Wspolczesna Onkol 2012; 16 (1): 60–63

DOI: 10.5114/wo.2012.27339

Case report

The prognosis of patients suffering from primary hepatocellular carcinoma (HCC) is unfavourable because the tumour usually develops in cirrhosis-affected liver and is typically not diagnosed until an advanced stage of the disease. The 5-year survival rate for HCC patients in Europe does not exceed 9%. On the basis of a clinical case, the present article discusses the strategy of treatment of HCC patients. Patients with advanced HCC, stage C according to the Barcelona Clinic Liver Cancer (BCLC) staging system, typically receive systemic chemotherapy with sorafenib. The standard management in the treatment of intermediate-stage HCC, i.e. BCLC's stage B, is chemoembolization (TACE). However, repeated TACE sessions activate factors involved in the process of angiogenesis such as hypoxia-inducible factor-1 (HIF-1) and vascular endothelial growth factor (VEGF), which can render the procedure ineffective. Therefore, there are scientific foundations for combining TACE with antiangiogenic agents such as sorafenib. Results of studies conducted to date indicate that the combination of sorafenib with TACE in patients with BCLC's stage B brings tangible therapeutic effects while being safe. The value of this therapeutic strategy is confirmed by the case described below, in which TACE + sorafenib have induced a partial regression of HCC.

Key words: hepatocellular carcinoma, HCC, sorafenib, TACE.

Effective therapeutic management of hepatocellular carcinoma – on the basis of a clinical case

Joanna Omyła-Staszewska[1], Andrzej Deptała[1,2]

[1]Department of Oncology and Haematology, Central Clinical Hospital of the Ministry of Internal Affairs and Administration, Warsaw, Poland
[2]Cancer Prevention Unit, Warsaw Medical University, Poland

Introduction

Primary hepatocellular carcinoma (HCC) is one of the most common tumours worldwide, accounting for 5.7% of all cancer cases [1, 2]. The HCC is the third most frequent cause of cancer deaths worldwide and the seventh most common cause of cancer-related deaths in Europe [3, 4]. A total of 1,300 new cases of primary hepatocellular carcinoma and nearly 2000 HACC-related deaths were recorded in Poland in 2007. Higher mortality relative to incidence suggests inadequate registration of HCC cases. Another fact worth noting is the ongoing increase in HCC incidence over the past 2-3 decades in countries with a high socioeconomic status, in which this cancer type was not an epidemiological problem until recently. The rise in incidence observed in the USA, Europe or Japan parallels the increase in the number of patients suffering from cirrhosis secondary to hepatitis C and the growing incidence of non-alcoholic steatohepatitis (NASH). The NASH, in turn, is a consequence of obesity causing insulin resistance and induction of oxidative stress due to chronic inflammation [5, 6]. The prognosis in primary hepatocellular carcinoma is poor because the disease is usually diagnosed at an advanced stage and the rate of 5-year survival in Europe does not exceed 9% [7]. Prolonged survival of HCC patients achieved as a result of introduction of sorafenib into cancer therapy has given rise to a number of trials and clinical practice observations with a view to establishing therapeutic management standards of HCC patients. Consequently, the present study seeks to outline an optimum management strategy in HCC therapy on the basis of a specific clinical case.

Case report

A man aged 56 years old, suffering from alcohol-induced cirrhosis, hypertension and insulin-treated type 2 diabetes was diagnosed with hepatocellular carcinoma (HCC) in early August 2008 on the basis of biopsy of the dominant tumorous lesion located in the right liver lobe. Abdominal CT scan performed on 30 Sept 2008 revealed abnormalities including hepatomegaly (liver measuring 176 mm in the c-c direction) and – in the arterial phase of the CT examination – heterogeneous hypervascular lesions (the largest focal lesion located at a border between hepatic segments 8 and 7, measuring 55 mm × 43 mm, and around a dozen satellite foci scattered throughout the liver) which were isodense with the liver parenchyma in the portal phase of CT. Other findings included multiple lymph nodes of borderline size. No signs of portal vein thrombosis or ascites were identified.

In December 2008, following consultation in the Department of General, Transplant and Liver Surgery of the Warsaw Medical University, the patient was excluded from surgery due to multifocal nature of the cancer process with coexisting liver cirrhosis. Instead, the patient was referred for local treatment using the method of transcatheter arterial chemoembolization (TACE). Two

TACE sessions were performed, on 2 Feb 2009 and 12 Mar 2009. The patient received injections of doxorubicin in lipiodol into the hepatic artery. Follow-up abdominal CT scan performed on 9 Apr 2009 failed to show a regression of lesions in the liver (compared to the examination of 30 Sept 2008), however provided evidence that their size and number had stabilized. Furthermore, calcifications were found within the largest lesion located at the border between segments 8 and 7, and less contrast enhancement was demonstrated in the other foci.

In March 2009 the patient was admitted to the Department of Oncology and Haematology of the Central Clinical Hospital of the Ministry of Internal Affairs and Administration in Warsaw to begin palliative chemotherapy with sorafenib. In view of the patient's stage B hepatocellular carcinoma (according to the BCLC classification), very good performance status (score 0 according to the ECOG scale) and lack of hepatic impairment (class A in the Child-Pough score = 5 points), targeted therapy with sorafenib (Nexavar) at 800 mg/day (2 × 400 mg) was initiated on 11 Apr 2009. Seven days after beginning the first chemotherapy cycle the patient reported quite severe abdominal pain and very intense reddening of the skin over the whole body, accompanied by large papular rash with a tendency to become bacterially infected. Due to observed grade 3 skin toxicity according to CTCAE (Common Terminology Criteria for Adverse Events), sorafenib was discontinued on day 8 of the first chemotherapy cycle. Abdominal pain subsided and skin symptoms were reduced to CTCAE toxicity grade 1 within 7 days from drug discontinuation. Sorafenib was then reinstituted at half of the original dose (400 mg/day). After reducing the dose, adverse skin reactions did not become more severe than toxicity grade 1 over the next two cycles of treatment. From June 2009 onwards, however, the patient's skin lesions occasionally progressed to CTCAE toxicity grade 2. The therapy was not discontinued, however due to previous adverse reactions no attempt was made to date to reintroduce the full standard dose of sorafenib. Another two TACE sessions were performed on 24 Apr 2009 and 5 June 2009, respectively.

Follow-up CT examinations conducted at regular 3-month intervals from April 2009 onwards demonstrated a gradual regression of the largest focal lesion located at the border between hepatic segments 7 and 8, and stabilization of the size of satellite lesions. Laboratory tests performed in December 2009 showed a very high concentration of alpha-fetoprotein (AFP), reaching 1,758 ng/ml. Laboratory tests, however, did not correlate with results of imaging studies (abdominal and chest CT) performed on 7 Jan 2010, which ruled out progression of the disease. Between February and June 2010, the AFP level was found to be gradually decreasing from 136 ng/ml to 107 ng/ml. The test performed on 2 Sept 2011 showed the AFP concentration to be 58 ng/ml. The best radiological response was demonstrated in the abdominal CT scan performed on 18 Oct 2010 revealing a reduction in dimensions of the largest focal lesion to 13 mm × 26 mm (vs. 55 mm × 43 mm at baseline), which according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumours 1.1) corresponds to partial response (PR). The latest abdominal CT scan, performed on 2 Sept 2011, confirmed stabilization of the cancer process – the largest lesion was 24 mm × 17 mm in size and the number and size of satellite foci were unchanged. The subsequent treatment cycle was started on 7 Sept 2011 and therapy has been continued ever since.

Discussion

The Barcelona staging system (BCLC) is commonly recognized as the optimum classification for assessing the stage of HCC [8]. Patients with good performance status and early-stage HCC (0 and A according to the BCLC) are potential candidates for surgery (tumour resection, liver transplant) or ablation therapy [9-11]. Ablation methods including PEI (percutaneous ethanol injection) or RFA (radiofrequency ablation) are recommended in cases of unresectable early HCC [10]. The preferred method of local treatment in this group of patients is RFA, with PEI being currently less popular in clinical practice. Patients with intermediate (BCLC stage B) and advanced (BCLC stage C) HCC undergo TACE (transarterial chemoembolization) or systemic therapy, respectively.

Transarterial chemoembolization is used in patients with unresectable HCC at BCLC stage B if no macroscopic vascular infiltration is identified in the liver and there is no evidence for extrahepatic metastases [8, 9, 11]. This applies to 30-40% of all HCC cases [12]. Patients with severe hepatic impairment (Child-Pough score C), portal hypertension and portal vein thrombosis do not qualify for the procedure despite local progression of the disease. A metaanalysis of randomized clinical trials has shown that TACE-based treatment of patients with BCLC stage B, good performance status (0-1), Child-Pugh score A (or B = 7 points) for liver function and without portal vein invasion makes it possible to extend overall survival to 11-20 months [13, 14]. The objective response rate for the therapeutic technique ranges from 16 to 61% [15].

Transarterial chemoembolization involves the infusion of cytotoxic agents in a mixture with lipiodol into hepatic arteries (in Europe usually doxorubicin, in Asia – cisplatin). Lipiodol occludes hepatic artery branches supplying blood to the tumour, while the cytostatic is released into cancer cells. The process causes cell apoptosis and, in the next stage, cancer tissue necrosis as a result of local inhibition of angiogenesis in HCC which is a well-vascularized tumour type. Consequently, a number of growth factors are activated including HIF-1α (hypoxia-inducible factor-1α) and VEGF (vascular endothelial growth factor) [16]. As the key inducer of angiogenesis, VEGF participates in all stages of the process. VEGF-mediated angiogenesis facilitates the interaction between cancer cells and blood vessels, thus opening up the way for cancer invasion. The most important regulator of VEGF expression is hypoxia. Hypoxia stimulates vascular growth via the signal pathway of hypoxia-inducible factors (HIFs), especially HIF-1α [17]. As a result of hypoxia, HIF-1 induces VEGF expression leading to the development of new blood vessels and increased oxygen supply. Li *et al*. confirmed a large elevation of serum VEGF concentration after TACE, which is a major factor promoting tumour growth [16, 17]. Therefore, the combined use of TACE and inhibitors with antiangiogenic properties seems justified.

Sorafenib (BAY43-9006), a drug which was introduced into clinical practice resulting in prolonged survival of HCC patients [18, 19], is a small-molecular multikinase inhibitor which

– by suppressing cytoplasmic serine/threonine kinases C-RAF and B-RAF (RAS-RAF-MAPK pathway) and receptor tyrosine kinases VEGFR-2, VEGFR-3, PDGFR-β, c-KIT and FLT3 – is able to inhibit tumour angiogenesis [20]. One of clinical studies conducted to date has shown that the sorafenib plus doxorubicin combination in the treatment of HCC patients prolongs median overall survival (14 months) versus doxorubicin alone (5.6 months) [21]. There are several strategies for combining sorafenib with TACE (with doxorubicin): the sequential approach (targeted therapy introduced after completing TACE sessions), the intermittent approach (sorafenib suspended for the duration of chemoembolization treatment) and the continuous approach [22]. The continuous regimen of sorafenib with TACE seems to be the most effective approach because of early onset of TACE-induced activation of growth factors, observed several hours after initiating the local treatment method [22].

A phase I trial [23] assessing the safety and tolerance of the TACE plus sorafenib combination in BCLC grade B patients suffering from HCC failed to identify significant differences in the frequency and severity of observed adverse reactions compared to results obtained in trials analyzing sorafenib [20] and TACE [24] used in monotherapy. The hand-foot syndrome occurred in 21% of patients. Diarrhoea was observed in 50% of patients, however the percentage of patients experiencing the adverse reaction at toxicity grade 3 was 8%. Abdominal pain was much more common in combination treatment (28%) than sorafenib monotherapy (8%), which is a likely consequence of the so-called post-embolization syndrome, a complication secondary to TACE. Acute cholecystitis, also associated with TACE, was observed in 7% of patients [23]. Thrombocytopenia was the only adverse reaction identified more commonly in combined therapy at toxicity grade 3. The reaction developed in 21% of patients vs. 4% of patients treated with sorafenib in monotherapy [20]. The same trial [23], in addition to assessing the safety and toxicity profiles, also sought to determine circulating VEGF levels at baseline and 20 hours after the first TACE session. A significant reduction in circulating VEGF concentration was obtained for the combined regimen, which corroborated the theoretical claim that the release of this growth factor could be effectively suppressed during TACE by administering molecularly targeted drugs [23].

Several phase II clinical trials are now under way to assess the safety and efficacy of the sorafenib plus TACE combination, and to establish an optimum management regimen for the treatment. During the American Society of Clinical Oncology conference held in 2010, Chung *et al.* announced preliminary results of their phase II clinical trial investigating the combination treatment in patients with unresectable HCC [25]. In the trial, sorafenib was combined with TACE in an intermittent regimen. The patients started systemic therapy 4 days after a TACE procedure, while sorafenib was interrupted for 4 days before each local treatment session. Out of 50 patients included in preliminary analysis, complete remission was observed in 18 (36%) patients, while partial remission or stabilization of the cancer process was achieved in 30 (60%) of patients. Cancer progression occurred in 2 patients (4% of assessed patients) [25].

Another multi-centre phase II trial (SOCRATES) [26] also evaluated the safety and efficacy of the therapeutic combination of sorafenib and TACE. The trial, however, used a different intermittent regimen for sorafenib and TACE administration than Chung *et al*. Sorafenib was introduced 2 weeks prior to the first TACE procedure and interrupted 3 days before the next chemoembolization session. Targeted therapy was resumed after local treatment, usually one day after the subsidence of signs of hepatic impairment. Preliminary results of the study, in the form of an abstract, were presented at the annual conference of the American Society of Clinical Oncology in 2011. Stabilization of the cancer process was achieved in the majority of patients (34 out of 45 study patients). There were no cases of complete remission, while partial clinical response was noted in one patient. Median TTP (time to progression) was 526 days, while medial overall survival – 562 days. High hopes for determining benefits of sorafenib-based targeted therapy combined with TACE in patients with intermediate cancer (BCLC stage B) are placed on results of the ongoing multi-centre randomized clinical trial (SPACE) [27]. The trial involves 300 randomized patients. Sorafenib is administered on a continuous basis, while chemoembolization is performed on day 1 of cycles 1, 3, 7, 13, and every 6 cycles of systemic treatment thereafter.

Results of studies completed to date confirm beneficial effects (in terms of efficacy and safety) of sorafenib used in conjunction with TACE in patients with inoperable HCC at the BCLC intermediate stage B. Despite a different (sequential) approach, the achievement of PR in the case described above corroborates other studies. It is hoped that treatment-associated toxicity could be reduced and the outcome improved thanks to using TACE with particles preloaded with doxorubicin (DEB-TACE). Results of phase III ECOG 1208 trial may be able to provide some answers to existing questions [28].

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108.
2. Boyle P, Levin B. World Cancer Report. IARC Press, Lyon 2008.
3. Bosch FX, Ribes J, Diaz M. Cleries R. Primary liver cancer world-wide incidence and trends. Gastroenterology 2004; 127 (supl. 10): 5-16.
4. El-Serag HB. Hepatocellular carcinoma: an epidemiologic view. J Clin Gastroenterol 2002; 35 (supl. 1): 72-8.
5. Sligte K, Bourass I, Sels JP, et al. Non-alcoholic steatohepatitis: review of growing medical problem. Eur J Intern Med 2004; 15: 10-21.
6. Neuschwander-Tetri BA. Non-alcoholic steatohepatitis and the metabolic syndrome. Am J Med Sci 2005; 330: 326-35.
7. Sant M, Allemani C, Santaquilani M, et al. EUROCARE-4. Survival of cancer patients diagnosed In 1995-1999. Results and commentary. Eur J Cancer 2009; 45: 931-91.
8. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-2.
9. Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. J Heaptol 2008; 48 (supl.1): S20-S37.
10. Sandhu DS, Tharayii VS, Lai JP, Roberts LR. Treatment options for hepatocellular carcinoma. Expert Rev Gastroenterol Heaptol 2008; 2: 81-92.
11. Bruix J, Llovet JM. Major achievements in hepatocellular carcinoma. Lancet 2009; 373: 614-6.
12. Camma C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: Meta-analysis of randomized controlled trials. Radiology 2002; 224: 47-54.
13. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003; 37: 429-42.

14. Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. Gastroenterology 2004; 127: S179-S188.
15. Li X, Feng GS, Zheng CS, Zhuo CK, Liu X. Influence of transarterial chemoembolization on angiogenesis and expression of vascular endothelial growth factor and basic fibroblast growth factor in rat with Walker-256 transplanted hepatoma: An experimental study. World J Gastroenterol 2003; 9: 2445-2449.
16. Sergio A, Cristofori C, Cardin R, et al. Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. Am J Gastroenterol 2008; 103: 914-21.
17. Li Z, Hu DY, Chu Q, Wu JH, Gao C, Zhang YQ, Huang YR. Cell apoptosis and regeneration of hepatocellular carcinoma after transarterial chemoembolization. World J Gastroenterol 2004; 10: 1876-80.
18. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-90.
19. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25-34.
20. Keating GM, Santoro A. Sorafenib. A review of its use in advanced hepatocellular carcinoma. Drugs 2009; 69: 223-40.
21. Abou-Alfa GK, Johnson P, Knox J, et al. Preliminary results from a Phase II, randomized, double-blind study of sorafenib plus doxorubicin versus placebo plus doxorubicin in patients with advanced hepatocellular carcinoma. Presented at: ECCO 14-European Cancer Conference. Barcelona, Spain, 23-27 September 2007.
22. Strebel BM, Dufour JF. Combined approach to hepatocellular carcinoma: A new treatment concept for nonresectable disease. Expert Rev Anticancer Ther 2008; 8: 1743-9.
23. Dufour JF, Hoppe H, Heim MH, et al. Continuous administration of sorafenib in combination with transarterial chemoembolization in patients with hepatocellular carcinoma: results of a phase I study. Am J Gastroenterol 2008; 103: 914-21.
24. Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: Which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol 2007; 30: 6-25.
25. Chung Y, Kim B, Chen C, et al. Study in Asia of the combination of transarterial chemoembolization (TACE) with sorafenib in patients with hepatocellular carcinoma trial (START): second interim safety and efficacy analysis. J Clin Oncol 2010; 28[15S]: 4026.
26. Erhardt A, Kolligs FT, Dollinger MM, et al. TACE plus sorafenib for the treatment of hepatocellular carcinoma: Final results of the multicenter SOCRATES trial. Presented at 2011 American Society of Clinical Oncology Meeting. Abstract 4107 General.
27. Lencioni R, Zou J, Leberre M. Sorafenib (SOR) or placebo (PL) in combination with transarterial chemoembolization (TACE) for intermediate-stage hepatocellular carcinoma (SPACE). J Clin Oncol 2010; 28: 15s.
28. Uller W, Wiggermann P, Gössmann H, Klebl F, Salzberger B, Stroszczynski C, Jung EM. Chemoembolization with epirubicin drug-eluting beads (DEB-TACE) to treat early and intermediate hepatocellular carcinoma. J Clin Oncol 2010; 28: 15s (abstract 4141).

Address for correspondence

Joanna Omyła-Staszewska
Klinika Onkologii i Hematologii
Centralny Szpital Kliniczny MSWiA
ul. Wołoska 137
02-507 Warszawa
e-mail: joannaomyla@gmail.com

Submitted: 19.09.2011
Accepted: 22.12.2011