Hormone-refractory prostate cancer and the skeleton

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Chapter 5

Strontium-89 (Metastron) and the bisphosphonate olpadronate reduce the incidence of spinal cord compression in patients with hormone-refractory prostate cancer metastatic to the skeleton.

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Abstract

Background: Spinal cord compression (SCC) is a devastating complication of metastatic cancer. We investigated the potential beneficial effect of two palliative therapies ^{89}Strontium (Metastron) and the nitrogen-containing bisphosphonate olpadronate on the incidence of SCC in hormone-refractory prostate cancer (HRPC) metastatic to the skeleton.

Patients and methods: We retrospectively studied 415 patients with histologically proven prostate cancer who underwent bone scintigraphy at the time of diagnosis and were followed up at the Leiden University Medical Center between 1990 and 1999. Medical or surgical castration was undertaken in 172 patients with evidence for skeletal metastases. Within 2 years, 147 of these patients (85%) developed HRPC associated with severe progressive bone pain. Palliative treatment was given to 131 patients in the form of local radiotherapy (n=10), ^{89}Sr (n=46) or intravenous olpadronate (n=66), with (n=57) or without (n=9) maintenance oral olpadronate. Nine patients received both ^{89}Sr and olpadronate at various intervals. Sixteen patients who did not receive any of these treatments were used as historical controls.

Results: There was no significant difference in baseline characteristics between treatment modalities. The incidence of SCC was 17% in the whole group, and highest in controls receiving no palliation (50%). None of the patients treated with local radiotherapy, only 4% of patients receiving ^{89}Sr and 21% of patients given olpadronate developed this complication.

Conclusions: Our findings suggest a significant reduction in SCC in patients with symptomatic HRPC metastatic to the skeleton who receive palliative therapies. Local radiotherapy completely prevents the incidence of SCC, ^{89}Sr leads to an important decrease in this complication and olpadronate induces a significant, albeit smaller decrease in the incidence of SCC. The use of these agents opens new avenues in the difficult management of patients with advanced prostate cancer who are most at risk of developing SCC.

Introduction

Prostate cancer is the most common cause of cancer in men[1]. In this malignancy, the development of skeletal metastases is associated with a significant increase in morbidity, mainly because of severe bone pain but also because of other complications of the metastatic state, one of the most devastating of which is spinal cord compression. Prostate cancer has been shown to represent the second most common cause of metastatic spinal cord compression[2-4] after lung cancer[5]. The mechanism of metastatic spinal cord compression and its clinical manifestations, diagnosis and treatment have been extensively described[2-8]. In prostate cancer, spinal cord compression is variably reported to occur in 1%-10% of patients, and the incidence of this complication is largely related to stage and grade of the primary tumour[9-11]. To date no single or combined therapy has been shown to significantly prolong survival in hormone-refractory prostate cancer. In the absence of effective second-line therapies, the mainstay of treatment of these patients is palliative[12]. Local radiotherapy by external beam irradiation is effective in the palliation of metastatic bone pain and is also used in the adjuvant treatment of established spinal cord compression[13]. The bone-seeking radiopharmaceutical ^{89}Strontium (Metastron) represents an attractive and cost-effective alternative to radiotherapy and is currently the most commonly used radionuclide for this purpose[13-23]. The nitrogen-containing bisphosphonate olpadronate has also been successfully used in the palliative treatment of metastatic bone pain[24]. The question arises as to whether these palliative interventions may be able to prevent or delay the occurrence of spinal cord compression in patients with hormone-refractory prostate cancer metastatic to the skeleton.

Materials and methods

We retrospectively studied data on all patients referred to the Department of Urology of the Leiden University Medical Center between January 1990 and October 1999 with a histologically confirmed diagnosis of prostate cancer. Data were available on 637 patients, a third of whom were referred back to their local hospitals for further investigation and management. A staging bone scintigraphy was undertaken in 415 patients who were followed up in our institution to establish the presence and extent of skeletal metastases.

Patients who demonstrated evidence for metastatic skeletal involvement (n=172) underwent medical or surgical castration. Of these 172 patients, 147 (85%) demonstrated hormone refractoriness after a mean period of 2 years, heralded by the development of

severe and progressive bone pain that was eventually refractory to escalating conventional analgesia in the majority of cases. Additional palliative therapy in the form of local radiotherapy, ^{89}Sr or olpadronate was administered to 131 patients. All patients had severe intractable bone pain and a WHO performance score of 2 or less at the time of treatment. There was no significant difference in severity of pain or performance status between treatment groups. Ten patients with localised metastatic bone pain were treated with local radiotherapy, 46 patients received ^{89}Sr (Metastron) and 66 patients were given the bisphosphonate olpadronate. This is a nitrogen-containing bisphosphonate obtained by the dimethylation of the nitrogen molecule of pamidronate, which increases its anti-resorptive potency by five- to tenfold[25]. Its clinical efficacy has been established in the management of Paget's disease of bone[26] and in that of hormone-refractory prostate cancer metastatic to the skeleton[24]. ^{89}Sr and olpadronate were administered as follows: in an open study design, 18 patients received intravenous ^{89}Sr at a single dose of 150 MBq (4 mCi) and 40 were given olpadronate (Gador S.A., Buenos Aires, Argentina), administered intravenously, at a total dose of 20 mg divided into five daily doses diluted in 250 ml 0.9% sodium chloride. All patients but nine in this latter group received maintenance treatment in the form of oral olpadronate at a dose of 200 mg/day after completion of the intravenous regimen. A further 54 patients with similar inclusion criteria to those in the open study were randomised to receive either olpadronate given intravenously as a single 20 mg dose diluted in 500 ml 0.9% sodium chloride (n=26) or ^{89}Sr (Metastron) at a single dose of 150 MBq (4 mCi) (n=28) as part of an as yet unpublished study comparing the cost-effectiveness of these two treatment regimens. It was necessary to repeat treatment at least once after a minimum of 3 months in 18% of patients receiving ^{89}Sr and in 10% of patients receiving olpadronate.

A subset of nine patients received both treatment modalities, first intravenous olpadronate and subsequently, 4 weeks (three patients) to 3-6 months later (five patients), ^{89}Sr because of failure to obtain adequate pain palliation or recurrence or progression of symptoms. In one patient, treatment with ^{89}Sr was given 2 years after initial therapy with i.v. olpadronate because of recurrence of symptoms. One of the nine patients in this subset developed spinal cord compression 3 months after ^{89}Sr therapy which was given 6 months following olpadronate treatment. However, because of the great individual variability in the timing of the second treatment (4 weeks to 2 years after the initial treatment), it was not possible to evaluate any potential synergism between the two treatment modalities. This subset was therefore excluded from the final analysis.

Hormonal treatment remained unchanged in all patients and none were given additional chemotherapy. None had received previous local radiotherapy. Analgesics, non-steroidal anti-inflammatory drugs and/or opiates were used as required.

Data on tumour stage and histological grading were available at the time of diagnosis (grade 1 = well differentiated, grade 2 = moderately differentiated, grade 3 = poorly differentiated and grade 4 = anaplastic). Bone scintigraphy was evaluated according to the Soloway grading[27]: *grade 1*, number of bone metastases less than six, each of which is less than 50% of the size of the vertebral body (one lesion about the size of a vertebral body would be counted as two lesions); *grade 2*, number of bone metastases between six and 20, size of lesions as described above; *grade 3*, number of metastases more than 20 but less than a "superscan"; and *grade 4*, superscan or its equivalent, i.e. more than 75% of the ribs, vertebrae and pelvic bones.

Treatment with either olpadronate or ^{89}Sr was successful in achieving pain palliation in 70%-75% of patients. Prospective data on changes in performance status were available only in the 54 patients randomly allocated to receive olpadronate or ^{89}Sr. In these patients, performance status improved in line with successful pain palliation.

The diagnosis of spinal cord compression was established clinically on the basis of progressive impairment of motor and sensory function, the finding of a segmental level of neurological impairment and radiological confirmation by plain X-rays of the spine and magnetic resonance imaging (MRI) or computerised tomography scanning (CT scan). After confirmation of the diagnosis of spinal cord compression, all patients were successfully treated with local radiotherapy and high-dose dexamethasone, leading to complete release of compression symptoms, with the exception of one patient who required surgical decompression owing to incomplete resolution of symptoms.

Statistical analysis. The incidence of spinal cord compression was compared between groups using the log rank test. The relative risk of spinal cord compression following treatment with local radiotherapy, ^{89}Sr or olpadronate was compared with that when using just analgesia and calculated using the Cox model.

Results

Baseline patients' characteristics are shown in Table 1. There were no significant differences in age, tumour grade or scintigraphic staging of skeletal metastases between the four groups studied. Spinal cord compression developed in 24 of the 138 patients studied. Sites of the spinal cord lesions were predominantly at the thoracic spine (n=12,

50%), followed by the lumbar spine (*n*=8, 33%). The other four lesions involved more than one level. Figure 1 illustrates the percentage of patients developing spinal cord compression in each group studied. In the group of patients treated conservatively with analgesia only and used as a control group, 8 out of 16 patients (50%) developed spinal cord compression. Fourteen of the 66 patients receiving olpadronate as a single infusion or in divided doses over 5 days developed spinal cord compression (21%). In contrast, only 2 of the 46 patients (4%) treated with ^{89}Sr developed the complication. None of the patients treated with local radiotherapy developed spinal cord compression. There was a statistically significant difference in the incidence of spinal cord compression between groups, clearly favouring local radiotherapy (P<0.001) or unsealed source radiotherapy using ^{89}Sr (P<0.001) compared with the group receiving no palliative treatment. Patients treated with olpadronate also demonstrated a significant, albeit more modest decrease in the incidence of spinal cord compression compared with controls (P=0.019). The cumulative incidence of spinal cord compression in the various groups is shown in Fig. 1. The relative risk of developing spinal cord compression after treatment with olpadronate or ^{89}Sr was 0.35 (CI: 0.15-0.84) and 0.07 (CI: 0.02-0.32), respectively.

Table 1. Patients' characteristics

	^{89}Sr (*n*=46)	Olpadronate (*n*=66)	Radiotherapy (*n*=10)	Controls (*n*=16)	P value
Mean age (years)	71	72	73	73	0.77
Tumour stage (T)					0.22
1	0%	2%	0%	9%	
2	8%	11%	0%	18%	
3	62%	32%	33%	27%	
4	31%	55%	67%	46%	
Tumour grade					0.13
1	7%	9%	33%	13%	
2	31%	56%	33%	38%	
3	45%	33%	22%	31%	
4	17%	2%	11%	19%	
Initial metastases	30%	38%	30%	38%	0.85

	^{89}Sr (*n*=46)	Olpadronate (*n*=66)	Radiotherapy (*n*=10)	Controls (*n*=16)	P value
Bone scintigraphy grading (Soloway)					0.64
1	9%	18%	33%	18%	
2	26%	18%	33%	27%	
3	37%	29%	22%	36%	
4	29%	35%	11%	18%	

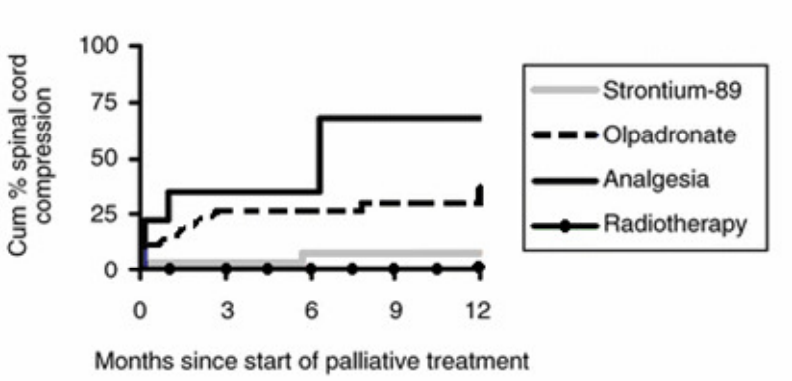

Fig. 1. Cumulative percentage incidence of spinal cord compression (SCC) within 12 months of starting palliative treatment in patients with hormone-refractory prostate cancer metastatic to the skeleton treated with local radiotherapy (*n*=10), ^{89}Sr (*n*=40), i.v. olpadronate (*n*=66) or no additional palliative therapy (controls, *n*=16). Treatment with ^{89}Sr and olpadronate resulted in a significant reduction in the incidence of SCC compared with controls (*P*<0.001 and *P*=0.019, respectively). None of the patients treated with local radiotherapy developed spinal cord compression.

Discussion

^{89}Strontium is the most commonly used radionuclide in the palliative management of bone pain in hormone-refractory prostate cancer metastatic to the skeleton[12,21-23,28]. In this malignancy, evidence for a significant palliative effect of bisphosphonates is also reasonably solid[12,24,28]. Whereas the beneficial effect of local radiotherapy is well established in complications of the metastatic process other than pain, the use of

radionuclides or bisphosphonates has not previously been studied in patients with advanced hormone-refractory prostate cancer metastatic to the skeleton. To our knowledge, this is thus the first report of an effect of either agent in reducing the incidence of spinal cord compression in this malignancy. In metastatic prostate cancer, compression of the spinal cord is epidural, most often caused by haematogenous spread of tumour cells to a vertebral body, which eventually collapses. The available literature describes an overall incidence of spinal cord compression varying from 1% to 10%. Our population consisted of patients who were at an advanced stage of this malignancy, which explains why the incidence of spinal cord compression in the historical control group was much higher than that reported in the literature. Analysis of the distribution of compression lesions in our series showed the thoracic region to be most frequently involved, followed by the lumbar region; this is in agreement with previous reports[3,10,11]. Multiple compression lesions were documented in four patients, which underlines the importance of performing MRI of the entire spine and not only of the suspected site if spinal compression signs develop[29]. In our study, MRI confirmed the diagnosis of spinal cord compression in the majority of patients. In a few patients in whom MRI could not be performed, CT of the spine delineated the extent of the lesion.

None of the patients who were treated with local external beam irradiation developed spinal cord compression, and it may be rightly argued that this is the treatment of choice in the prevention as well as the treatment of this complication. There are reservations, however, concerning the use of this treatment modality in multiple site metastatic disease because of its potential myelosuppressive effects if large areas are treated[30]. In practice, local radiotherapy is thus reserved for patients with localised metastatic involvement. Although there were no significant differences at baseline between the groups, the number of patients who received local radiotherapy was small, and the complete protection of this group against the development of spinal cord compression may still have stemmed from a relative population bias. Interestingly, however, ^{89}Sr was nearly as effective as local radiotherapy in protecting against the development of spinal cord compression. ^{89}Sr is a pure β-emitting radioisotope of strontium that has potential tumouricidal effects and shows selectively increased uptake in regions of increased osteoblastic activity[31]. Whole body retention of ^{89}Sr has thus been shown to be proportionate to the skeleton's metastatic burden[32]. At the currently recommended dose of 150 MBq it has been reported to be effective in the palliation of metastatic bone pain in some 75% of patients[21-23]. The mechanism by which ^{89}Sr may exert its protective effect on the skeleton is likely to be

through local irradiation by its ß-emitting properties, putatively resulting in a local decrease in tumour load, a mechanism comparable to that of treatment with local radiotherapy. The main limiting factor in the use of ^{89}Sr, however, is bone marrow suppression, which may be a significant feature of extensive metastatic bone involvement[13].

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and are extensively used in the management of disorders associated with increased bone resorption, such as Paget's disease of bone, multiple myeloma and hypercalcaemia of malignancy. The rationale for the use of bisphosphonates in the management of metastatic prostate cancer is not immediately obvious given the predominantly osteoblastic nature of the metastatic process. There is, however, ample evidence that prostate cancer metastases are associated with increased bone resorption, as determined by bone histology as well as biochemical markers of bone resorption[33-38]. Furthermore, the evidence for a beneficial effect of these agents in decreasing morbidity in symptomatic hormone-refractory prostate cancer metastatic to the skeleton is reasonably solid[12,24,28]. Our findings suggest that the use of bisphosphonates in the palliative management of metastatic bone pain is also associated with a decrease in the incidence of spinal cord compression as compared with that in patients who have a similar tumour load but do not receive palliative therapy. In the subset of patients receiving both olpadronate and ^{89}Sr, the great individual variability in time lapse between the treatment modalities precludes any judgment on the intriguing potential synergism achieved by their combination. Prospective studies should be specifically devised to address this question.

Whereas neither ^{89}Sr nor bisphosphonates have so far been shown to prolong survival in hormone-refractory metastatic prostate cancer, our data suggest that both agents have the potential to decrease the incidence of spinal cord compression and hence to reduce morbidity in this terminally ill group of patients at high risk of developing this complication. The largest beneficial effect appears to be associated with the use of ^{89}Sr although olpadronate may represent an attractive alternative, particularly in the presence of bone marrow suppression. Further studies are required to explore more fully the potential of these palliative therapies to decrease morbidity in hormone-refractory prostate cancer metastatic to the skeleton.

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