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THERAGNOSTICS OF SAMARIUM-153-EDTMP IN PATIENTS BEARING PROSTATE CANCER AND OSSEOUS SECONDARIES: PALLIATIVE BUT ALSO TUMOURICIDAL

Urology

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ABSTRACT

BACKGROUND: The radionuclide samarium-153 (^{153}Sm) in a chelated compound with ethylene-diamine-tetramethylene phosphonate (EDTMP) is mainly used as an alternative to palliative therapy of multifocal painful osseous metastases due to various primaries, especially prostate, breast, lung cancer, and osteosarcoma. Considering novel aspects of chemical properties attributed to ^{153}Sm, we aimed at evaluating the outcomes of solitary versus repeated ^{153}Sm-EDTMP or exclusive opiate therapy in patients with osseous secondaries from prostate cancer.

MATERIALS AND METHODS: In the present retrospective study, we included three groups of patients with hormone-refractory prostate cancer (HRPC) and multiple painful osteoblastic or mixed secondaries confirmed by bone scintigraphy. Forty-three patients (Group A) received 2 consecutive intravenous (i.v.) administrations of ^{153}Sm-EDTMP (37 MBq/kg of body weight each), twelve patients (Group B) received a solitary i.v. dose ^{153}Sm-EDTMP and 12 patients (Group C) used solely opiates due to exclusion criteria regarding radiometabolic therapy.

RESULTS: Pain palliation was reported by 90.7% of group A patients after the second injection. The repeated dose of ^{153}Sm-EDTMP improved the duration of pain response to 24±6 versus 8±2 weeks of the single dose treatment plan, without significant myelotoxicity. Group C patients were considered as non-responders owing to increased pain score and consumption of analgesics.

CONCLUSION: A repeated-dose ^{153}Sm-EDTMP treatment scheme consistently provides enhanced pain alleviation, thereby preserving quality of life in patients with skeletal metastases from HRPC. Interestingly, radiometabolic therapy with ^{153}Sm-EDTMP effectuates tumouricidal implications, thus upgrading a palliative agent to a disease theragnostics-targeted modifier, with anticipated survival benefit.

KEYWORDS

Samarium-153, EDTMP, hormone-refractory prostate cancer, pain palliation, radiometabolic therapy, tumouricidal

1. INTRODUCTION

Prostate cancer (PCa) ranks as the 2nd most common malignancy in men whilst also exhibiting up to 70% metastasis rate to the bones (Forman et al., 2014). The skeleton is the most frequently invaded tissue in patients suffering from hormone-refractory prostate cancer (HRPC) (Bantis et al., 2009). Pain is the most common related complication, being usually localized and sometimes intolerable. Not surprisingly, bone invasion can significantly lower both quality of life and survival expectancy of these patients (Keller et al., 2004).

Various therapeutic approaches have been hitherto tried in metastatic bone pain alleviation, specifically analgesics [non-steroidal anti-inflammatory drugs (NSAIDs) and opiates], hormones, radiotherapy, chemotherapy, local surgery or anaesthesia, immunotherapy, bisphosphonates, and, last but not least, radionuclide therapy. Multidisciplinary cooperation ensures the best individualized treatment in the correct sequence. In the framework of osteoblastic or mixed skeletal metastases with intense uptake on bone scintigraphy, pain relief can be achieved by the systemic administration of bone-seeking radiopharmaceuticals employing the physicochemical assets of β- and α-emitting radionuclides. In terms of theragnostics, the most widely applied relevant radiopharmaceuticals heretofore are β-emitters strontium-89-chloride ($^{89}SrCl_2$) (Baziotis et al., 1998), rhenium-186-etidronate or -hydroxyethylidene-1,1-diphosphonate (^{186}Re-HEDP), and samarium-153-ethylene-diamine-tetramethylene phosphonate, ^{153}Sm-EDTMP, ^{153}Sm-lexidronam). More recently, the α-emitter radium-223-dichloride ($^{223}RaCl_2$, alpharadin) has been introduced into clinical practice and authorized in the US and the European Union since 2013 (EMA, 2018). The choice of radiopharmaceuticals may vary in different countries depending on radiopharmaceutical availability (Table 1) (Bodei et al., 2008). Nowadays the focus shifts on exploiting multiple kinds of radiopharmaceuticals and combining radionuclide therapy mainly with chemotherapy to increase treatment efficacy (Sideras et al., 2012; Ferreira et al., 2012).

Table 1 ***Approval for the Clinical Use of Each Radiopharmaceutical May Differ Among Countries***

Radiopharmaceutical	Indication: skeletal secondaries imaged as osteoblastic or mixed lesions upon bone scintigraphy
$^{89}SrCl_2$	from primary breast or prostate cancer (established indications) or any other tumour type in Europe
^{153}Sm-EDTMP	
^{186}Re-HEDP	
$^{223}RaCl_2$	from HRPC without lymph node >3cm/visceral invasion

The radioisotope ^{153}Sm is chelated with the calcium salt EDTMP in the stable complex ^{153}Sm-EDTMP, which reduces pain by adhering to each bone metastasis, in terms of theragnostics. The average recommended ^{153}Sm-EDTMP administration dose (2590 MBq in commercial kit) yields a dose 20fold higher to each metastatic site than the dose to bone marrow (Quadramet, 2008). Still this effect is translated in 90% of patients into grade I or II thrombocytopenia and/or leukopenia, reaching a nadir during the 4th-6th week postinjection (p.i.) and consistently recovering at pretherapy values by the 6th-12th week. Consequently, inherent limitations of ^{153}Sm-EDTMP are anchored in possible side effects, including myelotoxicity and rarely hematuria, cough, nausea, vomiting, back pain, or fever. The purpose of this study

was to appraise the efficacy and safety of solitary versus dual ^{153}Sm-EDTMP or exclusive opiate administration in patients with multisite painful osseous metastases due to HRPC.

2. MATERIALS AND METHODS

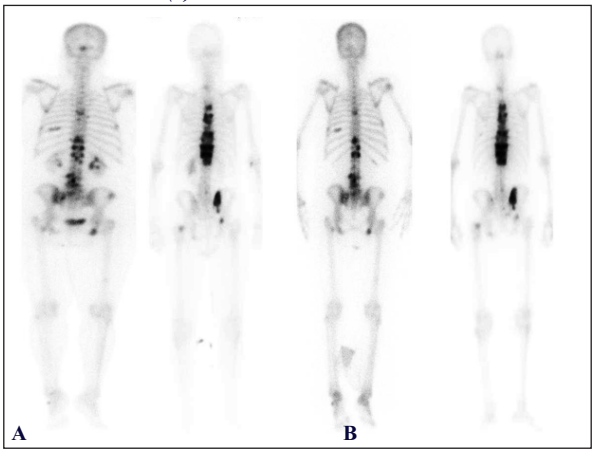
We retrospectively evaluated forty-three patients (Group A), 12 patients (Group B), and 12 patients (Group C) suffering from multiple painful skeletal secondaries due to HRPC, who were selected for repeated or solitary ^{153}Sm-EDTMP radionuclide therapy, and opiates, respectively (Table 2). Guideline-based eligibility criteria for radionuclide therapy (Bodei et al., 2008) were not fulfilled by Group C patients who were thus exclusively treated with opiates. Skeletal secondaries were detected on a baseline bone scintigraphy (BS) with technetium-99m-MDP (^{99m}Tc-MDP) within the previous 3-month interval on a single (Millenium GE, Milwakee, USA) or dual (Symbia Siemens, Erlangen, Germany) head γ-camera, using a 15% window centered at 140keV (Figure 1a). Parameters influencing the decision for choosing this treatment involved the extent of metastatic burden on BS, the hematological profile, recent supply of myelosuppressive treatment, performance status, and survival expectancy. Previous conventional treatment had been terminated at least 4 weeks prior to ^{153}Sm-EDTMP or opiates. None of the patients had received external hemibody radiotherapy and all provided written informed consent. There was no statistically significant difference between the three groups as to the duration of the disease.

Table 2 *Patient Characteristics*

	Group A	Group B	Group C
Number of patients	43	12	12
Age range (years)	54-81	65-80	58-79
Previous treatment modalities:			
Hormonal therapy	yes	yes	yes
Local Radiotherapy	yes	yes	yes

Patients from groups A (n=43) and B (n=12) received an intravenous injection of 37 MBq/kg of body weight (BW) of commercially available ^{153}Sm-EDTMP (Quadramet®, CIS bio international, Gif-sur-Yvette Cedex, France) on an outpatient basis. Injectable solutions of a ^{153}Sm-EDTMP Na(Ca) complex were obtained as single-dose 15 mL glass vials. Whole-body scans were performed 4 or 24 hours p.i. to confirm radiopharmaceutical retention in osteoblastic secondaries (Figure 1b). All Group A patients received further same dose treatment(s) within 3-5 months in up to 4 sessions, after recovery of their hematologic indices and symptom persistence or relapse.

Figure 1 *Whole Body Scans in Posterior Views with ^{99m}Tc-MDP (a) and ^{153}Sm-EDTMP (b) in Two Patients*



Pain was evaluated using a patient-rated pain intensity visual analogue scale (VAS). Each patient was asked to score pain on a 10-step scale, 0 being nearly no pain and 10 the maximum level of pain. An average weekly pain score was derived from the daily pain scores. The use of analgesics, their doses, and their use intervals were also recorded. Patients' responses were classified as complete (pain-free without analgesics), partial (VAS pain intensity attenuated for ≥2 steps for a minimum of two weeks, requiring NSAIDs but not opiates) and absent response (pain score increased). Myelotoxicity was evaluated by measuring full blood count weekly for an 8-week-period and then monthly; levels of WBC, PLT, and Hb were recorded. Absolute and percent variations of these parameters were calculated and compared with basal values obtained 1 week prior to treatment. The flare phenomenon, a transitory worsening of pain after treatment, was recorded as a greater-than-2-point increase in the pain scale within 5 days after the administration of ^{153}Sm-EDTMP. Six to nine months after treatment onset, all patients underwent a new BS which was compared with their baseline scan.

3. RESULTS

A total of 44 group A and B patients (80%) responded after one therapy with ^{153}Sm-EDTMP, implicating twenty-two with a complete response and twenty-two patients exhibiting a partial response (Table 3a). Pain palliation was reported by 90.7% of group A patients after the second injection. Out of the eight (group A) non-responders, 4 sufferers did ultimately respond after the second treatment cycle, experiencing a complete response. Also, five patients with a partial response to the first treatment actually became pain-free after the second ^{153}Sm-EDTMP cycle (Table 3b, Graph 1). Among the thirteen patients who demonstrated partial response after the second therapeutic cycle, two patients were administered another equal dose, one patient received 2 more doses and one patient 3 additional cycles. Four out of 43 patients unfortunately did not respond even after the second administration cycle and were not further treated with ^{153}Sm-EDTMP, in order to avoid possible cumbersome toxicity problems in the absence of any positive feedback.

Table 3a *Patient Response to Treatment, Duration of Response and Incidence of Myelotoxicity ^{CR}Complete Response, ^{PR}Partial Response, ^{NR}No Response*

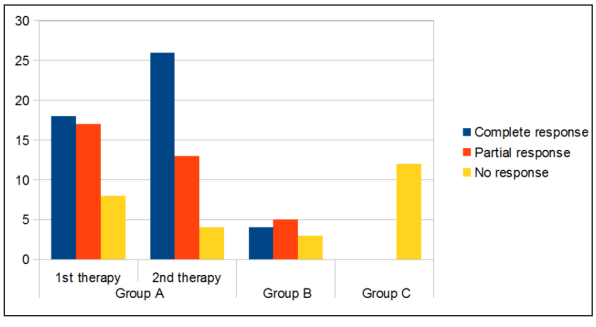
	Group A	Group B	Group C
Response to treatment (CR+PR)	39 (90,7%)	9 (75%)	NR
Duration of response (weeks)	24±6	8±2	-
Myelotoxicity	3 (7%)	-	-

Table 3b *Patients' Pain Response to Radiometabolic Therapy with ^{153}Sm-EDTMP*

	Group A		Group B
	1st therapy	2nd therapy	
	No of patients		
Complete Response	18	26	4
Partial Response	17	13	5
No Response	8	4	3

Graph 1

Patients' Pain Response to ^{153}Sm-EDTMP Solitary or Dual Radiometabolic Therapy versus Opiate Treatment

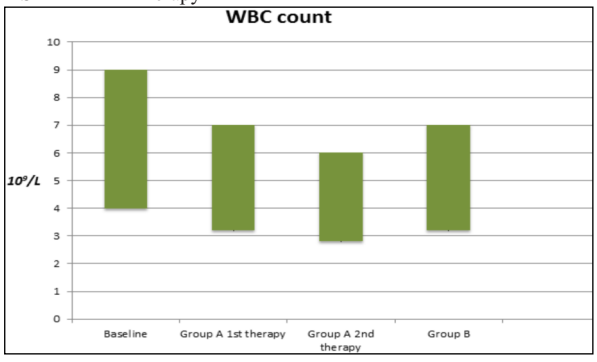


The therapeutic effect started to evolve at day four-to-7 after administration of radiometabolic treatment. The second injection of ^{153}Sm-EDTMP prolonged the analgesic effect in group A patients when compared with those of group B, who only received a solitary treatment cycle (24±6 weeks versus 8±2 weeks, respectively). The patients who received 3-5 radiopharmaceutical doses were statistically non-evaluable; yet, none manifested notable toxicity and all presented increasing alleviation of pain leading to a better quality of life. On the contrary, all group C patients endured a significant increase in their pain score during the entire follow-up period. These patients were

considered as non-responders owing also to the accompanying increase in the consumption of analgesics.Regarding adverse effects, a temporary and mild subsidence of hematologic parameters was observed in 40 group A patients and all group B patients (Graphs 2 and 3). With the exception of two patients, white blood cells and haematocrit did not drop more than 15% and 10%, respectively from baseline, whilst mostly remaining within normal limits, with the exception of only one patient who exhibited a significant reduction (32.5%) of his WBC count (nadir of $2.9x10^9$/L with baseline value: $4.3x10^9$/L) 2 weeks after the first therapy and recovered spontaneously within 5 weeks. Platelet counts never dropped more than 30% from baseline, except for two group A patients who showed relatively severe PLT count fall (nadir values: $46xl0^9$/L and $30xl0^9$/L with respective baseline: 135x $l0^9$/L and $120xl0^9$/L) two weeks after the second therapy. One of them also presented with a twelve-unit drop of his Hct value, i.e. 26% versus baseline value: 38.2%, leading to his hospitalization for blood transfusion. The other patient's grade 3 thrombocytopenia after the 2nd dose**,** was spontaneously revocable within 6 weeks.

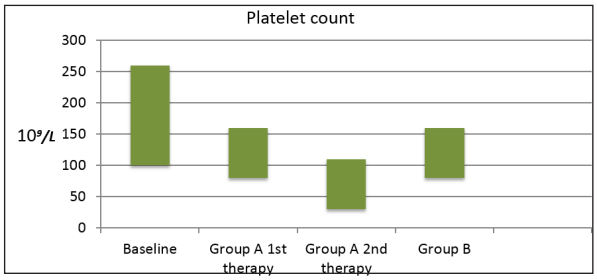
Graph 2

Patients' White Blood Cell Count at Baseline and After Solitary or dual ^{153}Sm-EDTMP Therapy



Graph 3

Patients' Platelet Count at Baseline and After Solitary or Dual ^{153}Sm-EDTMP Therapy



No other side effect was ascertained, apart from a small percentage (9%) of the flare reaction, which was reported by the responders and was conservatively handled with proper adjustment of their medication without, as expected, exceeding 5 days p.i. of ^{153}Sm-EDTMP.

4. DISCUSSION

Skeletal metastatic ontogenesis of PCa entails both site-specific molecular adhesive interactions and anatomical elements, videlicet the Batson venous plexus. A positive correlation has been established between the metabolites of type I collagen synthesis and breakdown, reflecting the sequent appearance of PCa bone metastases as osteoblastic or mixed rather than purely osteolytic (Zissimopoulos et al., 2009). Tumour cells harbouring bone provoke morbid bone remodelling with significant skeletal hindrances, including pain. Metabolic irradiation accomplishes destruction of both PCa cells and bone microenvironment, hence disrupts their complex cross-talk avoiding reappearance of metastases and improves clinical outcomes.

Therapeutic strategies against osseous secondaries, characteristically require both analgesic and antitumour compounds, while alternatives are explored for recalcitrant cases. Several tumor- and bone milieu-related factors of the metastatic cascade comprise therapeutic targets, since they appear to modulate cancer-related pain sensitization and/or actively partcipate in the processes of osteoblastogenesis, osteoclastogenesis, angiogenesis (Keller et al., 2004; Paterson et al., 2013), peritumoural lymphangiogenesis, and cancer cell division, with resultant increased invasion and metastasis leading to shortened survival (Page-McCaw et al., 2007). Blocking nuclear factor κB ligand (RANKL) (Keller et al., 2004) represents a well-established standard of care via denosumab (Weilbaecher et al., 2011)**.**

Similarly, systemic theragnostics utilizing bone-seeking isotopes like ^{153}Sm, has been rendered traditional from alternative (Scherr et al., 2003). The therapeutic action of ^{153}Sm-EDTMP is effectuated through the emission of radioactive beta particles deposited at multilevel metastatic bone burden based on targeted bone-avidity. The favourable physical characteristics of ^{153}Sm (Table 4), with a $t_{1/2}$ of 46.27h and maximum beta-particle energies of 0.81MeV (20%), 0.71MeV (50%), and 0.64MeV (30%) permit optimum internal radiotherapy whilst gamma emission of 103keV (29%) enables prospective individualized estimation of absorbed dose to metastases and bone marrow. Biodistribution with accumulation of applied ^{153}Sm-EDTMP into metastatic bone sites is routinely imaged on conventional γ-camera, with low exposure rate (Resche et al., 1993). Sm-153-EDTMP concentration in osteoblastic metastases has been estimated 5fold higher per gram than in the normal bone (Eary et al., 1993; Maini et al., 2004). The relatively brief $t_{1/2}$ of ^{153}Sm, delivers the metabolic irradiation dose within a short time interval at a high rate, thus allowing for dose fragmentation (Baziotis et al., 1998; Sinzinger et al., 2011). Keeping in mind the dose-dependent pattern of myelosuppression (Turner et al., 1991)**, t**he most cost-effective activity is 37 MBq/kg (Baziotis et al., 1998; Sinzinger et al., 2011; Turner et al., 1991; Baziotis et al., 2001), and this therapeutic dose is indicated for every patient bearing skeletal invasion irrespective of the primary cancer site (Bodei et al., 2008). Regardless of the dose, our experience invariably asserts the notion "the sooner, the better", as remarkably expressed by the colleagues who introduced the Vienna protocol **(**Sinzinger et al., 2011).

Table 4 *Physical Properties of Bone-Seeking Therapeutic Radionuclides ND Not Defined*

Physical property		$^{89}SrCl_2$	^{153}Sm-	^{186}Re-HEDP	$^{223}RaCl_2$
physical half-life (days)		50.5	1.95	3.72	11.4
maximum energy of principal emission: beta or alpha particle (MeV)		β: 1.46	β: 0.81	β: 1.07 (77%) 0.93 (23%)	α: 27.78
mean energy of principal emission: beta or alpha particle (MeV)		β: 0.58	β: 0.23	β: 0.349	α: 6.94
average soft tissue range (mm)		2.4	0.6	1.1	<0.01
abundant gamma emission (%) with a photo peak (keV)		0.01% 91	28% 103	9% 137	1.1% 81-84 (41%)
accummulation proportion in bone metastasis	versus healthy bone tissue	10/1	5/1	20/1	ND
	versus bone marrow	10/1	20/1	25/1	10/1
bone penetration (mm)		3.5	1.7	2.5	0.1
maximum soft tissue penetration (mm)		6.7	3.1	5	<0.1

Treatment with ^{153}Sm-EDTMP has been used in our country since the late 1990s as a palliative tool for painful bone metastases (Baziotis et al., 1998). The application of 0.37-37 Mbq/kg of this radiopharmaceutical has early provided promising results, with high pain relief rates effectuated within 5–10 days, coupled with a duration of 4-40 weeks (Turner et al., 1991; Turner et al., 1989; Farhanghi et al., 1992) and subsequent improved quality of life, sometimes with radiological and/or tumour marker melioration (Baziotis et al., 1998; Turner et al., 1989). Extended survival prospect is hitherto attributed to healthier eating and sleeping, less stress as well as easier cooperation. Re-treatment has been described to prolong the duration of pain response up to 52 weeks (Maini et al., 2004; Sinzinger et al., 2011; Turner et al., 1991; Baziotis et al., 2001; Higano et al., 2008) and increase survival from a median of 4 to 9 months (Turner et al., 1991).

Considering these setbacks and wishing to maximize the palliative effect of ^{153}Sm-EDTMP in patients with painful metastatic HRPC osseous lesions, we decided to administer the radioligand standard dose of 37 MBq/kg BW on two or more visits, leaving ample time inbetween for bone marrow recovery. By applying this repeated dose protocol, the observed palliative outcomes were satisfactorily augmented (90.7% versus 80%). All encountered haematotoxicity problems were of transient nature with spontaneous resolution, except for the one patient who had to be hospitalized for blood transfusion owing to grade 3 anemia (CTCAE v5.0, 2017), but soon recovered completely.

Long term follow-up of our patients after nine months, revealed osteoblastic lesion regression with partial recalcification of osteolytic metastases on BS as compared with corresponding baselines, insinuating a tumouricidal effect of ^{153}Sm-EDTMP, at least to a degree. The mechanisms for pain relief of skeletal secondaries through therapy with bone-seeking beta-emitters remain largely vague but include conjectural local effects of beta irradiation on bone metabolism and osteoblastic activity (Maini et al., 2004), which should be reappraised in conjunction with the EDTMP metal ion-chelatant properties that decouple osseous turnover. On one hand, bisphosphonates inhibit osteoclastic bone resorption and the EDTMP moiety in metabolic irradiation prefers the layer of osteoid undergoing mineralization due to intimate bond with hydroxyapatite crystals (Quadramet, 2004). On the other hand, targeted radiometal-based drugs are extraordinarily suited for hemisorption onto the shells of the skeletal hydroxyapatite in areas of accelerated bone turnover and undoubtedly have the ability to invoke a positive therapeutic effect on sufferers from skeletal secondaries, indicating that it is the samarium's affinity particularly for this interface between invading tumour and reactive bone that enables site-specific treatment (Weekes et al., 2016; Park et al., 2014).

Moreover, samarium's physical properties of a maximum penetration of 1.7mm in bone and 3.1mm in soft tissue can be sensibly perceived as both tumouricidal up to a degree and pain palliative through interrupting mechanical and humoral pain-inciting downstreams in the mileu of a mean±SD circulating PCa cell diameter of 7.97±1.81μm and cultured PCa cell of 13.38±2.54μm (Park et al., 2014), an osteoblast cell diameter of 20-50μm (Qiu et al., 2019), and around 50–70μm long endothelial cells (Félétou, 2011). Harnessing the physical and recently proven attractive chemical properties corroborates the achievement of site-specific concerted analgesic and tumouricidal implements of ^{153}Sm-EDTMP treatment on both bone lesions and microenvironment in the absence of grave adverse events.

In conclusion, even though this therapeutic scheme with ^{153}Sm-EDTMP was designed purely aiming at an augmented pain mitigation effect, the temporary arrest of disease evolution substantiates the appreciation of this radioligand as a disease theragnostics-targeted modifier in addition to its strong palliative outcome. Based on our continuing experience, repeated radiometabolic ^{153}Sm-EDTMP therapy may not halt PCa per se but halts further bone and potential lymphatic metastasis, ensuring patients' wellbeing with longer-lasting and more efficacious analgesia as well as anticipated survival benefit.

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