Metastatic Medullary Thyroid Cancer, Somatostatin Analogues and Markers

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Abstract

Background: Medullary Thyroid Carcinomas (MTC) are rare tumors that occur either sporadically or in a familiar form. It comprises 5-10% of all thyroid cancers. Except for some new drugs of tyrosine kinase inhibitors family that are effective in metastatic disease, multiple conventional chemotherapeutic regimens have been used without significant success and treatment with somatostatin analogues is still discussed.

Patients and methods: We report our experience of alternating treatment with somatostatin analogues Octreotide and Lanreotide in metastatic MTC.

In the period June 2011-May 2012 seven patients with medullary thyroid cancer were treated. We have evaluated clinical and biochemical response according to CEA, Calcitonin, Chromogranin A, and NSE levels after six courses of alternated therapy.

Results: The treatment was well tolerated, however, clear evidence of the clinical/biochemistry/radiological efficacy has not been found.

Conclusions: In the absence of conclusive data, this type of therapy could not be recommended outside of clinical trials.

Keywords: Myelodysplastic syndrome; Immunotherapy; Refractory anemia; Targeted therapy

Introduction/Epidemiology

Medullary Thyroid Carcinomas (MTC) are tumors comprising 5-10% of all thyroid cancers [1]: they can occur either sporadically or in a familiar form. Approximately 75% are sporadic and 25% are inherited and belong to multiple endocrine neoplasia type 2A (MEN 2A), multiple endocrine neoplasia type 2B (MEN 2B), and familial MTC not MEN associated [2]. Serum calcitonin is the tumor marker most commonly associated with MTC; serum calcitonin is widely considered a sensitive and specific marker of the disease [3]. However,

calcitonin is not the only tumor marker of MTC, as CEA is also secreted from the tumor and can be elevated in patients with MTC. CEA, in particular, has been associated with increased tumor aggressiveness and poor prognosis [4]. Moreover, it seems to be a better predictor of disease progression than calcitonin and chromogranin A [5].

The management of MTC relies heavily on surgical resection, consisting of total thyroidectomy and central neck dissection; however, recurrent disease develops in approximately 50% of patients with MTC [6]. Multiple conventional chemotherapeutic regimens have been used without significant success. Some new drugs as Tyrosine Kinase Inhibitors (TKIs) targeting signaling pathways essential for tumor cell survival, proliferation, differentiation, and metastasization have been recently tested as a single drug treatment (Sunitinib [7], Vandetanib [8], Sorafenib [9], Cabozantinib [10]), or in association (Sorafenib + Tipifarnib) [11] with promising results. In particular, Vandetanib has been recently approved for the treatment of locally advanced and/or metastatic MTC.

Somatostatin receptors are usually expressed on the surface of MTC cells. The various subtypes (SST1, SST2, SST3, SST4, and SST5) are differently expressed in the different endocrine tumors. The interaction between somatostatin analogues and multiple receptor subtypes induces a modulation of the tumor hormonal secretion providing a symptomatic improvement and biochemical responses (i.e. markers' decrease) in a significant percentage of cases. On the other hand, the objective/radiological responses are only anecdotal and generally lower than 10%. OCT was the first commercially available somatostatin analogue with a half-life of two hours. It has high affinity binding for SSTR2 and SSTR5, low affinity for SSTR1, SSTR4, and medium for SSTR3. OCT has been developed as a formulation for daily subcutaneous injection. LAN (another somatostatin analogue) has high activity binding for SSTR2 and SSTR5 and low affinity for SSTR1, SSTR4, and SSTR3 [12]. It is generally accepted that the two somatostatin analogues have similar efficacy in the treatment of carcinoid syndrome [13], but it is conceivable that there are some difference in their activity for the different binding profile; furthermore, it is known that there is no cross-resistance between them [14]. Treatment of advanced/metastatic MTC with somatostatin analogues is still debated [PACINI?]. Data from non-randomized studies in patients with MTC showed that somatostatin analogues are not effective [15] but Vainas, in a group of 22 patients with persistent or relapsed disease, reported that OCT and LAN treatment achieved a subjective and biological partial remission in one third and in one fourth of the MTC patients, respectively; on the other hand, they seemed to do not improve patients' prognosis [16]. It is believed that alternating the somatostatin analogues may increase the effectiveness and may overcame the resistance mechanisms, because of the different receptor expression even in the context of histologically similar neoplasia and the slightly different affinity for receptors of the two analogues.

The aim of this investigation has been to evaluate the activity (in terms of symptoms control, tumor markers plasma levels [calcitonin, CEA, neuronal specific enolase, chromogranin A] and/or radiological evidences) of an alternated OCT and LAN treatment in a cohort of metastatic MTC.

Patients and Methods

In the period between June 2011 and May 2012, seven patients with metastatic MTC (6 with sporadic tumor and 1 affected by MEN2A) were treated at Istituto Oncologico Veneto (IOV), Padova, Italy. Patients' characteristics, disease involvement and previous treatments are reported by table 1.

The performance status of all patients was between 0 and 1 according to Eastern Operative Oncology Group. All patients underwent a first LAN course (120 mg) and subsequently, after 4 weeks, an OCT course (30 mg), alternating the two drugs for a total of 6 cycles (3 administrations of LAN and 3 of OCT). Before treatment, all patients underwent CT scan (neck, chest, and abdomen), cardiologic evaluation (ECG, echocardiography), blood count, liver and kidney function tests, and markers (calcitonin, CEA, neuronal specific enolase [NSE], chromogranin A CgA). During treatment, physical examination, blood count, liver and kidney function tests and tumor markers were monthly evaluated. One month after the last cycle, CT scan was repeated in addition to blood count, liver and kidney function tests.

Pt	Sex, age	Period of disease (years)	Symptomatology	Sites of metastases	Previous treatments
N°1	F, 50	11	None	Cervical lymph nodes and lung	CT (DTIC and EPi)
					RT
N°2	M, 55	2	Diarrhea	Cervical lymph nodes and bone	CT (EPi and DDP)
N°3	M, 57	15	Asthenia, diarrhea	Cervical lymph nodes and lung	CT (Dacarbazine and 5-FU
					RT
					CT (DDP and EPi)
N°4	M, 64	2	Asthenia, diarrhea diffuse bone pain	Lung, mediastinal lymph nodes, liver, abdominal lymph nodes	None
N°5	F, 65	1	Diarrhea	Cervical lymph nodes, mediastinum, supraclavicular	CT (EPi and DDP)
N°6	F, 78	20	None	Cervical lymph nodes	None
N°7	M, 82	1	None	Liver	None

CT: Chemotherapy; RT: Radiotherapy; DTIC: Dacarbazine; EPi: E pirubicine; DDP: Cisplatin.

Table 1: *Patients' characteristics, sites of disease and previous treatments.*

Statistical analysis was performed by using T-test for paired samples. The data are expressed as average of differences between markers' levels at the beginning and at the end of treatment and as standard deviation of individual differences. A p-value < 0.05 was considered statistically significant.

Despite the fact that lenalidomide has been approved for del 5q subtype of MDS, European Medicines Agency raised concern over a potential risk of AML progression caused by lenalidomide in some lower-risk MDS with del 5q and has requested further analyses. However, the 3 available retrospective analyses comparing the long-term outcome of lower-risk MDS with Del 5q treated with and without lenalidomide have found no excess risk of AML with its administration.

Results

Side Effects

In the six courses with the two alternated drugs, the most frequent side effect was diarrhoea (4 patients). Patient's n°1 and n°6 did not report side effects during treatment; patient n°2 reported a progressive reduction in pre-existing diarrhoeic episodes (from 4-5/day to 2-3/day).

Regarding side effects, we report in detail that: (i) Pt n°3: diarrhea (from 2-3 episodes/day to 5-6/day) for three days only after the first administration of LAN; (ii) pt n°4: diarrhea (from 2 episodes/day until 10/day after LAN for 4 days); also one episode of mild hypotension after the 2nd administration of LAN. The patient attributed this side effect to the drug and he refused it. We replaced the 3rd (last) cycle of LAN with OCT; the hypotension solved itself without any treatment; (iii) pt n°5: gradual increase in diarrhoic episodes (from 6/day to 15/day) throughout the treatment; this symptomatology remained unchanged after the end of the treatment and until now, after eight months; (iv) pt n°7: diarrhea (4-5/day) for 3 days after the third and the fourth cycle of therapy.

Tumor Markers Evaluation

The markers assessed (normal values range: calcitonin 0.0-10.0 ng/l, CEA 0.0-5.0 ug/l, CgA 0.0-98.0 ug/l, NSE 0.0-17.0 ug/l) showed not homogenous trends in term of increase and/or decrease even in the same patient (the evaluation was monthly performed on the day of therapy and therefore their variations referred to the activity of somatostatin analogues administered four weeks before).

Patient	Chromogranin		CEA		Calcitonin		NSE	
	Mean	CI	Mean	CI	Mean	CI	Mean	CI
N°1	60,1	10,4	91,4	28,2	9.358,8	3.553,1	19,7	3,3
N°2	118,1	15,2	176,9	24,6	2.818,0	766,3	11,1	1,3
N°3	395,4	15,7	425,0	42,3	18.011,3	2.146,7	11,6	1,9
N°4	309,6	34,3	181,7	25,7	20.898,8	2.093,9	44,4	6,1
N°5	123,1	30,4	119,1	5,4	13.897,6	13.519,7	8,7	0,8
N°6	105,6	19,4	12,1	0,4	604,6	188,3	15,8	1,6
N°7	30,6	5,7	8,6	0,6	38,3	10,0	16,1	1,7

Table 2: Average and confidence interval for each patient.

Among the most significant markers' changes, there is an increase in calcitonin level in pt n°5 after OCT (2nd dose), followed a decrease with persistent return to baseline after LAN, until the end of observation. In the same period the CgA level decreased, while CEA and NSE were stable until the end of the 6th cycle.

It is worth noting the reset of CEA (pt n°1) 4 weeks after administration of the 4th course (OCT), followed by similar return to the original value after LAN.

The reduction of NSE was gradual and progressive in pt n°4.

In pt n°3 there was an immediate increase of CEA after the first administration of LAN with up and down in next five cycles of therapy before setting to a final value higher than the first one.

In addition, the concomitant trend of markers' levels is consistent in the following patients (evaluated from the baseline to the last cycle):
a. Patient n°2 with an increase of CEA (75% compared with baseline) and an increase of calcitonin (> 30%) (Table 3);
b. Patient n°4 with gradually decreases (more than 30%) of CEA and NSE value (Table 3).
c. Markers' changes instead are in contrast in the following patients:
d. patient n°1 with a decrease of CEA (> 40%) after the third course of treatment (LAN) and a subsequent increase up to the starting value after the fourth cycles (OCT) and an important increase of calcitonin (6-fold from baseline) (Table 3);
e. Patient n°6 with an increase of calcitonin (2-fold from baseline) after the third course (LAN) with successive gradual return to baseline value and a decrease of CgA (30%) (Table 3).

Patient	Δ%			
	Chromogranin	CEA	Calcitonon	NSE
N°1	↓18%	↑43%	↑518%	↓13%
N°2	↑17%	↑75%	↑43%	↑10%
N°3	↔	↑10%	↓39%	↓37%
N°4	↔	↓40%	↔	↓39%
N°5	↓54%	↔	↔	12%
N°6	↓38%	↓10%	↑42%	↔
N°7	↓43%	↑21%	↔	↓26%

↑ increase; ↓ decrease; ↔ stability

Table 3: Evaluation of markers after 6 doses (3 LAN and 3 OCT) from baseline.

Citation: Haralabos Koussis., *et al.* "Metastatic Medullary Thyroid Cancer, Somatostatin Analogues and Markers". *EC Cancer* 2.1 (2016): 45-51.

NSE was the marker with less variations, as expected, due to indolent trend of disease, except patient n°4, wherein its reduction was concomitant to CEA.

At CT scan performed four weeks after the 6th cycle and compared with the pretreatment one, all patients had stable disease.

Marker	t-test				
	Mean	CI	t	df	p-value
Chromogranin	30, 7	39,4	1,9	6	0,1045
CEA	-10,7	53,8	-0,5	6	0,6421
Calcinato	-598,8	5.071,6	-0,3	6	0,7824
NSE	4,6	7,5	1,5	6	0,1806

Table 4: *Paired t-test to compare markers' value at the beginning (t0) and at the end (t7) of treatment.*

Discussion

An indirect data about the effectiveness of Octreotide is the improvement in survival observed when comparing patients with NETs diagnosed in the period 1998-2004 with those diagnosed in earlier period [17]. Historically the survival rate at 5 years was 18%, and improved to 67% in patients treated with somatostatin analogues. These observations led to the hypothesis that Octreotide could have anticancer effects probably through direct stimulation of SSTR2. It can also mediate antitumor effects through indirect inhibition of ant apoptotic insulin-like growth factor-1, through ant angiogenesis and Immunomodulation. About two-thirds of patients with well-differentiated NETs treated with Octreotide have stable disease for more than 5 years, although only 5% has some objective response. In recent years, some studies have assesses the ant proliferative effect of the two analogs and a disease stabilization in 43-60% of cases has been reported. PROMID study (randomized, double-blind phase III, Octreotide vs placebo) was the first large randomized study that assessed the activity of Octreotide LAR in patients with metastatic well-differentiated intestinal NETs. 85 naïve patients were randomized to Octreotide LAR 30mg once monthly or placebo for 18 months until disease progression or death. In Octreotide LAR group, median time to progression was 14.3 months vs 6 months in the placebo group. After 6 months of treatment, a stable disease was reported in 64% and 37.2% of the patients treated with Octreotide LAR and placebo, respectively [18]. In another study of 71 patients who received Lanreotide Autogel for 6 months, 65% of patients had a more than 50% decrease in flushing episodes and 18% a more than 50% decrease in diarrhea [19]. Patient not tolerating Octeotride may benefit from Lanreotide [20]. In literature there is no experience about the alternation of the two analogues. We have tested this therapy to assess efficacy and tolerability beyond the biochemical response. Tumor markers can suggest the presence and the proliferative activity of a specific tumor. Despite the greater specificity of calcitonin, CEA levels reflect more precisely relapse and/or progression of disease [5]. It is known the importance of doubling time of CEA and calcitonin in prognosis. It's strange, however, the temporary increase in some markers (observed from a long-time) both here and by other authors. Of course, the possibility of a hypothetical stimulation of cell growth (expressed by increase of tumor markers) even temporary, should be investigated [5]. In a study of 2002 J. J. Diez reports a decrease of CEA and calcitonin in the treatment with somatostatin analogues (Octreotide or Lanreotide) two weeks after the administration, but similar return to the first values in 4-12 weeks [15].

In human cell lines of medullary thyroid cancer with expression of all subtype receptors, DNA synthesis is inhibited by selective agonists for SST2 and it is promoted by selective agonists for SST5. These selective agonists have contrasting effects, indicating a tissue-specific antagonism between SST2 and SST5 [21] [25].

Data from our previous experience, presented at the Thyroid Cancer Congress 3 (2002), and later at the Thyroid Cancer 4 (2004) [5] about seven patients with sporadic metastatic medullary thyroid cancer treated with Octreotide 30mg every 28 days for ten months values of calcitonin, CEA and Cg-A shows in some cases the same trend in the same patient. We have observed relevant increase and

relevant decrease of markers in a short time. Other authors report similar markers' trends during the treatment with RET inhibitors [22,23]. It is worth noting that, during the follow up, patients with metastatic disease has short duration increases of CEA and Calcitonin. These alterations are not correlated with clinical/radiological disease progression and the meaning is still unclear.

Conclusion

In conclusion, the unstable level of these markers over time may be the consequence of the variable expression of SSTR1, SSTR2, SSTR3, SSTR4, SSTR5; It is known through some experimental studies that SSTR2 is involved in the inhibition of proliferation while SSTR5 has an opposite effect. Also SSTR1 is involved in the inhibition of cell proliferation by significantly reducing the secretion of calcitonin and its gene expression. It would therefore be useful, to detect in advance the different subtypes of receptors in this slow-growing tumor, before proposing any treatment with somatostatin analogues [24].

Data from this study about 7 patients treated by alternating the two analogues for 6 monthly doses are uneven and often difficult to interpret. By alternating the two analogues Octreotide and Lanreotide, there were also significant changes in the values of markers. In addition we should consider the limited number of patients that makes it difficult to draw conclusions. In the absence of conclusive data, this type of therapy is not recommended outside of clinical trials.

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