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.

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
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 153Sm-EDTMP uptake varies greatly (~30% up to ~90%), the intra-individual one is rather stable (<7% deviation). Concomitant or even repeated application of bisphosphonates does not significantly affect the uptake. Bone uptake does not correlate with therapeutic benefit. Pretherapeutic dosimetry offers no advantage to the patient.

### Discussion

Samarium uptake in bone lesions has been shown to be identical to that by conventional technetium-99m diagnostic bone scintigraphy. 99mTc-EDTMP uptake studies do not provide any benefit, and the quality of data is poorer as compared to methylenediphosphonate (MDP) and others. 153Sm-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.
Conclusion

Early and repeated 153Sm-EDTMP is the key to improved therapeutic benefit in patients with painful bone recurrences. 153Sm-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 153Sm-EDTMP as far as they show up positively on bone scintigraphy.

The role of 153Sm-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 153Sm-EDTMP-treated prostate cancer patients might provocatively be considered in the future.

References


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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.