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Position paper

Clinical applications of newer radionuclide therapies

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ABSTRACT

When radio-iodine was first used in the treatment of metastasized thyroid carcinoma in 1943, its success in terms of tumour response, quality of life improvement and survival was considered a 'miracle', as in those days metastatic cancer was generally fatal. Inspired by this, many efforts have been made to apply radioisotope therapy to other tumours. Radionuclide therapy uses radioactive isotopes labelled with specific targeting agents that aim to deliver the irradiation of the isotope to the tumour, while sparing normal tissues. Its unique modality allows to systemically target radiosensitive tumours throughout the body. Another important principle is its so-called 'cross-fire' action, whereby, owing to the larger reach of the radiation in relation to the cell diameter, a tumour cell receives lethal hits also from isotopes in the neighbourhood that are not directly associated with this cell. The treatment is therefore less hampered by inhomogeneous distribution and metabolism than for example chemo- or immunotherapy. The European Association of Nuclear Medicine has issued guidelines on so-called 'established' therapies (www.eanm.org), i.e. hyperthyroidism, thyroid carcinoma, refractory synovitis, bone metastases, mIBG therapy, ^{32}P therapy and Lipiodol therapy. Newer therapies include radio-peptide therapy, radio-immunotherapy of lymphoma and microsphere therapy for liver cancer. The aim of a recently held workshop at the ECCO13 conference 2005 and this review is to inform the oncology community about these new developing therapies.

1. Radiopeptide therapy

Radiolabelled meta-iodobenzylguanidine (mIBG) – a norepinephrine analog and false neurotransmitter, and peptides specific to hormone receptors (mainly the somatostatin hormone analogue octreotide) are highly sensitive and specific for the detection of primary and secondary neuroendocrine tumours. This has led to their use as radiotherapeutic agents in neuro-endocrine tumours (NET).[1–3]

1.1. *Neuro-ectodermic NET*

As the sensitivity of radiolabelled mIBG scanning is higher than octreotide as a result of higher observed tumoural uptake in these type of neurogenic tumours,[4] the radiation dose delivered through ^{131}I-mIBG is also higher. This makes use of radiolabelled octreotide therapy in neuroblastoma and pheochromocytoma less feasible than ^{131}I-mIBG therapy.

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1.1.1. *Developments of ^{131}I-mIBG therapy in neuroblastoma*

Neuroblastoma is a high-grade malignancy of childhood, chemo- and radio-sensitive but prone to relapse after initial remission. ^{131}I-mIBG therapy has been used since the 1980s in Europe and the United States as a single palliative agent for chemo-refractory cases, or more recently in combination with myeloablative therapy before bone marrow rescue.[5] Other applications have been unresectable stage 3 disease, first-line therapy in combination with chemotherapy, and consolidation therapy after induction of a good partial remission. Sixty percent of neuroblastomas in young children are Stage 4 (undifferentiated and widely disseminated at diagnosis). In these cases, new treatment strategies are needed. Inclusion of ^{131}I-mIBG therapy modalities is highly desirable because of the high specificity of the agent and radiosensitivity of the primary and metastatic tumour.

In ^{131}I-mIBG therapy, the bone marrow is the dose-limiting organ. In a cohort of patients with neuroblastoma who had received prior intensive chemotherapy, it has been shown that the dose-limiting toxicity of single-fraction ^{131}I-mIBG is myelotoxicity at 2.5 Gy whole body dose. A total of 4.0 Gy whole body dose with stem-cell rescue is well-tolerated with no other short-term organ dose-limiting toxicity.[6] As a dose–toxicity relationship was previously established between bone marrow suppression and the whole-body dose, which can be used as a surrogate for marrow dose, pre-therapy dosimetry ^{123}I-mIBG scanning can be used to predict the individual degree of bone marrow toxicity.[7]

Following these premises, two major lines of ^{131}I-mIBG treatment development are taking place. Both involve ^{131}I-mIBG dose escalation to increase the tumoural radiation dose further, but differ in methodology. In the United States, the 'San Francisco approach' gives a high activity of ^{131}I-mIBG (15–18 mCi/kg, about 550–660 GBq/kg), with stem cell support available. This activity amount was previously established from toxicity–dose relationship phase I studies.[8] Whole body (and tumour) dose are calculated after therapy and a second treatment is administered if necessary, based on the correlation of radiation dose and observed toxicity.[7] The advantage is that there is no need for more or less acute planning/simulation. The disadvantages are the wide range of whole body (and tumour) doses that will still exist, the risk of individual under- or over-treatment and unpredictable myelotoxicity. Howard and colleagues reported the feasibility of repetitive ^{131}I-mIBG and achieved a 39% overall disease response in 24 heavily pretreated patients.[9]

The European 'ESIOP ^{131}I-mIBG-protocol' is dedicated to patients with high-risk neuroblastoma who failed to achieve adequate partial remission after induction chemotherapy. It uses high activities of mIBG, combined with topotecan,[10] in order to deliver a total combined whole body dose of 4.0 Gy in 2 fractions (Table 1). A stem cell rescue is required after the second fraction. Relatively simple dosimetry is performed after the first fraction and calculates the activity to be administered in the second fraction. This allows a very homogeneous total activity dose to the patients which also allows better study of the relevant parameters, i.e. whole-body and tumour doses. The feasibility of this protocol was recently tested in a Phase I study in eight children.[11]

Table 1 – ESIOP Phase II study in primary resistant neuroblastoma

Pre-therapy stem cell harvest	
Day 0	131I-mIBG dose 1: 444 MBq/kg (12 mCi/kg)
Day 0–4	topotecan 0.7 mg/m^2 daily
Post-therapy dosimetry to calculate received whole body dose	
Day 14	131I-mIBG dose 2: calculated to deliver a total combined whole body dose of 4.0 Gy
Day 14–18	topotecan 0.7 mg/m^2 daily
Day 24	Stem cell return

1.1.2. *Developments of ^{131}I-mIBG therapy in phaeochromocytoma*

Phaeochromocytoma is a rare disease arising from the adrenal gland that most commonly occurs in adults. It is usually benign and causes excess secretion of catecholamines. Early recognition of the presence of malignant phaeochromocytoma is critical in avoiding significant morbidity and mortality.

A recent study was performed in order to evaluate the performance of mIBG therapy with high activities in 12 patients with malignant phaeochromocytoma.[12] Three patients were in complete remission, including two patients with soft tissue and skeletal metastases: all three were alive without evidence of disease during a mean follow up of 45 months. Seven patients were in partial remission (two subsequently died of disease), two patients in progressive disease (both died of disease). Grade 3 platelet toxicity was noticed after 79% of therapies, and grades 3 and 4 neutrophil toxicity after 53% and 19% of therapies, respectively. All patients had stem cells harvested before therapy, but 11/12 patients reconstituted spontaneously and only one required stem cell return.

1.2. *Gastro-entero-pancreatic (GEP) NET*

The neuro-endocrine tumours of endodermic origin, also called gastro-entero-pancreatic tumours, are a heterogeneous group characterized by generally good prognosis, but important disparities of the evolutionary potential. In the aggressive forms, the therapeutic strategies are limited. Human somatostatin receptors (hSSTR 1–5), which mediate the antiproliferative effects of somatostatin are present in normal tissues and in several tumours. The systemic radionuclide therapy using radiolabelled peptides (essentially somatostatin analogues), which can act at the same time on the primary tumour and its metastases, constitutes a tempting therapeutic alternative currently in evolution. mIBG therapy plays a minor role, as this norepinephrine analog is well-taken up by the neuro-ectodermic tumours but far less by endodermic tumours.

1.2.1. *Developments in radiolabelled octreotide therapy*

Octreotide® is a somatostatin analogue with high affinity for hSSTR2, and a lower affinity for hSSTR3 and 5 (Table 2).[13,14] Labelled with ^{111}Indium (^{111}In-DTPA-D-Phe1-octreotide or Octreoscan®), the radiopharmaceutical is widely used as a diagnostic agent, particularly to image neuroendocrine tumours of endodermic origin thanks to its γ emission. However, it is also an important Auger electron emission which can be used therapeutically. ^{177}Lutetium-DOTA-Tyr(3)-Thr(8)-octreotide

Table 2 – Peptides affinities

Peptides	SST1	SST2	SST3	SST4	SST5
Somatostatin[28]	5	3	8	6	4
Octreotide	>10000	2	200	>1000	20
DTPA-octreotide	>10000	10	400	>1000	300
In-DTPA-octreotide	>10000	20	200	>1000	250
DOTA-octreotide	>10000	15	30	>1000	60
DOTA-lanreotide	200	2	2	2	2
Y-DOTA-lanreotide	>10000	20	300	>1000	15
DTPA-Tyr^3-octreotate	>10000	4	>10000	>1000	>1000
In-DTPA-Tyr^3-octreotate	>1000	1	>1000	430	>1000
DOTA-Tyr^3-octreotide	>10000	15	900	>1000	400
Y-DOTA-Tyr^3-octreotide	>10000	10	400	>10000	115
DOTA-Tyr^3-octreotate	>10000	2	>1000	500	600
Lu-DOTA-Tyr^3-octreotate	>10000	2	>1000	500	200
Ga-DOTA-Tyr^3-octreotate	>10000	0.2	>1000	300	380

Kd in nM; modified from Ref. [13,14].

(^{177}Lu-DOTATATE) has a lower β particle energy and shorter range and may be more effective in treating small lesions. ^{90}Yttrium-DOTA-D-Phe(1)-Tyr(3)-octreotide (^{90}Y-DOTATOC, or Octreother®) is more widely used, and may be more effective to larger tumours with its larger pathlength. Combinations of both may be feasible too. However, official registration as a pharmaceutical and commercial availability precludes wider applications of these products, which are therefore still to be considered as experimental therapy.

The preliminary results of peptide receptor-mediated radionuclide therapy are now encouraging. Two early studies[15,16] using ^{111}In-DTPA-D-Phe1-octreotide showed 0% and 8% objective response. Peptides labelled with a β-emitter radionuclide like ^{90}Yttrium and ^{177}Lutetium have been shown to be more effective. Three early studies[17–19] using ^{90}Y-DOTATOC showed objective responses on 7%, 24% and 9%. Bodei and co-workers subsequently reported on a large group of 141 patients with an objective response of 26%. Interestingly, patients with stable disease showed a non-significantly better objective response than patients with progressive disease (32% of 28 patients versus 23% of 113 patients). Symptomatic improvement was seen in 50%. It should be noted that these figures far exceed the results that can be achieved with "cold", non-radiolabelled octreotide, in which only 3–6% partial responses were achieved.[20] Recently, Kwekkeboom has reported the results of the Rotterdam group on 131 patients treated with ^{177}Lu-DOTATATE, reporting an overall response of 29% of patients, with a further stable disease in 35%. Best results were seen with high uptake, limited liver metastases, while progressive disease was more often associated with low performance scores and extensive disease.[21] Difference in results between studies may also be explained by differences in patient groups and response criteria.[22] Better responses are seen with a higher proportion of pancreatic GEP's as opposed to primaries from elsewhere. Localized disease is also generally better controlled than distant metastatic tumours.

During treatment, bone marrow as well as kidney are the dose-limiting organs for radiation damage. In particular, nephrotoxicity is the major limiting factor, because of high uptake and retention of the radiopharmaceutical after glomerular filtration. Pre-therapeutic assessment of kidney absorbed dose could therefore help to minimize the risk of renal toxicity.[23] As the therapeutic agent labelled with ^{90}Y is not suitable for quantitative imaging, octreotates labelled with ^{111}In or with the positron emitters ^{86}Y or ^{68}Ga can be considered appropriate chemical surrogates to measure the biodistribution and retention of the radiopharmaceutical before therapy. However, it is important to note that the dose calculations based on ^{86}Y-octreotate and ^{111}In-octreotide yields similar organ doses, whereas there are relevant differences in estimated tumour doses.[24] Moreover, a study showed that in rats, ^{111}In and ^{177}Lu labelled peptides are likely to have a higher threshold for renal damage than ^{90}Y labelled peptides.[25] In humans, it was recently established that radiation nephrotoxicity after octrother treatment is dose dependent and appears at 30 Gy.[26]

1.3. *Summary and future perspectives*

The field of radionuclide therapy in NET is steadily increasing. For ^{131}I-mIBG, current interest lies in dose escalation and further integration in multimodality therapy schemes for high-risk stage 4 neuroblastoma. Radiolabelled DOTATOC compares very well to traditional therapies such as streptozocin/5-FU, DTIC and other chemotherapies in terms of response and toxicity.[21] From an experimental point of view,

Table 3 – The present and the future of peptide receptor-mediated radionuclide therapy

Somatostatin (SMS) receptors
- Endodermic tumours
- Neuro-ectodermic tumours
- Other tumours: small-cell lung cancer (SCLC), medullary thyroid cancer, breast cancer, renal cancer, thyroid cancer, lymphoma
- Brain tumour: medulloblastoma and glioma (*topical application*)

Cholecystokinin B/Gastrin (CCK-2) receptors
- Medullary thyroid cancer, gastrointestinal stromal tumours (GIST), SCLC, GEP

Gastrin releasing peptide (Bombesin, GRP) receptors
- Prostate cancer, breast cancer

Vasoactive intestinal peptide (VIP) receptors
- GIST, other stromal tumours

Neurotensin (NT1) receptors
- Exocrine pancreatic cancer, meningioma, Ewing sarcoma

Neuropeptide Y (NPY) receptors
- Breast cancer (NPY-1), sex cord stromal ovarian tumour and adrenal tumour (NPY-1 and NPY-2)

Glucagon-like peptide-1 receptors (GLP-1)
- Insulinoma, gastrinoma

Corticotropin-releasing factor (CRF) receptors
- Pituitary adrenoma, paraganglioma

α-Melanocyte stimulating hormone (α-MSH) receptors
- Melanoma

Substance-P (SP) receptors
- Glioma (*topical application*)

Integrin {α}v{β}3 receptors
- Glioma (*topical application*)

combinations of isotopes and the use of other radionuclides, with different physical characteristics, like β emitting ^{188}Rhenium or α emitting ^{211}Astate,[27] are likely to be tried clinically in the near future. On the other hand, new radiopeptides will probably extend beyond the framework of the neuroendocrine tumours (Table 3). The efficacy of this type of treatment may also be further enhanced through the use of radiosensitizers, the upregulation of receptor expression on tumours, and increased organ protection.

2. Radionuclide therapy of haematological malignancies

Radionuclide therapy for haematological malignancies goes back a long time in history. In fact, the treatment of leukaemia by ^{32}Phosphorus (^{32}P) was the first therapy modality with radioisotopes in the early thirties of the previous century. Today ^{32}P is still used for polycythaemia vera and essential trombocythaemia. The French Polycythemia Study Group[28] concluded a few years ago, based on a study of 461 patients with a long follow-up, that ^{32}P is perfectly well-tolerated and efficient in elderly patients and induces a long survival with excellent quality of life. A similar study from Lund, Sweden indicated that ^{32}P was not associated with a shorter survival or higher incidence of acute myeloid leukaemia (AML) than treatment with chemotherapy like busulfan or hydoxyurea.[29] The therapy is furthermore cheap, easy to administer either orally or as an intravenous (i.v.) injection.

This 'old' therapy has lately received the company of a new, more sophisticated therapy by radioisotope labelled antibodies i.e. radioimmunotherapy (RIT) for various haematological malignancies, e.g. α- and β emitting radionuclides have been labelled with anti-CD33 antibodyHuM195 for the treatment of myeloid leukaemia.[30] High-dose RIT of myeloid leukaemia with β-emitting radionuclides is being investigated for intensifying anti-leukaemia therapy before stem cell transplantation. Another option is the use of targeted α particles with radionuclides such as bismuth-213 or actinium-225, which offers the possibility of selective tumour cell kill with less damage to surrounding normal cells.[30] As RIT constitutes the most significant clinical contribution to the treatment options of B-cell lymphomas, the following sections will focus on these haematological malignancies.

2.1. *RIT in B-cell lymphoma*

B-cell lymphomas are generally sensitive to treatment with chemotherapy and some are remarkably sensitive to radiotherapy. B-cell lymphomas express surface antigens, e.g. CD20 and CD22, which are successfully used as targets for therapy with unlabelled and radiolabelled antibodies.[31] Chemotherapy, in combination with anti-CD20 antibody, rituximab, is considered by many a standard treatment for diffuse large B-cell lymphoma,[32] as well as for follicular lymphoma. However, most patients with disseminated B-cell lymphoma are not cured. The need for improvements in the treatment of B-cell lymphoma and the radiosensitivity of the disease, provide the rationale for the study of systemic radiotherapy in this disease.

There are now two approved radiopharmaceuticals, Zevalin® (IDEC Pharmaceuticals, San Diego, CA and Schering AG, Berlin) and Bexxar® (Glaxo SmithKline, Philadelphia, PA) for the treatment of B-cell lymphoma. Both are directed against CD20, albeit not against the same epitope. The Zevalin regimen is ^{90}Y labelled ibritumomab, the rituximab parental mouse antibody, which is administered following a pre-load with unlabelled rituximab to improve dose distribution. The Bexxar regimen consists of ^{131}I labelled murine tositumomab, and unlike Zevalin, the same murine antibody i.e. unlabelled tositumomab is used for pre-load. Two further radiopharmaceuticals have been evaluated in clinical trials: epratuzumab (Lymphocide®, Immunomedics Inc., Morris Plains, USA), an ^{90}Y labelled humanised antibody directed against the B linage restricted antigen CD22; and Lym-1 (Oncolym®, Peregrine Pharmaceuticals Inc, Tustin, USA), a murine antibody directed against an aberrant HLA-DR10 antigen Lym-1 has been labelled with ^{131}I, ^{90}Y and ^{67}Cu. All these radiolabelled monoclonal antibodies (MAb) apart epratuzumab are of murine origin.

The Zevalin treatment is a single infusion of ^{90}Y-ibritumomab on day 8, preceded by 250 mg/m^2 unlabelled rituximab at days 1 and 8. Zevalin requires no dosimetry and the amount of radioactivity, i.e. ^{90}Y to be administered, is calculated per kg body weight to be 15 MBq/kg. When Zevalin was compared to four infusions of rituximab in a randomised study, patients receiving Zevalin showed higher overall and complete response rate but this did not translate into longer time to progression.[33] However, the study may not have been powered to do so. The rate of overall response was 80% for Zevalin versus 56% for rituximab ($P = 0.002$). Complete response (CR) rates were 30% and 16% in the Zevalin and rituximab groups, respectively ($P = 0.04$). Kaplan–Meier estimated median duration of response to be 14.2 months in the Zevalin group versus 12.1 months in the control group ($P = 0.6$), and time to progression was 11.2 versus 10.1 months ($P = 0.173$) in all patients. Durable responses of at least 6 months were 64% versus 47% ($P = 0.030$). In a study with patients refractory to rituximab, defined as no objective response to rituximab or time to progression within 6 months. Zevalin was shown to induce overall response rate of 74% and 15% CR indicating the superiority of the corresponding radiolabelled murine analogue.[34]

Bexxar (^{131}I tositumomab) is given as one dosimetric dose followed by a therapeutic dose both containing 450 mg unlabelled murine Mab tositumomab. The first infusion is carried out in order to calculate the patient-specific activity required to deliver a whole-body absorbed dose of 0.75 Gy. As referred to above, the response rate seems to vary with the treatment history of the patient. The highest response rate has been reported in 76 patients with previously untreated follicular lymphoma. Ninety-five percent of the patients exhibited objective response, and 75% showed complete response.[31] Moreover, a molecular remission was achieved in 80% of assessable patients who had a CR at six months after treatment. After a median follow-up of 5.1 years, the actuarial 5-year progression-free survival for all patients was 59%, with a median progression-free survival of 6.1 years. In reports regarding previously treated patients, the overall response rate was somewhat lower as illustrated by the pivotal trial for Bexxar, including patients with both indolent and transformed lymphoma. In that study with 60 patients, the efficacy of Bexxar

was compared to the efficacy of previous chemotherapy, last qualifying treatment (LQC). Partial response or CR was observed in 39 patients (65%) after Bexxar, compared with 17 patients (28%) after their LQC ($P < 0.001$). The "median duration of response" was 6.5 months after Bexxar, compared with 3.4 months after the LQC ($P < 0.001$). Two patients (3%) had a CR after their LQC, compared with 12 (20%) after Bexxar ($P < 0.001$). The "median duration of response" for CR was 6.1 months after the LQC and had not been reached with follow-up of more than 47 months after Bexxar. RIT has also successfully been combined with chemotherapy.[35] The overall response rate of CHOP followed by Bexxar for follicular lymphoma was 90%, including 67% complete remissions. This concept is now pursued in the form of a randomised trial for patients with previously untreated follicular lymphoma SWOG S0016.

2.1.1. *Immunotherapeutic effects*

The immunological effect of RIT may not be confined to targeting i.e. it may include antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis as well as radiosensitisation. Furthermore, since follicular lymphoma is a tumour with a known propensity to show spontaneous remission,[36] one may assume that the radiation dose delivered may also affect immunological anti-tumour determinants. This could be by changing the composition of the tumour infiltrating cells e.g. the elimination of regulatory T-cells as well as other immunosuppressive cells that may be of therapeutic value. There are furthermore reports of anti-CD20 antibodies being anti-proliferative in normal lymphocytes. It is of interest to note that antibodies are not equally effective in their ability to induce different mechanisms of action, and this is true for antibodies directed at the same target also.

2.1.2. *Radionuclide therapeutic effects*

Evidence of the existence of a dose–response relationship can be inferred from several observations. First, the highest CR rate has been reported in the setting of myeloablative RIT.[37] Second, the median duration of CR following treatment with Bexxar was significantly longer for patients with 0.65–0.85 Gy in total body dose than for patients receiving 0.25–0.55 Gy.[38] Third, in a different Bexxar study, using SPECT for dosimetry, and enrolling only previously untreated patients with follicular lymphoma, the relationship of tumour shrinkage versus absorbed dose to tumour approached statistical significance $P = 0.06$.[39] Fourth, volume reduction in responding tumours is not taken into account when dosimetry is performed. Since absorbed dose is energy per unit mass, this leads to an underestimation of the absorbed dose, if there is volume reduction during energy deposition.[40,41] One might presume that volume correction would improve the correlation of dose with response. The absence of a dose–response in most trials may be importantly related to shortcomings in dosimetry techniques and to patient heterogeneity in terms of lymphoma histology and treatment history.

2.1.3. *Anti-CD 20 RIT in different subtypes*

As in the treatment of lymphoma with external beam radiotherapy, data from RIT trials support the notion that there is a difference in sensitivity to treatment between different subtypes of B-cell lymphomas.[42,43] When an up-date of the results of the University of Michigan was published in 2000, the sensitivity of indolent and transformed lymphomas to RIT was confirmed[44] and 86% of the patients with indolent and 79% with the transformed, whereas significantly less 41% of the patients with de novo aggressive lymphoma, exhibited response. Of the 71 evaluable patients with transformed lymphoma who were treated with Bexxar in 5 trials, 25% showed CR with a median duration of 36.5 months.[45] Furthermore none of the patients with de novo aggressive lymphoma showed CR and response was short-lived. In contrast, in a study using Zevalin for the treatment of diffuse large cell lymphoma better response data were presented with encouraging duration, at least for patients previously untreated with rituximab.[46] The latter study implies that not only patients with indolent or transformed lymphoma but possibly also patients with diffuse large cell lymphoma may receive substantial clinical benefit from non-myeloablative RIT. Response rate in other indolent lymphoma has been reported and in an analysis comparing 89 patients with small lymphocytic lymphoma with 651 patients with follicular gradeS I and II the median duration of response was equivalent (19.3 months). The authors found however a lower response rate in lymphocytic lymphoma compared with follicular lymphoma, 42% versus 65%,[47] not unlike the situation with rituximab.

2.1.4. *Myeloablative RIT*

Radioimmunotherapy is limited by the absorbed dose to radiosensitive organs. The bone marrow is the first dose-limiting organ but myeloablation can be dealt with by stem cell support. In 2000 the Seattle group reported the long-term follow-up of their phases I–II myeloablative RIT of 29 patients with B cell lymphoma. The maximal tolerated dose was found to be 27 Gy to the cardiopulmonary system.[37] Following the phase I study, patients were treated to a calculated dose of 25–27 Gy to normal organs, corresponding to 12765–29600 MBq. Eight-five percent of the patients showed objective response and 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. Interestingly the 11 of 19 patients with indolent lymphomas in contrast with 3 of 10 patients with aggressive lymphoma remained in remission.

Myeloablative RIT using ^{131}I has also been combined with chemotherapy. In a group of patients with mantle cell lymphoma and unfavourable clinical characteristics (2–7 prior treatments) an estimated 3-year progression-free survival of 61% and an overall survival of 93%[48] has been reported. Furthermore, in a comparison between the combination of RIT followed by chemotherapy and external beam radiotherapy with chemotherapy, using a non-randomized control group, RIT compared favourably.[49]

The results of a phase I/II study using myeloablative therapy with high-dose Zevalin, intended to deliver dose of 10 Gy to highest normal organ followed by chemotherapy has recently been reported. The activity escalation was capped at 3700 MB, which is significantly lower than what has been reported using ^{131}I-tositumomab, but can possibly be increased.

Although the clinical outcome is encouraging after a median follow-up of 22 months, the 2-year estimated overall survival and relapse-free survival rates are 92% and 78%, respectively,[50] the study does not lend itself to comparison with other myeloablative RIT studies due to significant differences in patient characteristics.

2.2. *Summary and future perspectives*

The success of RIT in lymphoma can be attributed to the combination of radiosensitivity of the disease, the targeting of highly expressed antigens by signalling antibodies, and by antibodies that mediate other therapeutic effects in their own right. Clinically, as a single modality, RIT can induce a high percentage of remissions, some of which are of impressive duration, in indolent and transformed B-cell lymphoma. In the myeloablative setting, data are even more impressing. The role of RIT in other lymphomas and as a part of a combined treatment remains to be defined.

3. Loco-regional applications of radioisotopes for liver tumours

Liver tumours are an important cause of morbidity and mortality in the world. Colorectal carcinoma (CRC), the most important cause of liver metastases, is the second most mortal cancer in Europe. Primary liver cancer, or hepatocellular carcinoma (HCC) is worldwide the most important cancer. Secondary liver failure is a natural course of disease in many of these patients. For both liver metastases and HCC, surgery (resection, liver transplantation) is central for curative treatment. However, only 10–25% of cases are operable and postoperative recurrences are frequent. In CRC, several lines of systemic chemotherapy are used, more recently in conjunction with new antibodies to EGFR and VEGF. With these modalities, response rates have increased from 15% to up to 35%. In HCC there is no standard effective systemic chemotherapy. For these reasons, loco(-regional) therapy modalities have increasingly been employed, although its use varies enormously according to available interest and expertise.[51]

Today, the challenge is to combine these different therapies to an optimal cost-effectiveness of multimodality therapy and quality of life maintained survival.

3.1. *Trans-arterial radionuclide therapy of the liver*

Among these therapies, a distinction can be made between local-physical and loco-regional-(radio)chemical techniques. Percutaneous local ablative techniques are radiofrequency ablation (RFA), laser coagulation, ethanol injection, cryotherapy and microwave coagulation therapy. Trans-arterial regional techniques are hepatic artery chemotherapy (HAC), trans-arterial chemo-embolisation (TACE), trans-arterial radionuclide therapy, vena porta embolisation and isolated hepatic perfusion (± hyperthermia). Here we will focus on trans-arterial radionuclide therapy and refer the reader to recent reviews on the other techniques.[52–54]

Historically, radionuclide therapy for HCC and liver metastases dates back to the early seventies, when Phosphorus (P)-32 labelled with albumin colloids were first used. One line of development has been the use of micrometer sized particles: colloids, microspheres of resin or glass, and polymers. When injected into a hepatic artery, such particles preferentially lodge in the hypervasculature of liver tumours (small arterioles, capillary sinusoids) and internally irradiate the neighbouring tumour tissue. Today, two of these products are commercially available, i.e. resin microspheres (SIR-spheres®, SIRtex) and glass spheres (Theraspheres®, Nordion), both attached to ^{90}Yttrium(Y). Lipiodol is a fatty acid ester derivative of natural, iodine-rich seed oil previously used as CT contrast agent, commercially available labelled with ^{131}Iodine(I) (Lipiocis®, Schering S.A.). In another line of development, systematic or loco-regional applicable agents have targeted these tumours more specifically, such as radiolabelled monoclonal antibodies to α-foetoproteine, ferritine or CEA, and mIBG and DOTA-octreotide to metastases of neuro-endocrine tumours. An interesting development is the use of the isotope Holmium(Ho)-166 labelled with poly(L-lactic acid) microspheres[55] which has interesting radiation characteristics and can be used as a MRI contrast agent, and may directly connect diagnosis, dosimetry and therapy.

The important advantages of loco-regional radionuclide therapy for liver tumours are its good tolerability and feasibility of combination with other therapies such as systemic chemotherapy and limited liver resection. Secondly, treating the whole liver makes it more suitable for multiple tumours as compared to local-ablative strategies. The main disadvantage is the use of open source radiation which implies radiation protection measures. Another important disadvantage is that it cannot be used as a systemic treatment.

3.1.1. *Developments in lipiocis therapy*

Lipiocis therapy has not been used in recent years for liver metastases, after early disappointing results.[56] Although its biodistribution is similar to the SIR-spheres, this may be related to its lower particle radiation range and cross-fire as compared to ^{90}Y, which is a disadvantage in a more heterogeneous distribution, especially in larger tumours.

In HCC, lipiocis has been used mostly as single agent as palliative treatment of inoperable cases. A collection of published results[57–60] between 1986 and 2002 includes 319 patients. Overall, the average radiological response rate of these was 28% (range 13–100%) and the average 1-year survival 31%. However, the effect on survival remains uncertain as only one small study randomised patients in comparison with best medical support.[61] This study showed a significant difference in survival at 3- and 6-months (71% versus 10% and 48% versus 0%), but survival at 12 months was 0% in both groups. This may be importantly related to the grave prognosis of portal thrombosis in these patients, as observed by others.[58] One large prospective, randomized study comparing lipiocis with TACE found similar response rates and survival but far better tolerability of treatment, with severe side-effects occurring in 3% of lipiocis patients versus 29% in TACE, and a high number[56] treatment-related deaths in the TACE group, occurring within 15 days after treatment, while this was 0 in the lipiocis group.[62]

More recently, lipiocis therapy has been used as adjuvant therapy after resection. Indeed, for confined tumours without

vascular invasion, resection is the first option. However, recurrences are frequent and partly due to the multifocal nature of the disease and microscopic tumours developing elsewhere. A pilot study by Lau and colleagues[63] on 43 randomised patients found 28.5% of recurrences in the treated group versus 59% in the untreated control group, while 3-year survival was 86% and 46%, respectively ($P = 0.04$). This study was criticized for a premature termination, but subsequently supported by non-randomised, retrospective studies.[64,65] Microscopic subclinical tumours may be especially effectively treated with this approach, also because radionuclide therapy is less hampered by heterogeneous agent distribution because of the cross-fire effect. The feasibility of this concept has also been proven experimentally.[66] Small ranged isotopes such as iodine may be more suitable for this type of minimal residual disease patients, as more of the radiation energy will be absorbed in the neighbouring tumour cells than long range isotopes such as ^{90}Yttrium.

Liver transplantation is the preferred therapy for Child C liver cirrhosis and HCC tumours limited to 3 and $\leqslant$5 cm. Two studies have piloted the neo-adjuvant use of lipiocis.[67,68] 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%. These figures are very promising, probably also because of the limited disease and therefore better radiation penetration into the whole of the tumour. Larger, randomised studies are needed to assess its value. Given the lack of liver donors, the most important role may be in preventing patients to drop-out because of tumour progression while on the waiting list for transplantation.

An interesting new development in lipiodol therapy is the use of the isotope ^{188}Rhenium. This isotope has a similar radiation energy as ^{90}Yttrium but shorter half-life which increases the dose rate. Besides, it is readily available on a day-to-day basis by a generator similar to that of technetium, with which most of the nuclear medicine studies are done today. In comparison to iodine, no high-energy γ-rays are emitted which implies no hospitalisation and isolation for radiation protection. First clinical Phase I studies have been performed[69,70] and this is potentially a very important product development.

3.1.2. *Developments in SIR-spheres therapy (SIRT)*

SIR-spheres therapy has been used mostly for metastases of CRC.[71] Recently, promising preliminary results have also been reported for breast cancer metastases and HCC.[72]

One line of development followed an early study by Gray and co-workers,[73] in which a significant benefit was found in 74 Phase III randomized patients for hepatic artery chemotherapy (HAC) with SIR-spheres, as compared to HAC alone, in terms of objective response (44% versus 17%), median time to progression (15.9 versus 9.7 months) and a non-significant trend for survival (39% versus 29% after 2 years). Subsequently, such beneficial approach of combined chemotherapy and radionuclide therapy has been employed to standard systemic chemotherapy. In the first study, 21 untreated patients were randomized to 425 mg/m^2/day 5-FU plus 20 mg/m^2/day leucovorin during 5 days per 4 weeks alone, or combined with one cycle of SIRT on the third or fourth day of the second cycle. The results of the combined therapy were impressively different: objective response 73% versus 0%, median time to progression 18.6 versus 3.6 months, without differences in grade III/IV toxicity and quality of life.[74] In the Irinotecan Dose Escalation Trial with a irinotecan doses of 50–75–100 mg/m^2, and the FOLFOX Dose Escalation Trial with 30–60–85 mg/m^2 oxaliplatin, similar preliminary results were recently obtained.[75,76]

Another line of development is the use of SIRT before or after resection of hepatic tumours. Data from 226 tumours in 64 clinical trials, patients showed a median tumour decrease of 60%, irrespective of size, while >20% clinically disappeared. Downstaging to resection has been evident in 20% of first-line patients. These seem favourable prerequisites for further exploration of such indications.

Other interesting aspects under development are new ways to diagnose early response in oncology in general, and also in SIRT. Positron emission tomography (PET) with F-18-deoxyglucose (FDG) or others have the potential to assess metabolic/molecular response before anatomical/structural changes are seen on CT. PET scanning after SIRT has correlated FDG uptake in the tumours ("standardized uptake value" or SUV) with absorbed radiation dose (Gy) and subsequent radiological response (CT).[77] This may allow the early evaluation of the efficacy of initiated therapies, in order to individually optimize the relative use of certain therapies and decisions for therapy changes in the future.

3.2. *Summary and future perspectives*

Lipiocis is a unique loco-regional treatment modality. Especially its adjuvant use to resection of HCC seems a particular easy and effective modality, awaiting confirmation in a larger multi-centre trial. In palliative HCC therapy it is equally effective as TACE, but at the cost of far lower complicating morbidity and mortality.

SIRT is an adjunct, not a replacement for chemotherapy and has the potential for better local control and prognosis, without additional toxicity (New alinea). In both treatment modalities, patients may be downstaged to resection following treatment.

3.3. *Conclusion*

Radionuclide therapy is a unique treatment modality lying between chemotherapy and external radiotherapy. The challenge for the next years is to select the most promising and appropriate targets for (pre-)clinical use, while at the same time optimally integrate its unique capabilities into the increasing number of other anti-cancer treatment strategies available.

Conflict of interest statement

None declared.

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