Títol

SORAFENIB FOR THE TREATMENT OF METASTATIC THYROID CANCER PATIENTS

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FA CONSTAR,

que el treball titulat **"Sorafenib for the treatment of metastatic thyroid cancer patients**" ha estat realitzat sota la meva direcció pel llicenciat **Jaume Capdevila Castillón**, trobant-se en condicions de poder ser presentat com a treball d'investigació de 12 crèdits, dins el programa de doctorat en Medicina Interna/Diagnòstic per la Imatge (curs 2010-2011), a la convocatòria de setembre.

A Barcelona, 11 de Juliol de 2011,

Joan Carles Galceran

Director del Treball de Recerca

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SORAFENIB FOR THE TREATMENT OF METASTATIC THYROID CANCER PATIENTS

SORAFENIB PER AL TRACTAMENT DELS PACIENTS AMB CÀNCER DE TIROIDES METASTÀSIC

Keywords: Thyroid cancer, Sorafenib, Targeted Therapies.

Paraules Clau: Càncer de Tiroides, Sorafenib, Teràpies dirigides.

ABSTRACT

Introduction

Based on recent results of several phase II studies with tyrosine kinase inhibitors and the better knowledge of molecular aberrations that characterize thyroid carcinogenesis a retrospective analysis of patients with metastatic thyroid cancer treated with sorafenib was designed.

Patients and Methods

The primary end point was objective response rate. Secondary end points included toxicity, median progression-free (mPFS) and overall survival, and correlation between tumor marker levels (thyroglobulin, calcitonin and CEA) and efficacy. Patients received sorafenib 400 mg bid. Response was evaluated every 8-12 weeks using RECISTv1.0 (Response Evaluation Criteria in Solid Tumors).

Results

Thirty-four patients were included in the study between June 2006 and January 2010. 16 were differentiated thyroid carcinomas (DTC) (7 (23%) were papillary, 9 (26%) follicular), 15 (44%) medullary (MTC) and 3 (7%) were anaplastic (ATC). All patients were included in the intention-to-treat analysis. 11 patients (32%) reached partial response and 14 (41%) had stable disease beyond 6 months. Regarding histological subtype, response rates observed were 47% for medullary (7 of 15), 19% for differentiated (3 of 16) and 33% (1 of 3) for anaplastic. With a median follow-up of 11.5 months, mPFS were 13.5, 10.5 and 4.4 months for DTC, MTC and ATC, respectively. Tumor markers were evaluated in 22 patients and a statistically significant correlation was observed between response rate and decrease in tumor marker levels greater than 50% (p=0.033).

Conclusion

Sorafenib has showed anti-tumor efficacy in all histological subtypes of thyroid cancer in a population-based study and warrants further development in this setting.

RESUM

Introducció

Basat en els resultats recents de diversos estudis fase II amb inhibidors tirosina quinasa i del millor coneixement de les alteracions moleculars que caracteritzen el procés de carcinogènesi del càncer de tiroides, es va dissenyar un estudi retrospectiu de pacients afectes de carcinoma de tiroides metastàtic tractats amb sorafenib.

Pacients i Mètodes

L'objectiu primari de l'estudi era la taxa de respostes objectives. Els objectius secundaris incloïen toxicitat, mitjana de supervivència lliure de progressió (mSLP), supervivència global (mSG) i correlació entre els nivells de marcador tumoral (tiroglobulina, calcitonina i CEA) i eficàcia. Els pacients eren tractats amb sorafenib 400 mg dos cops al dia. La resposta s'avaluava cada 8-12 setmanes utilitzant els criteris RECIST v1.0

Resultats

Entre juny de 2006 i gener de 2010 trenta quatre pacients es van incloure en l'estudi. 16 eren carcinomes diferenciats de tiroides (CDT) (7 (23%) eren papil·lars, 9 (26%) fol·liculars), 15 (44%) medul·lars (CMT) i 3 (7%) eren anaplàsics (CAT). Tots els pacients van ser inclosos en l'anàlisi per intenció de tractar. 11 pacients (32%) van aconseguir una resposta parcial i 14 (41%) tenien malaltia estable més enllà dels 6 mesos. En funció del subtipus histològic, la taxa de respostes observada va ser del 47% per CMT (7 de 15), 19% per CDT (3 de 16) i 33% (1 de 3) per CAT. Amb una mitjana de seguiment de 11.5 mesos, la mSLP va ser de 13.5, 10.5 i 4.4 mesos per CDT, CMT i CAT, respectivament. Els marcadors tumorals es van avaluar en 22 pacients i es va observar una correlació estadísticament significativa entre la taxa de respostes i la reducció superior al 50% en els nivells dels marcadors tumorals (p=0.033).

Conclusió

Sorafenib ha demostrat una eficàcia antitumoral en tots els subtipus histològics de càncer de tiroides en un estudi poblacional i assegura un major desenvolupament en aquesta població.

INTRODUCTION

In the last decades the incidence of thyroid gland carcinoma has significantly raised becoming the most frequent tumor of the endocrine system[1]. The estimated number of new cases of thyroid cancer in the US for 2010 is 44.670 new cases with 1.690 estimated deaths[2]. Differentiated thyroid cancer (DTC) is by far the most common tumor type reaching 90% of cases and includes papillary and follicular carcinomas. Thyroid gland could develop other important tumor types such as medullary thyroid carcinoma (MTC) and anaplastic thyroid cancer far rarer than DTC[3].

The main therapeutic approaches for DTC are the surgical resection and radioactive iodine (^{131}I) ablation. These approaches reach a 10-year survival higher than 90% and achieve a complete remission of 60% of patients with local recurrence and 30% of patients with distant metastases[4]. So, the overall prognosis of thyroid cancer is excellent. However, overall survival dramatically falls when standard therapy fails and the 5-years survival rate decreases to less than 50% when radioactive iodine therapy loses its activity against DTC[5].

The traditional DNA damaging cytotoxic agents are of limited efficacy in the treatment of DTC. The activity of several agents has been evaluated for the treatment of patients with DTC with disappointing results. The best studies have shown response rates between 0-20%, of short duration, without complete remissions and no impact in overall survival. The most developed drug has been doxorubicin alone and in combination with other cytotoxics, mainly cisplatin, with no increasing in response rates but higher adverse events[6, 7].

Several translational and clinical studies have been designed based on the deeper knowledge of the main molecular steps that lead to the transformation of the normal follicular cell into an invasive thyroid carcinoma and have opened a more optimistic point of view for the treatment of these patients. Thyroid carcinogenesis has become

one of the most fascinating models and a particularly promising paradigm for targeted therapy.

A multistep model has been suggested involving the main genetic aberrations that carry out the tumor-initiating process from a follicular cell origin and also the so-called oncogenic addiction to these particular mutations that make them particularly interesting for directed therapy[8]. One of the most important activating genetic mutations involves the RET/PTC-RAS-RAF-MAPK axis. For hereditary medullary thyroid cancer (MTC) formation mutations in RET gene are essential in more than 95% of cases and also important are for the development of sporadic MTC (50% of cases)[9]. Activating mutations in protein kinase B-type RAF kinase (BRAF) up to 45% of cases play a key role in the carcinogenesis of papillary thyroid cancer (PTC), but also RAS mutations (10%) and rearrangements in RET gene (RET/PTC) between 5-30% of cases. These mutations have also been described in follicular thyroid carcinomas (FTC) affecting in more than 40% of cases the three RAS proto-oncogen family (HRAS, NRAS and KRAS) and also the genomic rearrangement in up to 50% of FTC involving a translocation event between chromosome regions 3p25 and 2q13 resulting in a fusion protein (paired box gene 8 (PAX8) with the peroxisome proliferator-activated receptor γ (PPARγ) gene). Genetic alterations in RAS-BRAF pathway have also been identified in poorly differentiated and anaplastic thyroid carcinomas that arise from PTC with accumulation of other important protein mutations that such as p53, β-catenin, or phosphatidylinositol-3-kinase (PI3K) mutations. Additionally, upregulation of vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor (PDGFR) expression has been well-described in thyroid cancer and correlated with tumor stage, size and lymphatic and distant tumor spread with a detrimental impact in survival[10].

Sorafenib (BAY 43-9006) is the first compound capable to inhibit all the RAF kinases that has reached the clinical practice. Moreover, sorafenib targets a panel of tyrosine kinase receptors such as VEGF receptors 1-3, PDGFR-β and RET that gives to

sorafenib not only proapoptotic properties, but also antiangiogenic effects which are of special interest in thyroid carcinomas[11].

A retrospective population-based study evaluating the activity of sorafenib in patients with metastatic thyroid cancer has been designed including consecutive patients of 7 referral centers of Spain: Vall d'Hebron University Hospital, Barcelona; 12 de Octubre University Hospital, Madrid; Clinic Hospital, Barcelona; La Fe University Hospital, Valencia; Miguel Servet Hospital, Zaragoza; Ramón y Cajal University Hospital, Madrid; and Virgen del Rocío University Hospital, Sevilla.

PATIENTS AND METHODS

Patients

Eligible patients were ≥ 18 years old with histologically confirmed thyroid carcinoma (papillary, follicular or anaplastic subtypes) for which no curative or standard palliative therapies were available. Patients had evidence of disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) in the 12 months prior to enter into the study and all patients had measurable disease by RECIST criteria. Previous therapies with radioiodine therapy, radiotherapy, chemotherapy or biologic treatment were allowed. Other inclusion criteria included Eastern Cooperative Oncology Group performance status ≤ 2, preserved renal, hepatic and bone marrow function. All patients provided written informed consent of the Spanish compassionate use program as well as hospitals' pharmacy and direction, and central government authorizations for off-label use were obtained for each patient included in this study[12].

Study design

The study was based on the evaluation of a Spanish off-label program of sorafenib in patients with metastatic thyroid carcinoma, including papillary, follicular, medullary and

anaplastic subtypes, performed in accordance with the local legislation in 7 Spanish referral centers. Sorafenib was administered at a dose of 400 mg twice a day as long as it provided clinical benefit or until unacceptable toxicity. A cycle was defined as 4 weeks and tumor evaluation was performed by CT scan or MRI every 8-12 weeks. Tumor marker evaluation, carcinoembrionary antigen (CEA), thyroglobulin and calcitonin, was performed every 8-12 weeks. Dose adjustments were made as per toxicity profile.

Study end points and Statistical analysis

The primary end point was efficacy assessment evaluated in terms of response rate (RR), median progression free survival (mPFS) and median overall survival (mOS) according to RECIST v 1.0 criteria[13]. Secondary end points included the toxicity profile, evaluated by means of the Common Terminology Criteria for Adverse Events, version 3.0. (CTC.AE v.3.0) and the correlation between efficacy and tumour marker levels: thyroglobulin for differentiated thyroid cancer (DTC) that included PTC and FTC, and calcitonin and CEA for MTC.

Statistical analyses of survival were performed using a one-sided log-rank of Kaplan-Meier survival estimates and Chi-square distribution for the correlation between tumor markers and efficacy.

RESULTS

Between June 2006 and January 2010, 34 patients were included onto study. Table 1 summarizes baseline characteristics of the patients entered onto study. Of the 34 patients with confirmed thyroid cancer, 7 (23%) were papillary, 9 (26%) follicular, 15 (44%) medullary and 3 (7%) were anaplastic. At baseline, 33 patients (97%) had undergone previous surgery, 19 (56%) had received radiotherapy, 13 (38%), radioactive iodine therapy, 32% (n=11) chemotherapy and 20% (n=7) somatostatin

analogues. All patients presented documented disease progression by RECIST criteria previous the inclusion in the trial.

Efficacy

A total of 32 patients were evaluable for radiological response, but all 34 patients were included in the intention-to-treat analysis. Eleven patients reached partial response (PR) and 14 stable disease (SD) beyond 6 month. The disease control rate (PR+SD) was 73%. The PR rate by histological subtype was 7/15 (47%) for patients with MTC, 3/16 (19%) for patients with DTC and 1/3 (33%) for patients with anaplastic carcinomas. Disease control rate for MTC patients was 87% and for DTC patients was 69% (Table 2). Image 1 shows an example of PR in a patient with advanced MTC.

With a median follow-up of 11.5 months, mPFS was 10.5 months (95 %CI, range 6, 13-14, 87) for the whole group of patients including all subtypes. As expected, mPFS was different according the thyroid carcinoma subtypes (Figure 1), from 4.4 months (95 %CI, range 2.30 - 6.57) in the anaplastic population to 13.3 months (95 %CI, range 6.28 - 20.45) in patients with DTC and 10.5 months (95 %CI, range 4.49 - 16.51) in those with MTC. In terms of OS, the median for the whole group of patients was 23.6 months, and when considering the different subtypes the figures were 5 months for the anaplastic tumor population, 23.6 months for the DTC population, whereas it was not reached for patients with MTC (Figure 2).

Marker Correlation

The correlation between the tumor marker decrease >50% and tumor response to sorafenib was analyzed. Thyroglobulin was used for DTC and calcitonin and/or CEA for MTC. Twenty-eight patients (82%) were evaluated for tumor marker response. In 16 patients there was a decrease in any tumor marker >50% from baseline value, 8 of whom achieved PR. Of the 12 patients that did not show a decrease in tumor markers, only 1 patient presented PR. A statistically significant correlation was observed

between > 50% of any tumor marker decrease and the probability to achieve a tumor response by RECIST criteria ($p<0.05$. Chi-Square analysis) (Table 5). Analysis by tumor subtype and tumor marker type was did not show statistical significance due to low number of patients in each group.

Toxicity

The most common side effects (frequency of ≥ 5%) were hand-foot syndrome, diarrhea, rash, fatigue, anorexia, stomatitis, hypertension and abdominal pain. The majority of side effects were controlled with treatment delays or dose reductions. Table 3 summarizes all the toxicity profile observed during the study period. Twelve patients (35%) required a dose reduction due to toxicity. There was one death from intracranial hemorrhage during the study, whose relationship with sorafenib cannot be ruled out.

DISCUSION

Until recently, medical management of advanced thyroid cancer refractory to standard treatments has been specially challenging. Classical DNA damaging drugs have demonstrated limited activity in this setting with no impact in survival. The knowledge of key mutational events in some genes including *BRAF* and *RET* that affect early stages of thyroid carcinogenesis has opened a new scene for targeted therapies. Sorafenib is the only available drug that target BRAF and RET and VEGF receptors also involved in the pathogenesis of thyroid cancers and offers a strong molecular rationale for the treatment of all thyroid cancer subtypes.

In this retrospective study, the activity and safety of an unselected group of patients with all thyroid cancer subtypes treated with sorafenib in an off-label program has been reported. The study has been carried out following the currently Spanish legislation and in referral centers with experience in the management of targeted therapies in order to

obtain realistic data and minimize at maximum the typical biases of retrospective studies. Showed data is considered as of special interest since patients included in this analysis are real patients of routine clinical practice in comparison of usually selected patients included in clinical trials.

The data obtained in this study are consistent with data obtained in previous studies with sorafenib and also with other tyrosine kinase inhibitors (TKIs) in DTC population in which the PR rate ranged from 6% to 49% (20% in this study), SD from 38% to 67% (50% in this study) and mPFS from 15 to 20 months (13.3 months in this study). However, certain discrepancies may be seen probably related to different inclusion criteria between studies, such as initial documented disease progression status (Table 4). Currently, there is a deep discussion about the best criteria to evaluate antitumor activity of targeted therapies, and it seems that RECIST criteria do not properly evaluate all the real benefit of new targeted agents in solid tumors. We chose RECIST v 1.0 criteria instead of RECIST v 1.1 criteria to try to assess the maximum number of target lesions in the same organ as RECIST v 1.1 criteria reduces the number of target lesions per organ and this could jeopardize the best evaluation of a disease that usually metastasize to one or two different organs with measurable disease (lymph nodes and lung)[14].

Data of sorafenib in MTC is clearly limited compared with data in DTC. Other TKIs have demonstrated promising activity against MTC, such as XL-184, sunitinib or motesanib, and specially vandetanib that has recently obtained the Food and Drug Administration (FDA) approval for the treatment of advanced MTC after the positive results of a placebo-controlled phase III study that demonstrated significant benefit in mPFS (19.3 months for the placebo group versus median not reached for the group of patients treated with vandetanib). The few data available with sorafenib in MTC patients has showed limited activity with PR rates <10% but higher SD rates especially in subgroup analyses of patients with tumor progression before study entry[15]. The data

reported in this study support the efficacy of sorafenib in MTC population reaching similar data compared with other TKIs in this setting (Table 4). Although trials are not directly comparable it seems that different TKIs are able to obtain significant benefit in MTC patients, regardless the affinity against wild-type or mutant RET receptor, raising the important issue about carcinogenesis mutations and tumor addiction.

In ATC patients, the number (n=3) renders it difficult to mainstream the data obtained from PR or SD. The results observed only generate the hypothesis of possible activity of TKIs in ATC. However, since TKIs may need some time to achieve active plasma concentration and reduction in tumor angiogenesis, these small molecules may be not as fast as desired, so their use in ATC should be considered carefully.

The toxicity profile observed in this unselected cohort of patients was similar to that observed in previous studies and was managed mainly with both symptomatic measures and sorafenib dose delay or reduction (35% in this study). It is of special interest the safety profile observed in routine clinic thyroid cancer patients since usually toxicity data reported in selected patients included in prospective studies does not exactly match the reality. Although few patients presented grade 3-4 related toxicity, most patients presented some grade 1-2 side effects, which in some of them, previously asymptomatic, could represent a worsening in quality of life that can jeopardize the compliance to the treatment. Quality of life assessment is strongly suggested for future regulatory clinical trials.

With regard to tumor markers and their role in the evaluation of clinical efficacy, a reduction in CEA/calcitonin and thyroglobulin higher than 50% was correlated with PR in this study. When data by tumor subtype and tumor marker type were analyzed the results were not significant due to the reduced number of patients. Data on this field are contradictory in phase II clinical trials and the results of this study only generate the hypothesis of possible predictive biomarkers for tumor response. These results should

be validated in prospective large phase III clinical trials and also provide information of the duration to achieve marker response (not available in this study) in order to recognize within few weeks, those patients who are very less likely/unlikely to get objective response and shorten drug exposure.

CONCLUSIONS

In summary, the results of this study show the efficacy and toxicity profile of sorafenib for the treatment of advanced and refractory thyroid cancer in an unselected population-based study that represents the scene of routine clinical practice. Similar efficacy data has been observed compared with other published studies with sorafenib in DTC patients. However, this study shows a cohort of patients with MTC with interesting clinical activity that warrants further development in this setting.

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Table 1. Patient Characteristics	
Total nº of patients	34
Gender M/F (Nº)	16/18
Median age (range)	57,3 years (range 28,8-84,6)
ECOG /PS	N (%)
0	5 (15)
1	20 (59)
2	9 (26)
Tumor subtypes	N (%)
Papillary	7 (23)
Follicular	9 (26)
Medullary	15 (44)
Anaplastic	3 (7)
Previous therapies	N (%)
Surgery	33 (97)
Radiotherapy	19 (56)
Radioiodine therapy	13 (38)
Chemotherapy	11 (32)
Somatostatin analogs	7 (20)

Table 2. Tumor Response by subtypes			
	PR	**SD**	**PD**
Papillary	14 % (1/7)	43 % (3/7)	43% (3/7)
Follicular	22 % (2/9)	55 % (5/9)	11 % (1/9)
DTC	19 % (3/16)	50 % (8/16)	25 % (4/16)
Medullary	47 % (7/15)	40 % (6/15)	7 % (1/15)
Anaplastic	33 % (1/3)	0%	66 % (2/3)

Table 3. Main Side Effects.				
N=34				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hand-Foot Syndrome	7 (20%)	6 (18%)	7 (20%)	1 (3%)
Stomatitis	6(18%)	9 (26%)	1 (3%)	
Diarrheas	6 (18%)	10 (29%)	5(15%)	
Alopecia	3 (9%)	2 (6%)	4 (12%)	
Hypertension	4 (12%)	2 (12%)		
Abdominal Pain	5 (15%)	5 (15%)	1 (3%)	
Rash	8 (23%)	2 (6%)	2 (6%)	
Dry Mouth	1 (3%)	1(3%)		
Fatigue	8 (23%)	6 (18%)	5 (15%)	
Anorexia	1 (3%)	3 (9%)	3 (9%)	
Xerosis	9 (26%)	1 (3%)	1 (3%)	
Dysgeusia	1 (3%)			
Arthromyalgia	1			
Elevated transaminases			1 (3%)	1 (3%)

Table 4. Main studies in advanced thyroid cancer with targeted therapies.

Authors	Drug	N	Tumor Type	Response Rate (%)	Stable Disease (%)	Median Progression-free Survival
Kloos[16]	Sorafenib	41	DTC & ATC	15	56	15 months
Gupta-Abramson[17]	Sorafenib	30	DTC	23	34	20 months
Hoftijzer[18]	Sorafenib	32	DTC	25	34	13.4 months
Ahmed[19]	Sorafenib	26	DTC & MTC	18*	82	NR
Sherman[20]	Motesanib	93	DTC	14	67	9.2 months
Cohen[21]	Axitinib	60	All	30	38	18.1 months
Ravaud[22]	Sunitinib	17	All	30	38	NR
Carr[23]	Sunitinib	33	DTC & MTC	32	48	NR
Bible[24]	Pazopanib	37	DTC	49	NR	11.7 months
Leboulleux[25]	Vandetanib	145	DTC	8.3	56.9**	11 months
De Souza[26]	Sunitinib	25	MTC	33	54	12 months
Kurzrock[27]	XL-184	37	MTC	29	41	NR
Wells[28]	Vandetanib/Placebo[+]	331	MTC	45	NR	19.3 months vs Not reached
Lam[15]	Sorafenib	21	MTC	6.3	87.5	17.9 months

*3 months median follow-up; **Disease control rate; [+] Phase III study; DTC: differentiated thyroid cancer; ATC: anaplastic thyroid cancer; MTC: medullary thyroid cancer; NR: not reported.

Table 5. Correlation of tumor marker decrease > 50% and response				
		Decrease > 50%		Total
		Yes	No	
Partial Response	Yes	8	1	9
	No	8	11	19
Total		16	12	28

P<0.05 Chi-Square

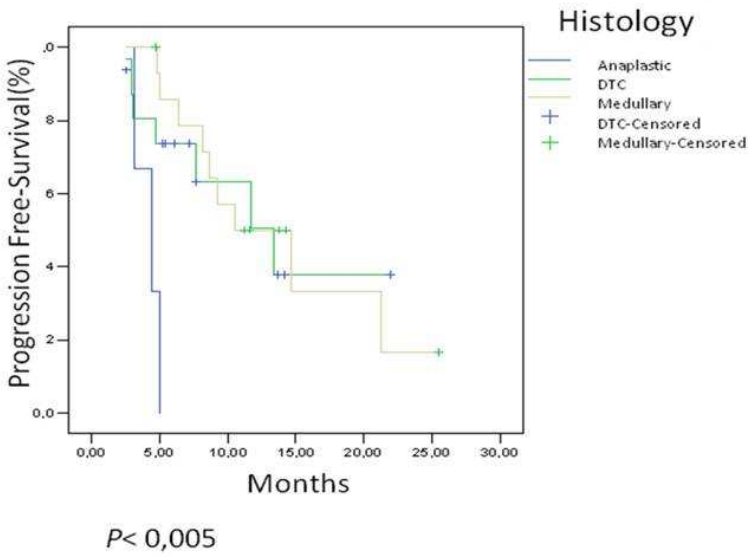


Figure 1. Median progression-free survival curves. Statistically significant differences were observed between DTC and anaplastic, and also between medullary and anaplastic. No differences were observed for DTC and MTC.

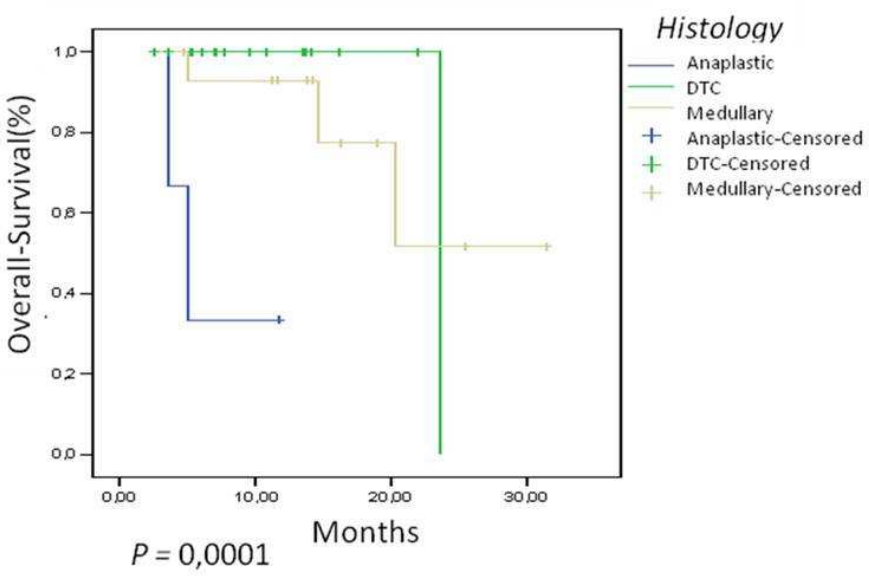
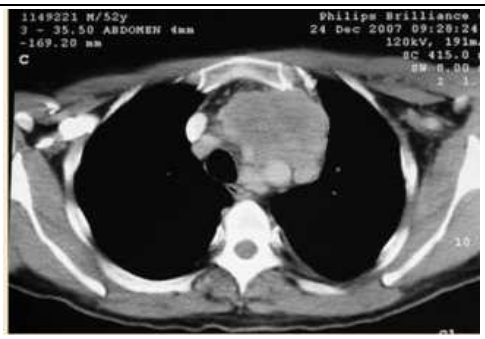


Figure 2. Median overall survival curves. Statistically significant differences were observed between DTC and anaplastic, and also between MTC and anaplastic. No differences were observed between DTC and MTC.

a) 

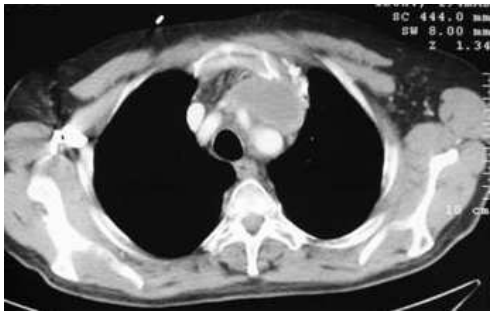
b) 

Image 1: a) On December 2007, baseline CT scan showed maximum diameters of 9 cm x 9 cm x 5 cm. b) On January 2009 a partial response was confirmed with maximum diameters of 5.5 cm x 5 cm x 4 cm.

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