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Sorafenib in advanced iodine-refractory differentiated thyroid cancer: efficacy, safety and exploratory analysis of role of serum thyroglobulin and FDG-PET

Short title: Sorafenib in advanced thyroid cancer

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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

ABSTRACT

Context: Radioactive-iodine is a crucial tool for treatment of differentiated thyroid cancer (DTC). In 5% of cases, DTCs lose I-131 avidity and assume an aggressive behaviour. Treatment options for iodine refractory DTC are limited. We report the experience of off-label use of the tyrosine-kinase inhibitor sorafenib for treatment of advanced iodine-refractory DTC.

Design: Patients with progressive DTC refractory to radioactive-iodine were treated with sorafenib used off-label independently from their performance status. Primary study endpoints were radiological response, progression free survival (PFS) and safety. Secondary endpoints were site-specific radiological response and overall survival (OS). An exploratory analysis of the role of serum thyroglobulin (Tg) and fluorodeoxyglucose (FDG) positron emission tomography (PET) was performed.

Results: Seventeen patients were included in the study. Median follow-up was 15.5 months. Clinical benefit was obtained in 71% of subjects (30% partial response and 41% stable disease). Sorafenib was mostly well tolerated but a high incidence of fatal events was reported (3 patients died from severe bleeding events and 2 from cardiac arrest). Median PFS was 9 months. Median OS was 10 months. The best responses were observed in lymph nodes and lung. Baseline Tg levels and the Tg response to treatment were correlated to both radiological response and PFS. Baseline FDG-PET assessment and early FDG-PET response were correlated to radiological response.

Conclusions: Sorafenib allows morphological disease control in the majority of patients with iodine-refractory DTC. Progression-free survival and overall survival were lower than in previous studies as a consequence of the worse clinical condition of our patients. Sorafenib is mostly well tolerated but could have been responsible for the reported fatal events. Baseline Tg and the Tg response to treatment could be useful for predicting morphological response and clinical outcome. Early FDG-PET response could be helpful for the timely identification of non-responding patients.

Introduction

Thyroid cancer is the most common endocrine malignancy (1) and its incidence and mortality are increasing worldwide (2). Differentiated thyroid cancer (DTC) accounts for 80-90% of all thyroid carcinomas and is the form mainly responsible for the increased incidence of such disease (3). Conventional treatment of DTC is based on a combined approach consisting of total thyroidectomy and radioactive iodine (RAI) followed by thyroid-stimulating hormone (TSH) suppression (3, 4). This approach is very effective and the prognosis of DTC is usually excellent with a 10 year disease-related survival of 85% (5). I-131 avidity is a crucial factor in the clinical course of the disease as RAI is used not only for post-operative ablation of the thyroid remnant (6) but also as primary tool for the treatment of loco-regional recurrences and distant metastases (7).

About 5% of patients with DTC develop an aggressive disease with distant metastases and loss of I-131 avidity. Patients with RAI-resistant DTC have a poor prognosis with a long-term overall survival of 10% (7).

To date, treatment of advanced DTC refractory to RAI represents a challenging task. Doxorubicin, the only chemotherapeutic agent approved by the *US Food and Drug Administration* (US FDA) for the treatment of DTC, achieves partial and short lasting responses and is associated with considerable toxicity (8). In the last several years many authors have focused on the pathogenesis of thyroid cancer, emphasizing the role of the MAP-kinase signalling pathway (9-11). Knowledge of thyroid cancer biology has led many researchers to assess compounds inhibiting the tyrosine-kinase (TK) pathway as tools for treatment of RAI-resistant DTC. Sorafenib is a non-selective kinase inhibitor already approved by the US FDA for the treatment of advanced renal and hepatocellular carcinoma and could represent an effective tool in this field as it is able to strike different steps of the MAP-kinase signalling pathway and control neo-angiogenesis, which is considered crucial for progression of the disease (12, 13).

The present study focuses on the experience of off-label use of sorafenib for the treatment of advanced RAI-refractory DTC.

Patients & Methods

Off-label treatment with sorafenib was offered to patients affected with DTC in post-surgical follow-up who showed refractoriness to RAI, as indicated by the absence of iodine uptake or by evidence of progressive disease after post-therapeutic whole body scintigraphy. All enrolled patients had documented progression of disease within the 6 months preceding treatment with the study drug according to RECIST criteria (14). Patients were treated independently from Eastern Cooperative Oncology Group (ECOG) performance status (15) and life expectancy.

Study design

This was a retrospective, longitudinal study assessing activity of oral sorafenib in patients with progressive RAI-refractory DTC. Sorafenib was administered at a starting dose of 400 mg bd. Clinical and laboratory

evaluations including complete blood count (CBC), chemistry panel, TSH, free-triiodothyronine (FT3), free-thyroxine (FT4), thyroglobulin (Tg), anti-thyroglobulin antibodies (AbTg) and urinalysis were performed at baseline and at 4-weeks intervals. Computed tomography (CT) scans were performed at baseline within 4 weeks of the first dose of study drug and at 12-week intervals or sooner if clinically indicated. Fluorodeoxyglucose (FDG) positron emission tomography (PET) assessment was performed at baseline after obtaining CT evaluation within 7 days of the first dose of study drug and repeated 15 days after the beginning of the treatment to assess early metabolic response. Contrast-enhancement was used for all CT scans. FDG-PET patient preparation and image acquisition were performed according to the NCI consensus guidelines (16). FDG-PET imaging was obtained after at least 6-hours fasting and plasma glucose levels were assessed before FDG injection to exclude significant hyperglycaemia. All FDG-PET scans were obtained while patients were on TSH-suppressive treatment without performing any procedure of TSH stimulation. All CT and FDG-PET examinations were performed in the same centre (Department of Biomorphological and Functional Sciences, Federico II University of Naples, Italy) by the same operators (L.C., R.F., M.S.). Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. All patients gave written informed consent for entering the data in our database. Ethical approval from the Institutional Review Board of the University Federico II of Naples was obtained.

Endpoints and definitions

Primary study endpoints were maximal radiological response (17), progression free survival (PFS) and safety. Secondary endpoints included the assessment of site-specific radiological responses and overall survival (OS). An exploratory analysis was performed to correlate serum Tg levels and FDG-PET with radiological response and PFS. Radiological response was defined according to RECIST criteria version 1.1 (14). Clinical benefit incorporates stable disease (SD) and partial response (PR). Durable response was defined as the presence of SD or PR for a minimum period of 6 months. Patients who achieved clinical benefit were defined as “responding” while subjects who experienced disease progression despite treatment were defined as “non responding”. Regarding biochemical response, a decrease of at least 25% in Tg levels was considered as PR, an increase of at least 25% was considered as progression of disease and

changes in Tg <25% were classified as SD. PFS was defined as the length of time after beginning treatment with the study drug in which the patient was living, and without progression of disease. OS was defined as the percentage of patients who were alive after they were treated with sorafenib.

Statistical analysis

Overall and site-specific radiological response, Tg response and FDG-PET response were computed as percent changes from baseline. Site-specific radiological responses were compared using one-way analysis of variance (ANOVA). ANOVA was used to compare baseline Tg levels, Tg response, baseline FDG-PET assessment and early FDG-PET response between patients achieving clinical benefit and subjects showing disease progression after starting treatment with the study drug. PFS and OS were assessed using the Kaplan-Meier method. Analysis of variables influencing survival was conducted using the log-rank test. We considered results with p–values <0.05 as statistically significant. Statistical analysis was performed using SPSS Version 17.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Between March 2010 and February 2012, 17 patients affected with progressive, iodine-refractory DTC were subjected to treatment with sorafenib used off-label (baseline characteristics are reported in Table 1). Disease progression was determined by a minimum 20% increase in the sum of diameters of known target lesions (TLs) in 9 patients (53%) and by development of one or more new metastasis in 8 subjects (47%), as defined by RECIST criteria (14). All subjects were included in our intention-to-treat analysis but 2 patients were not evaluable for radiological response since CT scans were not performed in our centre.

Radiological response

Maximal radiological responses are reported in Figure 1. Clinical benefit was observed in 12 patients (71%) while 3 subjects (18%) showed persisting disease progression despite treatment with the study drug. Among responding subjects, 5 (30%) achieved a PR while SD was observed in 7 cases (41%). A durable response was obtained in 8 (67%) of these patients. Among the 4 responding patients who did not achieve a durable response, 3 died from severe bleeding events and the other developed liver metastasis that were not present at the time of enrolment. Of the 8 responding patients who achieved a durable response, 2 died from cardiac arrest, one patient developed brain metastasis that were absent at baseline and one showed morphological progression of monitored target lesions (TLs) after 10 months of treatment. The remaining 4 patients (24%) are still on treatment and free of progression. Noticeably, in all but one subject having clinical benefit from treatment, disease progression was determined by death or detection of new metastasis while TLs identified at baseline were durably stabilized. Interestingly, among non-responding patients, disease progression was characterised by an increase of all monitored TLs (mean±DS increase 25.8%±19) while responding subjects showed shrinkage of all TLs (mean±DS increase 34.8%±14). Robust responses were obtained both in lymph nodes (including cervical and mediastinal; mean±DS decrease 62.8%±27) (shrinkage of a mediastinal lymph node at the level of the aorto-pulmonary window is reported in figure 2A) and lung (mean±DS decrease 39%±15) but shrinkage of lymph node lesions was significantly greater ($p=0.02$). Otherwise, radiological response of liver metastases was significantly less robust (mean±DS decrease 9%±12) ($p<0.001$). Interestingly the majority of lymph nodes and lung metastases showed a common trend of response with a dramatic decrease in the first 3 months of treatment followed by stabilization or mild size increase. All bone lesions, both irradiated and non irradiated, persisted despite treatment with sorafenib but did not show progression (Non CR/Non PD per RECIST). A quantitative assessment of tumour necrosis, as determined by measurement of density expressed in Hounsfield units (HU), was obtained for a limited number of metastases. We report in figure 2B a cervical lymph node showing a moderate reduction in dimensions but a dramatic HU decrease.

Survival

PFS and OS after treatment with sorafenib were plotted on Kaplan-Meier curves (Figure 3). The median PFS was 9 months (95% CI. 5.8 to 12.2). PFS was strikingly related to baseline ECOG performance status (p=0.001) and maximal morphological response (p=0.004). PFS was not influenced by gender (p=0.11), age (p=0.14), histology (p=0.3), stage (p=0.12), presence of liver (p=0.3) or bone metastases (p=0.78) and previous chemotherapy (p=0.64). The median OS was 10 months and the 12-months OS rate was 41.1%. OS was strikingly related to baseline ECOG status (p<0.001).

Tolerability and adverse events

Two (12%) patients discontinued sorafenib after 10 months of treatment because of uncontrollable diarrhoea and hand-foot syndrome (HFS) respectively. All patients needed dose reductions and/or transient drug interruption to control AEs. Median and mean time of the first dose reductions were 16 and 25 days respectively. Drug interruptions always induced a near-total regression of toxicity in less than 10 days. After transient discontinuation, treatment was usually better tolerated. In the majority of subjects (88%), AEs were fully managed by halving the starting dose of study drug (200 mg bd.), HFS being the main dose-limiting toxicity. The main AEs included HFS (88%), increased TSH levels requiring higher doses of levo-thyroxine (76%), constitutional symptoms such as fatigue (71%), weight loss (35%) and anorexia (35%), gastrointestinal symptoms such as diarrhoea (65%) and stomatitis (29%), and dermatological reactions other than HFS such as alopecia (53%). The main laboratory abnormalities were anaemia (47%) and hypocalcaemia (29%). The majority of toxicities were grade 1-2. HFS was grade 2-3 and always required drug reduction or interruption. A total of 5 patients (30%) died from the occurrence of fatal events while on treatment with the study drug. Three developed haemorrhage of the upper respiratory tract within the first 4 months of treatment. They had a grade 3 ECOG status at baseline and presented with wide tracheo-oesophageal neoplastic infiltration previously treated with external beam irradiation. The remaining 2 patients died from cardiac arrest after 10 months of treatment. They had no previous history of cardiac

dysfunction but developed grade 2 hypertension after starting treatment with sorafenib. In these patients blood pressure was successfully controlled by mono-therapy with angiotensin-converting enzyme (ACE) inhibitors.

Tg analysis

Thirteen patients (3 PR, 7 SD and 3 showing progressive disease per RECIST) were included in the present analysis. Tg assay was not feasible in two subjects who showed AbTg positivity. Baseline Tg levels were significantly higher in patients who showed disease progression compared with responding subjects ($p<0.001$) (figure 4A). Furthermore there was a clear correlation between baseline Tg and PFS ($p=0.04$). In all cases biochemical PR was achieved with a mean decrease of 75% and a median time of nadir of 3 months. The decrease in serum Tg levels was significantly greater in patients who achieved clinical benefit compared with non responding subjects ($p<0.01$) (figure 4B). Furthermore a strong correlation between Tg response and PFS was found ($p=0.01$).

FDG-PET analysis

Eleven patients (4 PR, 4 SD, 3 showing progressive disease per RECIST) underwent FDG-PET assessment at baseline and after 15 days of treatment as previously described. All TLs recorded on baseline CT scans showed significant metabolic activity with standardized uptake values maximum (SUVmax) greater than 3 in all cases (mean±DS 11.6±8.2). The average SUVmax of TLs monitored for radiological assessment was used to obtain a quantitative measure of FDG uptake. Baseline average SUVmax was significantly higher in patients who showed disease progression compared with responding subjects ($p=0.001$) (figure 5A) but no significant correlation with PFS was found ($p=0.07$). Early FDG-PET scans showed a reduction in average SUVmax in all cases (mean±DS decrease 29.9%±15.7). Early reductions in average SUVmax were more

robust in patients who achieved clinical benefit from treatment compared with non-responding subjects (p=0.002) (figure 5B) but no significant association with PFS was found (p=0.1).

Discussion

RAI is a crucial tool for treatment of DTC. To date, there is no effective therapeutic approach for iodine-refractory DTC. Genomic medicine is an emerging field that targets mutations involved in the initiation, maintenance and progression of cancer. Knowledge of the main mutational events involved in the pathogenesis of DTC provides a strong rationale for the application of target therapy in such disease. Several phase II and retrospective studies have assessed the activity of sorafenib in the treatment of metastatic thyroid cancer refractory to conventional therapies. Some of these papers included different histotypes of thyroid cancer (PTC, FTC, medullary thyroid cancer and anaplastic thyroid cancer) (18, 19) but the majority focused mainly or exclusively on patients with iodine-refractory DTC (20-23). We performed a retrospective analysis focused on a group of patients selectively affected with progressive RAI-resistant DTC and subjected to off-label treatment with the TK-inhibitor sorafenib in the same centre. In contrast to all previous studies which considered an ECOG score more than 2 as an exclusion criterion, we chose to include subjects independently from their performance status and life expectancy. Our aim was to define the actual role of sorafenib in this clinical context and to provide indications useful in clinical practice for the management of these patients.

In the present study, clinical benefit, which implies a halt of pre-treatment disease progression, was observed in 71% of patients (30% PR and 41% SD). These results were mainly consistent with data obtained from previous trials in which the percentage of clinical benefit ranged from 59 to 80% (PR from 15 to 25%, SD from 34 to 61%) (18, 21-23). In the current study, the majority (67%) of responding patients showed a durable response. Interestingly, responding patients achieved durable control of all TLs while subjects with persisting progression of disease showed size increase of all TLs. This suggests that the activity of sorafenib is not dependent on tissue-specific sensitivity but is rather related to intrinsic features of the neoplasm such as the presence of specific genetic mutations. A quantitative assessment of site-specific response to

treatment with sorafenib among subjects achieving clinical benefit was performed. Robust responses were observed in lymph nodes and lung while liver metastasis were less sensitive to treatment. In contrast to the findings in a previous study (22), radiological response was greater in lymph nodes than lung. Furthermore, while Cabanillas et al. (22) showed that irradiated bone metastasis were stabilized from treatment with sorafenib while non irradiated lesions showed clear progression, in our study, all bone lesions, whether irradiated or not, did not show progression (Non CR/Non PD per RECIST). Although the RECIST system is the most widely used in clinical trials, several authors have proposed using CHOI criteria (24) for the assessment of effectiveness of target therapies (25). Indeed, CHOI criteria include the quantitative evaluation of tumour necrosis by computing changes in tumour density while the RECIST system, which is based just on dimensional assessment, may underestimate response to treatment. The example reported in figure 2B seems to support this hypothesis. Unfortunately, we obtained quantitative assessment of tumour density in a limited number of cases and this represents a limit of our study.

The computed PFS in our paper was 9 months. This is lower than other studies in which median PFS ranged from 13.3 to 21 months (19-23). Furthermore OS was significantly lower than that reported by previous papers (18, 19, 22). These discrepancies can be attributed to the lack of exclusion criteria which led to the enrolment of a number of subjects with poor clinical condition. This hypothesis is sustained by the evidence that both PFS and OS were strikingly related to ECOG status at baseline. Beyond ECOG score, PFS was not influenced by any of the baseline clinical variables (gender, age, histology, stage, presence of liver or bone metastases, previous chemotherapy). As expected, a strong correlation between maximal radiological response and PFS was observed.

AEs reported in our paper were mainly consistent with those described in previous studies. Symptomatic treatment, transient sorafenib interruptions and dose reductions allowed acceptable control of AEs in the majority of patients (88% in this study). Nevertheless a high incidence of fatal events was reported in our patients while on treatment with the study drug. Three patients died for severe haemorrhage from the upper respiratory tract and 2 subjects from cardiac arrest. Inhibition of VEGF-signalling compromises the regenerative capacity of endothelial cells and causes defects that expose pro-coagulant phospholipids on

the luminal plasma membrane or underlying matrix, thus leading to thrombosis or haemorrhage (26). This explains why bleeding events can be considered as toxicities specifically associated with the use of TK-inhibitors (27, 28). Nevertheless endothelial cell defects alone are unlikely to explain the life-threatening haemorrhages that occurred in our patients. It is likely that mucosal damage induced by the tracheo-oesophageal neoplastic infiltration, which was reported in these patients, played a significant role in determining the fatal bleeding event. Furthermore all 3 patients had previously been treated with external beam irradiation of the neck. As some authors (29, 30) have reported an association between TK-inhibitors and fatal bleeding events in patients subjected to radiotherapy, we may hypothesize that previous radiotherapy may represent a concomitant condition contributing to the occurrence of fatal haemorrhage. In order to prevent bleeding complications we suggest excluding patients with mucosal damage related to neoplastic infiltration and those with previous haemorrhages. Furthermore, careful observation of subjects previously treated with external beam irradiation is needed. In addition, clinicians should maintain platelet counts over $50x10^9$/L and correct any haemostatic alterations during follow-up.

Sorafenib induces direct but reversible cardiomyocyte toxicity by inhibiting the kinases BRAF and RAF1 which play an important role in myocyte survival, thus determining cardiac apoptosis and fibrosis (31, 32). Furthermore the frequent occurrence of hypertension, which represents one of the most common adverse events in patients on treatment with sorafenib (33), could exacerbate this process leading to irreversible damage. The finding that persistent inhibition of VEGF signalling compromises the physiological response of cardiomyocytes to increased pressure load (34) further confirms the role of hypertension in this field. Therefore, adequate control of blood pressure (<140/90 mmHg) is required before starting treatment with TK-inhibitors and, once treatment has been initiated, patients should have blood pressure monitored at least weekly (35). If the blood pressure is above 140/90 mmHg, antihypertensive therapy should be initiated or adjusted. ACE-inhibitors, angiotensin receptor blockers (ARBs) or beta blockers (particularly carvedilol) should be preferred since these drugs do not interfere with sorafenib metabolism and, more importantly, exhibit a cardioprotective action (36). Although blood pressure could appear controlled, it is possible that patients treated with sorafenib or other TK-inhibitors develop undocumented episodes of

high blood pressure. This could explain why our patients developed cardiac damage despite hypertension being apparently controlled by antihypertensive treatment. Furthermore, microembolism may be involved and concomitant antithrombotic treatment may be reasonable. In conclusion we believe that a careful and individualized cardiovascular management is essential for these patients.

In order to provide useful indicators that could predict the morphological effectiveness of sorafenib and overall clinical outcome we performed an exploratory analysis of the potential role of serum Tg and FDG-PET. Baseline Tg levels were significantly higher in patients with progression of disease despite treatment with the study drug and showed a clear correlation with PFS. According to these findings, baseline Tg may represent a powerful tool to select patients who are likely to benefit from treatment with sorafenib in terms of both radiological response and clinical outcome. Nevertheless, larger and randomized studies are needed to confirm these data and to identify a cut off of Tg levels with corresponding probabilities of radiological response and acceptable PFS. All patients, both responding and non-responding, achieved biochemical PR. Tg response was significantly more marked among responding patients and was strikingly correlated to PFS. This means that Tg response could be useful for predicting radiological response and clinical outcome.

Baseline average SUVmax was significantly higher in patients with disease progression but showed no correlation with PFS. This means that FDG-PET assessment at baseline may predict radiological response but not clinical outcome. Larger and randomized studies are needed to confirm these findings and to verify whether FDG-PET evaluation may be useful in identifying patients with a higher likelihood of achieving a morphological response. Early FDG-PET assessment was performed as previous studies found that a reduction in metabolic activity could be an early predictor of response in other types of cancer treated with TK-inhibitors (37, 38). Furthermore Carr et al. (39) had previously observed that an early FDG-PET response was correlated to RECIST response in patients affected with iodine-refractory thyroid cancer treated with the TK-inhibitor sunitinib. An early reduction of average SUVmax was found in all patients but the percentage decrease was strikingly greater among responding subjects. According to this finding, an early FDG-PET scan could be useful for clinicians as it may allow identification of patients who are unlikely to

show a morphological response, thus anticipating suspension of treatment. Nevertheless larger and dedicated studies are needed for confirmation and standardization of the role of an early FDG-PET assessment in this clinical contest.

The present study was strikingly limited by its retrospective nature, the small sample size and the absence of randomization. This is why all our findings are not definitive and must be confirmed by the ongoing phase III DECISION trial (Study of Sorafenib in Locally Advanced or Metastatic Patients with RAI-Refractory Thyroid Cancer). Although retrospective, all included patients were treated in the same centre and the same diagnostic and therapeutic procedures were applied. This gives our study more power in comparison with previous retrospective papers. The peculiarity of the present paper was the absence of exclusion criteria typical of randomized trials, which allows us to assess more accurately the impact of sorafenib both in terms of efficacy and safety in actual clinical practice. Furthermore, an analysis of the role of serum Tg and FDG-PET was performed in order to provide indications useful in routine clinical practice for the management of these patients.

In conclusion, our study demonstrated that sorafenib allows morphological disease control in the majority of patients with iodine-refractory DTC. Nevertheless PFS and OS were lower than in other studies as a consequence of the worse baseline clinical condition of our patients. Sorafenib is mostly well tolerated but its activity may play a role in determining the occurrence of severe bleeding events and cardiac arrest, which led to the deaths of a significant percentage of our patients. Baseline levels of Tg and the Tg response to treatment could be useful for predicting the effectiveness of the study drug both in terms of morphological response and overall clinical outcome. Baseline FDG-PET assessment could be useful in predicting radiological response but not PFS. Early FDG-PET assessment could be helpful for clinicians for the rapid identification of non-responding patients, thus allowing timely suspension of treatment.

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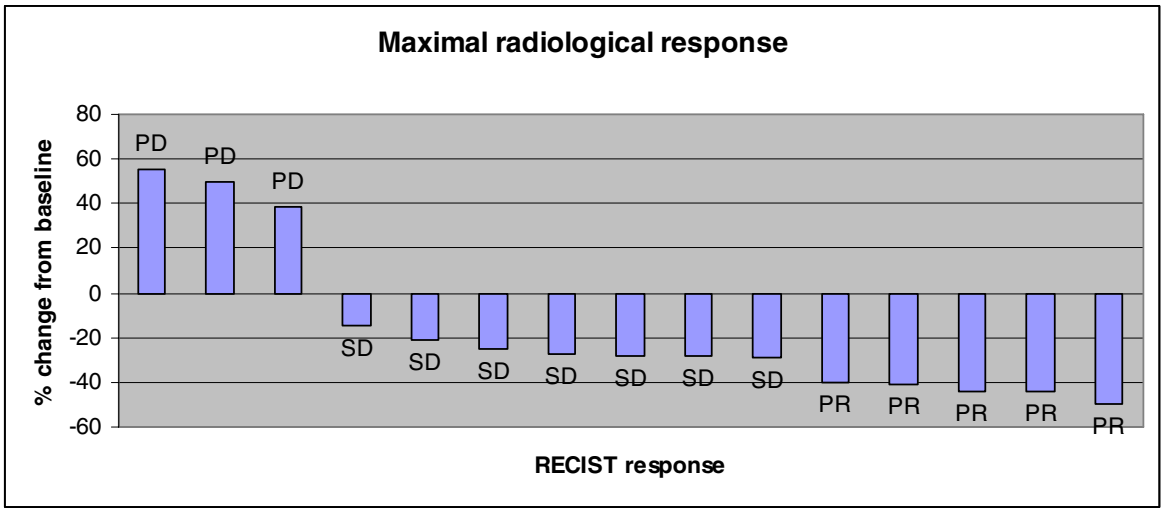
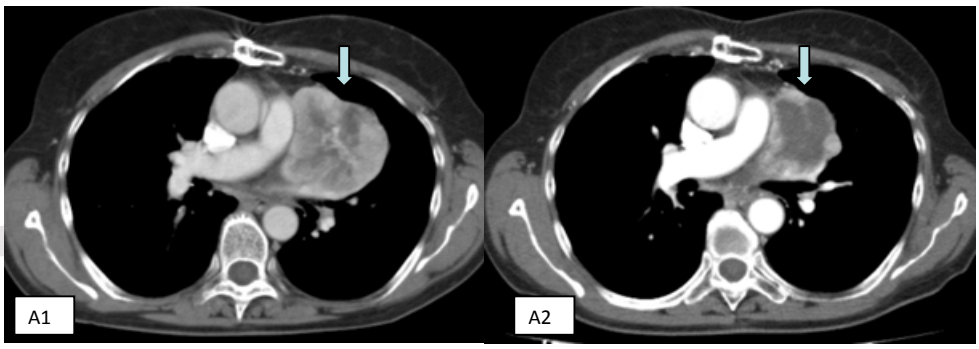


Figure 1. Waterfall plot of maximal radiological responses by RECIST criteria version 1.1.

%:proportion; SD:stable disease; PR:partial response; PD: progressive disease.

A



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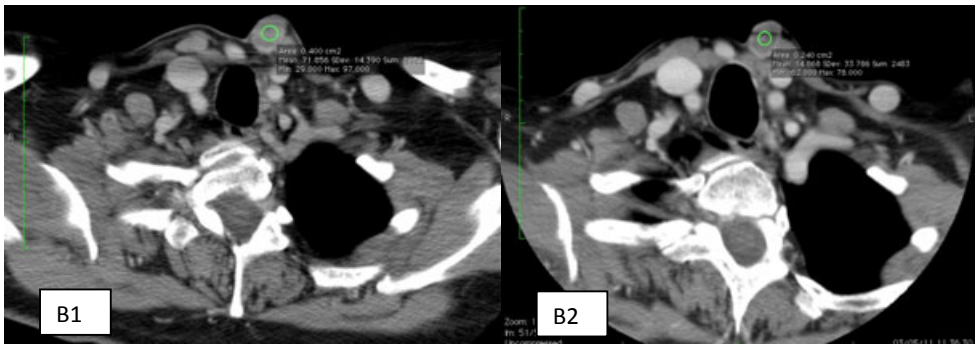


Figure 2: A: Contrast-enhanced multi-detector-CT in a 56-years old female with DTC refractory to RAI (patient 5). Baseline examination (A1) show a huge (diam. max 6.9 cm) mediastinal lymph node at the level of the aorto-pulmonary window. After 5 months of treatment (A2), considerable tumour shrinkage could be appreciated (diam. max 5.4 cm) along with associated tumour necrosis as best tumour response. B: Contrast-enhanced multi-detector-CT in a 60-years old female with DTC refractory to RAI (patient 8). Baseline (B1) and 4-months treatment examinations (B2) depicting a left anterior cervical lymph node are reported. The lymph-node exhibits a dramatic reduction in its density (14 vs 71 HU) despite a moderate size decrease (1.7 vs 1.3 cm). HU:Hounsfield units.

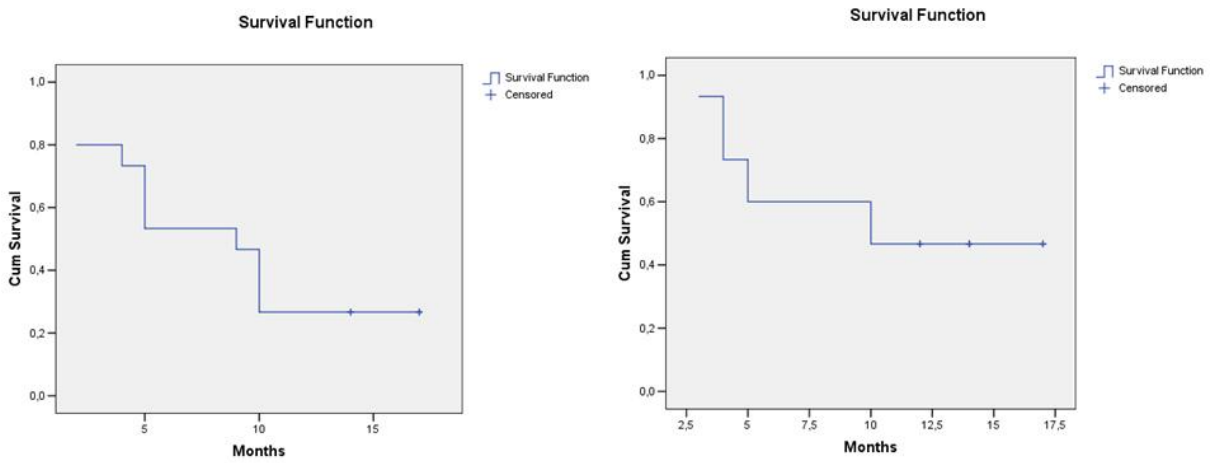
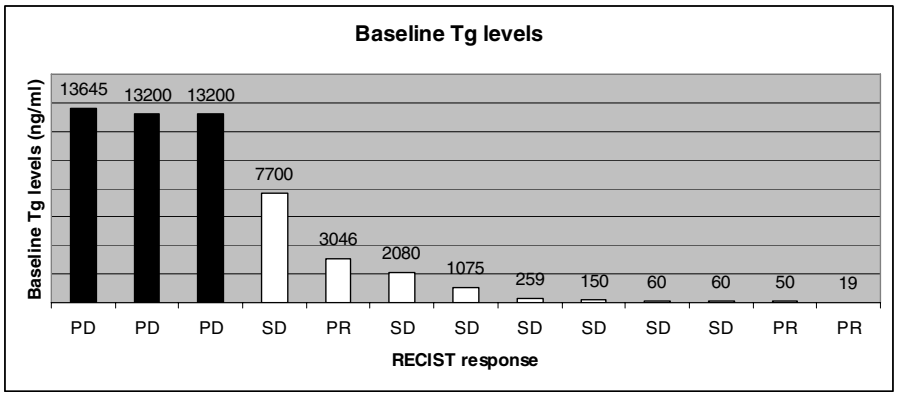


Figure 3. Kaplan Meier analysis of PFS and OS. Median PFS is 9 months. Median OS is 10 months. The twelve month OS rate is 41.1%

A



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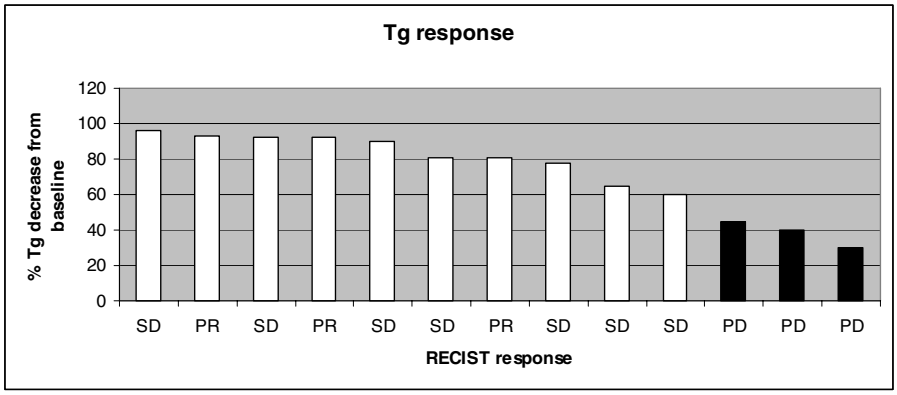
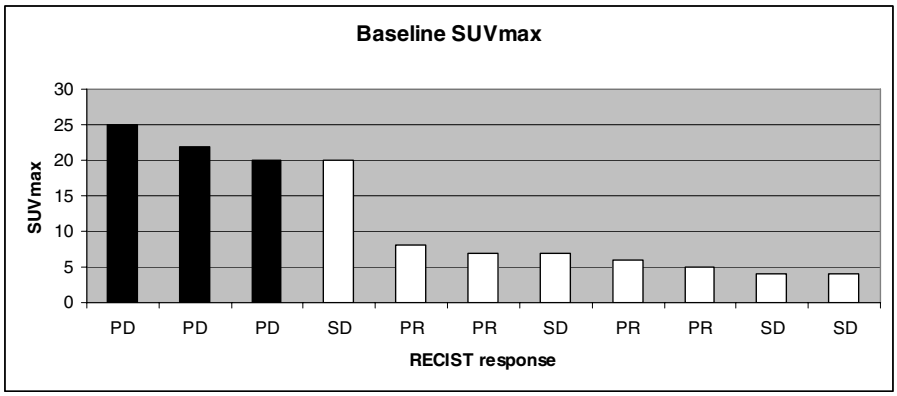


Figure 4. A: Baseline Tg levels. B: Tg response. Black columns indicate patients with PD while white columns indicate patients achieving clinical benefit (SD+PR).

Tg:thyroglobulin; SD:stable disease; PR:partial response; PD: progressive disease.

A



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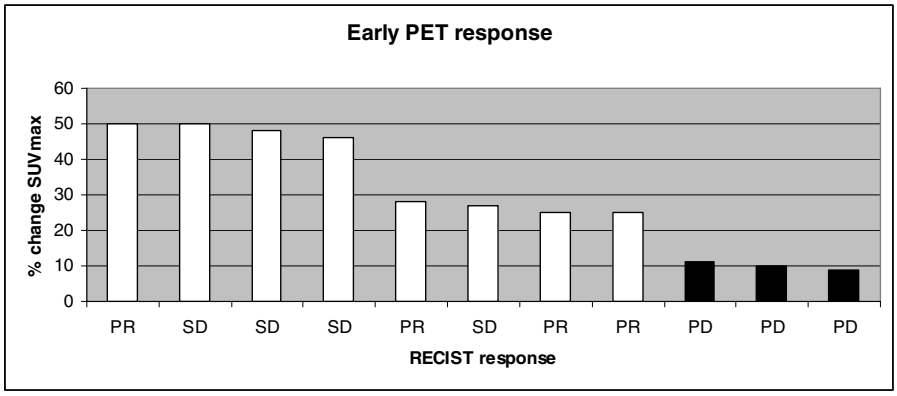

Figure 5. A: Baseline SUVmax B: Early FDG-PET response. Black columns indicate patients with PD while yellow columns indicate patients achieving clinical benefit (SD+PR).

SUVmax:Standard uptake value maximum; SD:stable disease; PR:partial response; PD: progressive disease.