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Palliation of Bone Metastases

BONE METASTASES are a major cause of serious morbidity from cancer, resulting in pain, hypercalcaemia, loss of function following pathological fracture and neurological symptoms from nerve compression.

The analgesic effects of radiation for bone metastases have been apparent since the beginning of this century but there has been little objective study of radiotherapy for bone pain. As a result a wide range of doses and fractionation schedules have evolved, each supported by small retrospective series demonstrating their efficacy. A review of this literature reveals no difference in reported results between various schedules ranging from low-dose single treatments to high-dose and hyperfractionated regimens [1]. The picture has not yet been completely clarified by the small number of prospective randomised studies published.

The largest of these from the Radiation Therapy and Oncology Group (RTOG) in the USA randomised 1006 patients into five different fractionation schedules ranging from 15 Gy in 5 fractions to 40.5 Gy in 15 fractions. The most recent analysis of these data [2] has shown a statistically significant relation between complete pain relief and the number of treatment fractions, but not the dose per fraction. An important criticism of the RTOG study is the use of insensitive pain measurement incorporating physician assessments at clinic visits. In contrast to this study three smaller prospective randomised studies have failed to show any difference between one or two treatments and a fractionated course. The largest of these compared 8 Gy as a single dose with 30 Gy in 10 daily fractions in 288 patients, using independently validated pain charts completed by the patient. No difference in onset, degree or duration of pain relief between the two patient groups was seen [3].

As yet there is no compelling evidence to show that for simple bone pain a high-dose fractionated schedule has any advantages over a single dose of around 8 Gy, and for uncomplicated bone pain this should be the initial treatment of choice. However, many factors which have not been addressed in the trials performed to date may complicate the aetiology of bone pain; these include the role of nerve root irritation, muscle spasm and pathological fracture. Many clinicians still feel that nerve pain and impending fracture may benefit from a higher dose fractionated schedule and this is common practice.

Bone metastases with few exceptions arise as a result of blood-borne spread from the primary site and multiple metastases are therefore usual. In this setting local irradiation can have only a limited role and systemic therapy would seem the most appropriate treatment in hormone or chemotherapy responsive tumours. However, response rates to chemotherapy for bone metastases are disappointing even in chemosensitive tumours, and the onset of response is often slow with a median time to pain relief of 32 weeks reported in breast cancer patients receiving various chemotherapy schedules [4]. Response rates for bone pain after hormone manipulation in breast cancer vary from around 20% with tamoxifen or progestogens to 35% with aminoglutethimide [5]. In contrast, high response rates of around 85% are seen after initial androgen deprivation for metastatic prostate cancer but second-line therapy on relapse is only occasionally of value. Early studies with biphosphonates in breast cancer and myeloma suggest that in the future these may have a role both in the treatment of established bone metastases [6] and in their prevention [7].

An alternative approach where several sites are symptomatic is wide-field hemibody irradiation (HBI). A prospective study of 168 patients having predominantly breast, lung and prostate cancer reported by the RTOG [8] found pain relief in 73% of patients with a 20% complete response rate. This is in keeping with other retrospective data. An interesting observation following HBI is that rapid pain relief, in many patients within 24 hours, is a common and consistent feature. Conventionally, doses of 8 Gy to the lower hemibody (LHBI) and 6 Gy to the upper hemibody (UHBI), lung corrected, are used but even at these dose levels toxicity is greater than with local irradiation. In particular there is gastrointestinal and bone marrow toxicity; and rarely, pneumonitis, which may be fatal, occurs.

In view of the potential toxicity of HBI, the requirement in many centres for hospital admission for HBI and the technical complexity of wide field irradiation, together with the limited efficacy of hormone and chemotherapy for bone metastases, alternative means of delivering radiation to multiple bone sites are attractive. The concept of a tumour-seeking radioactive isotope—the magic bullet—is familiar but has been elusive in practice. One exception is differentiated thyroid cancer which selectively concentrates radioiodine. Follicular carcinoma of the thyroid has a propensity to spread to bone and bone metastases will concentrate ^{131}I after oral administration. Paradoxically, however, whilst iodine uptake in affected areas of bone can be demonstrated, pain relief after radioiodine is poor and inferior to the use of external beam therapy [9].

Radioactive phosphorus (^{32}P) has been investigated for bone pain, but bone marrow suppression has limited its use for bone metastases. More recently, attention has been focused on the potential of strontium (^{89}Sr) in this context, and a number of prospective studies are now coming to fruition, one of the first of which appears in this issue (Lewington *et al.*, p.954). ^{89}Sr emits beta particles with an energy of 1.43 MeV and after intravenous administration to patients with bone metastases up to 70%, depending upon the extent of osteoblastic activity, will be taken up in the skeleton. Prolonged retention at sites of osteoblastic activity has been demonstrated for periods of up to 100 days. The biological half-life of ^{89}Sr has been estimated at 50 days enabling significant doses of radiation to be delivered at sites of uptake around metastases, comparable to that received after external beam therapy. Excretion of strontium is through the urine and radiation levels remain well within safe levels after therapeutic doses, the only contraindication to its use being in the incontinent patient, where safe disposal of radioactive urine cannot be guaranteed.

Early phase II studies with ^{89}Sr report response rates for bone pain of 51–86% with little or no bone marrow supression [1]. Attention has focused particularly on its role in prostatic metastases where there is a marked osteoblastic response and the study by Lewington *et al.* confirms the efficacy of strontium in a prospective randomised placebo-controlled study.

Currently, radiation remains the single most effective modality for the relief of pain from bone metastases, whether administered as a local external beam treatment, wide field therapy for multiple sites of pain or systemic radioisotopes of

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which ^{89}Sr may become the agent of choice. There remains, however, uncertainty as to the mechanism by which pain relief is achieved. There are a number of features which suggest that tumour shrinkage *per se* is not essential for pain relief. Firstly there is no clear dose-response relationship for pain relief, whether from external beam treatment or ^{89}Sr. Low doses are undoubtedly effective with significant pain relief being seen after single treatments of only 4 Gy [10]. No clear relationship between primary tumour type and response is seen and in particular, radioresistant tumours appear equally responsive in terms of pain relief as radiosensitive tumours [3, 11]. After strontium therapy in prostate cancer, no correlation is seen between pain relief and changes in acid phosphatase or bone scan. Another interesting observation is the rapid relief of pain seen particularly after HBI and which occurs with both UHBI and LHBI, excluding a specific endocrine effect. Little is known about the detailed pathology and radiobiology of bone irradiation in man nor of the neurophysiological mechanisms of bone pain due to metastatic disease; effects on humoral pain modulators, tumour secretions or nerve transmission have all been postulated as important factors in pain relief, but remain unproven. There is a need for studies to elucidate the biological basis for the analgesic action of radiation on bone metastases to reconcile the published clinical dose-effect data with current practice.

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Prevention Conference Overview

SINCE 1985 the International Council for Coordinating Cancer (ICCCR) has sponsored numerous conferences and symposia on cancer designed to provide a forum to discuss specific research findings, expand international communication and create research networks between scientists.

This year ICCCR announced that it would focus "nearly exclusively" on prevention research. Dr Vincent T. DeVita, Jr, president of ICCCR made this announcement just prior to the opening of ICCCR's first international Conference on Cancer Prevention: Facts, Maybes and Rumors. "There are various areas in cancer research that are uniquely international and poorly supported", Dr DeVita said. "Cancer prevention, some areas of AIDS research and the molecular biology of virus-related cancers are of special interest. In fact, most of our data on cancer prevention come from international population studies. However, a great deal of prevention research lacks support, either because the projects have their origins in more than one country or because of the multifaceted nature of the studies. In this case they cannot be submitted to funding agencies on a project by project basis".

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With this prevention vacuum in mind, the Steering Committee and its chairman, Dr C. Everett Koop, former US Surgeon General, organised a 2-day conference in February at the National Institutes of Health Campus in Bethesda, Maryland, which attracted more than 160 senior scientists and policy-makers from around the world. The stated aims of the conference were to define a more precise picture of current prevention research and to provide the opportunity for prevention experts to collaboratively define research agenda.

The Steering Committee felt that it would be critical to the stated long-term goals of the conference to establish the facts behind cancer causation that have been scientifically proven; the maybes that are intriguing and under active examination; and the powerful rumours that are unproven and often distort media and public opinion about cancer.

The conference was dedicated to the memory of Dr Joseph Cullen, a world leader in cancer prevention who as deputy directory of NCI's Division of Cancer Prevention and Control spearheaded the American government's campaign against tobacco use.

Presentations included four areas: tobacco and smoking; nutrition, diet and cancer; viruses/cancer risk factors and environment; and lifestyle and cancer. With a clearer understanding of the underlying causes of cancer, the conference