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Clinical Trial

A multicenter phase II study of sunitinib in patients with locally advanced or metastatic differentiated, anaplastic or medullary thyroid carcinomas: mature data from the THYSU study

Alain Ravaud [a,b,c,*], Christelle de la Fouchardière [d], Philippe Caron [e], Adelaïde Doussau [f], Christine Do Cao [g], Julien Asselineau [f], Patrice Rodien [h], Damien Pouessel [i], Patricia Nicolli-Sire [j], Marc Klein [k], Claire Bournaud-Salinas [l], Jean-Louis Wemeau [g], Anne Gimbert [m], Marie-Quitterie Picat [f], Delphine Pedenon [a], Laurence Digue [a], Amaury Daste [a,c], Bogdan Catargi [n], Jean-Pierre Delord [o]

[a] *Department of Medical Oncology, Bordeaux University Hospital, Bordeaux, France*
[b] *Clinical Investigational Center, CIC. INSERM CIC 1401, Bordeaux University Hospital, Bordeaux, France*
[c] *Bordeaux University, Bordeaux, France*
[d] *Department of Medical Oncology, Centre Leon Bérard, Lyon, France*
[e] *Department of Endocrinology, Toulouse University Hospital, Toulouse, France*
[f] *Methodology Research Unit, Bordeaux University Hospital, Bordeaux, France*
[g] *Department of Endocrinology, Lille University Hospital, Lille, France*
[h] *Department of Endocrinology, Angers University Hospital, Angers, France*
[i] *Department of Medical Oncology, Cancer Institute of Montpellier, Montpellier, France*
[j] *Department of Endocrinology, Marseille University Hospital, Marseille, France*
[k] *Department of Endocrinology, Nancy University Hospital, Nancy, France*
[l] *Department of Endocrinology, Lyon University Hospital, Lyon, France*
[m] *Pharmacovigilance Unit, Bordeaux University Hospital, Bordeaux, France*
[n] *Department of Endocrinology, Bordeaux University Hospital, Bordeaux, France*
[o] *Department of Medical Oncology, Institut Claudius Régaud, IUCT, Toulouse, France*

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* *Corresponding author*: Department of Medical Oncology, Bordeaux University Hospital, Bordeaux, France.
E-mail address: alain.ravaud@chu-bordeaux.fr (A. Ravaud).

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Abstract ***Purpose:*** Patients with advanced radioactive iodine resistant differentiated (MDTC) or medullary (MMTC) thyroid cancer had an unmet need. Early data showed promising efficacy of vascular endothelial growth factor receptor inhibitors. We investigated sunitinib in this setting.

Patients and methods: This phase 2 trial enrolled MDTC, anaplastic (MATC) and MMTC patients in 1st line anti-angiogenic therapy with sunitinib at 50 mg/d, 4/6w. Objective response rate was the primary end-point. Secondary end-points were progression-free survival, overall survival and safety.

Results: Seventy-one patients were enrolled from August 2007 to October 2009, 41 MDTC/4 MATC patients and 26 MMTC patients. Patients received a median of 8 and 9 cycles, respectively. In the MDTC/MATC group, 13% of patients and 43% of cycles and in the MMTC group, 23% of the patients and 48.8% of cycles remained at 50 mg/d, respectively. The primary end-point was reached with an objective response rate of 22% (95% CI: 10.6–37.6) in MDTC patients and in 38.5% (95% CI: 22.6–56.4) in MMTC patients. No objective response was seen in MATC patients. Median progression-free survival and overall survival were 13.1 and 26.4 months in MDTC patients, 16.5 and 29.4 months in MMTC patients. The most frequent side effects were asthenia/fatigue (27.8% $\geq$ grade 3), mucosal (9.9% $\geq$ grade 3), cutaneous toxicities, hand-foot syndrome (18.3% $\geq$ grade 3). Of all, 14.1% had a cardiac event. Nine unexpected side effects were reported, out of which, five induced deaths.

Conclusion: Sunitinib is active in MDTC and MMTC patients. Side effects were more severe than with previous reports. If using sunitinib, alternative schedule/dosage should be considered.

1. Introduction

Thyroid cancer incidence has increased worldwide. Differentiated thyroid cancer (DTC) accounts for 90% of all thyroid cancers. Anaplastic and medullary carcinomas account for less than 5% each.

Less than 20% of DTC develop local recurrence or distant metastatic radioactive iodine-refractory disease [1]. Patients with anaplastic carcinomas (ATCs) have the poorest outcome with rapid local progression and/or metastases [2]. Patients with medullary thyroid carcinoma (MTC) having residual or recurrent disease, or for those with distant metastases, display a short median survival with no appropriate treatment assessed, until recently [3].

In 2006, when the THYSU study was designed there was an unmet need for these populations having locally uncontrolled recurrent disease or advanced metastases.

These arguments were sufficient to justify the investigation of an anti-angiogenic drug in this setting. Assessment of angiogenesis using quantification of microvascular density in papillary thyroid cancers demonstrated an increase in tumour vascularity as compared with normal tissue or benign tumours [4,5] which may increase the risk of recurrence and shorter disease-free survival [6,7]. On the other hand, higher microvascular density is associated with a worse outcome in MTC [8]. Increased vascular endothelial growth factor is demonstrable in thyroid tumours when compared with normal gland or benign tumours [9,10]. Higher vascular endothelial growth factor expression is present in metastatic thyroid cancer when compared with non-metastatic disease [10].

Since the study started, drugs have been approved containing an angiogenic inhibitor targeting VEGFR tyrosine kinase inhibition but using additional pathway: BRAF (sorafenib) [11], cRET (lenvatinib) [12] in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer (MDTC) and cRet/EGFR (vandetanib) [13], cMET (cabozantinib) [14] in progressive medullary thyroid cancer (MMTC).

Here, we report mature data concerning sunitinib in patients with MDTC, anaplastic (MATC) and MMTC.

2. Patients and methods

2.1. Study design

This was an open-label multicentre phase II trial (NCT00510640). Stratification was done for MDTC/MATC in one arm and MMTC in the other. THYSU was sponsored by Bordeaux University Hospital and approved by the Bordeaux ethical committee (CPP). A signed, written, informed consent was obtained from all the patients before starting any procedure. The study was conducted in accordance with good clinical practice and the ethics principles of the Declaration of Helsinki.

2.2. Eligibility

The main eligible criteria were adult patients, with histologically confirmed radioactive iodine-refractory DTC, ATC or MTC which had been progressive $\leq$6 months prior entry using RECIST criteria (v1.0) [15],