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Complete pathological remission after palliative therapy with sorafenib in hepatocellular carcinoma — case report

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most frequent primary malignant liver cancer. The five-year overall survival (OS) in men diagnosed with HCC does not exceed 9%. Patients (pts) with advanced disease are treated with sorafenib (multikinase inhibitor). In randomised trials the OS advantage was within the range of three months for sorafenib. Stabilisation of disease was achieved in 71% of patients, and no case of CR was reported. We present a case of 60-year-old patient with locally advanced cT3aN0M0 (stage IIIA according to seventh TNM) bifocal HCC (12 × 10 cm and 10 × 8 cm). The diagnosis was confirmed by pathologic examination. Due to the clinical stage, palliative treatment with sorafenib was administered from January 2016 to February 2017. A clinical partial response (cPR) enabled surgery. In May 2017, left-sided liver bisegmentectomy and resection of residual lesion in segment 6 were performed. The pathological report revealed ypCR. Subsequently, pathology verification changed the primary diagnosis to PR. In September 2017 thermoablation of lesion in segment 5 of the liver was performed. The increased AFP (alpha-fetoprotein) level at baseline was normalised during treatment. The sorafenib therapy was completed after one year. The patient remains in follow-up with no evidence of relapse. Treatment with sorafenib in the presented case enabled radical therapy, so the palliative treatment turned out to be an induction treatment. Clinical CR (especially pCR) in advanced non-operable solid tumours after systemic treatment is quite rare (3–15%), and even less common in HCC. So far, only a few cases of achievement of CR during sorafenib therapy in HCC have been described.

Key words: hepatocellular carcinoma, sorafenib, complete response

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignant tumour. There are more than 600,000 new cases per year in the world (in Poland about 1–2 thousand cases are diagnosed annually). Hepatocellular carcinoma is the third cause of cancer-related death [1–4]. The five-year overall survival (OS) in male patients diagnosed with HCC does not exceed 9% [5]. The most common aetiological factors

leading to increased incidence include alcoholic liver cirrhosis or caused by hepatitis C or B virus (HCV or HBV) infection, diabetes, obesity, exposure to aflatoxins, genetic factors associated with congenital metabolic disorders such as haemochromatosis, tyrosinaemia (type I), galactosaemia, porphyria, or alpha 1-antitrypsin deficiency. Hepatocellular carcinoma is several times more frequent in male than in female patients, and the median of morbidity occurs around the age of 50–60 years [6, 7].

Standard chemotherapy is not used in the treatment of patients with advanced and inoperable HCC. The most scientific evidence concerns the use of doxorubicin, which produce remissions in approximately 10% of patients. Multidrug regimens do not increase the response rate but are associated with higher toxicity [8]. A breakthrough in systemic treatment of HCC has been the use of sorafenib, a multi-tyrosine kinase inhibitor.

Case report

In January 2016, a 60-year-old male patient diagnosed with HCC was admitted to the oncology department. The diagnosis was established on the basis of core needle biopsy (CNB) of hepatic lesions described in imaging studies performed in the course of routine internal diagnostics due to increased exercise intolerance in the last few months.

At admission, the patient was in a good general condition, the ECOG (Eastern Co-operative Oncology Group) performance status (PS) was 1, and the patient did not report clinically significant complaints. Concomitant diseases included well-controlled hypertension, type 2 diabetes, obesity, and mixed hyperlipidaemia.

Computed tomography (CT) imaging of the chest, abdomen, and pelvis was performed in January 2016 (Fig. 1) — it revealed hypervascular tumours with a wash-out effect and central disintegration. There were two lesions identified: in segment 6 with transverse dimensions 120 × 100 mm and in segments 2/3 with size 100 × 82 mm. No metastases outside the liver were found. Clinical stage was defined as cT3aN0M0 (IIIA according to TNM, seventh edition).



Figure 1. Baseline status before treatment — 04/01/2016. Tumours in the right and left liver lobe, examination in the venous phase after intravenous administration of iodine contrast medium

Infection with hepatitis B and C viruses (HBV and HCV) was excluded. The hepatic efficiency was assessed as Child-Pugh A (5 points), with no cirrhosis, and baseline alpha-fetoprotein (AFP) level before treatment was 83.88 IU/mL (N 0–5.8 IU/mL).

The patient was qualified for first-line palliative treatment with sorafenib in a daily dose of 800 mg orally.

From January 12, 2016 to February 6, 2017 the patient received 15 courses of treatment with good initial tolerance. Fatigue syndrome (Common Toxicity Criteria [CTC] 1) and hand-foot syndrome (CTC 1) were observed. The patient did not require reduction of initial sorafenib dose.

In subsequent imaging studies, a gradual decrease in the size of liver lesions was noted. In the follow-up CT study in February 2017 (Fig. 2, 3), two lesions were visible: in segment 6 (55 × 43 mm) and in segment 3 (55 × 37 mm). Clinical partial remission (cPR) was described, according to the RECIST (Response Evaluation Criteria in Solid Tumours) classification 1.1. Normalisation of AFP level was obtained after 12 weeks of treatment.

Due to a very good treatment response, the patient was qualified for radical surgical treatment. In May 2017, left-sided liver bisegmentectomy with resection of residual segments 2 and 3 and resection of liver segment 6 were performed. Complete remission (ypCR) was found — no cancer cells were detected in postoperative histological evaluation. Due to the fact that CR is an extremely rare phenomenon in this type of cancer, and because of the preoperative radiological response at the level of partial remission, re-evaluation of histological preparations was performed. It was found that HCC islands were visible in the postoperative material, surrounded by fibrosis and lymphocytic infiltrates, which corresponds to partial remission (ypPR) in response to preoperative treatment rather than complete remission as described in the primary material.

The follow-up CT imaging performed in June 2017 (Fig. 4) showed the state after resection of left-sided lobe segments — the presence of a tumour-resection bed in the right lobe, without features of local recurrence. In contrast, in the right lobe a new hypervascular nodule with wash-out effect was described (Fig. 5). In September 2017, thermoablation of the focal area, visible in imaging studies in segment 5 was performed. Due to the lack of lesions that can be monitored (measurable) in imaging studies and a very good effect of local treatment, the patient was considered cured and excluded from treatment within the drug program. The patient has not received systemic therapy with sorafenib since February 2017. He has been observed since then. The last CT scan was performed in September 2018 — the picture remained stable and there were no signs of recurrence or dissemination of the disease. AFP level

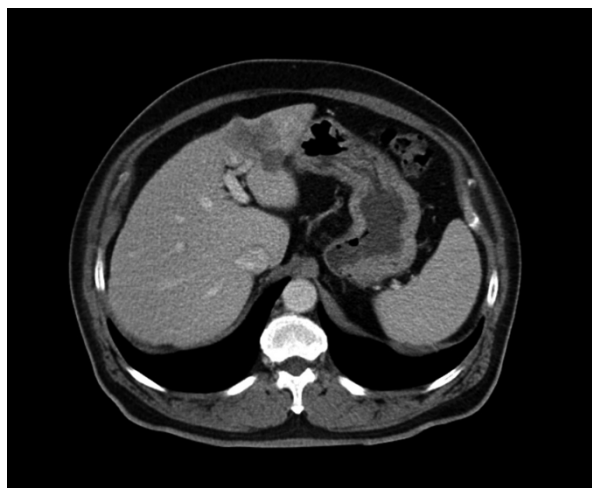


Figure 2. Status after sorafenib treatment—02/02/2017. Shrinkage of lesion in the left lobe, venous phase



Figure 4. Status after resection of the lateral segments (2 and 3) of the left lobe together with the tumour and segment 6—23/06/2017



Figure 3. Status after sorafenib treatment—02/02/2017. Shrinkage of lesion in the right lobe, venous phase

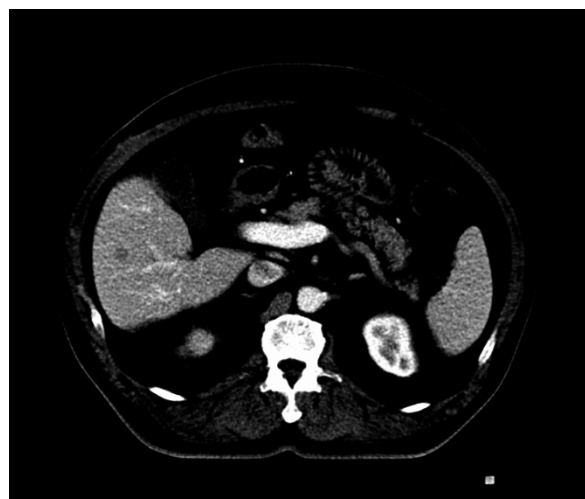


Figure 5. Status after surgery—23/06/2017. The control shows the metastasis in the right lobe

remained within normal limits. The patient has reached over 12 months of disease-free survival (DFS). The use of sorafenib in the described case allowed us to conduct a radical procedure, and the treatment, assumed to be palliative, became a remission-inducing and enabling resection.

Discussion

Patients with inoperable HCC are qualified for therapy with sorafenib, an inhibitor of tyrosine kinase of membrane receptor and serine/threonine kinases of the intracellular RAS/MAPK signalling pathway. Sorafenib is the first drug to be used in the prospective

randomised SHARP study and extended the median OS in patients with HCC by three months; 71% of patients achieved stabilisation of the disease, no CR was reported. Only 2% of patients achieved a clinical response at the PR level [9]. The results obtained were confirmed in the ASIA-PACIFIC study; however, the small sample size (226 compared to 602 patients in the SHARP study) requires caution in the interpretation of its conclusions [10].

To date, only a dozen CR cases have been described in the literature in patients with HCC during sorafenib treatment, and pCR has been found only in a few cases in the world [11].

In the recent years, several clinical trials have been completed with drugs that can be used in HCC systemic

treatment (e.g. sunitinib, erlotinib, everolimus, bri-vanib), but none of them has yet proved its effectiveness in HCC patients [12–15].

In 2016, a study with regorafenib (RESORCE) was completed, which showed a positive effect of the drug on progression-free survival (PFS) prolongation by approximately three months in comparison with placebo in second-line treatment [16].

The results of other studies have been published — in reference to the first-line treatment REFLECT study with lenvatinib compared to sorafenib, in further treatment lines in the CELESTIAL study with cabozantinib, and in the REACH-2 study with ramucirumab, which proved the effect of these drugs on extended survival versus placebo [17].

In 2018, very interesting results of a retrospective analysis were published on the basis of sorafenib treatment of over 800 patients diagnosed with HCC, among which a subgroup of 81 patients (10%) was identified receiving the drug for more than 12 months. In the group with long-term treatment 11 patients (13.7%) achieved radiological PR, and another five (6.3%) patients clinical CR. Two patients underwent liver transplantation, and three others underwent resection of a primary tumour. The authors of the study suggest that patients receiving sorafenib for over one year can have significant benefit in terms of long-term survival [18].

To date, predictive factors of response to treatment have not been identified in HCC patients receiving multi-kinase inhibitors. In the majority of patients, the results of treatment are not satisfactory. Currently, only sorafenib treatment in the first line is generally available in Poland (drug program). Treatment may be provided to patients without extrahepatic metastases, in good general condition, and without signs of liver failure. Due to the lack of availability of subsequent treatment lines, it was extremely difficult to decide about discontinuation of sorafenib treatment in the present case. Maintenance therapy with sorafenib after surgical intervention and thermoablation is a therapeutic option; nevertheless, its course is so non-standard that there are no guidelines for further treatment or evidence of the efficacy of continuing systemic treatment.

It is noteworthy that, based on previous experience, the results of adjuvant treatment with sorafenib in patients who underwent radical surgical treatment did not improve DFS or OS [19]. At present, the patient has been under observation for almost 1.5 years without the need to receive treatment — he lives in a sense of health and has returned to normal life and social roles.

New molecular targets that might be useful in the treatment of HCC patients are still being sought. The results were published of studies with anti-PD-1 (nivolumab, pembrolizumab), anti-PD-L1 (durvalumab), and anti-CTLA-4 (tremelimumab) drugs as well as

anti-PD-L1 (atezolizumab) in combination with bevacizumab [17]. These drugs are tested both in palliative and in adjuvant treatment. It may also be possible to identify the predictors of treatment response in patients with HCC undergoing immunotherapy.

There are first reports on the impact of PD-L1 expression level, baseline AFP concentration, and CD8+ T cell infiltration, which may correlate with response to immune checkpoint-targeted cancer immunotherapies [20, 21]. The correlations of immune response with microbiota or monocyte level in peripheral blood that are the subject of many ongoing studies are noteworthy [22].

Based on the aforementioned case report, the importance of the quality of histological evaluation results should also be underlined. In the presented case, the pCR described in another centre was questioned and, after consultation, finally described as pPR. Complete pathological remissions in HCC after using sorafenib should now be treated as anecdotal, and each of them should undergo independent histological evaluation in the reference centre.

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