Unusual Short-Term Complete Response to Two Regimens of Cytotoxic Chemotherapy in a Patient with Poorly Differentiated Thyroid Carcinoma

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Context: Treatment modalities for progressive iodine-refractory poorly differentiated thyroid carcinomas are not yet well defined. Molecular targeted therapy with multikinase inhibitors has recently shown promising results, and cytotoxic chemotherapy is generally considered of low efficacy.

Objective: We report the case of a 57-yr-old woman with an advanced iodine-refractory poorly differentiated thyroid cancer who was treated sequentially between October 2006 and March 2011 with two different regimens of cytotoxic chemotherapy and three lines of multikinase inhibitors.

Methods: Efficacy and adverse effects of the consecutive treatment modalities, i.e. vandetanib, doxorubicin-cisplatin combination, sorafenib, paclitaxel-carboplatin combination, and sunitinib, are reported.

Results: The patient presented a complete tumor response to a doxorubicin-cisplatin combination lasting 10 months and to a paclitaxel-carboplatin regimen lasting 5 months and had no or limited response to kinase inhibitors, i.e. progression after 3 months of vandetanib, progression after 4 months of sorafenib, and stable disease for 8 months with sunitinib treatment.

Conclusions: When tumor progresses with kinase inhibitors, cytotoxic chemotherapy may be an alternative in selected cases of advanced iodine-refractory poorly differentiated thyroid cancer. For those rare cases, clinical management should benefit from a multidisciplinary team approach through specialized networks. (J Clin Endocrinol Metab 97: 3046–3050, 2012)
then discuss the therapeutic tools currently used in radioiodine refractory patients.

Case Report

A 57-yr-old woman was referred to our institution in April 2002, a few weeks after total thyroidectomy. She had no medical history, including neck irradiation, and no family history of thyroid cancer. Pathology revealed a 4-cm tumor in the right lobe, which was a poorly DTC (PDTC) positive for thyroid transcription factor 1 and thyroglobulin (Tg) with minimal extension beyond the thyroid capsule, and a 1-cm infiltrating follicular variant of PTC in the left lobe.

Figure 1 summarizes the main treatments administered and their effects on serum Tg levels measured under L-thyroxine (LT4). The patient first received 4070 MBq 131I off LT4 in July 2002. Stimulated Tg level was 32 ng/ml (RIA-Tg-S Brahms; Brahms, Berlin, Germany; functional sensitivity, 0.4 ng/ml), in the absence of Tg antibodies (TgAb). Postablation whole body scintigraphy (WBS) only showed normal thyroid remnants. The tumor was then classified pT3NxM0. A second radioiodine treatment (4095 MBq) was administered off LT4 in January 2003 because serum Tg level remained detectable (2.4 ng/ml) on LT4 treatment 3 months after radioiodine ablation. Stimulated Tg level was 3.6 ng/ml and post-iodine WBS did not reveal any radioiodine avid lesions. In December 2003, Tg level on LT4 rose to 34 ng/ml (immunometric assay Tg-Kryptor; Brahms; functional sensitivity, 0.8 ng/ml) and led to a third radioiodine treatment (3922 MBq off LT4). WBS was again negative as well as 18-fluorodeoxyglucose positron emission tomography (18FDG-PET) and neck and thorax computed tomography (CT) scan.

In November 2004, serum Tg under LT4 treatment increased to 435 ng/ml. 18FDG-PET and CT scan demonstrated a nonsurgically removable 3-cm right hilar mass that was treated by external radiation beam therapy for a total dose of 50 Gy, which induced a grade 1 dysphagia lasting less than 1 month. Five months later, CT scan showed a 67% reduction of the target lesion, PET showed a decrease in 18FDG uptake, and serum Tg level fell to 242 ng/ml under LT4 treatment, providing evidence for partial remission (11). However, progressive disease with mediastinal nodal involvement and lung metastasis was evidenced in July 2006 (Tg = 6865 ng/ml). After local multidisciplinary discussion and advice from Pr. Martin Schlumberger (Institut Gustave Roussy, Villejuif, France), the patient received six cycles of doxorubicin 60 mg/m² associated with cisplatin 40 mg/m² every 4 wk between October 2006 and March 2007, with a complete response on CT scan and 18FDG-PET (Fig. 2). Tg level fell to 34 ng/ml. Astenhia (grade 1), nausea (grade 1 despite well-conducted treatment), alopecia (grade 3), and anemia (grade 1) were the main side effects. Cardiac function remained normal, and there were neither leucopenia nor infectious complications with preventive granulocyte colony-stimulating factor treatment.

In January 2008, recurrence was evidenced in the right paratracheal area and in the lungs, serum Tg level rose to 842 ng/ml (ECLIA, Cobas 6000; Roche Diagnostics, West Mannheim, Germany; functional sensitivity, 1.0 ng/ml), and the patient was included in a randomized therapeutic phase II trial, using either placebo or vandetanib (12). Tumor progression was observed after a 3-month placebo period. Disease continued to progress after crossover to vandetanib treatment (300 mg/d), which was stopped in July 2008. At that time, new lung metastases were visualized on CT scan, and Tg level reached 8781 ng/ml. Diarrhea (grade 2) and abdominal pain (grade 1) were the main adverse effects.

After a multidisciplinary web conference arranged by the French TUTHYREF network (for TUmeurs THYroïdiennes REFractaires), the off-labeled use of sorafenib was proposed to the patient. The treatment (800 mg/d) was begun in October 2008 with her informed consent. Although a 20% tumor shrinkage was observed at 1 month, disease had clearly progressed at 4 months (70% increase of the target lesions and appearance of new lesions). Digestive side effects with diarrhea (grade 1 to 2), nausea (grade 1), loss of appetite (grade 2) associated with asthenia (grade 1 to 2), and weight loss (grade 2) were noticed, as well as alopecia and hand-foot syndrome (grade 1). After another TUTHYREF web conference, it was decided to administer a second line of chemotherapy combining paclitaxel 175 mg/m² and carboplatin area under the curve 5 every 4 wk. A complete anatomical (13) and metabolic (14) tumor response was achieved after six cycles of
chemotherapy, with a decrease in serum Tg level on LT4 treatment to 170 ng/ml (Fig. 2). Chemotherapy was stopped in August 2009 for neurotoxicity (grade 2).

Unfortunately, disease progressed again in January 2010 with Tg level at 27,305 ng/ml, compressive right paratracheal mass, and new lung metastases. A surgical biopsy of the paratracheal lesion was performed with the patient’s informed consent. Pathological characteristics were similar to those of the primary PDTC. Recurrence was negative for a panel of mutations, i.e. BRAF, RAS, RET/PTC, and PAX8/PPARγ. BRAF V600E, NRAS codon 61, HRAS codon 61, and KRAS codons 12 and 13 mutations were searched for on tumor DNA by pyrosequencing. Translocations involving RET/PTC1, RET/PTC3, and PAX8/PPARγ were detected from RNA by RT-PCR as previously described (15). After giving informed consent, the patient received from March 2010 an off-label sunitinib treatment of 37.5 mg/d during 3 wk and a treatment holiday during the fourth week. She had grade 2 digestive toxicity and weight loss. Disease was first stable, but progression occurred in November 2010 and could not be controlled with higher doses of 50 mg/d. She died in March 2011 with pleural effusion.

**Discussion**

According to REsponse Criteria In Solid Tumors (RECIST) (11, 13) and also to PET Response Criteria In Solid Tumors (14), our patient with a progressive iodine-negative PDTC showed a complete response to two different regimens of cytotoxic chemotherapy. This response was associated with a dramatic decrease of Tg level. In contrast, only a minimal efficacy was achieved with three lines of TKI.

Chemotherapy is rarely effective in progressive radioiodine refractory thyroid cancer. Doxorubicin is the most frequently used cytotoxic agent in thyroid carcinoma, either alone (16) or in combination with cisplatin (17–19), and induces partial and transient responses in 0% to less than 20% with significant adverse effects, mainly cardiac and hematological. In the present case, the patient received six cycles of doxorubicin plus cisplatin and exhibited a complete response lasting 1 yr, and chemotherapy was well tolerated.

The use of taxanes has been reported in few patients with a modest activity in some (4, 20). Recently, Spano et al. (21) reported promising data in a retrospective analysis on 14 refractory patients (eight PTC, six follicular thyroid carcinoma), including six patients with a mixed component of poorly differentiated or undifferentiated carcinoma using the GEMOX regimen (1000 mg/m² gemcitabine plus 100 mg/m² oxaliplatin every 2 wk for 12 cycles). One patient (7%) achieved a complete response for more than 24 months, seven patients (50%) had a partial response, and four (28%) had stable disease. The combination was generally well tolerated. The most common adverse effects included asthenia, peripheral neuropathy, diarrhea, and hematological toxicity.

In recent years, molecular targeted therapy using TKI has shown promising results in radioiodine refractory patients. The patient described here received three lines of TKI. First, she received vandetanib in a randomized phase II trial but progressed rapidly. In this study including 145 patients, although progression-free survival was significantly improved in the treatment group (11 months) compared with the placebo group (5.8 months), no objective tumor response rate was seen (12). Secondly, our patient received sorafenib for 6 months. After achieving partial response at 2 months, she rapidly progressed. Data from phase II trials have been reported so far in four series including 19 to 41 DTC patients (6–8, 10). No complete response was reported, but partial response was obtained in 15 to 25% and stable disease was obtained in 34 to 82% of patients. Efficacy was lower in patients with PDTC, as in our patient, than in those with PTC. Thirdly, sunitinib was administered with disease stabilization during 8 months. In a phase II study performed in 28 DTC patients with FDG-avid tumors, sunitinib (37.5 mg) led to one complete response, seven (25%) partial responses, and 14 (50%) disease stabilizations (9). All these multikinase inhibitors induce a number of adverse effects that sometimes significantly impair quality of life. Our patient presented fatigue, weight loss, digestive and skin toxicity, which were limited to grades 1 or 2. Local treatment modalities,
such as surgery, radiation therapy, radiofrequency ablation, cryotherapy, cement injection or embolization, may control disease for significant periods of time and may enable postponing the initiation of a systemic treatment (2). Interestingly, our patient experienced partial remission lasting 15 months after the external beam radiation of a unique hilar mass.

Other molecular therapies have been tested such as motesanib (5) and axitinib (22), and more promising results were recently achieved with pazopanib (23) and lenvatinib (E7080) in phase II trials with partial response rates over 45% (24). Interestingly, lenvatinib showed similar efficacy in naive patients and in pretreated patients. Furthermore, preliminary data suggested that RAS mutated tumors showed better response to lenvatinib than wild types. Although controversial (7, 8), BRAF mutation may also predict response to sorafenib in PTC patients. In the recurrent tumor of our patient, no activating mutations were found in genes encoding signaling molecules of the MAPK pathway, i.e. BRAF, RAS, RET/PTC, though supposed to be initiating events in thyroid carcinogenesis. Other molecular abnormalities may be involved, and future research will focus on other relevant targets that may allow a more personalized treatment to be given.

This observation also underlines the relevance of expert multidisciplinary discussions for those complex and unusual clinical cases. In this regard, we have to point out the role and interest of the French TUTHYREF network, which was created in 2008 and includes more than 30 centers. It offers the opportunity for clinicians to present and discuss cases of refractory thyroid tumors during multidisciplinary web conferences arranged twice a month. The objective of this network is to harmonize clinical management modalities and to enable patients to have access to new treatments, especially in therapeutic trials.

Although recent data provide evidence for the use of molecular targeted therapy with TKI in first-line treatment of patients with progressive radioiodine refractory DTC, this case report shows that cytotoxic chemotherapy may be an option in patients who do not respond to these TKI. In any case, the development of new drugs or new treatment combinations is required as well as their assessment in appropriate trials.

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References


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