CASE REPORT

Complete radiographic remission with 5-fluorouracil and leucovorin after sorafenib failure in hepatocellular carcinoma: Is there a role for chemotherapy after targeted agents?

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SUMMARY

A 57-year-old Caucasian man with a history of Child's class A hepatitis C, cirrhosis and progressive multifocal hepatocellular carcinoma was treated with sorafenib but progressed after 7 months of stable disease. At progression he was given salvage chemotherapy consisting of 5-fluorouracil and leucovorin and went into complete radiographic remission after 12 cycles of treatment. He did develop a portal vein thrombosis but nevertheless his hepatic lesions continued to resolve. Throughout his therapy α -fetoprotein (AFP) levels decreased only minimally. He did not seek retreatment after 14 cycles of chemotherapy and presented 3 months later with relapsed disease on CT scans with markedly elevated AFP levels. He received one more chemotherapy cycle but was unable to tolerate further treatment, succumbing to his disease 3 months thereafter, and a total of 29 months after he was deemed a sorafenib failure.

BACKGROUND

The response rate of hepatocellular carcinoma to conventional 5-fluorouracil (5FU)-based chemotherapy has been traditionally marginal with few partial responders and stable disease at best. This is a case report of a patient progressing on sorafenib who subsequently experienced a significant radiographic response to salvage 5FU and leucovorin (LV). Sequential chemotherapy after tyrosine kinase inhibitor therapy may have a significant clinical effect and should merit further investigation.

CASE PRESENTATION

A 58-year-old Caucasian man with a history of Child's class A hepatitis C, cirrhosis and substance misuse was referred to the oncology clinic by our liver team for consideration of systemic chemotherapy. When he consulted us in April 2008 he had multiple hyperenhancing bilobar lesions on a triple-phase CT scan with at least six lesions measuring from 6 to 12 mm in diameter. He was originally diagnosed on 30 November 2006 with a 17×17 mm hyperenhancing right hepatic lesion which by appearance was consistent with hepatocellular carcinoma. For this he was treated with radio-frequency ablation (RFA) using a 3.5 cm LeVeen probe up to 120 W with good resolution of hyperenhancement. The procedure was preceded by a needle biopsy which confirmed the diagnosis of a

moderately differentiated hepatocellular carcinoma. He was followed closely over a year by the liver surgery team but developed rapidly enlarging multifocal disease which was documented on his subsequent March and April 2008 CT scans. At the time he was beyond Milan criteria and had poor family support plus active substance misuse and housing issues hence was no longer a candidate for liver transplantation, RFA or transarterial chemoembolisation. His case was discussed at our monthly liver multidisciplinary board and a recommendation was made to refer him to the oncology service for initiation of sorafenib. His baseline scan on 11 April 2008 showed multiple hyperenhancing hepatic lesions (at least 6) ranging from 6 to 14 mm in both lobes. He tolerated this oral treatment well and aside from occasional abdominal cramping he had no significant side effects. Imaging studies documented stable disease after 2 months of therapy but at 7 months showed tumour progression with a 31% increase in size by RECIST 1.1 criteria. His α -fetoprotein (AFP) level at this presentation was 1624.7 ng/mL. Total bilirubin was 0.5 mg/dL, aspartate aminotransferase (AST) 111 IU/L, alanine transaminase (ALT) 194 IU/L and alkaline phosphatase 48 IU/L. He was then given the option of supportive care only but he insisted on more treatment. Other than occasional abdominal pain which was controlled on a low dose of slow release morphine 40 mg orally twice daily plus breakthrough oxycodone 5 mg q6h prn, he was asymptomatic and had lost little of his baseline weight. Owing to his excellent performance status we felt it was reasonable to offer him more chemotherapy knowing that his options were very limited. He signed consent for intravenous 5FU and LV with the understanding that this is not a curative approach and moreover has a historically very low chance of response. On 15 December 2008 he received bolus 5FU at 370 mg/m² plus LV at 500 mg/m² which was administered by intravenous route for 5 consecutive days on a 28-day cycle.

INVESTIGATIONS

30 November 2006: The liver biopsy was positive for moderately differentiated hepatocellular carcinoma.

29 October 2008: The baseline CT scan at initiation of 5FU/LV showing at least six hyperenhancing lesions ranging from 10 to 24 mm in largest dimension (figure 1).

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Figure 1 Baseline scan after sorafenib failure but prior to starting 5-fluorouracil and leucovorin. Multiple hyperenhancing lesions.

Figure 3 After eight cycles of chemotherapy—significant improvement and resolution of previously hyperenhancing multiple hepatic lesions. Focal clot noted in the portal vein.

2 March 2009 and 28 May 2009 (after 3 and 4 cycles) stable disease SD by RECIST 1.1 criteria.

23 July 2009: After six cycles of 5FU LV chemotherapy—very mildly increased size of hyperenhancing hepatic lesions (figure 2).

17 November 2009: After eight cycles chemotherapy—significant improvement (over 50% shrinkage) and resolution of previously hyperenhancing multiple hepatic lesions. New focal clot noted in the portal vein. Non-complete partial response of target lesions by RECIST 1.1 criteria (figure 3).

Three-month chemotherapy break: November 2009 until January 2010 during which time dalteparin was started.

24 May 2010 CT scans: after 10 total cycles of chemotherapy near-complete resolution of previously hyperenhancing multiple hepatic lesions. Largest lesion remains in the dome of the liver at 22 mm. Focal clot noted in the portal vein. Two other ill-defined hypodense lesions in the posterior right hepatic lobe were consistent with treated lesions. Persistent right portal vein thrombosis (figure 4).

A positron emission tomography (PET) CT scan (6 August 2010) after 14 cycles showed no abnormal focal metabolic uptake in the liver parenchyma as compared to the one taken in

November 2009. He did have intense metabolic uptake conforming to the course of the posterior right portal vein.

TREATMENT

RFA was performed using a 3.5 cm LeVeen probe during the initial access. Starting at 50 W going up to 120 W, ablation of the 2 cm lesion in segment 5 of the liver was accomplished.

Sorafenib 400 mg was administered orally twice a day for 6 months (April–October 2008).

On sorafenib failure, he then received salvage chemotherapy with bolus 5FU at 370 mg/m² plus LV at 500 mg/m² intravenously for 5 consecutive days using a 28-day cycle which began on 15 December 2008.

OUTCOME AND FOLLOW-UP

After two cycles (March 2009) of 5FU-based chemotherapy he maintained his weight (losing only 3 lbs) and had less abdominal pain but his AFA had risen to 2254 ng/mL. Total bilirubin was 0.8 mg/dL, AST 78 IU/L, ALT 85 IU/L and alkaline phosphatase 39 IU/L. CT scans show that the target lesions have remained stable by RECIST 1.1 criteria. By cycle 5, his AFP finally peaked

Figure 2 After cycle 6 of 5-fluorouracil and leucovorin. Persistent but stable hypervascular liver lesions, with some slightly increased in size.

Figure 4 Sixteen months after starting on chemotherapy. Still with no hyperenhancement but persistent portal vein clot.

at 2787 ng/mL and then dropped to 1133 ng/mL on 6 July 2009 which was after cycle 6. Liver function testing remained within normal with total bilirubin 0.6 mg/dL, AST 116 IU/L, ALT 137 IU/L and alkaline phosphatase 61 IU/L, and he remained symptom free. Repeat CT scan on 23 July 2009 after cycle 6 still showed persistent but stable hypervascular liver lesions (figure 2). At this point we felt he had reached maximal response hence he was given a break from chemotherapy.

After 7 weeks (24 August 2009) on routine follow-up, his AFP rose again to 4051 ng/mL with liver function testing showing total bilirubin 0.4, AST 160, ALT 183 and alkaline phosphatase 60 IU/L. Physical examination was unremarkable and his weight remained steady at 160 lbs. Despite the AFP fluctuations, he was asymptomatic with good quality of life. He continued to volunteer and go about town independently.

Because he maintained his performance status but had rapidly rising AFP levels we restarted chemotherapy again on 14 September 2009.

By October 2009 he had received eight cumulative cycles and his AFP began to decline again, this time to 3107 ng/mL with CT scans showing evidence of many completely resolving hepatic lesions but now he was developing a new main portal vein thrombus extending into the right portal vein branches with areas of hypodensity in the right liver lobes consistent with areas of thrombosis (figure 3). For this reason chemotherapy was held and dalteparin anticoagulation was started at 200 IU/kg body weight subcutaneously daily was started followed by 150 IU/kg maintenance dose.

Chemotherapy was resumed in January 2010 after a 3-month break. AFP further dropped to 2380 ng/mL (March 2010). He thereafter continued to regularly receive his chemotherapy cycles without much incident other than post-treatment fatigue and by 24 May 2010 he received a total of 12 cycles of 5FU/LV chemotherapy. CT scans showed no visible hypervascular lesions in spite of a persistent portal vein thrombosis (figure 4).

On 7 June 2010 there was another upward fluctuation of AFP to 3661 ng/mL with no significant change in physical or subjective findings.

After 14 total cycles, in August 2010, chemotherapy was stopped. His weight had dropped by 5–15 lbs and he still had right upper quadrant abdominal pain which was reasonably controlled by opiate medication. His AFP was now 2433 ng/mL. Throughout most of his later clinical course, his AFP levels fluctuated within the 1500–4000 ng/mL range. Levels continued to decline without chemotherapy to 1635 ng/mL in October 2010. Follow-up sonogram showed no hepatic lesions, but a persistent thrombus in the right portal vein.

A PET CT scan at this time revealed no abnormal focal metabolic uptake in the liver parenchyma. Persistent intense metabolic uptake conforming to the course of the posterior right portal vein was still visible.

He was lost to follow-up for another 3 months, returning to my clinic 3 months later in January 2011 with renewed abdominal pain and a significantly elevated AFP of 25 686 ng/mL. CT scans confirmed recurrent areas of hyperenhancement and hypervascularity as well as further progression of the right portal vein thrombus.

He received one more cycle of 5FU and LV, after which he was taken off chemotherapy due to declining performance status and succumbed to his disease after 3 months in May 2011.

DISCUSSION

Little data exist on treatment alternatives after sorafenib failures in hepatocellular carcinoma. Conventional chemotherapy is

rarely utilised due to historically low response rates. This is a unique case because stable disease was achieved after only six cycles of chemotherapy with 12 months later achieving near complete-radiographic remission and an overall survival (OS) of 31 months after starting 5FU and LV. Of these 31 months 24 months were in good performance status. However, his disease-free survival after cessation of chemotherapy was only 5 months, nevertheless unexpected with 5FU-based chemotherapy even as first line.

His quality of life was maintained for 2 years while he remained on palliative chemotherapy, during which he was fully able to continue his volunteer work and live independently, reporting only chronic fatigue. After chemotherapy ceased, the disease accelerated within 6 months, resulting in his quick deterioration and eventual demise on May 2011, 29 months from the day he was deemed a sorafenib failure.

Sorafenib (Nexavar) is an inhibitor of several receptor tyrosine kinases such as vascular endothelial growth factor 2 (VEGFR2), platelet-derived growth factor receptor (PDGFR), FLT3, Ret and c-Kit. It also inhibits Raf kinase as well as angiogenesis and signalling through the RAF/mitogen-activated protein/(MEK)/extracellular signal-regulated kinase (ERK) cascade. These all play important roles in hepatocellular carcinoma development.¹

Kim *et al*² described the use of sorafenib after failure of systemic chemotherapy, specifically fluoropyrimidine plus platinum in which modest efficacy and tolerability were reported, among which 58% had stable disease, with a progression-free survival of 2.3 months and OS of 7.1 months in a series of 24 patients.

There has been no published report on effective systemic chemotherapy after sorafenib failure in hepatocellular carcinoma.

The only known salvage therapy with some efficacy is hepatic intra-arterial chemotherapy.

Cetuximab in combination with cisplatin and 5FU has resulted in partial to stable disease in 10 of 12 patients.³

Learning points

- ▶ This is a case of a significant response to conventional chemotherapy after sorafenib failure in a patient with hepatocellular carcinoma.
- ▶ In the presence of portal vein thrombosis, elevated α -fetoprotein levels are expected hence cannot always be used to predict the degree of radiological tumour shrinkage.
- ▶ Salvage with 5-fluorouracil-based chemotherapy after sorafenib failure may result in significant survival benefit as well as improvement of quality of life in selected patients with very good performance status.
- ▶ Prediction of response factors to chemotherapy as well as the use of chemotherapy sequentially or in conjunction with targeted therapies merits further investigation.⁴

Competing interests None.

Patient consent Not obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Liu L, Cao Y, Chen C, *et al*. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. *Cancer Res* 2006;66:11851.

- 2 Kim JW, Lee JO, Han SW, *et al.* Clinical outcomes of sorafenib treatment in patients with metastatic hepatocellular carcinoma who had been previously treated with fluoropyrimidine plus platinum-based chemotherapy. *Am J Clin Oncol* 2011;34:125–9.
- 3 Poggi G, Montagna B, Melchiorre F, *et al.* Hepatic intra-arterial cetuximab in combination with 5-fluorouracil and cisplatin as salvage treatment for sorafenib-refractory hepatocellular carcinoma. *Anticancer Res* 2011; 31:3927–33.
- 4 Boschetti G, Walter T, Hervieu V, *et al.* Complete response of hepatocellular carcinoma with systemic combination chemotherapy: not to get out the chemotherapy? *Eur J Gastroenterol Hepatol* 2010;22:1015–18.

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