A Case of Anaplastic Thyroid Cancer with Long-term Survival

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Abstract. *Anaplastic thyroid carcinoma (ATC) (less than 10% of all thyroid cancer) is a high-grade neoplasm, characterized by an aggressive clinical course and refractoriness to currently available local and systemic modalities of treatment. It is considered the most aggressive solid tumour, there is no adequate therapy for this disease and few patients with ATC live more than 1 year following diagnosis. We report herein an unusual case of ATC in a 59-year-old woman. She presented to our Institute in December 2004. She received many kinds of chemotherapeutical and multimodal treatment; we obtained a long period of localized disease (about two years) and an excellent response to therapy. She is still alive 58 months from diagnosis.*

Anaplastic thyroid carcinoma (ATC) is a high-grade neoplasm, characterized by an aggressive clinical course with brief survival, and is refractory to currently available local and systemic modalities of treatment. It represents fewer than 10% of all thyroid cancer cases, but accounts for up to 39% of thyroid carcinoma deaths; early invasion of local structures is as common as that of locoregional lymph nodes and distant metastasis (1-4).

There are approximately 420-900 new cases in Europe, 700-1200 new cases per year in the US. Due to the rapid death rate, the incidence (annual number of new cases) and prevalence (total number of cases present at any time) are essentially the same (3, 5, 6).

It is possible to find areas of ATC next to well-differentiated areas of carcinomas (papillary and/or follicular). This fact confirms the de-differentiation hypothesis on ATC genesis from pre-existing well-differentiated carcinoma. Risk factors for well-differentiated and anaplastic tumours, from this point of view, may be similar: ATC, in fact, is more common in people who have previous benign thyroid disease (1) and it more frequently arises in females and in patients older than 50 years (often between 60-70 years of age) (1, 4).

At present, it is considered the most aggressive type of solid tumour, with a median overall survival shorter than six months, while the percentage of patients surviving longer than one year is less than 20% (7).

Usually, ATC manifests itself as a neck lesion characterized by a rapid growth and the involvement of both thyroid lobes (8). The most frequent symptoms are due to local compression and include dyspnoea, dysphagia, vocal cord paralysis, superior cava vein syndrome, and headache. At the diagnosis, up to half of all patients have locally advanced disease with involved locoregional lymph nodes, and up to 40% have distant metastatic spread, involving mainly lung, bone and brain.

There is no adequate therapy for this disease. The treatment of ATC, whenever possible, is surgery, with radical intent. However, this approach is not always possible because the tumour is often locally advanced at diagnosis hence therapeutic options also include local radiotherapy and chemotherapy (9).

Some years ago, the most commonly used chemotherapeutic agent was adriamycin (or the analogous epirubicin); since then, other agents have been used such as cisplatin (or the analogous carboplatin) and more recently the taxanes (paclitaxel and docetaxel).

In the recent years, some new therapeutic drugs have been evaluated. Notably, inhibitors of RAF kinase (a non-specific serine/threonine protein kinase), such as sorafenib and some others, inhibit the growth of human tumor xenografts derived from ATC tumors in nude mice (10, 11). Another novel anti-cancer agent is combretastatin A4-

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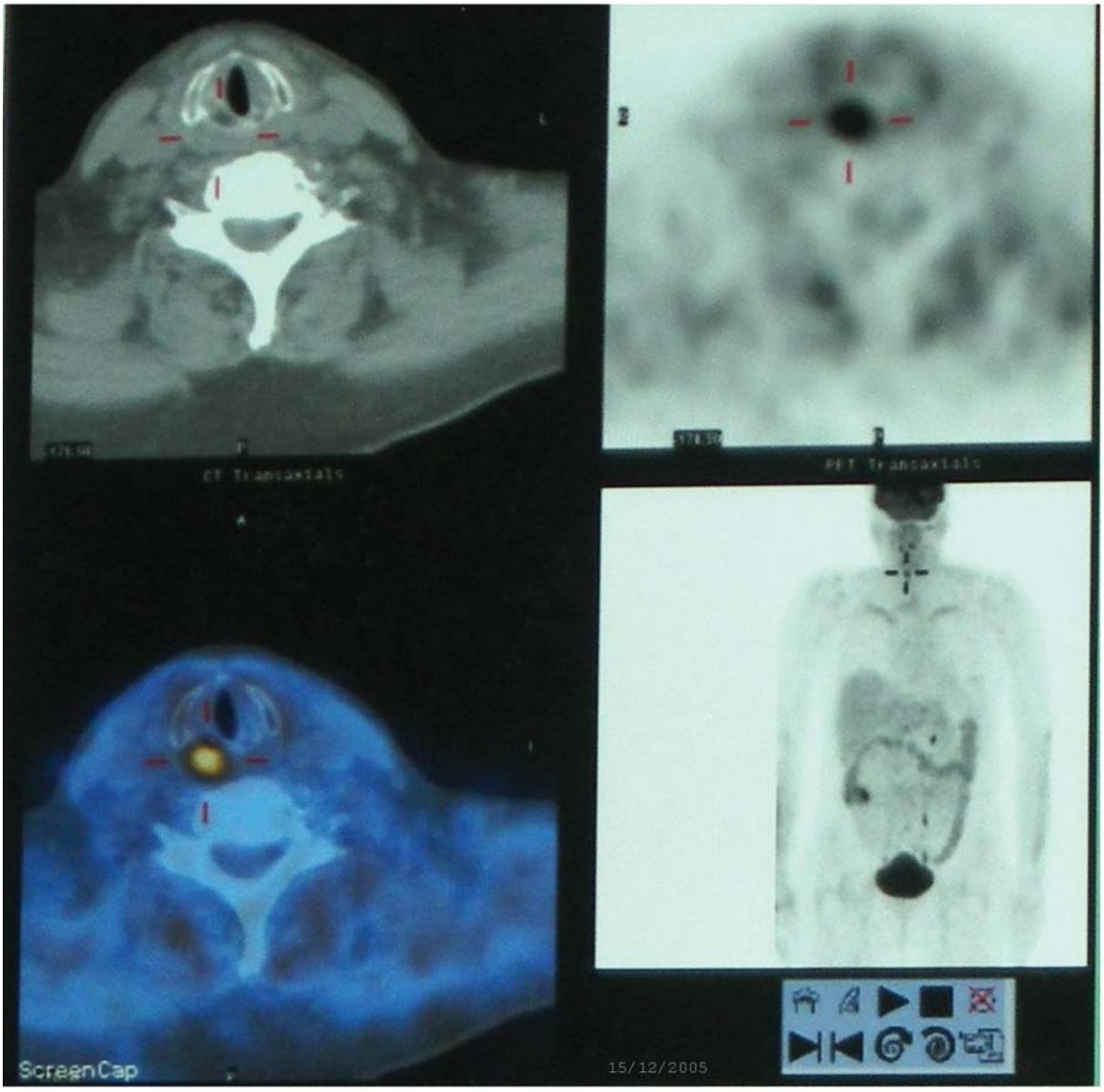

Figure 1. *PET-CT scan December 2005 (the lesion had almost disappeared).*

phosphate, which displays potent and selective toxicity towards tumour vasculature (12-14) and promises new valid approach to the disease (15-16).

The response rate to conventional chemo- and radiotherapy is often low and multimodality treatment remains the treatment of choice, even if the optimal sequence of multimodal treatment is not known.

Case Report

A 59-year-old woman presented to our Institute in December 2004 with history of cough and a progressive dyspnoea and dysphagia of some months' duration. She had a past medical history of surgery for an ovarian cystis in 1974, at the age of 25, and of non-insulin-dependent diabetes mellitus since 1998. She has never been exposed to radiation.

On admission, in December 2004, due to the evidence of a neck lesion, a computed tomography (CT) scan which revealed a 5 cm lesion at the base of the left neck originating from the left thyroid lobus, extending up to the mediastinal area. A thyroid biopsy was performed and confirmed the diagnosis of ATC. Excisional surgery was excluded because of the local invasion and the arterial compression.

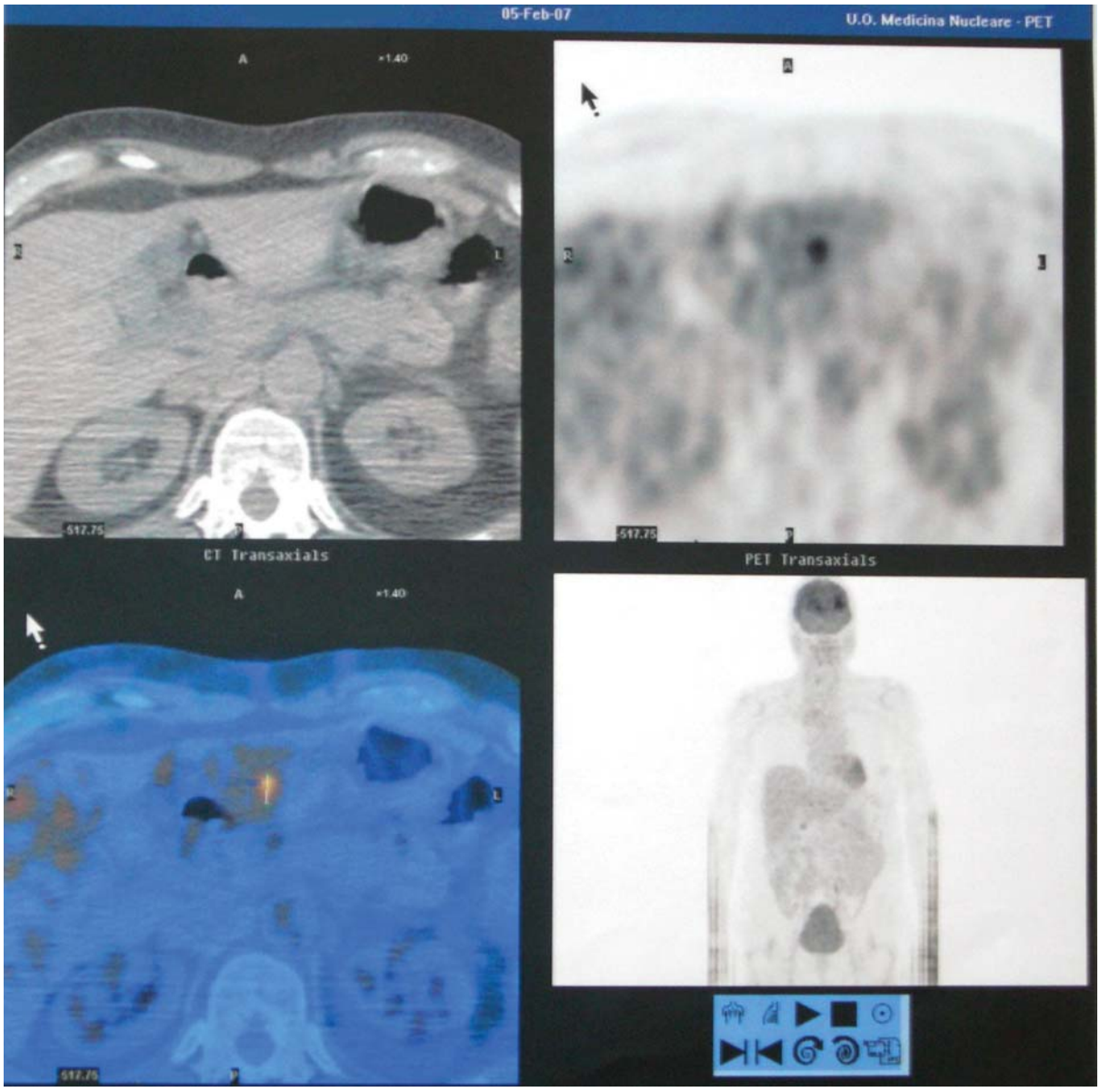

Figure 2. *PET- CT scan February 2007.*

The patient was treated with a multimodal treatment of cisplatin (50 mg total weekly) and local radiotherapy (2 Gy/day, total dose 28 Gy), for three weeks, without clinically significant toxicity.

In March 2005, a tracheotomy was performed, due to persistent dyspnoea; the patient started a new chemotherapeutic regimen of epirubicin at 50 mg/m^2 plus cisplatin at 60 mg/m^2, on day 1 and 2, every 21 days. After three cycles, a CT scan showed stable disease (SD) in April 2005. The chemotherapy was continued until June 2005 (four cycles total, with an adverse event of febrile neutropenia, treated with antibiotic therapy), associated with analgesic therapy (transdermal fentalyl) because of significant local pain of the neck.

In August 2005, the patient received a new chemotherapeutical treatment with docetaxel at 35 mg/m^2 on day 1, 8, 15, every 28 days (until November 2005).

At the end of 2005, a positron-emission tomography (PET)-CT scan was performed (Figure 1). It revealed only a small questionable area in the pharynx and the lesion had almost disappeared; however the patient reported significant pain localized in the right half of the neck, and dyspnoea.

Due to these symptoms, the patient started a new regimen of therapy receiving vinorelbine at 25 mg/m^2 on day 1, 8,

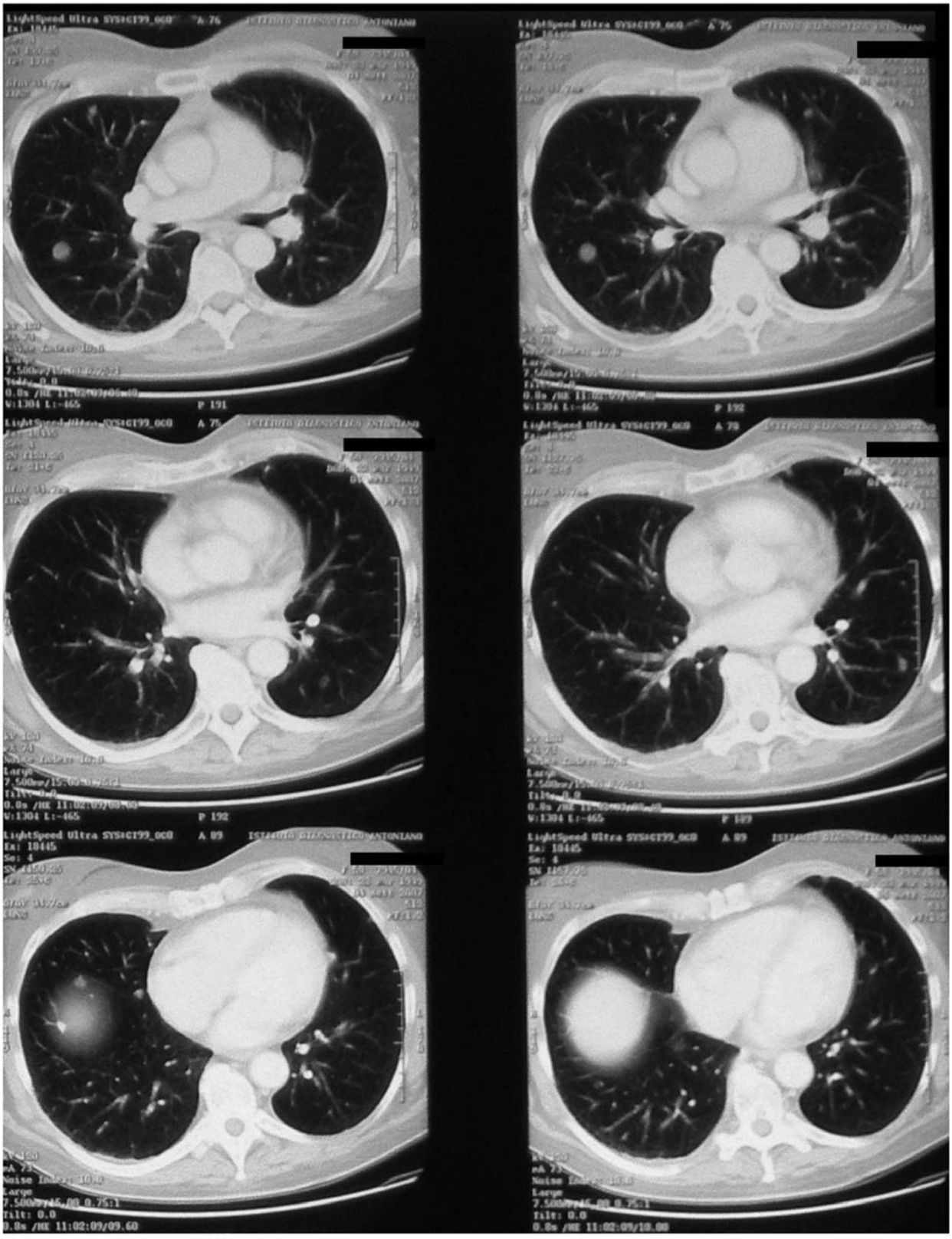

Figure 3. *CT scan October 2007, multiple lung metastases are apparent.*

every 28 days for two cycles until February 2006 (interrupted because of a hospitalization due to local pain). In March 2006, a new disease staging was performed: bone scintigraphy revealed high uptake in the right clavicle and in the eighth left rib; a CT scan demonstrated an area of inflammation and fistula from the tracheostomy to the half of clavicle, with focal osteo-necrosis (confirmed with magnetic resonance (MR) scan). Antibiotic treatment was given. The patient received another two cycles of chemotherapy with vinorelbine. From May to December 2006, because of the asthenia probably caused by vinorelbine, the patient again received therapy with docetaxel at 35 mg/m^2 weekly and appropriate analgesic therapy with opioid drugs because of local pain at the neck.

In February 2007, another PET-CT scan was performed, revealing only moderate uptake in thyroid cartilage [standardized glucose uptake value (SUV) 3.0] and in the right sternal-clavicular articulation (Figure 2). In April 2007, patient requested a six-month pause from therapy (weekly docetaxel). In October 2007, after the required pause from therapy, a further CT scan revealed multiple lung metastases (Figure 3). It was decided the patient would be treated again with docetaxel (35 mg/m^2 on day 1, 8, 15), which was the chemotherapeutic agent that demonstrated a good control of the disease of 4 and 8 months of SD for the two periods of therapy with docetaxel, without clinically significant toxicity.

In November 2007, due to further local progressive disease localized near the tracheotomy (with vocal cord paralysis), patient received liposomal doxorubicin at 40 mg/m^2 every four weeks. During further staging disease, SD was revealed on two consecutive visits with multiple lung metastases, sternal lysis and hepatic lesion (January 2008 and March 2008, CT scan). Liposomal doxorubicin was administered until August 2008, followed by therapy with sunitinib (37.5 mg for 28 days, every 42 days) from September 2008, due to progression of the disease.

Currently (September 2009), the patient is continuing sunitinib and has referred loss of weight and asthenia due to the disease and three episodes of local bleeding, probably due to the treatment.

The patient is still alive, with further local disease as shown by chest X-ray, 58 months from diagnosis.

Discussion

The reported case shows similarities and differences in comparison to the common course of ATC. The age at diagnosis, the rapid growth and the impossibility of a surgical treatment are common in this tumour type. On the other hand, the long period (about two years) of disease localized only in the neck and the excellent response to radiochemotherapy are the most important differences from standard ATC. The reason for disease control in this case is not clear, but in the scientific literature and in our experience, the multimodal approach may be an important factor in avoiding metastatic progression (17-19) even if this case does not meet the prognostic factors proposed by Kihara *et al*. (20).

Regarding the chemotherapy, our attitude was to be aggressive against this kind of cancer, giving the patient different courses of chemotherapeutic agents such as anthracyclines, platinum compounds and taxanes. The chemotherapy plus radiotherapy followed by an almost complete response, and weekly administration of docetaxel, in this patient allowed the control of the disease progression and resulted in an unusually long survival, against all expectations (21).

We also administered sunitinib to this patient. Sunitinib is an oral, small-molecule, multi-targeted receptor tyrosine kinase inhibitor. It acts against all receptors for platelet-derived growth factor and vascular endothelial growth factor, which play a role in both tumor angiogenesis and tumor cell proliferation (22). Some clinical trials are ongoing to demonstrate the activity of this new drug in ATC (23). Unfortunately, the decision of the patient regarding a six-month pause from therapy with docetaxel probably influenced the control of the disease, leading to distant metastatic spread.

The use of taxanes (paclitaxel, docetaxel) in our centre is based on the experience of some authors (24). Ain *et al*. demonstrated the activity of taxanes in ATC *in vivo* and *in vitro* (25); later they also demonstrated the use of paclitaxel (96-hour continous infusion) in ATC (1 complete response (CR) and 9 partial response (PR) in 19 patients) in a phase II clinical trial, with an important percentage of responses (PR+CR)(26).

Some other authors demonstrated the activity of paclitaxel *in vitro* (27) and in ATC with metastasis (28), and the activity of docetaxel (29). The use of taxanes in ATC is also under evaluation in a clinical trail ongoing in some centres, in association with the novel anticancer agent combretastatin A4-phosphate (15-17).

In our patient, chemo- and concomitant radiotherapy, followed by standard chemotherapy (adriamicyn, cisplatin) and the further chemotherapy with low-dose docetaxel allowed quite good control of the disease for some years, with almost complete response. For the patient, the use of taxanes doubtless provides advantage.

The use of taxanes appears to be of importance in some ATC cases, even if we do not have any predictive factor of response to this therapy. More clinical trials are needed to evaluate the action of taxanes in association with traditional chemotherapeutic agents or with new molecular target agents, such as combretastatin A4-phosphate, which is one of the best promising novel antivascular agents (12-16).

More studies are also needed to evaluate the activity of sunitinib, used as a single agent in metastatic or advanced ATC: first data highlight a quite good tolerance and an association with a high level of SD (24).

Presently, there is no standard approach to therapy in ATC; multimodal treatment seems to be the key to improvement in outcome against this lethal disease, even if the correct sequencing of therapy is not known.

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