**ISOTOPE TREATMENT AND BONE PAIN**

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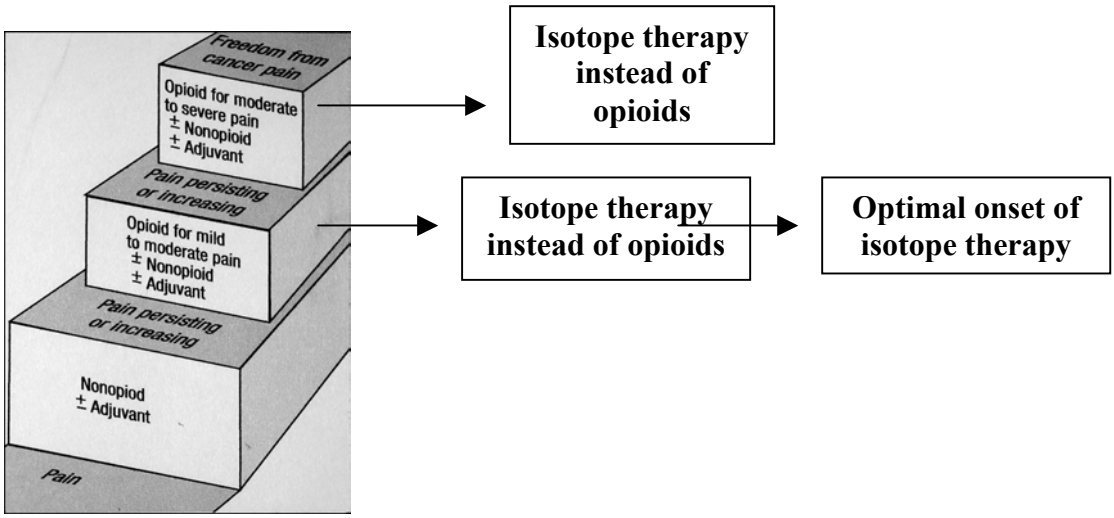
**Alleviation of pain arising from bone metastases** is a great challenge for medical science. Metastases to bones are frequent mainly in prostate and breast carcinomas, its frequency is 47 to 85% among breast cancer patients, whereas it is 33 to 85% among prostate cancer patients. The often torturous pain associated with bone metastases and the resulting limitation in motility considerably deteriorates the quality of patients' life. Subsequent to the appearance of distant metastases the average expected life time is 3 years, however many people may live up to 10 years with these symptoms often causing unbearable pain. The treatment of bone metastases is often a multidisciplinary area where Nuclear Medicine does have a role (1). Based on all these, it is crucial to know which method to choose for alleviating the pain and when.




The first attempts for the treatment of bone metastases with $^{32}P$ and $^{89}Sr$ isotopes came in 1942 (there are also current treatments with these isotopes) and it was only many years later, in 1974, that this therapy started its career when the broad range clinical trial of $^{89}SrCl$ (Metastron) began. The first publications also appeared at the same time (Firusian et al. (2)).

***What should an isotope be capable of and which isotope (radiopharmacon) should we use?***

In all cases, the isotope used is beta-emitting isotope with high energy emission and an effective range of only a few millimeters. It is important that the isotope should become selectively incorporated in the metastasis that is the isotope uptake of normal bones should be negligible as compared to that of the tumor. From the point of view of binding to bones, two groups of radiopharmacons can be discerned:

a) the isotope itself has affinity to bones – a Ca-analogue $^{89}SrCl_2$,
b) beta-emitting isotope is bound to a bone-binding inactive chemical, phosphonate ($^{90}Y$-, $^{155}Sm$ EDTMP etc), which transfers the isotope to the lesion.

*Its half-life should be long*, possibly many days, so that "local tumor irradiation" lasts for long time. It is a requirement that the isotope should *rapidly be excreted from blood and urine*, so that the organism should not be unnecessarily exposed to the emission of unbound isotopes. Having been administered, the isotope "locates" the bone metastases with increased osteoblast activity and directly exerts its effect to this area.

## MAIN PHYSICAL CHARACTERISTICS OF THE MOST FREQUENTLY USED THERAPEUTIC RADIOPHARMACONS

| | $^{89}Sr$ | $^{90}Y$ | $^{186}Re$ | $^{153}Sm$ |
|---|---|---|---|---|
| Half life (day) | 50.5 | 2.675 | 3.77 | 1.95 |
| $E_{,max}$ (MeV) | 1.49 | 2.25 | 1.07 | 0.81 |
| Effective range (mm) | | | | |
| Maximal | 8 | 12 | 5 | 3 |
| Average | | 3.6 | | 0.6 |
| Gamma-energy (keV) | - | - | 137 | 103 |
| Chemical specific to bone metastases (ligand) | klorid | EDTMP | HEDP | EDTMP |
| Industrial name of radiopharmacon | Metastron | Multibone | Osteopal-R Diphoter-R | Multibone |

We do not know the exact **mechanism of action** of isotopes applied in isotope therapies, however the essence of the mechanism is the energy transfer of beta particles to the metastasis and the surrounding bone.

The **indication** of isotope therapy can be established when the anti-tumor therapy and the non-narcotic analgesics are not sufficient even if combined (1, 3). It impacts only the bone process associated with *increased osteoblast* activity, for the measurement of which bone scintigraphy is the surest method. This is why preliminary bone scintigraphy is indispensable. It is not at all indifferent when such a scintigraphy is performed. On the one hand, for accurate measurement of the actual situation at the time of theraphy, an examination *more distant than 4 weeks is not* sufficient, and on the other hand such measurement *cannot be* performed *within 2 weeks* of therapy so as to prevent the decrease in therapeutic effect due to possible competition for bone binding sites. (Materials with high affinity to bones are used in diagnostics as well as in therapy.)

In the course of bone scintigraphy, bone marrow scintigraphy is also necessary to be performed to exclude or prove the existence of a non-densifying metastatic process. Comparison of bone and bone marrow scintigraphy will show us the purely lytic process for which therapeutic effect cannot be expected due to lack of increased osteoblast activity proving increased metabolism.

**Analgesic effect** is seen for 95% of patients, and among them full scale pain free status can be achieved for about 20%. The effect is permanent and lasts for some (3-6) months. Immediate effect cannot be expected as the development of analgesic effect takes

place within 1-2 weeks. For about 5% of patients this therapy has no effect. In some cases the metastatic lesion becomes smaller as can be shown using other imaging methods (4).

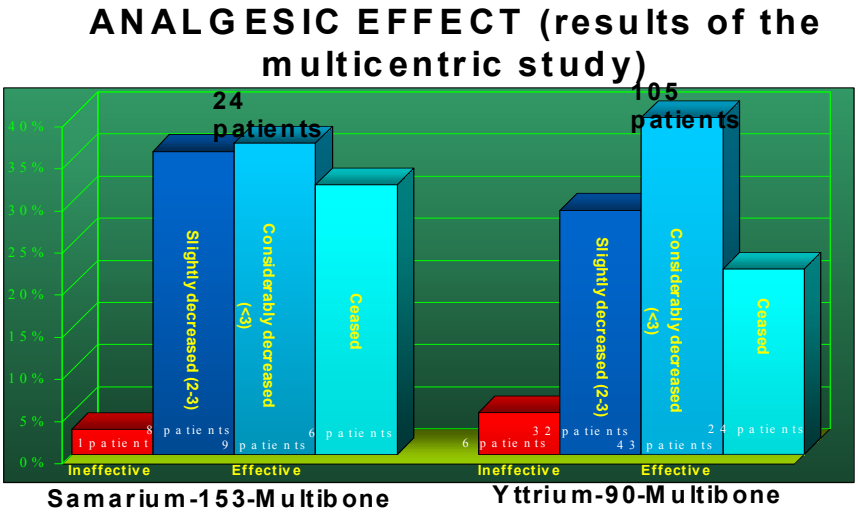
After successful therapy the treatment can be **repeated** when pain returns or within 2-3 months if the pain alleviated by therapy starts to increase.

There is no permanent irreversible **side-effect**. Provisional myelosuppression however will appear in all cases as a *late side-effect*. Due to this, cellular components of the blood must regularly be examined before and after therapy in about every 2 weeks. The alteration is qualitative blood count is expected after about 2-4 weeks subsequent to therapy and the lowest point is around the $6^{th}$ week, whereas spontaneous remission is experienced by the $12^{th}$ week. If the patient also receives chemotherapy or radiotherapy resulting in itself in bone marrow destruction, more frequent control of blood count is prescribed. *As an early side-effect* pain flare is frequent after about 2-4 days following pain alleviating therapy, which can be controlled by ordinary pharmaceutics and is automatically terminated after about 1 week. Very frequently, this forecasts the subsequent benign effect.

**Contraindication** resulting from those specified above: pregnancy, breast-feeding, impairment of renal function and severe myelosuppression. Therapy cannot be performed if creatinin is not >120 μmol/l, thrombocyte number is <100,000/l, leukocyte number is <3,000/l.

**Implementation of treatment**: after *intravenous administration* of the isotope the patient should be *observed* for 3-4 hours at the Department of Nuclear Medicine or the laboratory holding the license of ÁNTSZ (State Public Health and Medical Officer's Service) and performing the therapy and during this time abundant *hydration* of the patient can be ensured (to provide for necessary incorporation of the radiopharmacon and excretion of surplus amount) and the **radiohygenic rules and regulations** can be and should be observed. The largest amount of radiopharmacon rapidly excreted in the urine leaves the body in this period. This urine need not be collected or separated. It is exclusively the WC in the area of the Department of Nuclear Medicine that patients may use for urinating this urine during these 3-4 hours and such urine should be flushed a couple of times with large amounts of water. Subsequent to this observation period the patient may go home.

Results of our **multicentric retrospective** study, in which the data of therapeutic patients of four domestic Departments of Nuclear Medicine have been analyzed (5), proved favorable effects similarly to those described above (see figure below).




**In summary**, pain alleviation by application of isotopes is a ***systemic, selective and long-lasting beta radiographic treatment***. Isotope therapy, though will not cure the basic disease, can result in ***considerable increase in the quality of life*** if it is incorporated at the adequate time, with favorable indication in the complex and multidisciplinary treatment of the cancer patient. By applying isotope therapy, the use of narcotic analgesics with unfavorable side-effects can be prevented, the patient formerly lying in bed with unbearable pain can regain his/her ability to walk or perhaps become capable of working again.

By applying isotope therapy, such a considerable increase in the quality of life can be achieved for a long time without irreversible side-effects only by injecting one intravenous injection.

This therapy can be performed as an ***ambulant*** therapy.

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