British Association of
Urological Surgeons

Systemic Management of Metastatic Bone Disease

Guidelines on Treatment

The British Association of Urological Surgeons (BAUS) aims to promote the highest standard in the practice of Urology for the benefit of patients by fostering education, research and clinical excellence

A section from the BAUS Guidelines on the Management and Treatment of Metastatic Prostate Cancer

1.0 Recommendations

- Metastatic bone disease (MBD) is common in prostate cancer patients and has a high probability of leading to a skeletal-related event (SRE) such as bone pain, pathological fracture, spinal cord compression, or rarely hypercalcaemia
- In hormonally-naïve patients, the mainstay of therapy is androgen withdrawal. In hormone-resistant prostate cancer (HRPC), evidence suggests a role for early commencement of bisphosphonate therapy to reduce the risk and/or delay progression to an SRE. Zoledronic acid is the only bisphosphonate proven to reduce this risk
- For an established SRE, treatment options include bisphosphonates (if not already started), radiotherapy, surgery and analgesics

2.0 Clinical evidence

Introduction

Prostate cancer patients with MBD are at high risk of skeletal complications. These are often dramatic, and may initiate a rapid deterioration in quality of life in an already over-burdened patient.

Epidemiology

For the average district general hospital with a population of 250,000 – 500,000, there will be 100 to 200 new cases of prostate cancer diagnosed each year. Approximately 20 to 40 of these men will have bone metastases at diagnosis, whilst at least 65% to 75% will develop bone metastases through the course of their disease.[1]

Complications of Metastatic Bone Disease

Prostate cancer patients with bone metastases are at significant risk of developing skeletal-related events (SREs) such as spinal cord compression, pathological fractures, bone pain, and in some cases hypercalcaemia.[2,3] Clinical experience suggests that acute effects of SREs have a potentially significant impact on patient quality of life (QoL),[4] resulting in disability and reduced function. In addition, patients suffer the chronic threat of ongoing skeletal morbidity for a relatively long period of time.

On average, the metastatic prostate cancer patient will suffer his first SRE approximately 10 months after diagnosis.[5] The median survival time for this patient is about 40 months.[1] Epidemiological evidence has reported that pathological fractures in prostate cancer patients are associated with a shorter overall survival.[6]

Bone pain in patients with metastatic prostate cancer is frequently poorly localised, and often prominent during the night. Effective palliation is therefore essential to ensure an optimal QoL. Although not frequent in prostate cancer patients, hypercalcaemia is clinically important due to the associated morbidity.[1] If left untreated, moderate to severe hypercalcaemia (serum calcium >3.0 mmol/L) can lead to a number of debilitating side-effects, and may result in fatal cardiac arrythmias and renal failure.[1]

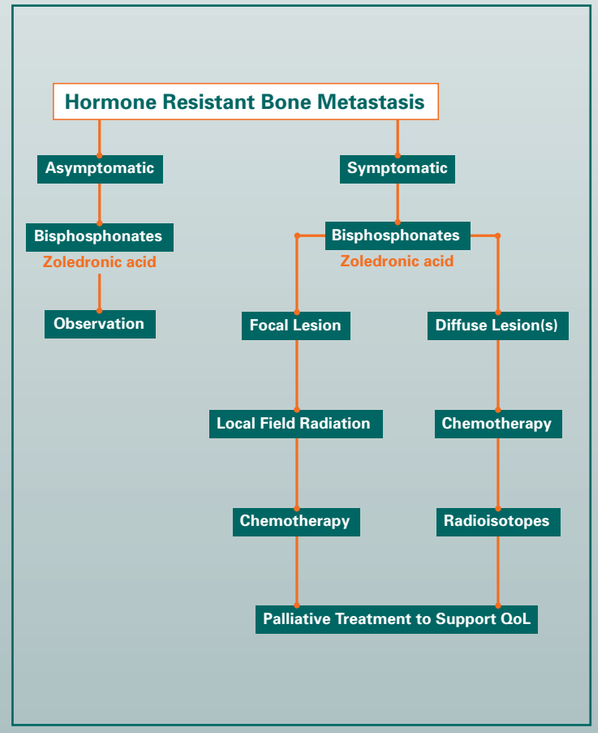
Regrettably, few therapies have been shown to delay the overall progression of metastatic prostate cancer. Consequently, since alleviating the complications of SREs has an immense impact on QoL, the principal goal of current treatment strategies is the prevention of these complications in both asymptomatic and symptomatic patients. Treatment options for prevention and palliation include bisphosphonates, radiotherapy, orthopaedic interventions and analgesics.

Treatment Options

Bisphosphonates

Bisphosphonates are stable analogues of the pyrophosphate molecule that inhibit bone resorption due to enzymatic hydrolysis by osteoclasts, as a consequence of their accumulation in the mineralised matrix of bone.[7] This family of synthetic drugs vary in clinical activity and potency due to differences in their chemical structure, resulting from variations in the combination of side-chains attached to a central carbon atom.[7] Often used as a supplementary approach to radiotherapy, bisphosphonates have now become part of the standard therapy for the treatment and prevention of SREs in patients with metastatic prostate cancer.[2] The use of bisphosphonates in SRE therapy is reflected in existing treatment algorithms (Figure 1).[8]

Figure 1: Algorithm for the Treatment of Symptomatic and Asymptomatic Hormone-Resistant Bone Metastases in Patients with Prostate Cancer [8]



In clinical trials[9,10,11] bisphosphonates have been shown to be an effective therapy for the treatment of bone metastases in other cancers. Recommended by the National Institute for Clinical Excellence (NICE), these drugs are now widely used to treat the skeletal consequences of advanced breast cancer.[12,13] A variety of bisphosphonates have been used for the treatment of bone pain in metastatic prostate cancer patients, either individually or in combination therapies. These include relatively low-potency drugs such as etidronate, clodronate, and pamidronate, and more recently, the high potency bisphosphonate, zoledronic acid. One major difference between breast and prostate cancer is that early generation bisphosphonates have failed to show a great benefit to metastatic prostate cancer patients.[14,15,16,17,18]

Etidronate and Clodronate

First generation, non-nitrogen containing bisphosphonates; etidronate and clodronate, were introduced clinically over 30 years ago.[7] Studies investigating the efficacy of these bisphosphonates in palliating painful bone metastases in patients with prostate cancer have shown them to be largely ineffective.

Table 1: Summary of Clodronate and Etidronate Trial Data

Author	Test Drug	n	Conclusion
Smith et al[14] 1989	Etidronate	51	No Treatment Benefit
Dearnley et al[15] 2003	Clodronate	311	No Significant Benefit
Elomaa et al[16] 1999	Clodronate	75	Non-Significant Symptomatic Benefit
Cresswell et al[17] 1995	Clodronate	27	Benefit short lived
Ernst et al[18] 2003	Mitoxantrone/Prednisone +/- Clodronate	209	No Significant Benefit

Pamidronate

Pamidronate, an example of a nitrogen containing bisphosphonate, has an aliphatic side chain containing a single nitrogen atom, and is a more potent inhibitor of bone resorption than the first generation drugs, clodronate or etidronate.[19] However, a recent combined analysis[20] of two multi-centre, double-blind, randomised, placebo-controlled trials consisting of 374 patients reported that pamidronate had no significant clinical benefit for the palliation of bone pain in metastatic prostate cancer patients.

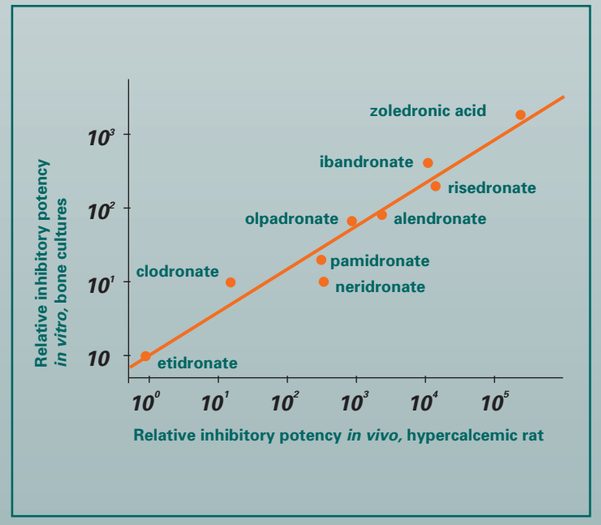
Zoledronic Acid

Zoledronic acid, a new generation high-potency bisphosphonate, is a heterocyclic nitrogen-containing compound with an imidazole ring side-chain containing two nitrogen atoms.[19] Due to its nitrogen content, this

compound inhibits protein prenylation and induces osteoclast apoptosis. In addition, it has been proposed that zoledronic acid has a direct inhibitory effect on osteoclast maturation, mature osteoclast cell function, and the recruitment of osteoclasts to the site of bone resorption.[21] Moreover, inhibition of tumour cell dissemination, as well as invasion and adhesion to the bone matrix has been demonstrated with this bisphosphonate in breast and prostate cancer cells.[22]

Zoledronic acid is currently the only bisphosphonate licensed for use in prostate cancer,[23] and has been shown to be a potent and effective treatment for the palliation and prevention of SREs in patients with advanced breast cancer, multiple myeloma and metastatic prostate cancer.[23,24,25] The substantially increased potency of this drug compared to other bisphosphonates has been attributed to its unique molecular structure, specifically the position of the second nitrogen atom (Figure 2).[19]

Figure 2: The Correlation between *in vitro* and *in vivo* Potencies of Bisphosphonates[19]



In a recent phase III, randomised, placebo-controlled trial[25] of 643 patients with HRPC and a history of MBD, patients were administered either 4 mg zoledronic acid, 8 mg (subsequently reduced to 4 mg) zoledronic acid, or placebo every 3 weeks for 15 months. Pathological fractures and the need for radiation to bone were the most frequently observed SRE, and treatment with 4 mg zoledronic acid was shown to significantly reduce the proportion of patients with a pathological fracture (13.1% versus 22%; p=0.015).[26] The significant incidence of pathological fractures in this trial implies that prostate cancer patients with osteoblastic lesions are at high risk of developing pathological fractures and other SREs that have traditionally been associated with osteolytic lesions. Therefore, the use of a potent bisphosphonate such as zoledronic acid that inhibits bone resorption may have a significant impact on the morbidity associated with osteoblastic lesions in metastatic prostate cancer patients.

There were no significant differences in time to disease progression (84 days), performance status, or QoL scores between treatment groups. Whilst zoledronic acid at 4 mg was well tolerated by patients, the 8 mg dose was associated with renal function deterioration. Patients treated with 8 mg zoledronic acid had a higher incidence of elevated serum creatinine levels than patients treated with 4 mg of zoledronic acid.[25] The authors of this study concluded that doses of zoledronic acid greater than 4 mg were therefore not recommended.[23]

In an extension phase of this study[23] lasting 9 months (total study time of 24 months), 186 patients who completed the 15-month core phase study were evaluated for the long-term efficacy of zoledronic acid. In terms of preventing further SREs, significantly fewer patients (38%) treated with 4 mg zoledronic acid every 3 weeks had an SRE, compared to 49% of the placebo group (p=0.028).[23] Furthermore, treatment with 4 mg zoledronic acid resulted in a significant advantage over placebo in delaying the time to the first SRE (488 days compared to 321 for placebo group; p=0.009).[23]

Long-term use of zoledronic acid also demonstrated a powerful and long lasting effect on bone pain.[23] Even though all patients showed a mean reduction in composite pain scores from baseline, periodic measures of BPI scores demonstrated a statistically significant and durable palliation of bone pain for those patients on 4 mg zoledronic acid every 3 weeks, compared to patients receiving placebo at 18 (p=0.075), 21 (p=0.014) and 24 (p=0.024) months.[23] For patients with a history of SREs, the long-term administration of zoledronic acid may therefore help to sustain QoL. Additionally, treatment early in the disease course may be beneficial for asymptomatic metastatic prostate cancer patients, through the prevention of a primary SRE. The use of zoledronic acid in patients with hormone-sensitive cancer that has metastasised to bone is currently the subject of an ongoing trial.[8] Currently, the licenced indication for zoledronic acid is for treatment of advanced malignancy involving bone, this includes both hormone-naïve and hormone refractory prostate cancer patients with bone metastases.

Radiotherapy

Radiotherapy is an established treatment for metastatic bone pain in patients with prostate cancer.[27] External beam radiation therapy is effective for the palliation of both localised and diffuse sites of pain, and pain relief can be both dramatic[28] and long lasting.[29,30] However, due to potential toxicities to visceral structures and difficulties in treatment set-up with external beam radiation therapy, radionuclides, which have no systemic toxicities other than effects on blood counts, have gained popularity in the treatment of patients with multifocal bone pain due to prostate cancer induced metastases. Strontium-89 is the most popular choice of radiopharmaceutical for the palliation of diffuse or widespread pain. The main limiting factor when using radionuclides is mild bone marrow suppression, which is also a feature of the late stages of prostate cancer.

Orthopaedic Interventions

Untreated pathological fractures rarely heal, and in the majority of cases primary internal stabilisation of the bone prior to radiotherapy is the treatment of choice. Patients with metastatic disease in the spine or long bones may be candidates for prophylactic fixation.[31] In these cases stabilisation of the spine is the only solution. Current systems for spinal stabilisation include the use of hooks and screws to attach rods to the posterior spine at multiple levels, stabilising the spine immediately. This allows the patient to be ambulatory on the first post-operative day, eliminating the need for body casts or prolonged periods of bed rest and leading to an improved quality of life.[31] Although spinal stabilisation is associated with significant morbidity and mortality, with careful patient selection, excellent results may be obtained.

Analgesics

The World Health Organisation (WHO) has determined guidelines for the management of pain that may be applied to manage metastatic prostate cancer patients. Treatment should be in line with this guidance, with medication given regularly (to prevent pain), and by the 'ladder': a stepwise progression from non-opioids, to 'weak' opioids, to strong opioids with appropriate adjuncts (including neuropathic agents, radiotherapy, chemotherapy, surgery etc).[32]

Critical Considerations

Critical issues that impact on a patient's QoL must be addressed when considering additional systemic treatment including anorexia, nausea, constipation, fatigue and depression. It is essential therefore to have a multi-disciplinary approach to palliation, with input from medical oncologists, radiation oncologists, urologists, nurses and social workers.[33]

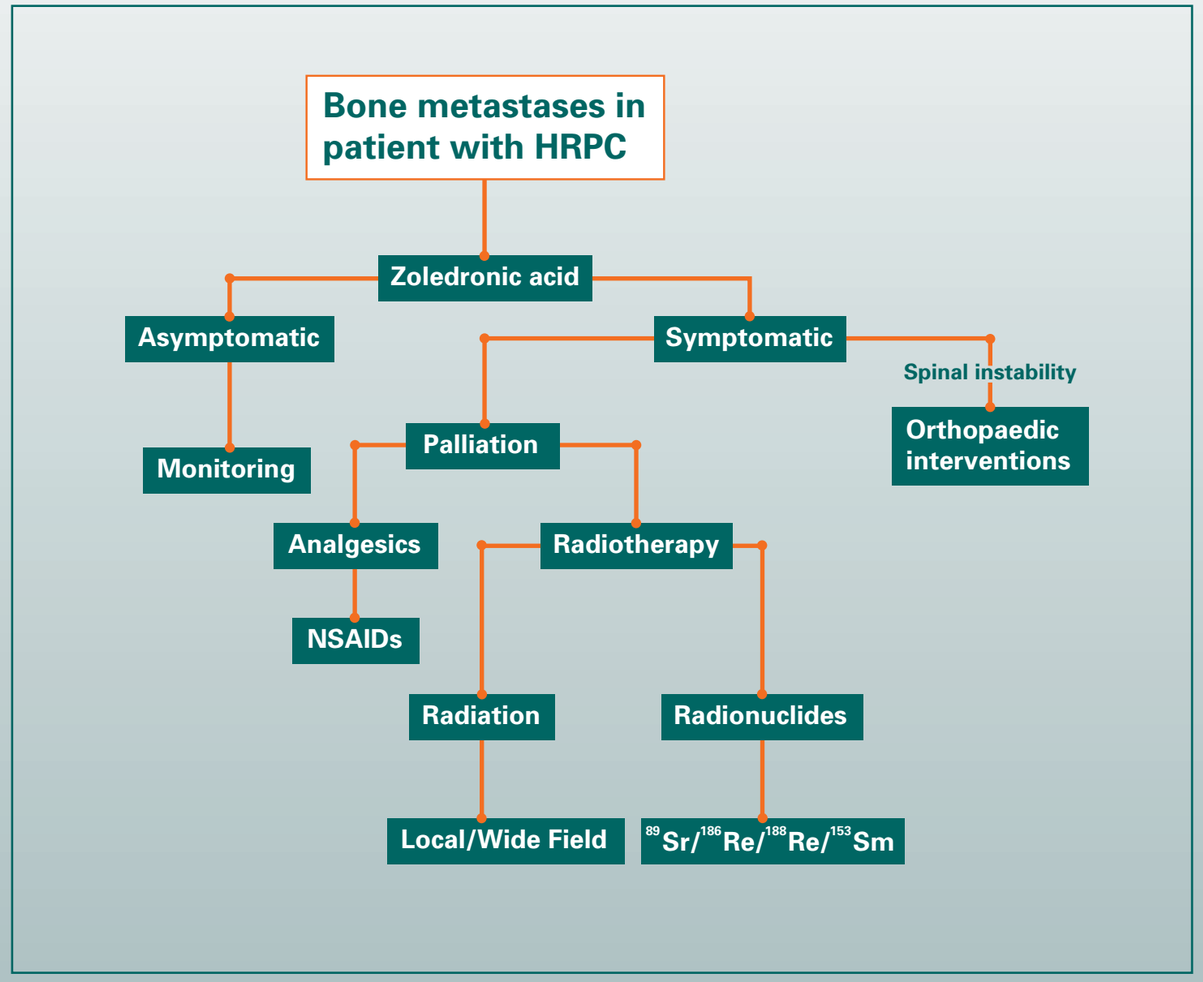
3.0 Conclusion

Although bisphosphonates have become part of the standard therapy for the treatment and prevention of SREs in patients with metastatic prostate cancer, the efficacy of some of this family of synthetic drugs remains unclear. Low-potency drugs such as etidronate, clodonate and pamidronate administered either alone or as combination therapies have failed to show significant differences in time to symptomatic progression,[14] overall survival,[14,15] or the palliation of pain.[18,20] In studies where a significant reduction in bone pain and the use of analgesics has been reported,[15,16] the duration of pain relief has been short lived.[16]

Zoledronic acid, a high-potency bisphosphonate, has been shown to be effective in bone pain, reducing the number of pathological fractures, and delaying time to first SRE.[22,24,25] Additionally, evidence suggests a role for the early treatment of asymptomatic metastatic prostate cancer patients with zoledronic acid in preventing primary SREs. A study by Brown *et al*[24] has reported that bone resorption markers may be useful to identify patients at high risk for SREs and therefore have the potential to facilitate the selection of patients for bisphosphonate therapy.

As yet, zoledronic acid has shown no significant difference in time to disease progression, performance status, or patient QoL when compared with placebo.[24] With careful patient selection, radiotherapy, orthopaedic interventions, and analgesics also play an important role in the management of MBD.

Figure 3: Management Algorithm



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