Relative Efficacy of ^{32}P and ^{89}Sr in Palliation in Skeletal Metastases

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^{32}P and ^{89}Sr have been shown to produce significant pain relief in patients with skeletal metastases from advanced cancer. Clinically significant pancytopenia has not been reported in doses up to 12 mCi (444 MBq) of either radionuclide. To date, no reports comparing the relative efficacy and toxicity of the two radionuclides in comparable patient populations have been available. Although a cure has not been reported, both treatments have achieved substantial pain relief. However, several studies have used semiquantitative measures such as "slight," "fair," "partial" and "dramatic" responses, which lend themselves to subjective bias. This report examines the responses to treatment with ^{32}P or ^{89}Sr by attempting a quantification of pain relief and quality of life using the patients as their own controls and compares toxicity in terms of hematological parameters. **Methods:** Thirty-one patients with skeletal metastases were treated for pain relief with either ^{32}P (16 patients) or ^{89}Sr (15 patients). Inclusion criteria were pain from bone scan-positive sites above a subjective score of 5 of 10 despite analgesic therapy with narcotic or non-narcotic medication, limitation of movement related to the performance of routine daily activity and a predicted life expectancy of at least 4 mo. The patients had not had chemotherapy or radiotherapy during the previous 6 wk and had normal serum creatinine, white cell and platelet counts. ^{32}P was given orally as a 12 mCi dose, and ^{89}Sr was given intravenously as a 4 mCi (148 MBq) dose. The patients were monitored for 4 mo. **Results:** Complete absence of pain was seen in 7 of 16 patients who were given ^{32}P and in 7 of 15 patients who were given ^{89}Sr. Pain scores fell by at least 50% of the pretreatment score in 14 of 16 patients who were given ^{32}P and 14 of 15 patients who were given ^{89}Sr. Mean duration of pain relief was 9.6 wk with ^{32}P and 10 wk with ^{89}Sr. Analgesic scores fell along with the drop in pain scores. A fall in total white cell, absolute granulocyte and platelet counts occurred in all patients. Subnormal values of white cells and platelets were seen in 5 and 7 patients, respectively, with ^{32}P, and in 0 and 4 patients, respectively, after ^{89}Sr therapy. The decrease in platelet count (but not absolute granulocyte count) was statistically significant when ^{32}P patients were compared with ^{89}Sr patients. However, in no instance did the fall in blood counts require treatment. Absolute granulocyte counts did not fall below 1000 in any patient. There was no significant difference between the two treatments in terms of either efficacy or toxicity. **Conclusion:** No justification has been found in this study for the recommendation of ^{89}Sr over the considerably less expensive oral ^{32}P for the palliation of skeletal pain from metastases of advanced cancer.

Key Words: ^{89}Sr; ^{32}P; bone metastases; palliation

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A major problem facing the physician is the treatment of intractable bone pain of advanced malignancy. Two common cancers, of the breast and of the prostate, metastasize to bone in almost half of all patients (*1*). Pain relief and improvement in mobility are often the principal or the only aims of management. External radiotherapy is effective in localized sites, in treatment of impending fractures and in imminent spinal cord compression. Bone metastases, however, are frequently multiple and need systemic treatment for pain relief. Treatment with radiopharmaceuticals aims to relieve pain, improve mobility and minimize dependence on narcotic or non-narcotic analgesics. ^{32}P and ^{89}Sr have been used for this purpose since they were shown to concentrate in normal bone (*2*). It was shown that osteoblastic metastases selectively concentrated ^{89}Sr, and patients achieved good clinical response after treatment (*3*). Both ^{32}P and ^{89}Sr were used to treat multiple myeloma unsuccessfully by Lawrence and Wasserman (*4*) in the late 1940s. In 1950, Friedell and Storaasli (*5*) used ^{32}P for metastatic breast cancer.

Combining testosterone with ^{32}P, Maxfield et al. (*6*) treated a large number of breast and prostate cancers. ^{89}Sr and ^{32}P uptake by bone is directly proportionate to the osteoblastic activity (*7*). Although treatment with ^{32}P was reported to produce good relief from bone pain, it was used sporadically for fear of significant bone marrow toxicity both from direct bone marrow incorporation into the cells and radiation from contiguous bone (*1,8*). It has been shown that ^{89}Sr turnover in metastases is significantly lower than in normal bone: it remains at the site for at least 100 d and achieves its effect over time (*9*). Marrow toxicity with ^{89}Sr has been reported as acceptable and low (*10,11*). Silberstein et al. (*12*) state that at doses up to 12 mCi (444 MBq), hematological toxicity with ^{32}P is not clinically significant and that it is not clear whether transfusions are necessary. ^{32}P has a half-life of 14 d. The longer 45-d half-life of cyclotron-produced ^{89}Sr is only a theoretical disadvantage because it is this longer half-life that is responsible for the therapeutic effect over time. In India, ^{89}Sr, ^{186}Re and ^{153}Sa are not readily available, the first two being cyclotron produced. However, ^{32}P is routinely made in our reactors for oral and intravenous use and is considerably less costly than the imported ^{89}Sr. It was important to compare the relative efficacy and toxicity of the two radionuclides to determine if the cheaper alternative of ^{32}P could produce comparable

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clinical benefits and acceptable toxicity so that patients need not be denied effective pain palliation.

MATERIALS AND METHODS

The Radiation Medicine Center in Bombay, India, participated in a multicentric study initiated by the International Atomic Energy Agency (IAEA, Vienna, Austria). Thirty-one patients were administered either an oral dose of 12 mCi ^{32}P (16 patients) or an intravenous dose of 4 mCi (148 MBq) ^{89}Sr (15 patients). Randomization of patients to the radionuclide was done at the IAEA, which then informed the center of the radionuclide to be used in a given patient. At our center, the selection criteria were (a) evidence of skeletal metastases as seen on a radionuclide bone scan; (b) pain from the scan-positive sites above a subjectively reported pain score of 5 of 10 on an analog scale (0 = no pain, 10 = unbearable pain) not relieved by therapy with non-narcotic analgesia or with narcotic medication; (c) a white cell count over 4×10^9/L (normal range, 5–11 $\times 10^9$/L); (d) a platelet count over 150×10^9/L (normal range, 150–400 $\times 10^9$/L; (e) a normal serum creatinine (0.8–1.5 mg/dL) and (f) no chemotherapy or radiotherapy within 6 wk preceding the treatment. The selection criterion of pain score was not part of the IAEA protocol but was a modification adopted at our center. A life expectancy of at least 4 mo was anticipated.

For each patient, an analgesic score was computed as the product of analgesic type and administration frequency, coded into integer form as follows. Type: 0 = none; 1 = non-narcotic; 2 = mild oral narcotics like codeine <30 mg; 3 = moderate oral narcotics, 30–60 mg codeine or equivalent; 4 = parenteral narcotics or sustained-release morphine. Frequency of administration: 0 = none; 1 = as needed but not daily; 2 = one tablet per day; 3 = one to four tablets per day; 4 = more than four tablets per day; 5 = parenteral narcotics.

Informed consent was obtained from every patient. A detailed history and physical examination were supplemented by pretreatment measurement of hemoglobin, total and differential white cell count, platelet count and serum creatinine.

The pain score was entered and the analgesic medication and score were recorded. The extent of bone metastases was determined from the bone scan by means of a bone scan index (BSI) as described by Blake et al. (*9*). Simply, 10 points each were assigned to the skull, shoulder girdle and ribs, pelvis and extremities, depending on the extent of skeletal metastases on the scan. Each vertebra was scored 1 and the total out of 24 was worked out as a factor of 10. The final figure was thus out of 50, which was then worked out as a percentage.

Mobility assessment included the following: (a) ability to sit and rise from a chair, (b) ability to dress/undress, (c) ability to wash oneself, (d) ability to work at home and (e) ability to travel outside the house. Each of these abilities had scores assigned to them as follows: 0 = unable; 1 = able with assistance; 2 = able unaided, but with some difficulty; 3 = normal activity. The scores for each item were totaled and averaged to get a single mobility score, in the range of 0 to 3.

Two responsible relatives of the patient were taken into confidence and the details of treatment, the stage of the disease and the expected outcome were explained. The relatives were educated on how to fill in the data sheets by making careful records of the pain and analgesic and mobility scores. The relatives were willing and even enthusiastic assistants and performed their assigned tasks conscientiously. A set of data sheets was given to the patient's relatives to fill out and return every 2 wk for at least eight follow-ups, or 16 wk. They were required to enter the pain and analgesic scores every day and the other parameters every 2 wk.

The IAEA recommendation of efficacy was at least a 25% reduction in pain scores. However, 25% response is often related to a "mild" or "fair" response, and it is difficult to be certain if the response is reliable. Therefore, we decided that pain scores should be reduced by at least 50% for the response to be considered satisfactory. This more stringent criterion is less vulnerable to the influence of a placebo effect due to autosuggestion.

The results were tabulated in terms of the following parameters: (a) achievement of complete or 100% pain relief, zero pain score and its duration; (b) achievement of 70%–100% pain relief and its duration; (c) achievement of 50%–70% pain relief and its duration; (d) reduction of analgesic requirement; (e) improvement in mobility; and (f) toxicity in terms of reduction in white cell count, granulocyte count, platelet count and rise of serum creatinine.

Grades for toxicity as recommended by the IAEA were as follows. White blood cell $\times 10^9$/L: grade 0 $\geq$ 4.0; grade 1 = 3.0–3.9; grade 2 = 2.0–2.9; grade 3 = 1.0–1.9; grade 4 < 1.0. Platelets $\times 10^9$/L: grade 0 = 150–400; grade 1 = 75–149.9; grade 2 = 50.0–74.9; grade 3 = 25.0–49.9; grade 4 < 25.0. Absolute granulocyte counts of less than 1000 were considered as significant toxicity.

^{32}P as an orthophosphate was made available by the Bhabha Atomic Research Center (BARC, a division of the Department of Atomic Energy). ^{89}Sr (Metastron) was provided by the IAEA on purchase from Amersham International (Amersham, Buckinghamshire, UK). Randomization of patients was performed at the IAEA.

RESULTS

Fifteen patients were given ^{89}Sr and 16 were given ^{32}P. Table 1 gives the basic information on the patients. The observed responses at 4-mo follow-up are shown in Table 2. Two patients treated with ^{32}P showed no response. One discontinued further participation after 6 wk, opting for other modalities of treatment, but the other sent in records of his progress until the end of the follow-up period. One patient who was given ^{89}Sr also had no response. At least a

TABLE 1
Primary Site, Pain Score and Bone Scan Index (BSI)

Variable	^{89}Sr	^{32}P
Number of patients	15	16
Primary site		
Breast	7	5
Prostate	5	8
Lung	1	2
Other	2	1
Age (y), mean and range	64.7 (36–81)	50 (40–69)*
Pretreatment mean pain score	7.5	7.4
BSI, median and range	26 (9–42)	27.6 (12–50)

*Apparent difference in mean ages was significant ($P < 0.005$ by the t test) but is most likely due to smallness in numbers rather than to any other reason. Randomization of patients, although performed outside our center by the International Atomic Energy Agency (IAEA), does not selectively include younger patients in the ^{32}P group. A larger sample would, we expect, show an absence of any significant difference.

TABLE 2
Pain Relief and Duration of Pain Relief

Pain relief and duration of relief	^{89}Sr	^{32}P
50%–70% pain relief	4/15 patients (26.6%)	2/16 patients (12.5%)
Duration in wk (mean and range)	10 (4–16)	9.6 (4–16)
70%–100% pain relief	3/15 patients (20%)	5/16 patients (31.2%)
Duration in wk (mean and range)	8.8 (2–16)	6.8 (2–12)
100% pain relief	7/15 patients (46.6%)	7/16 patients (43.75%)
Duration in wk (mean and range)	8 (2–16)	4.4 (2–6)
No response	1 patient	2 patients

At least 50% pain relief was experienced by 14 of 15 patients given ^{89}Sr and by 14 of 16 patients given ^{32}P.

50% reduction in pain scores was taken as indicative of clinically significant response. Table 2 gives the number of patients who reported complete absence of pain (100% relief), marked reduction of pain (70% pain relief) and good response (50% pain relief). No response was seen in 1 of 15 and 2 of 16 patients given ^{89}Sr and ^{32}P, respectively.

Analgesic requirements declined along with the decline in pain scores, and patients who attained 100% pain relief discontinued analgesic medication during the period they were totally pain free. A drop in analgesic medication was correspondent with pain relief. The onset of maximum pain relief varied widely among the patients. In the best of cases, pain relief occurred within 4 d after ^{89}Sr therapy and lasted throughout the follow-up period. In the worst of cases, the onset of maximum pain relief was at almost 16 wk, which means that the maximum pain relief experienced by the patient took nearly 4 mo.

Pain relief was analyzed statistically in four ways: (a) time to onset of therapeutic response (defined as 50% pain relief), (b) time to maximum pain relief, (c) duration of therapeutic response in weeks and (d) maximal pain relief. The results are shown in Table 3. None of these differences was statistically significant. As expected, improvement in pain relief was followed by reduction in the dosage of pain medication.

Improved mobility was understood to mean an improved quality of life. Table 4 gives the pretreatment scores and the best response achieved after treatment. Generally, improved mobility accompanied an improvement in pain scores.

The differences between maximal improvement in mobility and duration of maximal response, as well as differences between proportion of patients returning to normal mobility, were not significant between the two groups.

Deaths

Three patients died during the 4-mo follow-up period. One patient had cancer of the prostate and developed hemorrhagic cystitis. His platelet counts were 250 × 10^9/L at the time. The second death was a 65-y-old man with prostate cancer who improved so dramatically after ^{89}Sr that he went for a jeep ride, got into an accident and sustained a pathological fracture of the femur. After he was admitted to the hospital, he succumbed to multiple infections. The third patient died of a myocardial infarction.

Flare Phenomenon

Four patients experienced a flare phenomenon, 2 each after ^{32}P and after ^{89}Sr.

Toxicity

In both groups, the white cell and platelet counts fell below pretreatment levels in all patients at some point during follow-up. In no case did bleeding occur and no patient needed transfusion. The results are summarized in Table 5. (In Table 5, all patients having grade 2 toxicity are included in the set of patients with grade 1 toxicity.)

The difference between maximal decrease in absolute neutrophil count narrowly missed significance ($P = 0.059$), whereas the difference in decrease in platelet count was significant ($P = 0.04$).

Although the data were not a part of this study, patients returned completed data sheets for up to a year or more after the study. In all patients, the platelet levels returned to normal without transfusion within 6 mo of the therapy. There was no effect on hemoglobin values. Random fluctuations were noted, but there was no sustained pattern of change.

TABLE 3
Statistical Comparison of Pain Relief Parameters

Pain relief parameters	^{89}Sr	^{32}P
Onset of therapeutic response	7 wk (2–14)	6 wk (2–12)
Time to maximum relief	11 wk (4–16)	9 wk (2–16)
Maximal pain relief	80% (0%–98%)	74% (4%–99%)
Duration of response	10 wk (0–14)	10 wk (0–14)

Median is used rather than mean for both pain scores and mobility scores, because these two quantities are not interval measures and are not expected to follow a normal distribution.

TABLE 4
Improvement in Mobility (Median Scores)

Mobility	^{89}Sr	^{32}P
Pretreatment mobility score (median and range)	0.75 (0–2)	1 (0–2)
Post-treatment mobility score (median and range)	2.75 (0–3)	2.75 (0–3)
Duration of maximum response (median and range)	6 wk (2–10)	5 wk (2–14)
Return to normal mobility	8/15 patients	13/16 patients
No response	1 patient	2 patients

TABLE 5
Hematological Toxicity After Therapy

Toxicity	^{89}Sr	^{32}P
WBC count, grade 1 toxicity	2/15 patients	6/16 patients
WBC count, grade 2 toxicity	0 patients	2/16 patients
Platelet count, grade 1 toxicity	7/15 patients	7/16 patients
Platelet count, grade 2 toxicity	0 patients	6/16 patients
Maximal decrease in absolute neutrophil count (mean ± SD)	2519 (2104)	4018 (2145)
Maximal decrease in platelet count × 10^9/L (mean ± SD)	168 (63)	128 (65)

WBC = white blood cell.

DISCUSSION

We report the results of a single dose comparison between ^{89}Sr and ^{32}P treatment for the palliation of pain from skeletal metastases of advanced cancer. There is no report on the use of a single dose of 12 mCi ^{32}P. Although fractionated, 1.8 mCi doses every day for 7 d have been used in the past (*13,14*). However, several reports indicate the use of as much as 10 mCi as a single dose. The single dose of 12 mCi used in this study has not produced clinically significant toxicity needing therapeutic intervention in any patient, and it appears that this may be a safe single dose.

Oral ^{32}P as the orthophosphate has not been used often. This is probably because of the variability in its absorption and the influence of dietary calcium on the intestinal absorption of phosphate. It is known that insoluble phosphate complexes can be formed with it, thus retarding absorption. A similar effect may be present with iron, magnesium and aluminium in the intestine. The presence of sodium in the intestine, on the other hand, may enhance the absorption and lower concentrations may decrease absorption (*12*). No patient in this study was on oral calcium supplements and, although no information on the amount of calcium in their diets was available, they were not on calcium-rich diets. With the availability of injectable ^{32}P, it may be possible to lower the dose, although studies need to be done to establish this.

The first use of ^{32}P for palliation of painful skeletal metastases was reported by Friedell and Storaasli in 1942 (*5*). A dose of 20 mCi (740 MBq) was administered over a period of 1 mo to a 47-y-old woman in small installments and resulted in relief from pain. Subsequently, they reported that 83% of their patients obtained pain relief with ^{32}P therapy. Between 1941 and 1949, Maxfield and Maxfield (*15*) used ^{32}P for this purpose and found similar results. Androgen-stimulated ^{32}P treatment was found to increase uptake in stimulated cells by 15–20 times compared to nonstimulated cells (*16*). Albright and Reifenstein (*17*) also demonstrated an increase in phosphate uptake in new bone with androgen stimulation. Multiple doses of ^{32}P and androgen therapy were advocated by Maxfield et al. (*6*), who reported less undesirable effects than with a single dose. Multiple doses or the addition of androgen therapy were not a part of this study. Androgens were not used because they may be efficacious in breast cancer by themselves and may vitiate assessment of response to either radioactive treatment. Furthermore, occasional increase in bone pain and spinal cord compression have also been cited as undesirable effects of androgen therapy (*18*).

^{89}Sr was used by Pecher (*3*) in 1942 for treatment of skeletal metastases from carcinoma of the prostate. After it was used unsuccessfully to treat multiple myeloma (*4*), it was used in the 1970s to treat metastatic bone pain. Favorable reports of its use came from Europe (*19*) and from the U.S. (*1*) The initial reports of Robinson et al. (*20,21*) mentioned a 77% response rate in pain relief and quality of life. They found a higher response rate with breast carcinoma than with prostate carcinoma (83%–79%) and demonstrated a dose-response relationship—higher doses produced a better response. Approximately 30 μCi/Kg was considered the minimum dose and an ideal one is reported as 40–60 μCi/Kg (*22*). Other researchers have not found this dose-response relationship. We used a fixed 4 mCi dose and found no difference in response between breast and prostate cases. Our numbers, however, are small.

Laing et al. (*23*), reporting on the results of a multicenter study on 119 patients of prostate cancer, noted "a clinical response of some type" in 71%, of which 20% became effectively pain free at the end of a 12-wk follow-up period. They reported pain relief beginning between 10 and 20 d after ^{89}Sr treatment with the maximum benefit normally achieved by 6 wk. They found doses below 1.5 MBq/kg (0.04 mCi/kg) to be suboptimal and recommended a standard dose of 150 MBq for each patient for optimal relief.

Patients in this study, as pointed out, were given 4 mCi each and this would agree with the recommended dose of Laing et al. (*23*). With this dose, it has been possible to demonstrate therapeutic response (50% pain relief or better) within the first week itself in 14 of 15 patients and a complete absence from pain and significant reduction of analgesic intake in 7 patients. A further 7 patients obtained between 50% and 70% reduction of pain scores that could qualify as "substantial improvement" mentioned by Laing et al.

The study of Lainge et al. (*23*) was based on assessment at 12 wk post-treatment. They report, however, that the improvement lasted a mean of 6 mo and ranged from 4 to 15 mo. It is not clear how this was concluded. Although we had patients reporting back to us well after our 16-wk follow-up period, we have reported our findings only until the end of the 4-mo follow-up period. However, it must be mentioned that after ^{89}Sr therapy, sustained pain-free intervals lasted over 6 mo in

only 2 patients. In all the other 12 responders, the pain-free interval lasted on average 10 wk, ranging from 2 to 16 wk.

To our knowledge, no previous study has compared both ^{89}Sr and ^{32}P in a similar population. Our study seems to be the first to compare the two under fairly similar conditions and to attempt to quantify patient perceptions of improvement in pain and mobility. We believe that a quantitative approach is more reliable than impressions of dramatic or significant improvement that other workers have used.

^{32}P and ^{89}Sr were comparable in mean duration of therapeutic response (defined as 50% relief) and maximal pain relief. Although the proportion of patients attaining normal mobility was somewhat greater with ^{32}P than with ^{89}Sr (13 of 16 versus 8 of 15, respectively), the difference was not statistically significant.

The review of Silberstein et al. (*12*) mentions complete relief from pain in 20%–50% of ^{32}P-treated patients. Earliest response is after 3 d, response often occurs after 14 d and, at the latest, response occurs by 4 wk. Duration of pain relief is quoted as 5.1 ± 2.6 mo. Even though our study has demonstrated marginally better responses than Silberstein's study, we do not believe that this difference would be statistically significant.

We believe that this comparison has provided reliable data on the relative merits of both ^{32}P and ^{89}Sr and has found them identical in most respects. The smallness of the numbers is compensated by the elaborate parameters devised for pain relief, analgesic medication, mobility assessment and toxicity, the length of follow-up and patient compliance. Although there were occasional patients whose improvement lasted beyond 6 mo, a minimum of 50% relief lasted barely 3 mo with a proportional improvement in mobility.

The benefits and toxicity of the two radionuclides are comparable and real benefit was experienced, although it lasted for no more than 3 mo in most patients. There would, therefore, be a case to suggest that oral ^{32}P could be used very effectively in the palliation of pain from skeletal metastases. The considerably more expensive ^{89}Sr appears unwarranted, particularly in countries such as India. Even in countries with a more affluent population, the argument in favor of ^{89}Sr would be unsustainable in the light of the findings we have described.

The greater effect of ^{32}P on platelet counts over ^{89}Sr is expected, given the greater affinity for the former radionuclide for bone marrow. However, we note that in no case was the drop in counts sustained at or below 50,000/mL, that is, low enough to warrant intervention. Further, in all cases, counts eventually returned to normal. Our experience reinforces Silberstein's assertion that at doses up to 12 mCi, bone marrow toxicity with ^{32}P is not clinically significant. However, given our modest patient sample size, we cannot extrapolate our favorable experience to a much larger setting with absolute certainty. ^{32}P orthophosphate for parenteral use has now become locally available and studies need to be done to determine if lower doses can be used to achieve pain palliation.

It is feasible to repeat ^{32}P at the end of 3 mo or when pain recurs, whichever is later, for patients with a life expectancy of a few months in whom there is no reported cure despite occasional reports of reduction in PSA levels after ^{89}Sr therapy in prostate cancer (*11*) or radiographic evidence of bone regeneration after ^{32}P therapy (*24,25*). There have been arguments in support of administering either of these radionuclides in the absence of significant pain. This is not a practice to be encouraged because these medications have no curative value. Therefore, the mere demonstration of metastases on a bone scan in the absence of pain from the scan-positive sites should not qualify for this treatment. Pain not amenable to the usual analgesic medication should be present and must emanate from the areas shown to be abnormal on the bone scan. Pain not arising from these sites should not be considered for this treatment. Neither ^{89}Sr nor ^{32}P are true analgesics: they exert their effect by localizing in areas of osteoblastic activity.

CONCLUSION

^{89}Sr and ^{32}P were comparable in their effects on maximal pain relief, time to maximal relief, onset of therapeutic response to pain, duration of therapeutic response, degree of improvement of mobility and duration of maximal mobility improvement. In patients who obtained complete relief of pain, total withdrawal of analgesic medication was possible.

Although both ^{89}Sr and ^{32}P caused some depression of marrow function (and ^{32}P platelet toxicity was significantly higher than that of ^{89}Sr), in no patient was the hematological toxicity severe enough to require intervention. All counts eventually returned to normal.

Based on this data, we recommend that ^{32}P may be used instead of the expensive ^{89}Sr in the palliation of pain from skeletal metastases. This recommendation is subject to the caveat that bone marrow function needs to be monitored more carefully with ^{32}P.

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