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RESEARCH ARTICLE

IMPROVEMENT OF QUALITY OF LIFE IN PATIENTS WITH BONE PAIN IN ADVANCED CANCER: REINFORCING THE ROLE OF RADIONUCLIDE THERAPY FOR BONE PAIN PALLIATION

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ABSTRACT

Context: Patients with multiple bone pains due to metastatic cancer in bones presenting in the clinic are very challenging for all oncologists. Along with conventional medical and interventional techniques, the option of radioisotopes for bone pain palliation especially in the multiple bone pain setting is not very popular. **Aims:** We describe our initial clinical experience with Sm-153 EDTMP in a tertiary care centre set in a hilly state and briefly review the potential of radioisotope methods for bone pain palliation in such a setting. **Settings and Design:** Initial patients treated with Sm-153 EDTMP (1mg/kg) over first 6 months of the current year were included in the study. **Methods and Material:** Clinical assessment, haematological assessment and assessment of quality of life with a mini questionnaire was done at baseline and at 6-12 weeks after Sm-153 EDTMP. **Statistical analysis used:** Data from questionnaires was entered in excel for import to SPSS. Means were compared using paired t test while proportions were compared using chi square test for proportions. **Results:** Of the 26 patients included in the study 19(73%) showed subjective improvement in pain. Statistically significant improvement in quality of life was observed within 6-12 weeks. Quality of life improved in all the patients who experienced pain relief. None of the patients developed severe haematological toxicity. **Conclusions:** In the availability of a Nuclear Medicine department, Sm-153EDTMP can be used in a well selected group of patients for utilization for bone pain relief even in the setting of peripheral, smaller cities located away from metropolitan cities. Advantages include long duration of effect, ease of administration, low toxicity and repeatability of doses. It can have a positive impact in quality of life of patients with advanced cancer.

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INTRODUCTION

Originally being a disease of the developed world, over the years, the burden of cancer has shifted to less developed countries, which currently account for about 57% of cases and 65% of cancer deaths worldwide as documented by Torre El (2012). Thus, cancer burden is not a problem which can be over looked. In countries like India illiteracy, poverty, blind trust in alternative medicine and social taboos many patients present with advanced disease. These patients have high incidence of skeletal metastasis (Stage IV disease) and present with severe bone pain affecting quality of life and they desire relief from pain. Many patients may present to allied clinics like Orthopaedics, Neurology etc. for their pain. The attending physician in these cases needs to focus that the challenge remains to give adequate pain relief with or without definitive therapy by the Oncologist. The primary goal becomes maintenance of quality of life and performance status. The WHO guidelines (1990,1996) for pain relief mention the pain ladder for management of cancer pain which start with non-opioids analgesics and goes up to opioids, adjuvant drugs including steroids and nerve blocks. Pain palliation is usually initiated with non-opioid analgesics and can provide adequate pain relief, however as the disease progresses, increased doses as well as opioid analgesics are required.

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Table 1. Questionnaire

No.	Question	4	3	2	1
1	Are you in pain?	Constantly	Most of the time	Occasionally	Never
2	Are you able to sleep at night?	Not at all	Mostly disturbed	Yes but a bit disturbed	Yes
3	Are you able to perform your routine activities like bathing, toilet, moving around the house, going for a walk etc.?	Not at all	Sometimes	Most of the time	Always
4	What is your routine pain medicine intake pattern?	Daily >thrice	Daily 2-3 times	Daily once	Occassionally (<once a day)
5	Are you thinking about your disease/illness?	Constantly	Mostly	Occasionally	Almost never

Morphine, an important opioid analgesic drughas procurement restrictions leading to lack of availability. Other issues include association with increased adverse effects, including constipation and drowsiness. Chemotherapy or hormonal therapy may be used for both soft tissue and bone metastases and can be effective with tolerable side effects until the disease becomes refractory to these agents, this may be several weeks or months. External beam radiotherapy provides effective pain control with short courses of high dose per fraction and a low toxicity, if the metastatic disease is not extensive; however, the toxicity rapidly increases with wide radiation fields so it has limited use in widespread pain in multiple sitesas seen in studies by Hoskin PJ (1995), Dearnaley DP (1992), Serafini AN (1994), McEwan AJ (1997) and Serafini AN (2001). Bone seeking radionuclides can offer bone pain palliation in these patients with disseminated skeletal metastasis. Advantages include efficacy and low toxicity. Clinically useful Radionuclides suitable for systemic metabolic radiotherapy of bone pain include Phosphorous-32 (P-32), Strontium-89 (Sr-89), Rhenium-186 (Re-186) chelated with hydroxyethylidene diphosphonate (HEDP) and Samarium-153 (Sm-153) chelated with ethylene diamine tetra ethylene phosphonate (EDTMP).
In a resource challenged country like India, with lack of experts as well as palliative care teams - adequate pain relief may not reach the right person at the right time. Radionuclide therapy may be an option for such patients.

MATERIALS AND METHODS

The aim of this study was to evaluate pain relief and quality of life after radionuclide therapy with Sm-153-EDTMP in patients with advanced metastatic bone cancer with bone pain in one of the first radioisotope facilities in a tertiary care hospital in a hilly state in India. We included all patients treated with Sm-153 EDTMP for bone pain relief over six months of starting the facility of radioisotope therapy.

Inclusion Criteria: Patients with (i) bone pain (ii) in diagnosed cases of cancer (iii) with bone metastasis (iv) seen on bone scan (Figure 1A).

Exclusion Criteria: Absolute: Pregnancy, acute spinal cord compression, recent pathological fractures.

Relative Contraindications: Bone marrow suppression: Haemoglobin levels <nine gm%, WBCs < 3,500/cu mm and platelets <one lac /cu mm. All patients underwent a thorough clinical examination which included a detailed history and physical examination. Neurological deficits due to spinal cord compression and pathological fractures were ruled out. All patients answered a questionnaire at baseline and at 6-12 weeks (Table 1). The questionnaire had five questions with four-point response for each. It was devised with simple easy to understand questions to estimate quality of life.

The questionnaire was developed in bilingual (Hindi and English) format for ease of understanding of the patients.

Dose administration: Patients were planned for therapy and were called on the day of dose arrival in the department on outpatient basis. Blood profile performed within 7 days was documented. A dose of 1mg/kg intravenously of Sm-153 EDTMP was injected in all patients. A whole body scan was performed after four hours to see the bio distribution pattern of bone lesions (Figure 1B). Haematological parameters were kept in check weekly for the first month. Clinical assessment was done at two, four and six weeks and at three months.

Data analysis: The data was entered in excel and also imported into SPSS for performing data analysis. Proportions were calculated for different scores with respect to the questions asked. Also mean scores were calculated before and after the therapy. Means were compared using paired t test while proportions were compared using chi square test for proportions. P value less than 0.05 was considered significant.

RESULTS

26 patients (18 males) were included in the study. Diagnosis of malignancy was confirmed in all through proven histopathology and imaging results. Bone scan was performed within two weeks of therapy in all patients which demonstrated multiple osteoblastic lesions suggestive of skeletal metastasis at various sites including axial and appendicular skeleton. None of the patients had any symptoms of spinal cord compression or fractures. Patients had primary in breast (7), prostate (16) and at other sites viz. gall bladder (1), oral (1), unknown primary (1). Overall 19 (73%) patients experienced subjective improvement in the form of relief in painwithin 4-6 weeks. Objectively, changes in scores were noted in most patients (Table 2-6). None of the patients developed a serious /significant fall (< 7gm% or WBC <2000, Platelet < 50,000) in blood indices warranting blood transfusion or any other intervention after administration of Sm-153 EDTMP for the entire follow-up period. It was observed that the proportion of patients reporting constant pain or pain on most of the occasions decreased drastically after the therapy. More than half of the patients reported that they did not experience any pain after the therapy. The therapy was found to have a positive effect on frequency of pain experienced by the respondents. The differences observed were found to be statistically significant ($p < 0.05$). It was observed that the self reported sleep pattern of respondents improved after therapy and most of the patients reported good sleep after therapy. Four out of 26 patients reported a slightly disturbed sleep as compared to 10 out of 26 before therapy. The differences were found to be statistically significant. The ability of the patients to perform their routine activities also improved significantly from 58% to 82%. Proportion of patients taking pain medication also decreased significantly and about 70% of the

patients reported taking pain medication only once per day as compared to about 77% who were reported to take pain medication more than two times per day. No significant changes were observed in proportion of patients with respect to thoughts about their illness. The mean scores of patients before and after the therapy decreased significantly with respect to various questions except the thoughts about illness, thereby indicating a positive effect of the therapy on the subjective well-being of the patients. Phosphorous (P-32) by Freidell and Strontium (Sr-89) by Pecher were the first radioisotopes to be described used for bone pain palliation from metastatic disease. With hundreds of publications of literature over more than five decades, radionuclide therapy is an established modality for palliation of cancer pain from bony metastasis all over the world. Sm-153 EDTMP has been used as one of the safest and effective modalities in this context especially in patients with prostate cancer as seen by J Dolezal (2007) and Pradeep Thapa (2015) in the Indian context.

Mechanism of Action: A beta emitter is attached to a bone seeking molecule and is delivered at sites of osteoblastic activity i.e metastasis mostly corresponding to the sites seen on the bone scan. This accumulation exerts following local effects: i. Delivery of about 5-10 Gy of ionizing radiation dose to tumour site. ii. Local cytocidal effects of beta particles on radiation sensitive cells such as lymphocytes - an important mechanism to decrease cytokine induced pain. This dose is not sufficient to kill all tumor cells within marrow in a short time, and neither has any immediate impact on peritumoural edema or mechanical nerve entrapment. Shrinkage of metastatic tumour decreases the mechanical stimulation of periosteal pain receptors. These mechanisms have been reported by Lass P 2001, Finlay IG 2005, Mc Ewan 2000 and Baczyk M 2007 in various studies. Beta emitting radionuclides labelled with bone seeking radiopharmaceuticals form an armamentarium of agents for therapy. Commonly used agents include Sr-89-chloride, P-32-phosphate, Sm-153-EDTMP, Sn-117m –DTPA, Re-188(Sn) HEDP, and Re-186(Sn)HEDP. Recently, the U.S. Food and Drug Administration approved another therapeutic agent for bone pain palliation, 223Ra-chloride, which is an alpha-emitting radioisotope similar to calcium ions that accumulates in bone and targets osteoblastic metastatic sites.

The major advantage is targeting of multiple sites at one time, this is the advantage of radionuclide therapy in comparison to external beam radiotherapy, shown by Thapa P (2015). The goal of this therapy is not prolongation of survival, but improvement of quality of life of patients. Being able to "see what we treat" due to imaging possibility with gamma radiation in Sm-153 EDTMP is an added advantage. The images show lesions in which radioisotope has accumulated and will be effective. The challenges of inadequate pain relief of patients, in a hilly state of a resource challenged developing countries are huge so we explored the use of this radionuclide therapy with Sm-153 therapy in our patients. The minimum prerequisite for this radionuclide therapy is a Nuclear Medicine facility. Administration of Sm-153 therapy is a very simple and low resource consuming procedure. Sm-153 has a half-life of around 2 days which means that it would not require much logistics for procurement in major well connected cities. However, in our setting which is around 200km from the nearest metropolitan city (New Delhi) logistics for procurement of Sm-153 were a bit challenging as it is produced and supplied from BRIT in Mumbai, around 1700 km away from our Institute. Once completely evaluated and planned, we pooled our patients and order multiple doses. We called the patients on the same day and inject them preferably within the same hour of arrival of the dose. This made up for dose already lost by decay during the transit and prevents further loss of dose in radioactive decay. We administered a fixed dose of 1mCi /kg in all our patients. Most studies have shown that this dose is optimum for effective pain relief and higher or lower doses do not offer much advantages. In fact, doses of around 3mCi/kg have been shown to cause Grade 3 bone marrow toxicity which is highly undesirable considering that there is no significant difference in the degree of response with this dose. This dose was found to be cost effective too in our scenario. None of our patients developed haematological toxicity. This is seen in most studies significantly those by Oliver Sartor (2004) and Tripathi M (2006) in India. Sm-153is shown to have limited toxicity and nearly no incidence of grade 3 or 4 toxicity even on multiple dose administration.

Proper selection of patients: Radionuclide therapy is contraindicated inn patients with impending spinal compression or pathological fractures, it is ineffective in neurogenic pain. External beam radiation would be the option of choice in these scenarios. Bone scan must reveal osteoblastic metastasis usually multiple in numbers. Recent hemibody irradiation or myelosuppressive chemotherapy must be excluded in order to avoid serious marrow toxicity after radioisotopes. Such therapy should be avoided after radioisotope injection upto atleast 4 to 6 weeks. We evaluated pain relief and quality of life with a simple proforma devised by us comprising of only 5 questions for this pilot study. Various other QOL (quality of life index) proforma are available for evaluating the same, however, we introduced this simple chart so as to make it easy to collect and for patients to understand. We initially evaluated patients for baseline pain and recommended pain relief as per the WHO pain ladder until and upto 2 weeks after the radionuclide therapy dose. This helped to keep patients comfortable for the entire period. Our study reveals improvement in all aspects of quality of life of patients including pain relief in the form of reduction of medication, improvement in sleep patterns. In our patients we did not observe "flare" of pain. This phenomenon of mild increase in pain is noted in 10-30%of patients receiving Sm-153 therapy as per literature including Farhangi (1992) This could be attributed to small number in our study or lack of awareness to be able to exactly document the phenomenon or due to adequate pain relief with medications. However, another study by Tripathi M (2006), showed similar observations on flare. We observed a statistically significant response of pain relief in the form of improvement in overall pain intensity, reduction of pain medication dosage and improvement in sleep patterns, overall performance of routine activities . Response to thought about their disease was no statistically significant probably because of the short duration of follow-up. These results are in agreement with Thapa P (2015) and Tripathi M *et al* 2006. A single dose would be sufficient for providing pain relief for an average of 6 months and it can be repeated if necessary. We did not observe any major haematological toxicity in the current study. Dolezal *et al*. (2007) have reported of 32 patients with bone disseminated hormone-refractory prostate cancer and bone pain treated with 153Sm-EDTMP, mild and transient bone marrow suppression was observed as a side effect of treatment. Similar results were seen with Thapa P (2015) and Tripathi M (2006), none of the patients showed grade IV hematologic toxicity, and only 2 showed grade III (NCI-CTCAE).

Thapa P *et al* (2015) reported fall in markers for osteoblastic activity like alkaline phosphatase with radionuclide therapy. We did not perform any other investigations in the form of tumour markers or any other parameters as we intended to study purely degree of pain relief and quality of life in these patients also validated by Garnero P (2000, 2001). Challenges in radionuclide therapy include good selection of patients who have a median survival of atleast 3 months. Furthermore, short half-life of Sm-153(1.9 days) makes it more challenging for use in the periphery where supply may take a few days. This leads to escalation in cost. However, with appropriate use of communication and effective logistics, management we could perform this therapy in patients without escalating cost and wastage of doses. In our experience the three key steps for effective use of Sm-153 therapy are 1. Appropriate patient selection 2. Dose logistics and administration 3. Short term follow-up for haematological parameters and long term follow-up for assessment of clinical pain relief and possibility of retherapy.

Concluding Remarks

In a resource challenged country like India, with lack of experts as well as palliative care teams - adequate pain relief may not reach the right person at the right time. In the therapeutic algorithm radionuclide therapy for bone pain palliation should be located between conservative treatment and interventional therapeutic procedures/modalities. Radionuclide therapy for bone pain palliation does not require hospitalization or prolonged follow-up. Radionuclide therapy for bone pain palliation affects the patient's general condition, which is associated with eliminating pain and improving quality of life.

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