Sorafenib in advanced melanoma: a critical role for pharmacokinetics?

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BACKGROUND: Inter-patient pharmacokinetic variability can lead to suboptimal drug exposure, and therefore might impact the efficacy of sorafenib. This study reports long-term pharmacokinetic monitoring of patients treated with sorafenib and a retrospective pharmacodynamic/pharmacokinetic analysis in melanoma patients.

METHODS AND MATERIALS: Heavily pretreated patients with stage IV melanoma were started on sorafenib 400 mg twice daily (bid). In the absence of limiting toxicity, dose escalation of 200 mg bid levels was done every 2 weeks. Plasma sorafenib measurement was performed at each visit, allowing a retrospective pharmacodynamic/pharmacokinetic analysis for safety and efficacy.

RESULTS: In all, 19 of 30 patients underwent dose escalation over 400 mg bid, and 28 were evaluable for response. The overall disease control rate was 61% (95% confidence interval (CI): 42.6–78.8), including three confirmed responses (12%). Disease control rate and progression-free survival (PFS) were improved in patients with high vs low exposure (80% vs 32%, P = 0.02, and 5.25 vs 2.5 months, P = 0.005, hazard ratio (HR) = 0.28 (95% CI: 0.11–0.73)). In contrast, drug dosing had no effect on PFS. In multivariate analysis, drug exposure was the only factor associated with PFS (HR = 0.36 (95% CI: 0.13–0.99)). Diarrhoea and anorexia were correlated with drug dosing, while hypertension and hand–foot skin reaction were correlated with drug exposure.

CONCLUSIONS: Although sorafenib had modest efficacy in melanoma, these results suggest a correlation between exposure and efficacy of sorafenib. Therefore, dose optimisation in patients with low exposure at standard doses should be evaluated in validated indications.

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Sorafenib is an oral agent that inhibits a large spectrum of cellular targets (VEGFR-2, PDGFR, c-KIT, FLT-3, CRAF, wild-type BRAF or BRAFV600E; Wilhelm et al., 2004). The recommended dose of sorafenib in patients with hepatocellular carcinoma and advanced renal cell cancer is 400 mg twice daily (bid) (Strumberg et al., 2007). In preclinical studies, sorafenib efficiently inhibited BRAF activity in BRAF-mutated melanomas, leading to growth retardation in preclinical studies (Sharma et al., 2005; Wilhelm et al., 2008). A phase II trial of sorafenib in 37 metastatic melanoma patients reported a modest activity, with only three partial response (8%; Min et al., 2008). Another phase II randomized discontinuation trial confirmed these results, with no confirmed objective response, and only 19% of stable disease (Eisen et al., 2006). Unfortunately, BRAF mutations were not predictive of clinical outcome in several trials involving sorafenib in melanoma patients (Eisen et al., 2006; Flaherty et al., 2008; Amaravadi et al., 2009; Ott et al., 2010). Recently, the BRAFV600E inhibitor vemurafenib has shown significant clinical activity in patients with advanced melanoma (Chapman et al., 2011). Hence, it is unclear whether sorafenib exerts anti-tumour activity in melanoma through the inhibition of BRAF or other targets, such as c-Kit. For instance, imatinib, another c-Kit inhibitor, is active in KIT-mutated melanomas (Guo et al., 2011). NRAS, GNAQ and GNA11 are other potential molecular targets, particularly in uveal melanoma (Alisina et al., 2003; Van Raamsdonk et al., 2010).

Sorafenib dose-limiting toxicities (DLTs) included diarrhoea, hypertension and hand–foot skin reaction (HFSR). Notably, doses increases from 400 to 800 mg bid did not substantially increase sorafenib area under the curve (AUC) in phase I trials (Strumberg et al., 2007). However, intra-patient dose escalation has not been evaluated by pharmacokinetics. Owing to a large inter-patient variability (~50%) of sorafenib area under the plasma concentration–time curve over 12 h (AUC; Strumberg et al., 2007; Hornecker et al., 2011), a suboptimal exposure to sorafenib could result in a lack of anti-tumour activity in some patients. To date, this hypothesis could not be ruled out, as sorafenib exposure was not assessed in previous phase II and III trials. Otherwise, dose adjustment of sorafenib based on plasma exposure is not currently recommended. In addition, two clinical trials suggest potential benefit for sorafenib dose-escalation strategies in RCC, even after failure of sorafenib 400 mg bid dosing (Amato et al., 2008; Escudier et al., 2009).
In this context, we hypothesised that optimisation of sorafenib exposure might improve its efficacy in patients with metastatic melanoma, and that sorafenib AUC could be related to antitumor efficacy.

PATIENTS AND METHODS

From January 2008 to December 2009, consecutive patients with metastatic melanoma who progressed under previous therapeutic regimen containing one or more of the following: dacarbazine, fotemustine, interleukin-2, cisplatin, interferon or vaccine therapy, were offered sorafenib treatment in two academic cancer centres located in Paris, France (Cochin and Saint Louis Teaching Hospitals). At this time, vemurafenib was not available for patients with BRAF-mutated melanoma. BRAF mutation status was not assessed in our patients.

The schedule included an intra-patient dose escalation. A total of 30 patients with histologically confirmed metastatic melanoma started sorafenib. All patients provided written informed consent, and the study was approved by the Local Ethics Committee.

Treatment plan

Patients were treated with sorafenib at a starting dose of 400 mg bid. In the absence of acute-limiting toxicity, intra-patient dose escalation of 200 mg bid every 2 weeks was planned. No maximum dose was specified. Sorafenib daily doses were only adjusted based on adverse events and not on plasma sorafenib exposure as the values of sorafenib AUC were not transmitted to clinicians.

Assessments

The primary endpoint was safety. Safety was assessed every 2 weeks during the whole-treatment period. In addition to summaries of adverse events classified and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0, term and category, safety analyses included evaluation of clinically significant laboratory test results and vital signs. A DLT was defined as any toxicity leading to dose reduction or to discontinuation of treatment. Tumour response was assessed by CT scan using one-dimensional measurements made at baseline, every 8 weeks thereafter and at the end of the treatment period if applicable. Treatment activity was evaluated using the revised RECIST guidelines (Therasse et al, 2000).

Plasma exposure to sorafenib

Sorafenib plasma concentrations were assessed in one sample drawn every 2 weeks (at the end of each period of dose escalation) by high-performance liquid chromatography (Blanchet et al, 2009). The accuracy, within-assay precision and inter-assay precision of this method were 96.9–104.0%, 3.4–6.2% and 2.3–9.9%, respectively. A specific bayesian estimator developed in our institution allowed estimating sorafenib AUC with a limited precision of this method were 96.9–104.0%, 3.4–6.2% and 2.009). The accuracy, within-assay precision and inter-assay precision of this method were 96.9–104.0%, 3.4–6.2% and 2.009). The accuracy, within-assay precision and inter-assay precision of this method were 96.9–104.0%, 3.4–6.2% and 2.009). The accuracy, within-assay precision and inter-assay

RESULTS

Patients characteristics

A total of 30 patients with histologically confirmed metastatic melanoma were treated with sorafenib. Baseline patients’ characteristics are summarised in Table 1. The median daily dose was 800 mg bid (range 400–2600), and 19 patients (63%) underwent dose escalation (range 600–2600 mg bid). The median duration of treatment was 2.9 months (range 0.4–16.3).

Response and survival

Two patients discontinued treatment owing to severe toxicity before the first evaluation. Therefore, 28 patients were evaluable for response. One complete response and five partial responses were observed, including three confirmed responses. The overall response rate was 21% (95% CI: 6.2–36.6). The objective responses were assessed early, with a median time from time of treatment initiation of 2.3 months (range: 1.3–3.4 months). In all, 3 of 10 patients (30%) with cerebral metastasis had cerebral partial responses. Median duration of confirmed response was 6.1 months. In total, 11 patients (39%) had stable disease with a median duration of 4.4 months, for an overall disease control rate (PR + SD) of 61% (95% CI: 42.6–78.8).

After a median follow-up of 10 months (range: 3–20), median PFS was 3.6 months (95% CI: 2.5–5.6 months; 18% censored) and median OS was 11 months (95% CI: 5–15 months; 21% censored). The 1-year survival rate was 33% (95% CI: 19–52%). Median survival in patients with brain metastases was 5.6 months (95% CI: 2.5–9.6; 0% censored). In univariate analysis, significant (P < 0.05) prognostic factors were WHO PS ≥ 2 (HR = 3.72 (95% CI: 1.23–10.52)) and primary histological type, time as metastatic disease (> 15 months), number of previous treatment regimen (> 2) and primary histological type. Variable tested for PFS included: sex, WHO PS (≥ 2), age (> 59 years), AJCC stage, brain metastases, LDH baseline level (> ULN), time as metastatic disease (> 15 months), number of previous treatment regimen (> 2) and primary histological type. Variable tested for PFS included: sex, WHO PS (≥ 2), age (> 59 years), AJCC stage, brain metastases, BMI (> 25 kg m–2), primary histological type, time as metastatic disease (> 15 months), number of previous treatment regimen (> 2), LDH baseline level (> ULN), AUCmax (≥ 100 mg l–1 h–1), early grade ≥ 2 adverse events (at 2 months) including diarrhoea, hand–foot skin syndrome (HFSR), skin rash and hypertension considered separately or jointly. Then, multivariate analyses were conducted on all potential factors with P-value < 0.2 in univariate analysis using a stepwise Cox model with enter variable with P-value < 0.05 and remove if P-value > 0.1. The median served as the cutoff point when continuous variables (mean and max AUCs) were separated into two groups.

Missing data were not estimated or carried forward in any statistical analyses. All analyses were performed using the JMP 8.0.2 (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA). P-values were two tailed and considered significant when < 0.05.
Safety

A total of 18 severe adverse events (grade ≥3) occurred in 11 patients at the starting dose of 400 mg bid: 8 hand and foot skin reaction (HFSR), 5 skin rash, 2 stomatitis, 2 hypertension and 1 fatigue. Sorafenib was discontinued in the four patients who experienced both grade 3 rash and HFSR, and then reintroduced at 200 mg bid. Despite this daily dose adjustment, the severity of toxicity was unchanged; therefore the treatment was definitively discontinued. The four patients with isolated grade 3 HFSR were able to continue sorafenib for up to 5 months with a 50% dose decrease.

During the dose escalation, only two patients discontinued sorafenib because of toxicity: a symptomatic grade 3 pancreatitis in the first case, and a grade 4 diarrhoea in the second case. Dose escalation was associated with an increased rate of grade ≥3 diarrhoea (26% vs 3%, P = 0.03) and anorexia (26% vs 3%, P = 0.03). None of the other severe adverse events, especially hypertension and HFSR, occurred more frequently during dose escalation (Table 2).

The early toxicities (HFSR, rash, diarrhoea and hypertension) that occurred during the first cycle (2 months) were associated with a better PFS (18 vs 12 weeks, P = 0.024; HR = 0.38 (95% CI: 0.15–0.98)). In univariate analyses, none of the specific early grade ≥2 toxicity was associated with PFS gain (Table 3). Considering the whole-treatment period toxicities, patients experiencing either grade ≥2 hypertension or HFSR had improved PFS (19 vs 9 weeks, P < 0.0001; HR = 0.13 (95% CI: 0.04–0.39)) but not patients experiencing either grade ≥2 skin rash or diarrhoea (17 vs 13 weeks, P = 0.3; HR = 0.54 (95% CI: 0.17–2.02)).

Pharmacokinetics

During the whole-study period, 216 sorafenib plasma concentrations were assessed (Supplementary Table 1). The median sorafenib AUC was 63 mg l−1 h−1 (range: 16–2600 mg bid) in 19 patients allowed achieving a greater sorafenib exposure in 13 (68%) of them (Figure 2). Two and four patients stable and decreasing exposure, respectively.

The long-term drug exposure monitoring showed that AUC reached its maximum after treatment initiation. Maximal AUC occurred during the first 2 months in 18/27 patients (67%) and the median time to reach the AUCmax was 26 days (range 8–161 days). Sorafenib exposure tended to decrease over time in case of prolonged treatment. In 11 patients receiving sorafenib for

### Table 1 Baseline patients characteristics (n = 30)

|               | n   | %    |
|---------------|-----|------|
| Gender: male/female | 16/14 | 53/47 |
| Median age (range, in years) | 59 (31–80) |      |

**Primary melanoma**

|               | n   | %    |
|---------------|-----|------|
| SSM           | 17  | 57   |
| Nodular       | 4   | 13   |
| Uveal         | 3   | 10   |
| Unknown primary | 4   | 13   |
| Others        | 2   | 7    |

**AJCC stage IV**

|               | n   | %    |
|---------------|-----|------|
| M1a           | 1   | 3    |
| M1b           | 2   | 7    |
| M1c           | 27  | 90   |

|               | n   | %    |
|---------------|-----|------|
| > 2 metastatic sites | 22 | 73  |
| Lung metastases | 18 | 60  |
| Liver metastases | 19 | 63  |
| Brain metastases | 10 | 33  |

**LDH > N**

|               | n   | %    |
|---------------|-----|------|
| Previous chemotherapy | 28 | 93  |
| ≥ 2 Lines of chemotherapy | 22 | 73  |

**Performance Status (WHO)**

|               | n   | %    |
|---------------|-----|------|
| 0–1           | 24  | 80   |
| 2–3           | 6   | 20   |

**Median time from first metastasis (range, in months)**

|               | n   | %    |
|---------------|-----|------|
| 15 (1–59)     | 14  | 47   |

### Table 2 Adverse events by dose and AUC of initial occurrence (dose = 400 or >600 mg bid; AUC < 100 or >100 mg l−1 h−1). (Fisher’s exact test)

|               | All doses and AUC (n = 30) | Dose = 400 mg bid (n = 30) | Dose > 600 mg bid (n = 19) | Grade 3-4 |
|---------------|---------------------------|--------------------------|--------------------------|-----------|
|               |                           |                          |                           |           |
|               |                           |                           | OR (95% CI)               | P         |
|               |                           |                           |                           | AUC < 100 (n = 27) | AUC ≥ 100 (n = 15) | P  |
| HFSR          | 23 (77%)                  | 12 (40%)                 | 8 (27%)                  | 4 (21%)   | —           | 0.7 | 8 (29%) | 2 (13%) | 0.3 |
| Diarrhoea     | 22 (73%)                  | 6 (20%)                  | 1 (3%)                   | 5 (26%)   | 10 (2–71)   | 0.03*| 5 (21%) | 1 (7%)  | 0.4 |
| Fatigue       | 26 (87%)                  | 6 (20%)                  | 2 (7%)                   | 4 (21%)   | —           | 0.2 | 4 (14%) | 2 (13%) | 1   |
| Anorexia      | 13 (43%)                  | 6 (20%)                  | 1 (3%)                   | 5 (26%)   | 10 (2–71)   | 0.03*| 5 (18%) | 1 (7%)  | 0.4 |
| Cutaneous rash| 17 (57%)                  | 5 (17%)                  | 5 (17%)                  | 0 (0%)    | —           | 0.1 | 4 (18%) | 1 (7%)  | 0.6 |
| Hypertension  | 19 (63%)                  | 3 (10%)                  | 2 (7%)                   | 1 (5%)    | —           | 1   | 1 (4%)  | 2 (13%) | 0.3 |
| Stomatitis    | 6 (20%)                   | 3 (10%)                  | 2 (7%)                   | 1 (5%)    | —           | 1   | 1 (4%)  | 0 (0%)  | 1   |
| Neutropenia   | 5 (17%)                   | 3 (10%)                  | 2 (7%)                   | 1 (5%)    | —           | 1   | 3 (11%) | 0 (0%)  | 0.5 |
| Thrombocytopenia| 9 (30%)                 | 2 (7%)                   | 2 (7%)                   | 0 (0%)    | —           | 1   | 2 (7%)  | 0 (0%)  | 0.6 |
| Anaemia       | 8 (27%)                   | 1 (3%)                   | 1 (3%)                   | 0 (0%)    | —           | 1   | 1 (4%)  | 0 (0%)  | 0   |
| Atrial fibrillation| 3 (10%)              | 1 (3%)                   | 0 (0%)                   | 1 (5%)    | —           | 0.4 | 1 (4%)  | 0 (0%)  | 1   |
| Proteinuria   | 4 (13%)                   | 1 (3%)                   | 0 (0%)                   | 0 (0%)    | —           | 0.4 | 0 (0%)  | 1 (7%)  | 0.4 |
| Hypothyroidism| 3 (10%)                   | 1 (3%)                   | 0 (0%)                   | 1 (5%)    | —           | 0.4 | 0 (0%)  | 1 (7%)  | 0.4 |
| Pancreatitis  | 1 (3%)                    | 0 (0%)                   | 0 (0%)                   | 1 (5%)    | —           | 0.4 | 0 (0%)  | 1 (7%)  | 0.4 |
| Alopecia      | 1 (3%)                    | 1 (3%)                   | 3 (16%)                  | —         | 0.3         | 0.3 | 4 (14%) | 0 (0%)  | 0.2 |

Abbreviations: AUC = area under the plasma concentration–time curve over 12 h; CI = confidence interval; HFSR = hand–foot skin reaction; OR = odds ratio. Values are expressed as n (%).
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**Table 3** Parameters associated with time to disease progression by uni- and multivariate analysis (Cox proportional hazards model)

| WHO PS  | N     | Univariate HR | 95% CI | P-value | Multivariate HR | 95% CI | P-value |
|---------|-------|---------------|--------|---------|-----------------|--------|---------|
| 0–1     | 22    | 1             |        |         |                 |        |         |
| 2–3     | 6     | 1.77          | 0.62–4.35 | 0.26    |                 |        |         |

Time from metastatic diagnosis

| ≤ 15 Months | 9 | 1         |        |         |              |        |         |
| > 15 Months | 19 | 0.47     | 0.18–1.17 | 0.10* |             |        |         |

**Early hypertension**

| Grade < 2 | 17 | 1         |        |         |              |        |         |
| Grade ≥ 2 | 11 | 0.92      | 0.28–1.49 | 0.31   |              |        |         |

**Early HFSR**

| Grade < 2 | 14 | 1         |        |         |              |        |         |
| Grade ≥ 2 | 14 | 0.65      | 0.32–1.75 | 0.49   |              |        |         |

**Early rash**

| Grade < 2 | 7  | 1         |        |         |              |        |         |
| Grade ≥ 2 | 21 | 0.44      | 0.10–1.37 | 0.17* |             |        |         |

**Early diarrhoea**

| Grade < 2 | 19 | 1         |        |         |              |        |         |
| Grade ≥ 2 | 9  | 0.51      | 0.19–1.23 | 0.13* |             |        |         |

**Early toxicities**

| Grade < 2 | 8  | 1         |        |         |              |        |         |
| Grade ≥ 2 | 20 | 0.38      | 0.15–0.98 | 0.045* |             |        |         |

**AUC max**

| < 100 | 12 | 1         |        |         |              |        |         |
| ≥ 100 | 15 | 0.28      | 0.11–0.72 | 0.009* | 0.28         | 0.11–0.72 | 0.009* |

Abbreviations: AUC = area under the plasma concentration–time curve over (12 h); CI = confidence interval; HFSR = hand-foot skin reaction; HR = hazard ratio; N = number of patients; NS = variables not selected by the stepwise multivariate model; PS = performance status. Early toxicities included: hypertension, HFSR and diarrhoea during the first 2 months. *Variables included in the stepwise multivariate model. P-values < 0.05 are in bold.

Figure 1  Effect of dose escalation on inter patient sorafenib AUC (mg l⁻¹ h⁻¹). A total 119 AUCs from 29 patients are represented. Wilcoxon’s P-value: *<0.05, **<0.005, NS >0.05.

> 4 months, AUC had decreased in the last part of treatment (after 90 days; 77 vs 61 mg l⁻¹ h⁻¹, P = 0.002).

One month after treatment initiation, sorafenib median AUC was greater in patients with grade ≥ 2 hypertension compared with those with normal blood pressure (82 vs 54 mg l⁻¹ h⁻¹, respectively, P = 0.02). Each measurement of sorafenib was compared with the simultaneous safety report (n = 194 pairs). The median AUC was greater in case of grade ≥ 2 hypertension (84 vs 58 mg l⁻¹ h⁻¹, P < 0.0001), and grade ≥ 2 HFSR (76 vs 61 mg Lh, P = 0.0008). Besides, AUC was not correlated with other adverse events such as diarrhoea, anorexia, allergic and non-allergic skin rash. The rate of severe adverse events (grade ≥ 3) was not increased with AUCs ≥ 100 mg l⁻¹ h⁻¹ (Table 3).

Concerning the relation between plasma sorafenib exposure and efficacy, it was first noticed that five of six responses occurred at 400 mg bid but these patients had high exposure at this dose (with AUC of 102, 101, 84 and 75 mg l⁻¹ h⁻¹ in four patients, and AUC not available for the remaining patient). Then, the median AUCmax (100 mg l⁻¹ h⁻¹, range 51–206 mg l⁻¹ h⁻¹) was used to classify patients into high or low exposure on target lesions (86% vs 50%, P = 0.04, Figure 3). RECIST partial response or stable disease (80% vs 33%, P = 0.02) and PFS (21 vs 10 weeks, P = 0.005; HR = 0.28 (95% CI: 0.11–0.72); Figure 4; Table 3). The Youden index of the receiver operating characteristic (ROC) curve of the disease control relative to the AUCmax was 100 mg l⁻¹ h⁻¹ (data not shown). Maximal exposure had a positive impact on PFS in univariate analysis (Table 3) and confirmed by the multivariate analysis as AUCmax ≥ 100 mg l⁻¹ h⁻¹ (HR = 0.28 (95% CI: 0.11–0.72) was the only significant variable associated with PFS (Table 3).

Neither the AUC at 1 month after treatment initiation nor the mean AUC of the whole-treatment period were associated with a higher disease control rate (69% vs 46% P = 0.4 and 54% vs 64% P = 0.7, respectively) or a longer PFS (HRRs = 0.94 (95% CI: 0.84–1.05)).
DISCUSSION

In this multi-institutional experience with sorafenib dose-escalation in patients with metastatic melanoma, the main results consisted in the positive correlation between AUCmax, objective response and PFS. Although modest in melanoma, sorafenib efficacy was directly correlated with exposure, as seen with sunitinib in RCC and GIST (Houk et al, 2010) or pazopanib in differentiated thyroid cancers (Bible et al, 2010). Consistently with results from the phase I trials (Awada et al, 2005; Clark et al, 2005; Moore et al, 2005; Furuse et al, 2008; Minami et al, 2008; Miller et al, 2009) AUC increased infra-proportionally to the dose. However, the dose-escalation schedule increased AUC in 68% (13/19) patients. In this series, dose adjustments could effectively correct drug under-exposure.

To go further, the changes in sorafenib clearance and bioavailability with doses > 400 mg bid were described in a cohort of 71 patients treated with sorafenib in our institution, including the present series of melanoma patients (Hornecker et al, 2011). A one-compartment model with saturated absorption, first-order intestinal loss and elimination best described the pharmacokinetics of sorafenib. Absolute bioavailability significantly dropped with increasing daily doses of sorafenib. Area under the curve increased less than proportionally with increasing doses. Therefore, a split schedule three times a day might overcome absorption saturation, thereby leading to a higher exposure (Hornecker et al, 2011). Notably, tumour type did not seem to influence sorafenib pharmacokinetics. Only albumin was found to influence sorafenib clearance at standard doses (Tod et al, 2011). As well, in an independent cohort (Jain et al, 2011), no clinically important PK covariates were identified.

In this series, the highest AUC (AUC max) was correlated with antitumor efficacy while the other PK parameters were biased by the dose-escalation schedule: the AUC at 1 month was too early to be correlated to antitumor efficacy in our study. The Youden index of the ROC curve of the disease control relative to the AUCmax was 100 mg l⁻¹ h⁻¹, suggesting that highest exposures are responsible for efficacy. These properties of antiangiogenic treatments have been previously described and represented by a bell-shaped dose-response curve (Reynolds, 2009). Strikingly, only 15% of samples assessed at 400 mg bid had an AUC over 90 mg l⁻¹ h⁻¹ vs 36% of samples at 600 mg bid and more (P = 0.0003). With a target AUC of 90–100 mg l⁻¹ h⁻¹, these results pinpoint that most patients are underexposed to sorafenib at 400 mg bid, and that individualised dose adjustments would be required. In line with these results, a recent study (Motzer et al, 2011) has shown the superiority of sunitinib 50 mg daily 4 weeks out of 6 over a continuous daily dosing of 37.5 mg, pinpointing the need to reach a threshold exposure.
Long-term pharmacokinetic follow-up allowed detecting that the AUC decreased over time, as previously described in hepatocellular carcinoma (Arrondeau et al., 2011). This unexpected result could explain the clinical efficacy of sorafenib dose escalation after failure at standard doses (Escudier et al., 2009) and argue for long-term pharmacokinetic follow-up. This decrease of AUC over time could result from increased expression of drug efflux pumps, as seen with imatinib (Burger et al., 2005). We therefore suggest validating in a prospective trial the AUC as a surrogate marker to tailor sorafenib dose adjustments, thereby avoiding increasing sorafenib dose until intolerable toxicity. This approach could probably improve the therapeutic index of sorafenib in approved indications such as hepatocellular carcinoma and renal cancer.

The limitations of this study include the limited number of patients, the limited sampling strategy and the proportion of patients in whom sorafenib standard dose was not tolerated. Dose escalation was feasible and no unexpected severe adverse event was seen, even in highly pretreated patients with brain metastasis. Only two patients discontinued sorafenib during dose escalation. Several hypotheses on the pathogenesis of sorafenib-related adverse events could be raised. Indeed, toxicities could be classified in three categories according to their correlation with dose and exposure. Diarrhoea and anorexia were related to sorafenib dose but not to its AUC. Regarding diarrhoea, this result is in line with a previous hypothesis assuming that intestinal toxicity may be due to a local effect of poorly absorbed drug. Indeed, a low solubility of sorafenib in aqueous media hampers its complete dissolution in digestive tract at high doses. Thus, the fraction of sorafenib not absorbed could exert a direct toxic effect on enterocytes. Interestingly, patients with abnormal gastrointestinal functions are prone to develop diarrhoea under sorafenib (Lauritano et al., 2009), and patients with abnormal liver functions have a highest rate of diarrhoea without elevated exposure (Miller et al., 2009; Michels et al., 2010). As a consequence, diarrhoea per se may decrease sorafenib exposure, due to reduced intestinal absorption and interruption of entero-hepatic cycle.

Regarding prediction of toxicity, hypertension and HFSR were related to the AUC in the present series. To date, only one pharmacodynamic study identified a rare polymorphism of VEGFR-2 as a predictor of HFSR and hypertension (Jain et al., 2010). Regarding prediction of efficacy, biomarkers have failed to select patients who would respond to sorafenib. The results of four independent trials conclude BRAFV600E mutation is not a predictive biomarker of response to sorafenib (Eisen et al., 2006; Flaherty et al., 2008; Amaravadi et al., 2009; Ott et al., 2010). We propose optimised maximal AUC (>90–100 mgL⁻¹h⁻¹) as an alternative predictor for the activity of sorafenib, as illustrated presently in melanoma patients. Dose individualisation with drug monitoring might prevent under exposure to standard dose of sorafenib and favour antitumor activity in other tumour types. Dedicated phase II studies guided by pharmacokinetics are mandatory to prospectively confirm these results.

Conflict of interest

FG has worked as paid consultant for Bayer Healthcare and Pfizer. OM has worked as paid consultant for Roche. The other authors declare no conflict of interest.

Supplementary Information accompanies the paper on British Journal of Cancer website (http://www.nature.com/bjc)

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