and denosumab.

EGFR TKIs

Recent findings indicate that epidermal growth factor (EGF) signaling is an important mediator of bone metastasis in many cancers; indeed it has also been implicated in modulating functions of stromal cells in the tumor microenvironment [De Luca *et al.* 2008]. The balance between osteoblasts and osteoclasts can be perturbed by altering the activity of EGF signaling as it stimulates growth of bone metastasis directly by increasing tumor cell proliferation and indirectly with bone

stromal cell essential for the metastasis development [Lu and Kang, 2010].

It seems that gefitinib, an EGFR inhibitor, may block RANKL-mediated osteoclast activation for reduction in the synthesis of RANKL. Lu and colleagues showed direct evidence for reducing bone metastasis growth through inhibiting EGF signaling in bone stromal cells [Lu *et al.* 2009]. Tumor cells release three EGF-like factors – heparin-binding (HB) EGF, amphiregulin (AREG) and TGFα – which activate the EGFR pathway in adjacent osteoblasts through a paracrine mechanism and downregulate OPG expression. The increase of OPG favors osteoclastogenesis and contributes to the vicious cycle of osteolytic bone metastasis. Anti-EGFR agents reduced invasive capacity through the inhibition of molecules associated with tissue invasion like metalloproteinase and urokinase-type plasminogen activator (uPA), interfere with osteoclast differentiation and activation, and have an anti-angiogenic activity blocking the production of VEGF in stromal cells and in tumor cells [Normanno and Gullick, 2006].

It has recently been suggested that osteoblastic reactions were either present before receiving TKI and increased during treatment or appeared during treatment in areas considered to be free of metastases, and that bone condensation may increase or even appear within osteolytic lesions over time. The mechanism of the onset of this osteoblastic reaction is not fully understood – the action of the TKI can be considered as either having a direct therapeutic effect on the metastasis for which progression is thus impeded or as having an effect on the osteoblast's activity [Boyle *et al.* 2003]. Indeed, in a retrospective study in patients with NSCLC and osteoblastic lesions treated with a TKI, development of an osteoblastic reaction seems to be related to a more favorable outcome. The authors of this study concluded that osteoblastic reactions during treatment with a TKI, while primary tumor and metastases are stable or in response, should not be considered as disease progression [Pluquet *et al.* 2010]. A report showed osteoblastic responses in EGFR-mutated NSCLC and concluded that, in such patients, assessment of bone metastasis based on formal radiologic criteria alone is not recommended [Anse'n *et al.* 2010]. A Japanese study suggested that in addition to its antitumor effects, the TKI gefitinib has inhibitory effects on bone resorption, and in a series of patients it showed dramatic improvements of pathologic fractures [Okano and Nishio, 2008]. This clinical evidence must be confirmed and translated in clinical randomized prospective trials.

Brain metastasis in lung cancer

Metastatic brain tumors are the most common intracranial neoplasm in adults, the majority of brain metastases originate from lung cancer (40–50%) [Schouten *et al.* 2002]. Patients with brain metastases have median survivals of 3–6 months [Patchell *et al.* 1990]. Positive prognostic factors include Karnofsky's performance status, age >65 years, control of primary tumor and absence of extracranial metastatic disease [Schwer and Gaspar, 2006]. This metastatic site of disease contributes to the morbidity and mortality of these cancers: impairing sensory and motor neural functions, and causing headaches, vomiting and seizures. Lung cancer patients develop brain metastases early, within the first 2 years, after primary tumor diagnosis. In SCLC, 10% of patients have central nervous system (CNS) metastases at time of primary tumor diagnosis [Castrucci and Knisely, 2008]. Between 25% and 40% of NSCLC patients reportedly develop brain metastases during the course of their disease [Sørense *et al.* 1988]. The majority of brain metastases (80%) generally occur in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem [Delattre *et al.* 1988]. The management of brain metastases can be divided into symptomatic and therapeutic strategies. The mainstay of therapeutic strategies is radiation therapy.

Medical therapy

Symptomatic therapy includes corticosteroids to reduce peritumoraledema and anticonvulsants to prevent recurrent seizures. Other medications such as donepezil can improve cognition, mood, and QOL in patients with brain tumors [Shaw *et al.* 2006].

Dexamethasone is generally considered to be the steroid of choice with a starting dose of 4–8 mg/day in early supportive care [Robinson *et al.* 2010]. Use of routine prophylactic anticonvulsants is not recommended because of their significant adverse effects and for the lack of evidence showing some benefit from the prophylactic use of anticonvulsants for patients with brain metastases [Mikkelsen *et al.* 2010].

At the present time, there are no proven treatments for cognitive impairment following brain cancer and no known effective preventive strategies. Among the most studied drugs are those enhancing cholinergic neurotransmission. Both choline acetyltransferase and acetylcholine levels are significantly reduced in patients with neurological problems. A phase II trial showed encouraging results with donepezil and other angiotensin-converting enzyme (ACE) inhibitors in this population and warrants continued investigation [Mikkelsen *et al.* 2010].

Some improvement in QOL and cognitive function were noted with Ginkgo biloba in a recent phase II study; however, treatment with Ginkgo biloba was associated with a high dropout rate [Attia *et al.* 2012]. Methylphenidate did not result in an improvement in QOL and neurocognitive function in a phase III prospective trial [Butler *et al.* 2007].

Systemic and local treatments

Chemotherapy has a limited role in the treatment of brain metastases; the major impediment to treatment with cytotoxic agents is the blood–brain barrier (BBB) which creates a sanctuary site for metastatic tumors. However, it has been currently accepted that the integrity of the BBB is impaired in the presence of brain metastases. Several studies have reported that some patients might benefit from aggressive therapy including surgery, radiotherapy and chemotherapy [Harita *et al.* 2005]. Kim and colleagues analyzed retrospectively the outcome of chemotherapy only, upfront whole brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS) in NSCLC patients with asymptomatic brain metastases. There was no significant difference in OS among three groups but subset analysis of 110 patients suggested a potential role of systemic chemotherapy alone or upfront SRS followed by chemotherapy [Kim *et al.* 2010]. Recently, Galletta and colleagues, in a multicenter phase II study, analyzed the association of CDDP, fotemustine and whole-brain radiotherapy but this scheme does not represent a therapeutic option for patients with NSCLC [Galletta *et al.* 2011]. Antonadou and colleagues, in a study of 24 patients, showed that the combination of WBRT and low-dose (75 mg/m^2) daily temozolomide induced promising response rates (96% objective response rate, *versus* 66% in patients treated with WBRT alone) with acceptable toxicity in patients with newly diagnosed brain metastases but there was no difference in median survival [Antonadou *et al.* 2002]. A combination of local therapies and systemic chemotherapy may increase survival in NSCLC patients with brain metastases [Kim *et al.* 2005].

There are only a few randomized phase III studies of advanced or metastatic NSCLC evaluating different kind of treatments in patients with brain metastases. Generally, patients with brain metastases have been excluded from clinical trials because of poor prognosis – even if data from the study by Edelman and colleagues indicated that patients with or without brain metastases may experience similar outcomes when enrolled in clinical trials of systemic therapy with various regimens such as gemcitabine/CBCDA, gemcitabine/paclitaxel, or paclitaxel/CBCDA. The response rate was 28.9% for patients with brain metastases *versus* 29.1% without; OS was not significantly different, median survival 8.6 months *versus* 7.7 months with a slight trend favoring patients without brain metastases [Edelman *et al.* 2010]. A prospective, multicentric phase III trial by Neuhaus and colleagues, comparing WBRT alone with WBRT plus topotecan, showed no significant advantage for concurrent radiochemotherapy for patients with lung cancer; however, the recruited number of patients was too low (only 96 patients of 320 projected) to exhibit a small advantage of combined treatment [Neuheus *et al.* 2009]. In 2001, Robin and colleagues investigated differences in survival in patients receiving CDDP and vinorelbine as front-line therapy with early or delayed WBRT. The results based on 176 randomized patients, confirmed that different timing (early or delayed) of WBRT did not influence survival of NSCLC with brain metastasis treated with concurrent chemotherapy.

Chemotherapy options

CDDP has activity both as a single agent (response rates of 30%) and in combination with other chemotherapy – response rates and OS times were comparable to those in patients with metastatic NSCLC outside the CNS, again suggesting that the responsiveness of brain metastases is similar to the chemosensitivity of the primary tumor [Cortes *et al.* 2002; Bernardo *et al.* 2003]. Various drugs have been used in clinical trials; temozolamide generally used only in brain cancers has demonstrated modest activity in recurrent brain metastases from NSCLC, with response rates of 0–20% [Abrey *et al.* 2001;

Table 2. Treatment of brain metastases – summary of main studies.

Chemotherapy agents	Patients	Design	Histology	Response rate (%)	Overall survival	Reference
Gemcitabine–CBCDA, Gemcitabine–paclitaxel, Paclitaxel/CBCDA	194	Phase III	NSCLC	28.9	7.7 months	Edelman *et al.* [2010]
CDDP-based	110	Survey	NSCLC	27	10 months	Moscetti et al. [2007]
Vinorelbine–gemcitabine–CBCDA	22	Phase II	NSCLC	45	33 weeks	Bernardo *et al.* [2002]
CDDP–paclitaxel–vinorelbine/ gemcitabine	26	Phase II	NSCLC	38	21.4 weeks	Cortes *et al.* [2003]
Temozolamide	22	Phase II	NSCLC	–	6.6 months	Abrey *et al.* [2001]
Pemetrexed	39	Retrospective study	NSCLC	69	10 months	Bearz *et al.* [2010]
CDDP–pemetrexed	43	Multicenter phase II	NSCLC	34.9	7.4 months	Barlesi *et al.* [2011]
Gefitinib	41	Phase II	NSCLC	27	–	Ceresoli *et al.* [2004]
Gefitinib/erlotinib	23	Phase II	NSCLC(adk)	69.6	18.8 months	Kim *et al.* [2009]

adk, adenocarcinoma; CBCDA, carboplatin; CDDP, cisplatin; NSCLC, nonsmall cell lung cancer.

Christodoulou *et al.* 2001; Giorgio *et al.* 2005]. There are few data in the literature showing the use of pemetrexed on brain metastases from NSCLC. Bearz and colleagues, in a study of 39 patients, found interesting preliminary data that suggested some activity of pemetrexed in CNS metastases; response on cerebral metastases was good, with partial response (PR) in 11 patients (28.2%) and stable disease (SD) in 21 (53.8%), with a clinical benefit rate of 82% for cranial metastases and an OS of 10 months [Bearz *et al.* 2010]. In another study, pemetrexed and CDDP were given to chemonaïve NSCLC patients with brain metastases who were ineligible for radiosurgery [Barlesi *et al.* 2011]. In this study, median survival time and time to progression were 7.4 and 4.0 months, respectively; this regimen appeared a good option for treatment and might therefore replace frontline WBRT. The main studies reported in this review were summarized in Table 2.

EGFR TKIs

Limited data exist for the responsiveness of brain metastases to the EGFR inhibitors, gefitinib and erlotinib. It also appears that certain types of metastases respond particularly well to EGFR TKIs, particularly in the case of carcinomatous meningitis [Dhruva and Socinski, 2009].

Recently Park and colleagues, in a phase II study in NSCLC patients with brain metastases and EGFR mutation treated with erlotinib or gefitinib, showed 83% PR and 11% SD, with a disease control rate of 93%. Median progression free survival and OS were 6.6 months and 15.9 months, respectively [Park *et al.* 2012]. Patients who were treatment-naive were particularly responsive: a 70% CNS response rate was observed in 23 Asian never-smokers with brain metastases from a NSCLC primary treated with first-line erlotinib or gefitinib [Kim *et al.* 2009]. Another retrospective study correlated the sensitivity of brain metastases to gefitinib to that of extracranial disease and showed that gefitinib was effective against brain metastases, with a response rate equivalent to that obtained against extracranial disease [Hotta *et al.* 2004]. Ceresoli and colleagues reported 27% of disease control with gefitinib [Ceresoli *et al.* 2004]. The cerebrospinal fluid concentration of erlotinib and its active metabolite, OSI-420 can be higher than that of gefitinib even in wild-type EGFR gene cases and erlotinib treatment can be more effective for CNS metastases of NSCLC [Togashi *et al.* 2010]. The CNS responses seen with the first generation of small molecule EGFR inhibitors in properly selected patients suggest that the use of drugs that are highly effective is at least as important as drug delivery for treating patients with brain metastases.

Angiogenesis inhibitors

The studies of safety and efficacy of angiogenesis inhibitors in the treatment of stable and active brain metastases are ongoing because of risks regarding intracranial hemorrhage, but growing evidence in the treatment of patients with glioblastoma suggests that these agents are relatively safe and carry a low risk of bleeding. Angiogenesis agents can control peritumoral edema and reduce steroid dependence. A literature review of the available data on the incidence of CNS hemorrhage in NSCLC patients with brain metastases receiving anti-VEGF therapy showed no significantly increased risk of CNS hemorrhage in patients with NSCLC and previously untreated or pretreated CNS metastases. The authors concluded that bevacizumab-based therapy carries no appreciable increase in cerebrovascular risk in patients with primary or secondary brain malignancies [Sandler *et al.* 2012]. Only two prospective studies, PASSPORT (phase II study) and ATLAS (phase III study), were performed using bevacizumab in the treatment of NSCLC with brain metastases. In the PASSPORT study, patients received first-line bevacizumab every 3 weeks with platinum-based doublet therapy or erlotinib, and second-line patients received bevacizumab with single-agent chemotherapy or erlotinib, until disease progression or death. There were no grade ≥2 cerebral hemorrhages in 106 patients with brain metastases who received bevacizumab [Socinski *et al.* 2009]. In ATLAS, patients with previously untreated advanced nonsquamous or peripherally located squamous NSCLC received first-line bevacizumab in combination with different chemotherapy regimens, followed by maintenance bevacizumab with or without erlotinib until disease progression – no symptomatic brain hemorrhages were shown during the study by investigators [Miller *et al.* 2009].

Discussion and conclusion

Bone and brain metastases from lung cancer are associated with considerable negative effects on both patient QOL and survival. Such patients frequently require therapeutic intervention (radiation therapy, surgery and chemotherapy) that may add considerable cost to their end-of-life care. Also, total medical care costs of skeletal-related adverse events (pathologic fractures, surgery or radiotherapy, spinal cord and nerve root compression, and hypercalcemia of malignancy) are significant among patients with bone metastases in NSCLC. Zoledronic acid is the first and only bisphosphonate that has proven efficacy for the treatment of bone metastases in a randomized phase III trial. Future and ongoing trials will assess the efficacy of RANKL antibodies in lung cancer with bone metastases. Larger phase III trials are designed to investigate the effect of denosumab compared with zoledronic acid. The TKIs, gefitinib and erlotinib, are interesting options in bone and brain metastases treatment especially in EGFR-mutated patients but only a few studies have been conducted. Gefitinib seems to have important effects against bone resorption as well as antitumor effects.

In the past, treatments of brain metastases focused on symptom palliation with WBRT and steroids, but currently more aggressive approaches such as surgery, irradiation, stereotactic radiosurgery and chemotherapy have resulted in an improvement of neurologic outcomes, time to recurrence in the brain, and OS of patients with NSCLC. In patients with more metastases, recent evidence indicates that systemically effective chemotherapy may produce responses in the intracranial and extracranial disease states. The response rate of brain metastases to chemotherapy is similar to the response rate of the primary tumor and extracranial metastases. Many issues need to be investigated in future trials: the optimal combination of chemotherapy agents; the impact of TKIs in patients with specific mutation profiles; the timing of radiotherapy and chemotherapy (before or after?); and use of angiogenesis inhibitors.

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