CASE REPORT

Reproducible complete remission of advanced hepatocellular carcinoma with sorafenib in combination with clopidogrel

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SUMMARY

We present a 57-year-old Caucasian man with hepatocellular carcinoma (HCC) twice achieving complete remission with reduced dose sorafenib. His initial diagnosis of HCC rapidly improved with sorafenib and he achieved a complete biochemical and radiographic response within 7 months. Remission lasted only 5 months but we noted that the timing of his relapse was immediately after he incidentally discontinued clopidogrel. It was restarted and within 5 months of restarting clopidogrel he once again achieved complete remission. The course of his remission was followed and temporal association of sorafenib remission with use of clopidogrel was observed.

BACKGROUND

Only a handful of advanced hepatocellular carcinoma (HCC) cases worldwide were reported as complete responders to treatment with sorafenib. Clinical response after short-term treatment (less than 3 months) is extremely rare and is usually only partial.¹ Reduced dose sorafenib results in complete remission but only after a prolonged treatment period (over 8 months).² Outside of Japan, which reported 15 cases, complete remission with sorafenib monotherapy is a rare event.³

Sorafenib is an oral multikinase inhibitor used in the treatment of advanced HCC. In vitro and animal studies show that it causes interruption of multiple molecular pathways that suppress angiogenesis and lymphangiogenesis. It targets the VEGF (vascular endothelial growth factor) pathway via VEGF receptors 1, 2 and 3, which also belong to the PDGF (platelet-derived growth factor) receptor subfamily of receptor tyrosine kinases. Raf signalling is modified via the RAS/RAF/MEK or MAPK (mitogen-activated protein kinase formerly known as ERK (extracellular signal-regulated kinase)) pathway, which regulate translation and transcription. New vessel proliferation and tumour growth is suppressed and apoptosis or cell death increased.^{1–4} Sorafenib was approved by the Food and Drug Administration in the USA after two phase III randomised placebo-controlled studies showed an improvement in overall survival.^{5–6}

Clopidogrel (Plavix) is an oral antiplatelet that binds to ADP receptors found on platelets. One of these ADP receptors is P2Y₁₂ (a purinergic receptor)^{2–3} that, when bound, inhibits the glycoprotein IIb/IIIa pathway. Glycoprotein IIb/IIIa (also known as integrin α IIb β 3), is the most abundant receptor

on the platelet wall and helps to bind von Willebrand factor, fibrinogen, fibronectin, thrombospondin (TSP) and vitronectin. On binding it undergoes conformational changes, and increases platelet aggregation and adhesion.⁷

Besides maintaining haemostasis and promotion of thrombosis, there is growing evidence that platelets promote tumour growth, metastasis and angiogenesis. Reiss *et al* in 1872 first described a relationship between thrombocytosis and cancer but it was Gasic *et al* in 1968 who associated platelet number to increased metastatic potential.⁸ Marked thrombocytosis in patients with cancer is associated with poor survival.^{8–10} The exact mechanism is unclear.

CASE PRESENTATION

A 57-year-old man with a history of alcohol-related liver cirrhosis was incidentally found in May of 2011 with a hypervascular lesion in his right hepatic lobe while undergoing screening for orthotopic liver transplantation. Family history revealed that his father died of lung cancer and his mother is a lymphoma survivor at age 82. He is an ex-heavy smoker and drank heavily for 11 years until he developed cirrhosis. At age 33 he underwent a two-vessel bypass operation after suffering an acute myocardial infarction. Recently, he underwent coronary heart surgery and stenting and was started on the antiplatelet agent clopidogrel (Plavix). Owing to an increased bleeding risk from clopidogrel, he was ineligible for liver resection, radiofrequency ablation or transarterial chemoembolisation. He had an unremarkable physical examination.

INVESTIGATIONS

Baseline CT scans in August of 2011 showed an extremely cirrhotic liver with broad areas of confluent fibrosis, a 2.1×2.5 cm hypervascular lesion in segment 6 of his liver, plus a partially occlusive thrombus in the ventral aspect of the main portal vein (figure 1). His lesion was radiographically compatible with HCC and his initial α -fetoprotein (AFP) level was elevated at 148 ng/mL.

TREATMENT

We began sorafenib at 200 mg daily in November of 2011 but due to low platelet counts (range 60 000–90 000/mm³) used a reduced oral dose of 200 mg twice daily. Concurrent clopidogrel at a dose of 75 mg daily was started in October 2011 after he underwent a cardiac stenting procedure.

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Figure 1 Baseline scan. Hyperenhancing lesion in segment 6. Prior to sorafenib.

He was advised to stay on Clopidogrel for 12 months, however, he discontinued this at close to 10 months.

He was also continuously on baby aspirin at 81 mg daily from May 2011 to February 2014.

All three drugs (baby aspirin, clopidogrel and sorafenib) were continued until October 2012.

Clopidogrel was stopped after 10 months per cardiologist's recommendations.

Sorafenib was also briefly discontinued in November of 2013 due to issues with blood pressure control but restarted in December of 2013 at 200 mg per orally twice daily.

Clopidogrel 75 mg daily was restarted in May of 2013 when AFP indicated relapse (AFP=466 ng/mL) despite 5 months on sorafenib. At this point he was back on all three drugs (baby aspirin, clopidogrel and reduced dose sorafenib).

OUTCOME AND FOLLOW-UP

Sorafenib was started at 200 mg twice daily on 8 November 2011. The patient's baseline AFP level was 2254 ng/mL. He was already on 81 mg baby aspirin plus 75 mg of clopidogrel daily. Five days later, his AFP level was noted to rapidly rise to 3547 ng/mL. At week 7 his AFP level peaked to 7646 ng/mL and a CT scan was recommended; however, due to personal scheduling delays he was not scanned until week 8 (early January 2012). Images showed mixed findings with interval decrease in lesion hypervascularity while noting a new adjacent hypervascular lesion and increasing aortocaval and retrocaval lymph node size (figure 2). A left adrenal gland lesion increased in size and new bilateral lower lobe pulmonary nodules were suspicious for metastases. His AFP level at this time was already decreasing (AFP 3914 ng/mL). Owing to the mixed CT scan findings, declining AFP levels and his asymptomatic state, sorafenib was continued.

At week 12 (February 2012), CT scans showed no hypervascular lesions and no distant metastases and the patient's AFP dropped to 3914 ng/mL. By week 15 (23 February 2012) his AFP was down to 335 ng/mL, dropping further to 27 ng/mL on week 19 (22 March 2012) and CT scans showed no lung or hyperenhancing liver lesions (figure 3). By week 22 (12 April 2012) AFP levels had normalised to 7.8 ng/mL.

At week 29 (June 2012) follow-up the patient's AFP levels reached a nadir at 1.9 ng/mL and were still normal with an AFP level of 2.6 ng/mL in week 42 (September 2012). Radiographic

Figure 2 Eight weeks after starting sorafenib. Decrease in hypervascularity of original lesion. New adjacent hyperenhancing lesions.

first complete remission was achieved in less than 15 weeks and significant biochemical remission within 19 weeks.

At 51 weeks (31 October 2012), CT scans showed a new heterogeneous wedge-shaped hypodensity in the right hepatic lobe but normal AFP levels (5.8 ng/mL; figure 4). Sorafenib continued at the same 200 mg twice daily dose but AFP levels steadily rose to 16 ng/mL in December 2012 and continued to climb to 466 ng/mL in May 2013. It was felt that he was losing response to sorafenib.

The patient's medication list was reviewed at this time and it was noted that he had stopped his clopidogrel shortly before the rise in AFP (sometime in October 2012). He retained an extra medication bottle at home, which he was asked to consume at the same daily dose of 75 mg of clopidogrel. He maintained his excellent asymptomatic performance status, hence was allowed to continue sorafenib at 200 mg twice daily. One month after restarting clopidogrel his AFP levels again rose to 1129 ng/mL (June 2013). CT scans showed no change other than the wedge-shaped lesion with no suspicious areas of hypervascularity and he remained symptom free, hence we made no changes to his medication.

AFP peaked at 2342 ng/mL in August of 2013 and he was told to discontinue sorafenib. This was followed by a sharp decline in AFP to 487 ng/mL (3 September 2013), hence

Figure 3 Twelve weeks on sorafenib. Disappearance of hyperenhancing lesions.

Figure 4 New wedge-shaped heterogeneous areas. Followed by rising α -fetoprotein levels. Week 51.

sorafenib was resumed and AFP levels normalised to 5 ng/mL on 31 October 2013.

CT scans in December 2013 showed no hyperenhancing lesions (figure 5).

During his last check-up on February 2014 he was asymptomatic with a normal AFP level of 3.3 ng/mL. He has resumed sorafenib and remains in remission at the time of writing.

DISCUSSION

When HCC is treated with sorafenib, only a handful of cases achieve a complete response and rapid response is rare.^{1 2 4 10–14} Complete responses while on the full dose of sorafenib at 400 mg orally twice daily was seen as early as 4 months and as long as 6 months of treatment.^{10–14} Reduced dose sorafenib given at 200 mg orally twice daily produced a complete remission at 6 months.¹² Our patient showed a rapid biochemical response after only 4 months of reduced dose sorafenib. Rapid regression after short-term treatment has been previously reported, but clinical remission was short lived.¹⁴

Platelets are the source of >80% of the body's VEGF. Glycoprotein IIb/IIIa receptors activate platelets to release microparticles, factors and proteolytic enzymes, which increase cancer growth and invasiveness. Platelets also express platelet factor-4, TSP and endostatin, which inhibit angiogenesis and maintain cell homeostasis in the absence of malignancy. Tumours stimulate megakaryocyte growth to produce more platelets. Platelet clumps cloak tumour cells and protect them from natural killer cell activity, form platelet-tumour emboli and promote tumour spread.^{8–10 15 16}

Figure 5 December 2013 follow-up scans. No lesions. Normal α -fetoprotein.

Aspirin, another antiplatelet drug, inhibits metastasis in sarcoma and HCC laboratory models.^{17 18} Administration of clopidogrel in combination with cisplatin increases tumour cytotoxicity in breast cancer cell lines as well as in murine syngeneic breast cancer in vivo models. Clopidogrel inhibits P2Y12 receptors, which slows the PI3K-pAKT-mTOR pathway downstream, leading to upregulation of caspase-dependent apoptosis.¹⁹

HCC develops frequently from alcohol and hepatitis B/C-induced chronic liver inflammation and damage. In hepatitis B, activated platelets increase specific cytotoxic CD8 cells that produce inflammatory cytokines to combat the infection, but if unsuccessful they damage the remaining liver tissue. This repeated damage to the liver cells results in scarring and fibrosis. Hepatocytes lose their viral antigens, becoming unrecognisable by CD8 T cells, then develop cirrhosis and carcinoma.²⁰ Antiplatelet drugs will decrease platelet activation, decrease hepatitis B virus-specific CD8 cells, and thus block carcinoma formation. Antiplatelet therapy, however, was ineffective in mouse hepatoma models that do not have an inflammatory infiltrate.^{20–23} The use of this approach in combination with VEGF-directed targeted therapy could be synergistic.

This is the first case, to my knowledge, wherein a patient with advanced HCC achieved a complete biochemical and radiographic response at 4 months while on a reduced dose of sorafenib. He had initial worsening biochemical parameters prior to rapid improvement. Subsequent relapse on sorafenib coincided with withdrawal of clopidogrel. The patient regained remission by reintroduction of clopidogrel.

The temporal relationship seen with the discontinuation of and reinitiation of the antiplatelet clopidogrel in combination with sorafenib is interesting. Note that he was also on aspirin during that entire time but this was never discontinued.

HCC treated with sorafenib can result in a speedy complete remission even with reduced dosing. The reproducible rapid remission with the addition of clopidogrel suggests a synergistic effect between the three drugs.

Learning points

- Biochemical worsening (rising α -fetoprotein) may occur prior to complete remission and indicates tumour flare or necrosis rather than disease progression.
- A clinical picture of good performance status is a good gauge of disease stability in the event of worsening biochemical parameters.
- There is a possible synergy between sorafenib and antiplatelet therapy, specifically P2Y12 inhibitor clopidogrel and aspirin, in the treatment of hepatocellular carcinoma, which merits further corroboration.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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