A multicentre observational study of radionuclide therapy in patients with painful bone metastases of prostate cancer

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Abstract. A multicentre observational study was conducted by the Italian Association of Nuclear Medicine between 1996 and 1998. Twenty-nine Nuclear Medicine Departments participated. The aims of the study were to systematically evaluate the efficacy, toxicity and repeatability of radionuclide therapy of painful bone metastases (RTBM) in a large number of patients and to assess its incidence in patients with prostate cancer. Out of 818 treatments performed with a single i.v. dose of 148 MBq of strontium-89 chloride or 1,295 MBq of rhenium-186 hydroxyethylidene diphosphonate (HEDP), 610 could be evaluated (527 with ⁸⁹Sr and 83 with ¹⁸⁶Re-HEDP). Eighty-one patients received multiple (up to five) RTBM. The total number of retreatments was 100. Patients were followed up for a period of 3–24 months. Results, assessed according to pain relief and consumption of analgesic drugs, were expressed at four levels: 1, no response; 2, mild response; 3, good response; 4, excel-

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lent response. Responses were: level 1 in 19%, level 2 in 21.3%, level 3 in 33.3% and level 4 in 26.4% of cases. Retreatments showed significantly ($P<0.01$) worse responses (48% levels 3+4), in comparison to first RTBM. Duration of palliation was 5.0±3.5 months, and was longer in cases of excellent response, in first RTBM, in patients with limited metastases and when $^{89}$Sr was used. Better responses were found in cases of limited skeletal disease, under good clinical conditions, when life expectancy exceeded 3 months, and in radiologically osteoblastic or mixed bone lesions. The only statistically significant predictive factor was life expectancy ($P<0.001$). Flare phenomenon (14.1% of cases) did not correlate with the response. Haematological toxicity (mild to moderate in most cases) mainly affected platelets, and was observed in 25.5% of cases overall and in 38.9% of retreatments. RTBM did not seem to prolong life, though in some cases scintigraphic regression of bone metastases was observed. The two radiopharmaceuticals did not show any statistically significant differences in palliative efficacy and toxicity, either in first RTBM or in retreatments.

**Keywords:** Bone metastases – Strontium-89 – Rhenium-186-HEDP – Pain palliation – Radionuclide therapy

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### Introduction

Several studies [1, 2, 3] have proven that radionuclide therapy of painful bone metastases (RTBM) using bone-seeking, beta-emitting radiopharmaceuticals is an effective systemic, pain-palliative treatment in patients with disseminated bone metastases. These studies, however, were generally heterogeneous trials involving small groups of patients, who also differed with respect to primary tumours, stage of disease, radiopharmaceuticals, dosage, combination with other therapeutic modalities and methods of pain assessment.

Strontium-89 chloride is still the most widely used agent, but a variety of new radiopharmaceuticals have been introduced in recent years. Guidelines for RTBM have been released by both the SNM and the EANM, and these guidelines conflict in some respects regarding the choice of therapeutic agent. As a result, indications for RTBM are unclear and clinical protocols are not standardised. Recent European and U.S. studies [4, 5, 6] have demonstrated that nuclear medicine is under-utilised as a therapeutic modality, although RTBM is the second most frequent oncological therapeutic indication; moreover, oncologists perceive the appropriateness of RTBM as low, using it in less than optimal disease settings.

Observational studies are less cumbersome and expensive than randomised controlled trials, and recent reports [7, 8] show that they seem to be equally accurate for evaluating the effectiveness of various therapies.

The aims of this multicentre observational study, carried out by the Italian Association of Nuclear Medicine, were:

- To assess the efficacy and toxicity of RTBM on a large number of patients uniformly evaluated, in order to contribute to the standardisation of these procedures
- To evaluate the incidence of RTBM in metastatic prostate cancer in Italy

### Materials and methods

All information was collected by nuclear medicine physicians on pre-printed forms, which were jointly analysed by a central data bank (NuclearLink, Modena, Italy).

**Radiopharmaceuticals and administration modalities.** Therapy was carried out following the recommendations of the “EANM Radionuclide Therapy Committee”. Either $^{89}$Sr chloride (Metastrox, Amersham, U.K.) or rhenium-186 hydroxyethylidene diphosphonate (HEDP) (Osteopal, Byk-Gulden, Italy) was used in a standard single dose of 148 MBq (4 mCi) and 1.295 MBq (35 mCi) respectively. Centres were free to choose either radiopharmaceutical, according to their opinion and experience. The study had been approved by local ethics committees, and was performed in accordance with the ethical standards of the Helsinki Declaration. Therapy in most cases was performed on an out-patient basis. Written information about therapy and radioprotection issues was given to the patients. All patients gave their written informed consent prior to inclusion in the study.

**Patients.** Recruitment criteria were: bone pain originating from multiple skeletal metastases of prostate cancer; bone metastases intensively positive in a recent bone scan; therapies not changed/modified in the last 3 months; pain refractory to any other analgesic therapy; pain not originating from pathological bone fracture; absence of signs of spinal cord compression; life expectancy ≥3 months; absence of renal insufficiency; absence of signs of disseminated intravascular coagulation; white blood cells (WBCs) ≥2.4×10$^9$/l, platelets ≥60×10$^9$/l; absence of signs of rapid depletion of bone marrow reserve. Patients treated by chemotherapy or external radiotherapy in the 3 months before RTBM were excluded from the study. Simultaneous hormone therapy, as long as it had been started or changed at least 3 months earlier, was allowed. Retreatments were performed, when required, only in those individuals who had benefited from the first RTBM. The time interval between treatments on the same patient was at least 3 months; admission criteria and procedure modalities were the same as in the first RTBM. A maximum ceiling of total administered activity was not established.

**Pre-therapy assessment.** For each patient, data were collected about previous and current treatments for tumour and for pain palliation, other coexisting diseases, haematological and biochemical profiles, and prostate-specific antigen (PSA) levels.