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Targeted therapy in nuclear medicine—current status and future prospects

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In recent years, a number of new developments in targeted therapies using radiolabeled compounds have emerged. New developments and insights in radioiodine treatment of thyroid cancer, treatment of lymphoma and solid tumors with radiolabeled monoclonal antibodies (mAbs), the developments in the application of radiolabeled small receptor-specific molecules such as meta-iodobenzylguanidine and peptides and the position of locoregional treatment in malignant involvement of the liver are reviewed. The introduction of recombinant human thyroid-stimulating hormone and the possibility to enhance iodine uptake with retinoids has changed the radioiodine treatment protocol of patients with thyroid cancer. Introduction of radiolabeled mAbs has provided additional treatment options in patients with malignant lymphoma, while a similar approach proves to be cumbersome in patients with solid tumors. With radiolabeled small molecules that target specific receptors on tumor cells, high radiation doses can be directed to tumors in patients with disseminated disease. Radiolabeled somatostatin derivatives for the treatment of neuroendocrine tumors are the role model for this approach. Locoregional treatment with radiopharmaceuticals of patients with hepatocellular carcinoma or metastases to the liver may be used in inoperable cases, but may also be of benefit in a neo-adjuvant or adjuvant setting. Significant developments in the application of targeted radionuclide therapy have taken place. New treatment modalities have been introduced in the clinic. The concept of combining therapeutic radiopharmaceuticals with other treatment modalities is more extensively explored.
Key words: peptide receptor radionuclide therapy, radioimmunotherapy, radionuclide therapy, radioiodine therapy, radiopharmaceuticals, transarterial radionuclide therapy

introduction

In recent years, a number of new developments in targeted therapies using radiolabeled compounds have emerged. These vary from new insights in the treatment of thyroid cancer with radioiodine to the application of radiolabeled monoclonal antibodies (mAbs) and designer peptides. In this review, the current status and new developments in targeted radionuclide therapy are addressed.

new developments in radioiodine treatment of thyroid cancer

Radioiodine has been applied in millions of patients with benign and malignant thyroid diseases for >50 years. When administered systemically, I-131 is concentrated in thyroid tissue, achieving high intrathyroidal radiation doses thereby generating a therapeutic effect due to the emission of charged particles (electrons, β radiation). Due to the limited range, the cervical soft tissues are spared. I-131 accumulates in a given follicle, irradiates integral cellular structures such as cytoplasm and nucleus and may also irradiate neighboring cells and follicles. The aim of postoperative radioiodine therapy in differentiated thyroid cancer (DTC) is the selective irradiation of iodine-avid thyroid remnants and thyroid carcinoma [1–3].

Although DTC is relatively resistant to radiation, radioiodine treatment is an effective method due to the potentially high local dose that can be achieved [4]. Papillary and follicular tumors generally express the sodium iodide symporter (NIS), which is the key cellular feature for specific uptake of radioactive iodine [5, 6].

The target dose to the tissue is the determinant for successful therapy. Patients are commonly treated with standard ablative

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activities in the range of 1.1–3.7 GBq (30–100 mCi) of radioiodine [7]. An alternative approach is based on pretherapeutic individual dosimetry [8]. Dosing concepts were established based on quantitative dosimetry to estimate the activity needed to deliver an effective radiation dose (e.g. 300 Gy). This requires several measurements of the uptake of a tracer activity of radioiodine. Nevertheless, tumor doses exceeding 500 Gy can be achieved by systemic application of I-131, while external irradiation usually leads to <70 Gy [9].

Especially in high-risk patients, extending I-131 therapy to its limits may be beneficial. The indication for repeated 'high-dose' treatments should be considered after individualized risk stratification [10]. The effect of radioiodine treatment correlates inversely with tumor mass and extent. Younger age is predictive of favorable response. Figure 1 shows an example of successful treatment of diffuse pulmonary metastases by repetitive I-131 infusions.

Long-term adverse effects of I-131 therapy include salivary gland dysfunction, (transient) bone marrow depression and possibly hypofertility. There may be an elevated risk of leukemia and other secondary malignancies, but this has not been consistently demonstrated by follow-up studies and is therefore likely to be very small and dependent on other coexisting factors.

Elevated serum levels of thyroid-stimulating hormone (TSH) are a prerequisite for a selective uptake of radioiodine in both normal and cancerous thyroid-derived cells. Until recently, patients were treated with I-131 in a hypothyroid state after withdrawal of thyroid hormone therapy. Recently, administration of recombinant human TSH (rhTSH) without discontinuation of levothyroxine intake has been shown to be as effective for thyroid remnant ablation as conventional approaches on the basis of the discontinuation of the TSH-suppressive therapy with levothyroxine [11]. rhTSH has also been used in the treatment of distant metastases. However, no prospective, randomized studies have been conducted to date, and the published experience only reports individual cases or case series [12]. The main indications for rhTSH use in metastatic disease were insufficient endogenous TSH production, serious concomitant illnesses or high patient age and generally poor condition. In general, it is believed that a considerable proportion of patients derived some clinical benefit from rhTSH-aided radioiodine treatment, success rates being in the range of 30%–60% including partial remissions and stabilization of the disease [12]. The future role of rhTSH-aided radioiodine treatment of DTC, especially in the curative treatment, such as those with diffuse, miliary lung metastases, needs to be elucidated in further studies.

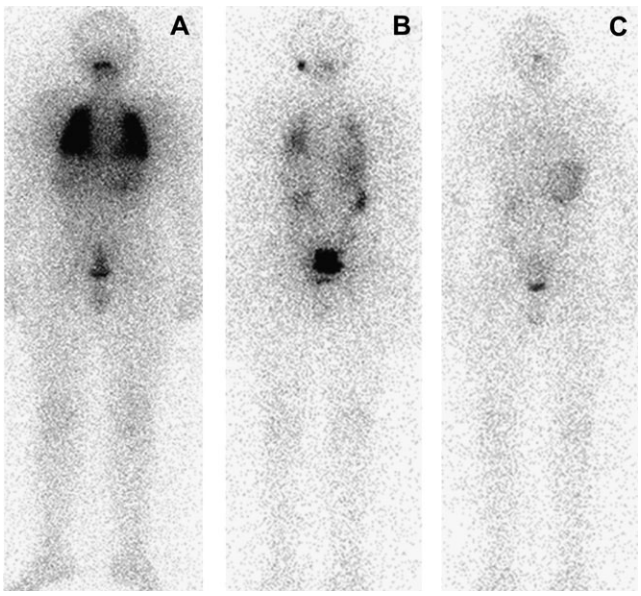

Figure 1. Successful treatment of pulmonary metastases of pT4N1M1 papillary thyroid carcinoma by repetitive high-dose I-131 infusions. (A). I-131 scintigraphy before treatment: diffuse pulmonary uptake of I-131 due to diffuse lung metastases. (B) I-131 scintigraphy after two administrations of I-131: decrease of the pulmonary uptake indicating response of the lung metastases. (C) I-131 scintigraphy after three administrations of I-131: no abnormal pulmonary uptake indicating complete response.

Up to one-third of metastasized or recurrent thyroid carcinomas may dedifferentiate over time, characterized by a loss of growth-regulating mechanisms mediated by TSH and/or a decline in iodine avidity making them eventually inaccessible to radioiodine therapy [13, 14]. This effect is commonly attributed to a lost or reduced expression of the thyroidal sodium/iodide symporter (NIS). Since a restoration of this essential biological feature would lead to a potential treatment options, various groups have investigated 'redifferentiating' agents such as retinoid acid and its derivatives. *In vitro* and *in vivo* studies showed that retinoids may inhibit proliferation of malignant cells. Retinoids bind to specific DNA sequences and modulate the transcription of retinoic acid responsive genes. Although retinoids showed a number of effects *in vitro*, they have so far failed to translate into a marked clinical effect. Response rates in the order of 20%–30% can be expected [13, 14]. Controlled clinical trials are warranted to establish better criteria for the pretherapeutic selection of patients. A more sophisticated approach may be on the basis of the determination of the individual receptor status.[15].

radioimmunotherapy with mAbs

hematological malignancies

Chemotherapy in combination with the anti-CD20 antibody rituximab is considered standard treatment of diffuse large B-cell lymphoma, as well as for follicular lymphoma [16]. Most patients with disseminated B-cell lymphoma are, however, not cured. The need for improvements in the treatment of B-cell lymphoma and the radiosensitivity of the disease provides the rationale for application of systemic radiotherapy in this disease.

Two radiolabeled anti-CD20 antibodies are currently available for radioimmunotherapy (RIT), i.e. Y-90-ibritumomab tiuxetan (Zevalin®, IDEC Pharmaceuticals and Schering AG, Berlin, Germany) and I-131-tositumomab (Bexxar®, Glaxo Smith Kline, Philadelphia PA) [17, 18]. Both radiolabeled mAbs are more efficacious at inducing remissions

compared with the respective unlabeled antibody, including rituximab [19] and also more effective than prior courses of chemotherapy in these patients [17]. A single course of I-131-tositumomab as initial therapy can induce 75% complete remissions (CR) in patients with advanced follicular lymphoma [20]. The authors found that 81% of the patients who had both a CR and molecular response with regard to the BCL2 gene, had a progression-free survival of 5 years, suggesting that this very favorable subset of patients (i.e. initial therapy of follicular B-cell lymphoma) may not benefit from additional or more intensive treatment.

Attempts to optimize the efficacy of RIT of B-cell lymphoma are ongoing for refractory/relapsed indolent and aggressive B-cell lymphomas. Three factors need to be considered: (i) choice of antibody/antigen, (ii) choice of radionuclide, (iii) choice of delivery system/schedule.

(i) The choice of the antibody/antigen: The vast majority of patients whose disease becomes refractory to rituximab still have lymphoma cells that express CD20 antigen, so they remain appropriate targets for anti-CD20-radiolabeled antibodies. Patients with unequivocal expression of the target antigen are reported to show a better response rate than those with a weak expression [21]. Quantitative flow cytometry analysis of the target antigen CD22 has shown to be a useful predictor of the outcome of therapy with epratuzumab, a Y-90-labeled humanized anti-CD22 immunoglobulin G antibody [21]. As the combination of epratuzumab (anti-CD22) with rituximab (anti-CD20) has shown to be well tolerated and having a significant clinical activity in aggressive and indolent B-cell lymphoma [22], a further development to explore could be the combination of different radiolabeled antibodies labeled.

(ii) The choice of the radionuclide: Beta-emitting radionuclides (i.e. Y-90, I-131, Cu-67, Lu-177) are mostly used for B-cell lymphomas in clinical trials. For the treatment of microscopic disease and leukemia, these radionuclides do have the disadvantage that their beta energy results in energy deposition beyond the targeted cell. Another option is the use of targeted alpha particles with radionuclides such as bismuth-213 or actinium-225, which offers both the possibility of selective tumor cell kill with less damage to surrounding normal cells and a higher radiobiological effectiveness [23, 24].

(iii) Choice of the delivery system/schedule: RIT is limited by the absorbed dose to radiosensitive organs (bone marrow, lung, liver and kidney). The bone marrow is the first dose-limiting organ but myeloablation can be circumvented by stem-cell support. To avoid toxicity of the other radiosensitive organs, other strategies must be used as pretargeting (discussed below) or affinity adsorption procedures [25].

In 2000, the long-term follow-up of a phase I–II high-dose myeloablative RIT of 29 patients with B-cell lymphoma was reported [26]. Following the phase I study, patients were treated to a calculated maximal tolerated dose of 25–27 Gy to normal organs to avoid cardiopulmonary toxicity, corresponding to 12 765–29 600 MBq of I-131-tositumomab. Approximately 85% of the patients showed objective responses with 79% CR. After a median follow-up of 42 months, 14 were free of progression. The overall and progression-free survival rates were 68% and 42%, respectively. When the pharmacokinetics of the chimeric I-131-labeled rituximab was studied, the kidneys were almost exclusively dose limiting [27]. These differences may be due to the significant difference in half-life between the two antibodies, the chimeric and the murine antibodies having plasma half-lives of 88 h and 56 h, respectively. Studies of myeloablative RIT using Y-90-labeled antibodies are ongoing and encouraging results have been reported [28].

A very interesting approach is the application of pretargeted RIT to increase the therapeutic window of RIT. The administration of the nonradioactive antitumor antibody is separated in time from the injection of small, radioactive molecules that can bind to the antibody. Thus, the tumor is targeted by the mAb, which is allowed to clear from circulation and normal organs. The small radioactive molecules which have affinity to bind to the pretargeted antibody have the advantage that they clear very fast from organs and tissues where no antibody is present, thereby reducing radiation-induced toxicity of normal organs, especially the bone marrow. Thus, these strategies provide increased tumor-to-background ratios and the delivery of a higher therapeutic dose. There are two reports on successful treatments of patients with B-cell lymphoma, using different pretargeting strategies [29, 30].

solid tumors

So far the application of radiolabeled antibodies for the treatment of patients with solid tumors has been less successful than in patients with malignant lymphoma. Several reasons can be identified. First, the generally lower radiosensitivity of solid cancers. Furthermore, solid tumors are targeted less efficiently with radiolabeled antibodies than lymphoma due to limited vascularization, elevated interstitial pressure and heterogeneous uptake of the radiolabeled antibody [31]. Due to the combination of these factors, treatment with radiolabeled antibodies results in tumor-absorbed radiation doses that typically do not exceed 15 Gy at dose levels when grade III/IV hematological toxicity is observed. As large tumor size further diminishes tumor uptake of radiolabeled antibodies, minimal residual disease is considered the most favorable condition for treatment with radiolabeled antibodies.

As most patients are studied in phase I/II clinical trials, most data are derived from heavily pretreated patients, mainly with bulky disease. Deriving efficacy data from dose-escalation studies will never yield data on the potential efficacy at the optimal dose in the patient population best suited for this type of treatment.

In colorectal carcinoma (CRC), the most commonly targeted antigen is carcinoembryonic antigen (CEA), as 95% of CRC express this antigen. The largest series of patients who were treated with I-131-labeled murine anti-CEA mAb NP-4 evaluated the antitumor activity of escalating activity doses of I-131-labeled NP-4 in 57 patients with CEA-expressing malignancies, of whom 29 had CRC [32]. Antitumor effects were reported in 12 of 35 patients, including one partial remission, four mixed/minor responses and seven stabilizations of previously progressive disease. Unfortunately, the tumor types of the responding patients were not specified. Because of the immunogenicity of the murine form (development of human anti-mouse antibodies), the antibody was humanized.

In patients with small-volume liver involvement, maximum tolerated dose (MTD) due to grade 4 hematological toxicity after administration of I-131-labeled hMN14 proved to be higher than in patients with bulky disease [33–35]. Seven of nine patients in whom RIT at MTD was administered in an adjuvant setting after resection of liver metastases did not show evidence of recurrence at a median follow-up of 27 months [34]. These favorable results were confirmed in a larger series of 23 patients, in whom a 5-year survival of 51% was reported, being an improvement as compared with historical and contemporaneous controls [36]. Still, these results need to be addressed cautiously as the patient groups are small and the studies lack appropriate controls. Wong et al. [37] evaluated the Y-90-labeled, high-affinity chimeric anti-CEA mAb cT84.66 in patients with CRC. In the study, combining Y-90-cT84.66 and 5-fluorouracil (5-FU), they did not observe responses, but did see stable disease (SD) (less than a 50% reduction and less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and the appearance of no new lesions according to the WHO standard criteria) in patients with previously progressive disease.

Ovarian cancer has been targeted in RIT trials using mainly antibodies directed against the mucin-1 (MUC-1) antigen and a few other tumor-associated glycoproteins, such as TAG-72 and gp-38 [38]. As ovarian cancer tends to stay confined to the peritoneal cavity during the course of the disease, radiolabeled antibodies have been administered intraperitoneally in many trials. Nevertheless, whether or not the intraperitoneal route of administration has significant advantages as compared with intravenous injection is not unequivocally proven. Based on a study by Nicholson et al. [39] who reported significantly better median survival than a matched historical control group and long-term survival (>10 years) after treatment with Y-90-labeled HMFG-1 mAb, a multicenter phase III randomized controlled trial was initiated, comparing the Y-90-HMFG-1 to best supportive care in 447 patients with ovarian cancer with no evidence of disease following cytoreductive surgery and platinum- or taxol-based chemotherapy, as confirmed by diagnostic laparoscopy. Unfortunately, no significant survival benefit was observed [40]. However, some suboptimal choices were made. First, the antibody dose was relatively high, which may have resulted in antigen saturation. Secondly, Y-90 is not the radionuclide of choice in minimal residual disease due to its high beta energy that results in energy deposition largely outside of the small tumor deposits.

Given the prevalence of breast cancer, the availability of several mAbs and its radiosensitivity, many mostly small clinical RIT trials have been conducted in patients with breast cancer with a variety of radiolabeled mAbs, as recently reviewed by DeNardo [41]. Although objective responses were reported, patient numbers are generally too small for more conclusive assessment.

In renal cell cancer, the antigen Carbonic Anhydrase IX is uniformly expressed in the vast majority of cases, which are mainly of the clear cell type. This antigen is very efficiently targeted by the mAb G250. Several clinical trials have been performed. In a phase I/II trial addressing the feasibility and efficacy of repeated high-dose I-131-labeled cG250 [42], no objective responses were recorded. However, four out of 15 assessable patients who received two therapy courses experienced stabilization of previously progressive disease for up to 6 months. When fractionating RIT instead of administrating the MTD, again SD was reported in 50% of assessable patients for 2–11 months [43]. Nevertheless, hematological toxicity was again dose limiting and no evidence of bone marrow sparing by fractionation was observed.

Most of the work using pretargeting strategies has been applied in solid tumors. Recently, the methodology using the (strept)avidin-biotin system or bispecific antibodies has been extensively reviewed [44, 45]. Very recently, a survival benefit has been reported in patients with medullary thyroid cancer treated with a bispecific antibody and a small radioiodinated peptide [46]. Furthermore, this approach is highly amendable to further biotechnological improvements, e.g. by creating trivalent antibodies that can target tumors more effectively [47].

radiolabeled MIBG

Uptake of meta-iodobenzylguanidine (mIBG), an arylalkylguanidine norepinephrine analogue, by the various organ systems reflects rich adrenergic innervation and/or catecholamine excretion [48–50]. Thus, radiolabeled mIBG enabled successful imaging of neuroectodermally derived tumors (neuroblastomas, pheochromocytomas, paragangliomas, medullary thyroid carcinomas, carcinoid tumors, Merkel cell tumors of the skin) [51, 52].

The high sensitivity and specificity of mIBG for the detection of primary and secondary tumor sites led to the development of I-131 mIBG treatment of neuroectodermally derived tumors [53, 54].

Neuroblastoma is a high-grade malignancy of childhood, chemo- and radiosensitive but prone to relapse after initial remission induction. Stage 1 and 2 tumors are usually cured by surgery alone. Many stage 3 tumors are rendered operable by neo-adjuvant chemotherapy. Sixty percent of neuroblastomas in young children are stage 4 (undifferentiated and widely disseminated at diagnosis). Many of these have biological markers for poor prognosis, such as MYCN amplification or 1p deletion [55, 56]. I-131 mIBG therapy has been used since the 80s as a palliative agent in relapsed patients [57, 58]. Figure 2 shows an example of a patient with metastatic neuroblastoma who was in remission after two cycles of I-131 mIBG. Later, the radiopharmaceutical was proposed in first-line therapy, as single agent or in combination with chemotherapy [59–61], in combination with myeloablative therapy before bone marrow rescue [62, 63], or in consolidation therapy after induction of a 'good partial remission' [64–68]. In second-line therapy after failed induction chemotherapy, I-131 mIBG can be combined with topotecan, a radiosensitizer and stem-cell rescue [69, 70].

In I-131 mIBG therapy, again the bone marrow is the dose-limiting organ [64, 71]. To optimize mIBG therapy, a toxicity–dose relationship for bone marrow suppression has been demonstrated [72]. Thus, pretherapy dosimetry can be used to predict the individual degree of bone marrow toxicity. In patients with neuroblastoma who had received prior intensive chemotherapy, dose-limiting toxicity (DLT) of a single fraction of I-131 mIBG was myelotoxicity at 2.5 Gy whole-body dose.

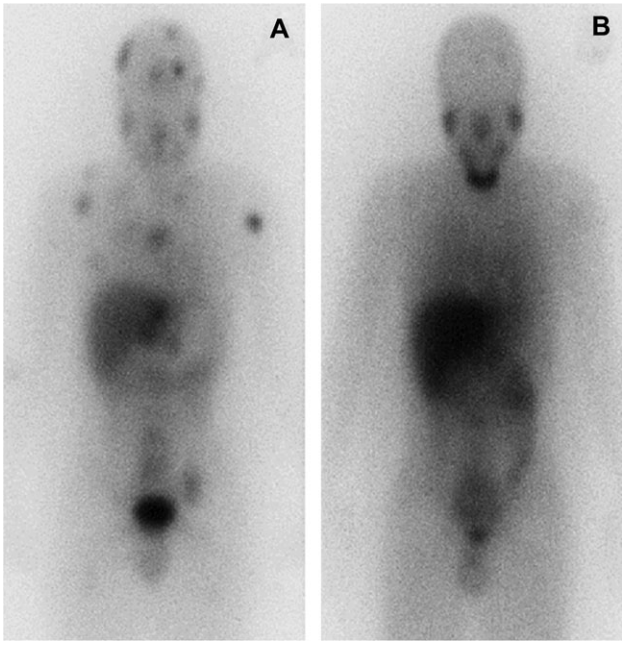

Figure 2. Treatment of metastatic neuroblastoma with I-131-meta-iodobenzylguanidine (mIBG). (A) I-131-mIBG scintigraphy before treatment: extensive bone metastases. (B) I-131-mIBG scintigraphy after two administrations of I-131-mIBG: no evidence of disease activity. Images courtesy of A. McEwan and E. Postema, Cross Cancer Institute, Edmonton AB, Canada.

A total of 4.0 Gy whole-body dose with stem-cell rescue is well tolerated with no other short-term organ DLT [73].

Currently, two major lines for further development of I-131 mIBG treatment are ongoing. Both involve I-131 mIBG dose escalation to further increase the tumor radiation dose. One approach is administration of high activity of I-131 mIBG with stem-cell support. The activity dose was established in toxicity–dose relationship phase I studies [71]. Whole-body (and tumor) doses were calculated after therapy and the dose of a second treatment is on the basis of the correlation of the radiation dose and observed toxicity [72]. Howard et al. [68] reported the feasibility of repetitive I-131 mIBG and achieved a 39% overall disease response in 24 heavily pretreated patients. The European ESIOP I-131 mIBG protocol includes patients with high-risk neuroblastoma who failed to achieve an adequate partial remission after induction chemotherapy. High doses of I-131 mIBG, combined with topotecan are administered [70] to deliver a total combined whole-body dose of 4.0 Gy in two fractions. A stem-cell rescue is required after the second fraction. Relatively simple dosimetry is performed after the first fraction, calculating the activity to be administered in the second fraction. This allows a very homogeneous total activity dose to the patients and better assessment of the relevant parameters, i.e. whole-body and tumor doses. The feasibility of this protocol was recently tested in a phase I study in eight children [69].

Phaeochromocytoma is a rare disease arising from the adrenal gland, mainly occurring in adults [74]. It is usually benign, but early recognition of malignant phaeochromocytoma is critical to avoid significant morbidity and mortality. In a small study, I-131 mIBG therapy was evaluated in 12 patients with malignant phaeochromocytoma [75]. Three patients were in CR and alive without evidence of disease after a mean follow-up of 45 months. Seven patients were in partial remission (two subsequently died of disease), two had progressive disease (both died of disease). Grade 3 thrombocytopenia was observed after 79% of cases and grade 3 and 4 granulocytopenia in 53% and 19% of cases. All patients had stem cells harvested before therapy, but only one required stem-cell return.

peptide receptor radionuclide therapy

Neuroendocrine tumors, which include pancreatic islet cell tumors, nonfunctioning neuroendocrine pancreatic tumors and carcinoids, are usually slow growing. The overexpression of somatostatin receptors enables treatment of tumor hypersecretion and of primary and metastatic lesion growth due to postreceptor signaling, triggered by the receptor–ligand internalization [76–79]. Treatment with somatostatin analogues yields symptomatic and biochemical responses in 73% and 77% of patients, respectively, but only 3%–5% objective responses are encountered in neuroendocrine tumors.

As a consequence of the scintigraphic localization of neuroendocrine tumors with radiolabeled somatostatin analogues, therapeutic approaches with radiolabeled peptides were developed. Peptide receptor radionuclide therapy (PRRT) can deliver radiation doses to tumors, which are adequate to achieve volume reduction [80]. The biological basis of PRRT is the receptor-mediated internalization and intracellular retention of the radiopeptide. Several clinical trials indicated that PRRT with radiolabeled somatostatin analogues is among the promising newly developed targeted tools in neuroendocrine tumors [81].

Initial studies were performed with the administration of high doses of the radiopeptide [In-111-DTPA^0]-octreotide. Objective responses were rare due to the short range of the emission and therefore the short tissue penetration of the particles (nanometers to micrometers). Among 40 patients treated with cumulative doses of 20–160 GBq, one partial remission, six minor remissions and 14 stabilization of disease were reported. Mild hematological toxicity was observed, but three cases of myelodysplastic syndrome (MDS) or leukemia occurred in the patients treated with high activities (>100 GBq). In another study in 27 patients with gastroenteropancreatic neuroendocrine tumors, partial responses (more than 50% reduction in size) occurred in two of 26 patients with measurable disease. Renal insufficiency was reported in one patient, although possibly not treatment related [82, 83].

The radiopeptide that has been most extensively studied is [Y-90-DOTA^0,Tyr^3]-octreotide. Despite differences in clinical phase I–II protocols from different centers, CR and partial remission were observed in 10%–30% of patients, a rate undoubtedly higher than that obtained with [In-111-DTPA^0]-octreotide. Moreover, survival of patients with metastatic gastroenteropancreatic neuroendocrine tumors was longer after [Y-90-DOTA0,Tyr3]-octreotide than [In-111-DTPA0]-octreotide [84]. In a first report, 29 patients were treated with a dose-escalating scheme consisting in four or more cycles of

[Y-90-DOTA^0,Tyr^3]-octreotide with cumulative activities. Twenty of these patients showed a disease stabilization, two had partial remission, four minor remission and three progressed [85]. In a subsequent study, 39 patients were treated with four equal intravenous injections, for a total of 7.4 GBq/m^2 of [Y-90-DOTA^0,Tyr^3]-octreotide [86]. The objective response rate was 23%, with CR in two patients, partial remission in seven and stabilization in 27. Neuroendocrine pancreatic tumors (13 patients) showed a higher objective response rate (38%). A significant reduction of clinical symptoms was recorded. Toxicity was generally mild and involved the kidney and the bone marrow. However, renal insufficiency was reported in five patients not receiving renal protection with amino acids during the therapy, while severe hematological toxicity occurred in those patients treated with high cumulative activities.

Dosimetric and dose-escalating studies with [^{90}Y-DOTA^0,Tyr^3]-octreotide, with and without renal protection showed no major acute reactions up to an administered dose of 5.55 GBq per cycle [87]. Reversible grade 3 hematological toxicity was found in 43% of patients injected with 5.18 GBq, which was defined as the MTD per cycle. None of the patients developed acute or delayed kidney toxicity, although follow-up was short. Partial and complete responses (according to the WHO standard criteria) were reported in 28% of 87 patients with neuroendocrine tumors [87]. In a multicenter phase 1 study, 60 patients received escalating doses up to 14.8 GBq/m^2 in four cycles or up to 9.3 GBq/m^2 in a single dose, without reaching the maximum tolerated single dose. All patients received renal protection. Three patients had DLT (liver toxicity, grade 4 thrombocytopenia and MDS). Four of 54 patients (8%) treated with the highest dose had partial response and seven patients (13%) had minor responses. The median time to progression (TtP) in the 44 patients with SD, minor or partial response was 30 months. Significant biochemical and symptomatic responses in functioning tumors were recorded [88, 89].

The newer somatostatin analogue [DOTA^0,Tyr^3]-octreotate has a nine-fold higher affinity for the somatostatin receptor subtype 2 compared with [DOTA^0,Tyr^3]octreotide [76]. In a preliminary report, 35 patients with neuroendocrine gastroenteropancreatic tumors were treated with escalating doses of [Lu-177-DOTA^0,Tyr^3]-octreotate, resulting in complete and partial responses in 38% of patients. No serious side-effects were observed [90]. In a subsequent study, 131 patients with somatostatin receptor-positive tumors were treated with up to a cumulative dose of 22.2–29.6 GBq of [^{177}Lu-DOTA^0]-Tyr^3-octeotate [91]. CR was observed in three patients (2%), partial remission in 32 (26%), minor response in 24 (19%) and SD in 44 patients (35%), while 22 patients (18%) progressed. Better responses were more frequent in case of high uptake on baseline In-111-DTPA-octreotide scintigraphy and in case of a limited number of liver metastases, while progression was significantly more frequent in patients with a low performance score and extensive disease at enrollment. Median TtP was >36 months, comparing favorably to chemotherapy. One patient developed renal insufficiency and another patient developed hepatorenal syndrome. Severe hematological toxicity occurred after <2% of the administrations. In addition, [Lu-177-DOTA^0]-Tyr^3-octeotate significantly improved the global health/quality of life and various function and symptom scales in patients with metastatic gastroenteropancreatic tumors [92].

Due to their marked radiosensitivity, the kidneys are the critical organs in PRRT. Proximal tubular reabsorption of the radiopeptide and the subsequent retention in the interstitium results in renal irradiation. Given the high kidney retention of radiopeptides, positively charged molecules, such as L-lysine and/or L-arginine, are used to competitively inhibit the proximal tubular reabsorption of the radiopeptide [93–96]. Despite kidney protection, renal function loss may become clinically evident years after PRRT. A median decline in creatinine clearance of 7.3% per year was reported in patients treated with [Y-90-DOTA^0,Tyr^3]-octreotide and of 3.8% per year in patients treated with [Lu-177-DOTA^0,Tyr^3]-octreotate. Cumulative and per-cycle renal absorbed dose, age, hypertension and diabetes are considered as contributing factors to the decline of renal function after PRRT [97].

Besides renal toxicity, bone marrow involvement must be considered although it appears not to be a principal dose-limiting factor. Acute hematological toxicity grade 3 or 4 is not uncommon, especially after [Y-90-DOTA^0,Tyr^3]-octreotide, and the possibility of a mild, but progressive impoverishment in bone marrow reserves has to be considered in repeated cycles [96]. In addition, MDS or overt leukemia may develop in patients receiving high bone marrow doses, especially in those previously treated with alkylating agents [81].

The majority of the studies with [Y-90-DOTA^0,Tyr^3]-octreotide are designed as phase I–II trials, thus not specifically addressing efficacy. In addition, the rates of tumor remission after [Y-90DOTA^0,Tyr^3]-octreotide treatment vary due to different administered doses and dosage schemes, as well as inhomogeneous patient characteristics, such as tumor type, tumor load and liver involvement. Uniform pathology-oriented phase II trials are required to assess the potential of peptide receptor radionuclide therapy. [91]. Furthermore, to establish which treatment scheme and which radiolabeled somatostatin analogue or combination is optimal, randomized clinical trials comparing different treatments are needed.

radionuclide therapy of liver tumors and metastases

Liver tumors are a very important cause of morbidity and mortality worldwide. For hepatocellular carcinoma (HCC), resection or liver transplantation is the only curative treatment available in the absence of extrahepatic metastases. However, only 10%–15% of patients are eligible. Systemic chemotherapy is generally no treatment option. In liver metastases of adenocarcinoma, multimodality treatment is employed to increase survival including surgery, systemic chemotherapy and a wide variety of locoregional therapies, such as percutaneous local ablative techniques (radiofrequency ablation, laser coagulation, ethanol injection, cryotherapy, microwave coagulation therapy) and transarterial regional techniques (hepatic artery chemotherapy (HAC), transarterial chemoembolization (TACE), transarterial radionuclide

therapy, vena porta embolization, isolated hepatic chemoperfusion). The big advantage of the locoregional administration of agents is the much higher dose that can be achieved in a single treatment.

Transarterial hepatic radionuclide therapy for HCC and liver metastases dates back to the early 70s, when albumin colloids labeled with Phosphorus-32 were first used. One line of research has been the further development of such micrometer-sized particles. When injected into a hepatic artery, such particles preferentially lodge in the hypervasculature of liver tumors (small arterioles, capillary sinusoids) and internally irradiate the neighboring tumor tissue. By the virtue of the dual blood supply, whereby the hepatic artery mainly perfuses tumors while the normal parenchyma is mainly perfused via the portal vein, a selective irradiation is achieved by the short ranged beta-emitting isotopes attached to the particle. Today, two of these products are commercially available, i.e. resin microspheres (SIR-Spheres®, Sirtex, Bonn, Germany) and glass spheres (Theraspheres®, Nordion, Fleurus, Belgium), both labeled with Y-90. Another agent, lipiodol is a fatty acid ester derivative of naturally occurring iodine-rich seed oil which was previously widely used as computed tomography contrast agent. Lipiodol labeled with I-131 is commercially available (Lipiocis®, Schering S.A., Berlin, Germany). This oily substance is trapped in the tortuous tumor vessels but, contrary to the spheres, is also taken up by tumor cells by endocytosis. Figure 3 shows the accumulation of I-131-lipiodol after intraarterial administration in a patient with HCC.

Important advantages of radionuclide therapy for liver tumors are its favorable toxicity profile and the feasibility of combination with other therapies such as systemic chemotherapy and limited liver resection without major toxicity. Serious side-effects may occur in ~5% (16/319) of patients for I-131-lipiodol. Grade 3 and 4 toxicity occurs in 7% (23/336) of patients for SIR-spheres therapy. Furthermore, treating the whole liver makes it more suitable for multiple tumors as compared with local ablative strategies such as radiofrequency ablation. Especially, microscopic subclinical tumors are also effectively treated with this approach. The feasibility of this has been demonstrated experimentally and clinically [98].

I-131-lipiodol therapy has not been used in recent years for liver metastases after early disappointing results [99]. This may be related to its lower cellular uptake, its lower particle radiation range and subsequently lower cross-fire radiation effects in larger tumors. In HCC, the largest experience has been with I-131-lipiodol as a single agent in palliative treatment of inoperable cases. A collection of publications between 1986 and 2002 included 319 patients [100–103]. Overall, the average radiological response rate of these was 28% (range 13%–100%) and the average 1-year survival 31%. As HCC has a median survival of only a few months, it appears that this treatment can extend survival. However, the effect on survival remains uncertain as only one small study randomized patients in comparison with best medical support. [104]. This study showed a significant difference in survival at 3 and 6 months (71% versus 10% and 48% versus 0%), but there was no survival at 12 months in both groups. However, this may be related to the grave prognosis of portal thrombosis, as observed by others [101]. One large prospective randomized study comparing I-131-lipiodol with TACE observed similar response rates and survival, but far better tolerability of I-131-lipiodol (severe side-effects in 3% after I-131-lipiodol versus 29% after TACE; six treatment-related deaths in the TACE group within 15 days after treatment, but no mortality in the I-131-lipiodol group) [105].

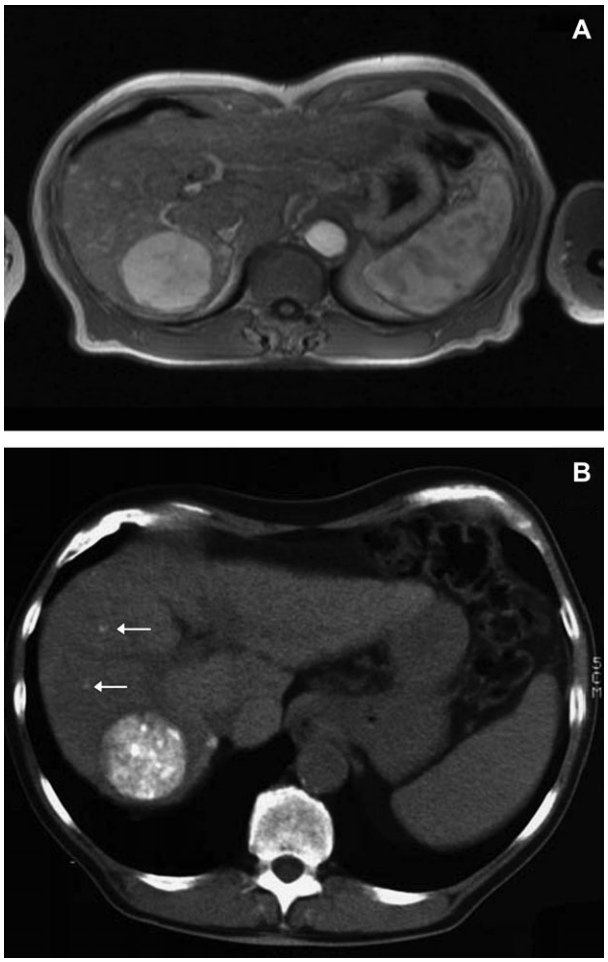

Figure 3. (A) Pretherapeutic T1-weighted magnetic resonance imaging (MRI) following gadolinium contrast in arterial phase showing a large, inoperable hepatocellular carcinoma (HCC) tumor in the right liver lobe. (B) High specific targeting is demonstrated on the computed tomography (CT) scan of the liver performed 7 days after administration of 2.2 GBq (60 mCi) I-131-lipiodol via selective canulation of the right hepatic artery. In addition, very small, subclinical lesions are also targeted (arrows).

More recently, I-131-lipiodol therapy has been used as adjuvant therapy after resection. A pilot study in 43 randomized patients reported 28.5% of recurrences in the treated group versus 59% in the untreated control group with a 3-year survival of 86% and 46%, respectively ($P = 0.04$) [98]. This study was criticized for a premature termination, but subsequently it has been supported by nonrandomized, retrospective studies [106, 107]. Low-range isotopes such as I-131 may be more suitable for these patients with minimal residual disease, as a larger fraction of the radiation energy will

be absorbed within the boundaries of the tumor as compared with long-range isotopes such as Y-90 that may irradiate to a larger fraction beyond such very small tumor cell clusters.

Two studies have piloted the neo-adjuvant use of I-131-lipiodol before liver transplantation [108, 109]. Objective radiological response in the first study was 50%. The second study reported 1- and 3-year recurrence-free survival rates of 91% and 83%, respectively. These figures are very promising, probably also because of the limited disease in these patients. Larger, randomized studies are needed to assess its value. Given the lack of liver donors, the most important role may be in preventing patients to dropout because of tumor progression while on the waiting list for transplantation.

A very interesting product development in lipiodol therapy is the recent use of the isotope Re-188, which yields higher dose rates and is readily available via a generator [110–112]. As no high-energy gamma rays are emitted, there is no need for hospitalization and isolation for radiation protection.

SIR-spheres therapy (SIRT) has been used mainly to treat liver metastases of CRC [113]. Recently, promising preliminary results have also been reported for small groups of patients with breast cancer metastases and HCC [114]. An early study by Gray et al. [115] in patients with CRC liver metastases reported a significant benefit in a phase III randomized trial in 74 patients in favor of HAC plus SIR-spheres, as compared with HAC alone. Objective response was 44% versus 17%, median TtP 15.9 versus 9.7 months and a trend for improved survival (39% versus 29% after 2 years). Given this beneficial effect of combined chemotherapy and radionuclide therapy, SIRT has been studied in combination with standard systemic chemotherapy. In the first study, 21 untreated patients were randomized to 5-FU plus leucovorin alone or combined with one cycle of SIRT. The results of the combined therapy were impressively different: objective response 73% versus 0%, median TtP 18.6 versus 3.6 months, without differences in grade 3/4 toxicity and quality of life [116]. In further studies by the same group, the combination of SIR-spheres with irinotecan or FOLFOX showed similar preliminary results [117, 118]. In the former trial, TtP in the liver was 9.9 months (range 1.5–27+), anywhere 6.0 months (1.5–15+) with the dominant site of progression being the lungs. Median survival in this challenging patient group was 13.6 months (range 2.8–34+), which compared favorably to phase III data from the literature of 6.4–9.4 months.

Another option is the use of SIRT before or after resection of hepatic tumors. Data from 226 tumors in 64 clinical trial patients show a median tumor decrease of 60%, irrespective the size, while >20% clinically disappear, the largest tumor 10 cm in diameter. Downstaging to allow resection was evident in 20% of first-line patients. These seem favorable prerequisites for further development of this indication. The future challenge is the optimal integration of locoregional radionuclide therapy into the increasing number of surgical, chemotherapeutic and targeted treatment options.

conclusions

In recent years, significant developments in the application of targeted radionuclide therapy have taken place, even in the well-established I-131 treatment of thyroid cancer. New treatment modalities, such as radiolabeled antibodies and peptides, targeting specific antigens or receptors have been introduced in the clinic. Local application of radiopharmaceuticals in liver tumors may become an asset to improve the still limited survival. The concept of combining therapeutic radiopharmaceuticals with other treatment modalities is more extensively explored. A gradual shift from treating patients with bulky disease to patients with minimal residual disease, for which radionuclide-based therapy is most suitable, is continuously considered.

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