CLINICAL STUDY

Analysis of the efficacy and toxicity of sorafenib in thyroid cancer: a phase II study in a UK based population

Merina Ahmed[1], Yolanda Barbachano[2], Angela Riddell[3], Jen Hickey[1], Katie L Newbold[1], Amaya Viros[4], Kevin J Harrington[1,4], Richard Marais[4] and Christopher M Nutting[1]

[1]Head and Neck Unit, The Royal Marsden NHS Foundation Trust, Fulham Road, London SW3 6JJ, UK, [2]Research Data and Statistics Unit, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, Surrey SM2 5PT, UK, [3]Department of Radiology, The Royal Marsden NHS Foundation Trust, Fulham Road, London SW3 6JJ, UK and [4]Signal Transduction Team, Chester Beatty Laboratories, Institute of Cancer Research, 237 Fulham Road, London SW3 6JB, UK

(Correspondence should be addressed to M Ahmed; Email: merina.ahmed@rmh.nhs.uk)

Abstract

Aim: To evaluate the tolerability and efficacy of sorafenib in patients with thyroid carcinoma.
Methods: Patients with progressive locally advanced/metastatic medullary thyroid carcinoma (MTC), or differentiated thyroid carcinoma (DTC) with non-radioiodine-avid disease, were treated with sorafenib 400 mg twice daily until disease progression. The primary endpoint was the radiological response rate (RR) at 6 months. Secondary endpoints were RR at 3, 9 and 12 months, biochemical responses, toxicity, biomarker analyses and progression free and overall survival (OS).
Results: A total of 34 patients were recruited to the study (15 medullary and 19 differentiated). After 6 months, the RR rate was 15% and a further 74% of patients achieved stable disease in the first 6 months. After 12 months of treatment, the RR was 21%. In the MTC patients, the RR at 12 months was 25% and OS was 100%. In DTC patients corresponding rates were 18 and 79% respectively. Median overall and progression-free survival points were not reached at 19 months. Commonest adverse events included hand–foot syndrome, other skin toxicities, diarrhoea and alopecia. Dose reduction was required in 79% patients. Median time on treatment was 16.5 months.
Conclusion: This study demonstrates that sorafenib is tolerable at reduced doses over prolonged periods of time in patients with thyroid cancer. Sorafenib leads to radiological and biochemical stabilisation of disease in the majority of these patients despite dose reductions.

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Introduction

Thyroid cancer is the commonest endocrine malignancy, presenting with ∼23 500 and 19 000 new cases per year in the United States (1) and European Union respectively (2). Differentiated thyroid carcinoma (DTC), which forms the predominant histopathological subtype, follows a relatively indolent course. Prognosis is excellent in young patients receiving optimum surgery and whose tumours are responsive to treatment with radioactive iodide (RAI). Late recurrences or metastases are not uncommon but most can be eradicated with RAI treatment. However, RAI resistance, which can occur *de novo* or many years after diagnosis, has a prevalence of ∼20% in metastatic DTC (3). These tumours are no longer curable due to loss of iodine sensitivity. Ultimately, 9% of all DTC patients will die of their disease (4).

Medullary thyroid carcinoma (MTC) is a less common but more aggressive disease. It is treated with total thyroidectomy ± lymph node excision, but is not amenable to RAI treatment. In the event of disease progression or relapse, these tumours, akin to iodine-resistant DTC, are difficult to manage. Response rates (RRs) to chemotherapeutic agents are poor and short-lived (5). Consequently, the advent of novel biological agents and increased understanding of thyroid tumorigenesis has generated much interest in the development of biologically targeted therapy for thyroid cancer.

A number of biological agents are being tested in thyroid cancer on the basis of thyroid tumour genotype. RAS and BRAF (6, 7) overexpression is adequately documented in differentiated thyroid cancer and the concept of aberrant signalling in the RAS–RAF–MEK–ERK pathway in thyroid cancer is established both in terms of tumour initiation and progression (8). N-RAS mutations correlate with follicular differentiation of thyroid tumours and may act as a tumour-initiating event (9). The *RET* gene represents a further potential biological target in thyroid cancer as oncogenic activation of *RET* due to *RET* gene rearrangement in papillary thyroid cancer (PTC) or point mutations in MTC are initiating events in the formation of both types of tumour (10). Sorafenib, a biaryl urea, targets the

serine/threonine kinases RAF1 and BRAF, and inhibits several tyrosine-kinase receptors (TKRs) including RET. Sorafenib is active against TKRs involved in tumour neovascularisation and progression including vascular endothelial growth factor receptors 2 and 3, platelet-derived growth factor receptor β, c-KIT and Flt3. The drug, therefore, potentially may inhibit thyroid cancer growth both through anti-proliferative and anti-angiogenic mechanisms.

A phase II clinical trial was designed to assess the clinical efficacy of sorafenib in patients with MTC and DTC and also its toxicity in this group of patients.

Patients and methods

Patients with histologically proven, progressive locally advanced/metastatic MTC, or DTC deemed not suitable for treatment with radioactive iodine, were entered into the study. Patients had to have documented evidence of measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria version 1.0. Key eligibility criteria are listed in supplementary Table 1 (see section on supplementary data given at the end of this article).

Study design and outcome measurements

Patients were commenced on sorafenib at a dose of 400 mg b.d. Radiological responses were measured by CT and bone scans using RECIST criteria version 1.0 (11). Biochemical responses in DTC patients were measured using thyroglobulin (Tg) in Tg secretors without thyroid autoantibodies. Calcitonin and CEA levels were measured in MTC patients to assess the biochemical response. A biochemical partial response (PR) was defined as a >25% decline in tumour marker (TM) level from baseline. Stable disease (SD) was defined as a 25% increase or decrease in TM level and progressive disease as 25% increase from baseline. Efficacy assessments were made at 3-month intervals. TM levels were also assessed at months 1 and 2 to assess for an early nadir response. Patients were taken off study if there was evidence of radiological progression.

Safety assessments consisting of medical history, physical examination, documentation of adverse events and full blood count, coagulation, renal, hepatic, bone and thyroid profiles were performed at months 1, 2, 3, 6, 9 and 12 and 3 monthly thereafter. Serious adverse events were documented and reported according to Ethics committee and Medicines and Healthcare Products Regulatory Agency (MHRA) regulations. Adverse event reporting was graded according to the Common Toxicity Criteria version 3.0. At the 12-month time point, subjects achieving SD or better were allowed to continue the study drug at the Investigator's discretion.

Dose-level reductions to 400 mg daily and 400 mg alternate days were implemented if patients developed severe toxicity. Drug interruptions were also permitted. All patients provided written informed consent before enrolment. This study was approved by the Institutional Review Board, Ethics Committee and MHRA (EudraCT number: 2006-006615-80) and complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki.

All MTC patients underwent RET genotyping during their initial diagnostic work up. Paraffin embedded archived tissue was obtained for DTC patients to evaluate *BRAF* mutational events and *BRAF* mutational analysis performed as described previously (12).

Endpoints

The primary endpoint of the study was the radiological RR following 6 months of treatment with sorafenib. Analyses were performed on an intention to treat basis.

A patient was said to have responded if they achieved a RECIST radiological response of a complete response (CR) or PR. The RR at a given time point was the best radiological response recorded up until that time point. Additional endpoints were RR at 3, 9 and 12 months, SD rates (also recorded as best response), biochemical RRs, adverse events, biomarkers, progression-free survival (PFS) and overall survival (OS).

Statistical analysis

The study adopted an exact single-stage phase II design. We considered a RR of 10% or less to imply that sorafenib has insufficient response benefit and a RR of 30% or more to indicate that sorafenib was effective in thyroid cancer. With a one-sided α of 0.05 and 90% power, 33 patients were required and sorafenib was to be considered worthy of further investigation if seven or more patients responded (13). PFS, defined as time from commencement of study drug to progression or death, was assessed by the Kaplan–Meier method as was OS. Comparisons between the histological subtypes were made by the log-rank test.

Results

Demographics

A total of 34 patients were recruited. Minimum follow-up period for all patients was 6 months. Thirty-one patients have been followed up more than 12 months and median follow-up was 19 months. Thirty-one patients had undergone total thyroidectomy. Patient demographics were as given in Table 1.

Of 28 patients had documented radiological evidence of progressive disease in the preceding 18 months. The remaining six patients had documented evidence of biochemical progression, i.e. >25% increase in the preceding 12 months.

Table 1 Patient demographics.

Demographic characteristics	Values (*n*)
Sex	
Female	15
Male	19
Age (years; median (range))	(55) 21–78
Histology	
Differentiated (Total)	19
Papillary	8
Follicular	5
Hurthle	4
Poorly differentiated	2
Medullary	15
Performance status (ECOG)	
0	21
1	13
Previous chemotherapy	4

ECOG, Eastern Co-operative Oncology Group.

Patients deemed not suitable for radioiodine treatment were classified as such if they had non-iodine-avid disease on therapy (17 patients) or diagnostic (one patient) scans in the presence of known radiological evidence of disease. In addition, one patient with hurthle cell cancer was deemed not suitable for iodine treatment due to large-volume disease adjacent to an airway. Medullary cancer patients were by definition not considered to be iodine avid.

Response

At 6 months, the RR recorded by patients in this study was 15% (95% confidence interval (CI) 5–31%). All responding patients obtained a PR and no CRs were observed. Confirmatory scan data was available for 80% of responses. Of the total patients, 73% achieved SD in the first 6 months. RR rates at 9 and 12 months were 16 and 21% (Table 2).

At 6 and 12 months, RR for MTC was 13 and 25% respectively. These data show that responses in MTC can occur beyond 6 months. Corresponding figures for DTC patients were RR of 16% at 6 months and 18% at 12 months. See waterfall plot (Fig. 1).

Survival

The median overall and PFS of patients in this study have not been reached. The 1-year OS and PFS rate was 88% (95% CI 72–95%) and 79% (95% CI 62–90%) respectively (Fig. 2A and B). In the medullary subgroup of patients, the OS rate at 1 year was 100% and PFS was 93%. The equivalent rates for the DTC group of patients were 79 and 68%. These differences were not significant (log-rank test $P = 0.094$) for OS and PFS.

Biochemical response

Biochemical responses were assessed in all patients with detectable TM. The biochemical RR (i.e. CR and PR) was 63% at 3 months, 57% at 6 months, 50% at 9 months and 48% at 12 months. In DTC patients, a drop in mean Tg levels was observed at 3 months but was not sustained and by 9 months the mean Tg returned to baseline levels. The subsequent drop observed at 12 and 15 months represents patients continuing on sorafenib with radiological PR or SD (Fig. 3A). In the MTC group, the mean calcitonin level demonstrated a dramatic reduction by $> 50\%$ in the first month (Fig. 3B). This was followed by a 'bounce' in months 2 and 3 following which the calcitonin levels reached a plateau. Mean CEA levels also showed initial reduction and then began to rise after 9 months (Fig. 3B).

Correlation of TM with radiological response using Pearson's coefficient was 0.4 ($P = 0.03$) for Tg and 0.3 for calcitonin ($P = 0.03$). The percentage change in CEA from baseline levels correlated with percentage change in calcitonin (Pearson's coefficient was 0.34, $P = 0.005$) suggesting both are useful markers for monitoring response in MTC patients.

Treatment tolerability

The median time patients remained on sorafenib was 16.5 months. Nine patients stopped treatment: five due to progressive disease, two because of toxicity and two died while on treatment; 82% of patients underwent a dose interruption for toxicity; 79% of patients required a dose reduction by one dose level to 400 mg daily and

Table 2 Radiological response and biochemical response rates at 3, 6, 9 and 12 months, as a percentage of all patients that have reached that time point.

	Radiological response rate (%)			Biochemical response (%)		
	PR*	SD	PD/NA	PR	SD	PD/NA
3	–	–	–	63	20	17
6	15 (5–31)	73	12	57	13	30
9	16 (5–33)	72	12	50	18	32
12	21 (8–40)	65	14	48	11	41

NA, those patients taken off study before reaching follow-up at that time interval.
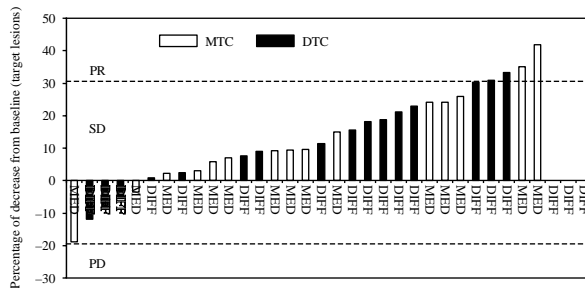* Presented as per cent best response (95% CI).

Figure 1 Waterfall plot of patients at 6 months. Best response recorded.

a third of these patients underwent a further reduction to the lowest dose level of 400 mg alternate days.

Median time to dose reduction for all toxicities was 14 days and the mean time to dose reduction was 35 days. The median time to dose reduction for hand–foot syndrome (HFS) was 14 days with a mean time to dose reduction of 32 days.

Adverse events

HFS occurred in 79% of patients and was the main dose limiting toxicity, with 44% of patients requiring a dose reduction. On reintroduction of the drug, all patients tolerated a lower dose level. 'Dermatology other' (i.e. all skin toxicities excluding HFS) was observed in 88% of patients; 27% of MTC patients also developed an acute hypersensitivity reaction in which they developed a florid erythematous rash associated with fever and systemic symptoms. This resolved on cessation of the drug. The drug was safely reintroduced in all patients at a lower dose. Other common adverse events (all grades) included diarrhoea (77%), infection (44%), fatigue (59%), abdominal pain, glossitis or glossodynia (35%), anorexia (29%), weight loss, haemorrhage (29%) and nausea (26%; Fig. 4 and Supplementary Table 2, see section on supplementary data given at the end of this article). Correlations between HFS and response were assessed but no relationship between the two variables was found to exist.

Laboratory values

In this study, 12% of patients developed an elevated TSH. As all patients were on thyroxine (T_4) replacement therapy and asymptomatic, this was interpreted as subclinical hypothyroidism and was corrected by increasing the T_4 dose in each patient. All patients were athyreotic and the TSH rise was not associated with low levels of free tri-iodothyronine (FT_3).

Sorafenib was found to be mildly myelosuppressive. There was one case of febrile neutropenia. Liver abnormalities were common with 32% of patients experiencing a grade 1/2 transaminitis; 15% of patients

developed grade 3 amylasaemia but no patients developed acute pancreatitis. Lipase levels were found to be raised in 22% of patients half of which were grade 3/4 (Supplementary Table 2).

Biomarker response

BRAF sequencing was performed on archived material and results for three out of ten DTC patients were obtained. One patient was identified as having a somatic mutation in BRAF exon 15 (V600E). This patient developed a dramatic PR within 3 months of commencing drug (Supplementary Figure 1, see section on supplementary data given at the end of this article).
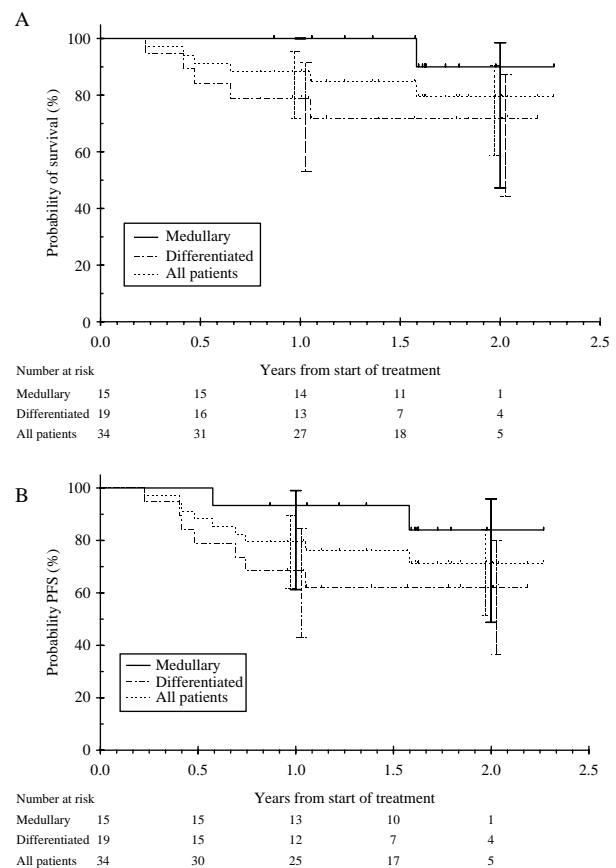

Figure 2 (A) Overall survival. The median survival has not been reached. The 1-year survival rate was 88% with (95% CI 72–95%). The 2-year survival rate was 79% with (95% CI 59–91%). Overall, survival at 1 year was 100% in MTC patients and 79% in DTC. At 2 years, it was 90% in MTC patients and 72% in DTC. The difference was not significant (log-rank test P value = 0.094). (B) Progression-free survival. The median progression-free survival has not been reached. The 1-year progression-free survival rate was 79% with (95% CI 62–90%). The 2-year progression-free survival rate was 71% with (95% CI 51–84%). The median follow-up for patients that have not died or progressed is 19 months. PFS at 1 year was 93% in MTC patients and 68% in DTC. At 2 years, it was 84% in MTC patients and 62% in DTC. As with OS the difference was not significant (log-rank test P value = 0.094).
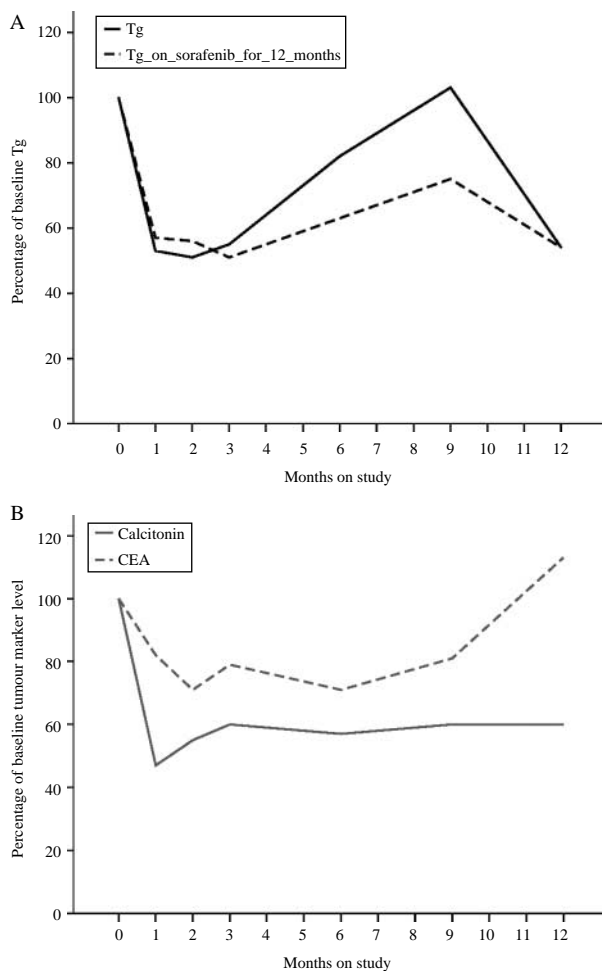
Figure 3 (A) Mean biochemical response of DTC patients (solid line). The decrease in Tg at 12 months is indicative of fewer patients at this time point. Patients who remained on sorafenib for 12 months demonstrated continuing evidence of decreased Tg (dotted line). (B) Mean calcitonin and carcino embryonic antigen (CEA) tumour marker levels for all MTC patients. For calcitonin levels a 'bounce' is observed after one month.

The two remaining patients were BRAF wild type and developed progressive disease by 9 months.

Three of the MTC patients had germline *RET* mutations (M918 MEN2B, V804 MEN2A and 634 MEN2A). All three patients continue to maintain SD but none has resulted in a PR. Six of the MTC patients tested for the *RET* gene were not found to have any genomic alteration of the gene and in fact all MTC patients who demonstrated a radiological PR were in this group. RET status for the remaining MTC patients are unknown.

Discussion

The study was designed such that a RR of 30% would deem sorafenib worthy of further investigation in thyroid cancer and a RR of 10% or less as insufficient

response. The RRs achieved in this study were only 15% at 6 months and 21% at 12 months suggesting that sorafenib was not as active as predicted. Our data revealed that PR can occur after 6 months and that a 12-month time point is more suitable to assess response. It is important to note that the clinical benefit rate (PR and SD) was high being 88% at 12 months.

The MTC patients appeared to have marginally improved PFS and OS compared with DTC (Fig. 2) but the numbers in each group are too small to make this conclusion and the difference was borderline significant. The PFS rate at 2 years in MTC patients was 84% and the OS rate was 90%. Corresponding rates for DTC patients were 62 and 72%. This difference may relate to the natural history of MTC compared with DTC but an (unplanned) analysis of the baseline characteristics of the two groups of patients reveal progression before study entry and baseline tumour measurements were not significantly different. This does not take into account non-measurable disease or TM doubling times making it difficult to draw any conclusions. However, it is clear that sorafenib has some activity in MTC as well as DTC.

Survival in this study remains high and sufficiently longer follow-up is required to assess median PFS and OS. At a median follow-up of 19 months PFS at 2 years was still 71%. This PFS is already longer than that observed in other phase II studies using sorafenib where median PFS ranged from 15 months (14) to 19.75 months (15, 16), and other tyrosine kinase inhibitors (TKIs) such as axitinib (16) and motesanib (17) with median PFS of 18.1 and 10 months respectively (Supplementary Table 3, see section on supplementary data given at the end of this article). Lam *et al.* (18) tested sorafenib in a similar cohort of MTC patients and demonstrated a median PFS of 17.9 months. However, these differences in PFS may simply be a reflection of the pre-study characteristics of our patient group.

The primary endpoint of RR at 6 months was chosen as it was expected that the maximum benefit from sorafenib would occur before 6 months. However, the increasing PR rate at 12 months implies that it may take many months before the full response to sorafenib is demonstrated. The patients who achieved a PR after 6 months had been progressing before study entry but had low-volume metastatic disease. One patient with PR at 3 months had large-volume pulmonary disease and this response was not sustained. Overall, PRs were observed in patients with liver and lung metastases but not in patients with thyroid or retrosternal masses and it may be that sorafenib is more effective against small-volume disease or that tumour vascularity is a key factor in determining response.

Sorafenib's effects on the MTC subgroup of patients in this study undoubtedly relate to VEGF inhibition as the majority of MTC patients did not have a *RET* mutation and the responses in the three familial MTC patients were not dramatic. Similarly, Lam *et al.* (18) were
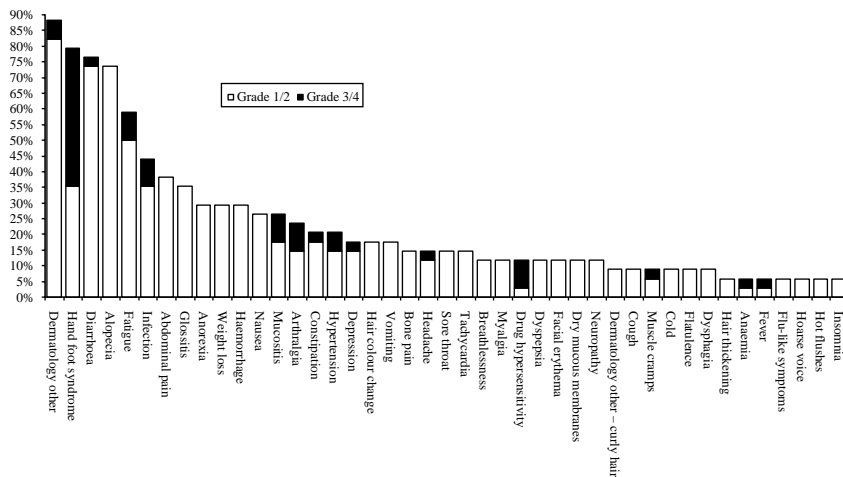
Figure 4 Adverse events occurring at > 5% incidence. Grade 3/4 events are indicated in black. 'Dermatology other' included follicular occlusions, dermatitis, xerosis and hypopigmentation of skin leading to photosensitivity.

unable to demonstrate striking responses in the hereditary MTC group. Interestingly, the PR observed in MTC patients occurred in patients who were known to be *RET* mutation negative while those patients who were *RET* mutation positive did not demonstrate a response. This suggests that sorafenib *in vivo* effects may not be RET inhibitory. Further testing of this drug in MTC is required to assess this.

One patient with a *BRAF* mutation demonstrated a dramatic response at 3 months (Supplementary Figure 1) despite the presence of large-volume disease. Unfortunately, BRAF status was not obtained for most patients. This was in part due to inaccessible disease for biopsy procedures. Furthermore, where tissue was obtained the DNA yield was low. This was attributed to paucicellularity of specimens and high Tg content.

In some studies the BRAF inhibitory effects of sorafenib *in vivo* have been brought into question by the poor anti-tumour efficacy of sorafenib in melanoma (12, 19), a tumour in which 66% of cases harbour activating point mutations (20). These studies raise the question of whether other novel BRAF inhibitors such as PLX4032 should be explored in DTC (21).

With the assumption that sorafenib is primarily a VEGF inhibitor, we were keen to assess this drug in thyroid cancer regardless of histological subtype and the statistical design of the study was formulated accordingly.

Our study highlights the difficulty of obtaining correlative biomarker data in metastatic thyroid cancer where patients often have small-volume disease. Further attempts should be made to obtain biomarker data (serum and tissue) in large numbers of patients. It is hoped that the current phase III study, 'DECISION' will provide a greater understanding of the molecular effects of sorafenib in DTC.

In the absence of alternative validated criteria, RECIST continues to be the mainstay of response assessment for targeted therapies although the adequacy of RECIST when assessing response to TKIs has been questioned on several occasions (22). RECIST is unable to differentiate stable lesions that became necrotic from those which remained solid. The issue of how functional imaging should be used is not always clear (14) but there is increasing evidence of its role as a predictive biomarker (23). In thyroid cancer there is the added advantage of monitoring the disease with TM. Tg is known to be an extremely sensitive TM for DTC in the absence of thyroid autoantibodies. In MTC, calcitonin and CEA are sensitive markers for detection of disease and predictors of survival (24). Calcitonin was selected as the predominant measure of biochemical response as calcitonin doubling times provide a more accurate prediction of survival than CEA doubling times (25, 26). However, the biochemical responses proved to be extremely erratic and there was poor correlation between radiological and biochemical responses. Our data suggest that Tg response in DTC patients does not correlate with radiological response and cannot be relied upon as a marker of response to treatment. Furthermore, the dramatic response of calcitonin levels to sorafenib highlights the fact that RET kinase inhibitors have pre-clinically been shown to have a physiological impact on calcitonin gene expression (27). The initial calcitonin drop is therefore an overestimation of biochemical response. A clinical consequence of sorafenib's effect on calcitonin synthesis is that the calcitonin-induced diarrhoea suffered by MTC patients may improve with this drug.

Tolerability of the drug at the standard dose level was poor. However, the lower dose level of 400 mg o.d. proved to be well tolerated with patients experiencing mostly grade 1/2 toxicity, the exception to this being HFS. Grade 3/4 HFS toxicity was high at 44% and proved to be the main dose limiting toxicity (DLT) for patients in this study. These levels appear relatively high compared with incidences in renal cell carcinoma (33% in the TARGET trial) (26) and 21% in hepatocellular

carcinoma in the SHARP trial (28). Our HFS incidence was also higher than those observed in sorafenib trials for DTC. This may be due to the number of young MTC patients who have a lower tolerance of HFS due to their active lifestyles and possibly an increased susceptibility. A high dose reduction rate of 76% compared with 79% in this study was observed in Lam's study. The dose reductions occurred predominantly in the first month of study entry and most patients were on this dose level throughout the study. It would appear that 400 mg o.d. is a more tolerable dose and efficacy at this dose level is maintained.

Diarrhoea was also a common toxicity but grade 3/4 toxicity was minimal at 3%. The assessment of diarrhoea in MTC was complicated by the fact that baseline diarrhoea levels were already fairly high due to hypercalcitoninaemia. Most MTC patients noticed a dramatic improvement in diarrhoeal symptoms in the first month of treatment with sorafenib but this was soon followed by a return to previously existing baseline levels of diarrhoea.

The drug hypersensitivity reaction observed in MTC patients in this study manifested as fever with no obvious infection, florid erythematous rash often with facial flushing and systemic symptoms. These symptoms subsided with lowering of the dose but frequently facial flushing remained. Although this reaction has not been mentioned in other studies, side effects such as facial flushing/erythema, chills and fever have previously been reported in MTC patients. The clinical significance of this reaction is not clear. Although the symptoms are alarming at the time the reaction did not preclude rechallenging with the drug at lower doses.

Raised TSH levels were recorded in 12% of patients in this study. As most patients were on TSH suppressive therapy the levels were managed by modifying the T_4 dose. The inference from other TKI studies with imatinib performed in athyreotic patients is that sorafenib interferes with clearance of T_4 and T_3. However, this would require induction of the UDP glucuronosyltransferase (UGT) enzymes. Sorafenib is primarily metabolised by CYP3A4 and undergoes glucuronidation by UGT 1A9. Sorafenib is affected by drugs that induce UGT1A9 enzymes but itself does not induce this pathway. In accordance with departmental policy at the time, all patients on T_4 suppressive therapy underwent assay of FT_3 levels only. Hence, there is no free T_4 data available for these patients. It is not feasible to postulate the cause of the TSH rise in these patients without this data.

This study suggests sorafenib exerts some anti-tumour efficacy in progressive medullary and differentiated subtypes of thyroid cancer. Radiological and biochemical stabilisation of disease was achieved in the majority of patients despite most patients requiring dose reduction and suggests that sorafenib is worthy of further investigation in these patients for whom conventionally there are no other treatment options available. The drug was tolerable at low doses while still maintaining efficacy but given the indolent nature of metastatic thyroid cancer the true test of this agent will be the effect on PFS and how this impacts on quality of life (QOL) particularly in a group of patients who for the most part maintain an excellent QOL without treatment. This hypothesis is to be tested in the international multi-centre randomised phase III trial in DTC patients (the DECISION study). However, our data are beginning to suggest that sorafenib has some efficacy in MTC and ultimately PFS and QOL will need to be assessed in a similar phase III setting in this group of patients.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-11-0129.

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.

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