Background, Reasons and Benefits Using the Vienna Protocol for the Treatment of Painful Bone Recurrences with ^{153}Samarium-EDTMP

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Abstract. *^{153}Samarium-ethylendiaminetetramethylenephosphonate (EDTMP) has become a treatment of choice for painful bone recurrences. The reasons and the background of the Vienna protocol in 1994 are outlined. A 30 mCi (1.1 GBq) dose exhibits comparable pain palliation with less hematotoxicity as compared to 1 mCi/kg, the conventional dose widely used, the 3 months interval as most of the patients (around 80%) show pain palliation for that period of time. Repeated administration furthermore allows lesion stabilization/regression and a tumor marker response. Other reasons are outlined in detail. The earlier ^{153}Sm-EDTMP is started the better; patients not only experience effective bone pain palliation, but also improved quality of life, lesion stabilization/regression and a prolonged survival.*

Up to 75% of patients suffering from prostate, breast or lung cancer go on to develop bone recurrences. Radionuclide therapy has been introduced for bone pain palliation using strontium-89, replaced later by rhenium (^{186}Re) and samarium (^{153}Sm). Originally directed at bone pain palliation treatment in final disease stages only, a variety of therapeutic schedules for ^{153}Sm-ethylendiaminetetramethylenephosphonate (EDTMP) has been used. Based on experimental data, Turner *et al.* were the first to propose the benefits of repeated treatment (1), a suggestion which has not been followed for quite a long time. This paper aims to explain why the Vienna protocol (2) was chosen to optimize the benefits of ^{153}Sm-EDTMP.

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Methods and Results

When ^{153}Sa-EDTMP was introduced into bone pain palliation it fast became evident that the strategy 'the sooner, the better' is preferable. Based upon the finding that a dose of 1 mCi/kg is not more beneficial (Table I) as compared to 0.5 mCi/kg (we generally use 30 mCi) concerning bone pain palliation (Table II) but does significantly more affect the bone marrow, in 1994 we started to treat patients according to the Vienna protocol (Table III) for the first time based on repeated treatments (Table IV) on a given schedule (3). Contraindication for the treatment is a platelet count $<100.10^3$/μl, a white blood cell count $<3.10^3$/μl and a red blood cell count $<3.10^6$/μl, hematocrit <30% and hemoglobin <12 g/l. However, if an abnormally low blood cell count is due to bone marrow suppression by tumor cell infiltration, a beneficial response and even an increase in peripheral blood cell count after therapy has been seen (4). Platelets are most affected by ^{153}Sm-EDTMP treatment followed by white and red blood cells. Usually, within 3 months (mainly between weeks 10 and 12) the peripheral blood cell count almost completely returns to the pre-values.

Therapy is performed 5 times at 3-month intervals (Table V), followed by 6-, 9- and 12- month intervals with 5 treatments each. The respective treatment intervals are shortened in case of proven disease progression (scintigraphy, magnetic resonance imaging (MRI)). Blood cell count is performed 3 and 6 weeks after therapy as well as immediately before the next scheduled one. Treatment is already indicated when more than 1 bone lesion and/or bone pains exist (Table VI) on an outpatient base (Table VII).

Repeated application clearly shows benefits beyond pain palliation such as tumor marker decrease and lesion regression, as monitored and proven by various imaging techniques (scintigraphy, MRI) (5, 6) (Figure 1 A-C). Prostate-specific antigen (PSA) after a few weeks may show a temporary increase, while in the majority of the patients (71%) it decreased after 3 months. Older bone lesions show a better therapeutic

Table I. *Pain response upon ^{153}Sm-EDTMP (in %).*

Week	Dose	
	0.5 mCi/kg	1.0 mCi/kg
8	100	100
9	97	95
10	93	93
11	89	90
12	79	81

n=100 each group.

Table II. *Why 30 mCi?*

- Mean response comparable with higher dose (1 mCi/kg)
- Fewer and less severe hematological side-effects
- Fast recovery of peripheral blood cell count
- Comparable influence on tumor markers (PSA, adhesion molecules)
- Possible on an outpatient base (radiation hazard, European legislation)
- Less oxidation injury (as compared to 1 mCi/kg)
- Less hematotoxicity after earlier chemo/radiotherapy
- Concomitant chemo/radiotherapy possible

Table III. *The Vienna protocol: 30 mCi (1.1 GBq) ^{153}Sm-EDTMP repeatedly intravenously.*

- On an outpatient basis
- Treatments 1-5 at 3-month-intervals, 6-10 at 6-month-intervals, 11-15 at 9-month-intervals, thereafter at 12-month-intervals
- Red and white blood cell and platelet count (3 and 6 weeks and before next treatment, respectively)
- Treatment interval reduced (by 3 months) in case of indicators of progression (radiography, MRI, scintigraphy, tumor marker ↑, pain ↑)
- Always: scintigraphy (more than 6 hours after radionuclide application)

Table IV. *Why repeated treatment?*

- Stabilization/regression of lesions (MRI, scintigraphy)
- Accumulated dose – less hematotoxicity
- Better pain control
- Tumor marker (indicator) decrease (PSA, ICAM, VCAM, E-selectin)
- No change in individual (^{153}Sm-EDTMP) uptake
- Maximum number of treatments to date 17 (=8.5 years)
- No complication to date throughout the first 10 treatments (>750 patients)

Table V. *Why 3 months?*

- About 80% still pain-free
- Faster decline in response rate starting after 3 months
- Recovery of blood cell count

Table VI. *Inclusion criteria for ^{153}Sm-EDTMP.*

- Bone pain and/or more than one positive lesion
- Scintigraphically proven uptake
- Haematological exclusion criteria for platelets, white blood cells, red blood cells (or hemoglobin, or hematocrit)
- Exception: one or more of the haematological exclusion criteria not met due to proven bone marrow infiltration

Table VII. *Why on an outpatient basis?*

1. Radiation protection law
2. Number of patients
3. Quality of life
4. Costs
5. Limited hospital facilities

Table VIII. *Therapeutic response to 30 mCi ^{153}Sm-EDTMP.*

Effect on lesions	Old	New
Complete regression	6	0
Most lesions regress	41	4
Significant regression	17	35
Minor regression	9	18
No change	15	12
Progression	12	31

n=100 each

response as compared to new ones appearing after first therapy (Table VIII). As yet, however, there is no individual predictor of response available. While the interindividual ^{153}Sm-EDTMP uptake varies greatly (~ 30% up to ~90%), the intraindividual one is rather stable (<7% deviation). Concomitant or even repeated application of biphosphonates does not significantly affect the uptake. Bone uptake does not correlate with treatment response. This indicates that pretherapeutic dosimetry is of low prospective value. A significant improvement in quality of life, pain score, Karnofsky score, WHO questionnaire results and reduction of analgesic consumption has been documented.

Discussion

Samarium uptake in bone lesions has been shown to be identical to that by conventional technetium-99m diagnostic bone scintigraphy. ^{99m}Tc-EDTMP uptake studies do not provide any benefit, and the quality of data is poorer as compared to methylenediphosphonate (MDP) and others. ^{153}Sm-EDTMP uptake studies may cause stunning (*i.e.* reduced uptake of second radionuclide dose) if carried out within a few days before scheduled treatment (unpublished data). As uptake does not correlate to therapeutic benefit, pretherapeutic dosimetry offers no advantage to the patient.

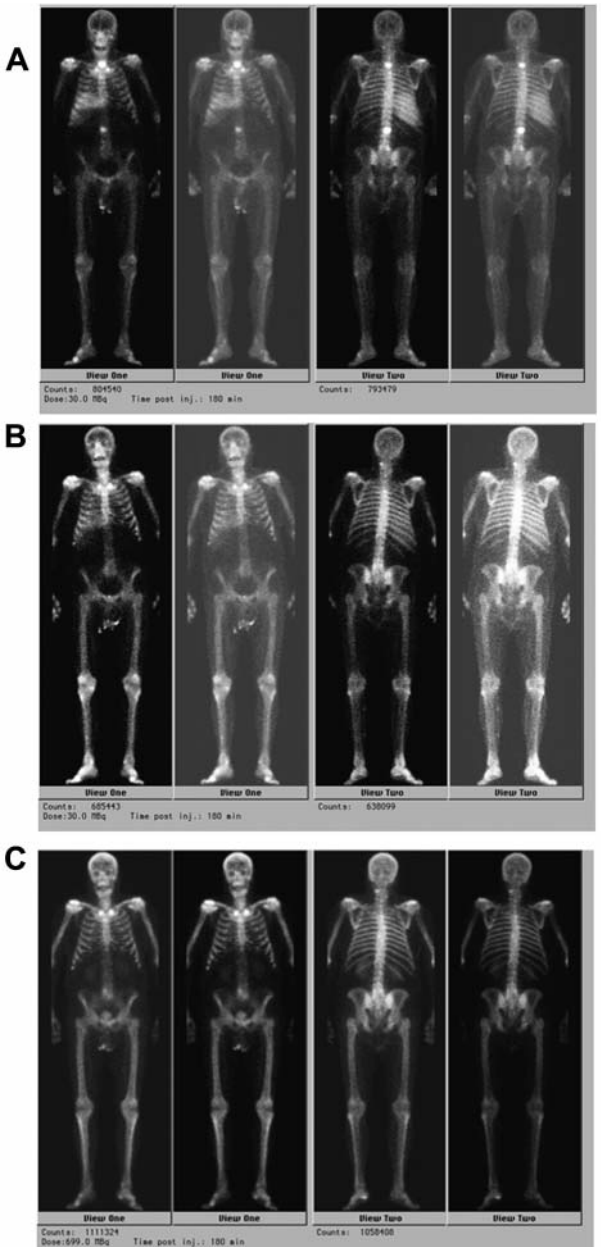

Figure 1. *Example of lesion regression in a 74-year-old male suffering from prostate cancer. Images from A) 1st therapy (28.3.2003): two hot spots in the vertebral column verified by (MRI) reflect recurrences; B) after 5 treatments (28.4.2004), the 2 abnormal uptake sites in the vertebral column are no longer visible; C) MDP-scintigraphy (26.1.2006), still no sign of recurrences in the skeletal system.*

Conclusion

Early and repeated ^{153}Sm-EDTMP is the key to improved therapeutic benefit in patients with painful bone recurrences.

^{153}Sm-EDTMP reduces bone pain, increases quality of life, diminishes lesion sites, tumor markers and tumor indicators and improves survival. Chances for regression of early-stage old lesions are significantly better as compared to new ones showing up during therapy. Concomitant chemotherapy indicates improved benefit (7). Even osteoclastic lesions beneficially respond to ^{153}Sm-EDTMP as far as they show up positively on bone scintigraphy.

The role of ^{153}Sm-EDTMP therapy in micrometastases still remains unclear. There is some reason to believe that concomitant statin treatment improves the benefit, as do a higher pretherapeutic red blood cell count and higher hemoglobin. Samarium, the sooner, the better, should be used. This approach is prior to conventional therapeutic schemes.

There are still a variety of open questions to be answered as to how histology, stage of the disease, osteoblastic *versus* osteoclastic lesions, the intervals, the number of treatments, concomitant (chemotherapeutic and statin) treatment, type and intensity, the level of hemoglobin (erythropoietin), sensitization, stunning, and many others might all influence the final therapeutic outcome (8).

Prospective studies should assess the benefit of this therapeutic regimen. Even later-stage surgery of ^{153}Sm-EDTMP-treated prostate cancer patients might provocatively be considered in the future.

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