Efficacy of Therapeutic Nuclear Medicine

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Introduction

Radionuclide therapy is a unique cancer treatment modality, which can selectively deliver radiation doses to tumors, is systemic and noninvasive, is associated with few immediate and late side effects, and has the advantage that the uptake and retention in the tumor can be assessed with a tracer study prior to administering a therapeutic dose. The basis for successful radionuclide therapy is a good and selective concentration and prolonged retention of the radiopharmaceutical by the tumor. In addition, several benign disorders, such as thyrotoxicosis and joint diseases, may be treated by radionuclides.

Specific metabolic characteristics and biological properties of the target (tumor or organ) are exploited as targeting mechanism for therapy. Radionuclides may be incorporated into the DNA of the cell's nucleus or into the cytoplasm via the metabolism, attached to the cell surface or brought into close vicinity of the tumor cell. For the choice of radionuclide it is important that the site of deposition is in accordance with the effective range ofthe alpha or beta-particles. The conditions for and the status of currently available forms of radionuclide therapy will be reviewed.

Clinical applications

1. I-131 therapy of thyrotoxicosis

More than half a century patients with thyrotoxicosis have been treated safely and effectively with doses of 131I as iodide, usually ranging 110-370 MBq, the major side effect being hypothyroidism (incidence related to absorbed dose). Compared with surgery, the treatment is equally effective and not associated with an increased risk of leukemia.

2. I-131 therapy of differentiated thyroid carcinoma

131I-therapy is also an integrated part of the clinical management of thyroid carcinoma: after total or near-total thyroidectomy doses of 131I ranging 1.1 - 5.5 GBq are used to ablate residual normal thyroid tissue in order to enable scintigraphic detection and eventually radionuclide treatment of metastases, which may not sufficiently concentrate 131I in the presence of thyroid remnants. Doses up to 7.4 GBq are applied for 131I treatment of recurrent or metastatic disease, with great efficacy and limited side effects.

3. P-32 therapy of myeloproliferative disease

32P as orthophosphate is used in the treatment of polycythemia vera and essential thrombocythemia, acting by incorporation into the nucleic acids of rapidly proliferating cells. In polycythemia vera, both chemotherapy and 32P treatment yield better results than phlebotomy alone, attaining objective remissions and prolonged survival.

4. I-131 MIBG therapy of neural crest tumors

131I-MIBG is used for the specific targeting of neuroblastoma, malignant pheochromocytoma, paraganglioma, medullary thyroid carcinoma and carcinoid tumors. Active uptake-1 at the cell membrane and granular storage provide the targeting mechanism. In children with neuroblastoma, having failed other treatment modalities, the cumulative response rate of 131I-MIBG therapy was 35%. Moreover, the treatment provides valuable palliation and improved quality of life, as its non-invasiveness is in contrast with that of chemotherapy. 131I-MIBG therapy is now being used with success preoperatively instead of combination chemotherapy in children with inoperable neuroblastoma. In pheochromocytoma and paraganglioma objective remissions and significant improvement of symptoms, lowering of blood pressure and pain relief are attained in about 60% of patients. In medullary thyroid carcinoma and carcinoid mostly palliative results are observed.

5. Radiolabelled peptides in neuroendocrine tumors

Radionuclide therapy using somatostatin analogs with b-emitting radioisotopes, interacting with somatostatin receptors on the tumor cell membrane, is being investigated. Attempts have been made to treat tumors with high doses of 111In-DTPA-octreotide, despite its unfavorable characteristics for therapy.

6. Radioimmunotherapy
A great variety of radiolabelled monoclonal antibodies or fragments have been developed for many tumors, but, till recently, their therapeutic application has met with limited success. More recently, however, considerably better results have been reported in leukemia and the treatment of lymphoma using 131I-anti-CD2O monoclonal antibodies, with objective response rates upto 70%. New developments of radioimmunotherapy include the production of chimaeric, "humanized" antibodies (no HAMA), bispecific antibodies and multistep targeting technology, the use of other labels and biologic response modifiers.
7. Palliative bone therapy of painful skeletal metastases
50 years after the initial therapeutic use of radioactive strontium, a revival of radionuclide bone therapy is observed in recent years, due to the fact that more suitable agents become available and possible an increasing appreciation of radionuclide therapy in general. Compared to external beam radiotherapy, radionuclide therapy is less invasive, better tolerated and produces a similar response rate (70-80%), limiting the radiation dose to the site of the metastases and sparing the normal tissues. 89Sr-chloride, 189Re-HEDP and 153Sm-EDTMP are used with more or less equal success and minimal side effects. Recently, also 117mSn-DTPA is investigated as a therapeutic bone seeking agent.
8. Radiosynoviorthesis
More than 60% of patients with reumaroid arthritis and other inflammatory joint disease experience a beneficial effect of intraarticular administration of radioactive colloids. Dependent on joint-size and synovial thickness either 90Y-citrate/silicate, 186Re-S-colloid or l69Er-citrate is used, the recommended administered dose and volume varying per joint.
9. Alternative approaches : intraarterial/intracavitary/intratumoral
Tumors, which are localized or regional, may be targeted via the intraarterial route using formulations which preferentially lodge in arterioles and capillaries of the tumor. 131I-Lipiodol, radiolabelled particles and 90Y-glass microspheres are used with success for i.a. therapy of liver tumors. For treatment of malignant effusions,

intracavitary administration of radiolabelled colloids, chelates or monoclonal antibodies can be applied to the pleural, pericardial and peritoneal cavities, intrathecally into the cerebrospinal fluid, and into cystic tumors, e.g. cystic craniopharyngioma. Examples of treatment by direct intratumoral injection of radioisotopes are the use of 131I-antibodies in glioma and 32P-colloids in pancreatic and hepatic tumors.

Side effects and longterm effects

Major series, in which patients treated with 131I have been followed up for decades, show that side effects are mild and that longterm complications of this treatment are hardly ever seen in practice. In fact, radionuclide therapy is associated with a much lower risk of leukemia and second cancers than chemotherapy and external beam radiotherapy.

Conclusion

The response of radionuclide therapy, reported to date, is promising. By incorporating this modality earlier in cancer treatment protocols, its efficacy in management of oncological disease can be optimized, appreciating that the invasiveness and toxicity compare favorably with that of chemotherapy, immunotherapy and external beam radiotherapy.