Original paper

The influence of Sm-153 therapy on bone marrow function

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Aim of the study: Studies about possible risks connected with β-emitter-radiotherapy concentrate mainly on potential myelotoxicity. Results of previously published analysis based on white blood cells (WBC) and platelet (PLT) counts – before and after radionuclide treatment – are quite varied. The aim of our study was to present the greatest possible impact of Samarium-153 on bone marrow function in clinical practice.

Material and methods: The study included the blood test results of 175 patients with bone metastases treated with Sm-153 in the years 2012–2014. We compared levels of WBC, PLT, red blood cells (RBC), and haemoglobin (HGB) from two blood tests – one performed directly before the therapy and the other 2–6 weeks after isotope injection.

Results and conclusions: The study showed decreased mean level of WBC in a control test performed after therapy in comparison to output results at about 27.1%. In our study 1.1% of patients developed the third-grade toxicity in CTCAE (Common Terminology Criteria for Adverse Events). Mean decrease of PLT was about 18%. Three patients (1.7% of all) result qualified as third-grade toxicity in a control test, one as fourth-grade. Analysis of RBC level showed 5.7% reduction of output values. The same calculation was seen for HGB – 5.1%. The greatest but acceptable decrease in haematological parameters was observed in WBC and PLT. Analysis of changes in WBC and PLT level showed them to be similar or smaller than was proven in previously published studies.

Key words: bone metastases, samarium, prostate cancer, breast cancer, radionuclide therapy, β-emitters.

Contemp Oncol (Pozn) 2016; 20 (5): 385–388
DOI: 10.5114/wo.2016.64598

Introduction

Systemic radionuclide therapy using strontium and samarium has been well known and successfully used for nearly thirty years now.

Samarium-153 is a β- and γ-emitter with a physical half-life around 46.8 hours. It has proven affinity to bone tissue and reticuloendothelial system. Combination with EDTMP (ethylenediamine tetramethylene phosphonic acid), known as Quadramet, was developed in order to increase affinity to bones. Studies showed that concentration of Sm-153 is 17-times higher in osteoblastic metastases than in healthy bone tissue. 35% of injected Sm-153 dose is uptaken by the skeletal system. The remaining part is excreted by the kidneys within about 12 hours.

The analgesic effect of Sm-153 therapy is associated with a local reduction of radioinflammation and subsequent induction of apoptosis in cancer cells.

These pathways decrease the pressure exerted on pain receptors located in the periosteum. As a result, the pain subsides or fully resolves. The effect occurs 4–6 days after the isotope injection and can last for up to 16 weeks. Sm-153 therapy can be repeated dependent on the patient's needs [1].

Sm-153 treatment is recommended for patients with multiple bone metastases with osteoblastic component, regardless of the primary tumour's location.

The effectiveness of Sm-153 therapy is already proven [2]. According to studies, about 70% of patients observe a decrease of pain scores after one dose, and as much as 80% after the third drug administration.

Despite the high effectiveness and wide employment of Sm-153 in other countries, Poland struggles to fully accept this method. This attitude is based on a common opinion that the isotope injection must not be applied along with a radio- or chemotherapy. However, recent research conducted on patients suffering from prostate cancer proves otherwise. It has been shown that Sm-153 acts synergistically with the chemotherapy to reduce PSA levels and subsequently alleviate pain [3, 4].

Risk of myelosuppression has also been indicated as another reason against isotope therapy in Poland; however, this concern was based on experience with the Sr-89 isotope itself.

We decided to investigate the greatest possible impact of the Sm-153 on bone marrow function.

Material and methods

Our retrospective study included blood test results of 175 patients with multiple bone metastases, treated in our Department with Sm-153 in the

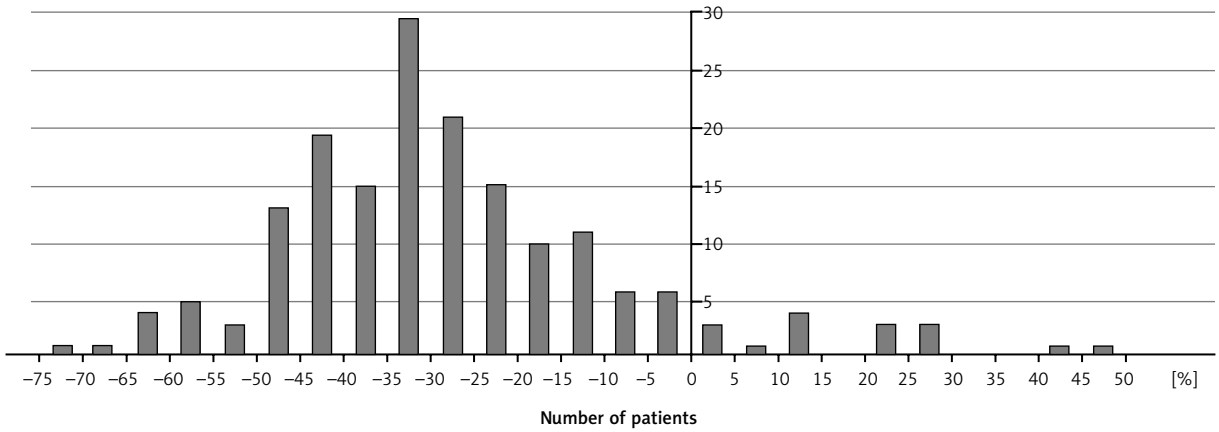

Fig. 1. Changes in WBC counts-decrease: increase in WBC level as a % of pretreatment result

years 2012–2014. The group consisted of 60 women, aged 33–86 years (mean 64.3 years) and 115 men, aged 53–87 years (mean 68.1 years). One hundred and four patients had prostate cancer, 44 – breast cancer, 7 – lung cancer, 6 – cervical cancer, 3 – endometrial cancer, 4 – kidney cancer, 1 – gallbladder cancer, 3 – colorectal cancer, 1 – urinary bladder cancer, 1 – leiomyosarcoma, and 1 – maxillary sinus cancer.

Patients were qualified for Sm-153 treatment based on up-to-bone scintigraphy and haematology results. Every whole body bone scan for therapy qualification was performed in our department 2–4 hours after injection of 800 MBq 99mTc-MDP. Scans were performed on a Symbia Truepoint SPECT/CT. Time of acquisition was 15–20 minutes.

Admitted patients received Quadramet intravenously at the dose of 37 MBq/kg. Injection took place in our Department. Every patient was obligatorily well hydrated with IV or per os before Sm-153 administration.

Table 1. Changes from baseline in WBC, PLT, RBC, and HGB

	WBC	PLT	RBC	HGB
Mean decrease (%)	27.1	18	5.7	5.1
Nadir as % baseline	71.7	88.8	47.9	47.1

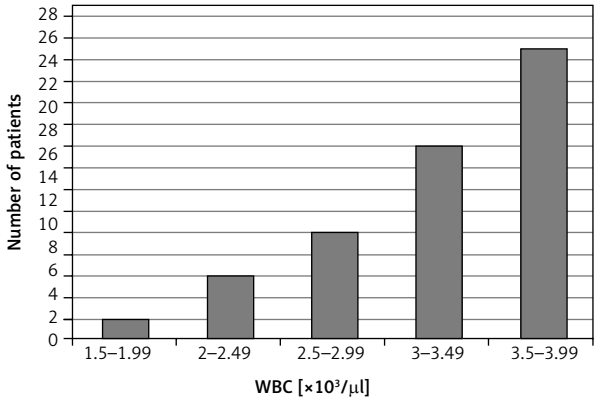

Fig. 2. Post-treatment WBC counts in the group of patients with the results under the lowest normal level (63 patients from 175)

We compared levels of white blood cells (WBC), platelets (PLT), red blood cells (RBC), and haemoglobin (HGB) from two tests – one test had been performed directly before the therapy, whereas the second one was done 2–6 weeks after isotope injection in order to show changes in blood parameters.

Blood tests were performed in the Department of Laboratory Diagnostics in The Franciszek Lukaszczyk Oncology Centre, Bydgoszcz on Sysmex XT-1800i and Sysmex XT-2000i analysers using flow cytometry with semiconductor laser beam, sodium lauryl sulphate (SLS), and conductivity methods.

Reference ranges for blood tests results:

- WBC 4–10 × 10^3/μl,
- PLT 130–350 × 10^3/μl,
- RBC 4–5 T/l for women and 4.5–5.5 T/l for men,
- HGB 12–16 g/dl for women, 14–18 g/dl for men.

Results

The study showed a decreased mean level of WBC count in the test performed 2–6 weeks after therapy compared with output values at about 27.1% (Fig. 1, Table 1).

Sixty-three patients out of 175, representing 36% of the whole group, showed results under 4 × 10^3/μl.

The important finding was that most of the results (n = 45) in this group (63 patients) were still above 3 × 10^3/μl, despite the general patients' decline. 1.1% of patients in our study developed third-grade toxicity in CTCAE [5]. There were no results qualified as fourth grade (Fig. 2).

Analysis of PLT levels showed a decreased mean number of platelets, at about 18%. Only 39 patients (22.2%) had platelet counts under the lowest normal level (130 × 10^3/μl). Within the group of 175 patients, three patients (1.7%) noticed a result qualified as third-grade toxicity in CTCAE and one (0.57%) as fourth grade (Figs. 3, 4).

RBC and HGB results showed 5.7% mean reduction for RBCs (from 4.1 ±0.5 T/l to 3.8 ±0.5 T/l and 5.1% for HGBs (from 12.1 ±1.5 g/dl to 11.5 ±1.6 g/dl). Only three patients noticed HGB level qualified as third grade in CTCAE. There were no patients with fourth grade.

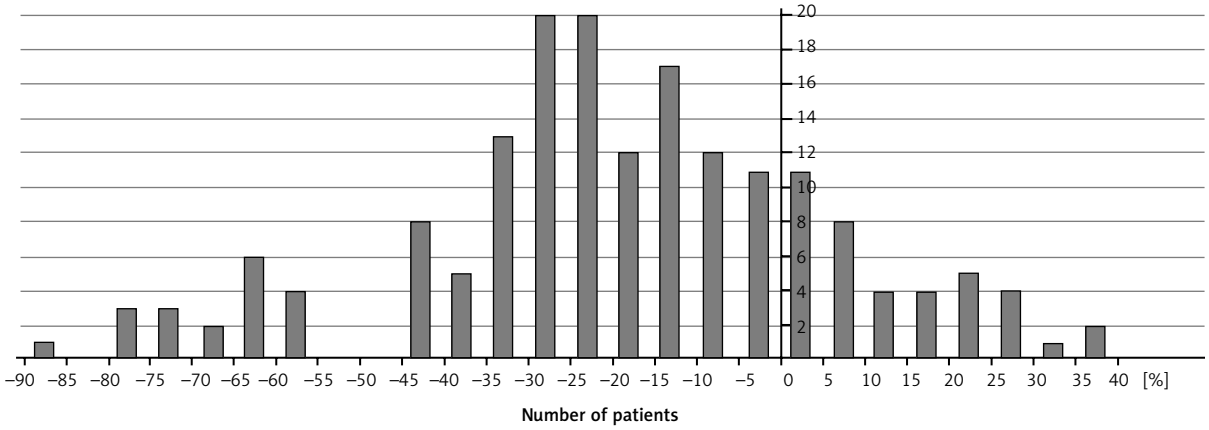

Fig. 3. Changes in PLT counts as a % of pretreatment results

Discussion

The effectiveness of the Sm-153 therapy was not the aim of this study, although we would like to remind about data regarding pain reduction as a result of radionuclide treatment.

In the prospective, randomised, placebo-controlled study published by Serafini *et al*. [6] 118 patients received single doses of placebo (n = 39) or Sm-153 of dose 0.5 mCi/kg (n = 40) or 1.0 mCi/kg (n = 39). During 16 weeks of follow-up pain relief was observed already in the first four weeks in 62–72% of patients who received higher dose of Samarium. Marked or complete pain relief was observed in 31% of patients. It had a direct impact on the opioid use ratio (mean daily opioid use relative to baseline), which four weeks after drug administration ranged between 0.6–0.7 for 1.0 mCi/kg dose. At the end of observation – after 16 weeks – 43% of patients still notified pain relief.

Another study published by Correa-González *et al*. [7] analysed pain palliation of 277 patients who received 37 MBq Sm-153 per kg of body weight. Pain intensity was measured by Visual Analogue Scale and Verbal Rating Scale three times – once before treatment and also 3 and 12 weeks after drug administration. The comparison showed a marked decrease in pain intensity, by about 54% after three weeks and 74% after 12 weeks.

Despite the proven efficiency of Sm-153 therapy, its use is still restricted by anxiety about potential adverse effects of the therapy.

The aim of our study was to present the greatest possible impact of Sm-153 on bone marrow function. For this purpose, we analysed the differences between results from tests performed 2–6 weeks after the isotope injection. It has been proven previously that the decreased levels of blood parameters are only temporary and is followed by a quick recovery phase [2, 8, 9]. Because of that confirmed fact, our study did not include subsequent blood test results.

The results of the WBC count obtained in our study seem very close to those published by Heron *et al*. [10], in which haematology results of 58 patients receiving Sm-153 1–8 times were analysed. In that study, following the treatment, WBC count decreased by 30% from a mean of 5.6 ±0.2 × 10^3/µl to 3.7 ±0.2 × 10^3/µl (respectively, 27.1%, 6.7 ±2.2 × 10^3/µl and 4.7 ±1.7 × 10^3/µl in our study). 11% of patients have been noticed to develop the third-grade toxicity in CTCAE. By comparison, in our study only 1.1% of patients developed third-grade toxicity in CTCAE.

Regarding PLT count, the difference was more significant. Our study showed 18% reduction of PLT from the mean 240.1 ±96.8 × 10^3/µl to 191.9 ±88 × 10^3/µl (respectively, 40%, 259 ±9 × 10^3/µl and 157 ±8 × 10^3/µl in the study by Heron *et al*.) [10].

Six per cent of patients from the study by Heron *et al*. [10] had results ranging from 25 to < 50 × 10^3/µl (respectively, 0.57% in our study). In both studies there was one patient with PLT count under 25 × 10^3/µl (fourth grade toxicity). In our study the lowest result was exactly 24 × 10^3/µl. As was previously stated in spite of PLT count decline, Sm-153 therapy is not associated with a significantly altered functional behaviour of platelets [11].

The WBC count results of our patients also showed smaller decreases compared to those published by Sartor *et al*. [2]. Following the Sm-153 therapy, 188 of patients in the study by Sartor *et al*. [2] had their WBC count decreased by 50% after the first dose of the isotope (in our study WBC

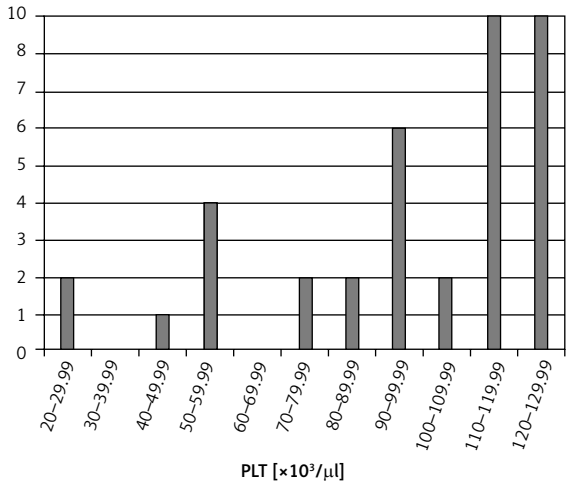

Fig. 4. Post-treatment PLT counts in the group of patients with the results under the lowest normal level (39 patients from 175)

count showed 27.1% decrease), whereas the PLT count was reduced by 44% (compared to 18% indicated in our study).

The final results of our study confirmed the small influence of Sm-153 on haematological parameters in patients treated with Sm-153. This may be a result of the high affinity of Sm-153 to osteoblastic metastases, and of the effect of low concentration of radionuclide in healthy bone tissue.

Taking in advance the low impact on the haematological parameters, radionuclide therapy should be considered in every case of a patient with multiple bone metastases with an osteoblastic component, regardless of the primary tumour's location and present or planned type of therapy.

The authors declare no conflict of interest.

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Submitted: 6.08.2015
Accepted: 9.03.2016