Effects of low-dose capecitabine on Samarium-153-EDTMP therapy for painful bone metastases

Sukanta Barai, Sanjay Gambhir, Neeraj Rastogi, Anil Mandani, Murthy Siddegowda

Departments of Nuclear Medicine, Radiotherapy and Urology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

ABSTRACT

Introduction: Samarium-153 (Sm-153)-EDTMP is routinely used for pain palliation in skeletal metastasis, however most patients report partial response. Many strategies have been contemplated to make radiation therapy for pain more effective, one of them being the use of radiosensitizers. Capecitabine is a chemotherapeutic drug and is routinely combined with external beam radiation to make the target more radio-sensitive. Aim of the study was to evaluate whether combining capecitabine in radiosensitizing dose with Sm-153-EDTMP produces superior analgesia compared to Sm alone. Materials and Methods: Forty-four patients with skeletal metastases from various primaries were randomized into two groups: The study group received 1 mCi/kg Sm-153-EDTMP plus capecitabine (1,650 mg/m²) orally for 8 days (equivalent to four t¹/² of 153Sm-EDTMP) and the control arm received 1 mCi/kg Sm-153-EDTMP plus placebo for the 8 days. After treatment, the patients were followed up for 12 weeks to evaluate the degree and duration of pain palliation and hematologic toxicity. Results: All 44 patients reported different degrees of pain relief with none reporting complete pain relief for the entire duration of 12 weeks posttherapy observation period. However the level of pain relief obtained in study arm was significantly better than the control arm with mean posttherapy pain score being 1.29 ± 1.05 and 3.59 ± 2.77 respectively with P of 0.001. Transient and mild hematologic toxicity, as determined by World Health Organization criteria, was apparent in both arms without significant differences. Conclusion: The addition of a low-dose of capecitabine significantly enhances the analgesic effect of Sm-153 without any additional side effects.

Keywords: Capecitabine, pain, radio-sensitization, Samarium-153-EDTMP, skeletal metastases

INTRODUCTION

Skeletal involvement accounts for substantial morbidity and mortality in patients with cancer. Advanced-stage solid tumors, notably those arising from the breast, prostate, and multiple myeloma are associated with a heavy burden of skeletal disease, with potentially debilitating or life-limiting skeletal-related events. The most common complication of skeletal metastasis is pain which typically worsens with time and is frequently refractory to conventional analgesic therapy. Bone metastases are the primary reservoir of treatment-resistant disease and are the most frequent site of disease relapse. A method of targeting the bone microenvironment, as well as irradiating tumor localized to bone, is through the use of bone-seeking radionuclides. Though the majority of the patients report various degree of pain relief from bone-seeking radionuclide therapy, typically the response is mostly partial. Many strategies have been contemplated to make radiation therapy for pain more effective, one of them being the use of radiosensitizing drugs. Many chemotherapeutic drugs have been found to have inherent radio-sensitizing property. Though chemotherapeutic agents are commonly used concurrently with external beam radiation to enhance the effect of radiation, the approach toward combination of bone-seeking radiopharmaceuticals and chemotherapeutic agent is very cautious, given concerns about additive marrow toxicity.

Capecitabine is an oral, tumor-activated fluoropyrimidine carbamate that delivers 5-fluorouracil (5-FU) preferentially to...
tumor cells via a three-step in vivo enzymatic conversion. It has radiosensitizing properties through several mechanisms even when used at low doses. Aim of the study was to evaluate whether the addition of capecitabine with Samarium-153 (Sm-153) in radiosensitizing dose produce better analgesic response compared to Sm alone.

MATERIALS AND METHODS

Patients
A total of 57 patients with painful skeletal metastasis referred for the radionuclide pain palliation therapy was assessed for eligibility. Thirteen patients were excluded due to the presence of one or more exclusion criteria, remaining 44 patients were randomized in two groups with 22 patients in group A or the study arm and 22 patients in control arm. Randomization numbers were generated by computer software developed by social psychology network, USA. The protocol was approved by the institutional review board. All patients furnished written informed consent.

Inclusion criteria
• Documented osteoblastic skeletal metastasis on bone scan with histologically proven cancer patients
• Willingness to give informed consent
• Projected survival of ≥ 3 months
• Hemoglobin (Hb) ≥ 7 gm/dl. Serum creatinine < 2.5 mg%
• Karnofsky performance score of at least 40
• Age of at least 18 years.

Exclusion criteria
• Patients with pathological fractures or clinically evident spinal cord compression
• Patients with brain metastasis
• Chemotherapy within 6 weeks prior to screening
• Clinically significant bleeding disorders; disseminated intravascular coagulation
• Platelet count < 80,000/ml; hemoglobin < 7 g/dl
• Serum creatinine > 2.5 mg%

Treatment protocol
• Group A (study arm) - received Sm-153 at a dose of one millicurie per kilogram body weight and capecitabine 1,650 mg/m² of body surface area per day for 8 days in two divided dose, which is equivalent to 4 half-life of Sm-153
• Group B (control arm) - received Sm-153 at a dose of one millicurie per kilogram body weight + placebo for 8 days.

Posttherapy follow-up
Patients were evaluated over a period of 3 months or till death, whichever was earlier. They were called for follow-up or contacted telephonically on 2nd, 6th, and 12th week posttherapy. Evaluation of the effect of therapy was documented by change in pain intensity as measured by visual analog scale (VAS) during the follow-up period. In addition, patients were asked to maintain a pain diary to record maximally perceived pain and analgesic intake.

Adverse effects
This outcome was evaluated by measuring changes in platelets, leukocytes, and Hb during the 12 weeks of follow-up and was classified by a 5-point toxicity score according to World Health Organization criteria.

Statistical analysis
Differences in pretherapy variables between the two arms were assessed by the t-test for paired data. The level of significance was set at the conventional value of P < 0.05.

RESULTS

Patients
Forty-four patients of various types of the primary malignancy having multiple painful skeletal metastases were enrolled onto the study. The demographic profiles of these patients are detailed in Table 1. The patients generally had been extensively pretreated; all having received different regime of chemotherapy, 75% of the patients had received some form of external radiation in the past. Nine patients received prior radiation to a metastatic site. Both the patient and physician evaluating the patients were blinded.

Pain palliation
One patient in study arm developed acute flare in pain within 24 h of administration of Sm, which responded favorably to increased dose of analgesic drugs. All the 44 patient reported different degree of pain relief. None of the patients in any arm reported complete pain relief for the entire duration of 12 weeks posttherapy observation period. However, the level of pain relief obtained in study arm was significantly better than the control arm with mean posttherapy VAS being 1.29 ± 1.05 and 3.59 ± 2.77 respectively with P of 0.001 [Table 2].

Table 1: The demographic profile in both the groups

| Criteria          | Study group | Control group |
|-------------------|-------------|---------------|
| Number of participants | 22          | 22            |
| Age               | 56.39±9.21  | 60.6±10.03    |
| Male:Female       | 12:10       | 14:8          |
| Site of primary tumor | Prostate (n=12) | Prostate (n=1) |
| Lung (n=3)        | Lung (n=2)  |               |
| Unknown primary (n=1) | Colon (n=2) | Nasopharynx (n=1) |

Table 2: The clinical profile in both the groups

| Parameter                  | Study group         | Control group        | P     |
|----------------------------|---------------------|----------------------|-------|
| Baseline VAS score         | 8.30±1.8            | 8.22±1.4             | 0.87  |
| Posttherapy VAS score      | 1.29±1.05           | 3.59±2.77            | 0.001 |
| Baseline Hb (g %)          | 11.16±1.47          | 11.19±1.28           | 0.94  |
| Posttherapy Hb (g %)       | 10.21±1.59          | 10.16±1.38           | 0.92  |
| Karnofsky performance score | 51.9±15.8          | 54.7±11.6            | 0.31  |
| Karnofsky performance score | 78.3±10.6          | 67.8±17.1            | 0.04  |

VAS: Visual analogue scale, Hb: Hemoglobin
Marrow toxicity

Study arm
All patients developed mild and transient hematological suppression which spontaneously returned to the baseline level at about 6 weeks posttherapy. However, one patient who was heavily pretreated with chemotherapy developed leukopenia with cell count < 2,000/ml along with pyrexia Recovery was prompt on granulocyte stimulating factor and antibiotic support for 5 days. Overall Hb level before and after therapy in both the groups were similar.

Control arm
All patients developed mild and transient hematological suppression which spontaneously returned to the baseline level at about 6 weeks posttherapy.

OTHER RESULTS

No side effects were clinically evident after capecitabine therapy. Prophylactic antiemetic therapy was prescribed in the form of oral ondansetron, and none of the patient reported any significant gastrointestinal complaints. One patient in study arm experienced an acute increase in pain, that is, a flare response, within 24 h of Sm-153-EDTMP injection. No patient showed any neurological signs or renal function impairment. The mean Karnofsky performance score which was similar at baseline in both group, was significantly better (P < 0.04) in the study arm, probably as a consequence to superior pain relief in this group compared to the control arm.

DISCUSSION

The main observation of this study was the synergistic effect of the addition of low-dose capecitabine on the analgesic effect of Sm-153-EDTMP in patients with painful skeletal metastasis. Most common complication of skeletal metastasis is pain which typically worsens with time and frequently such pain are refractory to conventional analgesic therapy. Only a small proportion of bone metastases become painful, and the factors that convert a painless lesion into a painful one are unknown.[9] Pain onset may represent an increase in neoplastic bone invasion and be an early marker of bone disease progression.[9]

Radiation to the affected bone leads to pain relief, and some form of radiotherapy is widely used for painful osseous metastasis.[10] Internal systemic radiation using Sm-153-EDTMP has widely been used for more than 25 years to relieve pain caused by skeletal metastases.[11] Although the clinical efficacy of Sm-153-EDTMP is evident in around 72% of patients, only a small percentage of these patients experience complete pain relief and only occasionally does objective evidence of tumor regression occur.[12] Many strategies have been contemplated to make radiation therapy for pain more effective, and one of them was the use of radiosensitizers.[13] Many chemotherapeutic drugs have been found to have inherent radio-sensitizing property. They act on the DNA of the tumor cell and produce break in the strand. When radiation is applied on the same cell, additional DNA breaks are produced, notably double strand break which are difficult to repair leading to increased tumor cell death.[14] This synergistic effect between chemotherapy and radiation leads to a higher number of tumor cell death than any of the modalities applied in isolation. The sites of skeletal deposits are intensely infiltrated by various cells of inflammations, and they are increasingly been recognized as important played in developing chronic pain state like cancer pain.[15] Part of the inflammatory cells are also ablated due to the effect of radiation, which probably contributes to analgesic effect of radionuclides. Previous studies have investigated the combination of other radionuclides like Sr-89 with doxorubicin or cisplatin in the treatment of patients with androgen-independent prostate carcinoma.[16,17] In the current study, we demonstrated the clinical efficacy safety of the combination of Sm-153-EDTMP with capecitabine.

For the purpose of radiosensitization, continuous 5-FU infusion is considered as the gold standard.[18,19] Capecitabine is a prodrug of 5-FU and is a potent radiosensitizer. Capecitabine acts on the S-phase of the cell cycle. Through its twice-daily oral administration, capecitabine approximates continuous infusions of 5-FU. The final step of conversion of capecitabine to 5-FU is mediated by the enzyme thymidine phosphorylase (TP), which is up-regulated in tumor tissue compared with adjacent healthy tissue.[20] Radiotherapy preferentially enhances TP expression in tumor tissues, with no upregulation in healthy tissue.[21] This upregulation of TP by radiation increases the preferential delivery of 5-FU to the site of the tumor following the administration of capecitabine. The dose of capecitabine of 1650 mg/square meter body surface area was based to standard accepted radio-sensitizing dose of the drug.[22,23] The duration of therapy was chosen such that the vast majority (~93%) of the energy of Sm-153 is deposited in the tissue while capecitabine radio-sensitizes the target tissue. Sm-153 has a half-life of 46 h, so by 8th day more than four half-life will elapse and ~93% of energy will be deposited at the sites of Sm retention. Capecitabine was started 4 h after administration of Sm in order to allow unbound Sm-153 to be excreted out of body.[24] A review of the literature did not reveal any study evaluating the combination therapy of capecitabine and Sm-153-EDTMP, hence no direct comparison could be made. Amato et al. evaluated 29 patients with progressive adenocarcinoma of the prostate with combination of Strontium-89 (Sr-89) and doxorubicin and concluded that combination chemohormonal therapies with Sr-89 produces a prolonged progression-free and overall survival with acceptable toxicity.[25] Tu et al. evaluated 36 patients of metastatic prostate cancer with a combination of Sr-89 and doxorubicin and reported improved survival and pain control compared to the control arm.[26] Ricci et al. evaluated 16 patients with a combination of Sm-153 and mitoxantrone and reported improved pain control and progression-free survival compared to the control arm.[27] Sciuto et al. evaluated 73 patients with skeletal metastasis with a combination of Strontium 89 and cisplatin and reported that the combination therapy produces superior effect.
when compared to Strontium therapy alone.[17] Unfortunately, data on the prevalence of pain palliation from most trials using radionuclide therapy are not comparable either with one another or with this study because of the small number of evaluable patients, the different or poorly defined criteria for evaluating responses, and the different inclusion criteria.

The addition of low-dose capecitabine in this study effectively enhanced the effect of Sm-153 as addressed by all endpoints. However, none of the patients in the current study achieved complete pain relief for the entire duration of 12 weeks of the observation period. This is primarily because malignant process continues to progress relentlessly, and these patients were having advanced metastatic disease at the time of entering into the study. Typically response duration of a single administration of Sm-153 is considered around 4 months and at the end of 3 months response tends to wane and requirement of supplementary analgesic medication increases to maintain round the clock analgesia.[18] Pain is a personal, subjective experience influenced by cultural learning, the meaning of the situation, attention, and other psychologic variables. Approaches to the measurement of pain include verbal and numeric self-rating scales, behavioral observation scales, and physiologic responses. The complex nature of the experience of pain suggests that measurements from these domains may not always show high concordance. Because the pain is subjective, patients’ self-reports provide the most valid measure of the experience. The VAS is commonly used as an outcome measure for such studies. It is usually presented as a 100-mm horizontal line on which the patient’s pain intensity is represented by a point between the extremes of “no pain at all” and “worst pain imaginable.” Its simplicity, reliability, and validity, as well as its ratio scale properties, make the VAS the optimal tool for describing pain severity or intensity.[20]

The current study demonstrates the successful integration of Sm-153 with cytotoxic drug capecitabine for management of painful osseous metastasis. Compared with continuous infusions of 5-FU, oral capecitabine in combination with radiotherapy is convenient for patients and health care professionals. Capecitabine also avoids the potential complications associated with indwelling central venous catheters, such as infections, sepsis, thrombosis, and blockage. Since capecitabine could possibly also exert its effect on nonskeletal sites, this could also indirectly play some role in overall therapy response. Evaluation of this effect was beyond the scope of this current study and a prospective study recruiting a larger number of participants should be done to address this issue. Whether a higher dose of capecitabine would have resulted in superior analgesia, requires further prospective evaluation.

**CONCLUSION**

Addition of capecitabine at radio-sensitizing dose significantly enhances the analgesic effect of a Sm-153-EDTMP without significantly increasing marrow toxicity.

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