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Review article

Targeted radionuclide therapy for bone metastases

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Abstract. Recent advances in targeted radiotherapy offer a new approach for the management of metastatic bone pain. This paper will review the scientific basis for radionuclide therapy and will examine the evidence for clinical efficacy. The therapeutic potential of targeted radiotherapy can only be appreciated by comparison with established treatments. Alternative treatment options will, therefore, be discussed, to bring the potential advantages and hazards of targeted radiotherapy into perspective and to define its place in routine management.

Key words: Bone metastasis – Bone pain – Targeted radiotherapy – Radionuclide – Toxicity – Myelosuppression

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Introduction

Bone metastases are the commonest cause of cancer pain (Twycross and Fairfield 1982) and predispose to immobility, pathological fracture, bone marrow failure, neurological symptoms and hypercalcaemia. Patients with predominantly skeletal metastases frequently survive longer than those with soft tissue involvement and therefore suffer prolonged periods of morbidity (Coleman and Rubens 1987). The reported incidence of bone metastasis varies according to tumour type. Post-mortem studies indicate that up to 85% of patients with breast or prostatic carcinoma develop bone metastases in comparison with 60% of patients with bronchogenic or thyroid tumours (Stoll 1983). These results are influenced by sampling errors and probably underestimate the true incidence of bone metastasis.

The mechanisms underlying the development of metastatic bone pain are poorly understood. Several factors have been implicated, some of which are apparently unrelated to direct bone invasion by tumour. These are summarised in Table 1. It is essential to establish the likely cause of symptoms in every patient in order to tailor treatment appropriately to individual needs.

The management of skeletal metastases is directed firmly towards symptom palliation and demands a multidisciplinary approach. Treatment may involve radiotherapy, oncology, surgery, nuclear medicine and palliative care, the contribution of each specialty being governed by tumour type, disease extent and local resources. A significant emotional component may affect the perception of metastatic pain and consideration must be given to other causes of chronic discomfort such as osteoarthritis and osteoporosis, which might be amenable to alternative treatments.

Many different treatments have been advocated to control metastatic bone pain. In order to assess the value of newer options such as targeted radiotherapy, it is important to consider the relative efficacies of existing therapies and to define the clinical context in which new techniques might offer an advantage. For this reason, the scientific background and clinical efficacy of established treatment options are discussed briefly below.

Analgesics. Either alone or in combination with other treatments, analgesics form the basis for managing metastatic pain. Guidelines for the sequential use of non-steroidal anti-inflammatory drugs (NSAIDs), NSAIDs with weak opiates, and finally strong opiates have been proposed by the World Health Organisation (WHO 1986). Anticipatory pain management may reduce total requirements and it is now recognised that drugs should be administered at fixed times depending on individual pharmacodynamic properties (Ventafridda et al. 1990). The efficacy of analgesics is often enhanced by concurrent administration of tricyclic antidepressants and phenothiazines.

The toxicity of NSAIDs and opiates is well known (Hoyan 1988) and the use of opiates for example, with-

Table 1. Suggested mechanisms for metastatic bone pain

Bone invasion and local destruction
– Mediated by prostaglandins E_1–F_2 and by $F_{1\alpha}$ parathyroid-related peptide osteoclast activating factor
Periostitis
Reflex contracture, muscle spasm
Nerve root compression
Pathological fracture, vertebral, collapse
Soft tissue infiltration
Joint instability

out prophylactic anti-emetics and laxatives, may increase rather than relieve morbidity in terminal disease.

Neurolysis. The introduction of longer acting morphine preparations together with a more liberal attitude to their use has led to a reduced demand for neurolysis. Procedures such as intrathecal blocks and percutaneous cervical cordotomy provide effective pain relief for around 10% of patients (Ventafridda 1989), but the anaesthesia induced is often unpredictable and of short duration (Evans 1990). Unilateral limb or pelvic pain responds well to this approach (Ventafridda 1989).

Systemic therapy. Systemic treatments for bone metastases can be considered within two distinct categories. The first approach is direct anti-tumour therapy, aimed at reducing cellular proliferation and tumour metabolism. This may involve chemotherapy or hormone manipulation, governed by the specific tumour type and staging. Direct anti-tumour therapy is included here for the sake of completeness, but detailed discussion of the various chemotherapy or endocrine protocols in current use is beyond the scope of this paper.

The indirect approach is inhibition of the effects of tumour mediators upon host cells, particularly osteoclasts. Pathological bone resorption in metastasees is predominantly mediated by osteoclasts (Galasko 1976). Tumours with a propensity for skeletal metastasis release a variety of cytokines including interleukin-1, transforming growth factor-alpha, parathyroid hormone-related peptide and tumour necrosis factor, all of which stimulate osteoclast activity. Inhibition of osteoclast function therefore offers a potential target for systemic treatment.

The most widely used agents in this class are the bisphosphonates. These are structural analogues of pyrophosphate which bind to bone mineral, disrupting hydroxyapatite crystal formation by preventing crystal aggregation. This inhibits bone resorption and, to a variable degree, mineralisation.

Bisphosphonates are used widely to treat Paget's disease and malignant hypercalcaemia. Several studies have demonstrated a significant analgesic effect in patients with breast cancer and myeloma using oral pamidronate or clodronate. In breast cancer, pain relief was associated with a reduced incidence of pathological fracture and a slower rate of development of new metastases in treated patients in comparison with control groups (Siris et al. 1983; Elomaa et al. 1985; van Holten-Verzantvoort et al. 1987). In all studies, however, specific antitumour therapy varied between treatment groups. Other than by preventing hypercalcaemia, there is no evidence that treatment confers any survival benefit although larger longitudinal studies are in progress.

A controlled study in myeloma demonstrated excellent pain relief with osteosclerotic repair of pathological fractures following pulsed intravenous clodronate therapy (Merlini et al. 1990). The trial has been criticised for using a suboptimal clodronate dose and was not placebo controlled, but the results are sufficiently promising to justify further studies.

There is conflicting evidence concerning the use of etidronate in prostatic cancer (Carey and Lippert 1988; Smith et al. 1989), and case reports suggest that pamidronate may be more effective (Adami et al. 1985; Masud and Slevin 1989). Pamidronate acts primarily by inhibiting osteoclastic resorption rather than by affecting osteoblastic activity. This implies a different mode of action in sclerotic as opposed to osteolytic metastases.

The bisphosphonates are not well absorbed orally, the major side-effects being nausea and vomiting. Unfortunately, the maximum tolerated oral doses tend to lie at the lower end of the dose-response curve. The potential of third generation aminobisphosphonates, which are significantly less toxic, is being studied.

Alternative inhibitors of osteoclastic activity include mithramycin and calcitonin. Significant pain relief has been reported using mithramycin in a small group of women with metastatic breast cancer, but this was not associated with bone healing (Davies et al. 1979). Mithramycin is both myelo- and hepatotoxic and has been largely superseded by the bisphosphonates. The clinical efficacy of calcitonin has been assessed in phase II and III trials (Roth and Kolaric 1986; Gennari et al. 1989). Treatment is associated with reduced analgesic requirements but has little effect on functional ability or tumour progression. The moderately frequent incidence of gastrointestinal side-effects and expense have again resulted in declining interest in favour of the bisphosphonates.

Radiotherapy

The analgesic effect of radiation for bone metastases has been recognised since the early 1900s but has been supported by relatively few controlled trials. Two techniques are widely used – local field external beam treatment for discrete, localised pain and wide field (hemibody) irradiation for multifocal symptoms.

Local radiotherapy. A variety of radiotherapy dose fractionation regimes and total dose schedules are reported to relieve focal pain in up to 80% of treated patients. Numerous retrospective studies have failed to demonstrate a dose-response relationship. Single fractions in the range 4–15 Gy are as effective as multiple fractions giving a total dose of 20–40 Gy (Penn et al. 1976). Stronger evidence is derived from controlled prospective studies comparing the efficacy of single fractions of 8 Gy with 24–30 Gy given in six to ten fractions. No differences were observed as regards response, the speed of onset of pain relief, response duration or tumour histology (Cole 1989; Price et al. 1986). Subsequent studies have demonstrated that single fractions of 4 Gy are also effective (Price et al. 1988).

Toxicity is minimal and local radiotherapy is general-

ly well tolerated. Potential toxicity to normal tissues frequently precludes further treatment, however, and recurrent pain within a previously treated field, particularly the spine, is a difficult management problem.

Wide field radiotherapy. Many patients develop multifocal bone pain in the presence of advancing skeletal disease. This is a particular feature of prostatic carcinoma, which is frequently associated with flitting pain. Under these circumstances, local radiotherapy becomes impractical and wide field, hemibody irradiation is the preferred approach in some centres.

Prospective studies have recorded pain relief in 73%–83% of patients treated using single fractions of 6–7 Gy to the upper hemibody and 6–8 Gy to the lower hemibody (Hoskin et al. 1989; Salazar et al. 1986). Response is typically rapid, occurring within 24–48 h of treatment, and is maintained until death in the majority of patients.

Sixty percent of patients develop treatment-related toxicity following hemibody irradiation. Gastrointestinal symptoms account for more than 50% of reported adverse effects (Hoskin et al. 1989), particularly nausea, vomiting or diarrhoea which occur within 12–48 h of lower hemibody irradiation. Toxicity can be minimised by intensive pre-hydration combined with antiemetics and steroids but symptoms may be more severe in up to 25% of treated patients. Upper hemibody irradiation is associated with alopecia if the skull is included in the radiotherapy field, but more importantly, with radiation pneumonitis, which may be fatal. Myelosuppression is reported in 10% of patients treated using single half body treatment, but affects virtually all patients who receive sequential upper and lower hemibody therapy (Hoskin 1991).

Thus, although a highly effective treatment for bone pain, the benefits of hemibody radiotherapy must be balanced against significant potential toxicity. It is also a relatively expensive option as careful patient preparation before treatment and subsequent aftercare necessitate inpatient admission.

Targeted radionuclide therapy

The concept of using tracer molecules to target radiation to tumour is well established. Radio iodine (^{131}I) and phosphorus-32 (^{32}P) have an accepted place in the management of follicular thyroid carcinoma and polycythaemia rubra vera respectively.

Targeted radiotherapy offers several advantages over conventional external beam radiotherapy. Treatment is tumour specific, with relative sparing of the surrounding, healthy tissues. This should reduce toxicity, an important consideration in palliative care. In comparison with external beam radiotherapy there is theoretically no limit to the absorbed dose that can be delivered to tumour

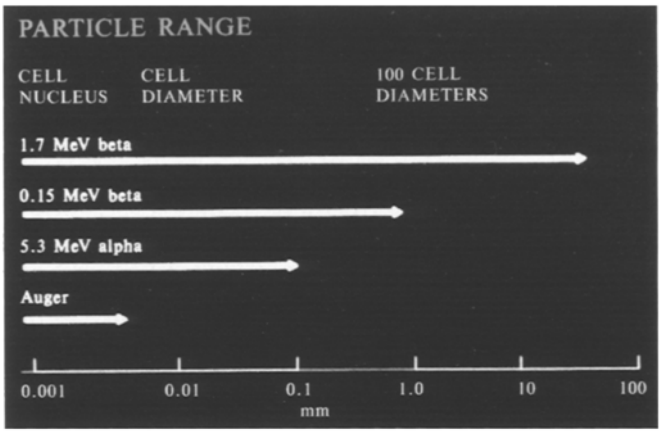

Fig. 1. Typical range or particulate emissions vs cell diameter

or to the number of individual treatments that can be administered.

The pathogenesis of metastatic bone pain and its alleviation by irradiation are not understood. Pain relief does not reflect a simple relationship between biological effect and cell kill; the absorbed radiation dose required to achieve a tumoricidal effect is far higher than the dose necessary for symptom palliation. This is an essential distinction that is of particular relevance to targeted radiotherapy. For the purpose of the following discussion, it is assumed that the intention of radionuclide therapy is to achieve cell kill. In practice, this may not be a realistic aim and pain relief alone should be regarded as a positive response, even in the absence of tumour regression.

The success of treatment depends critically upon the choice of an appropriate radionuclide and carrier molecule, where necessary, to ensure that the radionuclide is delivered directly to the tumour target. The suitability of an individual radionuclide for therapy is governed by several factors, outlined below.

Particle range. Appropriate particle range is governed by the precise site of localisation of the radiopharmaceutical in tumour. Therapeutic radionuclides can be conveniently considered in three categories – alpha, beta and internal conversion or Auger electron emitters. The relative ranges of a series of radionuclides is given in Fig. 1. The short range of Auger emitters, for example, means that the radionuclide must be incorporated into the nucleus, if not into DNA, to achieve cell kill. Alpha- and beta-emitting radiolabels are more suited to pharmaceuticals localising in the cell cytoplasm or cell surface. A range of several cell diameters allows for crossfire between adjacent cells, thus increasing the likelihood of cell kill. Conversely, a particle range exceeding 100 cell diameters is likely to damage healthy surrounding cells, leading to increased toxicity.

In theory, alpha emitters are suitable for therapy having a short range (50–90 μm) and high linear energy transfer, but complex decay schemes and unstable

Table 2. Physical properties of therapeutic radionuclides

	$T_{1/2}$	E_{max} (MeV)	Gamma emission (keV)
^{131}I	8.1 d	0.6	637; 365
^{90}Y	2.7 d	2.3	–
^{32}P	14.3 d	1.7	–
^{153}Sm	46.3 h	0.81	103
^{89}Sr	50.5 d	1.49	–
^{186}Re	3.7 d	1.07	137

Table 3. Metastatic bone pain: comparison of radiopharmaceuticals in current use

	^{89}Sr-Cl	^{153}Sm-EDTMP	^{186}Re-HEDP
Outpatient therapy	+	+	–
Imaging feasible	–	+	+
Time to response	>14 d	>48 h	>48 h
Response (% patients)	75	61–90[a]	80–90[a]

[a] Small series

daughter nuclides preclude the use of many alpha emitters. Astanine-211 and bismuth-212 are theoretically attractive but are cyclotron produced and have short half-lives which restrict their use outside specialist centres. For practical purposes, therefore, experience in targeted radionuclide therapy has focused predominantly upon beta emitters. These can be grouped according to particle range and energy, as shown in Table 2.

Physical half-life. It is essential that the physical half-life ($T_{1/2}$) of an individual radionuclide approaches the biological $T_{1/2}$ of the radiopharmaceutical in tumour. An additional factor is that a long physical $T_{1/2}$ may be associated with a suboptimal dose rate to tumour.

Low gamma yield. Gamma emission contributes to whole body absorbed dose, and, therefore, toxicity with minimal enhancement of tumour dose. A low gamma abundance in the range 100–200 keV may be of value for biodistribution and dosimetry calculations following treatment.

Chemistry and availability. It is important that the radionuclide is available in a chemical form suitable for complexing to produce a stable radiopharmaceutical in vivo. Availability and cost are necessary practical considerations.

In the context of radionuclide therapy for bone metastases, few radiopharmaceuticals have been assessed clinically. These are discussed below. The physical characteristics of each radionuclide are summarised in Table 3.

Iodine-131

Radioiodine was one of the first radionuclides to be used therapeutically and has an established place in the management of follicular thyroid carcinoma. It has been used successfully to treat both soft tissue and bone metastases although external beam radiotherapy for focal metastases may be more effective (Brown et al. 1984).

There is now good evidence to support the use of ^{131}I-labelled metaiodobenzylguanidine (MIBG) for the treatment of neuroectodermal tumours such as phaeochromocytoma (Lewington et al. 1991b) and neuroblastoma (Hoefnagel et al. 1987). ^{131}I-MIBG is of particular value for palliation of metastatic bone pain, and remineralisation of lytic metastases has been reported.

Phase I studies indicate that the ^{131}-labelled diphosphonate α-amino (4 hydroxybenzylidene) diphosphonate (^{131}I-BDP3) may have therapeutic potential for the treatment of disseminated bone metastases. Pharmacokinetic data from 18 patients with a variety of primary tumours suggest increased uptake and prolonged retention of ^{131}I-BDP3 in metastases, delivering tumour-absorbed doses of 0.75–1.9 cGy/MBq administered activity (Eisenhut et al. 1986). Clinical results from the same trial suggest 72% of patients benefitted from treatment using activities of 240–1900 MBq ^{131}I-BDP3. A standard dose of 860 MBq/m^2 has been proposed.

Yttrium-90

^{90}Y has appropriate physical characteristics for targeted radiotherapy and has been used for radiation synovectomy in the arthritides and for labelling monoclonal antibodies and glass microspheres for intracavity therapy. Experience using ^{90}Y to treat bone metastases has been limited by unacceptably high hepatic uptake (Eisenhut 1984).

Phosphorus-32

Wide experience has been gained using ^{32}P to treat bone metastases. Phosphorus localises in bone marrow and trabecular and cortical bone, influenced by the chemical form used – colloidal, phosphate or diphosphonate. The metastasis to normal bone uptake ratio is only in the order of 2:1 and a number of techniques have been advocated to enhance relative tumour uptake. Androgen priming stimulates osteoblastic activity adjacent to tumour (Hertz 1950; Maxfield et al. 1958; Burnet et al. 1990), increasing uptake in normal bone by a factor of 2–3 and by tumour by a factor of 15–20. Lasting pain relief has been reported in 50%–87% of patients with metastatic prostate cancer treated using a combination of testosterone and 200–800 MBq (5–20 mCi) ^{32}P administered in daily injections of 40–80 MBq (1–2 mCi) (Burnet et al. 1990).

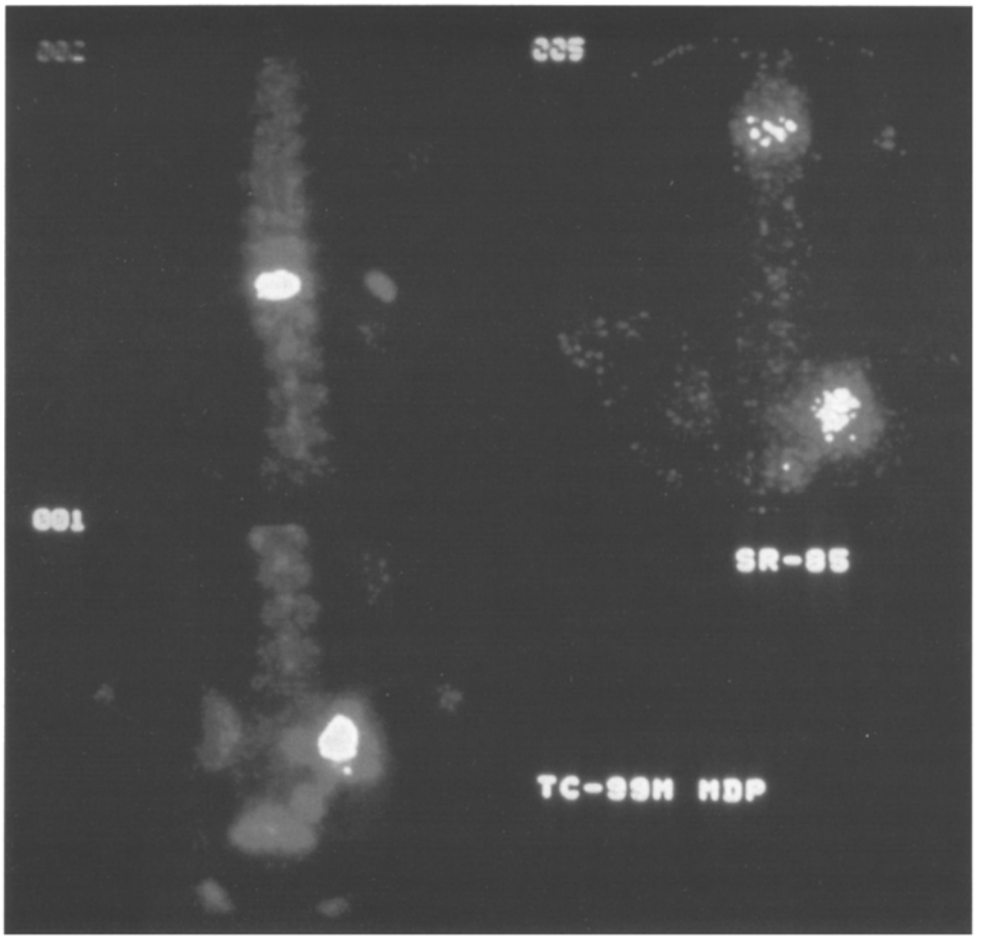

Fig. 2. ^{85}Sr vs ^{99m}Tc-MDP uptake in metastatic prostatic carcinoma

Androgen priming has obvious disadvantages in the context of a hormone-sensitive tumour. Soft tissue tumour growth may be stimulated and spinal cord compression is a recognised complication (Burnet et al. 1990). Many patients suffer a pain flare following testosterone administration which may necessitate hospital admission (Burnet et al. 1990).

An alternative technique involves the administration of parathyroid hormone (PTH) to induce bone resorption. Radiophosphorus uptake was increased during the rebound phase of increased osteoblastic activity following PTH withdrawal (Tong 1971).

The principal disadvantage of ^{32}P therapy is myelosuppression, the risk of which is considered unacceptably high. Transient pancytopenia is almost invariable, with aplastic anaemia in patients treated with repeated ^{32}P injections.

Strontium-89

The therapeutic potential of ^{89}Sr was first recognised by Pecher (1942) but was largely overlooked until the 1970s. Following intravenous injection, ^{89}Sr is cleared rapidly from the vascular compartment and selectively concentrates at sites of increased bone mineral turnover. Biodistribution studies have been undertaken using the gamma emitter ^{85}Sr in patients with disseminated prostatic carcinoma (Fig. 2). Strontium retention 90 days following injection ranges from 11% to 88% of administered activity, governed largely by tumour extent in the skeleton. Early retention is influenced by Sr plasma renal clearance, which is significantly reduced in patients with bone metastases compared with ICRP normal man (Blake et al. 1986). Absorbed doses to tumour in the range 20–24cGy/MBq have been calculated (Blake et al. 1987), giving a therapeutic ratio for metastasis to red marrow of 10:1 (Blake et al. 1988).

Following initial studies (Firusian et al. 1976; Silberstein and Williams 1985; Robinson et al. 1987), Laing et al. (1991) reported pain relief in 75% of patients with disseminated prostatic carcinoma treated with ^{89}Sr. Outcome was influenced by disease extent and patients with limited skeletal metastases responded better than those with more widespread tumour.

No clear dose-response relationship has been demonstrated. There appears to be a threshold of 1 MBq/kg below which ^{89}Sr is ineffective, but combined data from numerous small studies collated under the auspices of Amersham International indicate a response plateau

above activities of 1.5 MBq/kg. Dose escalation above this level results in increasing toxicity without enhancing pain relief. On the basis of these data, a standard dose of 150 MBq ^{89}Sr is recommended.

Toxicity is limited to temporary myelosuppression, the most sensitive indicator of which is the peripheral platelet count. Pletelet counts typically fall to 75% of pretreatment levels 4–6 weeks after ^{89}Sr therapy, with slow partial recovery over the next 3–6 weeks in patients with normal bone marrow reserve. The risk of toxicity is cumulative and regular haematological monitoring is essential following therapy. ^{89}Sr has been used safely in patients who have been heavily pretreated using wide field radiotherapy. McEwan et al. (1990) reported limited toxicity (RTOG grade 2 or 3) in only 12% of patients treated using 1.5 MBq/kg ^{89}Sr after wide field treatment.

A double-blind controlled study comparing the efficacy of ^{89}Sr with stable Sr as placebo concluded that Sr acts by the direct radiotherapeutic effect of the beta particle acting either on the tumour itself or on adjacent bone (Lewington et al. 1991 a). Symptomatic benefit is rarely associated with tumour regression or reduced osteoblastic activity, measured by radiology or bone scintigraphy. Similarly, pain relief does not correlate with a consistent decrease in biochemical markers such as alkaline phosphatase, acid phosphatase or prostatic specific antigen. This is in contrast to the effects of conventional radiotherapy which may lead to remineralisation of lytic metastases.

The clinical efficacy of ^{89}Sr and radiotherapy have been directly compared in a controlled, multicentre study (Lewington et al. 1992). Patients were grouped according to suitability for local or wide field treatment and were then randomised to receive either ^{89}Sr therapy or radiotherapy. Response was assessed at 3 months. The results indicated that ^{89}Sr is at least as effective as radiotherapy in relieving bone pain and, in comparison with local radiotherapy, may offer the advantage of delaying the onset of pain in new sites. Toxicity is higher following ^{89}Sr than after wide field radiotherapy, but this was not clinically significant.

The use of ^{89}Sr as an adjuant to fractionated radiotherapy has been assessed in a multicentre Canadian trial, the results of which are awaited.

Following an initial report by Buchali et al., increasing interest has focused on the question of survival benefit following ^{89}Sr therapy. The Berlin group used a fractionated treatment schedule and hormone manipulation was not controlled. Their work has not been repeated using conventional dose schedules and there is currently no evidence to suggest that ^{89}Sr, used as a single agent, has any effect on survival when administered for pain relief in advanced prostatic cancer. Consideration must be given to the therapeutic potential of introducing Sr earlier in the natural history of the disease with the intention of delaying the spread of bone metastases.

In summary, ^{89}Sr is of proven value for the relief of bone pain in metastatic prostatic carcinoma. Further research is required to established the optimal dose schedule and to investigate the effects of fractionation. In the light of previous uncontrolled studies (Robinson et al. 1987; Odavic 1991), trials are in progress to assess the value of ^{89}Sr for pain relief in other malignancies.

Samarium-153

^{153}Sm has a short physical half-life in comparison with other beta emitters. It has been shown that low LET radiation delivered at high dose rates is more effective than equivalent doses delivered at low dose rates (Hall 1978). ^{153}Sm might, therefore, be more effective than ^{89}Sr for palliation of metastatic bone pain.

A series of stable ^{153}Sm complexes have been synthesized using multidentate acetate and phosphonate ligands of which ^{153}Sm-ethylenediaminetetramethylene-phosphonate (^{153}Sm-EDTMP) exhibits the most favourable in vivo biodistribution (Goeckler et al. 1987). The radiopharmaceutical is stable in vivo and clears rapidly from the vascular compartment following intravenous injection with a $t_{1/2}$ of 3.7 ± 0.5 h. 40% and 60% of the injected activity is excreted in urine within 8 h of administration, the remaining activity concentrating in the skeleton, with preferential uptake at sites of increased osteoblastic activity (Kasi et al. 1991). Superior target to background and tumour to normal bone ratios are reported in comparison with technetium-99m methylene diphosphonate (Podoloff et al. 1991). Lesion to normal bone uptake ratios of 17:1 have been calculated (Goeckler et al. 1987). The gamma emission is ideal for imaging but has the disadvantage of necessitating hospital admission for 24–48 h following therapy injection.

Clinical experience with ^{153}Sm-EDTMP in man is relatively limited. Several small, uncontrolled studies have reported pain relief in 61%–90% of patients with bone metastases arising from a variety of primary malignancies (Turner et al. 1989; Turner and Claringbold 1991; Eary et al. 1991). Symptomatic improvement occurs within 2 weeks of treatment with median duration of benefit of 8 weeks (Turner et al. 1991). The short physical half-life of ^{153}Sm offers the option of fractionated treatment and response rates of 87% have been reported using a treatment interval of 4 weeks with activities of 20–40 MBq/kg per treatment (Kasi et al. 1991).

As with ^{89}Sr, toxicity is limited to myelosuppression which is dose related. Platelet recovery is typically slow and incomplete, with 25% of patients failing to achieve 65% of pretreatment platelet levels at 6 weeks (Turner et al. 1991). The risk of myelosuppression is cumulative and is invariable using activities of 22–36 MBq/kg. Turner et al. (1991) concluded that retreatment is safe provided that the radiation dose to red marrow is limited to 1.5–2 Gy on each occasion.

The first major phase II trial of ^{153}Sm-EDTMP, a multicentre, dose-ranging European study, is nearing completion.

Rhenium-186

Rhenium has similar chemical properties to technetium and forms a stable diphosphonate chelate with hydroxyethylidene diphosphonate (HEDP). In patients with osteoblastic bone metastases from prostate and breast carcinoma, 80%–90% response rates have been reported following a single treatment with 1.2–1.8 GBq ^{186}Re-HEDP (Maxon et al. 1991; Zonnenberg et al. 1991). Tumour to marrow absorbed dose ratios are double those achieved using ^{89}Sr (22:1 and 10:1 respectively) (Maxon et al. 1990). Toxicity is limited to temporary myelosuppression, with full recovery 8 weeks following therapy. This presumably reflects the high tumour to marrow ratio (Maxon et al. 1991). Like ^{153}Sm, ^{186}Re has the advantage of 9% gamma emission allowing post-therapy imaging, but by virtue of the high activities necessary for therapy, gamma emission also necessitates inpatient treatment.

In comparison with the results of ^{89}Sr, symptom relief occurs rapidly following treatment, and in this respect is similar to the rapid responses observed following wide field radiotherapy (Maxon et al. 1991). The Utrecht group report a transient pain flare in 50% of patients (Zonnenberg et al. 1991). The 5- to 7-week mean response duration is considerably shorter than that reported for ^{89}Sr (Zonnenberg et al. 1991) and no data have been published on the effectiveness or toxicity of repeated treatment. A small recent controlled study demonstrated a significant difference in clinical efficacy between ^{186}Re-HEDP and ^{99m}Tc-MDP as placebo (Maxon et al. 1991).

The relative advantages and disadvantages of the different radiopharmaceuticals currently used for targeted radiotherapy are summarised in Table 3.

Conclusion

Much of the morbidity and mortality associated with cancer can be attributed to skeletal metastases. Any improvement in effective treatment for metastatic bone pain must therefore represent a major advance in cancer management.

Analgesics alone are rarely adequate or appropriate for the long-term control of metastatic bone pain and the effectiveness of external beam radiotherapy is limited for patients with multifocal pain, particularly when pain recurs in a previously irradiated site. In this context, both the bisphosphonates and targeted radiotherapy offer the best chance of improving quality of life for patients with advancing malignancy. Comparative controlled trials will be necessary to assess the relative merits and specific indications for each treatment. It is important to appreciate that response to targeted radiotherapy is limited by the intensity of osteoblastic activity induced in the adjacent bone. Bone pain secondary to multiple myeloma, for example, is unlikely to respond to targeted radiotherapy and the bisphosphonates may offer a better treatment option in this condition.

With respect to targeted radiotherapy, current evidence suggests that in terms of clinical efficacy, there may be very little to choose between the different radiopharmaceuticals. The rapid onset of pain relief reported using ^{186}Re-HEDP, and ^{153}Sm-EDTMP may be an advantage in comparison with ^{89}Sr, although this must be balanced against the longer mean response duration reported for ^{89}Sr. It might be argued that a "cocktail" treatment could be used to maximise the advantages offered by the various beta emitters.

Factors such as ease of handling radiopharmaceuticals by hospital staff and the necessity for patient isolation after treatment for radiation protection purposes will assume increasing importance if targeted radiotherapy becomes an established treatment for routine management. Inpatient admission is unpopular with patients, inconvenient for their relatives and contributes enormously to the cost of treatment. In this respect, ^{89}Sr may have an advantage over the gamma emitters in that treatment can be safely administered on an outpatient basis.

All the trials published to date identify a hard core of 20%–25% of patients who fail targeted radiotherapy. From personal experience, it is virtually impossible to identify non-responders prior to treatment and further attention should be given to methods of predicting which patients are unlikely to benefit and to the reasons for treatment failure. Simple measures such as correcting anaemia may influence outcome by reducing tumour hypoxia, as in conventional radiotherapy, and the use of radiosensitisers, particularly in the treatment-resistant group, should also be considered.

An important consideration in the current climate of escalating costs for health care is the relative cost-effectiveness of treatment. It is essential that future studies for all the new therapeutic radiopharmaceuticals include detailed cost-benefit analysis in order that limited resources can be used effectively.

In conclusion, effective treatments are now available for the management of metastatic bone pain. It is essential that collective experience is pooled and that large, multicentre controlled trials are conducted to provide the weight of evidence that will convince clinicians of the therapeutic potential of targeted radiotherapy.

References

Adami S, Salvagno G, Guarrera G, Bianchi G, Dorizzi R, Rosini S (1985) Dichloromethylene disphosphonate in patients with prostatic carcinoma metastatic to the skeleton. J Urol 134:1152–1154

Blake GM, Zivanovic MA, McEwan AJ, Ackery DM (1986) Sr-89 therapy: Strontium kinetics in disseminated carcinoma of the prostate. Eur J Nucl Med 12:447–454

Blake GM, Zivanovic MA, McEwan AJ, Batty VB, Ackery DM

(1987) Sr-89 radionuclide therapy: dosimetry and haematological toxicity in two patients with metastasising prostatic carcinoma. Eur J Nucl Med 13:41–46

Blake GM, Zivanovic MA, Blaquiere RM, Fine DR, McEwan AJ, Ackery DM (1988) Strontium-89 therapy: measurement of absorbed dose to skeletal metastases. J Nucl Med 29:549–557

Brown AP, Greening WP, McCready VR, Shaw HJ, Harmer CL (1984) Radioiodine treatment of metastatic thyroid carcinoma: the Royal Marsden Hospital experience. Br J Radiol 57:323–327

Burnet NG, Williams G, Howard N (1990) Phosphorus-32 for intractable bony pain from carcinoma of the prostate. Clin Oncol 2:220–223

Carey PO, Lippert MC (1988) Treatment of painful prostatic bone metastases with oral editronate disodium. J Urol 32:403–407

Cole DJ (1989) A radiomised trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. Clin Oncol 1:59–62

Coleman RE, Rubens RD (1987) The clinical course of bone metastases in breast cancer. Br J Cancer 55:61–66

Davies J, Trask C, Souhami RL (1979) Effect of mithramycin on widespread painful bone metastases in cancer of the breast. Cancer Treat Rep 63:1835–1838

Eary JF, Collins C, Appelbaum FR, Nemiroff C, Ferency S, Richter KY, Gordon EE (1990) Sm-153 EDTMP treatment of hormone refractory prostate carcinoma. J Nucl Med 31:5; 755

Eisenhut M (1984) Iodine-131 labeled diphosphonates for the palliative treatment of bone metastases: organ distribution and kinetics of I-131 BDP3 in rats. J Nucl Med 25:1356–1361

Eisenhut M, Berberich R, Kimmig B, Oberhausen E (1986) Iodine-131 labeled diphosphonates for palliative treatment of bone metastases: II. Preliminary clinical results with iodine-131 BDP3. J Nucl Med 27:1255–1261

Elomaa I, Blomqvist C, Porkka L (1985) Diphosphonates for skeletal metastases. Lancet II:1063

Evans PJD (1990) Opioids in the treatment of cancer pain. In: Doyle D (ed) Royal Society of Medicine Services International Congress and Symposium Series No 146. Royal Society of Medicine Services Ltd

Firusian N, Mellin P, Schmidt CG (1976) Results of strontium-89 therapy in patients with carcinoma of the prostate and incurable pain from bone metastases: a preliminary report. J Urol 116:764–768

Galasko CSB (1976) Mechanisms of bone destruction in the development of skeletal metastases. Nature 263:507–508

Gennari C, Francini G, Chierichetti SM, Nami R, Gonelli S, Poilini M (1989) Salmon calcitonin treatment in bone metastases. Curr Ther Res 45:804–812

Goeckler WF, Edwards B, Volkert WA, Holmes RA, Simon J, Wilson D (1987) Skeletal localisation of samarium-153 chelates: potential therapeutic bone agents. J Nucl Med 28:495–504

Hall EJ (1978) Radiobiology for the radiologist. Harper & Row, Philadelphia, p 145

Hertz S (1950) Modifying effect of steroid hormone therapy on human neoplastic disease as judged by radioactive phosphorus (P32). J Clin Invest 29:821

Hoefnagel CA, Voute PA, de Kraker J, Marcuse HR (1987) Radionuclide diagnosis and therapy of nueroectodermal tumours using I-131 metaiodobenzylguanidine. J Nucl Med 28:308–314

Hoskin PJ (1991) Radiotherapy in the management of bone metastases. In: Rubens RD, Fogelman I (eds) Bone metastases: diagnosis and treatment. Springer, Berlin Heidelberg New York

Hoskin PJ, Ford HT, Harmer CL (1989) Hemibody irradiation for metastatic bone pain in two histologically distinct groups of patients. Clin Oncol 1:67–69

Hoyan DL (1988) Damage and protection of the human gastric mucosa. Am J Med 84[2A]:35–40

Kasi LP, Fossella F, Holoye P, Podoloff D, Kim E, Crane J, Gordon EE (1991) Evaluation of multiple dose Sm-153-EDTMP for bone pain palliation in cancer patients. Proc. 7th international symposium of radiopharmacology. Boston, Mass, p 11

Laing AH, Ackery DM, Bayly RJ, Buchanan RB, Lewington VJ, McEwan AJ, Macleod PM, Zivanovic MA (1991) Strontium-89 therapy for pain palliation in prostatic skeletal malignancy. Br J Radiol 64:816–822

Lewington VJ, McEwan AJ, Ackery DM, Bayly RJ, Keeling DH, Macleod PM, Porter AT, Zivanovic MA (1991) A prospective randomised double blind corssover study to examine the efficacy of strontium-89 in pain palliation in patients with advanced prostate cancer metastatic to bone. Eur J Cancer 27:954–958

Lewington VJ, Zivanovic MA, Tristam M, McEwan AJ, Ackery DM (1991b) I-131 mIBG therapy for malignant phaeochromocytoma. J Nucl Biol Med 35:280–283

Lewington VJ, Bolger PJ, Dearnaley DP, Kirk D, Quilty PM, Yardley J, Zivanovic MA (1992) Is strontium-89 an effective alternative to radiotherapy for prostatic metastases? Nucl Med Commun [Abs] 13:211–212 (abstr)

Masud T, Slevin ML (1989) Pamidronate to reduce bone pain in a normocalcaemic patient with disseminated prostatic carcinoma. Lancet I:1021–1022

Maxfield JR, Maxfield JGS, Maxfield WS (1958) The use of radioactive phosphorus and testosterone in metastatic bone lesions from breast and prostate. South Med J 51:937–327

Maxon HR, Schroder LE, Thomas SR (1990) Re-186[Sn]HEDP for treatment of painful osseous metastases: initial clinical experience in 20 patients with hormone resistant prostate cancer. Radiology 176:155–159

Maxon III HR, Schroder LE, Hertzberg VS, Thomas SR, Englaro EE, Samaratunga R, Smith H, Moulton JS, Williams CC, Ehrhardt GJ, Schneider HJ (1991) Rhenium-186[Sn]HEDP for treatment of painful osseous metastases: results of a double blind crossover comparison with placebo. J Nucl Med 32:1877–1881

McEwan AJB, Porter A, Venner P, Amyotte G (1990) An evaluation of the safety and efficacy of treatment with Sr-89 in patients who have previously received wide field radiotherapy. Antibodies, Immunoconjugates and Radiopharmaceuticals 3[2]:91–98

Merlini G, Parrinello GA, Piccinini L (1990) Long term effects of parenteral dichloromethylene bisphosphonate (CL2MBP) on bone disease of myeloma patients treated with chemotherapy. Haematol Oncol 8:23–30

Pecher C (1942) Biological investigations with radioactive calcium and strontium. Preliminary report on the use of radioactive strontium in the treatment of metastatic bone cancer. University of California Publications in Pharmacology 2:117–149

Podoloff DA, Kasi LP, Kim EE, Fossella F, Bhadkamkar VA (1991) Evaluation of Sm-153 EDTMP as a bone imaging agent during a therapeutic trial (abstr). J Nucl Med 32:918

Price P, Hoskin PJ, Easton P, Austin D, Palmer SG, Yarnold JR (1986) Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bone metastases. Radiother Oncol 6:247–255

Robinson RG, Spicer JA, Preston DF, Wegst AV, Martin NL (1987) Treatment of metastatic bone pain with strontium-89. Int J Rad Appl Instrum [B] 1:219–222

Roth A, Kolaric K (1986) Analgesic activity of calcitonin in patients with painful osteolytic metastases of breast cancer. Results of a controlled randomized study. Oncology 43:283–287

Silberstein EB, Williams C (1985) Strontium 89 therapy for the pain of osseous metastases. J Nucl Med 26:345–348

Siris ES, Hyman GA, Canfield RE (1983) Effects of dichloromethylene bisphosphonate in women with breast carcinoma metastatic to the skeleton. Am J Med 74:401–406

Stoll BA (1983) Natural history, prognosis and staging of bone metastases. In: Stoll BA, Parbhoo S (eds) Bone metastases: monitoring and treatment. Raven, New York, pp 1–4

Tong ECK (1971) Parathormone and P-32 therapy in prostatic cancer with bone metastases. Radiology 98:343–351

Turner JH, Claringbold PG (1991) A phase II study of treatment of painful multifocal skeletal metastases with single and repeated dose samarium-153 ethylenediaminetetramethylene phosphate. Eur J Cancer 27:1084–1086

Turner JH, Martindale AA, Sorby P, Hetherington EL, Fleay RF, Hoffman RF, Claringbold PG (1989) Samarium-153 EDTMP of disseminated skeletal metastasis. Eur J Nucl Med 15:784–795

Twycross RG, Fairfield S (1982) Pain in far advanced cancer. Pain 14:303–310

van Holten-Verzantvoort AT, Bijvoet OLM, Hermens J (1987) Reduced morbidity from skeletal metastases in breast cancer patients during long term bisphosphonate (APD) treatment. Lancet II:983–985

Ventafridda V (1989) Continuing care: a major issue in pain management. Pain 36:137–144

Ventafridda V, Sbanotto A, De Conno F (1990) Review article: pain in prostate cancer. Palliative Medicine 4:173–184

World Health Organisation (1986) Cancer pain relief. World Health Organisation, Geneva

Zonnenberg BA, de Klerk JMH, van Rijk PP, Quirijnen JMSP, van het Schip AD, van Dijk A, ten Kroode NFJ (1991) Re-186-HEDP for treatment of painful bone metastases in patients with metastatic prostate or breast cancer. Preliminary results (abstract). J Nucl Med 32:1082