A phase I/II trial of sorafenib and infliximab in advanced renal cell carcinoma

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BACKGROUND: There is clinical evidence to suggest that tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)) may be a therapeutic target in renal cell carcinoma (RCC). Multi-targeted kinase inhibitors, such as sorafenib and sunitinib, have become standard of care in advanced RCC. The anti-TNF-\(\alpha\) monoclonal antibody infliximab and sorafenib have differing cellular mechanisms of action. We conducted a phase I/II trial to determine the safety and efficacy of infliximab in combination with sorafenib in patients with advanced RCC.

METHODS: Eligible patients were systemic treatment-naïve or had received previous cytokine therapy only. Sorafenib and infliximab were administered according to standard schedules. The study had two phases: in phase I, the safety and toxicity of the combination of full-dose sorafenib and two dose levels of infliximab were evaluated in three and three patients, respectively, and in phase II, further safety, toxicity and efficacy data were collected in an expanded patient population.

RESULTS: Acceptable safety was reported for the first three patients (infliximab 5 mg kg\(^{-1}\)) in phase I. Sorafenib 400 mg twice daily and infliximab 10 mg kg\(^{-1}\) were administered to a total of 13 patients (three in phase 1 and 10 in phase 2). Adverse events included grade 3 hand–foot syndrome (31%), rash (25%), fatigue (19%) and infection (19%). Although manageable, toxicity resulted in 75% of the patients requiring at least one dose reduction and 81% requiring at least one dose delay of sorafenib. Four patients were progression-free at 6 months (PFS\(_6\) 31%); median PFS and overall survival were 6 and 14 months, respectively.

CONCLUSION: Sorafenib and infliximab can be administered in combination, but a significant increase in the numbers of adverse events requiring dose adjustments of sorafenib was observed. There was no evidence of increased efficacy compared with sorafenib alone in advanced RCC. The combination of sorafenib and infliximab does not warrant further evaluation in patients with advanced RCC.

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The treatment of metastatic renal cell carcinoma (RCC) has evolved rapidly since 2006 with the clinical development of targeted agents, such as sorafenib and sunitinib. Sorafenib is an inhibitor of multiple tyrosine kinases, including vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) receptors; the recommended dose is 400 mg twice daily; dose-limiting toxicities include diarrhoea, fatigue and skin toxicity (Strumberg et al, 2005). The activity of sorafenib in patients with advanced RCC has been demonstrated in the target phase III placebo-controlled trial in cytokine-pretreated patients (Escudier et al, 2007) that led to registration of the drug in this indication. A recently published randomised phase II study in previously untreated patients, however, did not show a progression-free survival (PFS) advantage for sorafenib in comparison with interferon-\(\alpha\) (5.7 vs 5.6 months, respectively) (Escudier et al, 2009).

Infliximab is a chimeric human–mouse monoclonal antibody to tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), a pro-inflammatory cytokine. Infliximab prevents TNF-\(\alpha\) binding to receptors, thereby neutralising its activity. In-vitro models suggest that this can induce cell death by complement-mediated lysis through the interaction with membrane-bound TNF-\(\alpha\) (Scallon et al, 1995). Although animal studies using TNF-\(\alpha\) in high dose can induce significant anti-cancer effects, (Locksley et al, 2001; Balkwill, 2002, 2006), lower levels of TNF-\(\alpha\) may be involved in cancer promotion, tumour growth and metastasis, either directly or by a network of cytokines, chemokines and matrix metalloproteinases (Moore et al, 1999; Locksley et al, 2001; Balkwill, 2006). TNF-\(\alpha\) also has a role in cancer cachexia and fatigue and is a putative autocrine and paracrine growth factor in RCC (Mizutani et al, 1994; Balkwill, 2006).

Infliximab is licensed for use in inflammatory diseases at doses of 3–10 mg kg\(^{-1}\). Large randomised trials have documented the safety of infliximab; the most common adverse events include injection site or infusion reactions, development of anti-nuclear antibodies and infection (Lichtenstein et al, 2009). In 2007, we published the results of two sequential phase II trials documenting the activity of the anti-TNF-\(\alpha\) antibody infliximab at dose levels of 5 and 10 mg kg\(^{-1}\) in patients with metastatic RCC previously treated with cytokine therapy (Harrison et al, 2006). Of the 37 patients treated, three patients achieved a partial response and 46% achieved clinical benefit (partial response or stable disease...
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Response and toxicity assessments
Response to therapy was assessed using the Response Evaluation Criteria in Solid Tumours (Therasse et al, 2000), with computed tomographic scans at baseline and every 12 weeks following the initiation of treatment. Adverse events were graded using the National Cancer Institute Common Toxicity Criteria version 3.0.

RESULTS
A total of 16 patients were recruited; six into the phase I and 10 into the phase II parts of the study. Baseline patient characteristics are shown in Table 1. Patients had an average age of 57 (range, 35–72), were predominantly male (13 of 16 patients) and most (12 of 16 patients) were in the low-risk Memorial Sloan-Kettering Cancer Centre prognostic risk category (Motzer et al, 2002). Cytokine therapy had been administered previously to five patients, and most patients (14 of 16 patients) had undergone previous nephrectomy. All patients except two had clear cell histology and all patients except one had documented disease progression at the time of study entry. The patient who did not have evidence of radiological progression at the time of study entry had multiple lung metastases requiring first line systemic treatment.

In phase I, no unexpected toxicities were seen in the three patients treated with sorafenib 400 mg bd and infliximab 5 mg kg\(^{-1}\); the next cohort of three patients was, therefore, dosed...
at sorafenib 400 mg bd and infliximab 10 mg kg⁻¹. One patient at
this dose level developed grade three fatigue and grade 3 rash and
the other two experienced grade 3 hand–foot–skin reaction. All of
these toxicities were considered attributable to sorafenib rather
than the combination of agents, and as a consequence these doses
were selected for further evaluation in the phase II part of the
study given our desire in the expansion to further evaluate the
efficacy and toxicity of infliximab and sorafenib at the recom-
ended therapeutic doses of both agents in RCC.

For the analysis of efficacy, data from the three patients dosed at
sorafenib 400 mg bd and infliximab 10 mg kg⁻¹ in phase I were
combined with data from the 10 patients treated in phase II. Four of
the 13 patients were PFS₆ (31%); an interim efficacy analysis was
performed and the trial was closed at this point
because the pre-specified target of ≥10 of 18 patients achieving
PFS₆ in stage one was not attainable. One patient achieved a partial
response, two patients had progressive disease and the remaining
10 patients had stable disease as their best response to treatment.
The Kaplan–Meier median PFS (Figure 1A) for all 16 patients from
phase 1 and 2 was 6 months (95% confidence interval 4.8–7.2
months) and the Kaplan–Meier median overall survival
(Figure 1B) for all patients was 14 months (95% confidence
interval 10–19 months).

One patient in phase I and three patients in phase II stopped
study treatment because of adverse reactions and two patients
remained on study treatment at the time of the last follow-up. Of
the four patients who stopped because of the adverse reactions,
two did so because of the serious infections, one because of allergic
reaction and one because of the development of multiple toxicities
that included hand–foot syndrome, fatigue and mucositis. All
other patients discontinued treatment because of the progressive
disease. Adverse events for all patients are summarised in Table 2.
There were no grade 4 adverse events and no treatment-related
deaths. Grade 3 adverse events were experienced by 13 of 16
patients and the three remaining patients all reported grade 2
adverse events. The most common grade 3 adverse events were
hand–foot syndrome (31%), rash (25%), fatigue (19%) and
infection (19%). The most frequent adverse events of any grade
were rash (88%), lymphopaenia (81%), diarrhoea (81%), alopecia
(75%) and hand–foot syndrome (75%). Serious haematological
toxicity was uncommon. Serious infection occurred in two
patients; both developed infections within primary renal tumours
and the surrounding renal parenchyma with associated abscess
formation. Allergic reactions were reported in two patients; one to
infliximab and one to sorafenib. Of 16 patients, 5 experienced dose
delays of infliximab and 13 had delays of sorafenib. A total of
12 patients had a reduction in sorafenib dose to once daily and,
of these, three had a further reduction to once every 2 days.

Table 2  Treatment-related adverse events (worst grades, all patients)

| Adverse event         | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Any Grade |
|-----------------------|---------|---------|---------|---------|-----------|
|                       | n   | (%) | n   | (%) | n   | (%) | n   | (%) | n   | (%) |
| Rash                  | 5   | 31  | 5   | 31  | 4   | 25  | —   | —   | 14  | 88  |
| Lymphopaenia          | 12  | 75  | —   | —   | 1   | 6   | —   | —   | 13  | 81  |
| Diarrhoea             | 10  | 62  | 2   | 12  | 1   | 6   | —   | —   | 12  | 75  |
| Alopecia              | 10  | 62  | 2   | 12  | —   | —   | —   | —   | 12  | 75  |
| Hand–foot reaction    | 3   | 19  | 4   | 12  | 5   | 31  | —   | —   | 12  | 75  |
| Anaemia               | 8   | 50  | 2   | 12  | 1   | 6   | —   | —   | 11  | 69  |
| Fatigue/lethargy      | 4   | 25  | 3   | 19  | 3   | 19  | —   | —   | 10  | 62  |
| Stomatitis/mucositis  | 6   | 37  | 3   | 19  | —   | —   | —   | —   | 9   | 56  |
| Infection             | 3   | 19  | 2   | 12  | 2   | 12  | —   | —   | 7   | 44  |
| Dyspnoea              | 6   | 37  | 1   | 6   | —   | —   | —   | —   | 7   | 44  |
| Nausea/vomiting       | 4   | 25  | 1   | 6   | 1   | 6   | —   | —   | 6   | 37  |
| Flushing              | 5   | 31  | —   | —   | 1   | 6   | —   | —   | 6   | 37  |
| Anorexia              | 4   | 25  | 1   | 6   | —   | —   | —   | —   | 5   | 31  |
| Constipation          | 3   | 19  | 1   | 6   | —   | —   | —   | —   | 4   | 25  |
| Leucopaenia           | 2   | 12  | 1   | 6   | 1   | 6   | —   | —   | 4   | 25  |
| Thrombocytopenia      | 4   | 25  | —   | —   | —   | —   | —   | —   | 4   | 25  |
| Hypertension          | —   | —   | 3   | 19  | 1   | 6   | —   | —   | 4   | 25  |
| Neutropaenia          | 1   | 6   | 1   | 6   | —   | —   | —   | —   | 2   | 12  |
| Other                 | 7   | 44  | 2   | 12  | 7   | 44  | —   | —   | 16  | 100 |

Figure 1  Kaplan–Meier plots of (A) progression-free survival (PFS) and
(B) overall survival (OS).
None of the patients had a reduction in infliximab dose. We did not observe a reduction of potentially TNF-α mediated constitutional symptoms, such as anorexia or lethargy.

**DISCUSSION**

We investigated the safety and efficacy of combining sorafenib with infliximab for the treatment of advanced RCC. To our knowledge, this is the first report of the combination of a multi-targeted kinase inhibitor with anti-TNF-α therapy in humans.

We evaluated a dose of sorafenib 400 mg twice daily and infliximab 10 mg kg⁻¹ every 4 weeks. Only four of 13 patients (31%) treated with this combination were free from progression 6 months after commencing treatment; this is lower than would be predicted with sorafenib alone. We enrolled a mixture of patients who were naive to systemic treatment and others who had progressed after immunotherapy. The activity of sorafenib in these settings may be regarded similar. In a randomised phase II trial of 189 previously untreated patients, the median PFS on sorafenib was 5.7 months with an estimated PFS6 47% (Escudier et al, 2009) and in a phase III trial of 903 previously treated patients (83% with cytokines), the median PFS on sorafenib was 5.5 months and estimated PFS6 43% (Escudier et al, 2007).

The lack of efficacy for the combination of sorafenib and infliximab cannot be explained by baseline patient factors given that the study population consisted mainly of patients of low or intermediate Memorial Sloan-Kettering Cancer Centre risk. Two patients had not undergone previous nephrectomy. In this study there was a considerably higher rate of sorafenib dose reductions, delays and treatment discontinuation in comparison with rates reported in the literature for sorafenib alone (Escudier et al, 2007, 2009). We observed a discontinuation rate because of the adverse reactions of 25%, a dose reduction rate for sorafenib of 75% and a dose interruption rate for sorafenib of 81%. In comparison, in the target study (Escudier et al, 2007) discontinuation and dose reduction rates were 10 and 13%, respectively, with dose interruptions in 21%. It is possible that the lower dose intensity of sorafenib treatment in our study due to these dose adjustments contributed to reduced efficacy, particularly as a dose-dependent increase in efficacy of sorafenib has been reported (Amato et al, 2007; Escudier et al, 2009).

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