The Vienna protocol and perspectives in radionuclide therapy

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The Vienna protocol for [153]Sm-EDTMP-therapy is based on the experience of the last two decades. Repeated treatments at a low dose are applied by several authors in order to achieve the maximum therapeutic effect with the lowest haematological toxicity. Significant benefits on pain palliation and some regression are documented. In contrast to earlier claims, [153]Sm-EDTMP treatment should be started as soon as more than 1 bone lesion appears in bone scintigraphy and/or bone pain becomes evident. Prospective randomized controlled studies, however, are urgently warranted in order to assess benefits beyond bone pain palliation on an evidence base. The combination with chemotherapy as well as radiotherapy may further improve the clinical results. Further research should be directed to identify underlying mechanisms of response and predictors of benefit and to elaborate an improved therapeutic schedule for further enhancing the response rate.

KEY WORDS: Samarium ethylenediaminetetramethylenephosphonate - Bone and bones - Neoplasm metastasis - Palliative care - Bone metastasis.

Advances in cancer treatment improve prognosis, extend life but also significantly increase the number of patients experiencing skeletal recurrences. The major clinical problems are bone recurrences and associated pain for some malignant diseases even in prostate cancer, without major involvement of other organs. Bone pains then become common and a challenge for treatment for a large group of patients. Radionuclide pain palliation therapy with the potential bystander benefits should gain increasing relevance in the routine management of these patients. Bone seeking agents ([32]P, [89]Sr) have long been used for bone pain palliation in metastatic disease. Radionuclide pain palliation therapy with the potential bystander benefit of effects should gain increasing relevance in the daily routine management of these patients. It was the merit of Turner's group to address the benefits of a new radiopharmaceutical ([153]Samarium- ethylenediaminetetramethylene phosphonate ([153]Sm-EDTMP)) for the first time in experimental models as well as in patients.[1] EDTMP was chosen as the preferred complex.[2] However, [153]Sm-EDTMP (as well as rhenium) is underutilized for treatment of cancer pain in the skeleton.[3] Samarium and rhenium isotopes are used for pain palliation mainly due to physical advantages. After

Acknowledgements.—We are greatly thankful to H. Ahmadzadehfar, K. Atefie, H. Fischer, J. Flores, Susanne Granegger, S. Hann, E. Havlik, J. Hiltunen, Ch. Kratzik, Susan Meghdadi, Irmgard Neumann, R. Palumbo, Margarida Rodrigues, M. Wenger and K. Weiss who over about 2 decades contributed to the experience presented in this overview.

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achieving the approval from the Ethics Committee, [153]Sm-EDTMP treatment was introduced at the Vienna University Medical Hospital in 1992. It originally was aimed to alleviate bone pains at a rather late stage of bone recurrences. As a consequence of some impressive single cases and a more systematical evaluation of the results we rapidly switched from late and single treatment to the early and repeated [153]Sm-EDTMP application.

The Vienna protocol

The Vienna protocol we introduced in the mid 90ies of the last century is characterized by repeated treatments with 30 mCi (1.1 GBq) [153]Sm-EDTMP on an outpatient base. The treatments are performed 5 times in 3 month intervals during the first year, followed by another 5 treatments at 6 month intervals, then 5 therapies at 9 month intervals and thereafter indefinitely in 12 month intervals. Treatment intervals are reduced by 3 months in case of disease progression (radiography, MRI, scintigraphy, increase in tumor markers or a marked increase in pain).[4] The repeated treatment intervals were chosen on the fact that most patients were experiencing pain control over a period of about 3 months and started to show a decline in response thereafter.

Reasons and background of the Vienna protocol

The considerations underlying the key points of the protocol [4] were as follows. Comparing the bone uptake we did not find any difference between the 0.5 and 1.0 mCi/kg dose while the pain response remained stable up to 12 weeks in most of the patients in both groups. This 3 month interval is in agreement with the original proposal by Turner.[5] Between the patients exhibiting an uptake below and above 50 %; there was no significant difference in pain response for both 0.5 and 1.0 mCi/kg dose groups (Table I). The calculation of the single dose was derived from the maximum total dose allowed per year, while introducing the 3 month interval outpatient treatment was for the convenience of patients and relatives, as well as for the cost effectiveness. Outpatient treatment improves quality of life and allows a large number of patients to be treated.

TABLE I.—*Influence of dose and bone uptake on (duration of) pain response. Pain response apparently does not depend on either the administered dose or the bone uptake. Response starts to decline at the end of the 3 month follow-up period during the initial treatment.*

<50%		Uptake	>50%	
1 mCi/kg	0.5 mCi/kg	week	0.5 mCi/kg	1 mCi/kg
89.5	93.0	7	92.0	93.5
84.2	90.0	8	91.0	90.3
84.2	86.0	9	88.0	87.1
84.2	84.0	10	85.0	83.9
78.9	80.0	11	81.0	80.6
73.4	76.0	12	78.0	77.5
19	100	n	100	31

Values in %

Indication

Indication for the treatment is the presence of more than 1 positive lesion in bone scintigraphy ± bone pain.

Contraindications

Contraindications beside haematological parameters include severe spinal cord compression In contrast to the package insert where kidney failure is listed as a contraindication, it was reported that the effectiveness and safety have been proven in a haemodialysis patient.[6] After adjusting dose according to kidney function and considering haemodialysis intervals, treatment is rather easy to perform due to the rapid clearance of the agent from the blood stream after application. An earlier claim to introduce an 8 week interval between concomitant chemo- and radiotherapy can no longer be upheld. Our earlier *in vitro* data showed the highest uptake of [153]Sm-EDTMP by osteoblastic and osteosclerotic lesions as compared to osteoclastic ones, irrespective whether of primary or secondary origin.[7]

Hematological toxicity

Treatment with [153]Sm-EDTMP is well tolerated; no serious adverse events are seen. The red bone marrow is the critical organ. Haematological toxicity

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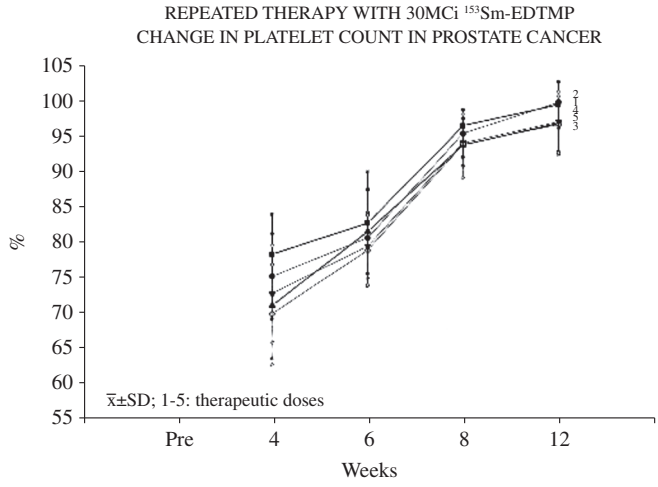

Figure 1.—Peripheral platelet count shows the nadir at 4 weeks with a prompt recovery thereafter. No difference is seen between treatments 1-5.

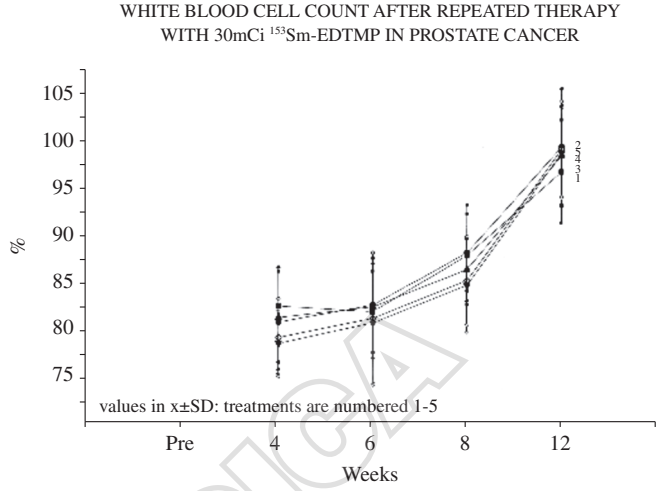

Figure 2.—White blood cell count is the lowest 4 and 6 weeks after treatment returning to pre-values at week 12. The variation is much smaller as compared to red blood cells;no difference can be seen between the number of treatments.

depending on the radionuclide used especially with [153]Sm-EDTMP is mild and transient. Platelets are the critical cells mostly affected.[8, 9] The nadir of platelet and white blood cell count has been reported to occur between weeks 2 and 5,[10] recovering quickly in 90 % of the patients at week 8.[11] The haematological toxicity seems to be dose-dependent[9, 12] and mainly influenced by the concomitant chemo- and/or radiotherapy as well as the number of treatments.[13] We saw the nadir of peripheral platelet count (Figure 1) at a mean of 27 days after therapy, followed by white blood cells (Figure 2) (30.7 days) and red blood cells (Figure 3) (37.7 days); (N.=200).[14] Uptake shows no correlation with both response and toxicity.[15] On this basis, the value of pre-therapeutic dosimetry may be questioned. Earlier chemo- and/or radiotherapy do not change type and extent of response, only pre-values may be lower. Up to 10 treatments we never saw a significant hematological problem. Even patients being treated more than 10 times according to the Vienna protocol (N.=104) did not exhibit severe haematological concerns. A particular challenge is the patient with diffuse bone marrow infiltration not meeting the usual (platelets $>1.10^5$/µL, red blood cells $>3.10^6$/µL, haemoglobin >12 g/l, hematocrit >30 %, white blood cells 3.10^3/µL) haematological inclusion criteria. Treating these patients under special surveillance surprisingly revealed excellent results (pain palliation, regression) even increasing rather than decreasing number of

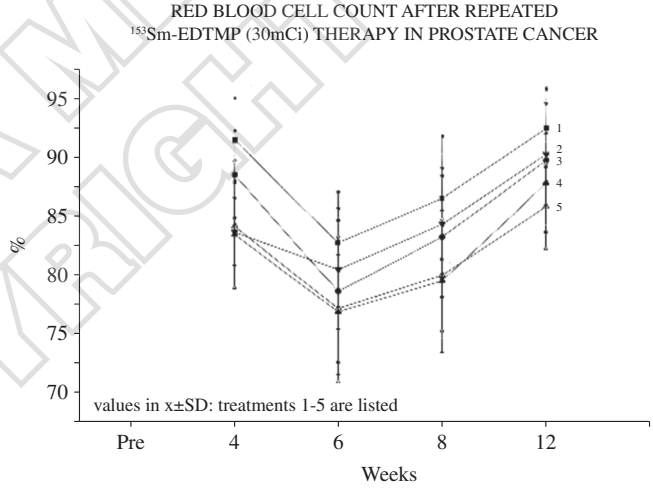

Figure 3.—The number of red blood cells shows the nadir at 6 weeks after treatment returning close to pre-values after 3 months. The number of treatments (1-5 in the Figure) does not significantly affect the behavior despite a wide inter-individual variation.

peripheral blood cells in most patients. Interestingly, assessing platelet function by various tests revealed that the decrease in peripheral platelet count is balanced by an increased functional activity per cell, while the total activity (expressed by the platelet aggregation response, thromboxane formation or platelet proteins determination) being almost unchanged.[16, 17]

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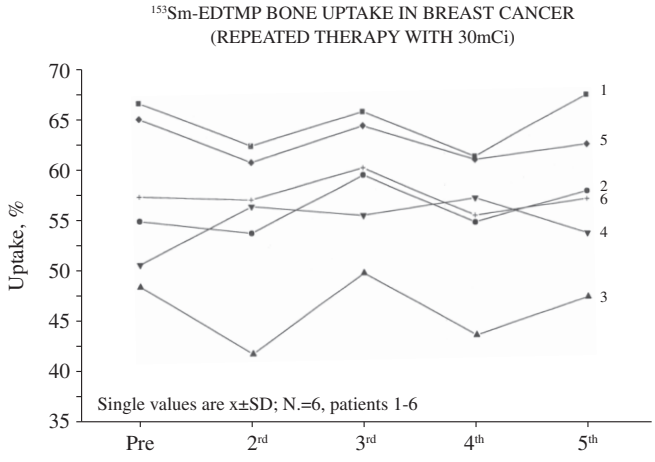

Figure 4.—The bone uptake remains rather stable during the first year with 5 treatments in 3 month intervals.

Dosimetry

Various investigations of dosimetry and calculation of the optimal dose have been performed [18] including the measurement of whole body retention at 6-24 hours, 24 hours urine excretion and determination of biodistribution by whole-body imaging and quantitation by regions of interest.[19-21] Measurements were done directly after [153]Sm-EDTMP administration [22] or using surrogate agents.[23] The calculation of both, bone-surface and bone-volume using the Monte Carlo article transport model, revealed that usually administered doses of [153]Sm-EDTMP are significantly low by about 37 %.[24] No proven value of dosimetry exists for the therapeutic outcome.

Attempts to use [99m]Tc-EDTMP instead of MDP dosimetry were not advantageous, because of the known problems with the preparation as well as the potential stunning effect if applied in short intervals.

Bone uptake

There is general agreement that MDP bone scanning reveals identical lesion sites as compared to [153]Sm-EDTMP.[3, 25, 26] Pretherapeutic scintigraphic identification of positive bone lesion uptake is mandatory.

Bone uptake has been reported to range between 29.0% and 86.6% (mean 56%).[27] These authors found a relation between the uptake and the benefit of the treatment while others did not.[15] Intraindividually, bone uptake seems to be rather constant (±5%) over repeated treatments (Figure 4), while the interindividual uptake varies considerably. Mixed osteoblastic/osteoclastic recurrences do not necessarily show a lower uptake as compared to pure osteoblastic ones. Introducing an interval to androgen oblation might influence tracer uptake as it has been shown with chemosensitization. In a retrospective analysis we found that the uptake was significantly lower ($P<0.01$), by about 5%, (48.7; 49.5; 47.6; 48.8 and 49.1% after the intake of antioxidant vitamins at 5 repeated treatments *vs* 52.9; 54.2; 53.4; 53.7 and 54.0% without antioxidant). Influence of the type and interval of dosing, to intake is unknown. The antioxidants might reduce resorption and uptake by inducing a shift in pH in the ruffled resorbing zone of osteoclasts.[28] Whether this also affects clinical outcome remains to be determined.

Bisphosphonates

Bisphosphonates affect osteoclast-mediated bone resorption and diminish skeletal complication rate. Combined application of bone seeking radiopharmaceuticals and bisphosphonates in the early days was considered as a contraindication assuming that there was a competition between the phosphate compounds at the bone level. However, later findings apparently revealed no clinically relevant interaction.

Sartor *et al.* excluded patients who received bisphosphonates less than 6 weeks before [153]Sm-EDTMP therapy.[29] There was no difference in uptake of [153]Sm-EDTMP in a patient treated with zoledronic acid two days before [153]Sm-EDTMP therapy.[30] Zoledronic acid treatment in combination with [153]Sm-EDTMP even resulted in a total pain relief and a significant decrease of PSA.[30] The number of reports showing no influence of bisphosphonates on bone uptake is overwhelming.[31, 32]

Flare phenomenon

A temporary increase in bone pain, usually occurs between 12 and 48 hours after the administration.[33] The information on the flare phenomenon, is greatly differing among several reports. The highest rate reported on the flare phenomenon reached 18.2%,[34] while others found 10%.[35] In a double-blind

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prospective multicenter trial flare appeared in 7.5% of patients on verum and 5% on placebo, reflecting a true rate of 2.5%.[36] In various subgroups of the patients we treated, prevalence of flare never exceeded 6%. In contrast to Tripathi *et al.* who claimed that the pain flare could predict a reduction in bone pain and therapeutic response we were unable to confirm this assumption.[37] Pain flare usually disappears completely between 7 and 10 days. In one patient, however, we observed a persistence of flare for over 5 weeks. Notably, regression response in this particular patient was large, while we were unable to discover any correlation in all our patients.

Pain palliation

There are a number of publications on the extent of pain palliation,[38] however, as the methodology of judging the benefit differs, the response is hardly comparable. An overview of the different judging criteria in breast cancer is reported by Maini *et al.*[9] Our patients' population was aged from 36 to 94 years. After a single therapy, the analgesic effect may last over half a year or even more in some patients, reaching the maximum of 50 weeks in one patient.[39] No difference in pain response has been reported between the prostate and breast cancer patients [15, 37, 40] or even hypernephroma patients (unpublished data) the lesions being more osteoclastic in nature. Histology of primary tumor apparently has no significant influence. It was claimed that generalized bone infiltration reveals better results as compared to a localized one. An earlier response was reported in patients with rib recurrences [41] in 136 patients. Another report found no correlation between bone scan patterns and response.[15] There is some disagreement whether pain response is dose-related or not, some authors report it,[42] others do not.[9, 41, 43, 44] Uptake was independent of dose and pain response in our patients (Table I).

Pain response usually starts early, in most cases within 5-7 days.[35, 36] Coronado *et al.* report that the mean duration of the analgesic effect is about 3 months.[45, 46] The Vienna protocol results in 85% response rate (21% complete, 40% moderate, 24% minor). Liepe reported a similar pain response between 70 and 80%.[10, 47]

Evaluating the improvement in mobility and decrease consumption of analgesics, Dolezal *et al.* reported 44% significant, 31% mild and 25% no response one month after the [153]Sm-EDTMP treatment.[48] The benefit at 3 months was decreased by 6% in significant responders and an increased in mild responders.[48] An improved Karnovsky score and a decreased analgesics consumption was also reported in the majority of reports.[48] Quality of life assessment revealed a significant improvement throughout the Vienna protocol treatment schedule (unpublished data). Papatheofanis *et al.* demonstrated that an improvement in the quality of life achieved by [153]Sm-EDTMP was comparable to that obtained with the use of opioids.[49]

Repeated therapy

Turner *et al.* 1991 in a phase II-study were the first to report on the success of repeated treatment.[5] His group originally introduced repeated treatment to maintain the analgesic effect claiming also a better pain control and survival. In the beginning they chose a 3-month interval in order to allow the recovery of peripheral blood cells and a decline in analgesic efficiency at the same time (Table I). The safety of repeated sequential multiple dosing has been confirmed later on by several authors,[50] without fixed schemes.[47, 51, 52] There has been no claim for a decreased quality of response with successive treatments.[11, 53] In our large series we did not observe any alteration in pain response.

Menda *et al.* reported that a patient receiving 11 doses of 1 mCi/kg, over a period of 28 months exhibited no significant hematological problems.[54] The maximum number of treatments reported until this date is 17, performed by our group, monitoring patients for more than 5 years, while 26 patients received more than 15 treatments until this date.[4]

Benefits beyond bone pain palliation

Regression/stabilization

Experimental studies revealed a delay in tumor growth and a postponed development of recurrences.[55] A cytostatic effect was reported by several authors. A 54-year old patient with multiple bone recurrences in the spine and the pelvic region, showed a negative whole-body scintigraphy and a PSA below 0.5 ng/mL, 7 months after treatment with 100 mCi (3.7 GBq) [153]Sm-EDTMP, the benefits per-

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TABLE II.—*Therapeutic response.The regression effect is significantly better for already existing lesions at the time of the treatment initiation as compared to the ones appearing during treatment.*

Lesions	Old	New
Compl. regression	6	0
Most lesions regressed	41	4
Significant regression	17	35
Minor regression	9	18
No change	15	12
Progression	12	31

Values in %

sisting for more than 3 years.[56] A tumoricidal effect as well as a PSA-decrease (judged on > 20% change) was reported even after single therapy with 1 mCi/kg.[36] A higher dose was claimed to be more effective by Collins *et al.*[42] The most pronounced response we have ever seen was in a 91 year old patient who has been treated for almost 5 years resulting in a PSA decrease from 541 to 14 ng/mL.[39] The patient finally died due to cardiomyopathy. An unexplained finding currently is that the lesions already existed at the initiation of [153]Sm-EDTMP treatment have responded significantly better as compared to the ones appeared during treatment (Table II). Disappearance of recurrences has not only been proven by scintigraphy, but also by computed tomography (CT) and magnetic resonance (MR).[14] Despite the small number of cases we demonstrated that even osteoclastic lesions favourably respond to [153]Sm-EDTMP therapy as seen on bone scintigraphy.[7] Baczyk *et al.* reported a better response in osteoblastic as compared to mixed bone lesions.[57] Figures 5, 6 are demonstrating lesion regressions in two cases. Figure 5 shows lesion regression in a patient even after a single dose of 30 mCi [153]Sm-EDTMP.

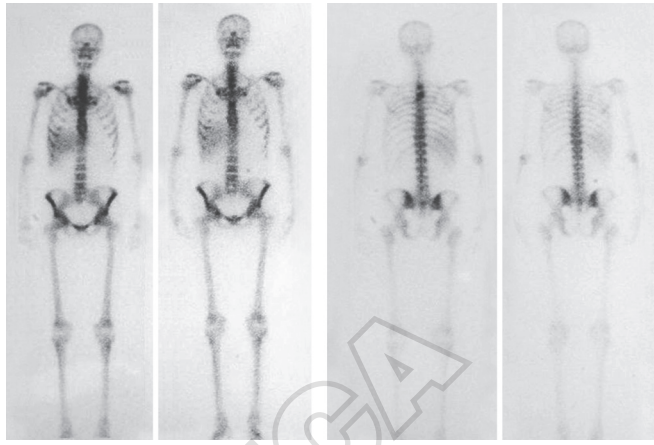

Figure 5.—Disappearance of recurrences in the vertebral column 3 months after first therapy with 30 mCi [153]Sm-EDTMP in a 44 years old male patient (P.M.) with lung cancer.

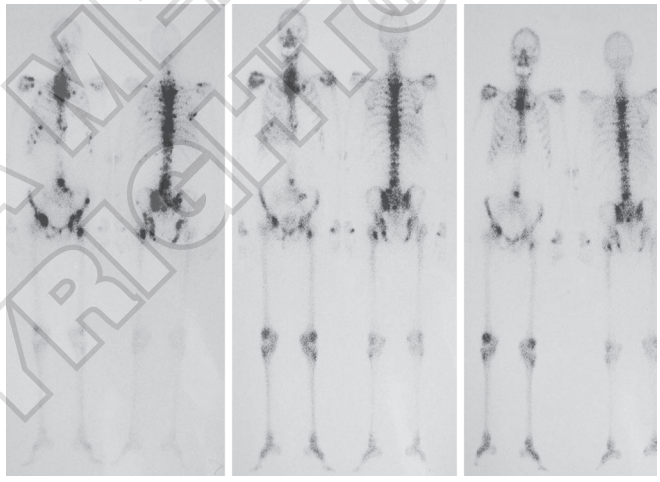

Figure 6.—Seventy-three-year old male (H.L.) suffering from hormone refractory prostate cancer;Post-therapeutic scans demonstrate regression after treatments 1, 3 and 4.

Tumor marker (indicator) response

In our prostate cancer patients PSA decline was more pronounced if the blood cell count was above $4.5x10^6/\mu L$ indicating the significant role of providing the source of free oxygen radicals. We also observed a correlation between haemoglobin and PSA-decline.

Comparing [153]Sm-EDTMP with cold [152]Samarium, Sartor *et al.* found a significant decrease in PSA in a prospective randomized, double-blind trial.[58]

A significantly greater reduction in PSA and serum prostatic acid phosphatase levels was seen in patients receiving higher doses.[42] We found no difference on the PSA response between 0.5 and 1.0 mCi/kg [153]Sm-EDTMP doses (Table III). Similarly, PSA-values throughout the initial treatment (Table III) showed that findings were quite com-

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TABLE III.—*Influence of dose and bone uptake on PSA-response. PSA shows a decline following a temporary increase after [153]Sm-EDTMP injection in the majority of the patients before the next therapy. This seems to be independent of the dose administered as well as of the extent of bone uptake.*

	<50%		Uptake	>50%	
	1 mCi /kg	0.5 mCi/kg	Dose	0.5 mCi/kg	1 mCi/kg
Week 3-9	63.2	66.0	↑	65.0	64.5
	10.5	7.0		9.0	9.7
	26.3	27.0	↓	26.0	25.8
Week 12	21.0	22.0	↑	24.0	22.6
	5.3	6.0		8.0	9.7
	73.7	72.0	↓	68.0	64.5
	19	100	N	100	31

↑increase; ↓decrease; unchanged (values in %)

parable in both dose groups, as well as in patients with an uptake below and above 50%, indicating that the higher dose does not offer a significant advantage.

Apparently, there are 3 types of PSA-response,[59] an immediate decrease in about a quarter of the patients, similarly a continuous increase despite therapy and a drop after a temporary increase (Table III). In breast as well as in prostate cancer patients we have observed a significant decrease in adhesion molecules known to determine metastatic spread in a wide range of malignancies.

Patients' survival

A prolonged patients' survival has been reported with high [153]Sm-EDTMP doses by Collins *et al.* and Resche *et al.*[42, 60] Resche observed a significantly better pain score using 1 mCi/kg (N.=55) *vs* 0.5 mCi/kg (N.=59). The survival was also better with the higher dose in breast cancer patients.[60]

Influence of statins

In this context it is of interest that statins as well as bisphosphonates are inhibitors of tumor proliferation inducing apoptosis along the cholesterol synthesis pathway and via the antiangiogenic properties.[61] Statin use was associated with a lower PSA, being most pronounced with simvastatin.[62] How [153]Sm-EDTMP even further enhances this benefit or interacts with these mechanisms is unknown.

Retrospective analysis of patients being on statins for treatment of hyperlipidemia revealed no difference in uptake of [153]Sm-EDTMP, flare phenomenon and haematological response. The effect of therapy on PSA in prostate cancer patients (32 *vs* 18% [1st therapy], 35 *vs* 17% [2nd therapy], 37 *vs* 17% [3rd therapy])[63] and on the adhesion molecules (ICAM, VCAM, E-selectin) were significantly (P<0.01) more pronounced (unpublished data). Whether dosing, substance specificity, extent of lipid lowering or duration of therapy are causative, remains to be established. Treating patients to target lipid values with statins, anyway, may be recommended meanwhile. In our hands, 53% of the prostate cancer patients and 42% of breast cancer patients meet the criteria of lipid lowering treatment according to the Austrian cholesterol consensus.[64]

Concomitant chemotherapy

Concomitant chemotherapy seems to enhance therapeutic benefit.[65] Retrospective analysis in patients receiving concomitant chemotherapy showed a significantly enhanced benefit concerning PSA, pain palliation and survival without additive toxicity.[8] On the other hand, the great many therapeutic scientific studies particularly in patients with prostate cancer do not allow any concomitant treatment such as [153]Sm-EDTMP minimizing the oncologists' motivation for referral. Vice versa, the repeated chemotherapies in breast cancer patients make it difficult to judge the benefits of [153]Sm-EDTMP beyond bone pain palliation.

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TABLE IV.—*Total radiation dose for red bone marrow due to [152]Eu, [154]Eu and [156]Eu after repeated therapies. Radiation dose due to Eu-impurities significantly increases because of the repeated [153]Sm-EDTMP therapy and longer patient survival.*

Therapies	Interval to first therapy	Total dose 1 year after last therapy (mGy)	mSv	Total dose 5 years after last therapy (mGy)	mSv
1	_	9.4	1.1	41.2	4.9
5	1 y	69.7	8.4	223.6	26.8
9	3 y	219.2	26.3	475.5	57.1
12	5.25 y	429.9	51.6	742.9	89.0
15	8, 25 y	744.5	89.3	1091.1	130.9

Mean values of 6 measurements each and 5-years calculation

Europium contamination

Ramamoorthy *et al.* were the first to address the issue of [154]Eu-contamination[66] followed by others.[67] In his thesis on the Vienna protocol, Fischer *et al.*[68] reported that the influence of impurities may become significant in patients receiving repeated treatments. We should consider that there are substantial differences in [153]Sm-EDTMP preparations available which are not only limited the impurities. These differences in preparation may influence therapeutic efficacy significantly. Investigations using clinical shadow shield whole-body counter with activity profile device revealed the presence of [152]Eu (half-life 13.33 years), [154]Eu (half-life 8.8 years) and [156]Eu (half-life 15.19) in patients. The distribution of Europium (Eu) isotopes contamination was assessed by inductively coupled plasma sector field and mass spectrometry in aliquots of the probe applied to the patients.[68] An enormous interprobe variability by more than one order of magnitude was seen (unpublished findings). The impurities with Eu in profile scanning appear at identical sites as [153]Sm, indicating identical biodistribution. The Eu-isotopes contribute to about 1.0-1.5% to the effect of [153]Sm in a single therapy. This may not be of great relevance in the case of a single application, however, applying repeated treatments according to the Vienna protocol [152]Eu and [154]Eu may finally account for up to 20% or even more of the total radiation dose (Table IV, Figure 7). With up to 17 therapeutic applications of [153]Sm-EDTMP until this date, and in the light of longer survivals of patients, the contribution of the impurities to the therapeutic benefit as well as from the point of radiation biology should be seriously considered. Furthermore, it should be also noted that the [154]Eu impurities may cause radiation alarms [69] at airports or security controls which necessitates that a respective informational sheet should be delivered to the patients similar to that initiated with radioiodine.[70] Meanwhile we have routinely started providing this document for [153]Sm-EDTMP treated patients.

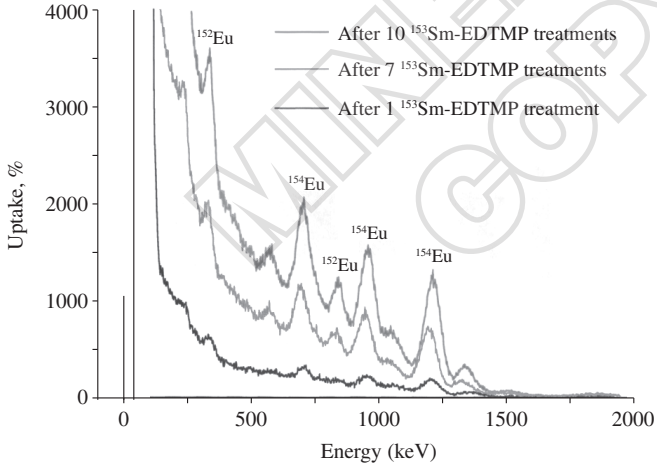

Figure 7.—Whole body scanning in a patient shows significant accumulation of Europium who received multiple doses of [153]Sm-EDTMP (scans after treatments 1, 7 and 10 are presented).

Cost effectiveness

Costs are currently an increasing concern in health care. On the basis of prices in Portugal Macedo *et al.* showed that [153]Sm-EDTMP-treatment for bone pain palliation is more cost effective as compared to conventional analgesic treatment.[71] Cost savings (mainly hospital stay) has originally been among the 5 lead-

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ing arguments for the Vienna protocol for treating patients on an out-patient base.

EANM-guidelines

Administration of [153]Sm-EDTMP in patients is associated with a significant pain reduction, improved mobility, decreased analgesics consumption, and improved quality of life. Benefits beyond, such as lesion stabilization, regression and tumor marker response, indicate a tumoricidal benefit. New therapeutic strategies combined with chemo- and/or radiotherapy as well as sensitizers such as cis- or carboplatin may further improve therapeutic response without additional toxicity.

Recently, the EANM guideline on the use of bone-seeking radiopharmaceuticals has been revised.[72] According to the new guideline, patients with a better prognosis and better clinical condition may benefit from being treated with long-lived radioisotopes. We feel that short-lived radioisotopes but not (as stated) long-lived ones are a better choice in this patient group. These patients may require chemo- and/or radiation therapy or combined radionuclide/chemotherapy at a later stage. The combined treatments seem to further improve the benefit from bone seeking therapeutic agents. Furthermore, in this particular group of patients a repeated radionuclide therapy may be required. Abiding the ALARA rule, the radiation dose for the patient should be kept as low as possible.

The guidelines also say that the quality of the therapeutic response may decrease with re-treatments. To our knowledge there is not a single evidence-based study on this issue available in the literature. Our experience with more than 550 patients mainly with prostate and breast cancer on repeated treatments (maximum treatment 17 times with 30 mCi [153]Sm-EDTMP) showed no change in pain response throughout repeated application as evaluated by questionnaire data (unpublished results).

If a patient is receiving treatment with a radioisotope that is also emitting a gamma-ray component, a post-therapeutic scintigraphy should be mandatory rather than done only when feasible. This is in order to obtain the maximum benefit for the patient keeping the radiation dose as low as reasonably achievable.

A statement on the optimal interval for post-therapeutic scintigraphy is missing. For [153]Sm-EDTMP this interval should be at least 6 hours (we routinely do it on the next day) in order to allow complete blood clearance and to optimize imaging quality. All these facts together question the value of longer-lived bone-seeking therapeutic compounds in general which showed no higher clinical benefit until today.

Conclusions

Although available for a long time, radionuclide therapy for bone pain palliation is still not widely used and undervalued. Provided that a regular haematological monitoring is done, treatment with [153]Sm-EDTMP is remarkably safe. Patients should be treated early[73] when symptoms appear rather than being referred at a late stage after chemotherapy, radiotherapy, bisphosphonates, analgesics or other therapeutic measures fail.[35] There is an evidence for lesion regression and improved survival. Prospective controlled studies are urgently required to assess the benefit and discover predicting factors of treatment success.

A new scientific tool is not usually presented in a way that it convinces its opponents … rather the opponents gradually die off and a rising generation becomes familiar with the truth from the start (Max Planck, Nobel Laureate 1918).

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