Complete regression following sorafenib in unresectable, locally advanced hepatocellular carcinoma

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Sorafenib (SO) was the first targeted agent to produce significant improvements in overall survival in patients with advanced hepatocellular carcinoma (HCC). We report the case of a cirrhotic patient with chronic hepatitis C virus infection; locally advanced, unresectable, multinodular HCC, and portal vein tumor thrombosis, who achieved complete tumor regression following SO treatment. The patient was treated with SO 400 mg twice daily, which was subsequently reduced to 200 mg twice daily due to the occurrence of hand–foot skin reaction. The patient also received the following concomitant medications: Synchro-Levels® (Alphrema, Varese, Italy), silymarin and vitamin E. Long-term treatment with reduced SO dosage and Synchro-Levels resulted in a sustained radiological and clinical response with normalization of α-fetoprotein levels. Observed side effects were mostly low grade and manageable following dose adjustments. After 44 months of treatment the patient was in good physical condition, which suggests that a complete response with long-term SO is achievable in patients with locally advanced HCC.

Hepatocellular carcinoma (HCC) is a complex and heterogeneous disease that is the sixth most common solid malignancy and is the third leading cause of cancer-related death worldwide. It is often associated with other chronic liver diseases, such as cirrhosis, and in the majority of patients it is only diagnosed at an advanced stage, resulting in poor prognosis [1,2].

In Phase III trials, sorafenib (SO) has been shown to significantly improve overall survival in patients with unresectable HCC [1,2]. These results led to the recommendation of SO for the first-line treatment of patients with advanced HCC and for patients not suitable for locoregional treatment [3,4]. In the neoadjuvant setting, recent data from a Phase II trial reported that the combination of SO with transarterial chemoembolization and doxorubicin-eluting beads can be an effective and safe therapy [5]. In addition, a Phase III trial evaluating the effects of SO–transarterial chemoembolization in this group of patients is currently ongoing (Eastern Cooperative Oncology Group [ECOG] 1208) [5].

However, the situations and clinical challenges faced in everyday clinical practice differ largely from the experimental conditions applied to clinical trials in order to guarantee their robustness [6]. It has been suggested that observational analyses and case reports can expand upon outcomes of randomized controlled trials, as they may provide important information on long-term effectiveness and safety [6].

In clinical practice, treatment with SO is sometimes discontinued prematurely owing to the onset of adverse events [7]. This approach is, at least partially, in contrast with recent evidence that indicates that the optimal strategy may be to successfully manage side effects and tailor the dosage regimen to the characteristics of the patient, rather than discontinuing treatment at the first signs of intolerance [7,8]. In addition, treatment adherence is a key factor in optimizing responses to therapy and improving clinical outcomes [7].

Synchro-Levels® (Alphrema, Varese, Italy) is a product containing stem cell differentiation stage factors, proposed in 2005 by Livraghi *et al.* [9,10] for patients affected by advanced HCC, and is capable of improving the performance status and tumoral response, with some cases of complete response, of advanced HCC patients. Mono-Select® Silybum® (PharmaExtracta, Piacenza, Italy) is a phytosome-complexed form of silymarin that exerts a long-lasting hepatoprotective action through multiple mechanisms, such as inhibition of lipid peroxidation and prevention of toxins binding to hepatocytes. Ephynal®, α-tocopheryl acetate (vitamin E; Bayer, Milan,

Keywords
■ complete response ■ hepatocellular carcinoma ■ silymarin ■ sorafenib ■ Synchro-Levels®

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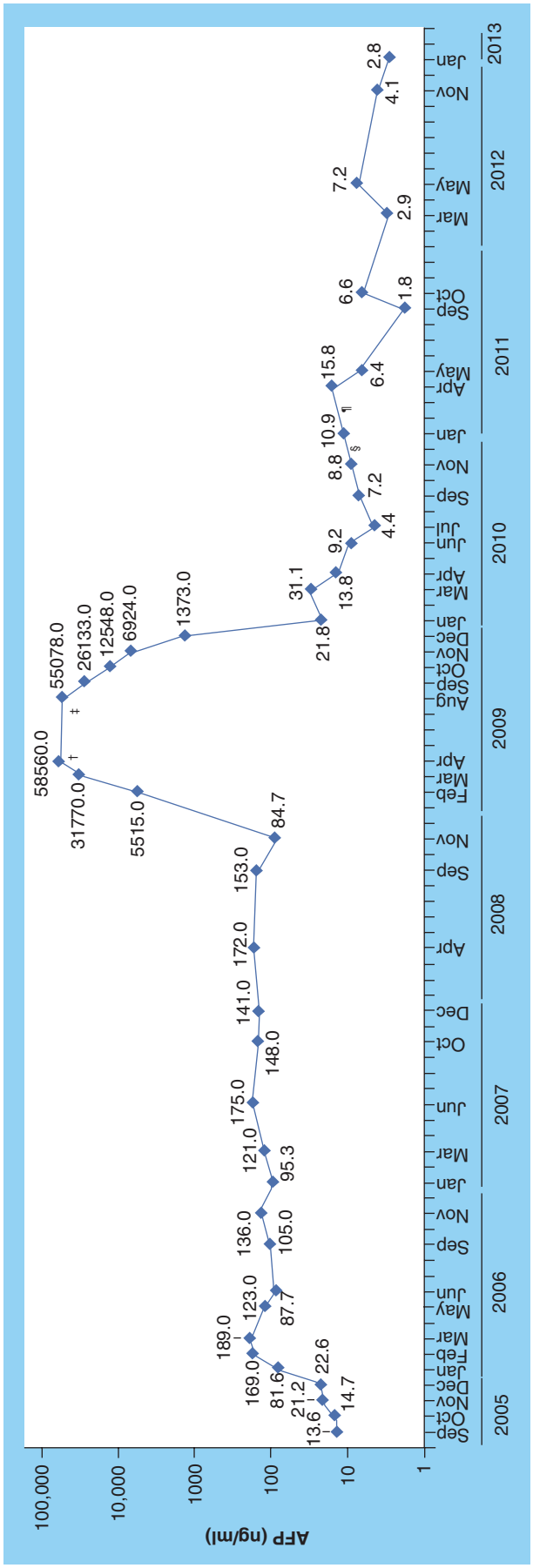

Figure 1. Changes in α-fetoprotein levels over time. Data are expressed on a log scale.
†Initiation of sorafenib; ‡Reduction of sorafenib; §Complete disappearance of hepatocellular carcinoma lesions at MRI; ¶Suspension of sorafenib.
AFP: α-fetoprotein.

Italy), is a physiological antioxidant that acts as protector of lipid structures and stabilizer of cell membranes.

We present the case of a 81-year-old male with advanced HCC who achieved complete remission following SO in combination with the above-mentioned compounds for a total of 21 months.

Case report

Since 2002, a male patient, then aged 71 years, with chronic hepatitis C virus (Knodell–Desmet grading: 9 and staging: 3), genotype 2a–2c with high viral load (2–3 MUI/ml), has been attending our unit (Infectivology Unit, Ospedale di Circolo di Busto Arsizio, Busto Arsizio, Italy). He was treated initially with IFN-α-2b and ribavirin, then with PEGylated IFN-α-2b plus ribavirin and, following an intolerance, with leukocyte IFN-α with amantadine, which was also stopped owing to adverse events. In 2005, despite short but numerous treatments performed and a favorable genotype, the hepatitis C virus was not eradicated and a hepatic cirrhosis with α-fetoprotein (AFP) levels between 13 and 22 ng/ml was diagnosed; in 2006, the AFP level began to increase, reaching its maximum of 189 ng/ml (the lowest value was 81.6 ng/ml) in March 2006 (Figure 1).

In 2007, after a slight lowering of AFP levels, a CT scan diagnosed multifocal micronodules in the liver (segments IV and VII). The patient, after MRI, was started on Synchro-Levels and vitamin E at a dosage of 1 ml (0.5 plus 0.5 after 2 min) sublingually twice daily; diagnosis of HCC was suspected, but not yet confirmed. In September 2008, a MRI did not show significant differences from previous scans and AFP showed a continuous reduction (from 172 to 84.7 ng/ml). Synchro-Level treatment was stopped, while silymarin and vitamin E were continued. Despite a high viral load (>2 MIU/ml), hepatic function was maintained and the patient remained in good general condition (his Child–Pugh score was A5).

This situation allowed performance of a successful surgical intervention to remove an atheroma stenosis in the right carotid artery in January 2009.

In the following month, an ultrasound scan of the abdomen with contrast media showed portal vein thrombosis (Figure 2), the AFP level increased (to 5515 ng/ml) and a subsequent CT scan showed portal thrombosis (portal fork), dense lesions in the IV and VII segments, and another marked increase of AFP levels (Figure 1).

In April 2009, histological examination after ultrasound-guided fine needle aspiration demonstrated evidence of poor-/medium-differentiated trabecular HCC, and contrast-enhanced MRI confirmed the diagnosis of multiple confluent nodal HCC (9 cm) (Figure 3A). Due to the size of the lesion, the multifocal setting and portal vein involvement, locoregional treatment and surgery were excluded.

In May 2009, serum AFP levels reached a maximum of 58,560 ng/ml and therapy with SO (400 mg twice a day) was started in combination with Synchro-Levels (silymarin and vitamin E had been taken since 2006). The patient's Child–Pugh score was A, with a model for endstage liver disease score of 10 and a performance status of 0 according to the ECOG score. After 2 months the SO dosage was reduced to 200 mg twice a day as the patient experienced grade II hand–foot skin reaction (HFSR). At the same time, ultrasound showed a 6-cm lesion in segment VIII surrounded by smaller nodules (10–12 mm) and tumor spread in numerous ipsilateral portal vein branches. Reduction of the dosage of SO led to a reduction in the severity of adverse events. The application of a careful management program of HFSR and other adverse events made it possible to continue SO therapy.

In September 2009, anemia was treated with darbepoetin-α.

In October 2009, MRI showed tumor progression with multifocal expansion and a partial obstruction of the portal vein and its main branches, but importantly, the AFP level had begun to decrease, reaching 1373 ng/ml in December 2009.

Finally, in January 2010, MRI showed a decrease in tumor mass (Figure 3B), a reduction of the thrombosis, and a continued steady decrease in AFP level (to 21.8 ng/ml). In February 2010, suspension of SO was considered as the patient experienced grade II neutropenia; however, the multidisciplinary team decided that SO should be continued and that filgrastim should be given in addition to erythropoietin. The patient's general state of health gradually improved (no asthenia despite anemia, no weight loss and AFP of 31.1 ng/ml) with moderate peripheral edema and minimal palmar dermatitis. In July 2010, oral iron therapy was begun in order to treat the anemia.

On continuation with treatment, a grade II thrombocytopenia also appeared that indicated drug withdrawal but, in agreement with the patient, the team decision was to proceed with the therapy, with frequent monitoring of

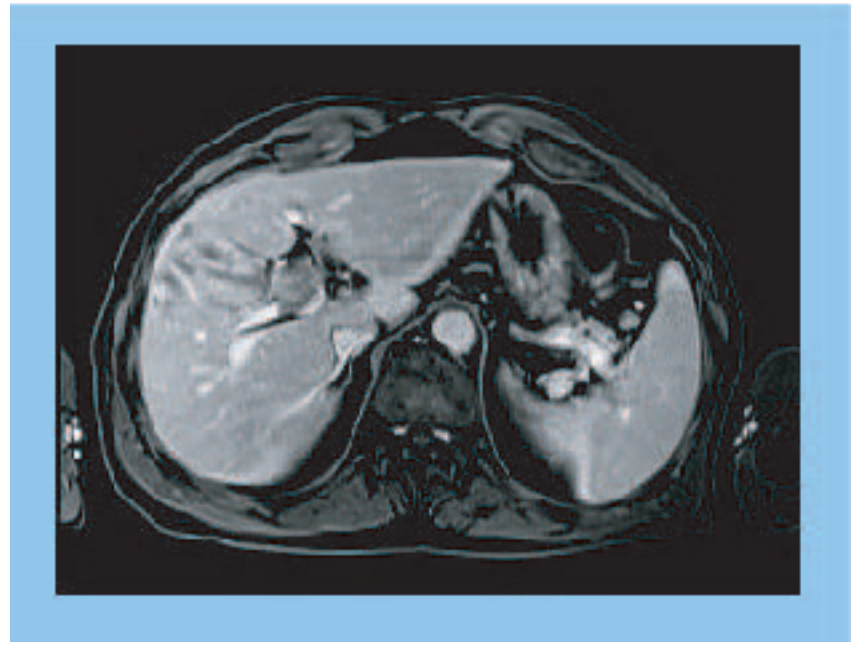

Figure 2. MRI scan showing main portal vein tumor thrombus before sorafenib treatment.

the patient. In November 2010, a MRI showed the complete disappearance of the HCC lesions and recanalization of the portal vein, despite worsening anemia and edema. A repeat MRI in January 2011 (Figure 3C) confirmed the complete regression of locally advanced HCC and SO was stopped. The patient continued taking Synchro-Levels daily along with MonoSelect Silybum and Ephynal periodically. Clinical investigations continued in order to establish the cause of his edema and anemia. No cardiac abnormalities, apart from previously noted hypertension, were detected, but a gastroscopy revealed esophageal varices (degree F1) that were considered to be the causes of his anemia. In March 2011, the patient was diagnosed with grade III renal failure, and therapy with diuretics was established. In June 2011, the patient's HCC continued to be in complete remission and the patient was in relatively good general health despite the presence of renal failure (his Child–Pugh score was A5).

In December 2011, the patient, owing to nephropathy, was not subjected to MRI; however, following the advice of the radiologists, we decided to perform a triphasic CT scan of the abdomen (Figure 3D). The patient was hospitalized for precautionary reasons at another Hospital (Nephrology Department of Cuggiono Hospital, Cuggiono, Italy). The outcome of the investigation was negative.

In mid-April 2012, again for nephropathy, an abdominal contrast-enhanced ultrasound was performed at our hospital, which did not

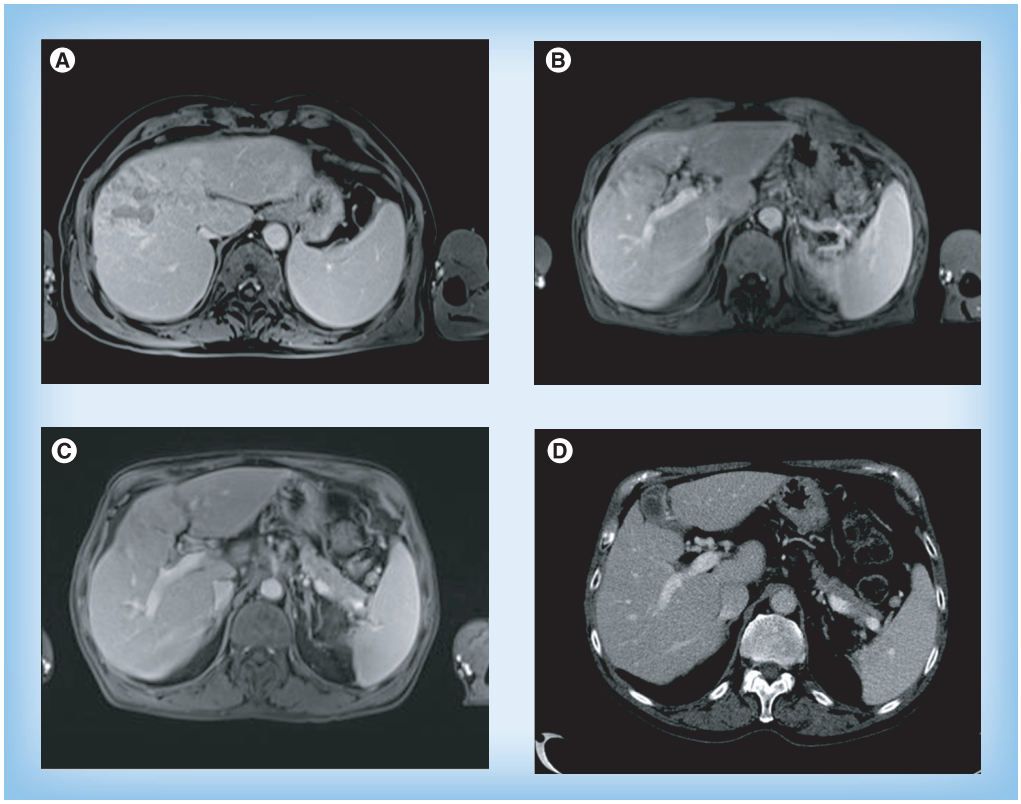

Figure 3. Progression of the neoplastic lesion over time. (A) Contrast-enhanced MRI showing multiple confluent nodal hepatocellular carcinoma (April 2009). **(B)** MRI showing a decrease in the tumor mass (January 2010). **(C)** MRI showing complete regression of locally advanced hepatocellular carcinoma (January 2011). **(D)** Triphasic CT scan of the abdomen, showing a lack of neoplastic lesions according to the radiologists of our unit (December 2011).

reveal any heteroplastic injury. The AFP level was always within the normal range (Figure 1). We decided to follow the patient with a 4-monthly contrast-enhanced ultrasound and annual CT scan of the abdomen. In October 2012, the patient was submitted to an abdominal contrast-enhanced ultrasound that detected no reccurrence of tumor.

In March 2013, the patient underwent another contrast-enhanced ultrasound that was, once again, negative. The new AFP level in January 2013 was 2.8 ng/ml. The patient is, at the time of writing, in good health and has returned to his usual daily activities.

Discussion

In this complex case presentation, long-term treatment with SO caused a complete response in advanced HCC, in line with the results of some recent reports from clinical practice [8,11]. During the course of SO therapy several adverse events occurred. A summary of the main toxicities, including grades and supportive treatments, is reported in Table 1. The outcome of this case report raises a number of interesting points.

First, dose reductions could be considered if adverse events occur that may impact on the patient's quality of life. The maintenance of long-term SO therapy could possibly maximize its clinical benefits and control tumor growth. HCC is a challenging disease and, therefore, during long-term SO therapy, the expertise of a multidisciplinary team, as outlined by Cabibbo *et al.* [7], should be considered in order to prevent and manage adverse events so that SO therapy can be continued. The present report provides a successful example of such multidisciplinary cooperation.

Second, the observed recanalization of the portal vein in this patient provides further evidence of a dual-mechanism activity of SO – its direct antineoplastic action and its effect on PVTT through the inhibition of the VEGF pathway [12].

Moreover the patient was treated with Synchro-Levels, silymarin and vitamin E before, during and after SO therapy. Synchro-Levels is a product containing stem cell differentiation stage factors taken from zebra fish embryos during the differentiation process of totipotent

Table 1. Main adverse events that occurred during sorafenib treatment.

Toxicity	Grade	Duration	Supportive treatment
Hand–foot skin reaction	II	–	Vitamin E plus reduction in sorafenib from 400 to 200 mg twice daily
Anemia	II	September 2009–January 2011	Darbepoetin-α (erythropoietin) plus oral iron therapy plus two sessions of hemotranfusion (four bags)
Neutropenia	II	February–March 2010	Filgrastim
Thrombocytopenia	II	–	Frequent monitoring
Renal failure	III	March 2011 (ongoing)	Diet, diuretics, allopurinol, vitamin D and calcium

–: Exact duration not available.

stem cells [13]. An *in vitro* study showed that the administration of zebra fish embryonic extracts was able to significantly slow cell proliferation in five different tumor cell lines (glioblastoma, melanoma, kidney adenocarcinoma, breast carcinoma and lymphoblastic leukemia), thus suggesting its possible use in cancer therapy [14]. This product may exert some effects on the inhibition of tumor cell proliferation through the control of genes involved in the regulation of the cell cycle, such as *p53* and *pRb* [13]. Several other *in vitro* and *in vivo* studies have reported the efficacy of factors present in embryos and the pregnant uterus in regulating abnormal cell proliferation and in delaying tumor growth and metastasis formation [15–17].

It is not possible to clearly establish whether SO or Synchro-Levels played the major role in inducing HCC remission; based on the results of our study, we can assume that a synergic action may exist between SO and Synchro-Levels in HCC treatment. However, this is only a speculation derived by a single clinical case; further studies are required to explore the potential effect of Synchro-Levels in HCC treatment and to clarify a potential synergy between the two molecules.

Silymarin has beneficial effects on patients affected by chronic liver disease and can be useful as an adjuvant therapy in some neoplastic diseases. Several *in vitro* and *in vivo* studies have also demonstrated the chemopreventive effect of silymarin on HCC. This product can significantly reduce tumor cell proliferation and angiogenesis, as well as insulin resistance, and an effect on the reduction of metastasis development has also been detected with this molecule [18].

The administration of vitamin E seems to play an important role in the reduction of HFSR induced by SO. A recent study showed that the addition of vitamin E to SO therapy was effective in treating grade 2–3 HFSR without reduction in SO dose or treatment interruption [19].

Another group of Italian authors developed a strategy to combine vitamin K1 with SO to treat HCC, and found that the above combination enhanced SO-induced HCC cell growth inhibition [20]. They suggested that c-Met–PI3K–Akt signaling pathway-mediated inhibitory c-Raf phosphorylation may play a central role in the inhibition of HCC cell growth by the synergy of vitamin K1 plus SO.

Interestingly, data from our case study support the prognostic value of AFP, a molecule secreted in approximately 70% of HCCs, which has been the foremost biomarker used for HCC diagnosis [21]. The change in AFP level throughout the illness and the recovery of the patient support the findings of a recent study that proved that a decrease in AFP correlates with overall survival in patients treated with SO, thus suggesting that this molecule can be used to capture SO activity in contrasting HCC [21]. Another study reported the normalization of AFP levels following SO treatment in a patient affected by HCC who achieved complete response. This case report also suggested that a complete response to SO may be possible in a small subgroup of patients affected by advanced HCC, owing to the specific mechanism of action of SO [22].

Conclusion

In conclusion, the above-reported case represents one of the few examples of a complete response observed following long-term SO treatment in a patient with advanced HCC and concomitant hepatitis C virus infection and it emphasizes the importance of dose adjustments rather than discontinuations to allow prolonged administration of SO in a setting of clinical practice. In addition, this case underlines the positive action of coadjuvants, such as silymarin and vitamin E, in

the management of HCC. Finally, the results of this report might give some support to a potential synergic action between SO and Synchro-Levels in HCC remission; however, the existence of a possible synergy between these two molecules in treating HCC deserves further evaluation.

Future perspective

The introduction of SO into clinical practice has provided advanced HCC patients with a valuable therapeutic option that may prolong overall survival. In addition, SO is being tested – alone or in combination – in patients at an earlier stage of disease.

Despite its importance in the therapeutic armamentarium for HCC patients, SO is sometimes prematurely discontinued in clinical practice, with detrimental consequences on treatment outcomes. We believe that in the coming years research will focus on how to best individualize this therapy with the aim to prolong its administration and, therefore, extend its benefits. One potential strategy to optimize the use of SO can be the concomitant administration of coadjuvants such as those described in this case report. Clinical research on these molecules is active, and studies on their potential synergy with more established drugs, such as SO, are to be expected in the years to come.

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Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

Executive summary

Background

- Sorafenib (SO) is the first targeted agent that has been shown to improve overall survival in patients affected by unresectable hepatocellular carcinoma (HCC).
- SO treatment poses some challenges in clinical practice and it is frequently discontinued prematurely owing to the occurrence of severe adverse reactions.

Case report

- A patient affected by advanced HCC achieved complete remission after long-term treatment with SO.
- During SO treatment several adverse events occurred (hand–foot skin reaction, anemia, neutropenia, thrombocytopenia and renal failure) that were managed with dose adjustments and supportive treatment (Synchro-Levels® [Alphrema, Varese, Italy], silymarin and vitamin E).

Discussion

- A multidisciplinary approach in managing adverse events associated with SO treatment may be useful to avoid discontinuation of the therapy, thus maximizing SO clinical benefits
- A possible synergic activity may exist between SO and Synchro-Levels in HCC treatment; further studies are required to assess this hypothesis.
- Coadjuvants, such as silymarin and vitamin E, might be useful in combating tumor growth or in treating adverse drug reactions associated with SO.

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