Peptide receptor radionuclide therapy with radiolabelled somatostatin analogues

Bodei, Lisa

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2009

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 7

RECEPTOR RADIONUCLIDE THERAPY WITH ⁹⁰Y-DOTATOC IN PATIENTS WITH MEDULLARY THYROID CARCINOMAS

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Abstract
Metastatic medullary thyroid cancer (MTC) shows a progressive course. Surgery is the only curative treatment. In advanced disease, chemo- and radiotherapy show poor results. Newly developed somatostatin analogue \([\text{DOTA}^0, \text{Tyr}^3]\)octreotide (DOTATOC) labeled to ⁹⁰Y is administered in patients with endocrine tumors expressing somatostatin receptors, like MTC. Preliminary studies demonstrated that ⁹⁰Y-DOTATOC could be safely administered, resulting in objective responses in 27% of patients. Aims: To evaluate the efficacy of ⁹⁰Y-DOTATOC therapy in metastatic MTC patients with positive OctreoScan, progressing after conventional treatments. Twenty-one patients were retrospectively evaluated after therapy, receiving 7.5–19.2 GBq in 2–8 cycles. Results: Two patients (10%) obtained a complete response (CR), as evaluated by CT, MRI and/or ultrasound, while a stabilization of disease (SD) was observed in 12 patients (57%); seven patients (33%) did not respond to therapy. The duration of the response ranged between 3–40 months. Using biochemical parameters (calcitonin and CEA), a complete response was observed in one patient (5%), while partial response in five patients (24%) and stabilization in three patients (14%). Twelve patients had progression (57%). Complete responses were observed in patients with lower tumor burden and calcitonin values at the time of the enrollment. Conclusions: This retrospective analysis is consistent with the literature, regarding a low response rate in medullary thyroid cancers treated with ⁹⁰Y-DOTATOC. Patients with smaller tumors and higher uptake of the radiopeptide tended to respond better. Studies with ⁹⁰Y-DOTATOC administered in earlier phases of the disease will help to evaluate the ability of this treatment to enhance survival. New more specific peptides and new radionuclides will also represent the key of a better treatment of MTC.

Introduction
Medullary thyroid carcinoma is a rare neuroendocrine tumor arising from parafollicular C cells of the thyroid. Such C cells embryologically originate from the neural crest, therefore medullary thyroid carcinoma is able to secrete calcitonin, CEA and a number of proteins and peptides in-cluding neuron-specific enolase,
chromogranin, gastrin-releasing peptide, and somatostatin. About 80% of cases are sporadic, while the rest are in three familial forms: multiple endocrine neoplasia Type 2A (MEN 2A), multiple endocrine neoplasia Type 2B (MEN 2B), and familial medullary thyroid carcinoma not associated with MEN (FMTC). The clinical course is variable, from indolent to particularly aggressive forms, and is related to the stage of disease at the time of diagnosis. Symptoms are usually related to local invasion and to hormonal hypersecretion. Survival rates are clearly worse than for patients with differentiated thyroid cancer. Survival at 10 years is 95% for patients with tumors limited to the thyroid, while it drops to 55%–70% in patients with persistent or recurrent disease [1–4]. Distant metastases are the main cause of death. So far, surgery is the only established curative treatment. Total thyroidectomy and complete cervical lymph node dissection are associated with a lower incidence of recurrences and better survival [5]. Medullary thyroid cancer remains a challenge for multimodality therapy. In metastatic advanced disease, any standard therapeutic approach, namely radiotherapy, chemotherapy, or biological therapy, show limited results [6]. In vitro data has demonstrated that medullary thyroid carcinoma cells not only produce somatostatin, but also express corresponding receptors on their membranes [7,8]. In a immunohistochemistry study of the distribution of the five somatostatin receptors subtypes (sst1–5) in medullary thyroid cancer specimens, a heterogeneous expression of somatostatin receptor subtypes was detected, with an expression of octreotide sensitive types (sst2, sst3, and sst5) in 75% of cases [9]. However, probably because of the low density of expression of sst2, only about 50–70% of medullary thyroid cancer can be visualized by scintigraphy with radiolabeled octreotide [7,10]. Newly developed somatostatin analog [DOTA0,Tyr3]octreotide (DOTATOC), labeled with Yttrium-90, is presently used in therapy trials in patients affected by endocrine tumors expressing sst2 receptors [11–13]. In our previous Phase I-II studies, we determined that 90Y-DOTATOC possesses favorable pharmacokinetic and dosimetric parameters [14], and can be safely administered up to 5.18 GBq per cycle (MTD) [15,16]. In a following study, 111 patients affected by sst2 positive tumors were treated with cumulative activity >7.4 GBq: 27% objective therapeutic responses. and 49% disease stabilization were observed [11]. We continued treating patients with a cumulative activity of 7.4 GBq, which is suitable to induce an objective response [12], thus reaching a total number of 141 patients (including a subgroup of 21 medullary thyroid carcinomas). The aim of this study was to retrospectively evaluate the therapeutic efficacy of receptor radionuclide therapy with 90Y-DOTATOC in the subgroup of 21 patients affected by metastatic medullary thyroid carcinoma that received a cumulative activity of at least 7.4 GBq.

Patients and methods
From February 1998 to September 2002, 21 patients (8 females and 13 males, ages 31–78 years, median 53) with histologically proven medullary thyroid carcinoma and positive OctreoScan scintigraphy were included in the study. All patients suffered from non-resectable loco-regional and/or distant metastases after total thyroidectomy. Six patients had also received radiotherapy, two were treated with chemotherapy, and one with cold somatostatin analogs (Table 1). Patients were treated with 90Y-DOTATOC with cumulative activities ranging from 7.5 to 19.2 GBq, divided in 2–8 cycles, according to clinical requirements. The somatostatin
analogue DOTATOC (DOTA: 1,4,7,10-tetra-azacyclododecane-N,N',N',N'''-tetracetic acid) was synthesized at the Division of Radiological Chemistry University Hospital, Basel according to a described procedure [17]. $^{90}$Y chloride was purchased from MDS Nordion (Ottawa, Ontario, Canada). DOTATOC was radiolabeled according to a previously published procedure [11]. Prior to initiation of therapy, all patients underwent physical examination, routine biochemical profile with determination of serum calcitonin and CEA values, and imaging-based (CT, MRI, or US) evaluation of the disease. These examinations were repeated 6–8 weeks after at least two cycles of therapy and then every 3 months. $^{90}$Y-DOTATOC was injected intravenously over 20 minutes in 100 mL of physiological saline. Repeated administrations were performed with at least 6–8-week interval. A typical administration consisted in 80 μg of DOTATOC labeled with 2.96 GBq of $^{90}$Y. According to current concerns for renal protection, all patients received an infusion of positively charged amino acids, namely lysine and/or arginine, immediately before and after therapy. Response to therapy was defined according to SWOG criteria as follows: complete response (CR) as total regression of all known lesions for at least 1 month; partial response (PR) as regression of all known lesions by more than 50% lasting at least 2 months; stable disease (SD) as no change in lesion size; progressive disease (PD) as increase of all known lesions by 25% or more. Biochemical response was evaluated by measurement of serum calcitonin and CEA. Response was defined as follow: CR: serum marker value below the cut off level (calcitonin: 15 pg/mL; CEA: 5 ng/mL); PR: a decrease of 50% or more in the basal marker values; PD an increase of 25% or more in the basal marker values; SD: when all above were excluded. After discharge, patients underwent the following tests: renal and hepatic function, LDH, and uricaemia every 15 days for the first 2 months; complete blood count 3 days after therapy and then every 2 weeks for the first 2 months. Toxicity was evaluated according to World Health Organization criteria. Given the small number of patients, we used the binomial distribution to calculate confidence intervals for proportions, (indicated in text with 95% CI), and Fisher’s exact test to assess the potential association between factors.

**Results**

The treatment was well tolerated and no acute side effect was reported in any of the treated patients. The median (min, max) number of cycles, in this group of patients, was 4 (2,8) with a median cumulative activity of 10.4 GBq (min = 7.5, max = 19.2). Both the cumulative activity and the maximum activity per cycle were quite homogeneous in this sample and not associated with either objective or biochemical response. The routine evaluation of hematological toxicity parameters did not show any significant toxicity resulting from $^{90}$Y-DOTATOC, except in one patient. In fact, according to our previous studies [16], we maintained single cycle activity below the MTD (Table 2, column 5), with a median value of 3.7 GBq. The patient showing Grade 3 hematological toxicity on WBC received a relatively low activity per cycle, and had no bone metastases or bone marrow invasion, as demonstrated by bone marrow biopsy. Permanent renal toxicity has not been observed with 3–40 months of follow up. At the time of analysis (April 2003) 15 patients were alive and two were lost from follow-up. The clinical benefit (objective response plus stable disease) was
67% (95% CI = [43%, 85%]), however morphological complete response was
doctrumented only in two patients, while no partial response was observed. Seven
patients (33%, 95% CI = [15%, 57%]) did not respond to the therapy and
progression continued. The duration of this response (CR plus SD) ranged from 3
to 40 months. Patient 12, a 56-year-old male affected by latero-cervical and
mediastinal lymph-node metastases from MTC, showed stabilization of disease by
CT scan and biochemical complete response, resulted in normalization of
calcitonin and CEA serum levels for 12 months. Another five patients (24%, 95%CI = [8%, 47%]) responded with biochemical partial remission (≥50% of initial values),
while three (14%, 95%CI = [3%, 36%]) showed stabilization in serum markers.
Twelve patients (57%, 95%CI 5 [34%, 78%]) had biochemical progression. Figure
1 reports an example of objective response in Patient 5, a male affected by cervical
lymph node metastases from MTC and treated with 8.92 GBq of 90Y-DOTATOC.

Discussion
In patients with metastatic medullary thyroid cancer no effective treatment has
been found, except for surgery, when feasible. Various chemotherapy regimens
have been tested. All studies have been performed in small cohorts of patients and
report limited results. The most active molecule is Adriamycin, with maximum partial
remission in 1 of 4 patients in single regimen and in 3 of 8 patients in combination
schemes.6 Nevertheless, cardio- and myelotoxicity limits the patients’ quality of life.
Previous Phase I radioimmunotherapy studies with high-dose 131I-MN-14 F(ab)_2
anti-CEA monoclonal antibody, combined with autologous hematopoietic stem cell
rescue (AHSCR,) in 12 patients with rapidly progressing metastatic medullary
thyroid cancer, yielded promising results (one partial response, one minor
response and 10 stabilizations) [18]. Other kinds of targeted radiotherapy, such as
131I-MIBG (131I-metaiodobenzylguanidine) have also been studied in medullary
thyroid carcinoma. Results obtained with 131I-MIBG have been modest: only
approximately 35% of medullary thyroid carcinomas show sufficient 131I-MIBG
uptake to be considered for therapy [19,20]. In patients with suitable 131I-MIBG
uptake, palliation was frequently achieved. Objective responses were recorded in 6
of 18 patients [21]. The expression of somatostatin receptors in medullary thyroid
cancer cells offers a treatment. Octreotide, administered in short or long term
fashion in symptomatic patients, results in improvement of neuroendocrine
symptoms, especially diarrhea and flushing [22], however reports of objective
tumor responses are only sporadic. Since a combination of human recombinant α-
interferon and octreotide increased the response rate in metastatic neuroendocrine
tumors of the gastro-entero-pancreatic area, the same combination was tested in
medullary thyroid cancer. No objective responses were demonstrated with this
combination regimen and only symptomatic benefit was achieved in some patients
[23,24]. Still, somatostatin receptors can be exploited for receptor radionuclide
therapy with 90Y-DOTATOC. The rational basis of this therapy relies on the
receptor-mediated internalization of a radiolabeled octreotide analog that carries
the beta-energy of Yttrium-90 inside the tumor cell. For 5 years, phase I–II studies
with 90Y-DOTATOC have been performed in patients affected by tumors
expressing sst_2. The results are encouraging. Objective response rate ranges from
19 to 27% [15,11–13]. Although presently all sst_2-expressing tumors are
considered to be suitable for radiolabeled octreotide therapy, the evaluation of the
first trials performed in wide populations of tumors suggest that response rate differs with different histotypes. The best responses seem to be obtainable in gastro-entero-pancreatic neuroendocrine tumors, and particularly in pancreatic ones [13]. This presumptions is in part confirmed in this report, where $^{90}\text{Y}-\text{DOTATOC}$ therapy of advanced medullary thyroid cancer resulted only in 10% objective response rate (2/21 patients, CR only). On the other hand, since all the patients had progression at enrolment, a clinical benefit can be described in 67% of patients (objective responses plus stable disease). Patients with smaller tumors and higher uptake of the radiopeptide tended to respond better. Biochemical responses were more frequently encountered than morphological ones (28.6% of cases). Six of the 14 (43%) patients who had morphological response had also a biochemical one. The reduction in calcitonin values is of particular interest in clinical setting, since it represents an index of functional activity of the disease and it may follow the course of patient's symptoms. Our results are consistent with the experience reported by Waldherr [25]. In their study of 20 patients with advanced thyroid cancer, 12 of which had medullary thyroid cancer, only stable responses were observed. Phase II studies on larger cohorts are needed to better assess the efficacy of $^{90}\text{Y}-\text{DOTATOC}$ therapy in medullary thyroid carcinoma. Analyzing the characteristics of response and the difference in the efficacy of $^{90}\text{Y}-\text{DOTATOC}$ in neuroendocrine tumors and medullary thyroid carcinoma, the radiosensitivity must be taken into account. Medullary thyroid carcinoma probably has a radiosensitivity that falls between that of differentiated and anaplastic thyroid carcinoma. In a series of 29 patients with gross residual disease from medullary thyroid carcinoma after surgery, local control was achieved in 4 of 21 patients treated with external radiotherapy [4]. Similarly, Fife [26] reported a 24% survival at 5 years in patients with gross residual disease and a complete response in 30% of patients after external radiotherapy. Resulting from our previous dosimetric studies, tumor lesions received variable absorbed doses, mainly lower than requested to induce an objective response (at least 60–70 Gy), especially in cases of moderate uptake of the radiotracer. In fact, sst$_2$ receptor expression in medullary thyroid cancer is generally not very high. It is possible, therefore, that the maximum cumulative activity, administrable without exceeding the renal threshold dose for toxicity, is not sufficient to deliver a curative absorbed dose to the tumor. Finally the receptor status must be taken into account. Medullary thyroid carcinoma cells express a number of receptors. Probably sst$_2$ receptor is not the optimal target to deliver radiation doses to the tumor. CCK receptors and bombesin receptors are extensively expressed in medullary thyroid carcinoma and new radiolabeled analogs directed towards these receptors will probably represent another way to treat such cancer [27]. Furthermore, the potential for treatment of newly introduced beta-emitter Lutetium-177, that seems more effective in small sized lesions [12], must be evaluated. In conclusion, $^{90}\text{Y}-\text{DOTATOC}$ in metastatic medullary thyroid carcinoma is a safe treatment, able to induce mainly stabilization of disease, and objective responses in some patients with very small residual disease and calcitonin values. Based on this experience we would propose $^{90}\text{Y}-\text{DOTATOC}$ in earlier phases of the disease to assess the exact potential of $^{90}\text{Y}-\text{DOTATOC}$ therapy to extend the time to progression and overall survival in medullary thyroid carcinoma.


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PD, progressive disease; L, lymph nodes; L.c., latero-cervical; S, surgery; R, radiotherapy; C, chemotherapy; LAR, octreotide LAR.
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<td>8</td>
<td>3.44</td>
<td>IV c</td>
<td>0</td>
<td>SD</td>
<td>PD</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
Figure 1. An example of objective response in patient #5 affected by cervical metastases from MTC. (A) OctreoScan, anterior and posterior whole-body sections, before (a: November 1999) and after (b: November 2001) $^{90}$Y-DOTATOC. (B) Calcitonin course $^{90}$Y-DOTATOC therapy. Arrows represent calcitonin assay before each cycle of $^{90}$Y-DOTATOC.