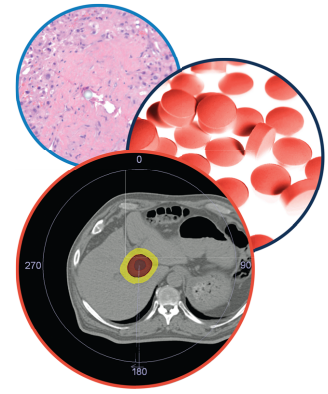
Case Series



Hepatic Oncology

Long-lasting remission in a metastatic hepatocellular carcinoma patient after combined regorafenib therapy and surgery

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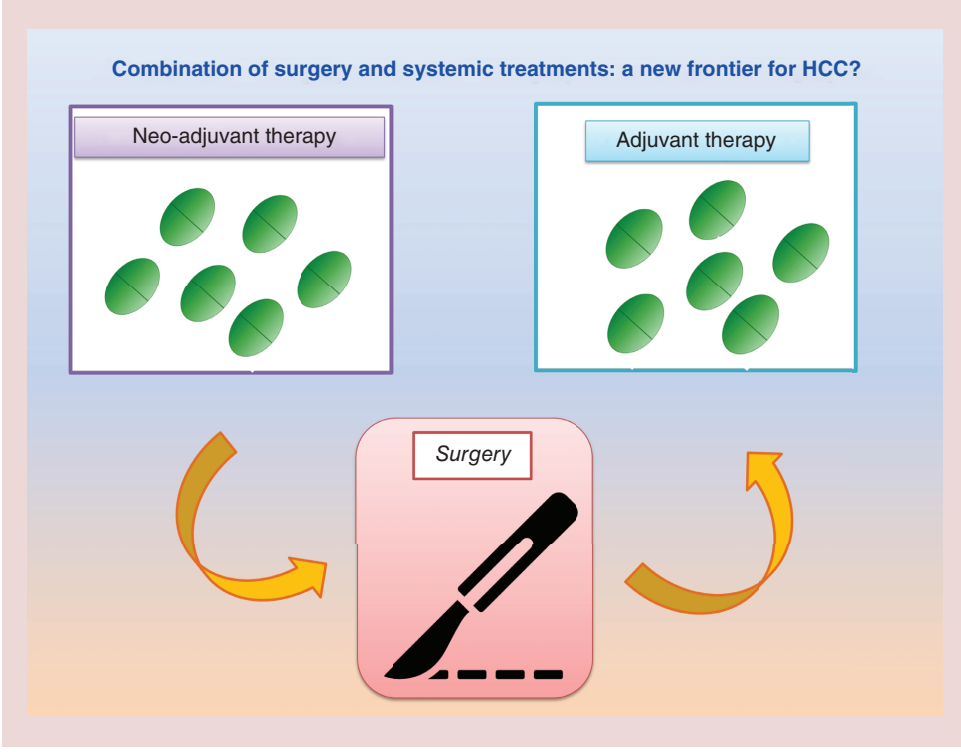
Aims: The therapeutic scenario of systemic treatments for hepatocellular carcinoma (HCC) is rapidly changing. There is much interest in the possibility of combining new therapies with surgery, but clinical data is lacking. We aimed to provide an example of such integration. **Patients & methods:** We report a patient with metastatic HCC who received regorafenib in the setting of the RESORCE trial. **Results:** A brilliant response led to a tumor downstaging and a subsequent adrenal metastasectomy with radical intent. **Conclusions:** New agents will change the therapeutic perspectives in advanced HCC and lead to a higher rate of objective responses, with possibilities of associating systemic therapy and surgery. Thus, the management of HCC will require more and more of an integrated, multidisciplinary and personalized approach.

Graphical abstract:



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Future Medicine

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death in the world [1]. Its incidence is increasing further due to the worldwide epidemic of nonalcoholic steatohepatitis [1]. Despite the availability of multiple treatment modalities, the prognosis of HCC remains poor. In particular, the median overall survival in the advanced stage is about 10–12 months in patients receiving sorafenib, a multitarget tyrosine kinase inhibitor available since 2008 [2,3]. This scenario will improve with the availability of the combination of the immune checkpoint inhibitor atezolizumab plus the anti-VEGF agent bevacizumab, whose combination significantly outperformed sorafenib in a recent trial [4]. Additionally, the availability of new anti-angiogenic agents, such as lenvatinib (in the frontline setting), regorafenib, cabozantinib and ramucirumab (in the second-line setting) will further ameliorate the prognosis of advanced HCC [5].

The possibility of combining these new therapies with surgery or with locoregional treatments is intriguing, as it could theoretically provide better outcomes. This hypothesis has not yet been evaluated in clinical trials since the approval process of the leading regulatory agencies for these new drugs is either very recent or still ongoing.

We report a case illustrating an objective response to regorafenib, leading to a tumor downstaging with the subsequent possibility of achieving an oncological radicality through an adrenal metastasectomy. The patient provided a written informed consent to report his medical history anonymously.

Case description

In September 2012, a 64-year-old overweight Caucasian male (BMI: 27 kg/m^2), affected by Type 2 diabetes underwent routine laboratory tests. Increased values of γ-glutamyl transpeptidase and alkaline phosphatase were found, prompting an imaging evaluation. Both sonography and computed tomography detected two focal liver lesions highly suspicious for malignancy. He underwent a bisegmental liver resection, receiving a diagnosis of poorly differentiated HCC (grade 3 according to Edmondson) on a precirrhotic nonalcoholic steatohepatitis. In the following 2 years, multiple intrahepatic recurrences were treated with percutaneous ablation therapies (radiofrequency ablation on three occurrences, percutaneous ethanol injection in a single occurrence). Also, right adrenalectomy was performed to treat a localized extrahepatic spread. Sorafenib was started in February 2015, following a contralateral adrenal spread that was judged as not suitable for resection at that stage (Figure 1A). A full dose of 800 mg/day was prescribed, but a permanent reduction to 400 mg/day was necessary to manage drug-related adverse events (diarrhea grade 3, weight loss grade 2 and symptomatic hypophosphatemia grade 2). Six months after the beginning of sorafenib, progressive disease was documented, with both a dimensional increase of the existing adrenal lesion (from 30 to 45 mm) and evidence of multiple new lung lesions (Figure 1B). A parallel increase of AFP was registered (from 1967 to 52,652 ng/ml).

In September 2015, the patient was, therefore, sent to our attention for possible enrollment in a second-line clinical trial. He was screened and enrolled in the RESORCE study, a Phase III randomized clinical trial evaluating the efficacy of regorafenib versus placebo in patients who had progressed to sorafenib [6]. At the baseline, the adrenal lesion (56 mm) and the largest lung lesion (11 mm) were chosen as target lesions. The baseline AFP was 99,587

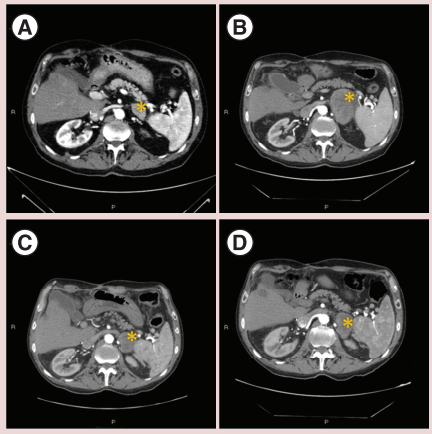

Figure 1. Modifications of the left adrenal lesion during sorafenib and regorafenib sequential treatment. Imaging of the left adrenal metastasis **(A)** at the start of sorafenib; **(B)** after progression to sorafenib and before the start of regorafenib; **(C)** 6 months after the start of regorafenib (best response); **(D)** 9 months after the start of regorafenib (progressive disease).

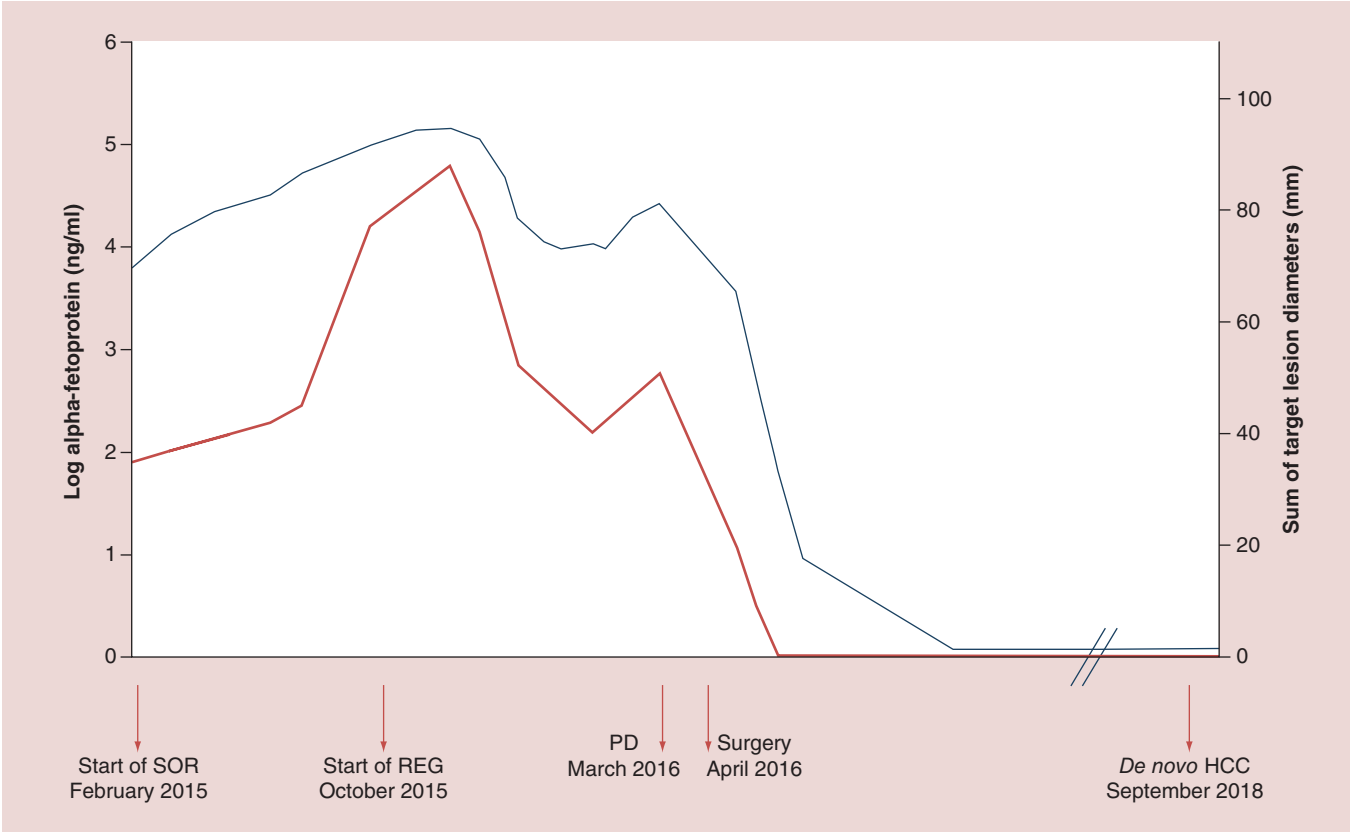

Figure 2. Changes in alpha-fetoprotein levels (reported in log scale – blue) and tumor burden (red) throughout the clinical course of the case. To better reflect the tumor burden in this graph, the second largest lung lesion was considered as a target lesion, even if it measured <10 mm.
HCC: Hepatocellular carcinoma; PD: Progressive disease; REG: Regorafenib; SOR: Sorafenib.

ng/ml. The patient was staged as Barcelona Clinic for Liver Cancer stage C (advanced), with liver function tests entailing a Child–Pugh score A5. The treatment was well tolerated without dose reductions. The first and second follow-up imaging (Figure 1C) showed a dimensional reduction of the adrenal metastasis (down to 40 mm) and complete disappearance of the lung nodules. In parallel, AFP dropped to 18,438 ng/ml.

Unfortunately, a new increase in the adrenal lesion (51 mm) defining progressive disease was documented 9 months after randomization (Figure 1D). AFP also increased to 26,543 ng/ml. As per the protocol procedures, the study drug was permanently stopped. The patient was proposed again for left adrenalectomy. This time, in the setting of a multidisciplinary team, the surgeons agreed after considering the brilliant response to the systemic treatment, the excellent general conditions and the absence of any other therapeutic options. Left adrenalectomy was performed 20 days after the last dose of the study drug without relevant postoperative complications. Hormone replacement therapy was swiftly initiated and titrated. The surgical specimen analysis confirmed an adrenal metastasis of HCC, with microvascular invasion and infiltration of the adrenal capsule. Considering the high risk of recurrence, the patient received off-label adjuvant treatment with metronomic capecitabine. The postoperative thorax-abdominal computed tomography (CT) scan (performed 3 months after surgery) showed no residual malignancy. The complete response was confirmed by the normalization of AFP (2.4 ng/dl) (Figure 2). Randomization to the regorafenib treatment arm was confirmed at the unblinding of the RESORCE trial. There was no recurrence of the treated tumor. A switching of three pre-existing high-grade dysplastic nodules of the liver toward an overt *de novo* HCC was documented 30 months after surgery (September 2018). Due to the impossibility of locoregional treatments, regorafenib was restarted on a compassionate basis. Treatment was continued until June 2019, when the previously excellent conditions of the patients rapidly deteriorated due to progressive disease, leading to his death in July 2019.

Table 1. Previous reports of bilateral adrenalectomy for metastasis of hepatocellular carcinoma following liver-direct treatments.

Study (year)	Age (years)	Sex	Initial treatment	Time to recurrence	Adrenalectomy type	Outcome	Ref.
Morimoto (1999)	65	M	Liver resection	15 months	Two-step	Disease free after 10 months	[13]
Castroagudin (2002)	51	M	OLT	5 months	Two-step	Disease free after 35 months	[14]
Uenishi (2005)	73	M	TACE	10 months	Simultaneous	Death from HCC after 9 months	[15]
Kondo (2008)	58	M	Liver resection	Simultaneous†	Two-step	Disease free after 10 months	[16]
Fujimoto (2016)	59	M	Liver resection	Simultaneous †	Simultaneous	Disease free after 6 months	[17]

†In these cases, the adrenalectomy was performed simultaneously with the liver resection.
HCC: Hepatocellular carcinoma; OLT: Orthotopic liver transplantation; TACE: Transarterial chemoembolization.

Conclusion

We reported a case in which a brilliant response to a systemic treatment paired with the aggressive use of surgery obtained a dramatic change in the prognosis of a HCC patient. Our case illustrates the importance of two different but equally important points.

The first peculiarity of our case was the dramatic tumor response to an oral multitarget tyrosine kinase inhibitors (TKIs), a possibility still considered rare after a 10-year experience with sorafenib. This scenario is poised to change with the advent of the new generation of TKIs and immune checkpoint inhibitors. In the case of regorafenib, its ability to block aggressive tumor pathways such as *AXL* and Ang2 (which are not targeted by sorafenib) can lead to a striking response even in cases of massive HCC [7]. Even more intriguing news came from the Imbrave150 Phase III trial of atezolizumab plus bevacizumab versus sorafenib, where the overall response rate was 27% in the combination treatment arm [4]. Similar response rates (31%) were also reported for a combination of immune checkpoint inhibitors (nivolumab plus ipilimumab) in a second-line setting [8]. As for single-agent immune checkpoint inhibitors, both nivolumab (15%) and pembrolizumab (17%) showed an interesting rate of objective responses, although they failed to demonstrate a survival benefit in comparison with sorafenib in the frontline and placebo in the second-line setting, respectively [9,10]. Indeed, the role of tumor biomarkers will be critical for the proper identification of patients who might benefit from these drugs. In our specific case, somatic next-generation sequencing of the tumor performed right before the start of regorafenib would have brought interesting insights regarding the molecular basis, which led to this brilliant response. Unfortunately, the tumor lesions at that time were not easy to reach for a fresh biopsy. Also, this procedure was not required by the study protocol, and its possible complications would have deprived the patient of the possibility to be included in the trial.

The second peculiarity of our case was the choice of performing surgery in a patient coming from the advanced setting and two previous therapeutic lines. The benefit of an aggressive but potentially curative approach for HCC has been hypothesized and demonstrated in recent times. In particular, Vitale *et al.* reported that resection could result in survival benefit over other therapies for HCC patients regardless of their stage, provided that both liver function and performance status are preserved [11]. Also, according to the guidelines of the European Association for the Study of the Liver, surgical interventions can be extended to nonearly stages of HCC, once effective tumor downstaging is achieved by nonsurgical means [12].

Based on this scientific rationale, an already established partial adrenal failure, and the personal preference of the patient, the multidisciplinary team opted for a surgical intervention that was discarded in a previous stage. Although other cases of bilateral adrenalectomy have been reported after a previous surgical or transarterial treatment of the primary liver tumor (Table 1) [13–17], this was the first case of completion of two-time adrenalectomy following a systemic treatment.

Future perspective

Regorafenib and other agents (such as immune checkpoint inhibitors) will likely change the therapeutic perspectives in advanced HCC. In particular, the possibility to achieve a relatively high rate of objective responses offers ever-increasing possibilities of associating systemic therapy and surgery. The possibility of neoadjuvant treatments is currently being explored in different Phase I and II clinical trials (NCT03222076, NCT03510871, NCT03337841 and NCT03299946). At the same time, our case also demonstrates that the management of HCC requires more and more of an integrated, multidisciplinary and personalized approach in real-life clinical practice.

Summary points

- New systemic drugs are becoming available for hepatocellular carcinoma including multitarget kinase and immune checkpoint inhibitors.
- We report a case of brilliant response to the multitarget kinase inhibitor regorafenib.
- The patient had already undergone a right adrenal metastasectomy and failed sorafenib.
- Thanks to an objective response to regorafenib, the patient achieved tumor downstaging, after a total regression of other metastatic lesions, only a left adrenal lesion remained.
- The patient underwent a left adrenalectomy, remaining disease-free for 30 months.
- We highlight the importance of combining surgical and systemic treatments.
- We analyze the ability of the new systemic drugs to achieve objective responses, adjuvant and neoadjuvant treatments will likely become available in the coming years.

Author contributions

All of the authors equally contributed to description of this case and to the review of the pertinent literature, and approved the final version of this manuscript.

Financial & competing interests disclosure

F Tovoli is a consultant for Bayer; E Goio, L Ielasi, F Benevento and M Renzulli have no conflicts of interest to declare. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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