SECTION I

Clinical spectrum of hormone-refractory prostate cancer
Chapter 1

General Introduction

R.C.M. Pelger¹, V. Soerdjbalie-Maikoe¹, N.A.T. Hamdy².

From the Departments of Urology¹ & Endocrinology and Metabolic Diseases²,
Leiden University Medical Center, Leiden, The Netherlands.

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1.1 Epidemiology and clinical spectrum of skeletal metastases.

In the skeleton, metastatic lesions are much more frequently encountered than primary malignancies and are usually multiple. Solitary osseous metastases are rare except in patients with renal cell carcinoma or neuroblastoma in whom 5% to 10% may have a single site skeletal metastasis. Overall, the skeleton is the most common site of cancer metastasis, closely followed by lung and liver.

The most common primary tumours developing bone metastases are those arising in breast, bronchus and prostate. In these malignancies autopsy studies have shown metastases in over 80% of patients dying from the primary tumour. In breast and prostate cancer, the prevalence of bone metastases has been shown at autopsy to be as high as 84%, whereas it is 50% in thyroid cancer, 44% in lung cancer and 37% in renal cancer.

Within the skeletal system, metastases are distributed centrally, with rare peripheral involvement. This is because metastatic foci are located predominantly in red bone marrow, so that more than 80% of metastases are to the axial skeleton and the spine, pelvis and ribs are consequently the most commonly involved sites, followed by the proximal ends of long bones, sternum and skull. Spinal metastases predominantly occur in the vertebral bodies, affecting most often the lumbar vertebrae, followed by thoracic, cervical and sacral sites.

**Prostate cancer (PC)** is the most common non-cutaneous malignancy and the second leading cause of cancer-related deaths in the USA. Across the world, the incidence of PC varies widely from country to country. It is thus relatively high in North America and in Northern Europe, intermediate in Southern Europe and Central and South America and low in Asia. In Europe, PC is the second most frequently diagnosed cancer. In the Netherlands the incidence of PC has increased from 22 per 100,000 between 1955 and 1959 to 33 per 100,000 between 1990 and 1994 with 6,535 new cases reported in 1998.

The apparent worldwide increase in the incidence of prostate cancer is likely to be due to an increased use of prostate specific antigen (PSA) measurement in screening for the malignancy.

PC metastasizes most commonly to lymph nodes, with bone being the second most common metastatic site and autopsy studies demonstrating skeletal metastases in up to 84% of patients. In patients with PC and skeletal metastases, prognosis varies widely between individuals because of general factors such as age and performance status.
at the time of diagnosis. Other prognostic factors such as extent of involvement on skeletal scintigraphy, rate of tumour growth, evidence of hypercalcaemia or leucoerythroblastic anaemia and the level of serum alkaline phosphatase activity and renal function at the time of presentation also play a role\textsuperscript{10,32}.

1.2 Pathophysiology of skeletal metastases.

The ability of malignant cells to invade a host’s normal tissues resulting in metastases is the most fearsome and disastrous aspect of cancer because of its prognostic implications. Despite remarkable advances in diagnosis and treatment using surgery and adjuvant local or systemic therapies, metastases remain the leading cause of death in patients with cancer. This is due to several obstacles encountered in the management of metastatic disease\textsuperscript{2}. Micrometastases are thus commonly missed at the time of diagnosis. Metastases may also be located in several organs at diagnosis and treatment may be complicated by organ toxicity. However, the most important reason for failure of successful treatment seems to be the biological diversity of the metastatic tumour cells. This heterogeneity results in differences in response of individual metastases to therapy. At the time of diagnosis, metastatic lesions may be fairly large so that eradication of all metastatic cells is not achieved, resulting in further biological heterogeneity. Better understanding of the metastatic process and of the heterogeneity of cancer cells should provide a basis for the development of more effective therapies for metastasized cancer.

Skeletal metastases occur as a result of haematogenous dissemination of cancer cells\textsuperscript{120}. Micrometastatic tumour cells can be detected in the bone marrow of 25-75\% of patients with common malignancies\textsuperscript{118}. However, not all such cells will grow or alter the structure of bone to become clinically significant metastases, reflecting the tumour specific nature of bone metastases formation. In 1889, Stephen Paget suggested that the formation of bone metastases is not a matter of chance, but that it demonstrated a dependance of the seed upon the soil\textsuperscript{119}. The pathogenesis of cancer metastases is described by Fidler\textsuperscript{1,2}, summarized by Nielsen\textsuperscript{3} and extensively reviewed by Guise and Mundy\textsuperscript{60}.

Metastasis to the skeleton is attributed to a combination of anatomical factors and other determinants of site of metastases such as tumour cell phenotype and suitability of the metastatic site for tumour growth.

- Within the anatomical factors, the plexus containing the portal, pulmonary and caval systems, plays a mayor role. Batson\textsuperscript{7} describes in detail a low-pressure high-volume
system of valveless vertebral veins in which the spinal and intercostal veins communicate independently of the pulmonary, caval or portal systems. Through extensive injection studies of the prostatic plexus and venules of the breast in male and female cadavres as well as in animals, Batson described the vertebral veins as a system consisting of the epidural veins, the perivertebral veins, the veins of the thoraco-abdominal wall, the veins of the head and neck and the veins of the walls of blood vessels of the extremities; of valveless vessels that carry blood under low pressure; subject to arrest and reversal of blood flow; that parallels, connects with, and provides by-passes for the portal, pulmonary and caval systems. This plexus may serve as a major channel by which certain malignancies such as prostate and breast cancer metastasize to bone.

The concept that the vertebral system of veins acts as a direct conduit for the specific spread of prostatic carcinoma to the skeletal system was refuted however by Dodds et al. After analyzing $^{99m}$technetium bone scans in patients with bone metastases due to prostate cancer, these authors found that the distribution of metastases was indeed virtually identical in patients with prostatic and non-prostatic tumours.

Determinants of the site of metastases (seed and soil) are very important in understanding the metastatic process. A cascade of linked sequential events must be completed before a secondary tumour is established in bone. These steps are described as follows:

1. Detachment of the tumour cell from its primary site.
2. Entrance of the tumour cell in the vasculature to reach the peripheral circulation.
3. Survival of the tumour cell to the host immune response and to physical forces encountered in the peripheral circulation.
4. Arrest of the tumour cell in a distant capillary bed.
5. Escape of the tumour cell from the capillary bed.
6. Proliferation of the tumour cell in the metastatic site.

The morphological changes associated with bone invasion fall into two separate components: bone destruction (osteolysis) and bone formation (osteosclerosis). In most cancers, especially breast cancer, osteolytic lesions predominate whereas osteosclerotic metastases most commonly occur in patients with prostate cancer and in some breast and lung cancers. However, mixed osteolytic and osteoblastic lesions are often evident in both breast and prostate cancer, and the appearance of osteolytic and osteosclerotic metastases is characteristic, but not specific, with no qualitative differences.
between both types microscopically\textsuperscript{3,6}. The proportion of bone destruction and bone formation varies also between different types of metastatic lesions. In osteolytic lesions, destruction predominates and bone formation is minimal, whereas in osteosclerotic lesions the situation is reversed\textsuperscript{6}, with radiological appearances merely reflecting the net result of both processes\textsuperscript{3,8-12}. Lesions thus appear osteolytic when bone destruction predominates and osteoblastic when bone formation predominates\textsuperscript{3,6,11}. It is the osteoblastic response which provides the morphological basis for the scintigraphic changes\textsuperscript{6}. Radiologically mixed lesions demonstrate a combination of bone formation and bone destruction\textsuperscript{11}.

The process of \textit{bone destruction} (osteolysis) is initiated by osteoclasts under the influence of osteoclast-stimulating factors locally produced by metastatic tumour cells or by the host’s stromal cells\textsuperscript{3,6,9,13,14}. Bone is unique among metastatic target tissues since it undergoes continual remodeling under the influence of systemic hormones and of locally released bone-derived growth factors, of which TGF-\(\beta\) and IGF-1 are the most important\textsuperscript{60,62}. During the normal remodeling process, these growth factors are released from the bone matrix by the process of normal or enhanced osteoclastic bone resorption\textsuperscript{60,63}. In order for a cancer cell (the seed) to grow in bone (the soil), the cancer cell must possess the capacity to cause bone destruction. Breast cancer is the most common tumour associated with osteolytic lesions so that study of the pathophysiology of cancer-mediated osteolysis has focused on this type of cancer\textsuperscript{60}. Histological review of breast cancer metastatic to bone reveals that tumour cells are found adjacent to bone-resorbing osteoclasts\textsuperscript{60,64-66}, indicating that breast cancer cells possess the capacity to stimulate osteoclast-mediated bone resorption. This may occur as a result of inducing osteoclastic differentiation of haematopoetic stem cells, activating mature osteoclasts or stimulating both processes by releasing soluble mediators or by cell-to-cell contact\textsuperscript{60}. Clinical and experimental studies suggest that tumour-produced PTHrP represents a major factor in the induction of the osteoclast-mediated bone resorption observed in breast cancer metastatic to the skeleton\textsuperscript{67-69}. PTHrP has thus been detected by immunohistochemistry\textsuperscript{67} and by in situ hybridization\textsuperscript{68} in 92% of skeletal breast cancer metastases compared to only 17% of similar non-skeletal metastases: an observation that prompted speculation that production of PTHrP as a bone-resorbing agent may contribute to the ability of breast cancer cells to grow in bone\textsuperscript{60}. No consistent correlations have been observed, however, between PTHrP expression and progression-free survival in primary
breast tumours. The first step in the process of osteolysis after arrival of the tumour cell (seed) in bone is the stimulation of osteoclastic bone resorption by secretion of PTHrP. This results in release and activation of growth factors present in the bone matrix, such as TGF-ß, IGF-1 and IGF-1. TGF-ß increases in turn tumour production of PTHrP and of IGF-1 which further stimulates tumour cell growth. Local concentrations of bone-derived growth factors result in an increase in PTHrP production, in tumour cell growth and in chemotaxis, further amplifying the metastatic process.

The concept that bone is a fertile soil for tumour cells further enriched by the process of osteoclastic bone resorption, has led to the trial of bisphosphonates in the management of skeletal metastases. Having demonstrated the ability of these agents to decrease the number of bone metastases as well as the tumour burden in animal models, clinical studies indeed demonstrated that bisphosphonates, potent inhibitors of bone resorption, significantly reduce skeletal morbidity in advanced breast cancer. By decreasing osteoclastic bone resorption, bisphosphonates appear to alter “the soil” thus resulting in a bone micro-environment that is less fertile for the growth of tumour cells.

In the process of bone formation, a process mediated by osteoblasts, two mechanisms are described named stromal and reactive. Stromal bone formation is the earliest less important process consisting of the development of intra-membranous ossification areas within the fibrous stroma. Reactive new bone formation is the most important of the two processes, in which bone is laid down as a response to stress on the weakened bone, analogical to the development of callus in fracture healing.

Osteoblastic metastases are predominant in prostate cancer. Over the past few years, several animal models have provided insight into the pathophysiology of prostate cancer metastatic to the skeleton. Thalman et al. reported that the subcutaneous or orthotopic inoculating of an androgen-independent clone of the LNCaP human prostate cancer cell line into castrated male nude mice resulted in spontaneous metastasis to bone in 11-50% of mice and that new bone formation was histologically observed at the metastatic sites. Greenberg et al. developed a transgenic mouse model of spontaneous prostate cancer, in which the simian virus 40 (SV40) large tumour T antigen is driven by the rat probasin promotor to target the dorso-lateral epithelium of the prostate (TRAMP mice). In this model, 100% of mice develop distinct pathological lesions in the dorso-lateral epithelium of the prostate by 10 weeks of age that range from mild intra-epithelial hyperplasia to...
large multinodular malignant neoplasia\textsuperscript{90}. Distant metastases occur as early as 12 weeks in common sites such as peri-aortic lymph nodes and lungs and in less common sites such as kidney, adrenal glands and bone\textsuperscript{91}. Gingrich et al\textsuperscript{91} reported that one of these TRAMP mice developed paraplegia and was found to have metastases in the spinal canal. As prostate cancer is more frequently associated with osteoblastic metastases, prostate cancer cells must possess properties different from tumour cells associated with osteolytic metastases\textsuperscript{60}. Several studies indeed indicate that prostate cancer cells are a source of osteoblast-stimulating activity\textsuperscript{60}. Conditioned media from Xenopus oocytes injected with total RNA from the human prostate cancer cell line PC3 stimulated both mitogenesis and alkaline phosphatase activity in osteosarcoma cells with the osteoblast phenotype\textsuperscript{93}. In foetal rat calvarial cells, PC3-conditioned media stimulated osteoblast proliferation\textsuperscript{94}. Koutsilieris et al\textsuperscript{95} found that extracts of prostate cancer tissue and normal prostate tissue stimulated proliferation of bone cells.

The following tumour products have been proposed to be important in the genesis of the osteoblastic response to tumour cells in bone: transforming growth factor-\(\beta\) (TGF-\(\beta\)), insulin-like growth factor (IGF-1 and 11), the proteases (PSA, uPA), FGFs, bone-morphogenetic proteins (BMPs) and Endothelin-1. TGF-\(\beta\), isoforms 1 and 2 in particular, are produced by prostate cancer cells and local concentrations appear to be greater in this malignancy than in the normal prostate or than in benign prostate hypertrophy\textsuperscript{96}. Although data-based evidence is lacking to demonstrate a direct relationship between tumour-produced TGF-\(\beta\) and the development of osteoblastic metastases, the fact that TGF-\(\beta\) is produced by prostate cancer cells coupled with its effect on bone formation suggests the implication of this growth factor in the pathophysiology of cancer-mediated osteoblastic metastases\textsuperscript{60}. Insulin Growth Factors (IGFs) are potent mitogens for the growth of human prostate cancer cells and primary cultures of prostate epithelial cells demonstrated expression of IGFs, IGF receptors and IGF-BPs\textsuperscript{97}.

Proteases. PSA (prostate specific antigen) is a serine protease, single chain glycoprotein with a trypsin-like and chymotrypsin-like enzymatic activity\textsuperscript{98}. PSA was initially believed to be produced exclusively by prostate epithelial cells so that it has been widely used as a marker for prostate cancer\textsuperscript{99}. An increased serum PSA concentration may actually be observed in three different clinical situations: prostate cancer, benign prostatic hypertrophy and acute bacterial prostatitis\textsuperscript{100}. Androgenic hormones increase the production of PSA via transcriptional regulation\textsuperscript{102}. In patients with prostate cancer,
serum PSA concentration has been shown to be of significant value in predicting disease outcome after radiation therapy for local and regional prostate cancer\textsuperscript{101}. Serum PSA has also been shown to correlate significantly with the presence of bone metastases on radionuclide scanning\textsuperscript{103}. In a large study of 521 men with newly diagnosed untreated prostate cancer, Chybowski \textit{et al}\textsuperscript{104} demonstrated that only 1 of the 306 patients with a serum PSA concentration less than 20 ng/ml had a positive bone scan for skeletal metastases. Serum PSA concentration was indeed demonstrated to be the best predictor of bone scan findings when compared with tumour grade, local clinical stage, serum acid phosphatase and prostate acid phosphatase\textsuperscript{104-106}. In the light of their findings the authors concluded that a bone scintigraphy may not be necessary in a newly diagnosed patient with prostate cancer in the presence of a serum PSA concentration of less than 10 ng/ml and in the absence of skeletal symptoms\textsuperscript{103}. Although it was believed that PSA was exclusively a product of prostate epithelial cells, immunoreactive PSA has also been recently demonstrated in 27\% of 174 patients with breast cancer\textsuperscript{107}. This breast-derived PSA was identical to prostate-epithelial PSA\textsuperscript{108} and has been shown to be also produced at ovarian metastatic sites for breast cancer\textsuperscript{109}.

The function of PSA in prostate cancer remains unclear, although its proteolytic activity may prove to be important in the genesis of an osteoblastic response to prostate cancer tumour cells in bone\textsuperscript{60}.

Bone Morphogenetic Proteins (BMPs) induce ectopic bone formation in vivo and one of these proteins, BMP-6, is highly expressed in skeletal metastases from prostate cancer\textsuperscript{110}.

In prostate cancer, the process of osteoblastic metastasis as currently proposed can be summarized as follows. Tumour factors such as TGF-\(\beta\), FGFs, BMPs and ET-1 directly stimulate osteoblastic activity and subsequent bone formation, whereas proteases such as PSA, uPA and cathepsin D activate latent TGF-\(\beta\), release IGFs from binding proteins and inactivate PTHrP. Although osteoblastosis is a common phenotype of metastases in prostate cancer, osteolysis is likely to be necessary for prostate cancer cells to colonize bone\textsuperscript{117}. Induction of radiologically detected extensive osteolysis due to increased osteoclasts at the bone surface can indeed be demonstrated after injection of PC3, an androgen-insensitive cell line derived from metastatic lesions, intracardially or into tibiae of athymic male mice\textsuperscript{131}. At the site of metastases, bone-resorbing factors such as macrophage-colony stimulating factor (M-CSF), parathyroid hormone-related peptide (PTHrP) and interleukins (IL-1 and IL-6)\textsuperscript{131} were found to be expressed, with PTHrP
being the most robustly resorbing factor\textsuperscript{111-113}. Prostatic cancer cell’s expression of PTHrP is associated with regulatory effects and interactions that are important in the development and progression of prostate carcinoma\textsuperscript{111}. Recent studies provide evidence for a role of PTHrP expression in the development of bone metastases in patients with prostate cancer\textsuperscript{111-114}. The association of PTHrP expression with the development and progression of bone metastases has already been established for breast carcinoma. Corresponding studies have been reported in prostate cancer\textsuperscript{112,113,115-117}. Tatsuo et al\textsuperscript{132} recently described two members of the tumour necrosis family, RANK-ligand (osteoclast differentiation factor) and the receptor for M-CSF. RANK-ligand reacts with RANK, the receptor activator of NF-kB, which is localized in haematopoetic osteoclast-precursors and stimulates osteoclast formation. Molecular studies demonstrated allelic loss present in more than 50\% of cases on chromosomes 8p, 10q and 16q\textsuperscript{272} to be a common finding in prostate cancer. The presence or inactivation of tumour suppression genes may also play a role in carcinogenesis.

1.3 Pathology of prostate cancer.

In the last decade, the introduction of the automated spring-loaded 18-gauge core-biopsy gun signaled the dawn of a new era in sampling the prostate for histologic diagnosis. Needle biopsy samples tissue from the peripheral zone of the prostate, unlike TURP, which samples tissue from the transition zone, urethra, periurethral area, bladder neck and anterior fibromuscular stroma. Studies of radical prostatectomies performed after TURP reveal that the resection does not usually include tissue from the central and peripheral zones, and that not all of the transition zone is removed. Well-differentiated cancer found incidentally in TURP chips usually represents cancer that has arisen in the transition zone. These tumours are frequently small and may be completely resected by TURP. Conversely, poorly differentiated cancer found in TURP chips usually represents part of a larger tumour that has invaded the transition zone after arising in the peripheral zone. Gleason scoring should be undertaken and reported in all prostate needle biopsies, even in those with small amounts of tumour. When compared with matched prostatectomy specimens, needle core biopsy underestimates tumour grade in 33-45\% of cases and overestimates tumour grade in 4-32\% of cases\textsuperscript{268}. Prostatic intraepithelial neoplasia (PIN) represents the putative pre-cancerous end of the morphologic continuum of cellular proliferation of prostatic ducts, ductules and acini\textsuperscript{269}. Two grades of PIN are identified
(low-grade and high-grade) and high-grade PIN is considered to be the pre-invasive stage of invasive prostate carcinoma.

The peripheral zone of the prostate, the area in which the majority of prostatic carcinomas occur (70%), is also the most common localisation for PIN\textsuperscript{270}.

Diagnosis of prostate adenocarcinoma relies on a combination of architectural and cytologic findings. It usually consists of a proliferation of small acini lined by atypical luminal epithelial cells with nuclear and nucleolar enlargement with a complete lack of basal cell layer\textsuperscript{271}. In problematic cases, it may be useful to use monoclonal antibodies directed against high molecular weight keratin (e.g. 34β-E12) to evaluate the basal cell layer. Perineural invasion is common in prostate adenocarcinoma and represents strong evidence of malignancy, although not pathognomonic of it. The histologic pattern of prostate cancer correlates significantly with biological malignancy. The Gleason grading system, based on the Veterans Administration Cooperative Urological Research Group (VACURG) study of more than 4000 patients between 1960 and 1975, is the de-facto grading standard. It is based on the degree of glandular differentiation, reflecting tumour heterogeneity by assigning a primary pattern for the dominant grade and a secondary pattern for the non-dominant grade. The histologic score is derived by adding the two patterns. Gleason noted that more than 50% of cancers contained two or more patterns. The Gleason grade is one of the strongest predictors of biological behaviour in prostate cancer. There is general agreement that low Gleason grades (1-6) reflect localized prostate cancer and that the higher grades (8-10) correlate with a higher incidence of advanced invasive disease. A Gleason grade of 7 is accepted to be the cut-off point for discriminating local from invasive disease.

Despite the fact that benign prostate hypertrophy and prostatitis can elevate serum PSA concentrations, this remains the most accurate and clinically useful biochemical marker for diagnosing prostate cancer.

**1.4 Natural history of prostate cancer.**

Prostate cancer metastases frequently to the skeleton, most commonly to the vertebrae, pelvic bones and lower extremities. Patients may present de novo with advanced disease and painful skeletal metastases, but this is uncommon\textsuperscript{258}. Androgen ablation, first described ± 60 years ago\textsuperscript{121}, is the treatment of choice for metastatic prostate cancer.
Androgens are essential for the normal development of the prostate and are predominantly formed in the testicles (95%), with a small amount being produced by the adrenals (5%). Adrenal androgens are transformed into testosterone in target cells such as the prostate and adipose tissue. It is only the free, unbound fraction of testosterone (2%) which is physiologically active because bound testosterone is unable to cross the cell membrane. The effectiveness of androgen ablation in the management of advanced prostate cancer is based on the androgen dependency of prostate cancer cells. These cells express androgen receptors, which after complexing with dihydrotestosterone, are transduced into the nucleus and bind dimerally to the androgen response element in the genome, inducing cell growth\(^{122}\). Androgen ablation results in apoptosis of these androgen-sensitive cells and can be achieved by surgical castration or by medical castration using oestrogens, anti-androgens, luteinizing hormone-releasing hormone (LHRH) analogues or progestational agents\(^3\). Castration is the gold standard of hormonal therapy in advanced prostate cancer. Most patients respond to this procedure with a significant reduction in bone pain due to regression of metastases and survival is prolonged\(^3,17\). Medical castration in the form of LHRH agonists, steroidal/non-steroidal anti-androgens or combined endocrine therapy is equally effective and may be more appropriate\(^3,17\). 70-80% of previously untreated patients with advanced prostate cancer are expected to respond favourably with significant regression or disappearance of metastases\(^287\). This is illustrated in bone scintigraphy images obtained in a patient with prostate cancer metastatic to the skeleton prior and 6 months after androgen deprivation (Figure 1). This therapy has, however, a substantial impact on the patient’s quality of life because of symptoms associated with androgen deprivation, such as impotence, hot flushes, anaemia, obesity, muscle atrophy, gynaecomastia, mood changes and depression. An increased risk for osteoporotic fractures\(^123\) and a reduction in plasma levels of high density lipoprotein cholesterol with subsequently increased risk for cardiovascular disease, has also been reported\(^288\).
1.5 **Hormone-refractory prostate cancer (HRPC).**

In most patients with prostate cancer, the tumour becomes unresponsive to androgen deprivation within 2 to 3 years of androgen ablation and patients are diagnosed as having hormone-refractory prostate cancer (HRPC). Hormone-refractoriness is associated with rapid disease progression heralded by progressively worsening bone pain due to unchecked spread of skeletal metastases. Standard therapeutic options for patients with HRPC include additional hormonal therapies (LHRH-agonists or antiandrogens) or chemotherapy. The use of intermittent androgen appears promising. In this latter form of treatment, periods of androgen-ablation are followed by periods of androgen-restitution, a treatment schedule which appears to significantly improve quality of life. It has been suggested that the regrowth and presence of androgen-dependent cells may have a prohibitive effect on the growth of androgen independent cells. This may result in longer survival and progression-free survival. Although secondary hormonal manipulations may produce a subjective response in approximately 25% of patients, the benefit is usually short-lived (approximately 4 months). Novel therapeutic agents are
being explored in these patients. An understanding of the mechanisms of resistance associated with HRPC is necessary to develop these agents. Several genetic alterations seen in advanced prostate cancer may lead to hormone-refractoriness. Overexpression of oncogenes or mutations in tumour suppressor genes have been implicated in the development of the hormone-refractory stage of prostate cancer. For example the bcl-2 oncogene is highly expressed in HRPC\textsuperscript{122}, whereas patients with hormone-sensitive disease have low levels of bcl-2 expression\textsuperscript{328}. Bcl-2 belongs to a family of proteins that control apoptosis or programmed cell death characterized by active participation of the cell in its own demise by providing the enzymes and energy for the process\textsuperscript{327}. Overexpression of bcl-2 prevents apoptosis by dimerization with Bax and inhibits the death of prostate cancer cells\textsuperscript{122,326}. Bax is a member of the family of proteins related to bcl-2.

Point mutations in the ras gene family leading to abnormal growth and transformation of tissue have been found to correlate with the progression of prostate cancer\textsuperscript{329}. Mutations in p53, a tumour suppressor gene, are also associated with progression of prostate cancer to a hormone-refractory stage\textsuperscript{330,331}. Increased levels of mutant p53 have been found in HRPC cells\textsuperscript{331}.

The Rb (retinoblastoma) gene, a tumour suppressor gene, and the myc oncogene, along with other genetic changes play an as yet undefined role in the progression of prostate cancer to HRPC\textsuperscript{332,333}.

Although use of chemotherapy has been shown to be associated with longer survival and progression-free survival\textsuperscript{258} and the taxane class of antimicrotubule chemotherapy agents such as paclitaxel and docetaxel have shown promise as second line therapies in hormone-refractory prostate cancer\textsuperscript{159,160}, there is still no consensus on the chemotherapy regimen of choice in advanced stages of prostate cancer, so that the mainstay of treatment remains to date largely palliative.

\subsection*{1.6 Skeletal-related events in HRPC.}

\textit{Bone pain}

Up to 62\% of patients have bone metastases at the time of diagnosis of prostate cancer\textsuperscript{53} and bone pain due to metastases is the presenting symptom in 10-20\% of patients. The exact mechanism of bone pain associated with skeletal metastases is not known. It is
likely to be mediated by locally released cytokines or prostaglandins, which may stimulate local pain receptors. It has also been suggested that an increase in bone resorption, infiltration or compression of nerve roots and reflex muscle spasms may also contribute to metastatic bone pain\textsuperscript{17}. Management of cancer-related bone pain requires a knowledge of specific clinical syndromes, of the associated neurological (spinal cord compression) and orthopaedic (pathological fractures) primary morbidities and of the secondary morbidity due to extensive use of narcotic analgesics with attendant variable efficacy and side effects. In the end stages of prostate cancer, quality of life is dramatically decreased both by the sequelae of prostatic cancer itself and by endeavours to manage pain. Androgen-ablation (tumour-specific treatment) is the primary treatment of choice resulting in significant regression of metastases and control of bone pain. However, most patients relapse within 2-3 years when the mainstay of treatment is so far palliative.

\textit{Pathologic fractures}

Prostate cancer metastasizes frequently to the skeleton. Both osteolytic and osteoblastic long bone metastases are associated with an increased risk of pathologic fractures in instances particularly when more than 50\% of the circumferential cortical bone has been destroyed. The risk of fracture is also increased when weight-bearing pain persists, increases, or recurs despite adequate local irradiation. At this point, pathological lesions are visible on plain films or CT scans. Bone scintigraphy is more sensitive than plain X-rays in detecting skeletal metastases.

The most commonly encountered metastatic lesions of the proximal femur are at high risk for fracture if they are in excess of 2.5 cm in any dimension or if they are associated with avulsion of the lesser trochanter. Such lesions should be treated aggressively by prophylactic internal fixation. This will avoid the development of a secondary fracture often associated with delayed healing despite adequate fixation. When internal fixation is chosen for a large metastasis with extensive cortical destruction, the procedure should be augmented by debulking of the lesion and by packing it with methylmethacrylate polymer in situ. Such an expedient not only improves the efficacy of subsequent radiotherapy, but also prevents shortening of the bone with weight bearing while enhancing the torque capacity and sheer resistance inherent to the metal fixation device\textsuperscript{350}. Maurer \textit{et al}\textsuperscript{351} described the diagnostic and therapeutic considerations of pathological fractures. They observed 131 patients between 1983 and 1993 with 143 pathological
fractures, 10 of whom were treated conservatively and the remaining 133 were treated surgically. In 68 of the surgically treated patients, average survival was 11.6 months. Gainor et al\textsuperscript{352} observed 123 patients with 129 pathological fractures. Survival was about 6 months in the whole group. 74\% of the fractures united in time. Behr et al\textsuperscript{353} studied pathological proximal femur fractures in the elderly, observing fracture union in 89\% of patients with a postsurgical survival of 9 months.

*Spinal cord compression*

Prostate cancer is the second most common cause of metastatic spinal cord compression after lung cancer\textsuperscript{125-128}, variably reported to occur in 1-10\% of patients\textsuperscript{129}, although a higher incidence of 17\% was described in one study\textsuperscript{130}. Lesions are most common at thoracic levels (46-48\%), but can occur anywhere along the spine including lumbar (18-48\%) and cervical (5-14\%) sites\textsuperscript{53}. The most common clinical manifestations of spinal cord compression are back pain (75-100\%) and pain along a specific nerve root distribution. Motor weakness may rapidly progress to paraparesis or paraplegia. Sensory deficits (68\%) and autonomic dysfunction such as neurogenic bladder and faecal incontinence (40\%) occur less frequently\textsuperscript{273}. MRI is the best tool for diagnosing spinal cord compression. Immediate treatment with corticosteroids is required to decrease spinal cord oedema. Local radiation therapy is successful in relieving symptoms in most cases. Surgical decompression is the treatment of choice in case of failure of local radiotherapy.

*Disorders of calcium homeostasis*

In prostate cancer, disturbances in calcium homeostasis are only seldom observed, occurring mainly in the form of hypocalcaemia\textsuperscript{278,280,282-285} likely to be due to increased utilisation of calcium by the metastatic osteoblastic process\textsuperscript{274-280}. The mechanism is similar to that described in association with osteoblastic metastases in breast cancer\textsuperscript{281,282}. Raskin observed hypocalcaemia in 31\% of 75 patients with skeletal metastases at some stage during the clinical course of prostate cancer\textsuperscript{280}. Hypercalcaemia, which is relatively frequently encountered in the late stages of other malignant diseases, is observed in only 1\% of patients with prostate cancer metastatic to the skeleton. However, mild elevations in serum calcium concentrations are described at some stage during the natural course of prostate cancer in some 9\% of patients during long term follow-up\textsuperscript{286}.
Osteoporosis

About 5% of men with prostate cancer who are older than 50 years have osteoporosis and 30-50% have osteopenia. Osteoporosis is more frequently encountered in patients with advanced prostate cancer treated with androgen deprivation and fracture risk is 5-fold increased\(^{337-342}\).

1.7 Palliative management of HRPC-related bone pain.

Analgesic drugs

Until very recently, the skillful use of analgesia has represented the mainstay of the palliative treatment of HRPC metastatic to the skeleton\(^ {258}\). The World Health Organization (WHO) proposes a ‘three–step ladder’ scheme for the management of cancer-related bone pain. This scheme recommends the use of non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin for mild pain, ‘weak’ opioids (such as codeine, oxycodone and dextro-propoxyphene) for moderate pain and ‘strong’ opioids (morphine derivatives such as hydromorphone and methadone) in addition to NSAIDs in the management of severe pain\(^{54}\).

The NSAIDs ketoprofen and ketorolac are particularly useful in the management of musculoskeletal pain\(^ {54}\). However these agents may result in renal and hepatic toxicity when used in high doses. Moreover, these agents possess antiplatelet activity, and their use may become contraindicated in the late stages of prostate cancer when extensive metastases may be associated with myelosuppression\(^ {54}\).

Opioids induce analgesia by interacting with opioid receptors. The same result is achieved with the use of opioid (partial) agonists such as tramadol and buprenorphine that also bind to opiate receptors resulting in opioid-like activity. Agonist-antagonist agents demonstrate mixed effects\(^ {55}\). Because of the adverse effects associated with the long-term use of opiates, which include opioid tolerance, physical dependence, sedation and gastrointestinal side effects (constipation, nausea and vomiting), other modalities of treatment should be explored in order to maintain quality of life for as long as possible.

Radiation therapy

Local-field external beam radiation therapy is highly effective in the treatment of one or more well-defined metastatic foci and can be given as a single treatment of 8 Gy\(^ 3\). Retrospective and prospective trials have reported relief of pain in about 80-100% of
patients\textsuperscript{53}. Complete pain relief is observed in 30\% of patients, with a mean duration of remission of 6 months\textsuperscript{260}. Toxicity after local irradiation is minimal\textsuperscript{53}. Local radiotherapy may also be effective in patients with multiple bone metastases and as adjuvant therapy in the treatment of patients with pathological fractures or spinal cord compression\textsuperscript{53}. However, many patients progress to develop widespread painful lesions, which are no longer suitable for local treatment. In patients with multiple sites of metastatic bone pain, wide field radiotherapy is indicated, administered as upper or lower hemibody irradiation (HBI) or as sequential hemibody therapy\textsuperscript{17}. A single fraction of 6-7 Gy to the upper half and of 7-8 Gy to the lower half of the body is administered with a 2-4 week interval\textsuperscript{53}, with pain relief reported in 55-100\% of patients. Complete palliative efficacy is reported in 5-50\% of patients\textsuperscript{53}. Wide-field radiotherapy is a less frequently used option because of its associated adverse effects reported in 2-32\% of patients, which include thrombocytopenia and gastrointestinal symptoms\textsuperscript{53}.

\textit{Bone-seeking radionuclides}

The potential of unsealed source therapy using bone-seeking radionuclides in the palliation of metastatic bone pain was recognized in the early 1980s\textsuperscript{214}. By the mid-1980s results of the first clinical trials of \textsuperscript{32}P (Phosphorous) and of \textsuperscript{89}Sr (Strontium) were reported. \textsuperscript{153}Sm-EDTMP (samarium ethylenediamine-tetramethylene phosphonic acid), \textsuperscript{186}Re-HEDP (rhenium hydroxy ethylidene diphosphonate) and \textsuperscript{117}Sn-DTPA (tin diethylene triamine pentaacetic acid) have recently been recognized as promising alternative agents\textsuperscript{289-291}. Krishnamurthy \textit{et al}\textsuperscript{265} suggested that the goals and objectives of using radionuclides for metastatic bone pain in the new millennium should be separated in two major categories: pain palliation and pain palliation plus disease control. \textsuperscript{32}P would be the class winner for pain palliation because of its low costs. \textsuperscript{89}Sr and \textsuperscript{153}Sm and other potentially beneficial radionuclides would be reserved for patients for whom the clinical goal is both pain palliation and disease control. Table 1 illustrates the radiopharmaceuticals in current use for palliation of bone pain. The underlying principle of the use of any form of unsealed source therapy is that the dose absorbed by the tumour cells should be high enough to produce a significant clinical effect while the maximal toxicity to the target organ, usually the bone marrow, should be low enough to avoid significant adverse effects. The dose absorbed by an individual metastasis is a function of the accumulated radioactivity in the tumour cells, which is in turn dependent on the concentration and retention of the radiopharmaceutical, the physical relationship between
the radiopharmaceutical and the metastasis, and the half-life and β-particle energy of the radionuclide. In 1942, Pecher was the first to report the possible therapeutic role for the β-emitting radionuclide Strontium in the palliation of metastatic bone pain. Strontium imitates calcium in vivo by localising in bone mineral, especially at the sites of increased bone turnover. Although unsuccessful in the treatment of multiple myeloma, several clinical studies have demonstrated the efficacy of Strontium in the palliative treatment of pain due to metastatic bone lesions in other malignancies, Table 2. Strontium chloride has been shown to localize efficiently and for some 90 days at the sites of metastatic bone lesions in patients with prostate cancer. The calculated tumour/marrow absorbed dose ratio was found to be 10:1. Pain relief was demonstrated in up to 80% of treated patients probably as a result of a decrease in tumour load due to selective β dose-irradiation to metastatic sites. Most of a dose of administered Strontium (90%) is excreted by the kidneys, with the excretion being highest within the first two days following injection. The remainder undergoes biliary excretion. The main limiting factor with the use of Strontium is myelosuppression, which may restrict the use of this agent in the very advanced stages of prostate cancer when extensive metastatic involvement is associated with significant bone marrow suppression.

The efficacy, toxicity and repeatability of radionuclide therapy was evaluated in a multicentre study. Up to 60% of patients with multiple skeletal metastases experienced substantial pain relief or became pain free (26%). Patients previously treated with external beam radiotherapy and/or chemotherapy did not demonstrate a superior palliative response. Radiologically, osteoblastic and mixed metastases demonstrated a better response than purely osteolytic metastases. Duration of palliation was 5.0 ± 3.5 months and retreatments demonstrated significantly worse responses (p<0.01) compared to first treatments. Haematological toxicity mainly affected platelets and was observed overall in 25.5% of cases and in 38.9% of retreatments. Survival was not prolonged, though in some cases scintigraphic regression of bone metastases was observed in post-therapy bone scans. Attempts to sterilize metastases by radionuclide therapy have been made with some promising results in vivo, but human studies are so far limited. The biological behaviour of radionuclides is at least in part determined by their physical half-life and by the nature of the radioactive emissions. β-emissions contribute to irradiation of the bone marrow compartment and often lead to temporary myelosuppression 4 to 6 weeks after applying therapy. In principle, severe myelosuppression should be preventable by using radionuclides that have a half-life in the order of days rather than weeks and that emit less...
energetic $\beta$ particles. The physical half-life of $^{89}$Sr, the most commonly used radionuclide in the palliative management of skeletal metastases, is 50 days which matches its residence time in bone metastases of 90 days. It has now been established that using radionuclides with much shorter half-lives such as $^{117m}$Sn (13.6 days), $^{186}$Re (3.8 days) or $^{153}$Sm (46 hours) results in much less severe myelosuppression than using $^{89}$Sr$^{290}$. It has also been shown that radioactive agents with shorter half-lives, $^{153}$Sm-EDTMP and $^{186}$Re-HEDP, produce higher dose rates and result in earlier pain relief than agents with longer half-lives$^{290,291}$. $^{153}$Sm-EDTMP is a 1:1 complex of radioactive $^{153}$Sm and a tetraphosphonate (EDTMP) approved for routine use in the palliative management of patients with metastatic bone pain$^{292-294}$. Pain palliation was achieved in over 70% of patients, in most of whom conventional pain therapies had failed$^{295-299}$. Consistent with the physical characteristics of $^{153}$Sm-EDTMP (high dose rate delivered over a short period because of short half-life and $\beta$ particle energy levels), there is an early onset of pain relief which lasts for 3 to 5 months, associated with a significant decrease in analgesic needs. Only mild transient myelosuppressive effects are reported. Individualised dosimetry, limiting the dose to 2 Gy, additionally secures an adequate clinical response with minimum myelotoxicity$^{300}$. Multiple dose administration of $^{153}$Sm-EDTMP has been shown to be well tolerated, feasible and efficacious in patients with hormone-refractory prostate cancer metastatic to the skeleton$^{301,302}$. Additional radiopharmaceuticals with short half-lives under investigation are $^{186}$Re-HEDP$^{303,304}$ and $^{117m}$Sn-DTPA$^{305}$. There is evidence that combining radionuclide therapy with chemotherapy may prolong survival as shown with the use of $^{89}$Sr and doxorubicin$^{306-307}$. Combining “hot” bisphosphonate-labelled $^{153}$Sm with a “cold” bisphosphonate may hold additional benefits over their individual use. However, sequential rather than concomitant use of “hot” and “cold” bisphosphonates is advocated, as both “hot” (i.e. radiolabelled) and “cold” (non-radiolabelled) bisphosphonates would combine with hydroxyapatite and may restrict the usefulness of the second administered agent. Efficacy of such a combined regimen is currently under investigation.
Table 1. Radiopharmaceuticals in use for the palliation of cancer-related bone pain.

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Pharmaceutical</th>
<th>Half-life (days)</th>
<th>Maximum ßEnergy MeV</th>
<th>Mean ßEnergy MeV</th>
<th>Maximum range in tissue (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{89}$Sr</td>
<td>Chloride</td>
<td>50.5</td>
<td>1.46</td>
<td>0.583</td>
<td>6.7</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>Orthophosphate</td>
<td>14.3</td>
<td>1.71</td>
<td>0.695</td>
<td>8</td>
</tr>
<tr>
<td>$^{186}$Re</td>
<td>HEDP</td>
<td>3.8</td>
<td>1.07</td>
<td>0.349</td>
<td>4.7</td>
</tr>
<tr>
<td>$^{117m}$Sn</td>
<td>DTPA</td>
<td>13.6</td>
<td>NA</td>
<td>0.129/0.153</td>
<td>0.3</td>
</tr>
</tbody>
</table>

NA=not available

Table 2. Review of studies in which $^{89}$Strontium was given for the palliation of painful skeletal metastases due to various primaries.

<table>
<thead>
<tr>
<th>Author</th>
<th>Ref</th>
<th>Year</th>
<th>Evaluable patients</th>
<th>Patients responding</th>
<th>Responding (%)</th>
<th>Administered activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silberstein</td>
<td>218</td>
<td>1985</td>
<td>45</td>
<td>23</td>
<td>51</td>
<td>1-4.5 mCi</td>
</tr>
<tr>
<td>Reddy</td>
<td>219</td>
<td>1986</td>
<td>47</td>
<td>43</td>
<td>91</td>
<td>30-40 µCi/kg</td>
</tr>
<tr>
<td>Kloiber</td>
<td>220</td>
<td>1987</td>
<td>10</td>
<td>5</td>
<td>50</td>
<td>10-60 µCi/kg</td>
</tr>
<tr>
<td>Robinson</td>
<td>221</td>
<td>1987</td>
<td>109</td>
<td>81</td>
<td>74</td>
<td>30-40 µCi/kg</td>
</tr>
<tr>
<td>Tennvall</td>
<td>222</td>
<td>1988</td>
<td>11</td>
<td>5</td>
<td>45</td>
<td>3-6 mCiF</td>
</tr>
<tr>
<td>Buchali</td>
<td>223</td>
<td>1988</td>
<td>21</td>
<td>14</td>
<td>67</td>
<td>3x2 mCiF</td>
</tr>
<tr>
<td>McEwan</td>
<td>224</td>
<td>1990</td>
<td>26</td>
<td>20</td>
<td>77</td>
<td>40 µCi/kg</td>
</tr>
<tr>
<td>Laing</td>
<td>225</td>
<td>1991</td>
<td>83</td>
<td>62</td>
<td>75</td>
<td>20-80 µCi/kg</td>
</tr>
<tr>
<td>Fossa</td>
<td>226</td>
<td>1992</td>
<td>23</td>
<td>11</td>
<td>48</td>
<td>4 mCi</td>
</tr>
<tr>
<td>Dearnany</td>
<td>227</td>
<td>1992</td>
<td>24</td>
<td>23</td>
<td>96</td>
<td>30-60 µCi/kg</td>
</tr>
<tr>
<td>Mertens</td>
<td>228</td>
<td>1992</td>
<td>18</td>
<td>10</td>
<td>55</td>
<td>4 mCi+Cispl*</td>
</tr>
<tr>
<td>Kovner</td>
<td>229</td>
<td>1993</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>4.8 mCi</td>
</tr>
<tr>
<td>Hansen</td>
<td>230</td>
<td>1993</td>
<td>26</td>
<td>25</td>
<td>95</td>
<td>40 µCi/kg</td>
</tr>
<tr>
<td>Guerrieri</td>
<td>231</td>
<td>1994</td>
<td>13</td>
<td>9</td>
<td>69</td>
<td>4 mCi</td>
</tr>
<tr>
<td>Robinson</td>
<td>232</td>
<td>1995</td>
<td>310</td>
<td>252</td>
<td>81</td>
<td>40-55 µCi/kg</td>
</tr>
<tr>
<td>Quilty</td>
<td>233</td>
<td>1995</td>
<td>153</td>
<td>103</td>
<td>67</td>
<td>1.6 mCi</td>
</tr>
</tbody>
</table>
Pyrophosphate is produced by many anabolic processes. It is rapidly hydrolysed to its two constituent phosphate groups. If the linking oxygen atom in the pyrophosphate molecule is replaced by a carbon atom, a bisphosphonate is formed. These analogues are completely resistant to hydrolysis and are chemically extremely stable. Like pyrophosphate, the bisphosphonates bind to the hydroxyapatite crystals of bone and prevent both their growth and their dissolution.

Bisphosphonates are chemical agents known since the middle of the 19th century. They were first synthesised in Germany in 1865\textsuperscript{132} to be used as industrial agents, mainly as corrosion inhibitors or as complexing agents in the textile, fertiliser and oil industries.

Knowledge of the biological characteristics of bisphosphonates dates back to more than 40 years ago. In the early sixties, plasma and urine were shown to contain compounds which inhibit calcium phosphate precipitation and part of this inhibitory activity was found to be due to inorganic pyrophosphate\textsuperscript{135}. Pyrophosphate was thus demonstrated to impair the \textit{in vitro} formation and dissolution of calcium phosphate and carbonate crystals.
a property which led to its extensive use in the manufacture of washing powders. Because of their high avidity for Ca\(^{2+}\) ions, pyrophosphates have also been used diagnostically as bone-scanning agents when coupled to a \(\gamma\)-emitting radioisotope such as \(^{99m}\)Tc (technetium). Failure of pyrophosphates to act when given orally and their rapid hydrolysis when given parenterally, prompted the search for more stable analogues with similar physicochemical activity but resistance to enzymatic hydrolysis, which led to the development of the bisphosphonate compounds. Bisphosphonates, originally called diphosphonates, are compounds characterised by a P-C-P (phosphorus-carbon-phosphorus) bond. Unlike the unstable nature of P-O-P (phosphorus-oxygen-phosphorus) bonds in pyrophosphates, the P-C-P structure of bisphosphonates confers to these synthetic agents resistance to hydrolysis under acidic conditions and protection against degradation by pyrophosphatases. Varying the structure of geminal bisphosphonates, either by changing the lateral chains on the carbon atom (R1, R2), or esterifying the phosphate groups, results in a variety of compounds with specific physicochemical and biological characteristics and potency (structure-activity relationship). The introduction of a nitrogen-containing side chain thus increases the anti-resorptive potency and specificity of a bisphosphonate, while methylation of one of the phosphate groups reduces its potency by 1000-fold and activity of a bisphosphonate is completely lost by methylation of both phosphate groups.

Bisphosphonates can efficiently inhibit ectopic calcification and ossification in vivo, not only by decreasing mineral deposits but also by decreasing the accumulation of elastin, collagen and cholesterol in the arteries of the animals studied. Bisphosphonates have also been reported to decrease the formation of urinary stones and dental calculus. In humans, etidronate has been used for the prevention of ectopic calcification and heterotopic ossification, but the results have been disappointing. Better results are observed in urolithiasis and in the prevention of dental calculus, one of the main reasons behind the use of these agents as additive in toothpastes. The most important in vivo effect of bisphosphonates, however, is inhibition of osteoclast-mediated bone resorption. In animals, inhibition of endogenous bone resorption has been documented by \(^{45}\)Ca kinetic studies and by changes in markers of bone resorption. In humans, inhibition of bone resorption has been documented histologically and biochemically in patients with metastatic prostate cancer and breast cancer. The decrease in bone resorption results in an increase in calcium.
balance and in the mineral content of bone. Some studies suggest that in patients with metastatic prostate cancer, skeletal pain is associated with an increased bone resorption and that suppression of bone resorption may lead to a decrease in bone pain.\textsuperscript{41,52,162,163}

The cellular and molecular mechanisms of action of bisphosphonates have been recently elucidated. Depending on the presence or absence of a nitrogen molecule in their structure, bisphosphonates act either by resulting in direct apoptotic cell death of osteoclasts or by interfering with specific intracellular pathways in osteoclasts, thereby inducing their apoptosis.

First-generation, non-nitrogen-containing bisphosphonates, such as etidronic acid (1-hydroxyethylidene-1,1-bisphosphonate), clodronic acid (dichloromethylene-1,1-bisphosphonate) and tiludronic acid, induce both necrotic and apoptotic cell death after metabolism of the drug to the nonhydrolyzable adenosine triphosphate analogue, adenosine 5-triphosphate.\textsuperscript{164,165}

In contrast, nitrogen-containing bisphosphonates such as pamidronic acid (3-amino-1-hydroxypropylidene-1,1-bisphosphonate, Aredia\textsuperscript{R}, Novartis Pharmaceuticals Corp, East Hanover, NJ), alendronic acid (Fosamax\textsuperscript{R}; Merck and company, Inc; West Point, PA), ibandronic acid (Bondronat\textsuperscript{R}; Hoffmann-La Roche Inc; Nutley, NJ), olpadronic acid (3-dimethylamino-1-hydroxypropylidene)-1,1-bisphosphonate or dimethyl-pamidronate), risedronic acid (Actonel\textsuperscript{R}; Proctor and Gamble Pharmaceuticals, Inc; Cincinnati, OH) and zoledronic acid (Zometa\textsuperscript{R}; Novartis Pharmaceuticals Corp.), induce apoptosis by interfering with mevalonate metabolism by inhibiting prenylation.\textsuperscript{166-170} In 1982, Reitsma et al.\textsuperscript{171} demonstrated a cytotoxic effect of clodronic acid and pamidronic acid on macrophages. Cytotoxic cellular effects as a result of induction of apoptosis, have been recently observed with the use of bisphosphonates not only in macrophages and osteoclasts, but also in myeloma and breast carcinoma cells.\textsuperscript{172-175} The \textit{in vitro} adhesion of breast and prostate cancer cells to bone slices has also been found to be inhibited by various bisphosphonates,\textsuperscript{176,177} suggesting an additional potential beneficial effect of these agents on the pathophysiology of skeletal metastases in both malignancies. Since the first publication in 1979\textsuperscript{195} of the beneficial effect of treating tumour-induced osteolysis in normocalcaemic patients with bisphosphonates, considerable interest has developed for the use of these agents in patients with tumour-induced osteolytic lesions such as those observed in breast cancer, multiple myeloma or in patients with tumour-induced osteoblastic lesions and increased bone resorption such as those seen in prostate cancer.
The osteoprotective effect of bisphosphonates has been demonstrated in several animal studies\textsuperscript{84,85,178-188} and in clinical trials in humans, both as primary or secondary prevention\textsuperscript{42,44,46,86,189-194}, with several publications reporting the beneficial palliative effect of these agents in the management of skeletal metastases-associated morbidity in breast and prostate cancer and in multiple myeloma.

\textit{Bisphosphonates in the management of skeletal complications of cancer.}

**Etidronic Acid (Etidronate): Dronetel\textsuperscript{®}.**

![Etidronic Acid Structure](image)

A double-blind, placebo-controlled study using etidronic acid, a first generation bisphosphonate\textsuperscript{50,197}, did not confirm earlier promising results on palliation of pain reported in two small, non-blinded studies\textsuperscript{40,196}. Table 3 illustrates a schematic overview of these studies.

**Table 3. Studies with etidronic acid as palliative therapy for painful bone metastases.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year/N</th>
<th>Study type</th>
<th>Dose (mg/kg/day)</th>
<th>Duration</th>
<th>Favourable effects on</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schnur\textsuperscript{196}</td>
<td>1984/6*</td>
<td>OC</td>
<td>5-7 po</td>
<td>3 weeks</td>
<td>Pain, analgesic consumption.</td>
</tr>
<tr>
<td>Carey\textsuperscript{40}</td>
<td>1988/12#</td>
<td>OC</td>
<td>15 po</td>
<td>4 weeks</td>
<td>Pain, analgesic consumption.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 po</td>
<td>3 months</td>
<td>-</td>
</tr>
<tr>
<td>Smith\textsuperscript{197}</td>
<td>1988/57#</td>
<td>DBPC</td>
<td>7.5 mg/kg iv</td>
<td>3 days</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>400 mg/d po</td>
<td>1 month</td>
<td>-</td>
</tr>
<tr>
<td>Belch\textsuperscript{50}</td>
<td>1991/173@</td>
<td>DBPC</td>
<td>5 po</td>
<td>Until death</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{*}=various primaries \quad \textsuperscript{OC}=open, controlled \quad \textsuperscript{po}=oral

\textsuperscript{#}=prostate cancer \quad \textsuperscript{DBPC}=double-blind placebo-controlled \quad \textsuperscript{iv}=intravenous

\textsuperscript{@}=multiple myeloma \quad \textsuperscript{N}=number of patients \quad \textsuperscript{-}=no favourable effects
Clodronic Acid (Clodronate): Bonefos® or Ostac®.

Several studies have evaluated the use of clodronic acid in the palliative management of patients with metastatic bone lesions and breast cancer, prostate cancer, multiple myeloma and in metastatic disease due to other malignancies. Clinical improvement in bone pain was observed in open studies of clodronic acid in patients with metastatic prostate cancer. Results from the only published double-blind placebo-controlled study are confounded by the concomitant use of antitumour treatment. Table 4 illustrates a schematic overview of these studies. A number of studies have addressed the potential role of clodronic acid in the prevention of skeletal-related events in patients with metastatic breast cancer.

Further studies have addressed the use of clodronic acid in the reduction of the number of metastatic lesions.

Table 4. Studies with clodronic acid as palliative therapy for painful bone metastases in various malignancies.

| Author | Year/N Study type | Dose (mg) | Duration | Favorable effect on/
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Siris</td>
<td>1980/10@ DBPC</td>
<td>3200/d po</td>
<td>8+8 weeks Cross-over</td>
<td>Pain, Hypercal.</td>
</tr>
<tr>
<td>Delmas</td>
<td>1982/13@ DBPC</td>
<td>1600/d po</td>
<td>18 months</td>
<td>Pain, stabilization Rö lesions.</td>
</tr>
<tr>
<td>Siris</td>
<td>1983/10$ DBPC</td>
<td>3200/d po</td>
<td>8+8 weeks Cross-over</td>
<td>Pain, Hypercal.</td>
</tr>
<tr>
<td>Elomaa</td>
<td>1983/34$ DBPC</td>
<td>1600/d po</td>
<td>12 months</td>
<td>Pain, Hypercal.</td>
</tr>
<tr>
<td>Jung</td>
<td>1983/10* DBPC</td>
<td>8/kg iv 2400/d po</td>
<td>2 weeks 1 month</td>
<td>Hypercal.</td>
</tr>
<tr>
<td>Adami</td>
<td>1985/17# O</td>
<td>300 iv 3200/d po</td>
<td>2 weeks 4-11 weeks</td>
<td>Pain, Hypercal, regression Rö lesions.</td>
</tr>
<tr>
<td>Elomaa</td>
<td>1987/$ O</td>
<td>600/d</td>
<td></td>
<td>Pain, Hypercal.</td>
</tr>
<tr>
<td>Adami</td>
<td>1989/92# O</td>
<td>300/d iv</td>
<td>10 days</td>
<td>Pain.</td>
</tr>
<tr>
<td>Merlini</td>
<td>1990/68@ O</td>
<td>300/d iv</td>
<td>7 days</td>
<td>Pain, Hypercal.</td>
</tr>
<tr>
<td>Name</td>
<td>Year/ID</td>
<td>Treatment</td>
<td>Route</td>
<td>Duration</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>-----------</td>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>Ernst</td>
<td>1991/24*</td>
<td>DBPC</td>
<td>IV</td>
<td>1 infusion</td>
</tr>
<tr>
<td>Martoni</td>
<td>1991/38$</td>
<td>DB</td>
<td>IV</td>
<td>7 days</td>
</tr>
<tr>
<td>Neri</td>
<td>1992/20$</td>
<td>O</td>
<td>IM</td>
<td>10 days</td>
</tr>
<tr>
<td>Elomaa</td>
<td>1992/75#</td>
<td>PC</td>
<td>PO</td>
<td>1 month</td>
</tr>
<tr>
<td>Lahtinen</td>
<td>1992/350@</td>
<td>DBPC</td>
<td>PO</td>
<td>24 months</td>
</tr>
<tr>
<td>Francini</td>
<td>1992/76*</td>
<td>O</td>
<td>IV</td>
<td>7 days</td>
</tr>
<tr>
<td>Kylmäla</td>
<td>1993/99#</td>
<td>O</td>
<td>IM</td>
<td>14 days</td>
</tr>
<tr>
<td>Vorreuther</td>
<td>1993/41#O</td>
<td>O</td>
<td>IV</td>
<td>8 days</td>
</tr>
<tr>
<td>Kylmäla</td>
<td>1994/16#</td>
<td>O</td>
<td>IM</td>
<td>6 days</td>
</tr>
<tr>
<td>Robertson</td>
<td>1995/55*</td>
<td>DBPC</td>
<td>PO</td>
<td>2 months</td>
</tr>
<tr>
<td>O’Rourke</td>
<td>1995/84*</td>
<td>DBPC</td>
<td>PO</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Cresswell</td>
<td>1995/27#</td>
<td>O</td>
<td>IV</td>
<td>10 days</td>
</tr>
<tr>
<td>Heim</td>
<td>1995/170@</td>
<td>O</td>
<td>PO</td>
<td>3 months</td>
</tr>
<tr>
<td>McCloskey</td>
<td>1998/609@</td>
<td>DB</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Heidenreich</td>
<td>2001/85#</td>
<td>O</td>
<td>IV</td>
<td>8 days</td>
</tr>
<tr>
<td>Paterson</td>
<td>1993/173$</td>
<td>DBPC</td>
<td>PO</td>
<td>14 months</td>
</tr>
<tr>
<td>Rizzoli</td>
<td>1996/67$</td>
<td>O</td>
<td>PO</td>
<td>9 months</td>
</tr>
</tbody>
</table>
**Prevention of metastases**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Type</th>
<th>Dose</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanis*44</td>
<td>1996</td>
<td>DBPC</td>
<td>1600/d po</td>
<td>3 days</td>
<td>↓Number of patients with and ↓number of bone metastases.</td>
</tr>
<tr>
<td>Diel*86</td>
<td>1998</td>
<td>NPC</td>
<td>1600/d po</td>
<td>2 years</td>
<td>Significant ↓ osseous+ visceral lesions.</td>
</tr>
<tr>
<td>Powles*192</td>
<td>1998</td>
<td>NPC</td>
<td>1600/d po</td>
<td>2 years</td>
<td>No change in osseous lesions; ↑visceral lesions.</td>
</tr>
<tr>
<td>McCloskey*48</td>
<td>1998</td>
<td>DBPC</td>
<td>1600/d po</td>
<td>2 years</td>
<td>Significant ↓ in osseous lesions.</td>
</tr>
<tr>
<td>Saarto*193</td>
<td>1999</td>
<td>DBPC</td>
<td>1600/d po</td>
<td>3 years</td>
<td>Significant ↓ in osseous lesions + visceral lesions.</td>
</tr>
</tbody>
</table>

* *=various primaries  
#=prostate cancer  
$=breast cancer  
N=number of patients  
DBPC=double-blind  
OC=open controlled  
NPC=non placebo-controlled  
po=oral  
im=intramuscular  
iv=intravenous  
PC=placebo-controlled  
Hypercal=hypercalcaemia  
Rö=röentgenological  
d=day  

---

**Pamidronic Acid (Pamidronate): Aredia®.**

*Pamidronic acid* is a nitrogen-containing bisphosphonate, with a potency some 100-fold greater than that of etidronic acid. The efficacy of pamidronic acid in inhibiting bone resorption was first documented in 1979 and resulted in the use of this bisphosphonate in the treatment of metastatic bone disease. A number of studies reported clinical improvement of skeletal pain in patients with metastatic bone disease. The ability of pamidronate to modulate the metastatic process has also been addressed. Table 5 illustrates a schematic overview of these studies.
Table 5. Studies with pamidronic acid as palliative therapy for painful bone metastases in various malignancies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year/N</th>
<th>Study type</th>
<th>Dose (mg)</th>
<th>Duration</th>
<th>Clinical response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Holten Verz\textsuperscript{72}</td>
<td>1987/131$</td>
<td>OC</td>
<td>300/d po</td>
<td>13 months</td>
<td>Significant ↓fractures and bone pain. Analgesic effect (32%).</td>
</tr>
<tr>
<td>Coleman\textsuperscript{246}</td>
<td>1988/28$</td>
<td>O</td>
<td>30 iv/2 weeks</td>
<td>4 months</td>
<td>↓bone pain. Analgesic effect (32%).</td>
</tr>
<tr>
<td>Pelger\textsuperscript{76}</td>
<td>1989/7#</td>
<td>O</td>
<td>15 iv</td>
<td>7 days</td>
<td>↓urine/serum Ca; ↓pain.</td>
</tr>
<tr>
<td>Dodwell\textsuperscript{256}</td>
<td>1990/22$</td>
<td>O</td>
<td>30 iv/week + 30 iv/2 weeks</td>
<td>4 weeks 6 months</td>
<td>Significant ↓bone pain.</td>
</tr>
<tr>
<td>Lipton\textsuperscript{257}</td>
<td>1991/25*</td>
<td>O</td>
<td>30 iv-90 iv</td>
<td>Variable</td>
<td>Significant ↓bone pain and serum Ca.</td>
</tr>
<tr>
<td>Hacking\textsuperscript{255}</td>
<td>1991/20$</td>
<td>O</td>
<td>90 iv</td>
<td>1 infusion</td>
<td>↓bone pain.</td>
</tr>
<tr>
<td>Bachouchi\textsuperscript{254}</td>
<td>1991/22$</td>
<td>O</td>
<td>60 iv/2 weeks</td>
<td>6 months</td>
<td>↓bone pain.</td>
</tr>
<tr>
<td>Thürlimann\textsuperscript{253}</td>
<td>1991/34*</td>
<td>O</td>
<td>30 iv-90 iv</td>
<td>2,3 or 4 weeks variable 3 weeks, 9 months</td>
<td>↓bone pain.</td>
</tr>
<tr>
<td>Millward\textsuperscript{250}</td>
<td>1991/82*</td>
<td>O</td>
<td>30 iv</td>
<td>Variable</td>
<td>No favourable response.</td>
</tr>
<tr>
<td>Van Holten Verz\textsuperscript{35}</td>
<td>1991/144$</td>
<td>O</td>
<td>300/d po</td>
<td>18 months</td>
<td>↓bone pain+impairment mobility. Analgesic effect (57%).</td>
</tr>
<tr>
<td>Thiébaut\textsuperscript{245}</td>
<td>1991/18$</td>
<td>O</td>
<td>Variable</td>
<td>Variable</td>
<td>↓bone pain.</td>
</tr>
<tr>
<td>Panagos\textsuperscript{252}</td>
<td>1992/20</td>
<td>O</td>
<td>6 months</td>
<td>Variable</td>
<td>↓bone pain.</td>
</tr>
<tr>
<td>Radziwill\textsuperscript{251}</td>
<td>1992/23</td>
<td>OC</td>
<td>Variable</td>
<td>Variable</td>
<td>↓bone pain.</td>
</tr>
<tr>
<td>Glover\textsuperscript{71}</td>
<td>1994/61$</td>
<td>O</td>
<td>3 months</td>
<td>Analgesic effect (49%).</td>
<td></td>
</tr>
<tr>
<td>Tyrrell\textsuperscript{78}</td>
<td>1994/69$</td>
<td>O</td>
<td>60 iv/ every 2 Weeks</td>
<td>6 months</td>
<td>Analgesic effect (61%).</td>
</tr>
<tr>
<td>Purohit\textsuperscript{48}</td>
<td>1996/22S</td>
<td>O</td>
<td>120 iv once</td>
<td>3 months</td>
<td>Analgesic effect (68%).</td>
</tr>
<tr>
<td>Vinholes\textsuperscript{247}</td>
<td>1996/52*</td>
<td>DBPC</td>
<td>120 iv every 4 weeks</td>
<td>2 months</td>
<td>Analgesic effect (53%).</td>
</tr>
<tr>
<td>Study</td>
<td>Year(s)</td>
<td>Design</td>
<td>Dose</td>
<td>Duration</td>
<td>Outcome Measures</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------</td>
<td>--------</td>
<td>------</td>
<td>----------</td>
<td>------------------</td>
</tr>
<tr>
<td>Hultborn</td>
<td>1996</td>
<td>DBPC</td>
<td></td>
<td></td>
<td>TIH, ↓bone pain/FR/need for R(X).</td>
</tr>
<tr>
<td>Hultborn</td>
<td>1999</td>
<td>DBPC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Holten Verz</td>
<td>1993/161$</td>
<td>O</td>
<td>300-600/d or 20 months</td>
<td>↑Time to first SRE/nonvertebral FR, ↓bone pain/need for R(X) or surgery/TIH/Rö response in bone.</td>
<td></td>
</tr>
<tr>
<td>Hortobagyi</td>
<td>1996/382$</td>
<td>DBPC</td>
<td>90 iv/every 4 weeks.</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Theriault</td>
<td>1996/372$</td>
<td>DBPC</td>
<td>90 iv/every 4 weeks.</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Berenson</td>
<td>1996/392@</td>
<td>DBPC</td>
<td>90 iv/every 4 weeks.</td>
<td>↓bone pain, FR, need for R(X).</td>
<td></td>
</tr>
<tr>
<td>Theriault</td>
<td>1999/372$</td>
<td>OPC</td>
<td>90 iv/every 4 weeks.</td>
<td>Significant ↓skeletal morbidity. ↑time to first SRE.</td>
<td></td>
</tr>
<tr>
<td>Conte</td>
<td>1996/295$</td>
<td>OC</td>
<td>45 iv/every 3 weeks.</td>
<td>No ↓in number of bone lesions.</td>
<td></td>
</tr>
<tr>
<td>Van Holten-Verz</td>
<td>1996/124$</td>
<td>O</td>
<td>300/d po</td>
<td>No ↓in number of bone lesions.</td>
<td></td>
</tr>
<tr>
<td>Ford</td>
<td>1998/304@</td>
<td>DBPC</td>
<td>300/d po</td>
<td>No ↓in number of bone lesions.</td>
<td></td>
</tr>
<tr>
<td>Ford</td>
<td>1998/610$</td>
<td>DBPC</td>
<td>150/d po</td>
<td>No ↓in number of bone lesions.</td>
<td></td>
</tr>
</tbody>
</table>

* = various primaries  
#= prostate cancer  
$= breast cancer  
N= number of patients  
DBPC= double-blind  
DB= double-blind  
O= open  
po= oral  
im= intramuscular  
NS= non-significant  
TIH= tumour-induced hypercalcaemia  
R(X)= radiotherapy  
SRE= skeletal related events  
@= multiple myeloma  
DB= double-blind  
O= open  
IV= intravenous  
FR= fractures
Olpadronic Acid (Olpadronate): dimethyl-APD®.

*Olpadronic acid* has a 5-to 10-fold greater potency than pamidronic acid\(^{264}\) of which it is the dimethylated form. An additional advantage of olpadronate is that the agent is well-tolerated after oral administration\(^{260,263,309}\). Table 6 illustrates a schematic overview of these studies. When administered intravenously and followed by oral maintenance therapy, olpadronic acid has been shown to be effective in the palliation of pain in 60-70% of patients with metastatic prostate cancer\(^{263}\). These results have subsequently been confirmed in a larger number of patients\(^{309}\). Clinical response has been shown to parallel biochemical changes in bone resorption\(^{263}\). Olpadronic acid appears to be as effective as Strontium in the palliative management of metastatic bone pain in patients with hormone-refractory prostate cancer.

**Table 6. Studies with olpadronic acid as palliative therapy for painful bone metastases in various malignancies.**

<table>
<thead>
<tr>
<th>Author(^{ref})</th>
<th>Year/N Study type</th>
<th>Dose (mg)</th>
<th>Duration</th>
<th>Clinical response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelger(^{263})</td>
<td>1998/28@ O</td>
<td>4/day iv +200/day po</td>
<td>5 days 3 months</td>
<td>+ (76%)</td>
</tr>
<tr>
<td>Soerdjbalie(^{309})</td>
<td>2000/46@ O</td>
<td>4/day iv +200/day po</td>
<td>5 days 3 months</td>
<td>+ (67%)</td>
</tr>
</tbody>
</table>

N=number of patients  
iv=intravenous  
po=oral  
O=open  
@=prostate cancer  
Clinical response=favourable effects on bone pain (hypercalcaemia, pathological fractures).

Ibandronate (Ibandronic Acid): Bonviva®.

Ibandronate is approximately 50 times more potent than pamidronate and 500 times more potent than clodronate in inhibiting osteoclastic bone resorption in animal models. Heidenreich *et al*\(^{354}\) reported a significant reduction in pain and a significant decrease in the daily consumption of analgesics in 92% of 25 patients with hormone-refractory prostate cancer who were treated with 6 mg ibandronate every 4 weeks in an open
prospective study. In a review study Heidenrich et al mentioned improved quality of life and patient functioning after treatment of breast cancer patients with ibandronate.

**Zoledronic acid (Zoledronate): Zometa®.**

Zoledronic acid is a potent nitrogen-containing bisphosphonate, structurally similar to other bisphosphonates, having the required phosphorus-carbon-phosphorus core and a hydroxyl group at the RI position. It is distinguished by an imidazole group attached to the R2 position.

Zoledronic acid is a potent inhibitor of bone resorption. This results in interference with osteoclastic activity by inhibiting osteoclast formation and by inducing osteoclast apoptotic cell death. Zoledronic acid exhibits concentration-dependent binding to bone that is similar to pamidronate but ~2-fold greater than clodronate, which lacks the RI hydroxyl group. Several clinical trials (Table 7) have assessed the tolerability and efficacy of zoledronic acid in multiple myeloma and in bone metastases from solid tumours. Patients with metastatic renal cell carcinoma showed significantly lower SREs than placebo-treated patients, after treatment with zoledronic acid.

In contrast to clodronate and pamidronate, zoledronic acid (4 mg in a 15-minute infusion every 3 weeks) demonstrated a statistically significant reduction in the incidence of skeletal related events (SREs) and sustained palliation of bone pain over 2 years in patients with hormone-refractory prostate cancer and bone metastases. These results were first reported at 15 months and then after 2-years of treatment. Comparing placebo with zoledronate, Coleman et al demonstrated a significantly longer time to first SRE by approximately 6 months in zoledronate-treated patients. A sustained palliative effect was also demonstrated by Saad et al, who also demonstrated that a potent intravenous bisphosphonate can lead to a lower incidence of SREs in patients with bone metastases.

**Table 7. Studies with zoledronic acid as palliative therapy for painful bone metastases in various malignancies.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year/N</th>
<th>Study type</th>
<th>Dose (Z, mg)</th>
<th>Duration</th>
<th>Clinical response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berenson</td>
<td>2001/59#,*</td>
<td>O</td>
<td>0.1-8, iv,</td>
<td>3 months</td>
<td>-inhibition BR.</td>
</tr>
<tr>
<td>Reference</td>
<td>Date</td>
<td>Study Design</td>
<td>Treatment</td>
<td>Duration</td>
<td>Results</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
<td>--------------</td>
<td>-----------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>Berenson 317</td>
<td>2001/44</td>
<td>O</td>
<td>1-16, iv</td>
<td>once</td>
<td>-inhibition BR.</td>
</tr>
<tr>
<td>Berenson 318</td>
<td>2001/280</td>
<td>R</td>
<td>0.4-4, po vs 90 PAM iv</td>
<td>every 4 weeks for up to 10 months</td>
<td>-↓ pain in both groups. - 0.4 mg Z was significantly less effective than PAM. - 2 and 4 mg Z comparable in efficacy with PAM 90 mg.</td>
</tr>
<tr>
<td>Rosen 319</td>
<td>2001/1648</td>
<td>R</td>
<td>4 or 8 po vs 90 PAM</td>
<td>every 3 weeks during 15 months</td>
<td>-↓ BR markers. -↓ pain scores in all groups. - no difference in analgesic scores between groups.</td>
</tr>
<tr>
<td>Saad 320</td>
<td>2002/643</td>
<td>RP</td>
<td>4 or 8 po</td>
<td></td>
<td>-↓ bone markers. - no difference between groups for survival or performance status.</td>
</tr>
<tr>
<td>Rosen 321</td>
<td>2003/773</td>
<td>RP</td>
<td>4 or 8 po</td>
<td></td>
<td>- no differences in pain or quality of life.</td>
</tr>
<tr>
<td>Berruti 322</td>
<td>2003/643</td>
<td>RP</td>
<td>4 or 8 po Every 3 weeks during 15 months</td>
<td></td>
<td>-↓ SRE in patients treated with Z4 mg. -↓ pain, quality</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Type</td>
<td>Dosage</td>
<td>Frequency</td>
<td>Results</td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
<td>-------</td>
<td>--------</td>
<td>-----------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Zekri</td>
<td>2001</td>
<td>RP</td>
<td>4 or 8 po</td>
<td>Every 3 weeks during 15 months</td>
<td>↓SRE.</td>
</tr>
<tr>
<td>Saad</td>
<td>2004@</td>
<td>RP</td>
<td>4 or 8 po</td>
<td>Every 3 weeks during 15 months</td>
<td>↓SRE. ↓lower risk for SRE.</td>
</tr>
<tr>
<td>Coleman</td>
<td>2004@,#</td>
<td>RP</td>
<td>4 or 8 po</td>
<td>Every 3 weeks during 15 months</td>
<td>-longer time to first SRE.</td>
</tr>
<tr>
<td>Saad</td>
<td>2004@</td>
<td>RP</td>
<td>4 or 8 po</td>
<td>Every 3 weeks during 15 months</td>
<td>-smaller increases from baseline bone pain after Z than in placebo.</td>
</tr>
<tr>
<td>Saad</td>
<td>2003@</td>
<td>RP</td>
<td>4 or 8 po</td>
<td>Every 3 weeks during 15 months</td>
<td>-palliation of bone pain.</td>
</tr>
<tr>
<td>Lipton</td>
<td>2004!</td>
<td>RP</td>
<td>4 or 8 po</td>
<td>Every 3 weeks during 15 months</td>
<td>↑SRE ↑longer time to onset of SRE. ↑bone lesions.</td>
</tr>
</tbody>
</table>

*=breast cancer  #=multiple myeloma  @=prostate carcinoma
$=lung carcinoma ^=lymphoma  !=renal cell carcinoma
Second line therapy in the management of HRPC.

Over the past decade it has become increasingly evident that systemic chemotherapy may play an important role in the management of hormone-refractory prostate cancer. In contrast with the use of mitoxantrone and prednisone, phase I and II studies using docetaxel demonstrated a significantly beneficial clinical and biochemical response. Two multicenter randomized trials, the TAX 327 and SWOG study have demonstrated a survival advantage of docetaxel-based chemotherapy over mitoxantrone. In the TAX 327 study 1006 patients were included and received docetaxel 75 mg/m$^2$ every 3 weeks, docetaxel 35 mg/m$^2$ weekly and mitoxantrone 12 mg/m$^2$ every 3 weeks. Overall survival was significantly better in the docetaxel arm than in the mitoxantrone arm (18.7 versus 16.9 months, p=0.009).

In the SWOG study 770 patients were treated with docetaxel-estramustine or mitoxantrone-prednisone. The difference in survival was significant in favour of the docetaxel arm (17.5 versus 15.6 months, p=0.02).

The survival advantage of docetaxel created a place for this agent as standard therapy in the treatment of HRPC. This anti-cancer agent is also approved for the treatment of patients with locally advanced or metastatic breast cancer and non-small cell lung cancer (NSCLC). At the recommended dose of 60-100 mg/m$^2$ given every 3 weeks, severe neutropenia is the dose-limiting toxicity and a major concern especially when treating patients at high risk from myelotoxic complications. A less toxic schedule involving weekly docetaxel administration was developed for patients with poor performance status, poor haematological reserves and for the elderly.

Other potential agents in the treatment of HRPC.

- The oncogene bcl-2 is highly expressed in HRPC. A potential attractive method for decreasing the overexpression of bcl-2 is the use of antisense oligonucleotides. Use of these agents is associated with in vitro improved response rates when given with chemotherapeutic agents.

- One of the hallmarks of tumours is the unregulated growth of tumour cells, which leads to de-differentiation and aggressive invasive behaviour. Agents such as vitamin D are...
capable of inducing the *in vitro* differentiation of malignant cells to cells with normal physiologic function. The active metabolite of vitamin D3, 1,25-dihydroxyvitamin D3 has been shown to be able to induce the differentiation and proliferation of various human prostate cells in culture\(^{336}\). L-377202, a conjugate consisting of the peptide co-valently linked to the aminoglycoside portion of doxorubicin, which is cleaved by PSA to leucine-doxorubicin and doxorubicin, is also a novel agent which has been demonstrated to lead to a decrease in PSA concentrations in patients with HRPC.

### 1.8 Summary and Conclusion.

The development of bone metastases is very common in prostate cancer and is associated with the development of bone pain which eventually becomes intractable despite maximal analgesia. Androgens play a major role in the development of prostate cancer, so that androgen deprivation is the treatment of choice for patients presenting with skeletal metastases. Androgen-deprivation can be achieved by surgical or medical castration, resulting in regression of metastatic lesions and disappearance of pain. Hormone-refractoriness as defined by disease progression in the presence of adequate androgen suppression is associated with reappearance or progression of skeletal metastases and progressive disabling bone pain. If metastatic foci are unifocal, local radiotherapy is very successful in relieving symptoms. However skeletal metastases are often multiple, in which case bisphosphonates and radionuclides are the treatment of choice. Second line therapies such as Docetaxel (Taxotere) and Paclitaxel (Taxol) are very promising. Whether novel agents such as bcl-2, vitamin-D and inhibitors of the Epidermal Growth Factor (EFG) may be of additional or superior value, remains to be established.
References


155. Fleisch H: The bisphosphonate ibandronate, given daily as well as discontinuously, decreases bone resorption and increases calcium retention as assessed by \textsuperscript{45}Ca kinetics in the intact rat. \textit{Osteoporosis Int} 6: 166-170, 1996.


Presented at: What is new in bisphosphonates? Seventh workshop on bisphosphonates-from the laboratory to the patient, March 24-26, 2004, Davos, Switzerland.


