THERAPY OF BENIGN THYROID DISEASES

Recently the human Na+/I- symporter (hNIS), which is responsible for iodine uptake in the thyroid gland, has been cloned and characterised\textsuperscript{16}. This transporter is located on the basolateral membrane of the thyroid follicular cells and iodine transport is made possible by an energy (Na\textsuperscript{+} / K\textsuperscript{+}-ATPase) dependant co-transport mechanism that is driven by an inwardly directed Na\textsuperscript{+} gradient. This transporter is the basis of thyroid scintigraphy and radioiodine therapy, which is clinically used since more than 50 years since the initial \textsuperscript{131}I human thyroid uptake studies performed by Hamilton and Soley\textsuperscript{25, 57}.

Graves’ disease

Indication

\textsuperscript{131}I has become the most commonly used therapy for Graves’ disease in adults in the United States, but this predominant \textsuperscript{131}I therapeutic use is not followed in Europe and Asia where antithyroid drug therapy is initially preferred\textsuperscript{69}.

Once the diagnosis of Graves’ disease is established the physician must discuss with the patient likely therapeutic outcomes of the various available options, antithyroid drug therapy, surgery or radioiodine therapy. Each of these modalities has advantages and disadvantages. No option is clearly superior or inferior to the other modality. Because a lot of studies demonstrated clearly that a antithyroid drug therapy of at least one year offers a spontaneous long-lasting remission for the patients, Europeans prefer to treat first with antithyroid drugs, if after one year hyperthyroidism recurs or antithyroid drug therapy cannot be stopped or even reduced in dose, a definitive treatment of hyperthyroidism is discussed with the patient, where actually two options, near total thyroidectomy and radioiodine therapy has to be discussed.

The situation in Europe due to the iodine deficiency areas all over the continent is different. In the USA most of the patients with Graves’ disease have normal sized glands, in Europe and especially in Germany patients have additionally goiters sometimes with nodules. In this situation surgery should be preferred to radioiodine therapy, if there are additional cold nodules being suspicious to be malignant, large goiters with mechanical problems in the neck and situations where an immediate stop of hyperthyroidism and antithyroid drug therapy has to be guaranteed, such as allergic or liver and hematologic side effects of antithyroid drugs.

In all the other situations radioiodine therapy is the treatment of choice, because there is no real side effect, no hypoparathyroidism, no voice cord paralysis and no risk of anesthesia.

The radiation risk is negligible, because the radiation burden of the patients receiving 185MBq of \textsuperscript{131}I is comparable to one or two x-ray studies of the kidneys.

Therapy strategy

Due to the European preferred antithyroid drug pre-treatment, most of the patients are euthyroid under ongoing antithyroid drug therapy. But before radioiodine dosimetry and radioiodine treatment antithyroid drug therapy should be stopped, because it is well documented that this leads to an increase of intrathyroidal halflife of radioiodine\textsuperscript{58}. The explanation for that
is that antithyroid drugs inhibit thyroid peroxidase which binds iodine to thyroid hormone precursors. If iodine and also radioiodine is not bound to i.e. monoiodothyrosin it rapidly is excreted out of the thyroid cell. Also prevented must be the use of iodine containing contrast agents or other drugs such as cordarex, because then the thyroid gland would be overloaded with iodine and no sufficient radioiodine uptake would be any longer possible for therapy.

Radioiodine is given as a standard activity or as an individually calculated activity. Standard activities are more common in the United States, probably due to the most likely normal-sized thyroid glands, where individual dosimetry is preferred in Europe. A prospective study in Germany^2^ demonstrate that standard doses of 555MBq ^131^I lead to a higher number of hypothyroidism in small glands, a higher number of treatment failure in large glands etc.

For the dosimetry the Marinelli algorithm:

\[
\text{Activity} = \text{thyroid volume (sonography)} (\text{ml}) \times \text{dose} (100-300 \text{ Gy}) \times 24.8 \times \frac{\text{highest}\% \text{ radioiodine uptake} \times \text{biological half-life (days)}}{}
\]

is used. For dosimetry, which is performed as a 24 h uptake test or optimally as a 5 days radioiodine uptake test, between 3.7 to 7 MBq radioiodine are administered.

Since 1997 in the USA the NCR has appropriately liberalized the previous 30mCi restriction for outpatient therapy by promulgating the so-called Patient Discharge rule. Patients may now be released when the total dose of a member of the public exposed to the patient is not likely to exceed 5mSv in a year. This allows nearly all Graves’ patients in the USA to be treated on an outpatient basis. This is more strictly regulated in most European countries with the maximal permissible dose to outpatients varying from 185MBq (Switzerland, Austria, The Netherlands) 555MBq (Poland, Finland, Greece, Hungary) 740MBq (Belgium, France, United Kingdom) to 1100MBq in Italy. In Germany every intention to treat a patient with radionuclides makes him obligatory an inpatient for at least 48 hours. He may be then released with a restactivity of less than 250MBq.

**Results and side effects**

The comparison of the results of radioiodine therapy in the literature is difficult, because the way to treat the patients is very different.

After low doses to the thyroid between 20 and 50 Gy about 35% of the patients remain hyperthyroid after 1 year of follow-up. Only after repeated applications of therapeutic ^131^I activities, which are necessary in 20% to 70% of the cases, the percentage of hyperthyroidism can be lowered to approximately 4% after 5 years of follow-up. The incidence of hypothyroidism increases from 18% after the first year to approximately 25% after 5 years. In long-term follow-up after 10 years, 50% of the patients develop hypothyroidism, the remaining 50% being euthyroid.

For intermediate doses between 60 and 100 Gy, the percentage of patients with persistent hyperthyroidism is about 10% after 1 year. Also in this group repeated doses are necessary to abolish hyperthyroidism. After 5 years of follow-up approximately 35% of the patients are hypothyroid. As in the low dose group this percentage increases to 50% after 10 years remaining 50% of euthyroid patients.

In the high dose group with doses between 120 and 150 Gy hyperthyroidism can be rapidly controlled. Only 5% of the patients show hyperthyroidism after 1 year. 1% of patients remain hyperthyroid after 5 years. On the other hand 70% of these patients are hypothyroid after one year and this increases to approximately 80% after 5 years. Possible further increase of the hypothyroidism rate are not available in the literature. These figures have been taken from three already older studies in the literature covering about 4,700 patients. In the own department we have to use 300 Gy for hyperthyroidism to come the same results as are published in the high dose group. Perhaps this general German experience is due to the difficulties to differentiate between Graves’ disease and disseminated functional autonomy. From these data it clearly can be concluded, that the higher the dose is, the higher is the elimination of hyperthyroidism, but the higher is also the induction of hypothyroidism.

So it depends from the strategy to treat patients, whether you prefer to have a high succes rate in elimination of hyperthyroidism and substitute most of the patients life long with thyroid hormone drugs or whether take into account to treat them several times with radioiodine and to guarantee half of them to be euthyroid for the rest of the life.

As all other treatments also radioiodine has risks and side effects. The general rule should be to use for an individual the modality with the lowest risk and the highest benefit 7, 8, 10, 11, 18, 23, 24, 26, 30, 32, 40, 49, 54-56. Main risks of surgery are irreversible paresis of the laryn-
geal nerve and hypoparathyroidism (risk of 3\textsuperscript{rd} order). Perioperative mortality which increases with age and accompanying disease is a risk of 4\textsuperscript{th} order.

Radiation induced carcinogenesis and mutagenic effects have to be taken into consideration as possible risks of \textsuperscript{131}I-treatment. It has to be stressed that these risks are hypothetical since they have not been proven to be of statistical significance in all available follow-up studies.

So in conclusion radioiodine therapy of Graves’ disease is safe without severe side effects.

**Graves ophthalmopathy and Graves disease**

Graves’ophthalmopathy is an autoimmune process initiated and maintained by antigen(s) shared by the thyroid and the orbit. A matter of argument concerns the choice of the method of treatment of Graves’hyperthyroidism when clinically evident ophthalmopathy is present. Restoration of euthyroidism appears to be beneficial for ophthalmopathy. The rational for a definitive therapy of Graves’hyperthyroidism is a permanent control of the hyperthyroidism, ablation of thyroid tissue may result in the removal of both the thyroid orbit cross reacting antigens and the major source of thyroid autoreactive lymphocytes.

The relationship between radioiodine treatment and the course of ophthalmopathy is a matter of controversy and some authors have suggested that radioiodine administration may be associated with a worsening of preexisting ophthalmopathy.\textsuperscript{61} This is not observed when radioiodine treatment was associated with a three month oral course of prednisone.\textsuperscript{4}

This development or progression of ophthalmopathy in Graves’patients might be due to the release of thyroid antigens following radiation injury and to subsequent exacerbations of autoimmune reactions directed towards antigens shared by the thyroid and the orbit.

The glucocorticoid treatment should be limited to patients with evident ophthalmopathy and to those without ophthalmopathy but with other known risk factors, such as smoking.\textsuperscript{43}

**Therapy of toxic nodular goiter (thyroid autonomy; Plummers disease)**

Besides Graves’disease functional thyroid autonomy (Plummers’disease) is still the most frequent cause of hyperthyroidism, especially in iodine deficiency areas. In these countries thyroid autonomy is four to fivefold more frequent than in areas with a sufficient iodine supply. Thyroid autonomy can be further differentiated into uni-, multifocal or diffuse (disseminated) TSH-independent thyroid hyperfunction by quantitative thyroid scintigraphy with \textsuperscript{99m}Tc pertechnetate.

**Dosimetry**

The aim of radioiodine therapy (RIT) in autonomy is the destruction of autonomous tissue with restoration of euthyroidism. Some groups have successfully used standard activities.\textsuperscript{46} Others modify the fixed dose by giving larger activities per gram multiplied by the estimated thyroid weight and normalised to the 24 hours uptake value. In Germany radiation protection authorities require the estimation of therapeutic activity by a radioiodinetest. For dose estimation Marinelli’s formula is generally used:

\[
\text{MBq} \times 131\text{I} = \text{Gy desired } \times \text{weight of target thyroid tissue} \times 24.8 \times \text{maximal uptake (\%)} \times \text{effective half life (d)}
\]

Many investigators used ultrasonographic volumetry in the determination of the weight of the target volume in patients with unifocal autonomy. Agreement exists that in these patients an empirical dose of 300-400 Gy should be delivered to the autonomous tissue. Because it is impossible to measure the autonomous volume in multifocal or disseminated autonomy by ultrasonography with certainty, the sonographic approach to determine the target volume has been replaced by a so called «compromise». For this concept the thyroid gland as a whole was taken as the target volume and the target dose was reduced to 150-200 Gy. Using this concept sufficient therapeutic success could only be achieved in patients whose TCTU was smaller than 3.2\%, indicating that higher doses were necessary in a certain thyroid volume if the amount of autonomous tissue exceeded a critical limit. As a consequence the original approach was modified by adapting the target dose in autonomy to the TcTUs-values. This modified concept uses the total thyroid volume as a target with stepwise increasing the target doses between 150-300 Gy which are given dependent of the pretherapeutic TcTUs. Recently preferable results were published for this method.
A more functional approach in the determination of the target volume was developed by authors who made an attempt to estimate the «autonomous volume» directly by a linear correlation between the sonographic volume of unifocal thyroid autonomy without any regressive changes and their corresponding TcTU values. In order to estimate the autonomous volume independently of its distribution form of thyroid autonomy.

**Indications**

Thyroid autonomy is very common in longstanding goiters, so not only the diagnostic proof of a thyroid autonomy is an indication to radioiodine therapy or even surgery as the most common alternative treatment regimen. Thyroid autonomy should definitively be treated in patients having hyperthyroidism, borderline thyrotoxicosis, because of proven higher cardiac risk, and euthyroid patients where the TCTU under suppressive conditions (TCTUs) is higher than 2.0%.

**Results**

Own results demonstrate that after a 18 months follow-up radioiodine therapy is successful (TSH > 0.5 and or TCTUs < 1.6%) in 84%. Of these patients 91% were euthyroid with or without thyroxine and 9% borderline hypothyroid (TSH > 4 uU/ml). A dose of 350-450 Gy to the autonomous tissue resulted in a success rate of 97% in the unifocal and 78% in multifocal or disseminated autonomy. A negative influence comes from high therapeutic volume of the gland, high pretherapeutic TCTUs, multifocal and disseminated autonomy and low target doses.

The results are normally given after 6 to 12 months with a complete elimination of the autonomous tissue.

Treatment startegies differ from country to country. Also the possibility of an outpatient or inpatient treatment is different and is the same as described for Graves’ disease.

**Treatment of non toxic goiter**

Radioiodine is not classically used in the first-line treatment of non toxic goiter. Surgery is more common. However there may be a great benefit for some patients from radioiodine therapy, particularly when surgery is contraindicated as in elderly patients with cardiopulmonary diseases or not accepted by the patient for various reasons.

A thyroid relapse after surgery represents another indication for radioiodine therapy. The use of $^{131}$I in nontoxic goiter has certainly been reinforced by the general safety of this treatment.

Overall median thyroid volume reduction averages 50% after 24 months. In this indication also standard activities and dosimetric activities are reported, using the Marinelli algorithm.

Again modalities of therapy differ from country to country in Europe.

**Therapy of inflammatory joint diseases (radiosynovectomy)**

The principle of radiosynovectomy means, that the inflamed synovia will be normalized or cured after application of radionuclides in the joint and the inflammatory process will be stopped.

**Radionuclides and activity**

For radiosynovectomy only beta-emitting radionuclides are applied. The beta-emitters have to penetrate and cure the swollen synovia and the underlying cartilage has to be protected. The radioisotopes have to be fixed to particles small enough to be phagocytosed, but large enough for not leaving unspecifically the joint. The optimal size seems to be 2-5 um

For this reason different radionuclides are available and used because the thickness of the synovia in different joints is different. In smaller joints radionuclides with a short pathway in larger joints radionuclides with a longer pathways are used.

**Rhenium-186-sulfid**

The mean beta-energy of $^{186}$Re is 1.07 MeV and additional a gamma-energy of 137 keV is available, which allows gammacamera imaging. The pathway of the beta-energy is 3.7 mm and the physical halflife is 3.7 days. As a chelating agent sulfat is used. $^{186}$Re
is used for wrist, elbows and ankle joints with an activity of 74 MBq and for shoulders and hip with a dose of 111 MBq.

**Yttrium-90-citrate**

The mean beta-energy of \(^{90}\text{Y}\) is 2.26 MeV with a maximal pathlength of 11 mm in soft tissue. The physical halflife is 2.7 days. Due to its pathlength it is only used for injection into the knee joints with an activity of 185 MBq.

**Erbium-169-citrate**

The maximal beta energy of this low activity isotope is 340 keV with a short pathway of 1 mm in soft tissue. The physical half life is 9.5 days. The low energy is optimal for small joints just as in finger joints. Normally no more than 37 MBq are injected per joint.

**Therapeutic principle**

 Autoradiographic studies with colloidal coupled radionuclides show a preliminary superficial binding of the radionuclides and shortly afterwards also a deeper accumulation without damaging the cartilage of the joint. In accordance with an external radiation beam therapy the effect of radiation synovectomy can be described as an initial hyperemia, increased capillary leakage, increased leucocyte migration and dead with a subsequent increased cellular and humoral defense reaction. The final consequence can be described as reduction of local hyperemia with reduction of inflammation and inactivation of infiltration. Following this first step fibrosis of the synovia without damage of the cartilage are the consequence. The fibrosis can first be detected 2-3 months after instillation of the radionuclides. One of the consequences is the reduction of filtration and resorption of synovial fluids. After therapy it is recommended to fix the joint for at least 48 h via lying the patient in the bed or via a cast to prevent efflux of the radionuclides out of the joints into the lymphatic vessels and the regional lymphnodes.

 The application should be performed under x-ray control or preinjection of \(^{99m}\text{Tc}\)-pertechnetate under gammacamera to make sure that the radionuclide homogenously distributes. At a single time point more than one joint can be treated, but a total administered radioactivity of more than 400 MBq should not given per year.

**Indications for therapy**

Radiosynoviortheses is indicated in different joint diseases, such as rheumatoid arthritis and other inflammatory joint diseases, hemarthros in patients with hemophilia, villonodular synovalitis and osteoarthritis. Before therapy an active inflammation in the joint to treat has to be documented via three phase bone scintigraphy with increased blood pool activity or in a pertechnetate scintigraphy of the joint. This diagnosis of activity allows a semiquantitative reevaluation of the joint after therapy. Via sonography the inflammatory activity can be judged by the determination of the thickness of the synovia.

**Results**

In all the patients after 6 months a reduction of the thickness of the synovia of about 50% can be documented, whereas the reduction of the inflammatory process starts earlier and is about 40% after the first month. This can be documented by three phase scintigraphy and sonography. Pain relief starts early at 1 month after application and reaches its maximum at three months posttherapy.

**Side effects**

If a reflux or an instillation of part of the radionuclid happens into the puncture channel skin necrosis may happen. In 2% of the patients increased body temperature is described. Also in about 2% joint effusion happens immediately, which is not permanent. This can be prevented by a coinjection of steroids. Systemic side effects are not reported.

**Therapy of spondylitis ankylosans**

Spondylitis ankylosans is a common rheumatoid disease with inflammation of the small joints of the
spine and the iliosacral joints with pain and immobilisation of the spine as well as inflammation of the tendons of the central skeleton.

Recently the old, but for a long time not longer available $^{224}$Ra-chlorid ($^{224}$Ra) is available again. The injection of this drug leads to a target dose at the surface of the bones of 6 Gy.

**Therapy**

The use of $^{224}$Ra-chlorid is based on a low dose scheme with a 10 times weekly repeated injection of 1 MBq. A repetition of the therapy is recommended not earlier than 10 years afterwards.

**Indication for $^{224}$Ra-Radiumchlorid and results**

The indication is only given, if the disease is proven but should be performed early in the course of disease. This is important to start radiation at the time of inflammation and not when inflammatory lesions have gone. The treatment results in good pain relief and better mobilisation of the spine. Earlier described tumor induction is based on significantly higher activities used in earlier times.

**THERAPY OF MALIGNANT DISEASES**

**Therapy of thyroid cancer**

Thyroid cancer is a rare malignancy with wide interethnic and geographic variations. The overall incidence is increasing slightly in recent years. The most common types of cancer are papillary (60-80%) and follicular cancers (10-20%). The relevant prognostic indicators are tumor stage and distant metastases. The mean survival rates in papillary cancer usually exceed 90%, whereas in follicular cancer the amount is about 80%. The standard treatment procedure in these thyroid cancer types is total thyroidectomy and radioiodine therapy if the TSH level is higher than 30 mU/l. The short ranging beta-radiation (maximum range 2 mm in soft tissue) of $^{131}$I (8 days half-life) allows to administer tumor doses of higher than 500 Gy in tumor tissue. Percutaneous radiation therapy only achieves about 70 Gy. The basis for this therapy is the expression of the sodium-iodine-symporter, which specifically accumulates radioiodine in benign and malignant thyroid tumor tissue.

The expression is lower in tumors as in normal thyroid tissues, which explains that presurgically these nodules always are cold, because the surrounding benign tissue accumulates nearly all of the iodine. But after removing the normal thyroid tissue thyroid cancer tissue accumulates enough radioiodine for therapy. The indications for a routine ablative dose after surgery for patients having differentiated papillary or follicular thyroid cancer are:

— Elimination of the benign or potentially malignant remnant in the neck as a good basis for thyroglobulin follow-up.
— The adjuvant therapy of potential small circulating tumor cells or tumor cell clusters in lymphnodes or other organs.
— Curative or palliative treatment of inoperable tumor or metastases.
— Staging procedure, because high radioiodine doses are significantly better than low doses for imaging small metastases such as small disseminated pulmonary metastases in lymphangioses carcinomatosa of the lung.

In patients with medullary and anaplastic thyroid cancers no radioiodine uptake has to be expected. In oncocytic differentiated carcinomas an effective radioiodine accumulation can be demonstrated not very often, so it should be tried to treat these patients because they may benefit from radioiodine therapy.

The effect of radioiodine therapy is inversely correlated with the tumor mass. The higher the tumor volume, the lower the therapeutic benefit. So before radioiodine therapy it should always be considered together with the surgeon to remove as much tumor tissue as possible.

The only contraindication for radioiodine therapy is pregnancy. So pregnancy should be excluded before therapy and also breast feeding has to be stopped, because radioiodine is excreted in breast milk.

Therapeutic strategy

In the ablative situation the patients is treated between 3 to 4 weeks after surgery. At this time the TSH level is usually higher than 30 mU/l which is accepted to be high enough for radioiodine uptake in tumor tissue. Between surgery and radioiodine therapy thyroid hormones, iodine containing drugs and contrast agents are contraindicated. The urine iodine excretion should be checked, if possible.

The radioiodine uptake test should be done with low activities of radioiodine to prevent stunning. Activities of 10-20 MBq are recommended.

300 Gy are sufficient to ablate thyroid remnants. 1-3 GBq 131I deliver doses of more than 300 Gy if the tissue of the remnant is small enough. Some authors prefer to administer radioiodine on a dosimetric basis of the Quimby-Marinelli formula. But in general this is impossible, because the volume of the remnant can not be determined exactly.

The therapy itself should be combined with high hydration of the patient to facilitate urinary excretion and by oral stimulus of salivary gland excretion, i.e lemon juice, to keep the radiation exposure of the patients as low as possible. Recently Amifostine has been used to reduce radiation exposure to the salivary glands. In patients with large local remnants and with no further option of surgery non-steroidal antiphlogistics should be administered to prevent radiation induced thyroiditis.

In curative or palliative therapy of tumor residues, recurrences lymphnode or distant metastases if not performed immediately after surgery, the thyroid hormone suppressive therapy has to be stopped for 3-5 weeks to achieve TSH stimulation of higher than 30 mU/l. In the future perhaps recombinant human TSH may be injected to induce radioiodine uptake.

In general diagnostic or dosimetric studies should not be performed immediately before radioiodine therapy, because stunning could prevent acceptable radioiodine uptake in the tumor tissue. So most of the authors administer standard activities between 5-10 GBy.

In patients with high thyroglobulin but without radioiodine positive diagnostic scans some authors recommend also to perform radioiodine therapy. The benefit of the patients is around 50-60% of the cases, but the benefit is only measured as a disappearance of an elevated tumor marker. In patients with faint radioiodine uptake in the tumor tissue retinoic acid for some weeks may induce 131I uptake again, but these data have still to be confirmed.

Therapy of neuroblastoma

The targeting of neuroblastoma with radiopharmaceuticals is based on the characteristic features of neuroblastoma such as the metabolism of MIBG, via receptor binding or via antibody targeting. The active uptake-1 mechanism at the cell membrane and the neurosecretory storage granules in the cytoplasm of the neuroblastoma are responsible for the uptake of 131I- or 123I labelled MIBG. The radiopharmaceutical may be released from the granules, but a reuptake mechanism prolongates the retention in the tumor cells. In non adrenergic tissue there is a passive diffusion only. The peptide receptors on top of neuroblastoma cell lines, which have been used for neuroblastoma imaging are the somatostatin receptor and the vasoactive intestinal peptide receptor. Reubi has shown that somatostatin receptor is expressed in 86% and VIP receptor in 57% of all the cases.

Goldman y cols. and Cheung y cols. reported successful radioimmunoscintigraphy with a 131I-labelled UJ13A and a 123I-labelled 3FB antibody (oncalfetal antigen ganglioside GD2). Nowadays studies in nude mice demonstrate a high specific tumor uptake with an antibody against a cell surface glycoprotein chCE7. First clinical results have been reported. Potentially due to the high radiation sensitivity of neuroblastoma cells MIBG therapy, peptide therapy with 90Y-DOTATOC or labelled VIP and radioimmunotherapy would be possible approaches.
**Indication and contraindication**

The largest experience nowadays is based on $^{131}$I-MIBG therapy. The indication for such a therapy are TNM stage III and IV, where chemotherapy and surgery, sometimes high dose chemotherapy with stem cell transplantation are the basis of therapy. Radiation therapy may follow. Due to the bad prognosis of the disease other therapy strategies are warranted.

Contraindications for $^{131}$I-MIBG therapy are severe myelosuppression and renal failure. Unstable clinical conditions which do not allow to isolate the patient in a specific unit is a relative contraindication. $^{131}$I-MIBG therapy is given in the following clinical settings: in recurrent or progressive disease after all other modalities have been used, preoperatively at the start of the treatment protocol in inoperable stage III and IV disease and in combination with hyperbaric oxygen therapy.

**Therapeutic strategy**

Generally a fixed does of 3.7-7.4GBq (100-200mCi) of $^{131}$I-MIBG with a high specific activity (up to 1.48 GBq/mg) is intravenously injected during 30 min to 60 min. For thyroid protection 200 mg potassium iodide is given orally daily.

**Results**

Different results in small series have been published and demonstrate a low response rate but sometimes a very impressive palliative effect. The review of pooled results of in total 273 treated patients indicated an overall objective response rate of 35%. Most of these patients had progressive and intensively pretreated diseases in stage IV disease. The therapy and the isolation of the patients is generally well tolerated. Thrombocytopenia may selectively occur due to a radiation of the bone marrow but also due to selective uptake of MIBG in platelets. In patients with bone marrow involvement the use of stem cells or bone marrow for transplantation is recommendable. Troncone described hypertensive crisis shortly after administration of the drug.

The objective of introducing $^{131}$I-MIBG therapy as the first therapy was to reduce the tumor volume, enabling adequate surgical resection and to avoid toxicity and the induction of early drug resistance. An additional advantage of such an approach was that the child’s general condition is unaffected or improved before it undergoes surgery. In this approach chemotherapy is reserved to treat minimal residual disease. In their initial results Hoefnagel and cals. demonstrated that the objective response rate was better than after conventional treatment and 70% had complete or > 95% resection of the primary tumour or did not require surgery at all. The toxicity after such a first-line therapy was only mild thrombocytopenia and moderate myelosuppression, because in these patients the bone marrow was not infiltrated. In conclusion the first line treatment is at least as effective as combination with chemotherapy but is combined with significantly less toxicity. The combination of both was reported to be associated with severe toxicity.

Several new applications are nowadays discussed, such as the use of Auger-electron emitters like $^{125}$I-MIBG or alpha-emitters like At-211-MABG. Also the combination with other uptake and retention increasing radiopharmaceuticals are discussed, i.e interferon, retinoic acids etc.

First results have also been reported on the use of radioimmunotherapy as is described above.

**Therapy of pheochromocytoma and paraganglioma**

Pheochromocytomas and paragangliomas are rare catecholamine-producing tumors which arise from chromaffin tissue. When there is the suspicion of a pheochromocytoma the biochemical confirmation is based on 24 hour urinary excretion rates of catecholamines and their metabolites (metanephrines, VMA etc.). Non invasive imaging techniques such as CT and MRI and $^{123}$I-MIBG scintigraphy are performed to localize the tumor and / or metastases. $^{111}$In-octreotide may also be applied, especially in head and neck chemodectomas. Malignant paragangliomas of adrenal or extraadrenal origin show a variable natural history from a locally invasive indolent tumor to a highly aggressive tumor. Surgery with complete resection or debulking of the primary tumor is standard treatment. External radiotherapy or chemotherapy are not very effective. An alternative therapy is here the use of $^{131}$I-MIBG.
**Indications and contraindications**

$^{131}$I-MIBG is mainly indicated in disseminated and unresectable pheochromocytoma with a good tracer uptake, so that $^{131}$I-MIBG is able to deliver at least 20 Gy to the target. Another indication is the treatment of small postsurgical residual tumors to complete surgery. The aims of the treatment are 1) symptom palliation 2) reduction of tumor function due to the secretion of catecholamines 3) stable disease, partial or complete response.42

**Therapy strategy**

Imaging studies with $^{123}$I- or $^{131}$I labelled MIBG should demonstrate a good tracer uptake and retention and dosimetry are recommended before therapy. Before imaging and dosimetry drug intake interfering with MIBG uptake has to be stopped 7 days before starting scintigraphy or therapy, thyroid has to be blocked with Potassium-perchlorate or high doses of iodine (200 mg) or Lugols solution. 18.5-37 MBq $^{131}$I-MIBG is slowly intravenously injected and whole body and spot images are performed. Dosimetry should be performed according MIRD formulations taking into account $^{131}$I-MIBG tumoral uptake (% of 24 hr), retention of the tracer dose (effective halflife), the tumor volume estimated by CT or ultrasound.

3.7-9 GBq of $^{131}$I-MIBG is infused controlling heart rate, blood pressure and ECG.

The treatment can be repeated within of 4 to 6 weeks, but usually within of 3-12 months. Cumulative doses of 30 GBq have been reported. Reinjection of treatment doses should be dependent from the toxicological profile (platelets > 150 000/l).

**Results**

Troncone and Rufini report in a multicenter metaanalysis of 137 treated patients a biochemical response in 52 patients, a complete response in 8, partial response in 25, stable disease in 60 patients progressive disease in 29 and not evaluable were 15 patients. But it is important to keep in mind that the therapeutic response depends on the tumor size, the number of metastases, the MIBG uptake and retention etc.

In advanced stages nearly in all treated patients a symptomatic improvement could be achieved. A partial response (6 months to 4 years) was observed in 68% of the patients. Soft tissue lesions better responded than bone metastases. Smaller lesions responded better than larger lesions. Therefore debulking should always precede MIBG therapy. In these advanced stages a complete response was rare (5.8%). In patients with less advanced disease longer lasting complete responses have been achieved.

In malignant paragangliomas partial responses were observed in most cases and symptom palliation in all of them. The largest series is reported by Virotta y cols. with 22 patients with chemodectoma. 10 patients were only evaluable but all showed subjective benefit, 1 had tumor shrinkage and 9 showed stabilisation of disease.

**Side effects and toxicity**

Some patients complain immediately after infusion nausea and anorexia accompanied by vomiting, which easily can be handle by diet and antiemetic drugs. Some patients demonstrate increase of blood pressure, due to catecholamine displacement in the periphery, but this can be handle by reducing infusion rate. Myelotoxicity is low, but a few patients have minor and transient myelosuppression with leukopenia and thromocytopenia. This typically occurs 4 to 6 weeks after therapy. The risk is highest in patients with bone metastases. The development of hypothyroidism has also been reported.

**Therapy of neuroendocrine tumours with somatostatin analogues**

It is well known that peptide receptor scintigraphy with the radioactive somatostatin-analogue ($^{111}$In-DTPA) octreotide is a sensitive and specific technique to show in vivo the presence and abundance of somatostatin receptors on various mainly neuroendocrine tumours. With this technique primary tumours and metastases of neuroendocrine tumours as well of other cancer types can be localized. Based on this knowledge the use of peptide receptor radionuclide therapy, administration of high doses of $^{111}$In- or $^{90}$Y-labeled octreotide analogues is now in prospective clinical trials. Due to the experimental status of this the-
therapy the comments on it will be short, because the therapy is only available in a few centers.

The Rotterdam group treated thirty end-stage patients with mostly neuroendocrine progressing tumours with $^{111}$In-DTPA octreotide with up to a maximal cumulative patient dose of about 74 GBq in a phase I trial. There were no major clinical side effects after up to 2 years treatment except that a transient decline in platelet counts and lymphocyte subsets can occur. Promising beneficial effects on clinical symptoms, hormone production and tumor proliferation were found. Of the 21 patients with progressive disease at baseline and who received a cumulative dose of more than 20 GBq $^{111}$In-DTPA octreotide 8 patients showed stabilisation and 6 a reduction of tumor size. There is a tendency to a better result in patients having higher tumor uptake\textsuperscript{17}.

In a phase II study 40 patients were treated in the Basel group with 4 intravenous injections of a total of 6000MBq/m\textsuperscript{2} Y-90-DOTATOC administered at intervals of 6 weeks. 82% of patients suffered from a tumor progression before therapy. According to WHO criteria the tumor response was as follows: complete remissions in 3\%, partial remission in 20\%, minor response in 13\% stable disease in 50\% and progressive disease in 15\%. The tumor response according to WHO criteria was 23\%, and 36\% in case of endocrine pancreatic tumors. Up to now these results have been calculated after a nine months follow-up. More than 90\% of the patients had improvement of the subjective syndromes. Side effects were only mild lymphopenia lasting 3-5 weeks after injection in 20\% of the patients\textsuperscript{68}. It could be nicely shown that in patients with a positive antitumor effect there was a good correlation with the dose to the tumor, calculated with $^{90}$Y-DOTA TYR Octreotide\textsuperscript{44}. A coinfusion of aminocids is renal protective, which is very important, because the kidneys are the critical organ with the highest dose.

This therapy is one of the most promising therapies and has to be forwarded to patients with smaller tumor load, who probably have better therapeutic results.

Metastatic bone pain palliation

Pain is both a blessing and curse for humanity. The onset of pain serves as a benefactor when it convinces the patient to seek medical aid early, at a time when the pathophysiologic process is still reversible. However, the same benefactor becomes a curse in the terminal stages of patient’s lives, especially for those with metastatic bone cancer.

The therapy of bone metastases with radionuclides is known since 40 years. Besides osteotropi radiopharmaceuticals especially the pure beta emitter will be used such as $^{89}$Sr and $^{90}$Y. Disadvantage of $^{89}$Sr is the long physical half-life of 50.6 days. This is the reason why $^{90}$Y was preferred, which itself is incorporated in the bone metabolism, has a shorter half-life of 2.7 days and a higher betaenergy. Comparable results were known from P-32 but due its incorporation in the bone marrow as well myelosuppression is the consequence.

A new group is the combination of bone seeking radiopharmaceuticals such as $^{186}$Re-HEDP and $^{153}$Sm-EDTMP. For all this radiopharmaceuticals the aim is bone pain palliation, which leads to a lowering of the dose of drugs and increases life quality.

Therapy

After a conventional bone scan, where the metabolic activity of metastases have been proven the therapy can be started. The scintigraphic control can be performed with a gammacamera using the Bremsstrahlung and the gamma energy of the radionuclides.

The usual activities are: 40-150 MBq (1-4 mCi) for $^{90}$Y, 35-100 MBq (1-3 mCi) for $^{89}$Sr, 1.3GBq (35 mCi) for $^{186}$Re-HEDP and 2.6 GBq (79 mCi) for $^{153}$Sm-EDTMP. These doses are recommended for patients with 70 kg.

Indication and results

This kind of therapy is indicated in advanced stages of bone metastases mainly of prostatic and breast cancer, but all kinds of cancer metastases can be treated. The only relevant question is the metabolic activity of the osteoblastic metastases, which has to be proven by bone scintigraphy. About 80\% of the injected radiopharmaceutical is metabolized in the bone metastases whereas the rest is excreted via the kidneys very fast, so a treatment as an inpatient is recommended but not necessary.

The effect of bone palliation is hard to document because most of these patients are in an advanced

stage of the disease. Normally pain relief starts after some days (doses to the metastases 4 Gy). The duration of this effect is strongly correlated to the dose to the metastases. If the tumor to bone ratio is 10 : 1 a dose of up to 40 to 50 Gy can be delivered.

The rate of success is variable and ranges between 60 and 90%.

Side effects and complications are rarely documented. After several injections bone marrow depression is reported. This therapy is mainly indicated and of benefit, if the pain is diffuse of large areas of the bone where local external radiation is not possible to perform.

**Future developments**

Some authors report the use of higher doses of the radiopharmaceuticals to control not only pain but also the disease. $^{153}$Sm-EDTMP was injected in five cycles using 30 mCi each and a significant decrease in the number of bone metastases and a decrease of PSA in patients with prostate cancer was reported. This remission of bone metastases in the bone scan is remarkable and was also reported by McCready and colleagues. He used $^{186}$Re HEDP in a dose escalation study and found that metastases from prostate cancer in the bone can successfully ablated by therapy activities of rhenium-186 and that higher activities are even more effective. But in these cases bone marrow toxicity has to be considered and even stem cell transplantation may be necessary.

**Intraperitoneal and intrapleural therapy**

Another palliative approach is the intraperitoneal or intrapleural injection of $^{99}$Tc-colloids. The colloids prevent resorption. The application of the radionuclide is performed under sonographic control in the left lower quadrant of the abdomen, or at the typical side of pleural effusion. Very important is the primarily reduction of the volume of the ascites or the pleural effusion to prevent a dilution of the injected radionuclide. Before the therapeutic radionuclid is injected the homogenous distribution of the injected radionuclide should be demonstrated using $^{99m}$Tc labelled colloids. After the therapeutic injection the distribution should be controlled with a Bremsstrahlung image.

**Indication and results**

The indication for this kind of therapy is a recurrent ascites or pleural effusion in malignant diseases. The aim of the therapy is to stop or to reduce the volume of ascites or pleural effusion. In about 50-80% of the treated patients the result starts but not earlier than 3 months after injection. Patients with chylic effusion, large tumor masses in the abdomen or chest or patients with circumscribed fluid cysts should not be treated.

**Therapy of polycythemia**

Polycythemia is a myeloproliferative syndrome and mainly gets manifest in elderly patients. The disease leads to splenomegaly and proliferation of red cells but also platelets. The aim of the therapy is normalisation of the blood cell counts to reduce the danger of thrombosis and normalisation of the size of the spleen. Primarily blood letting and chemotherapy is used.

**Therapy**

After intravenous injection of $^{32}$P as natrium-dihydrogenphosphat, which is incorporated in cells with high turn over, predominantly in bone marrow cells and in the calciumphosphat of the bone. Before therapy blood lettings should be performed to stimulate proliferation activity of the bone marrow and to increase the rate of incorporation of $^{32}$P into the stem cells when stem cell proliferation starts.

The recommended activities are empiric. At the beginning 70-110 MBq (2-3 mCi) $^{32}$P / qm body surface or a standard activity of 185 MBq (5 mCi). After 3 to 4 months therapy could be repeated if no therapeutic results can be detected. It is recommended to inject a 25% increased activity. A repetition of therapy is possible if the single dose is not higher than 250 MBq (7 mCi). The effective half life is about 20 days and the absorbed dose is 5-14 mGy/MBq for the bone marrow. 5 to 10% of the activity is renally excreted within of the first 24 h. The cumulative urinary excretion is up to 50%. In Germany a 48 h indoors therapy is necessary.
Indications and results

A primary success of the therapy can be expected in 60-85% of the patients with a time of remission of 6 to 24 months. The mean survival time increases from 1 to 2 years up to 11 to 16 years. There is no significant difference in comparison to chemotherapy.

Acute side effects just as bone marrow aplasia and pancytopenia are rare, but due to this fact blood specimens for control are recommended. Late side effects is leukemia. The frequency increases from 1 to 2% up to 10 to 15%. Chemotherapy with Busulfan chemotherapy shows the same effect. But nowadays other chemotherapeutics are recommended.

Pregnancy, age under 40 years and leuco- or thrombocytopenia are contraindications. This kind of therapy can be performed in polycythemia but also in thrombocytopenia.

NEW THERAPEUTIC STRATEGIES

Intraarterial hepatocellular carcinoma therapy with \(^{131}\)I-labelled lipiodol

Recently in different asian, french and german group the use of \(^{131}\)I-lipiodoltherapy was reported. The \(^{131}\)I-lipiodol has to be delivered via an intrarterial catheter during hepatic angiography. The therapeutic efficacy is dependant on tumor mass. Side effects due to the radiopharmaceutical were tolerable and mainly consisted of a transient rise of liver enzymes.

These results are encouraging for tumors up to a moderate mass.

Local radioimmunotherapy of malignant gliomas

The high grade malignant gliomas (anaplastic astrocytoma and glioblastoma) have a very bad prognosis since the available methods of treatment (surgery, radio therapy and chemotherapy) are unable to control the progression of the disease for long. The use of specific monoclonal antibodies labelled with a suitable isotope (iodine-131 and yttrium-90) represents an effective approach to hamper tumour growth. Some authors have injected the antibodies intravenously, or have tried to increase the tumour / background ratio with the avidin / biotin system. In many cases the monoclonal antibodies were injected directly into the tumoral bed after surgery. The largest series uses antitenascin antibodies labelled with \(^{131}\)I and recently with \(^{90}\)Y for direct local injection. The clinical results demonstrate the ability of this technique to control, for a long time, the growth of the tumour. The glioblastoma median survival was prolonged to 25 months (\(^{131}\)I-therapy) or 31 month (\(^{90}\)Y-therapy). The response rate which comprises partial response, complete response and no evidence of disease was 47.1% (glioblastoma \(^{131}\)I-therapy) or 40% (glioblastoma \(^{90}\)Y therapy). The use of \(^{90}\)Y proved to be more favourable in bulky lesions and reduced the radioprotection problems.

Radioimmunotherapy of Non-Hodgkins-Lymphoma

Rationale

Few patients with relapsed non-Hodgkin’s lymphoma are curable with conventional doses of chemotherapy or radiotherapy. In contrast, high doses of chemotherapy and radiotherapy in conjunction with autologous peripheral stem cell or bone marrow transplantation can offer long term disease-free survival for between 20 to 50% of such relapsed patients. However conventional chemotherapy conditioning regimens used for autologous transplantation are associated with high morbidity and 3-15% treatment-related mortality from infections, venoocclusive disease of the liver, interstitiell lung disease, and renal failure. Furthermore relapse rates remain high, with 40 to 80% of patients eventually developing progressive lymphoma.

Based on this background the clinical promise of radiolabelled antibodies has been recently verified by several authors.

Results

Press y cols. have documented in an \(^{131}\)I-labelled murine monoclonal anti CD20 (anti-B1) trial with myeloablative doses of \(^{131}\)I complete responses in 83% of their patients and many of these responses have been durable. The patients received therapeutic infusions of 234 to 777 mCi of \(^{131}\)I labelled antibody (58 to 1168 mg). In a median follow-up time of 42
months the overall and progression free-survival rates were 68% and 42%.

The use of a cold chimeric anti-CD-20 antibody (IDEC-C2B8) is also well documented. Maloney (44) injected 375 mg/m² and documented 46% complete responses.

Kaminski (35) y cols. administered non-myeloablative doses of I-anti-B1 (anti-CD20) mAb (34-161 mCi) and documented 50% complete response. The median duration of response exceeded 16.5 months. The therapy in these patients is dosimetry based. Delivering 75 Gy to the tumor, this group reported a 57% response rate, a complete response in 35%. The median duration of response was 9.9 months.

Knox y cols. (38) reported a 72% overall response rate and a 33% complete response rate with a non-myeloablative dose (13.5-50 mCi) of an Y labelled murine anti-CD20 antibody (IDEC-Y2B8). Later on the same group with the same antibody (0.4 mCi/kg) reported an overall response rate of 67% for low grade disease a response rate of 82%, for intermediate grade 43% and for mantle cell disease 0% (70).

Another approach is the use of an anti-CD22 antibody. Vose y cols. (66) report in a dose escalating study a total response rate of 33%.

**Side effects**

Dose dependant side effects were seen from the bone marrow, which had to be substituted by stem cell transplantation in high dose therapy schemes. The side effects then are comparable to bone marrow aplasia after radiation or high dose chemotherapy. They were expected, because the antibody delivers its activity also to the normal non malignant bone marrow cell. In a low number of patients hypothyroidism occurred in the iodine labelled antibody therapy group although there was a high blocking of the thyroid uptake. Using murine monoclonal antibodies, a limited number of patients developed human antimouse antibodies (HAMA). The HAMA rate is low because all these patients are immunocompromised due to their disease. Other side effects like moderate fatigue, nausea fever, vomiting, pruritus and rash were reported in a frequency between 10% to 70%.

Patients with bulky disease and splenomegaly were appointed as unfavourable in the biodistribution, because in bulky disease the total uptake was normally low, in splenomegaly most of the injected antibody goes to the spleen and for the rest of the tumour there is not enough antibody left. But also in these situations responses are reported.

Summarizing the results of these published studies the highest number of responses and progression free survival rates are reported in the high dose I approach. The disadvantage is the handling of high doses of I, the long inpatient status of these patients, whereas the low dose I has a shorter period of inpatient stay and can be performed in some countries on an outpatient basis. The use of yttrium-90 has the disadvantage of having no gamma emission, which is also an advantage, because this offers a higher safety profile to medical personnel but does necessitate the use of another radioisotope (In) for imaging studies.

**Future directions**

Several independent groups have now documented impressive efficacy with minimal toxicity of anti-CD20 monoclonal antibodies and radioimmunoconjugates. Future studies will be aimed at integrating this exciting group of radiopharmaceuticals in conventional chemotherapy in the setting of minimal residual disease, investigating upfront therapy for previously untreated patients, amplifying radiation delivery to tumor cells using the avidin-biotin pretargeting strategy and optimizing the application of these reagents to potentially curative high dose regimens.

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