Medullary thyroid cancer treated by capecitabine

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Medullary thyroid carcinoma with distant metastases is generally incurable, with 20% overall survival at 10 years. The treatment goal is palliative. Chemotherapy has a limited role, with low response rates and high toxicities with the different regimens. Here, we report the case of 64-year-old man with metastatic medullary thyroid carcinoma in progression after primary treatment with cisplatin–doxorubicin. The patient received capecitabine 2000 mg/m^2 total per day × 14 days followed by 1-week rest. He received 41 cycles, and presented prolonged and objective tumor response (30 months), without any toxicity. *Anti-Cancer Drugs* 18:831–834 © 2007 Lippincott Williams & Wilkins.

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Introduction

Medullary thyroid carcinoma (MTC) accounts for 5–10% of all thyroid cancer. It occurs as a sporadic form in about 70–75% of the cases, whereas the remaining 25–30% are familial forms. The clinical course of patients with MTC is largely related to tumor stage at the time of diagnosis. Survival rate at 10 years is 95% for patients of stages I and II, whereas it is 55% for patients of stages III and IV [1].

The management of metastatic disease is primarily oriented towards the relief of symptoms. Chemotherapy can be recommended for patients presenting rapidly progressive metastatic tumors; however, the rate of response to the different chemotherapeutic regimens is generally low [2].

Capecitabine, an oral 5-fluorouracil (5-FU) prodrug, has been shown to be effective in breast cancer and gastrointestinal tumors. We report on a case of a remarkable outcome in a patient with metastatic MTC treated by capecitabine.

Case report

A 64-year-old man with neither personal nor family history of thyroid disease presented progressive thyroid enlargement and cervical pain. Local examination revealed a 4-cm nodule on the right thyroid lobe, associated with ipsilateral cervical nodes. Baseline serum calcitonin (CT) level was 5000 pg/ml.

The patient underwent total thyroidectomy with dissection of ipsilateral, central neck compartments and anterosuperior mediastinum lymph nodes. Histological examination found a 5-cm MTC involving the right lobe, the isthma and part of the left lobe, with capsular effraction. Immunohistochemical staining was positive for CT, chromogranin, synaptophysin and cytokeratin. Examination revealed amyloid deposits. Tests for mutations of the RET proto-oncogene were negative, confirming the sporadic origin.

Postoperative chest and abdominal computed tomography was normal, as well as technetium-99 m bone scintigraphy. Two months after surgery, CT level was 345 pg/ml.

The patient received additional external radiotherapy to a total dose of 45 Gy over 5 weeks and was maintained on thyroxine (150 μg/day).

CT levels increased progressively during 1 year to 5000 pg/ml. Total body tomodensitometry images were normal. Fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography indicated multiple bone metastases, confirmed by technetium-99m bone scintigraphy. Clinically, the patient had diarrhea but no bone pain.

After four cycles of chemotherapy associating doxorubicin (50 mg/m^2) and cisplatin (90 mg/m^2), the CT level increased to 5220 pg/ml. The patient remained pain-free and no longer had diarrhea. We considered that he had stable disease and decided to add 5-FU to the combination. Furthermore, because it was impossible to insert an implantable site, we used capecitabine instead, at 1000 mg/m^2 total per day × 14 days followed by 1-week rest. The patient received three additional cycles with capecitabine–doxorubicin–cisplatin.

Patient evaluation after these three cycles revealed a progressive disease with CT increased to 9147 pg/ml and appearance of one hepatic metastasis. We decided to stop doxorubicin–cisplatin and continue capecitabine with doses increased to 2000 mg/m^2 total per day. The patient also underwent radiofrequency ablation of his hepatic metastasis.

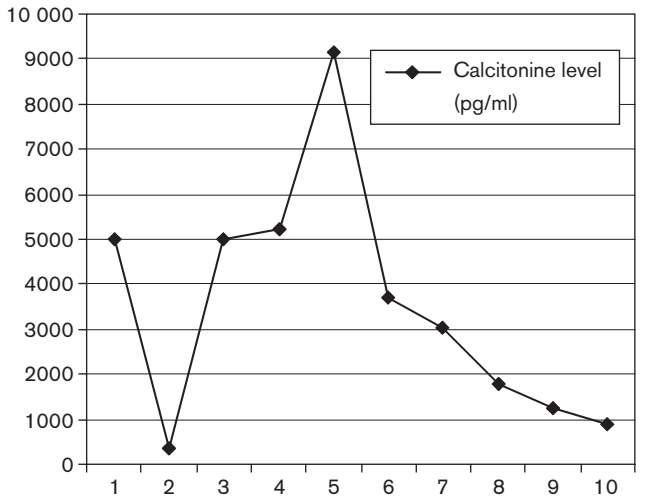
He presented a prolonged and objective response (30 months) and received 41 cycles of capecitabine alone. The CT level decreased progressively to 882 pg/ml (Fig. 1). Bone metastases were stable, with reduction of scintillation signal on technetium-99m scintigraphy. Chest and abdominal tomodensitometry results were normal. The chemotherapy was well tolerated, with no diarrhea or hematologic toxicities.

Discussion

The 10-year survival rate of patients with clinical MTC is approximately 65%. Distant metastases are the main cause of MTC-related death. Chemotherapy can be recommended to patients presenting a rapidly progressive metastatic tumor, which represents an unpredictable event in the natural history of the disease.

MTC is a well-differentiated endocrine tumor, therefore MTC patients have so far been treated with drugs with demonstrated activity against other well-differentiated endocrine tumors (such as carcinoids or islet cell carcinomas). Various combinations of doxorubicin, cisplatin, 5-FU, bleomycin, dacarbazine and streptozocin have produced similar response rates (about 20%) with symptomatic improvement in some patients, but no survival benefit has been found [3,4]. Many factors can explain the low chemosensitivity of MTC. One of these is the low rate of mitosis, the target of many cytotoxic drugs. Another reason could be the overexpression of the *mdr*-1 gene product by tumor cells. *mdr*-1 encodes a transmembrane glycoprotein, p-170, that antagonizes the intracellular accumulation of cytotoxic agents of natural derivation and confers the multidrug resistance phenotype to tumor cells [5].

Fig. 1



Evolution of calcitonin level (pg/ml). Before surgery (1); after surgery (2); at relapse (3); after four cycles of doxorubicin–cisplatin (4); after three cycles of doxorubicin–cisplatin–capecitabine (5); before radiofrequency (6); 2 months after radiofrequency (7); after 22 cycles of capecitabine (8); after 31 cycles of capecitabine (9); after 40 cycles of capecitabine (10).

Few cases of complete response have been described in the literature: one with doxorubicin [6], one with doxorubicin and cisplatin [6], and one with dacarbazine and 5-FU [7].

Capecitabine is a carbamate derivative of doxifluridine that is absorbed through the intestine in prodrug form. It is converted to its only active metabolite, 5-FU, by thymidine phosphorylase. This enzyme is present at higher levels in some tumors compared with normal healthy tissues. This theoretically allows for selective activation of the drug and lower systemic toxicity [8,9].

The activity of capecitabine is thought to mimic continuous infusion of 5-FU. The recommended dosage is 1250 mg/m^2 administered orally twice daily for 2 weeks followed by 1-week rest in 3-week cycles [10]. Thus, dose reductions because of capecitabine toxicity are frequently required in the patients [11,12], suggesting that a lower starting dose may be beneficial.

In vivo, this drug has shown antineoplastic activity in a variety of xenograft models, including greater inhibition compared with FU or the tegafur/uracil combination in selected models [8,13]. It has also shown activity in tumors known to be resistant to FU [14].

In clinical trials, capecitabine compares favorably with 5-FU in two phase III trials for first-line therapy in patients with metastatic colorectal cancer. The toxicity profile consisted most commonly of gastrointestinal and dermatologic effects [11,12]. In phase II noncomparative trials, the combination of capecitabine with oxaliplatin [15,16] or irinotecan [17,18] has yielded overall response rate and median survival results similar to regimens associating 5-FU with the same agents.

Capecitabine has also been approved for use as a single agent in metastatic breast cancer patients resistant to both anthracycline-based and paclitaxel-based regimens, and in combination with docetaxel after failure of prior anthracycline-based regimens [19]. The ease of administration of the drug also leads to specific investigations in

elderly patients (> 65 years) in whom it produced interesting results with acceptable toxicity [20,21].

In patients with prostate, renal cell, ovarian or pancreatic cancers, capecitabine has shown various degrees of efficacy, mostly in the form of partial response and stable disease. Combination therapy in these patients appears to be more beneficial than single-agent capecitabine [19].

Recently, some phase II clinical trials using capecitabine in the treatment of metastatic MTC have been published [22–24]. The associated drugs were different and so were the results.

Fine *et al.* [22] gave a combination of capecitabine and temozolomide to 10 patients with progressive metastatic neuroendocrine tumors. They obtained six objective responses: one complete response, two partial responses, one minor response and two stable diseases.

Hoff *et al.* [23] designed a phase I/II trial testing capecitabine, dacarbazine and imatinib in 13 patients with advanced solid tumours, including seven MTC. The combination of the three drugs yielded no objective response, but was associated with considerable toxicity.

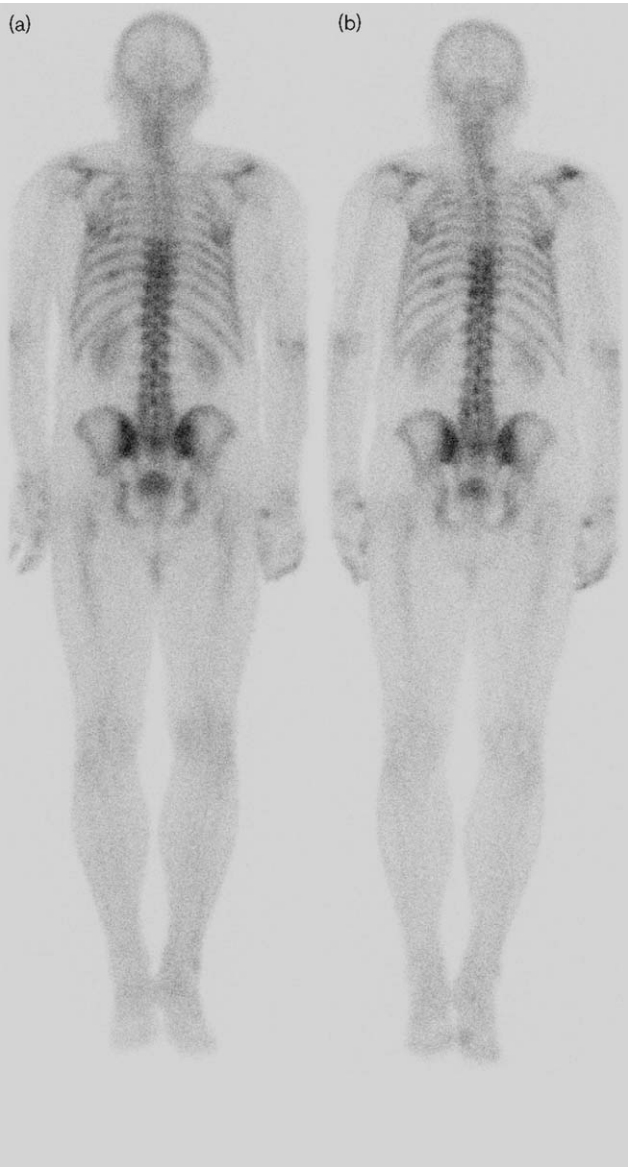
Droz *et al.* [24] conducted a phase II trial of capecitabine and irofulven in patients with advanced thyroid cancer. Of the five patients with MTC, three had disease stabilization.

The problem with these trials is the small number and the heterogeneity of the patients, thus complicating the assessment of results specific to MTC (not distinguished from other well-differentiated tumors).

The current case exemplifies a potential activity of capecitabine on MTC, with the drug achieving significant, objective and prolonged tumor response in one patient who had failed previous chemotherapy regimens. A progressive and continued decrease of CT levels was observed, concomitant to a partial response detected by bone scintigraphy (Fig. 2). These biological and radiological responses were confirmed by the clinical status of the patient who still had performance status 1 and neither diarrhea nor bone pain.

Capecitabine was well tolerated at the total dose of 2000 mg/m^2 per day. Diarrhea and hand–foot syndrome, two of the major adverse effects reported with this agent, were not observed. We chose to increase the administered dose progressively because we had no information about the tolerance of MTC patients to capecitabine, especially with diarrhea being a possible toxic effect of the drug or a symptom of the disease.

Fig. 2



Posterior whole-body Tc-99m bone scintigrams [(a) before capecitabine; (b) after 40 cycles of capecitabine] show decreased uptake at the posterior arch of the ninth rib, the anterior arch of the fourth rib and the lumbar vertebrae. The increased uptake at the right acromioclavicular articulation was considered a sequel of traumatism.

CT is a good tumor marker in the follow-up treatment of MTC [25]. Postoperative serum CT is the central criterion for diagnostic decision making, whether or not incomplete tumor extirpation or tumor recurrences are present [26]. In some cases with poor prognosis, CT levels may decrease simultaneously with disease progression when the tumor dedifferentiates [27,28]. For the patient presented here, however, CT level decrease was associated with radiological and clinical responses, thus confirming tumor regression.

As far as we know, this is the first report demonstrating the activity of single-agent capecitabine in medullary thyroid carcinoma. This drug may represent a reasonable therapeutic alternative for patients with metastatic disease. Further prospective studies including larger numbers of patients and evaluating the dose and schedule of capecitabine administration for the treatment of MTC are warranted.

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