Samarium-EDTMP administration followed by hematopoietic stem cell support for bone metastases in osteosarcoma patients

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Background: Bone metastatic patients with osteosarcoma have a very poor prognosis. Targeted radiation therapy has been pursued as a valid alternative. The primary end point of this study was progression-free survival (PFS) at 4 months.

Patients and methods: Twenty-two osteosarcoma patients were treated with Samarium-153 ethylenediaminetetramethylene phosphonic acid (153Sm-EDTMP) at various dosages. Administered activities ranged from 150 (3 mCi/kg) to 1140 MBq/kg (30 mCi/kg). Autologous hematopoietic stem cell infusion was carried out on day 14 after the 153Sm-EDTMP infusion.

Results: The median PFS was 61 days (18–436 days) and the median overall survival (OS) was 189 days (31–1175 days). PFS and OS for the entire patient population were 32% [95% confidence interval (CI) 16–50] and 76% (95% CI 52–89) at 4 months, respectively. No statistical differences emerged according to 153Sm-EDTMP administered or 24-h retained activity. One-month pain palliation was only observed in a minority of subjects and in none at 4 months.

Conclusions: Based on our series, the PFS is dramatically short even when higher activity of 153Sm-EDTMP is administered. This would mean that, even at high level, 153Sm-EDTMP is itself ineffective against relapsed osteosarcoma or the residual activity is too low to be active on these particular subsets of patients.

Key words: hematopoietic stem cell rescue, metastatic osteosarcoma, 153samarium-EDTMP administration

Introduction

New strategies are needed to improve the prognosis of relapsed osteosarcoma, which could not achieve surgical resection, especially for patients with high-risk features such as bone metastases whose cure rate is <15% [1–4]. This concept has been pointed out in a recently published series in which long-term survivors could be found only among patients who achieved surgical remission [5]. Moreover, osteosarcoma is a relatively radioresistant tumor [6] and only transient disease control was obtained with doses of <60 grays. Such doses limit the application of external radiotherapy because of significant normal tissue toxicity.

Targeted radiation therapy has been pursued as a valid alternative and Samarium-153 ethylenediaminetetramethylene phosphonic acid (153Sm-EDTMP) has been investigated as a radiopharmaceutical agent selectively delivering radiation to osteoblastic skeletal lesions, due to a high affinity for skeletal tissue and chemiabsorption in areas of enhanced activity [7]. 153Sm has a half-life of 47 h, allowing safe administration in an outpatient setting. Due to its half-life and beta emissions, a high dose rate can be delivered to regions adjacent to enhanced osteoblastic activity over a short period of time with little residual long-term activity being left in the bone marrow [8].

153Sm-EDTMP was initially developed as an agent for the palliative treatment of bone metastases. The Food and Drug Administration approved 153Sm-EDTMP in April 1998 for pain palliation in patients with bone metastasis at a standard dose of 1 mCi/kg. Thereafter, 153Sm-EDTMP was used in high-risk osteosarcoma patients as a single or combined agent. Anderson et al. [9, 10] found that the administration of high-dose 153Sm-EDTMP (1140 MBq/kg) with autologous stem cell support is feasible, with only hematological toxicity, and its association with gemcitabine as a radiation sensitizer allows partial transient responses.
In this retrospective multicenter study, we investigated the role of $^{153}$Sm-EDTMP followed by hematopoietic stem cell (HSC) rescue in high-risk osteosarcoma patients together with the correlation of the delivered and retained activity and the clinical outcome. The primary end point was progression-free survival (PFS), while the secondary end points were toxic effects, pain relief and the correlation between delivered and retained activity when $^{153}$Sm-EDTMP was administered at various dosages.

**materials and methods**

**patient selection**

Eligibility criteria were: a biopsy-proven diagnosis of high-grade osteosarcoma; metachronous bone metastasis [11]; age <50 years; normal liver, kidney and cardiac function with an ejection fraction over 50%; a white blood cell count >3 × 10^9/l and >50 × 10^9/l platelets; no previous treatment with $^{153}$Sm-EDTMP; and cryopreserved HSC rescue with >2 × 10^6/kg CD34+ cells.

Before entering the study, all patients underwent an accurate physical examination, total body computerized tomography (CT) or magnetic resonance imaging (MRI) of the primary lesion and metastatic sites and a radionuclide bone scan. All these patients were centralized at the Regina Margherita Children’s Hospital (Turin) or the Institute for Cancer research and Treatment (Candiolo). The local ethical committee (EC) approved the study. Since it was the first study designed as a curative treatment, in order to monitor toxic effects, the first group of patients had to be treated with a low dosage of $^{153}$Sm-EDTMP followed by $^{153}$Sm level escalation. All patients or their parents provided informed consent consistent with local institutional review board guidelines.

**end points**

The primary end point of this study was PFS [12, 13]. The first tumor restaging following treatment was assessed on day 60 and then every 2 months [14]. The secondary end points were toxicity, according to common toxicity criteria adverse events [15], pain palliation and dosimetry [16–22].

**treatment plan**

All patients had successful peripheral blood HSC collection following cyclophosphamide (4 g/m²) and etoposide (600 mg/m²) treatment according to the chemotherapy protocol in which patients were enrolled before radiometabolic treatment. After hematological recovery following chemotherapy, all patients underwent complete restaging by CT scan or MRI and bone scan.

$^{153}$Sm-EDTMP was administered via slow i.v. injection in single doses and the patients were hospitalized for at least 12 h. Administered activities ranged from 150 (3 mCi/kg) to 1.140 MBq/kg (30 mCi/kg).

After administration, whole-body radioactivity was continuously measured with a time interval of 2 h through Geiger–Müller probes localized on the patient’s bed; to ensure repeatable evaluations and the correct measuring position, the patient received an audible warning. The total number of measures for each patient was determined on the basis of the hospitalization time (12–42 h). According to the EC instructions, various dosages of $^{153}$Sm-EDTMP were delivered: six patients received ≤10 mCi/kg, nine patients >10 to 20 mCi/kg and finally seven patients >20 mCi/kg.

HSC infusion was carried out on day 14 after the $^{153}$Sm-EDTMP infusion in all patients.

**biodistribution and kinetics**

Studies on dose evaluation in the therapeutic use of $^{153}$Sm-EDTMP for pain palliation demonstrated that only skeletal tissues adsorb the radiopharmaceutical drug and that nonskeletal tissues sites received negligible doses. In this work, we regarded the source organ to be the bone, without distinguishing between normal bone and tumor, since total body measurements did not allow us to make a distinction between the kinetics of the two tissues. The retention curve (fraction of injected activity versus time) was obtained by normalizing every measurement to the maximum, which also identified the initial reference time. From this curve, the fraction of injected activity retained in the body after 24 h from i.v. injection is also evaluated [16–22].

**statistical analysis**

Data were analyzed as of October 2010. The PFS was analyzed by Kaplan–Meier method [23] and the differences between curves by log-rank test [24]. PFS was defined as the length of time from study entry to the date of documented progression or death, whichever occurred first. Overall survival (OS) was calculated from the date of $^{153}$Sm-EDTMP infusion to death for any causes. The statistical analysis for dichotomic variables was carried out through Fisher’s exact test [25]. The following variables were analyzed for their impact on outcome: site of disease (bone only versus bone and extra-osseous disease), activity of $^{153}$Sm-EDTMP administrated (≤10 versus >10 to 20 versus >20 mCi/kg), disease status at $^{153}$Sm-EDTMP treatment (progressive disease (PD) versus non-PD) and 24-h retained activity of $^{153}$Sm-EDTMP (≤3 versus >3 to 7 versus >7 mCi/kg).

**results**

**patient characteristics**

Twenty-two patients entered this study between December 2005 and August 2009 (Table 1).

At study entry, all patients had bone lesions (17 both osseous and extra-osseous; 5 only osseous). Three patients had primary refractory disease, including 1 patient with previous allogeneic HSC transplantation; 10 patients were treated at the time of first disease recurrence (one patient with secondary osteosarcoma following retinoblastoma); 7 patients at second relapse and 2 patients following a subsequent relapse. Following chemotherapy, 1 patient was in complete response, 4 patients in partial response (PR), 10 had stable disease (SD)
and 7 were in PD (Table 2). There were no significant comorbidities. All patients were under opiate treatment.

All 22 patients were assessable for efficacy and toxicity; 15 patients were assessable for correlation between delivered and retained activity. No patients were lost at follow-up. The median follow-up was 189 days (55–1175 days).

153Sm-EDTMP administration
The 153Sm-EDTMP activity level was ≤10 mCi/kg (≤370 MBq/kg) for six patients, >10 to 20 mCi/kg (>370 to 740 MBq/kg) for nine patients (one female patient received a tandem infusion of 153Sm-EDTMP at 9 mCi/kg) and >20 mCi/kg (>740 MBq/kg) for seven patients (Table 2).

Tumor response
At day 60 after 153Sm-EDTMP infusion, 10 (45%) patients had SD and 12 (55%) progression disease. No objective response was documented. When we analyzed the tumor response for patients with bone and extra-osseous disease (combined disease) to others (bone disease only), SD was obtained in 35% of patients with combined disease and in 80% of those with other location of metastases (four patients, P = 0.98). Only 28% (two patients) of patients with PD who received samarium had tumor growth arrest compared with 46% (seven patients, P = 0.003) of those who had PR or SD following previous treatment. According to the 153Sm-EDTMP activity administered, SD was obtained in 83%, 33% and 28% of patients who received ≤10, >10 to 20 and >20 mCi/kg, respectively, (P = 0.77).

Finally, when we considered the 24-h retained activity (4.13 mCi/kg being the median value), SD was obtained in 71% of patients with a bone uptake lower than the median value and in 37% for patients with median higher activity.

PFS and OS
As reported in Figure 1, the median PFS was 61 days (18–436 days) and the median OS was 189 days (31–1175 days). PFS and OS for the entire patient population were 32% and 76% at 4 months and 9% and 50% at 6 months, respectively.

At the end of the study, one patient (in PR before 153Sm-EDTMP treatment) with SD at day 60 and tumor progression (both osseous and extra-osseous) 14 months after treatment is still alive with active disease. One patient treated with a tandem infusion (total activity 18 mCi/kg), with SD after the first administration, had osseous progression 4 months after the second one and died of disease at 34 months from the first therapy. As reported in Figures 2 and 3, no statistical differences emerged according to the 153Sm-EDTMP administered or 24-h retained activity. In brief, patients who were given ≤10 mCi/kg had a median PFS of 57 days, patients with >10 to 20 mCi/kg had a median PFS of 60 days and patients with >20 mCi/kg had a median PFS of 64 days (P = 0.71). The analysis of PFS according to 24-h retained activity showed PFS of 48 (31–182 days), 54 (31–153 days) and 100 days (18–152 days) for patients with <3 mCi/kg, ≥3 to 7 mCi/kg and ≥7 mCi/kg at 24 h from treatment, respectively (P = 0.55). When we considered patients with combined disease to patients only with osseous disease, the median PFS was 61 and 114 days (P = 0.47), respectively. Patients having PD at 153Sm-EDTMP had a median PFS of 47 days compared with 61 days (P = 0.81).

The comparison of 1-year OS for patients treated with 153Sm-EDTMP >20 mCi/kg to others showed a no statistically significant higher survival for the first group (50% versus 22%, P = 0.48); the role of 153Sm-EDTMP benefits on survival was also confirmed when patients were stratified according to 24-h retained activity. OS was 379 (range 56–439) and 221 days (range 31–1175) for patients with ≥7 24-h retained activity.

Toxicity
All patients were examined for toxicity. No immediate 153Sm-EDTMP infusion-related toxic effects were observed. No treatment-related deaths were documented, and none of the patients experienced life-threatening extra-hematological toxicity.

After HSC infusion, the median time to recover an absolute neutrophil count >0.5 × 10⁹/l was 10 days (0–37), median time to >50 × 10⁹/l platelets was 18 days (13–47) and median time to Hb >10 g/dl was 20 days (0–32). One female patient with iliac bone disease (lesion of 7.5 × 5.5 × 5 cm) did not recover until tumor progression and finally died of disease. Severe infectious complications occurred in one patient; six patients had gastrointestinal toxicity (in two cases, grade III–IV).

Pain palliation after 153Sm-EDTMP
The pain relief following 153Sm-EDTMP was minimal because of early pain flair following radiometabolic treatment together with rapid disease progression in most cases. In brief, only 1 out of 16 assessable patients had pain relief at 1 week (6%), 9 patients (56%) at 1 month and none at 4 months.

Biodistribution and kinetics
Figure 4 shows four examples of retained activity curves in which the large patient dependence of uptake can be observed. The kinetics of 153Sm-EDTMP consists of two clearly different phases: a first phase of ~6 h in which the urinary excretion
Table 2. Main characteristics of patients at study entry, $^{153}$Sm-EDTMP data, response and pain relief

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>State at entry</th>
<th>Previous treatment</th>
<th>Disease at entry</th>
<th>Pain at entry</th>
<th>State at $^{153}$Sm-EDTMP</th>
<th>Dose level (mCi/kg)</th>
<th>24-h activity (mCi/kg)</th>
<th>Best response (day 60)</th>
<th>Time to progression (days)</th>
<th>Site of progression</th>
<th>Clinical benefit at 4 months</th>
<th>Pain relief at 1 week</th>
<th>Pain relief at 1 month</th>
<th>Pain relief at 4 months</th>
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<td>&gt;7</td>
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AWD, alive with disease; CE, Cyclophosphamide–Etoposide; SX, surgery; DOD, dead of disease; extra, extra osseous; HD-IFO, high-dose ifosfamide; HDCT, high-dose chemotherapy; MAP, standard methotrexate–doxorubicin–cisplatinum; ND, not done; NE, not evaluable; NR, refractory; PD, progressive disease; PR, partial response; refractory, oss, osseous; oss + ex, osseous and extra-osseous; Rec, recurrence; SD, stable disease; TG, Taxotere/Gemcitabine; CR, complete response.
and the bone uptake are completed and a second phase in which activity decreases as a single exponential function.

For the 15 patients with data available, the residual 24-h activity was calculated multiplying the fraction of injected activity for administered activity; the results are reported in Table 2. The median time lapse was 30.3 h (range 8.7–42.9), the median residual 24-h activity was 33% (range 11%–77%) of the delivered activity, confirming a large intrapatient dependency, resulting in a median 24-h activity of 4.13 mCi/kg (range 1.37–12.46).

We did not observe any significant differences when we compared the time lapse for patients receiving ≤10, >10 to 20 or >20 mCi/kg 153Sm-EDTMP. When we compared the 24-h retained activity, we observed significant differences between patients having received >20 mCi/kg compared with others (8.35 versus 3.08 mCi/kg, P = 0.001). Finally, when we compared the percentage of 24-h retained to the given activity, there were no significant differences [33%, 31% and 32.5% for patients receiving ≤10, >10 to 20 or >20 mCi/kg, respectively (P = NS)].

**discussion**

This study of 22 unselected consecutive bone metastatic patients with heavily pretreated recurrent osteosarcoma confirms the poor prognosis of patients with skeletal metastatic disease from osteosarcoma.

Three recent papers reported the outcome in patients with nonmetastatic osteosarcoma, treated with surgery and chemotherapy, who first relapsed with bone metastases. The Rizzoli experience reported a 5-year OS of 13% in 52 patients with bone metastases [26]. Aung et al. [27] reported in 23 patients treated at Memorial Sloan–Kettering Cancer Center a 5-year post-relapse survival of 33%. Patients having relapse-
free interval (RFI) longer than 2 years had a 5-year disease-free survival of 61% while it was only 8% in case of a shorter RFI. Jaffe et al. [28] reported that 5 of 11 patients survived 20–50 months following bone metastases.

Targeted radiotherapy with high-dose $^{153}$Sm-EDTMP might represent an option for both its antineoplastic effect and for pain control in patients who had multifocal osteosarcoma, with no possibility of surgical removal or having progressed after first- or second-line chemotherapy [13]. High-dose $^{153}$Sm-EDTMP for osteosarcoma patients has been proposed since 2002 by the MD Anderson group and their experience showed good tolerability together with significant low toxicity when radiometabolic treatment was followed by stem cell rescue. Other groups recently reported on osteosarcoma bone metastatic patients given low doses up to 44.8 MBq (1.21 mCi/kg). These authors reported on 13 assessable patients in whom 5 (38%) had SD at the end of the study while the median estimates for PFS was 51 days. Thereafter, the same group treated 11 high-risk osteosarcoma patients with tandem doses of $^{153}$Sm-EDTMP (37–51.8 and 222 MBq/kg) followed by stem cell rescue after the last infusion, with a limited toxicity and evidence of disease stabilization and tumor necrosis in 44% of patients. Nevertheless, all the patients had tumor progression with a median time of 79 days [29, 30].

In our study, $^{153}$Sm-EDTMP was delivered at various dosages and was followed by autologous HSC rescue. Even when administrated at >20 mCi/kg, we did not observe objective response. This would mean that, also in the case of higher 24-h retained activity, $^{153}$Sm-EDTMP is ineffective against relapsed osteosarcoma or the residual activity is too low to be active on these particular subsets of patients. As reported by Essman et al. [31], some areas of bone lesions may have poor $^{153}$Sm-EDTMP uptake due to the intrinsic heterogeneity of the tumor and that could result in undertreating parts of tumor which lack bone formation. Besides, there may be some tumor cells that did not receive enough activity because of the radiobiological characteristics of a beta emitter, such as $^{153}$Sm, in particular its pattern of energy deposition in the track of the particles and the induced DNA damage [32, 33]. The areas undertreated, due to these probable and other unknown variables, may be the ones that progress most rapidly, even in the patients having received higher $^{153}$Sm-EDTMP.

In fact, this might explain no advantage in terms of PFS compared with patients having received lower $^{153}$Sm-EDTMP. The PFS is dramatically short even when higher doses of $^{153}$Sm-EDTMP are administrated and the 1-year Kaplan–Meier estimates of PFS are substantially homogeneous when comparing the administrated and residual 24-h activity. The clinical benefit at 4 months was reached for only 32% of the whole patient cohort. It was also 32% for patients who received >20 mCi/kg. The 4-month clinical benefit was observed only in patients with SD (five patients) and PR (two patients). No patients with PD at $^{153}$Sm-EDTMP benefited from even higher $^{153}$Sm-EDTMP and, more importantly, no patient following $^{153}$Sm-EDTMP treatment underwent surgery.

We observed a 4-month clinical benefit for patients whose 24-h retained activity was over 7 mCi/kg, in which the 4-month PFS was 60%. However, these few patients also experienced tumor progression by day 155, except one patient who had SD for 14 months. As reported above, the analysis of OS did not significantly differ when we compared the delivered activity of $^{153}$Sm-EDTMP to its residual 24-h activity, being 28% at 1 year.

According to the MD Anderson data, the comparison of 1-year OS for patients treated with higher $^{153}$Sm-EDTMP than others showed a higher probability of survival for the first group (50% versus 22%, $P = 0.48$); the role of $^{153}$Sm-EDTMP benefits on survival was also confirmed when patients were stratified according to 24-h retained activity. We were thus able to demonstrate an OS advantage for patients with 24-h retained activity >7 mCi/kg compared with patients who had 24-h activities <3 mCi/kg or 3–7 mCi/kg (data not shown). This data should be kept in mind when patients are considered for $^{153}$Sm-EDTMP for palliation. In such cases, a provisional bone scan with a monitoring of 24-h residual activity might suggest the earliest timing for HSC reinfusion to reduce hematological toxicity.

Despite the absence of significant extra-hematological toxicity, the benefit of this approach is minimal in regard to...
observed responses and in terms of PFS. This remains when we also consider the uptake of $^{153}$Sm-EDTMP; however, it should be mentioned that higher uptake means longer survival. The discrepancy in terms of OS and PFS might simply be supported by the low number of patients treated with this protocol. Furthermore, all relapsed patients underwent further therapies that might have an independent role on survival. A number of patients experienced pain relief soon after $^{153}$Sm-EDTMP administration, and this was followed by pain relief only for a minority of patients. Since the aggressiveness of the disease, none of the patients discontinued opiate treatment. In particular, $^{153}$Sm-EDTMP gave a significant benefit for only 2 out of 5 pediatric patients with unresolved bone pain on analgesic drugs. Following tumor progression, some patients received external beam palliative radiotherapy, but also in these cases, it was a short-lasting benefit.

In conclusion, we found that radiometabolic treatment with $^{153}$Sm-EDTMP followed by HSC rescue is feasible also for highly treated patients. However, its role in controlling osteosarcoma progression is minimal in a large portion of patients, even when it is administered at high dosages, and, finally, this approach offers no distinct advantages over other palliative approaches.

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disclosure

The authors declare no conflicts of interest.

references