Original Article

Palliation of Bone Pain in Prostate Cancer Using Chemotherapy and Strontium-89. A Randomized Phase II Study

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Abstract

Strontium-89 is an established alternative for the alleviation of bone pain in prostate cancer. There are few data evaluating the effect on pain of palliative chemotherapy. The aim of this randomized phase II study was to assess and compare the analgesic efficacy of strontium-89 and chemotherapy (FEM = 5-FU, epirubicin, and mitomycin C) in 35 patients with disseminated, hormone-refractory prostate cancer suffering from persisting bone pain despite analgesic treatment. In order to minimize the risk for imbalances regarding the two patient groups, a double-blind randomization was performed. A significant reduction in pain intensity and pain frequency was registered in both patient groups ($P < 0.01$ in both groups after 3 weeks). Side effects were generally mild in the strontium-89 group and significantly more severe in the FEM group. The effect of FEM on pain is surprising as chemotherapy has generally only limited effect on tumor growth in bone metastases due to prostate cancer. A possible explanation is that FEM has an inhibitory activity on the inflammatory component of metastases. J Pain Symptom Manage 2005;29:352–357. *© 2005 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words

Neoplasms, pain, prostate, strontium, chemotherapy, inflammation

Introduction

Bone pain is a major problem in metastatic prostate cancer. Analgesics, administered according to the World Health Organization (WHO) recommendations,[1,2] and palliative radiotherapy[3,4] constitute mainstays of treatment. The efficacy of palliative radiotherapy at single sites is very convincing, both in retrospective[5,6] and prospective studies,[7–9] with partial or total pain relief and reduction in stiffness in up to 80–90% of the reported cases. According to a recent meta-analysis of 20 studies, radiotherapy produced complete pain relief at

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one month in 395/1580 (25%) patients, and at least 50% relief in 788/1933 (41%) patients at some time during the trials.[3]

Focal radiotherapy may be relatively less helpful in the population with metastatic prostate cancer because metastatic spread is generally diffuse and widespread, with manifestations in considerable parts of the skeleton. Hemibody irradiation constitutes a treatment option in theses cases, with a good documented effect on pain.[10–12] However, the toxicity is considerable and the dose-planning is complicated, which limits its use.

As radiotherapy obviously is effective for the treatment of pain and stiffness in metastatic prostate cancer, the systemic administration of radiopharmaceuticals constitutes a viable alternative to external radiotherapy. Strontium-89 was initially used in 1941 in a patient with metastatic prostate cancer[13] and it has been used for the alleviation of bone pain in several studies since the 1970s.[14–18] Positive effects on pain and quality of life have been observed in a majority of the patients.[19] The efficacy is better in patients with moderate than extensive bone involvement.[20,21]

The pain-relieving effect of chemotherapy in prostate cancer has only occasionally been reported.[22–29] However, these studies indicate that palliative chemotherapy might have an effect on pain, with pain reduction generally in about 40–50% of the treated patients; some studies report responses as high as 70–90%.[25,26] Such effects might be significant also in those patients whose tumors do not respond objectively to the given treatment.[30]

Interesting studies have also been performed in order to evaluate the additive effect of strontium-89 and chemotherapy. In two recent studies, such effects were found:[31,32] Pain control was significantly improved when low-dose cisplatin and strontium-89 were combined,[31] and survival was improved.[32]

In our departments, palliative treatment with FEM (5-FU, epirubicin, and mitomycin C) has been administered to pilot patients with prostate cancer suffering from refractory bone pain despite adequate analgesic treatment. A rapid, encouraging effect has been noted in several patients. These data have constituted the rationale for a prospective study to compare the analgesic effect of strontium-89 with FEM. The primary endpoint of this exploratory phase II study was analgesia and the aim was to determine whether the previously unstudied chemotherapy regimen FEM produces clinically significant analgesia comparable to the effects of an established alternative (strontium-89).

Methods

A total of 35 patients were included in this randomized study. Mean age was 68 years. Inclusion criteria included primary or secondary hormone-refractory prostate cancer, skeletal metastases, persisting pain despite analgesic treatment, and life expectancy more than 3 months. The main exclusion criteria were significantly impaired renal function or previous administration of strontium-89 or chemotherapy.

Eighteen patients were randomized to strontium-89 and 17 patients received FEM. Patients receiving strontium-89 (Metastron) were administered a dose of 150 MBq by the intravenous (IV) route. The FEM regimen consisted of 5-fluorouracil (750 mg/m^2), epirubicin (40 mg/m^2) and mitomycin-C (0.1 mg/kg). All drugs were administered IV on two consecutive days. The follow-up was performed every 3 weeks for 12 weeks or until progression of pain. Previous treatments (surgery, radiotherapy, hormonal treatment) were comparable in both groups.

Pain intensity at a maximum of three original sites was assessed using a verbal rating scale, where pain intensity was classified as 0 = none, 1 = mild, 2 = moderate, 3 = severe, or 4 = intractable. Pain frequency was registered for each site and classified as 1 = occasional, 2 = intermittent, 3 = frequent, and 4 = constant. Baseline values and assessments after 3, 6, 9, and 12 weeks were recorded. Analgesic consumption was registered during the study period and related to outcome.

The statistical analyses used Wilcoxon signed rank test to identify changes from baseline, and the Wilcoxon-Mann-Whitney test to compare the treatment groups. For patients who had missing data, or who prematurely withdrew, the previous post-treatment result was used in the analysis. The study was approved by the respective local ethics committee board and all the patients provided written informed consent.