Treatment of Advanced Medullary Thyroid Carcinoma with a Combination of Recombinant Interferon α-2b and Octreotide

Giovanni Lupoli, M.D.,[1]
Edvige Cascone, M.D.,[1]
Francesco Arlotta, M.D.,[1]
Giovanni Vitale, M.D.,[1]
Luigi Celentano, M.D.,[2]
Marco Salvatore, M.D.,[2]
Gaetano Lombardi, M.D.,[1]

[1] Department of Molecular and Clinical Endocrinology and Oncology, School of Medicine, University "Federico II", Naples, Italy.

[2] Department of Nuclear Medicine, School of Medicine, University "Federico II", Naples, Italy.

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Address for reprints: Giovanni Lupoli, M.D., Via Nicolardi 145, Parco Arcadia n.8, 80131 Napoli, Italy.

BACKGROUND. The medical treatment of advanced medullary thyroid carcinoma (MTC) is still questionable. Results of chemotherapy are disappointing with almost no curative responses, few partial responses, and many side-effects. A recent report has suggested the activity of combination recombinant interferon α-2b (rIFN-α-2b) and octreotide, a somatostatin analogue, in the treatment of a metastatic carcinoid tumor. This new therapeutic schedule may be used in other neuroendocrine tumors. In this study we evaluated the therapeutic effectiveness of octreotide and rIFN-α-2b in patients with advanced MTC.

METHODS. Eight patients affected by advanced MTC received octreotide at a daily dose of 150 μg for 6 months and subsequently at a daily dose of 300 μg for another 6 months, subcutaneously, and rIFN-α-2b at a daily dose of 5.000.000 IU intramuscularly 3 times a week for 12 months. Plasma calcitonin, carcinoembryonic antigenic levels, and morphologic staging were evaluated at 0, 1, 3, 6, and 12 months.

RESULTS. The therapy was stopped in two patients because of diarrhea and toxicity of drugs used. Pre-existing diarrhea in four patients and flushing in one significantly improved during treatment. A maximum decrease of calcitonin was reached after 1 month in 2 patients and after 3 months in 4. In all of the patients carcinoembryonic antigen levels decreased during treatment. No significant changes of size of metastases were observed.

CONCLUSIONS. The combination of octreotide and interferon is well tolerated and can be recommended for the treatment of advanced MTC. ***Cancer* 1996; 78:1114–8.**

KEYWORDS: medullary thyroid carcinoma, octreotide, recombinant interferon-α-2b, calcitonin, carcinoembryonic antigen.

Medullary thyroid carcinoma (MTC) develops from the thyroid parafollicular or calcitonin-producing cells (C cells). These cells are derived from the neural crest and have amine precursor uptake and decarboxylation characteristics. MTC not only releases calcitonin (CT) and carcinoembryonic antigen (CEA), but also, occasionally, other peptides (serotonin, chromogranin, gastrin-releasing peptide, substance P, pro-opiomelanocortin-derived products and somatostatin).[1–4] Approximately 50% of MTC has somatostatin receptors.[5–10]

The treatment of MTC consists, where possible, of total thyroidectomy in combination with lymphonodal dissection and surgical excision of recurrences, evaluated by echography, computerized tomography, 131-I-metaiodobenzyl-guanidine, 99mTc(V) dimercaptosuccinic acid, and selective venous catheterization.[11–12] Recurrence occurs in about 50% of the patients and is often preceded by high serum CT and/or CEA concentrations. The success of re-operation derives from

early detection of secondary disease.[13-14] The medical treatment of advanced MTC is still questionable. Results of chemotherapy are disappointing with almost no curative responses, few partial responses, and many side-effects.[15-17] External beam radiotherapy is indicated only as a palliation for those cases with brain metastases, symptomatic liver metastases, and mediastinic metastases with an upper vena cava syndrome, or for those patients with compression of the vital organs.[18] Considerable interest exists in the use of somatostatin analogues for the treatment of symptomatic metastatic MTC. This treatment of MTC has proven to be an important adjuvant for the relief of clinical symptoms in a considerable proportion of patients, although, so far, no evidence has been given that somatostatin analogues can reduce metastases or tumor mass, or prolong life expectancy.[19-25]

The use of interferon (IFN) has been tried in many types of tumors and has been shown to possess some therapeutic effects on neuroendocrine tumors with metastases.[26-33] Recombinant α-IFN (rIFN-α) has been shown to have inhibitory effects on oncogene expression, DNA replication, and protein synthesis. Tumor cell division is mainly blocked in the G0–G1 phase, but a definite cytotoxic effect has not yet been demonstrated. Control could also be indirect and occur through the activation of the immunoregulatory system.[34-35] A recent report has suggested the activity of combination rIFN-α-2b and octreotide, a somatostatin analogue, for the treatment of patients with a metastatic carcinoid tumor. Therefore this new therapeutic schedule may be used in other neuroendocrine tumors.[36]

The aim of this study was to evaluate the therapeutic effectiveness of octreotide and rIFN-α-2b in patients with advanced MTC.

PATIENTS AND METHODS

Eight patients, 3 men and 5 women between the ages of 32 and 56 years, with histologically proven MTC and with metastases were included in this study. Patients with severe heart, liver (serum total bilirubin $\geq$ 25 μmol/L), or kidney impairment (creatinine clearance $\leq$ 60 mL per minute) were excluded from the study. Somatostatin receptors were visualized in all patients after intravenous (i.v.) administration of 111In-diethylenetriamine pentaacetic acid (DTPA)-octreotide. All had a sporadic form of MTC. They had been treated previously with total thyroidectomy and lymphadenectomy. Local recurrences occurred in two patients and they underwent radical neck dissection. Later, all patients had unresectable local-regional and/or distant metastases (three with mediastinal metastases; one with hepatic, skeletal, and cervical metastases; and four with mediastinal and pulmonary metastases). Six patients reported the development of intractable diarrhea and one developed flushing.

All patients had persistently elevated plasma CT and CEA levels. The staging procedures, performed before and during therapy, included physical examination, biochemical profile, thyroid hormones, tumor markers (CT, CEA), chest X-ray, 111In-DTPA-octreotide scintigraphy (Mallinckrodt Medical, Holland), neck and hepatic ultrasound, total body computerized tomography, and/or magnetic resonance (MR).

CT was evaluated using a double antibody radioimmunoassay (RIA) method (DPC-USA); normal value $<$ 14,63 pmol/l, sensitivity 4,68 pmol/l, CV intrassay 3%, CV interassay 6%. CEA was evaluated using an immunoradiometric assay (IRMA) (CIS-France); normal value $<$ 5 μg/l, sensitivity 0,3 μg/l, CV intrassay 2%, CV interassay 5,3%. Appropriate dilutions were made to measure the high values of both CT and CEA.

Octreotide at a daily dose of 150 μg was administered by means of 3 subcutaneous (s.c.) injections for the first 6 months, the dose was then increased to 300 μg per day for another 6 months. rIFN-α-2b was administered in doses of 5.000.000 I.U. intramuscular (i.m.) 3 times a week for 12 months.

All patients gave informed consent to participate in the study. Patients were admitted to our department for the initial treatment, which was then self-administered.

RESULTS

Treatment was well tolerated in most of the patients. The therapy was stopped after 2 to 3 weeks in 2 patients, because of aggravation of pre-existing diarrhea and severe toxicity of rIFN-α-2b treatment (fever, leukopenia, anorexia, and myalgia).

The characteristics of the 6 treated patients are summarized in Table 1. Pre-existing diarrhea (Patients 1, 2, 4, and 6) and flushing (Patient 5) significantly improved during long-term treatment. All patients expressed a feeling of well being.

The evolution of CT and CEA is shown in Figures 1 and 2. A maximum decrease of CT was reached after 1 month in 2 patients (Patients 1 and 6), the decrease was respectively 56% and 34% from the basal CT values, and after 3 months in 4 patients (Patients 2, 3, 4, and 5), the decrease was respectively 88%, 34%, 36%, and 42%. Subsequently, CT values increased moderately in all patients; therefore, after 12 months, the final decrease of plasma CT levels variation in Patients 1, 2, 3, 4, 5, and 6 was, respectively, 12%, 15%, 18%, 20%, 24%, and 22% from the initial levels. In all patients, a decrease of CEA levels was already reached after 1 month and a maximum decrease was obtained

TABLE 1
Patients Characteristics and Results of Treatment with Octreotide + rIFN-α-2b

Patients no.	Sex	Age	Disease extension	Symptoms	CT (pmol/l) Months of treatment					CEA (μg/l) Months of treatment				
					0	1	3	6	12	0	1	3	6	12
1	M	32	Liver, bones, cervical nodes	Diarrhea	31.483	13.986	21.293	26.411	27.705	213	209	185	150	145
2	M	46	Mediastinum	Diarrhea	1.901	1.765	231	1.499	1.616	119	75	59	49	44
3	F	42	Lung, mediastinum	—	41.013	31.015	27.067	32.154	33.631	430	310	280	200	185
4	F	56	Mediastinum	Diarrhea	4.506	3.160	2.890	3.307	3.605	30	26	24	18	16
5	F	46	Lung, mediastinum	Flushing	14.835	12.333	8.626	10.150	11.275	60	48	40	30	28
6	F	44	Lung, mediastinum	Diarrhea	8.385	5.546	5.837	5.925	6.540	145	140	121	92	87

rIFN-α-2b: recombinant interferon-α-2b; CT: calcitonin; CEA: carcinoembryonic antigen.

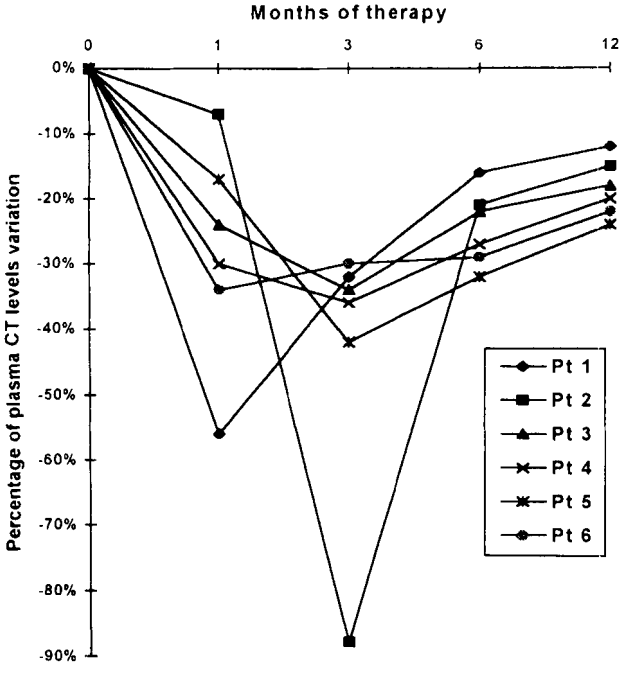

FIGURE 1. Individual variation of calcitonin (CT) plasma levels (%) during the therapy with octreotide and interferon-α-2b in six patients. Percentage of plasma CT levels variation is calculated in comparison with basal plasma CT.

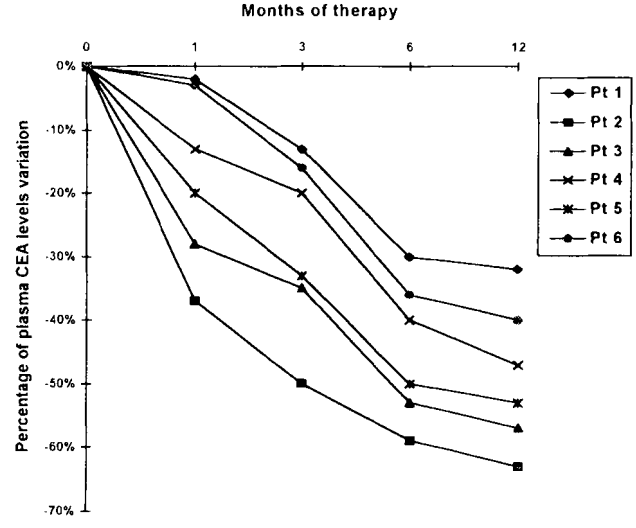

FIGURE 2. Individual variation of carcinoembryonic antigen (CEA) plasma levels (%) during the therapy with octreotide and interferon-α-2b in six patients. Percentage of plasma CEA levels variation is calculated in comparison with basal plasma CEA.

after 12 months (32%, 63%, 57%, 47%, 53%, and 40%). The side effects observed in all of the patients during treatment were fever, which rarely exceeded 38.5 °C and myalgia. Anorexia, nausea, and headache were observed in one patient (Patient 1), leukopenia and fatigue in three patients (Patients 3, 4, and 5).

No significant changes in metastases size were observed by echography, total body computerized tomography, and MR.

DISCUSSION

Some recent reports have suggested the activity of high doses of long-acting somatostatin analogues in the management of MTC and other neuroendocrine tumors.[37-38]

Contradictory results regarding the therapeutic effect of octreotide have been described in MTC. In the literature high doses of octreotide were usually necessary to obtain significant response without obtaining normalization of CT plasma levels. Mahler et al.[21] reported on 3 patients with metastatic MTC treated with high doses of octreotide (up to 2.000 μg per day) for 3 to 17 months. Symptoms of diarrhea, malaise, and weight loss improved in all of the patients. Serum CT levels decreased to a minimum of 47%, 52%, and 81% of the initial levels, but these ones finally increased again to 67%, 68%, and 127%. Serum CEA levels also decreased to 45%, 60%, and 63% of the basal levels, but later increased again to 50%, 84%, and 105%. Modigliani et al.[23] administered octreotide (up to 1500 μg

per day for 1 to 2 months) to 18 patients with MTC, 12 of whom had metastases. During treatment serum CT levels decreased by more than 20% in 8 patients, whereas CEA levels did not decrease. In two of nine patients, diarrhea improved dramatically, and in four of five there was a definite improvement of other symptoms such as flushing or malaise. These authors observed a decrease in CT levels more frequently in a group of patients with normal or minimally elevated CEA levels, hence considered to have a better prognosis.

A study by the Italian Trials in Medical Oncology Group[28] confirms the efficacy of rIFN-α-2a in the treatment of neuroendocrine tumors, with subjective relief of symptoms being obtained in 64% of patients. In particular, 1 patient affected by MTC with mediastinal nodes 3 cm in greatest dimension assessed by computed tomography scan experienced a complete remission.

Our study suggests that the combination of octreotide and IFN can be recommended in advanced MTC, obtaining an initial decrease of CT values (a maximum decrease was 34–88% from the basal values) and a permanent reduction of CEA levels (a maximum decrease was 32–63% from the basal values). For all of the patients treated for 12 months this schedule was well tolerated, and the quality of life greatly improved, obtaining alleviation of flushing and diarrhea. We haven't obtained a significant reduction of primary tumor and metastases, but the decreases in CT and CEA levels may indicate inhibition of further tumor growth.

In conclusion, the results obtained indicate that the combination of octreotide and IFN may have synergistic effects in therapy of advanced MTC and it may prevent or retard the need to increase the dose of octreotide with time. Therefore this schedule can be recommended for its good level of tolerability in patients and the relief of clinical symptoms and the decrease of tumor markers.

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