

Handbook of Cancer-Related Bone Disease

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and P Hadji

Published by
BioScientifica 



Euro House, 22 Apex Court, Woodlands, Bristol BS32 4JT, UK
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Published March 2010

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British Library Cataloguing in Publication Data
A CIP catalogue record for this book is available from the British Library

ISBN-13: 978-1-901978-28-5

ISBN-10: 1-901978-28-1

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Coloured X-ray of a malignant tumour in the humerus.
This is a secondary bone cancer; the cancer had metastasised from the primary site, which was a thyroid cancer.

Typesetting by Academic + Technical, Bristol, UK
Printed in the Malta by Gutenberg Press Limited, Tarxien, Malta

Contents

Contributors		vii
Preface		xi
Chapter 1	Bone biology and pathology	1
	Brendan F Boyce	
Chapter 2	Assessment of bone health	19
	Eugene McCloskey	
Chapter 3	Pathophysiology of bone metastases	33
	Ingunn Holen	
Chapter 4	Clinical features of metastatic bone disease	53
	Allan Lipton	
Chapter 5	Bisphosphonates: mechanisms of action	69
	Anke J Roelofs, Michael J Rogers	
Chapter 6	Bone health in breast cancer	91
	Michael Gnant	
Chapter 7	Bone health in prostate cancer	115
	Philip J Saylor, Matthew R Smith	
Chapter 8	Bone health in myeloma	131
	G David Roodman	
Chapter 9	Management of bone pain	145
	Sebastiano Mercadante	
Chapter 10	Radiotherapy for bone metastasis	161
	Peter Hoskin	
Chapter 11	Radio-isotope treatments for bone metastases	173
	Øyvind S Bruland, Oliver Sartor	
Chapter 12	Hypercalcaemia of malignancy	191
	Jean-Jacques Body	

Chapter 13	Orthopaedic treatment for skeletal metastases	203
	Andreas A Kurth	
Index		221

**Sponsored by an educational grant from
Amgen (Europe) GmbH**

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His particular research interests are tumour bone disease and osteoporosis. He was involved in numerous trials in cancer patients with all the bisphosphonates available in Europe including denosumab. He has a long standing interest in the biochemical markers of bone turnover in metastatic bone disease and in osteoporosis. More recently, he became interested in risk factors for fractures in postmenopausal women.

Brendan F Boyce MD

Professor Brendan Boyce is currently Director of Anatomic Pathology at University of Rochester Medical Center, Rochester, New York, USA. He is a general diagnostic surgical pathologist, who received his MD in Glasgow in 1972, completing his training at the Royal Infirmary Glasgow and at the University of Lyon, France. An interest in the pathology of metabolic bone disease developed in 1976 when he began to collaborate with Dr Iain Boyle and his group in Glasgow and after the move to Lyon in 1977, with Dr Pierre Meunier.

His current research interest is the study of the regulation of the formation, activation and survival of osteoclasts. In recent years, many genes have been identified as regulators of these aspects of osteoclast function, and his research team are presently focussed on the roles of NF- κ B and src tyrosine kinase in osteoclasts and the role of NF- κ B in the regulation of chondrocyte differentiation. With his colleague, Dr Lianping Xing, along with members of the Center for Musculoskeletal Research in Rochester, they are also studying the

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Eugene McCloskey MB MRCP MD FRCPI

Eugene McCloskey is Professor of Adult Bone Disease at the University of Sheffield. He has worked in the field of calcium and bone disorders since 1986. Following medical school at Trinity College, Dublin, Ireland, Dr McCloskey initially trained in general medicine and endocrinology, and subsequently in rheumatology before specialising in metabolic bone diseases. He has a long-standing interest in the mechanisms of malignant hypercalcaemia and osteolytic bone disease. This led to several clinical trials of bisphosphonates in multiple myeloma and breast cancer that have established the role of anti-osteoclastic therapy in malignant disease. Within the field of osteoporosis, Dr McCloskey has been principal investigator in a large number of MRC and pharmaceutical funded studies. He is an acknowledged expert in the fields of vertebral fracture definition and epidemiology as well as non-invasive assessments of bone strength and fracture risk. He is on the board of the Bone Research Society and is a member of the IOF Committee of Scientific Advisors.

His current research interests encompass benign and malignant bone disease. Within osteoporosis,

interests include the evaluation of techniques used in the diagnosis and management of osteoporosis, fracture risk assessment and the development of the WHO Risk Algorithm (FRAX). In breast cancer and multiple myeloma, research interests have focussed on the development of bisphosphonates as inhibitors of bone complications and metastases.

Michael Gnant PhD MD

Professor Michael Gnant is Professor of Surgery at the Medical University of Vienna, Austria, and is President of the Austrian Breast and Colorectal Cancer Study Group. His medical career began in 1988 when he graduated in medicine in Vienna. He specialised in surgery (1994) and surgical oncology. In 1997–1998 he worked at the National Cancer Institute, NIH, Bethesda, USA, and in 2004 he became Professor at the Medical University of Vienna.

His research interests include several fields of surgical oncology, in particular breast and pancreatic cancer, immunotherapy using antibodies, vaccination with dendritic cells, endocrine intervention, dormant tumor cells, and the use of bisphosphonates. He has been the principal investigator of more than 20 clinical trials.

Ingunn Holen BSc MSc PhD

Dr Ingunn Holen obtained a BSc, MSc, and a PhD from the University of Oslo, Norway. She worked at the Cancer Research Centre at the Norwegian Radium Hospital 1989–1995 and since 1995 has worked in various research groups at the University of Sheffield, UK with a focus on bone biology and metastatic bone disease. She is currently Reader in Bone Oncology and Head of the Laboratory Research Team in the Academic Unit of Clinical Oncology at the University of Sheffield.

Dr Holen has wide experience in the studies of tumour-induced bone disease, with particular emphasis on therapeutics, including bisphosphonates. Her main research interests are the molecular mechanisms involved in tumour cell:bone cell interactions in breast and prostate cancer, and how these can be targeted by combining current therapies. The aim is to establish promising drug combinations in laboratory models of bone metastases in breast and prostate cancer, and to subsequently take these forward to clinical studies.

Peter Hoskin MD FRCP FRCR

Professor Peter Hoskin is Consultant Clinical Oncologist at Mount Vernon Cancer Centre, Northwood UK and Professor of Clinical Oncology at University College London. He trained in clinical oncology at the Royal Marsden Hospital. This included a time as research fellow there and at St Bartholomew's Hospital London studying pain control in advanced cancer. He has extensive experience in the management of bone metastases with radiotherapy and is widely involved in research into radiotherapy fractionation, and its use in combination therapy for bone pain. His current research interests include the role of bone markers in predicting response to local radiotherapy and evaluation of radiotherapy against bisphosphonates and in combination with pregabalin for bone pain. He is European Co-Chair of the International Consensus Group on Palliative Radiotherapy responsible for developing guidelines and consensus statements in this area.

Andreas A Kurth

Professor Andreas Kurth is Director of Orthopaedic Surgery at the University Medical Center of the Johannes Gutenberg University Mainz, Germany. Professor Kurth studied Medicine and Sports Science at the University of Frankfurt and Zurich. After graduation he trained in Orthopaedics and Trauma (surgery) at DOES Darmstadt and the University Clinic Frankfurt. He completed his scientific and clinical training at Harvard Medical School, USA. After the return from the USA he specialised in orthopaedics and was made Consultant of Orthopaedic Oncology at University Clinic in Frankfurt. Over eight years he developed the reconstructive orthopaedic oncology services at Frankfurt University Hospital. Professor Kurth joined Johannes Gutenberg University Mainz in 2009 to establish innovative surgical and medical methods on the spinal column and joints, and to conduct further research into the biological basis for the development of medical procedures to reconstruct diseased bone.

Allan Lipton MD

Professor Allan Lipton is a specialist in internal medicine and medical oncology at Pennsylvania State University College of Medicine in Hershey, Pennsylvania, USA. He is also Chief of the Division of Oncology at the Milton S Hershey

Medical Center, Pennsylvania, USA. Professor Lipton received his medical degree from New York University School of Medicine and completed an internship and residency at Cornell Medical Division, Bellevue Hospital, New York, USA. He completed a fellowship in haematology at Memorial Hospital for Cancer and Allied Diseases and New York Hospital, and a clinical fellowship in the Division of Medical Oncology at Memorial Hospital for Cancer and Allied Diseases and the Division of Chemotherapy Research at the Sloan-Kettering Institute.

Sebastiano Mercadante MD

Professor Sebastiano Mercadante is Director of Anesthesia & Intensive Care Unit, Pain Relief & Palliative Care Unit, La Maddalena Clinic for Cancer, Palermo, Italy. Awarded an MD in 1979 from University of Palermo, Professor Mercadante specialized in Anesthesiology in 1980 and in the Science of Nutrition in 1984 before becoming Professor of Palliative Medicine at the University of Palermo.

La Maddalena Cancer Center opened 1999 and the Pain Relief & Palliative Care Unit was soon established. The aim of the Unit is to diminish the physical and psychological distress of patients during the treatment of oncological diseases, as well as during the end stage, when curative approaches are no longer possible. In contrast to many palliative care facilities, the unit has developed a unique acute and aggressive treatment in response to cancer-related symptoms. Research interests include opioid switching, opioid pharmacokinetics, breakthrough pain, bowel obstruction, opioid toxicity and possible alternative therapies.

Anke J Roelofs MSc PhD

Dr Anke Roelofs graduated from the University of Groningen in the Netherlands in 2003 with an MSc in Medical Biology. She then moved to the Institute of Musculoskeletal Sciences at the University of Oxford where she obtained a PhD working in the laboratory of Professor Graham Russell investigating the anti-tumour mechanisms of the action of bisphosphonates and related compounds.

Since 2005, she has worked with Professor Mike Rogers and colleagues in the Bone & Musculoskeletal Research Programme at the University of Aberdeen, where she is currently a post-doctoral

research fellow. Her main research interests are the pharmacology and mechanisms of action of bisphosphonates, as well as the mechanisms of breast cancer metastasis.

Michael J Rogers BSc (Hons) PhD

Professor Mike Rogers is Professor of Musculoskeletal Pharmacology at the University of Aberdeen, UK. He studied Biochemistry in the Department of Molecular Biology & Biotechnology at the University of Sheffield, receiving his doctorate in 1993, before moving to the University of Aberdeen in 1997. In 2003 he was awarded a personal chair and currently heads a laboratory research group studying the molecular pharmacology of bisphosphonates, the role of the mevalonate pathway in bone metabolism, and the signalling pathways involved in regulating osteoclast activity and apoptosis.

Current research interests seek to address some unanswered questions about the pharmacology of bisphosphonates, including potential differences between bisphosphonates in their distribution, the molecular basis of adverse effects, and how bisphosphonates disrupt intracellular signalling pathways by affecting protein prenylation.

G David Roodman PhD MD

Professor David Roodman is Professor of Medicine at the University of Pittsburgh School of Medicine, PA, USA. He received an MD from the University of Kentucky College of Medicine in 1973, and a doctorate in biochemistry from the University of Kentucky in 1975. His postdoctoral training included an internship in internal medicine at the University of Kentucky, as well as a residency in medicine and a haematology fellowship at the University of Minnesota. Professor Roodman currently serves as Director of the Myeloma Program at the University of Pittsburgh Cancer Institute and Vice Chair for Research in the University of Pittsburgh School of Medicine's Department of Medicine.

Research interests focus on the cellular and molecular events that control the formation and activity of osteoclasts in normal and pathologic states. Professor Roodman also heads a Program Project Grant (Pathobiology of Paget's Disease) to investigate the role of measles virus in the pathophysiology of Paget's disease and the role of genetics in the pathologic process.

Oliver Sartor MD

Professor Oliver Sartor is the Piltz Professor of Cancer Research in the Departments of Medicine and Urology at the Tulane University School of Medicine, New Orleans, LA, USA. Professor Sartor graduated from Tulane University's School of Medicine in 1982 and completed his residency at Tulane in 1986. Professor Sartor was chief of Hematology-Oncology and director of the Stanley S Scott Cancer Center at LSU Medical Center, New Orleans for eight years before taking a post as associate professor in the Lank Center for Genitourinary Oncology at Harvard's Dana-Farber Cancer Institute in Boston, USA. Professor Sartor returned to Tulane in 2008.

Current research interests include clinical trials in advanced prostate cancer with novel agents and novel combinations of agents, including trials with alfaradin a novel bone-seeking isotope. His collaborative projects include novel concepts in germ line assessment of prostate cancer risk and treatment response.

Philip J Saylor MD

Dr Philip J Saylor is an oncology fellow and has accepted a position as an Instructor in Medicine at Harvard Medical School, Boston, MA, USA. Dr Saylor received an MD from the University of Pittsburgh, School of Medicine. He then continued

his training with an internal medicine residency at the University of California San Diego and an oncology fellowship at the Dana Farber Cancer Institute and Massachusetts General Hospital Cancer Center, Boston, MA, USA. Upon completion of his fellowship, his clinical appointment will be Assistant Physician in the Division of Hematology and Oncology at the Massachusetts General Hospital Cancer Center.

Current research interests include clinical trials in genitourinary cancer treatment and survivorship. His investigative efforts particularly focus on prostate cancer survivorship and the metabolic consequences of androgen deprivation therapy.

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Professor Matthew R Smith is an associate professor of Medicine, at Harvard Medical School, Boston, MA, USA and the Director of Genitourinary Medical Oncology at Massachusetts General Hospital Cancer Center, Boston. He received a PhD from Duke University, Durham, NC, USA in 1991 and an MD from Duke University in 1992. Professor Smith completed his training with a residency at Brigham & Women's Hospital, Boston, a fellowship at the Dana Farber Cancer Institute, Boston, and a post-doctoral fellowship at Massachusetts Institute of Technology, Cambridge, MA, USA.

Preface

The optimal treatment of cancer requires a wide-ranging, multidisciplinary approach to appropriately apply to patient care the quite remarkable progress that has been made across all fields of oncology. This handbook summarises current knowledge of cancer-related bone diseases and describes appropriate management, not only for patients with advanced malignancy affecting the skeleton, but also for those at risk for treatment induced morbidity.

Bone is the most common site for metastasis and is of great clinical relevance in breast, prostate and lung cancers as well as in multiple myeloma. Bone metastasis causes pain, structural damage and adverse effects on both quality of life and physical function, as well as consuming a large amount of health care resources. Our understanding of the pathophysiology of metastasis to bone has resulted in the application of bone-targeted treatments to prevent skeletal morbidity and treat complications that may result from both the disease itself as well as those induced by the cancer therapy.

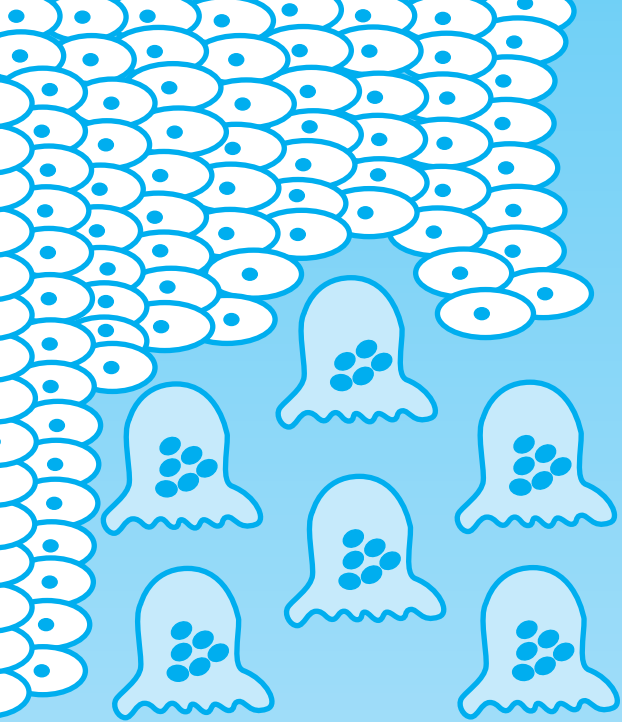
The bisphosphonates have been the mainstay of treatment alongside radiotherapy, orthopaedic intervention, appropriate systemic treatments and supportive care including analgesics. More recently,

our understanding of the biological cross talk between osteoblasts and osteoclasts has led to the definition of new therapeutic targets resulting in exciting treatment options that show great promise for future patient care.

The interactions in the bone microenvironment between stem cells, osteoclasts and osteoblasts, and cancer cells are of fundamental importance to the processes that underpin metastasis. Extensive preclinical investigations, and a widening range of clinical trial results, suggest that treatments able to interrupt these inter-relationships can reduce the risk of metastasis and may offer far more to the patient than just supportive care.

This handbook brings together the expertise of the foremost experts in this rapidly developing field and presents a clear summary of clinically relevant information with recommendations for treatment. We hope that the content and format will be of value across the spectrum of clinicians, scientists and health care professionals involved in the management of bone disease in cancer.

*Robert Coleman
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11

Radio-isotope treatments for bone metastases

Radio-isotope treatments for bone metastases

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Introduction

The scope of this chapter is to discuss the clinical indications and current data for bone-seeking radiopharmaceuticals (BSR) in a conceptual manner. Several helpful comprehensive reviews have recently been published and we also highlight the significant randomized trials of importance. Some radiobiological aspects will be emphasized with a particular focus on radiation dose deposition within the skeletal metastases and the feasibility of repeated dosing. Furthermore, we cover a new class of BSR in clinical development based on targeted alpha-irradiation. Lastly, we discuss advances in combining BSR with bisphosphonates and/or chemotherapy. Taken together, recent achievements in this field suggest that BSR will play a significant and growing role in the future of cancer therapeutics. The hypothesis that BSR can improve survival will be definitively tested by trials currently in progress.

Bone is the most common site of symptomatic cancer metastasis. Two thirds of patients with advanced breast cancer and over 90% of patients with advanced prostate cancer have skeletal metastases. Lung, thyroid, and renal carcinoma metastasize to bone in approximately 30–40% of cases. Multiple myeloma, though not usually thought of as a metastatic disease, involves the skeleton in nearly 100% of cases.

Skeletal metastases may have a devastating impact on a patient's quality of life and lead to

significant debilitation. Pain is the usual dominating symptom. Furthermore, additional clinically serious implications are pathological fracture, nerve entrapment, spinal cord compression, bone marrow insufficiency and hypercalcaemia.^{1–4} These are of particular concern to cancer patients with a long expected survival; e.g. those with the diagnosis of skeletal metastases as the first and sole metastatic event.

Patients with skeletal metastases should be treated by a multidisciplinary team. The appropriate combination of analgesic medication, radiotherapy, surgery, chemotherapy, hormone treatment, bisphosphonates and/or BSR is mandatory. Choices depend on the biology of the disease, extent of skeletal involvement, symptoms, the availability of effective systemic therapies, and the life expectancy of the patient. While external beam radiation therapy remains the mainstay of pain palliation in solitary lesions, BSR have an established role in the therapeutic armamentarium for the treatment of multiple painful osteoblastic lesions and for those patients with pain recurrence at multiple sites after external beam radiation.

Tumourbiological aspects

Development of bone metastasis involves a complex pathophysiology between host and tumour cells. Tumour cell migration, adhesion and invasion into the skeleton induces stimulation of osteoclastic

and osteoblastic activity – a process mediated by cytokines and tumour-derived factors.⁵ Studies performed in the early 1970s clearly demonstrated the importance of stromal factors in prostate epithelial cell growth.⁶ These initial findings were expanded both in concept and scope by the observation that cancerous prostate growth was markedly enhanced by the presence of stromal elements from selected sources.⁷ Co-inoculation experiments with bone stroma derived fibroblasts and human prostate cancer cell lines demonstrated clear synergy of growth,⁸ thereby presenting a heuristic concept and intellectual framework for subsequent studies both *in vitro* and *in vivo*. The exquisite tropism of prostate cancer cells to bone⁹ and factors secreted by the prostate cancer cells that promote the formation of new bone matrix¹⁰ contribute to the sclerotic phenotype of such metastases,¹¹ and render BSR an attractive treatment that targets the lethal phenotype of this disease.^{12,13}

Therapeutically speaking, targeting stromal elements that promote cancerous growth is an attractive alternative to targeting cancer cells from advanced epithelial malignancies given the unstable phenotypes and genotypes typical of these cancer cells.¹⁴ Stromal elements are less likely to have a genetic heterogeneity and thus a stromal-targeted therapy has the potential to overcome some of the difficulties and mechanisms of resistance associated with more traditional cytotoxic chemotherapies. The concept of stromal targeted therapy has rapidly evolved in recent years given the development of anti-angiogenesis inhibitors such as bevacizumab. Recognizing that stromal elements other than blood vessels are important in the growth of diverse tumour types helps to provide an intellectual framework for the development of new stromal targeted therapies.

The propensity of cancer cells to metastasize to bone and the ability of BSR to target the extracellular matrix as well as stromal cells such as fibroblasts, osteoblasts, osteoclasts and endothelial cells suggest an alternative, attractive method to approach cancer therapeutics that should be theoretically effective, despite significant heterogeneity within the actual cancerous cell.¹⁴ BSR provide a multi-targeted approach aimed at both the tumour cell and the tumour microenvironment, and have the advantage of being able to target

cells, regardless of genotype, within the diverse tumour microenvironment. No non-isotopic therapy under development has the opportunity to have such multiplicity of actions, and thus we believe that BSRs have a unique role to play in the development of the next generation of cancer therapies.

External beam radiotherapy – relevance to radio-isotopes

Skeletal metastases are the single most frequent indication for palliative radiotherapy and external beam irradiation effectively relieves pain from single sites of painful skeletal metastases.^{15–17} Chapter 10 in this book reviews this in detail. Here only aspects with relevance to BRS will be mentioned.

Metastases to bone are usually multiple and distributed throughout the axial skeleton thus providing a significant limitation to the use of external beam therapy (Figure 11.1). When larger or multiple fields of irradiation are necessary, such as for diffuse metastases in the axial skeleton such as vertebra and pelvis, bone marrow suppression increases substantially.

Radiation doses needed to achieve pain palliation seems to be different from that which results in long-term local tumour control. International consensus advocates the standard use of a single fraction (8.0 Gy) in most patients in whom the clinical indication is ‘pain relief’.^{15–18} Patients not responding to treatment or those with new pain arising at a previously irradiated site should be offered retreatment. In contrast, when the aim is ‘local tumour control’ in patients with solitary bony metastases and long life expectancy, or when medullar compression is present, fractionated external beam radiotherapy is advisable (3.0 Gy × 10, or even conventional 2 Gy fractions to higher total doses) in selected cases.¹⁸ This seems also to be the case in patients with imminent fractures because re-mineralization is reported to be more favorable after fractionated irradiation.¹⁹

Experiences from re-treatment suggest that effective palliation may be achieved with localized radiation doses as low as 4.0 Gy.²⁰ This might be of relevance to the use of BSR where dosimetry is much more complicated and less accurate. However, it should be realized that external beam

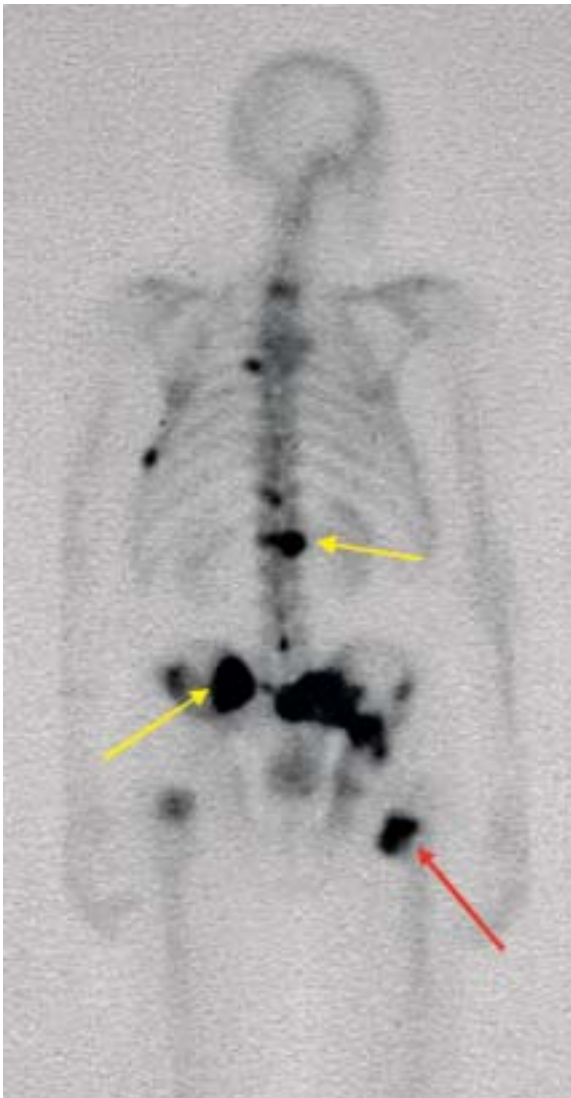


Figure 11.1 Bone scintigraphy (^{99m}Tc MDP diagnostic bone-scan) in a man with multiple skeletal metastases from prostate cancer. The scan provides a biodistribution image of the class of bone-seeking radiopharmaceuticals. Red arrow: site of pain; yellow arrow: non-symptomatic lesions.

irradiation is delivered with a very high dose-rate as compared to that of BSR (see below).

► Bone-seeking radiopharmaceuticals

Currently, two principal chemical classes of therapeutic bone-seeking radiopharmaceuticals are

regulatory approved – cationic and anionic bone seekers (i.e. calcium analogues and radiolabelled polyphosphonates). In commercially available formulations the radioisotopes involved are beta-emitters. Strontium-89 dichloride (Metastron, GE Healthcare, Chalfont St. Giles, United Kingdom) is approved in the United States and in most European countries, and more recently, ^{153}Sm -EDTMP (^{153}Sm -lexidronam, Quadramet, Schering AG, Berlin, Germany and EUSA, Oxford, UK) has been approved. In the latter, the beta-emitter samarium-153 is in complex with ethylene-diaminetetramethylene phosphonic acid.

While each of these agents is shown to have efficacy in the treatment of painful osseous metastases derived from prostate cancer, they may also have utility in the treatment of skeletal metastases from breast cancer and perhaps from non-small cell lung cancer. As noted above, histological cancer type and the organ of cancer origin is less important for the BSR as compared to more conventional therapeutic agents. Furthermore, BSR offer an effective alternative to external beam irradiation in patients with multiple skeletal metastases.

The target for BSR is calcium-hydroxyapatite which is particularly abundant¹¹ and avid in sclerotic metastases from prostate cancer (Figures 11.1 and 11.2) but also present, though more heterogeneously distributed, in mixed sclerotic/osteolytic metastases e.g. breast cancer. This is evident from the biodistribution image (Figure 11.1) common to all BSR – exemplified as ‘hot-spots’ visualized on a routine diagnostic bone-scan (by ^{99m}Tc -MDP, a radiolabelled bisphosphonate). Following administration, a selective delivery of ionizing radiation to targeted areas of amplified osteoblastic activity occurs, and multiple (symptomatic and asymptomatic) metastases are targeted simultaneously (Figure 11.1).

BSR effectively relieves pain, and this has been the basis for regulatory approvals. Their salient characteristics and usefulness in controlling pain from widespread metastatic bone disease have been thoroughly reviewed.^{21–26} Important characteristics of the various BSR are presented in Tables 11.1 and 11.2. In addition to the commercially available formulations mentioned above, ^{186}Re or ^{188}Re -hydroxyethylene diphosphonate (HEDP) are still under clinical development.^{27–30} ^{179m}Sn -DTPA emits conversion electrons and is also associated



Figure 11.2 Sclerotic skeletal metastases from HRPC. Spiral CT – Coronal section: note the bony phenotype of metastases of various sizes. Matrix containing calcium is present throughout the lesions.

with effective palliation of pain but clinical development has been halted.^{31,32} Lastly, a new generation of BSR that emits alpha-particles (see below) and is based on the bone-seeking properties of radium-223 has shown encouraging results in phase-II clinical development.³³

Randomized trials represent the best source of data for assessing pain responses. As a rule regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have required randomized and placebo controlled assessments for palliative

agents given the high rate of success for placebos in studies evaluating pain as an endpoint.

As mentioned above, BSRs are approved for the palliative treatment of advanced bone metastatic cancers but have not gained a wide acceptance in the oncological community. The reasons for this lack of general usage may include both economic and licensing issues. Particularly in the United States, oncologic care is controlled by medical oncologists that are not certified in radiopharmaceutical administration and, hence, are financially incentivized to deliver chemotherapy.

Table 11.1 Decay, bone and marrow doses of bone-seeking radiopharmaceuticals

RADIO PHARMACEUTICAL	HALF-LIFE (DAYS)	PARTICLE	MEAN DECAY ENERGY (MeV)	MAXIMUM SOFT TISSUE RANGE (mm)
¹⁵³ Sm-EDTMP	1.9	Beta minus	0.27	3.4
⁸⁹ SrCl ₂	50.5	Beta minus	0.58	6.0
²²³ RaCl ₂	11.4	Alpha	28.2*	<0.1
¹⁸⁶ Re-HEDP	3.8	Beta minus	0.34	4.4
¹⁸⁸ Re-HEDP	0.7	Beta minus	0.78	10
³² P	14.3	Beta minus	0.70	8.5
^{117m} Sn-DTPA	13.6	Conversion electrons	0.15	<0.3

* Includes daughter radionuclides

Data from Nuclides 2000, Nuclide Explorer, version 1.2, Institute for Transuranium Elements, Karlsruhe, Germany

Table 11.2 Photon emissions from bone seeking radiopharmaceuticals gamma emissions allow scintigraphic documentation of tumour targeting

RADIONUCLIDE	COMPLEX	ENERGY (keV)	ABUNDANCE (%)	IMAGING
^{99m} Tc	MDP	141	(89%)	Yes (ideal)
¹⁵³ Sm	EDTMP	103	(29%)	Yes (fair)
¹⁸⁶ Re	HEDP	137	(10%)	Yes
¹⁸⁸ Re	HEDP	155		Yes
²²³ Ra	Cl ₂	154	(6%)	Yes (poor)
		271	(10%)	
		269	(14%)	
		81	(15%)	
		84	(26%)	
⁸⁹ Sr	Cl ₂	none	(0%)	No
³² P	PO ₄	none	(0%)	No
^{117m} Sn	DTPA	159		Yes

Studies with ³²P

Phosphorous-32 is an older radiopharmaceutical that is also available in several countries. ³²P as orthophosphate has been used for over 50 years in the palliative treatment of multiple painful osseous metastases. In fact, this agent was the first BSR used in clinical medicine and was used to target bone metastases in patients with breast and prostate cancer in the 1950s.^{34–36} The main disadvantages of this BSR are dose-limiting myelosuppression³⁶ and the lack of randomized trials performed with this agent limiting the interpretation of data. However, one more recent trial³⁷ is covered below in the portion of the chapter covering a comparison of BSRs. The clinical use of ³²P in pain palliation today is relatively limited in most of the developed world.

Strontium-89 study review

Strontium-89 is, due to its earth alkaline metal characteristics, a bone-seeking radionuclide, with similarities to calcium. As a calcium homologue, ⁸⁹Sr tracks calcium after administration. Patients may benefit from a single i.v. infusion of 148 MBq (4 mCi) of Metastron (⁸⁹SrCl₂ – physical half-life (t_{1/2}) of 50.5 days), and pain relief may occur

within the first few weeks and can sometimes lasts for several months. Clinical phase-II studies with ⁸⁹Sr have shown effective palliation of pain in some but not all studies in metastatic prostate cancer. Initial reports using a non-blinded trial design suggested palliative responses in up to 75% of the patients, with as many as 25% being able to stop taking analgesics.^{38–40} Double-blind studies have compared radioactive and stable strontium and confirmed the therapeutic effect of Metastron.⁴¹ However, effective pain palliation was observed in a lower percentage of the patients than that reported in the non-placebo controlled phase-II trials.

The initial randomized studies with ⁸⁹Sr were small. In a trial reported by Lewington and colleagues⁴¹ assessing metastatic prostate cancer and comparing ⁸⁹Sr to placebo, only a single time point 5 weeks post-dosing was assessed and only 26 of 32 patients were included in the efficacy analysis. The authors concluded that pain relief occurred with ⁸⁹Sr and that one third of patients had a complete response. Assessment methods and analgesic reporting were, however, sparsely described. Duration of pain relief and analgesic consumption changes could not be ascertained from this initial randomized report.

Another small study involving 49 patients with castration resistant prostate cancer (CRPC) utilized

^{89}Sr at an intravenous dose of 2 mCi or placebo administered monthly for three doses. This trial noted no pain differences in the treatment groups. However, the BSR group had a longer survival than the placebo group.⁴² No other randomized trial of ^{89}Sr monotherapy has demonstrated prolonged survival so this data needs to be taken with caution.

In the first large ($n = 126$) multi-centre placebo controlled study of ^{89}Sr , bone-metastatic CRPC patients requiring external beam radiation for palliation of bone pain were randomized to 10 mCi of ^{89}Sr or placebo immediately after completion of the external beam.⁴³ The dose utilized in this trial, conducted in multiple Canadian centres and termed the Trans-Canada Study, was higher than in any other of the randomized trials. Pre-defined endpoints for this trial included analgesic use, new painful sites of metastatic bone disease, reduction of pain at the sites originally radiated, and overall survival. No differences were noted in survival or the pain relief at the primary site, however there was a significant improvement in the ^{89}Sr arm for discontinuing analgesics (17% vs 2%) and in new sites of bone pain assessed three months after treatment. A subsequent follow-up prostate specific antigen (PSA) analysis in this trial was conducted in a subset of 54 patients.⁴⁴ This subset analysis indicated that the mean time to PSA progression was relatively prolonged in the ^{89}Sr group; 19 vs 6 weeks with placebo, suggesting the possibility of a direct anti-tumor effect (at least as assessed by PSA). The findings in the Trans-Canada study were contradicted by results from a Norwegian study.⁴⁵ However, the discrepancy might result from the considerable difference in injected dose, as the latter used the standard approved dose of 148 MBq (4 mCi).

In a comprehensive multi-centre study performed in 203 patients by the European Organization for Research and Treatment of Cancer (EORTC), ^{89}Sr at a dose of 4 mCi was compared to local field radiation therapy for patients with pain and bone-metastatic CRPC.⁴⁶ Time to subjective progression was 3 months for each treatment arm and duration of pain response (among patients with a response) was approximately 4.5 months for each treatment. There were no statistically significant differences between the treatment arms for either the time to subjective progression or

duration of pain response in responding patients.⁴⁶ The survival of ^{89}Sr treated patients was statistically significantly shorter as compared to the patients treated with local field radiotherapy alone (median 7.2 vs 11.0 months). Though no other trial has demonstrated shorter survival for ^{89}Sr treated patients, this relatively large randomized multi-centre trial raises concerns that survival could be compromised in certain settings by treatment with this particular BSR.

In another large multi-center prospective randomized trial, Quilty *et al.*⁴⁷ evaluated intravenous ^{89}Sr versus external beam radiation in a total of 284 men with advanced bone-metastatic CRPC. Patients were randomized between 5.3 mCi (single dose) and external beam radiation. A variety of well defined endpoints were assessed including pain at an index site, new painful sites, need for additional external beam radiation, and overall survival. External beam radiation was administered either focally to the painful areas or as hemi-body radiation. For pain at the index site, each modality was effective in 61–66% of patients and no differences were noted between the various treatments. ^{89}Sr was more effective than the focal external beam in terms of preventing new painful sites and fewer patients in the BSR arm required subsequent external beam therapy. Median survival was only 21 weeks in this trial, but no differences were noted by trial treatment arm. The median survival in this trial suggests that patients had an advanced disease stage when randomized as few trials in prostate cancer have demonstrated such limited survival post-treatment. Toxicity was reported as being minimal in each arm but patient follow up was limited given the short life-expectancy of patients enrolled in the trial.

Samarium-153 study review

A bone-seeking radiopharmaceutical with shorter physical half-life, such as the tetrakisphosphate ^{153}Sm -EDTMP ($t_{1/2}$ of 1.9 days) may have the potential to facilitate more rapid bone marrow recovery. The first major randomized trial using ^{153}Sm was performed by Resche *et al.*⁴⁸ This was a multi-centre, randomized, dose-controlled study performed in patients with a variety of tumours with painful bone metastases. One hundred and fourteen patients received a single dose of

0.5 mCi/kg (n = 55) or 1.0 mCi/kg (n = 59). Most patients (59%) had prostate cancer and 32% had breast cancer. Efficacy was evaluated by patient reported outcomes using evaluations of pain with visual analogue scale (VAS) score and diaries of opioid analgesic use. VAS scores significantly decreased for the 1.0 mCi/kg group, 3 and 4 weeks post-dosing but the lower dose did not induce statistically significant changes. Long term follow-up revealed a significantly longer survival among breast cancer patients receiving the higher dose compared to those treated with the low dose. However, such differences in survival were not observed in the prostate cancer patients.⁴⁸ No other trial of ¹⁵³Sm has demonstrated a survival advantage thus caution is urged in interpreting data from this small trial.

Serafini *et al.* conducted the first double blind, placebo controlled randomized study in a variety of cancer patients with bone metastases.⁴⁹ A total of 118 patients were randomized 1:1:1 to receive single doses of placebo or ¹⁵³Sm at doses of 0.5 or 1.0 mCi/kg. Most patients had prostate cancer (n = 80) or breast cancer (n = 21). Patients who received the 1.0 mCi/kg dose of active drug exhibited significant improvements (as compared to the placebo group) in both pain scores at each of the first four weeks post-dosing. In contrast, the 0.5 mCi/kg dose demonstrated improvement in pain scores at week 1, but not for any other week. For patients receiving the 1.0 mCi/kg dose, two thirds of those responding at week 4 were still responding at week 16.

In a trial targeted only to bone metastatic CRPC patients, Sartor *et al.* performed a multi-center placebo controlled study and enrolled 152 patients.⁵⁰ Patients were randomized in a 2:1 ratio to ¹⁵³Sm or placebo and were followed for up to 16 weeks. Pain was measured twice daily by patients using a VAS or a pain descriptor scale. Analgesic scores were also recorded daily. Patients randomized to receive the ¹⁵³Sm exhibited significant improvements in the VAS pain scores for weeks 2–4 ($P < 0.02$) and in the descriptor pain scores for week 1 through 4. Cross-over for non-responding placebo-treated patients at four weeks prevented statistical analysis beyond that time point. Patients treated with ¹⁵³Sm also had significant decreases in opioid analgesic use during week 3 and week 4.

Comparison of different BSR

One trial has compared, in a direct randomized fashion, ⁸⁹Sr to ¹⁵³Sm-EDTMP.⁵¹ Baczyk *et al.* performed this study in a single Polish institution and randomized patients to receive either BSR. The study involved 100 patients, 60% with prostate cancer and the remainder with breast cancer. ⁸⁹Sr was used at a single dose of 4 mCi and ¹⁵³Sm at a single dose of 1 mCi/kg. Responses were measured two months after treatment and only this one time point was assessed. The authors concluded that 80% of patients responded in both arms. Analgesic use at the 2 month post-dosing time point was reduced by 45% and 55% in the ¹⁵³Sm and ⁸⁹Sr arms, respectively. Adverse events were not recorded in the usual fashion but 5 cases of severe pancytopenia were noted – 3 patients treated with ⁸⁹Sr and 2 patients treated with ¹⁵³Sm. Timing of the pancytopenia was not commented upon, neither were the kinetics of the response nor was toxicity accurately assessed. This small and limited trial suggests that at two months after injection, both of these isotopes are effective in palliation.

A single institution German trial³⁰ evaluated ¹⁸⁸Re-HEDP, ¹⁸⁶Re-HEDP, ¹⁵³Sm-EDTMP and ⁸⁹Sr in 79 bone-metastatic patients (61 with prostate and 18 with breast cancer). The study was not a randomized study but pain scores and analgesic use were determined weekly after each treatment. Thirty one patients were treated with ¹⁸⁸Re-HEDP, 15 patients with ¹⁸⁶Re-HEDP, 15 with ¹⁵³Sm-EDTMP, and 18 patients with ⁸⁹Sr. No apparent differences between the treatments were reported in this small and non-randomized study; approximately 70% of patients receiving each treatment had pain improvements as measured using a visual analogue scale (VAS).

As noted above, one trial has compared ³²P and ⁸⁹Sr but this trial also had a number of limitations. This single institution small randomized comparative trial conducted in India yielded similar outcomes.³⁷ Thirty-one patients with painful metastatic bone disease were treated with oral ³²P at 12 mCi or intravenous ⁸⁹Sr at 4 mCi. Pain score declines of >50% were observed in 14/16 subjects in the ³²P arm and in 14/15 subjects in the ⁸⁹Sr arm. Surprisingly, no toxicity issues were noted after either treatment. This trial emphasizes the continued utility of ³²P as a palliative agent and has implications for cost-conscious health systems

given the relatively low costs of procuring this radiopharmaceutical in most countries.

Repeated BSR dosing

The number of studies with repeated BSR dosing are limited, and $^{153}\text{Sm-EDTMP}$ and ^{223}Ra (see below) are the only BSRs to date with significant trials reporting repeated dosing. For ^{153}Sm , retreatment has primarily been reported in the setting of an initial palliative response followed by symptom recurrence in patients with good bone marrow function. Sartor *et al.* reported on 54 multiple administrations to 18 patients (range 2–11 doses/patient) with prostate ($n=15$) and breast ($n=3$) cancer.⁵² Percentage decreases from baseline in white blood cells (WBC) and platelet (PLT) counts did not increase as a function of an increasing number of administrations and there was no significant increase in the percentage of patients with Grade 3 or 4 haematologic toxicities.

Alpha-particle emitting BSR

Radium-223 (Alpharadin) is a natural bone-seeker that decays with a physical half-life of 11.4 days by releasing alpha-particles.⁵³ Alpha-emitters are relatively heavy charged particles (helium nuclei with two positive charges) that produce high-linear energy transfer (LET) radiation with a range of <100 micrometres. In contrast, beta-emitting radioisotopes have a relatively low radiobiological effectiveness and a track length in tissues of up to several millimeters (Tables 11.1 and 11.2). In comparison with ^{89}Sr and $^{153}\text{Sm-EDTMP}$, a bone-seeking alpha-emitter might therefore have a greater anti-tumour effect, by virtue of the densely ionizing high-LET radiation, but with relative sparing of the bone marrow due to the short track length. This much more energetic and localized radiation is virtually dose-rate independent resulting in potent cell-killing (Table 11.3). The induction of predominantly non-reparable double DNA-strand breaks renders an alpha-emitting BSR such as Alpharadin an intriguing alternative to beta-emitters.^{53,54} Such dense irradiation may provide an important

Table 11.3 Comparison of alpha and beta emissions from bone-seeking radioisotopes

CHARACTERISTIC	ALPHA	BETA
Range (μm)	40–90	25–6000
Linear Energy Transfer (LET; $\text{keV}/\mu\text{m}$)	60–230	0.02–0.4
Relative mass	7000	1
DNA hits to kill a cell	1–5	100–1000
Cytotoxic against G_0 cells	Yes	No
Effective against 'radio-resistant' cells?	Yes	No

advantage in patients with chemoresistant disease. In addition, micrometastases with dormant clonogenic tumor cells residing in cell cycle growth phase G_0 may be eliminated by high-linear energy transfer irradiation from alpha-emitters.⁵⁵

In its chloride formulation ^{223}Ra has been studied extensively in pre-clinical models. In mice, the biodistribution of ^{223}Ra has been shown to correspond to that of ^{89}Sr , with targeting of the bony skeleton, and with retention of its daughter isotopes in the bone matrix.⁵⁶ Modelling the dose deposition in relation to tumour deposits within the bone marrow suggest a significant reduction in dose to the normal bone marrow with ^{223}Ra in comparison with ^{89}Sr .⁵⁶ In a rat model of metastatic breast cancer, ^{223}Ra showed significant anti-tumor effects in the absence of bone marrow toxicity.⁵⁷ Animals treated with ≥ 100 kBq/kg ^{223}Ra had 40% survival beyond the 67-day follow-up period compared to 0% in control animals. Treatment with conventional chemotherapeutics, a beta-emitting BSR or the bisphosphonate pamidronate gave no survival benefit in this animal model.

More recently, a phase I trial of a single i.v. injection of Alpharadin was performed in 25 patients with metastatic bone disease, comprising 15 patients with HRPC and 10 with metastatic breast cancer.⁵⁸ Administered activities of up to 250 kBq/kg were well tolerated; with grade 3 leucopenia in 3/25 patients and no grade 2+ thrombocytopenia. Dose-limiting toxicity was not observed.

Results from a phase-II randomized clinical trial of external beam radiation plus either saline or ^{223}Ra injections (given 4 times at 4-week intervals), have recently been published.³³ Radium-223 treatment resulted in a statistically significant decrease from

baseline compared with placebo both in bone alkaline phosphatase and PSA. A favorable adverse event profile was observed with minimal bone marrow toxicity for patients who received ^{223}Ra . Importantly, survival analyzes from this phase-II trial showed a significant overall survival benefit for ^{223}Ra .³³ This alpha-pharmaceutical for repeated injections is currently in phase-III clinical development.

The dosing regimen for the phase-III trial (see www.alsympca.com for details) is straight forward being 50 kBq/kg every 4 weeks for 6 cycles. The randomized trial is a global phase-III with around 750 patients being required (about 80 sites) which has started in Europe, Australia, Canada and so far enrolled more than 300 patients. The US sites have recently joined as well. With a 2:1 randomization of the compound vs placebo, and best standard of care, eligible patients are those with castrate-resistant prostate cancer – generally docetaxel failures.

Alpha-emitters are more toxic and mutagenic than beta-emitters when comparing effects on single cells. These adverse properties can be compensated for by using targeted therapy which has the potential to irradiate much smaller volumes of normal cells when alpha-emitters are targeted against tumour cells.^{53,54} This feature helps treat skeletal metastases because the short alpha radiation tracks cause smaller dose delivered from the bone surfaces to the bone marrow cells within the bone marrow-containing cavities.⁵⁶ On the other hand, the spatial distribution of the hydroxyapatite target within an osteoblastic tumour would facilitate a volume distribution of the radionuclide and make it less likely that tumour cells evade the alpha-particles despite the limited track lengths. The promise of targeting stem cells has been much discussed¹⁴ and this may provide an approach capable of eliminating the stem cells thought to be at the source of the problem in metastatic solid tumours.

► Combination therapy

Combination of BSRs and chemotherapy

Several clinical studies to date have reported on the feasibility of combining BRSs and chemotherapy.^{59–64}

A renewed interest is seen nowadays,⁶⁵ with recent studies employing concomitant use of BSRs and chemotherapy demonstrating that apart from feasibility, the combination also seems to be effective.

Provocative randomized studies with BSRs (^{89}Sr) and chemotherapeutics were reported nearly a decade ago in prostate cancer.⁵⁹ The largest ^{89}Sr /chemotherapy trial was performed at MD Anderson in bone-metastatic CRPC patients and the randomization was between ^{89}Sr in combination with weekly doxorubicin for 6 doses or doxorubicin alone following an ‘induction’ chemotherapy.⁶² A total of 103 patients received the induction chemotherapy consisting of ketoconazole, adriamycin, vinblastine, and estramustine and 72 patients were randomized. Patients that were unable to tolerate the chemotherapy, or those patients who progressed despite the induction were not randomized. In patients randomized to ^{89}Sr , median progression free survival (PFS) (13 vs 7 months) and median overall survival (28 vs 19 months) were significantly improved as compared to doxorubicin alone. Follow-up data from larger trials are currently lacking but these results are both substantial and important and need verification in an independent and larger study.

Recent studies have renewed the interest in combining BSRs and chemotherapy. Both of these recent studies used ^{153}Sm -EDTMP and docetaxel in bone metastatic CRPC patients. Morris *et al.* used docetaxel at 75 mg/m² administered once every 3 weeks (q 3 weeks) – (considered as the standard of care for this agent) – and added a dose escalated ^{153}Sm -EDTMP in a repetitive fashion.⁶⁶ Interestingly full doses (1 mCi/kg) of ^{153}Sm q 6 weeks could be relatively safely administered in combination with 75 mg/m² docetaxel q 3 weeks. Dose-limiting toxicity was thrombocytopenia in this small phase-I trial. A small number of deemed ‘docetaxel-refractory’ patients responded to a combination of ^{153}Sm -EDTMP and docetaxel suggesting that the combination of these agents is able to reverse docetaxel resistance. If confirmed, these findings have major significance. Randomized studies are planned using these agents in combination for patients with advanced prostate cancer.

In another recent study reported by Fizazi *et al.*, estramustine/docetaxel q 3 weeks were planned and stable/responding bone metastatic prostate cancer patients after 4 cycles were treated with a single

dose of ^{153}Sm -EDTMP combined with docetaxel doses at 20 mg/m^2 q week \times 6 doses.⁶⁷ Toxicity was minimal, only two episodes of grade 3 thrombocytopenias were observed after combined therapy. The median overall survival was 29 months which is excellent for patients with this disease state. Large trials with docetaxel alone suggest median survivals in the range of 19 months. Additional studies will be needed to determine if these results can be replicated but both the Fizazi and Morris studies indicate the promise of a combined modality approach, at least in prostate cancer patients.

Studies with ^{223}Ra and taxotere in bone metastatic CRPC are planned in the near future. This combination of agents may be particularly interesting given the relatively low myelosuppression of the alpha-emitter, its potential effectiveness in prolonging survival, the possible synergy between these two agents, and the ability to deliver repeated doses of ^{223}Ra .

Combination of BSRs and chemotherapy has also been reported in osteosarcoma with several interesting results. The characteristic feature of osteosarcoma is the formation of osteoid; i.e. primitive bone matrix produced by the malignant cells per se. In the initial experiences with ^{153}Sm -EDTMP alone,^{68,69} fourteen patients with osteoblastic lesions were treated with a large dose of (30 mCi/kg) ^{153}Sm -EDTMP and gemcitabine, a known radiosensitizer, administered 1 day after ^{153}Sm . Patients then received autologous stem cell reinfusion 2 weeks later.⁷⁰ Toxicity was restricted to bone marrow suppression which was important to know given that the other potential toxicity (e.g. gastrointestinal adverse effects) was considered to be a possibility prior to therapy. At the 6–8-week assessment, there were six partial remissions and two mixed responses but unfortunately these responses were not durable.⁷⁰

Combination of BSRs and bisphosphonates

Several studies have shown that the combination of BSRs and bisphosphonates is feasible and seems effective.^{71–74} In a study by Storto *et al.* ^{89}Sr was used concomitantly with zoledronate to treat patients with pain refractory to conventional treatments.⁷¹ Patients received either 6 infusions

of zoledronate (4 mg) every 3 weeks, followed by a single dose of 150 MBq ^{89}Sr (group A), or strontium alone (group B), or zoledronate alone for 8 months (group C). Even though a statistically significant pain reduction was noted for all groups, for group A patients pain response was more pronounced. Additionally, 68% of group A patients had a pain response ≥ 4 points, as compared to 15% and 9% for groups B and C respectively.⁷¹

In a different study, women with breast cancer and disseminated bone metastases were treated with either ^{186}Re -HEDP and pamidronate, or ^{186}Re alone.⁷² The authors reported that the bisphosphonate injection did not interfere with radionuclide uptake or effect. Additionally the pain reduction documented by the VAS was similar and statistically significant for both groups.⁷²

In an additional study with rhenium,⁷³ 48 patients with metastatic bone disease from breast cancer were managed with either ^{188}Re -HEDP (group A), pamidronate alone (group B), or ^{188}Re -HEDP plus pamidronate (group C). Pain relief for groups A–C was 73.3, 80 and 100% respectively and the corresponding rates for bone metastases response was 40, 33.3 and 67.7%. The authors concluded that the combined treatment resulted in a significantly better therapeutic effect ($P < 0.05$).

Limited studies of ^{153}Sm -EDTMP and bisphosphonates have been published and conclusions are limited to skeletal uptake and toxicity.⁷⁴ Patients with bone-metastatic hormone-refractory prostate cancer were treated with isotope weeks 1, 3 and 15. Treatment with zoledronic acid began in week 3 and continued every 4 weeks through week 23 with the zoledronic acid administered 2 days before the isotope. In the analysis neither urinary excretion nor skeletal uptake was altered by the interaction between the bisphosphonate and ^{153}Sm -EDTMP.

Multiple myeloma is not usually viewed as a target for BSRs given the predominance of lytic metastases but pre-treatment with bisphosphonates may change the equilibrium of the lytic/blastic cycle sufficiently such that BSR can be targeted to exert a positive action. This may also be of significance in other cancers such as breast cancer (Figure 11.3) and lung cancer. Trials in multiple myeloma are limited but recent data combining ^{153}Sm -EDTMP with bortezomib have been published with

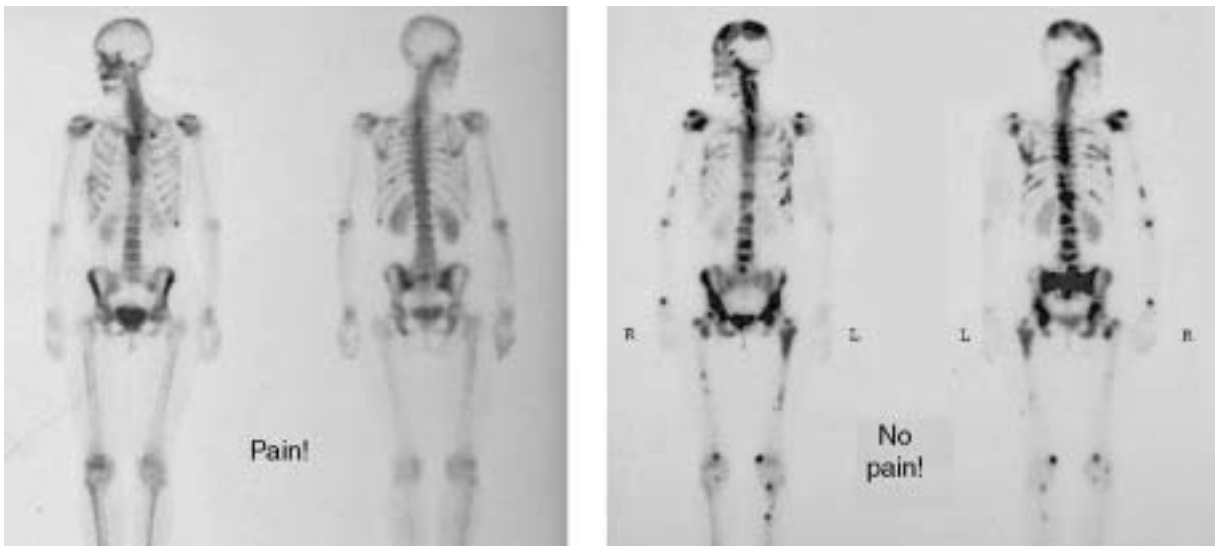


Figure 11.3 Woman with breast cancer and skeletal metastases. Increased osteoblastic/sclerotic phenotype induced following 6 months of bisphosphonate therapy. Lesions have changed to a sclerotic phenotype – hence will more readily take up BSR.

promising results.⁷⁵ Patients were enrolled in six cohorts and given bortezomib either 1.0 or 1.3 mg/m² on days 1, 4, 8, and 11 and ¹⁵³Sm in an escalating dose (0.25, 0.5, or 1.0 mCi/kg) on day 3 of a 56-day cycle. The most common toxicities were neutropenia and thrombocytopenia. Dose-limiting toxicity was reached at 0.5 mCi/kg ¹⁵³Sm-EDTMP in combination with 1.3 mg/m² bortezomib in the

schedule noted above. Responses occurred in some patients refractory to bortezomib alone suggesting synergy between the two agents.

Another experience might be of relevance to the clinical potential of combining BSR and bisphosphonates. This comes from the combination of external field radiotherapy and bisphosphonates that brings about significant pain relief and

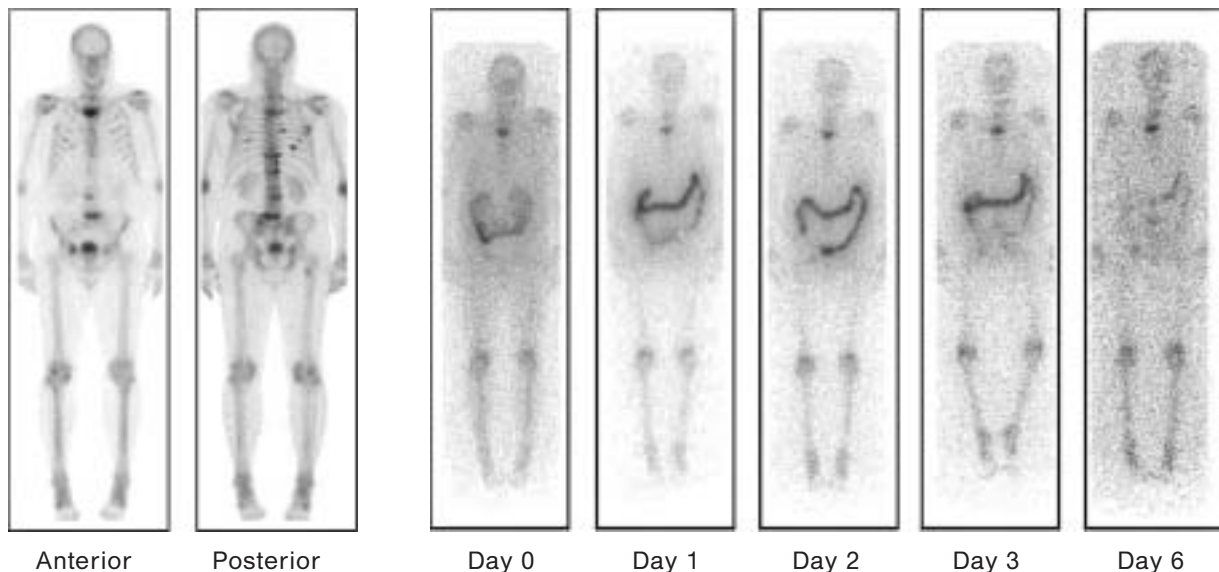


Figure 11.4 Gamma camera images of Radium-223 (left) and a diagnostic bone-scan by Technetium-99m MDP (right) illustrating corresponding uptake in osteoblastic bone metastases in a patient with prostate cancer. Images courtesy The Royal Marsden Hospital.

improvement of QoL and performance status (PS) that seem to be superior to that achieved when either therapy is applied alone.^{76,77} Synergy between the two modalities has in animal studies been shown to induce an enhanced re-ossification in metastatic lesions and to bring about an improved biomechanical strength, stability and bone microarchitecture.^{78,79}

Current clinical indications and future perspectives

BSR therapy today is clinically indicated in the context of bone pain attributable to cancerous bone lesions with avid tracer uptake on a diagnostic bone scan. Imaging studies are necessary given that the presence of an osteoblastic reaction provides the target necessary for selective uptake of the BSR (Figure 11.1). Virtually all clinical studies utilized patient populations with osteoblastic lesions, typically those having increased uptake on a ^{99m}Tc-MDP bone scan.

Following i.v. administration of a beta-emitting BSR, the bone marrow is an innocent bystander and unequivocally the dose-limiting organ. Due to the millimetre range of the emitted electrons (Tables 11.1 and 11.2), the cross-irradiation of the bone marrow represents an ever-present concern. Leukopenia and, in particular, thrombocytopenia severely limits the clinical use of beta-emitting BSRs,

especially when dosages are increased to deliver potential anti-tumour radiation levels and/or repeated treatments are attempted. Furthermore, disease-associated bone marrow suppression, and suppression associated with previous or concomitant chemotherapy, is often already present in these patients.

In slight contrast to the experience from selected patients in published clinical trials, the general clinical experience is that beta-emitting BSRs too often may result in delayed and unpredictable recovery of bone marrow function. Clinical trials were predominantly performed in chemo-naïve patients but in practice, many patients have been pre-treated with chemotherapy before BSR are administered. The other concern is that the use of future chemotherapy will be compromised and some studies addressing the topic may be interpreted in this way.⁶³ Economic issues regarding chemotherapy and BSR use is also an issue that has influenced usage in the United States.⁸⁰ Economic incentives for chemotherapy administration have decreased in recent years, thus perhaps newer BSRs may have more favourable usage patterns in the future as compared to the past.

BSR therapy should be viewed in the context of other therapeutic choices (Box 11.1). For patients with extensive soft-tissue and/or visceral disease, bone lesions may represent only a small proportion of the cancer volume and thus use of BSRs may be inappropriate. For patients with diseases known to be highly chemo- or hormonally-responsive, systemic treatment with appropriate non-isotopic

Box 11.1 Current assessments for bone seeking radiopharmaceutical consideration

- Histologic diagnosis of cancer required
- Increased uptake on a diagnostic radionuclide bone scan mandatory
 - Lack of uptake (such as osteolytic lesions) implies poor BSR targeting
- Bone pain attributable to the cancer, requiring analgesic medications, and correlated with bone scan findings
 - Significant soft-tissue component of the pain make BSR a sub-optimal choice
- Assessment for spinal cord compression, pathologic fracture, or high risk for pathologic fracture
 - These conditions require specialized and non-BSR management strategies
- Ascertainment of past therapeutic interventions and current options
 - Single lesions or regional pain may best be treated with external beam radiation
- Assessment of bone marrow function and reserve by complete blood counts
- Assessment of renal function to assess disposition of the radioisotope
- Careful discussions with patients regarding possibility of pain flare and post-injection monitoring requirements (isotope dependent)

agents may be appropriate. For patients with limited symptomatic bone disease, external beam radiation is a leading option. For those patients with risk of pathologic fractures or spinal cord compression, priority must be given to treatment of those conditions.

In addition to indications such as those listed above, contraindications to BSR should also be reviewed prior to administration (Box 11.1). Current approved BSR may induce leucopenia and thrombocytopenia thus hematological analysis is required pre-treatment. For ^{153}Sm -EDTMP, clearance is via renal excretion and experience in patients with compromised renal status is quite limited. ^{89}Sr , too, is partially cleared via the kidneys, thus caution is also advised for those with poor renal function. Interestingly ^{223}Ra appears to be excreted primarily via the small bowel and this isotope may prove to be safe in those with renal compromise.

Future perspectives in the field of BSRs are bright. A new agent with a promising effect on survival in preliminary CRPC studies is now being tested in phase III trials designed to determine in a definitive way if a BSR can prolong survival. In addition, novel studies with ^{223}Ra are being planned to take advantage of a potential synergy between this novel BSR and chemotherapy. Promising results with beta-emitters have been reported and the possibility of reversing chemotherapeutic resistance while prolonging survival has been raised. Additional studies on these concepts are planned and the questions regarding patient benefit will be available within the next few years.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this scientific work.

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