32-PHOSPHORUS FOR BONE PAIN PALLIATION DUE TO BONE METASTASES, ITS SAFETY AND EFFICACY IN PATIENTS WITH ADVANCED CANCER*

J. FETTICH
University Clinic, University Medical Centre, Ljubljana, Slovenia

G. NAIR
International Atomic Energy Agency, Vienna

A.K. PADHY
AIIMS, New Delhi, India

J. STARE
Institute of Biomedical Informatics, Ljubljana, Slovenia

N. NAIR
RMC (BARC), Mumbai, India

R. MORALLES
Instituto Peruano de Energia Nuclear, Lima, Peru

M. TANUMIHARDIA
Bandung, Indonesia

G. RICCABONA
Universitätsklink für Nuklearmedizin, Innsbruck, Austria

Abstract. Bone pain due to bony metastases can seriously affect a patient's quality of life. External irradiation, narcotic drugs and polyphosphates may cause important side effects or are expensive, therefore in many patients radionuclide treatment using a single dose of beta emitting bone seeking radiopharmaceuticals has become widely accepted. Except 32-Phosphorus (32-P) all of them are expensive and difficult to obtain in certain countries. The aim of the study was to evaluate safety and efficacy of 32-P for palliation of bone pain due to bony metastases by comparing it to 89-Strontium (89-Sr), the most commonly used radiopharmaceutical for bone pain palliation in the framework of a prospective IAEA co-ordinated multicenter study. A very strict protocol for unified patient inclusion and follow up was used. 93 cancer patients with osteoblastic bony metastases were included into the study, 48 were treated by 89-Sr (150 MBq) and 45 by 32-P (450 MBq). Pain score, analgesic consumption, quality of life, and indices of bone marrow depression were monitored 2 weeks pre- and up to 4 months post treatment. Favourable response to treatment was recorded in 75% of the patients treated with 89-Sr and in 60% of those treated with 32-P (p=0,122). There was no significant difference between the duration of favourable effect for both radiopharmaceuticals. Moderate decrease of white blood cell (WBC) and platelet counts, and haemoglobin (Hb) levels was detected more often in the 32-P treated group. Although 32-P appears to be more toxic, no toxic effects requiring specific treatment were seen in either group. Due to its comparable efficacy and safety, general availability and low cost its more widespread use should be encouraged to increase quality of life and reduce cost of medical care of patients with intractable bone pain due to cancer metastases.

1. INTRODUCTION

Bony metastases ultimately develop in over 80% of patients with metastatic breast and prostate cancers, and bone can be the sole site of metastatic spread. Bone metastases are frequently multiple and diffuse. A prominent symptom caused by bony metastases is pain, which can seriously affect a

* Work performed within the framework of the International Atomic Energy Agency Co-ordinated Research Project.

patient's quality of life [1]. Only a few patients with hormone resistant prostate cancer achieve significant clinical benefit from chemotherapy. For breast cancer, hormonal therapy and chemotherapy can palliate symptoms for a short duration, but complete responses are infrequent. Radiation therapy can provide significant palliation in up to 70% of the cases, but median time of relief to pain is often measured in weeks. Hemibody or total body external irradiation may cause important side effects such as bone marrow suppression, gastrointestinal symptoms, and radiation pneumonitis. Pain palliation using narcotic drugs also causes considerable side effects, while prolonged treatment with polyphosphates is expensive [2, 3].

Therefore in many patients with a large number of metastatic lesions radionuclide treatment using single dose of beta emitting bone-seeking radiopharmaceuticals has become widely accepted. 32-Phosphorus orthophosphate and polyphosphate, 89-Strontium, 90-Yttrium EDTA and several 131-Iodine, 186-Rhenium and 153-Samarium labelled diphosphonates have been evaluated [4, 5]. Except 32-Phosphorus all of them are expensive and difficult to obtain in certain countries.

32-Phosphorus decays by beta radiation of maximum energy of 1,71 MeV with mean range of beta particles in tissue of 3 mm and maximum range of 8 mm. It's physical half life is 14,3 days. Its biological half-life in the bone marrow is 7–9 days. Since it is incorporated into the nucleic acids of rapidly proliferating cells as well as into cortical bone concern was raised that bone marrow toxicity with possible severe consequences can outweigh benefit of bone pain palliation [6].

2. THE AIM

The aim of the study was to evaluate safety and efficacy of 32-P for palliation of bone pain due to bony metastases. For this purpose safety and efficacy of 32-P was compared with safety and efficacy of 89-Sr (7), the most commonly used and thoroughly evaluated radiopharmaceutical for bone pain palliation in the framework of a prospective IAEA co-ordinated multicentric study.

3. PATIENTS AND METHODS

Methods

To assess efficacy of both radiopharmaceuticals intensity of bone pain was recorded once daily on 1–10 subjective scale, and consumption of analgesics was determined as type of analgesic multiplied by daily frequency (analgesic index) for 14 days before treatment and for 4 months after treatment. General quality of life data were also recorded.

To assess safety of 32-P and 89-Sr total white blood cell (WBC) and differential count, platelet count, haemoglobin (Hb) concentration were measured 14 days before application of the radiopharmaceutical, on the day of treatment and every 14 days after treatment for 4 months to assess bone marrow suppression. Creatinine concentration was measured simultaneously to assess renal function. Presence of bleeding, infection, gastrointestinal problems etc. was recorded.

Patients

A very strict protocol for unified patient inclusion and follow up was used. Inclusion criteria were as follows. Confirmed multiple osteoblastic bony metastases, the extent of metastatic spread was semiquantified as 'Bone scan index' [8].

Pain should be caused by bone scan positive site, but spinal cord lesions and/or pathologic fractures were excluded. Patients had to have been on analgesic or narcotic therapy. Consumption of analgesics was determined using analgesic index.

No radiotherapy or chemotherapy was allowed during the last 6 weeks and no change in hormone therapy during the last 3 months before the injection of radiopharmaceuticals.

There had to have been no signs of bone marrow suppression (white blood cell count over 5000/mL and platelet count over 150 000/mL) and no significant renal failure (creatinine level below 200 umol/L).

Life expectancy had to have been more than 6 weeks and in case of female patients pregnancy had to be excluded. Written informed consent for the study was obtained from all patients.

Patients conforming to the above mentioned criteria were randomised to receive either 32-P (450 MBq 32-P as orthophosphate orally) or 89-Sr (150 MBq 89-Sr as chloride intravenously). The patients were unaware of the form of treatment they received. 93 patients who completed at least two months follow up were included into the study. 45 of them received 32-P and 48 89-Sr.

Profile of the patients before treatment is described in Table I. There were no statistically significant differences between the two groups as far as gender, age, metastatic spread, and degree of pain, as well as haematological values was concerned. Most patients had bony metastases due to prostate and breast cancer, but lung, colorectal, ovarian, bladder and even thyroid cancer patients were also represented. Most patients were treated by surgery, chemotherapy, radiotherapy, and hormonal therapy as indicated previous to radionuclide therapy.

TABLE I. PROFILE OF PATIENTS TREATED WITH 32-P AND 89-SR BEFORE TREATMENT (N OR MEAN VALUE)

	32-P	89-Sr	p
N	45	49	
Gender			0,147
Female	9 (20%)	16 (33%)	
Male	36 (80%)	33 (67%)	
Age	61,2	62,4	0,668
Bone Scan Index	39,9	45,7	0,234
Pain Score	6,5	6,7	0,633
Analgesic Index	6,1	6,9	0,349
Hb (g/L)	108,8	109,1	0,917
WBC	8030	7570	0,072
Platelets (10*3)	273	256	0,350
Primary cancer			0,261
Prostate	32	27	
Breast	9	16	
Other	4	5	

Statistical analysis

T-test and chi-square test for univariate comparison of treatment groups was used. Logistic regression was used when the outcome variable was considered to be dichotomous (e.g. response versus no response) and Cox's proportional hazards model was used to calculate the duration of effects.

4. RESULTS

Efficacy

The patients were classified as responders or not-responders at a meeting of all contributing investigators taking into account changes in individual pain score and analgesic index. Also duration of the favourable effect was determined in responders using the same criteria. 68% of all patients were considered to respond to treatment with radionuclides. 60% of patients responded to treatment with phosphorus and 75% to treatment with strontium. While difference between number of patients who responded favourably to 89-Sr and 32-P is not significantly different (p = 0,122), the probability of success in the 89-Sr treated group is 1,25 times greater than in the 32-P treated group (Table II).

TABLE II. EFFICACY: NUMBER OF PATIENTS TREATED WITH 32-P AND 89-SR WITH PAIN RELIEF (RESPONSE)

Treatment	Response		Total
	Yes	No	
32-P	27 (60,0%)	18 (40,0%)	45 (100%)
87-Sr	36 (75,0%)	12 (25,0%)	48 (100%)
	p=0,122		
Total	63 (67,8%)	30 (32,3%)	93 (100%)

For responders duration of the response was also considered important. We compared the length of response between both treatment groups using the methods of survival analysis. The time of interest, 'survival time', was time elapsed between the beginning of the response and end of the response. At any time point proportion of patients still having good effect of treatment with each radiopharmaceutical is calculated. No significant differences between both groups were observed (p = 0.737).

Safety

Other than changes in platelet and WBC counts and Hb concentration no adverse effects were observed in either group.

Greater proportion of decrease for all three haematological parameters was observed in the group of patients treated with 32-P than with 89-Sr and also pathological decreases of all three were more common in the 32-P treated group. Since this was a multicentric trial with different ranges of normal values for haematological parameters in their laboratories, adverse effects were evaluated as being present or absent.

Significant decrease of WBC was seen in 42% of patients treated with phosphorus and in only 19% of patients treated with strontium. This difference was statistically significant. Also platelet count decreased significantly in 56% of patients treated with phosphorus and in one third of patients treated with strontium. Also this difference was statistically significant. Haemoglobin levels dropped in 69% of patients treated with phosphorus and approximately in half of those treated with strontium. This difference was statistically not significant (Table III).

TABLE III. SAFETY: NUMBER OF PATIENTS TREATED WITH 32-P AND 89-SR WITH PATHOLOGICAL DECREASE OF WBC, PLATELETS, AND HB CONCENTRATION

	32-P	89-Sr	Total	p
N	45	48	93	
WBC	19 (42%)	9 (19%)	28 (30%)	0,014
Platelets	25 (56%)	16 (33%)	41 (44%)	0,031
Hb	31 (69%)	26 (54%)	57 (61%)	0,145

5. DISCUSSION

Both 89-Sr and 32-P are used mainly to suppress hyperproliferative cell lines rather than to eradicate them, therefore expected effect of such treatment is predominantly palliation of bone pain rather than treatment of bony metastases. Favourable response to treatment was recorded in 75% of the patients treated with 89-Sr and in 60% of those treated with 32-P, overall response being 67,8%. These values are in accordance with published figures for success of bone pain palliation using different radiopharmaceuticals in patients with different types of cancer (4,7).

"Survival time curves" were used to assess the duration of favourable effect. At any time point these curves give proportion of patients still having good effect of treatment for each radiopharmaceutical. There was no significant difference between the duration of favourable effect for both radiopharmaceuticals.

No statistically significant differences between the two groups of patients receiving different radiopharmaceuticals were found in efficacy indices.

Limiting side effects using radiopharmaceuticals for bone pain palliation is temporary myelosuppression, the severity of which can be influenced also by the extent of the tumour involving bone marrow, previous radiotherapy and chemotherapy as well as patient's general condition. Decrease of WBC and platelet counts were recorded significantly more often in the patients treated with phosphorus than with strontium while no statistically significant differences was seen in frequency of Hb concentration decrease. Since 32-P is accumulated not only in the growing bone, as is 89-Sr, but also in the rapidly proliferating cells, such as bone marrow, more myelotoxic side effects could be expected in patients treated with 32-P than with 89-Sr.

Nevertheless decrease of WBCs, platelets, and haemoglobin levels was moderate and was clinically not considered important, since no toxic effects requiring specific treatment were seen in either group. Known risk of developing acute leukaemia several years after treatment with 32-P was not considered important in patients with widespread metastatic disease.

6. CONCLUSION

According to our results 32-P is slightly but not significantly less effective than 89-Sr for palliation of bone pain due to bony metastases. Although 32-P appears to be more toxic it is important to note, that no toxic effects requiring specific treatment were seen in either group. It seems that 32-P is as safe as 89-Sr using doses up to 450 MBq.

Due to its comparable efficacy and safety with other radiopharmaceuticals for bone pain palliation, general availability and low cost more widespread use of 32-Phosphorus should be encouraged to increase quality of life and reduce cost of medical care of patients with intractable bone pain due to cancer metastases.

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