VIA MEDICA

REVIEW ARTICLE

Ewa Klank-Sokołowska[1], Mariola Kucharewicz[1], Marek Z. Wojtukiewicz[1, 2]

[1]Department of Clinical Oncology, Comprehensive Cancer Centre of Białystok, Poland
[2]Department of Oncology, Medical University of Bialystok, Poland

Cabozantinib in the treatment of advanced hepatocellular carcinoma patients

Address for correspondence:
Prof. dr hab. n. med.
Marek Z. Wojtukiewicz
Klinika Onkologii Uniwersytet Medyczny
w Białymstoku
Białostockie Centrum Onkologii
ul. Ogrodowa 12, 15–027 Białystok
e-mail: onkologia@umb.edu.pl

Oncology in Clinical Practice
2019, Vol. 15, No. 4, 195–201
DOI: 10.5603/OCP.2019.0007
Translation: dr n. med. Dariusz Stencel

ISSN 2450–1654

ABSTRACT

Hepatocellular carcinoma (HCC) is the sixth most frequently diagnosed malignancy in the world, with the number of cases steadily increasing. Currently, around 850,000 new cases are diagnosed annually. In the majority of patients, HCC is diagnosed at an advanced stage mainly due to the lack of early symptoms. Risk factors for HCC are well known. HCC usually develops in cirrhotic liver; the exception is a form of fibrolamellar carcinoma arising in healthy liver. Hepatocarcinogenesis is a multistage process in which many pathways of intracellular signal transduction are disturbed, which leads to various biological characteristics of the disease. During foetal life, liver cells produce multiple factors, e.g. epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), or platelet-derived growth factor (PDGF), which play a significant role in organogenesis. In adults, the production of many of the factors decreases or does not exist. As a result of organ damage (e.g. after injury), hepatocytes start the synthesis again, but only temporarily. In a chronically damaged liver, a dysregulation of the production of these factors takes place, it is continuous and leads to hepatocarcinogenesis. Understanding the HCC pathogenesis has allowed the synthesis of compounds that can directly interfere with the molecular pathways associated with the growth and progression of tumours. Cabozantinib (an oral tyrosine kinase inhibitor) targets VEGF, MET, and AXL receptors. It may be an option in patients with HCC with disease progression after one or two lines of systemic treatment (e.g. after sorafenib therapy). The use of cabozantinib in the treatment of patients with advanced HCC was evaluated in a prospective phase III study, which demonstrated prolongation of overall survival (OS) and progression-free survival (PFS) compared to patients receiving placebo. Based on the results of the study, the use of cabozantinib provides an opportunity to further improve treatment outcomes in patients with advanced HCC.

Key words: hepatocellular carcinoma, cabozantinib, multikinase inhibitor, signal transduction pathways, treatment outcomes

Oncol Clin Pract 2019; 15, 4: 195–201

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Hepatocarcinogenesis is a complex, multistage process, in which the disorders of many intracellular transduction pathways occur, subsequently leading to heterogenous biological characteristics of the disease. During foetal life, many growth factors are produced by hepatocytes and this plays a significant role in organogenesis — these are epidermal growth factor (EGF), insulin-like growth factors (IGF), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and transforming growth factor-α and -β (TGF-α, -β). In the healthy liver of an adult human the production of many of them is reduced to a minimum or does not exist. In turn, when regenerative processes after organ damage (e.g. injury) require the production of these factors, adult hepatocytes synthesise them for a transitional period (EGF, TGF-α, IGF, and VEGF). However, this process is dysregulated

in chronically damaged liver, leading to permanent mitogenic signalling. Like other growth factors (FGF, PDGF), HGF is produced and released from sources other than hepatocytes (e.g. activated hepatic stellate cells, myofibroblasts, endothelial cells, Kupffer cells, and bile duct epithelium), which can contribute to hepatocarcinogenesis. There is no single dominant signal pathway in the pathogenesis of HCC; however, the introduction of molecular target-directed drugs (targeted therapies) significantly expanded the possibilities of systemic therapy of patients with HCC [1, 2].

The first drug with documented impact to extend overall survival (OS) in patients with HCC in advanced clinical stages was sorafenib, a small-molecule multikinase inhibitor. Clinical efficacy has also been confirmed for regorafenib in the second-line treatment. Regorafenib has molecular targets similar to sorafenib — in patients with advanced HCC after sorafenib failure it showed a significant prolongation of OS by almost three months compared to the control group.

A novel drug with proven effectiveness in the treatment patients with HCC is cabozantinib, an oral tyrosine kinase inhibitor targeted against VEGFR, MET, and AXL. Cabozantinib is indicated for use as monotherapy in adult patients with HCC previously treated with sorafenib. The aim of the study is to present the value of cabozantinib in patients with advanced HCC.

Epidemiology

The most common primary liver cancer is HCC (approximately 85–90%), which accounts for about 4% of all newly diagnosed cancers in the world and is the sixth cancer in terms of prevalence worldwide (about 850,000 new cases annually) and the tenth cause of cancer-related deaths. HCC morbidity is constantly increasing. Gender diversity is observed — HCC applies more than twice as much to men than to women. In Poland about 3000 new cases are diagnosed annually. Unlike other human malignancies, risk factors for HCC are well understood [2–7]. There is also clear geographical differentiation of HCC, which is undoubtedly related with exposure to hepatitis B (HBV) and C virus (HCV) infections. More than 80% of all HCC cases occur in developing countries, mainly in China and Southeast Asian countries and in sub-Saharan Africa. In Western countries the incidence of HCC is low except for in Southern Europe, where morbidity among men is higher.

The risk of developing HCC increases with age. The highest incidence is observed in people aged around 50–60 years, but some young people at the age of 20–30 years are also affected; they have a rarely occurring form of so-called fibrolamellar carcinoma (FLC).

Aetiology

In 70–90% of cases, HCC develops on the grounds of liver cirrhosis, caused by chronic hepatotropic virus infection (HBV, HCV) or toxic liver damage (alcohol, *nonalcoholic fatty liver* disease [NAFLD], aflatoxin — produced by *Aspergillus flavus*), and it is seen much less often metabolic diseases (especially hemochromatosis — about 300-fold increased risk of HCC) and alpha-1 antitrypsin deficiency. Other factors that increase HCC risk are associated with obesity and insulin resistance. Research is currently underway to determine the impact of genetic disorders on HCC development. Mutations, translocations, amplifications, deletions within suppressor genes (*TP53*, *DLC1*, Wnt pathway), oncogenes and growth factors (EGFR, VEGFR, Ras, mTOR pathway, HEDGEHOG, HGF, IGF), and cell cycle regulators (cyclin-dependent kinase inhibitor 2A [p16] or cell cycle regulator p27). Understanding genetic disorders allows the use of targeted therapies. The targets for molecular drugs are intracellular signalling pathways responsible for cell proliferation and tumour growth, but also influencing tumour angiogenesis and dissemination [1, 7, 8].

HCC development is a complicated, multistage process. A transformation from a regenerative nodule into cirrhosis, through the dysplastic nodule, to cancer usually takes many months. Enlarging the lesion to about 2 cm in diameter takes about 12 months [9–11].

Pathology

Hepatocellular cancer is adenocarcinoma in a single-focal, multifocal, or disseminated infiltration form. It can have various degrees of histological maturity — from G1 (reminiscent of normal hepatocytes) to G4 (undifferentiated). FLC is a specific type, found mainly in young people, with no relation to cirrhosis, appearing in unchanged liver without connection to viral infection, and characterised by increased AFP serum concentration.

Diagnostics

Symptoms

Early HCC symptoms are unspecific. They may result from coexisting liver cirrhosis. The course of liver cirrhosis in compensated phase may be asymptomatic or minimal symptoms may be found. General symptoms include: asthaenia, loss of appetite, weight loss, low-grade fever, nausea, vomiting, diarrhoea, and pain in the right subcostal region of the abdomen or epigastrium. The liver can be enlarged, hard, painless, and with

nodular changes. Increasing portal hypertension leads to development of collateral circulation, oesophageal varices, haemorrhoids, and characteristic "Medusa's head" (widened capillary network in the chest and abdominal wall). Impairment of hepatic function can lead to thromboembolic complications or haemorrhagic diathesis. The symptoms may also include jaundice, ascites, or encephalopathy in advanced states. In the course of HCC, symptoms of paraneoplastic syndromes can occur: dermatomyositis syndromes, gynecomastia, polyglobulia, hypercalcaemia, hypercholesterolaemia, hypoglycaemia, or dysfibrinogenaemia [10, 12].

Laboratory tests

In patients with HCC, abnormal results of laboratory tests are observed. In the complete blood count (CBC) some features of anaemia are observed, as well as thrombocytopaenia, that can transform into thrombocythaemia. Coagulation system disorders are also present (reduced prothrombin plasma level, prolonged activated partial thromboplastin time [APTT]), as well as disorders of lipid (hypocholesterolaemia, sometimes leading to hypercholesterolaemia) and protein (hypoalbuminaemia, reduced total protein plasma level) metabolism. Hyperbilirubinaemia is observed, increased aminotransferase levels with common predominance of aspartate aminotransferase (AST) over alanine aminotransferase (ALT) — de Ritis ratio > 1, glucose intolerance or type 2 diabetes, and, rarely, hepatorenal syndrome (HRS).

The only serological marker used in HCC diagnosis is AFP serum concentration [10, 12]. The value of AFP does not show a close relationship with HCC stage. In a significant group of patients with HCC, an increased AFP (α-fetoprotein) concentration is observed, but in approximately 40% of patients there is no increase in the concentration of this protein. About 30% of patients with cirrhosis may have an elevated AFP concentration without HCC. In patients with FLC the concentration of AFP may be normal.

Non-invasive diagnostics

In the majority of patients the diagnosis of HCC is based on imaging examinations. The most commonly used method in the initial diagnosis, especially in surveillance of patients with cirrhosis, is abdominal ultrasound examination (USG). The sensitivity of this method ranges between 65 and 80%, and the specificity is above 90%. The basic diagnostic methods include three-phase computed tomography (CT) examination with contrast medium and magnetic resonance imaging (MRI). The radiological picture is characteristic: there is contrast enhancement in the arterial phase of the study and delayed contrast washout during venous and delayed phases. According to the guidelines, a typical radiological image justifies HCC diagnosis without histopathological examination [13–15].

Positron emission tomography (PET) in combination with CT (PET-CT) is not recommended for recognition of early cancer forms but may be useful in later stages to exclude a retrohepatic tumour location.

Invasive diagnostics

HCC diagnosis is based on histological or — less valuable — cytological examination. As recommended by experts and European guidelines (EASL 2018 guidelines), in the case of cirrhotic liver with nodule below 1 cm, which neither changes its nature nor grows, abdominal USG should be repeated every four months. If the tumour grows to a diameter of 1–2 cm, detailed imaging diagnostics (CT, MRI) should be performed. A change of 1–2 cm requires confirmation in two imaging tests with contrast. In the case of nodules greater than 2 cm, a typical radiological image (as described above) in a single imaging study is sufficient to diagnose HCC.

Clinical staging of HCC helps in selecting the optimal treatment strategy. In addition to the need to perform imaging tests, it is also required to assess patient's performance status (PS) and liver function. There are several systems for HCC clinical classification. The TNM classification only assesses the stage of the disease and does not take into account the accompanying hepatic impairment according to Child-Pugh scale. Okuda staging system (Okuda's scale), including information about tumour and liver function, is currently rarely used. In Europe the most popular classification is the Barcelona Clinic Liver Cancer (BCLC) staging system, which assesses all of aforementioned factors (tumour stage, liver efficiency according to the Child-Pugh scale, and PS). The BCLC classification divides patients into five categories (0, A, B, C, and D). The BCLC division is helpful when assessing patients' eligibility for treatment [3, 4, 13, 16–18].

Surgical treatment

Eligibility criteria of HCC patients for surgical treatment and transplantation are highly restrictive but give a chance of a complete cure. Cancer resection in cirrhotic liver may be considered in patients with BCLC stage 0 or A. In patients without cirrhosis, surgery is the treatment of choice because the resection of even a large volume of the organ does not put the patient at risk of liver failure. Classical eligibility criteria for liver transplantation in patients with HCC are the so-called

Milan criteria: patients with one nodular change in the liver less than 5 cm or a maximum of three lesions in the liver not exceeding 3 cm can be qualified for transplantation. In practice, extended criteria are often used, the so-called "up to seven" criterion — the size of the largest lesion expressed in centimetres and the number of remaining lesions summed to a maximum of seven [13, 19–21].

Local methods of treatment

In a properly selected group of patients with recurrent diseases after surgery or ineligible for resection or transplantation a significant improvement of prognosis, and even long-term remission, can be obtained using local methods of treatment, which include: radiofrequency ablation (RFA), percutaneous ethanol injection therapy (PEIT), radioembolisation, transarterial embolisation (TAE), or cryoablation [22–24].

Systemic treatment

Advances in understanding the pathogenesis of HCC have led to the development of drugs that can interfere directly with the molecular pathways associated with cancer growth and progression. Sorafenib has proven impact on OS in HCC patients; it is an oral small-molecule inhibitor of many tyrosine kinases (Raf, VEGFR, PDGR-b, KIT, FTL-3, RET) and is characterised by anti-angiogenic and anti-proliferative activity. The basis for the registration of sorafenib for use in HCC treatment was an international, multi-centre phase III clinical trial with the acronym SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol). The results of the study showed a significant OS improvement in HCC patients treated with sorafenib, compared to the placebo group. In total, 602 patients with advanced HCC were enrolled in the study (approximately 90% from European sites). Treatment with sorafenib was rarely associated with an objective response to treatment – the partial response (PR) rate was seen in 2.3% of patients only; more often stabilisation of the disease (SD) was observed (about 71%). The median OS in sorafenib patients was 10.7 months, that is almost three months longer than in the control group [25, 26]. In another phase III clinical trial with similar design to the SHARP study, the efficacy of sorafenib in the Asian population was evaluated; a significant reduction of the disease progression risk (by 42%) and risk of death (by 33%) were observed. Note the difference in statistical power of both studies and the difference in the aetiology of HCC — in the Asian study patients with hepatitis B virus (HBV) constituted about 75% of the study population, while in the European study it was about 30% of patients. The Asian study also included patients in a worse general condition and with more advanced HCC compared to the European study; hence, both prognosis and treatment results in Asian countries were generally worse [27, 28]. In Poland, sorafenib is reimbursed within a drug program. This agent is indicated in the treatment of patients with HCC with advanced disease, which prevents surgical treatment of patients with relapse after radical surgery, after failure of previously used local treatment methods, or when they are unavailable.

Another option of systemic treatment of patients with HCC is regorafenib, which is a multi-kinase inhibitor with similar molecular targets to sorafenib (the structure differs only by one substituent). Regorafenib is indicated for second-line treatment in patients with advanced HCC, who received sorafenib in the first-line therapy with good clinical tolerance but, progression of the disease was found after a beneficial period. In a clinical trial regorafenib was compared with placebo, and OS was the main efficacy outcome assessed. Regorafenib was shown to prolong the OS — the median was 10.6 months, compared with 7.8 months in placebo group [29]. Currently in Poland regorafenib treatment is not reimbursed.

A new drug with proven efficacy targeting the molecular pathways associated with tumour growth and HCC progression is cabozantinib [30, 31]. Cabozantinib may be considered in patients with disease progression, who have received one or two systemic treatment lines and have normal liver function and performance status 0–1 according to the Eastern Cooperative Oncology Group (ECOG) scale. On November 12, 2018, the European Medicines Agency (EMA) approved cabozantinib for use as monotherapy in the treatment of adult HCC patients who had previously received sorafenib.

Cabozantinib is an oral non-selective, multi-kinase inhibitor directed against VEGF receptor type 2 (VEGFR2), the *mesenchymal epithelial* transition factor *receptor* (*Met*), and AXL receptor tyrosine kinase (Fig. 1) [32, 33]. Through the inhibition of tyrosine kinases, cabozantinib affects processes associated with tumour growth, angiogenesis, metastasis, bone remodelling, and drug resistance. Effects on VEGF pathway are a known therapeutic target in HCC, but clinical benefits are inadequate. Inhibition of additional intracellular transmission pathways can successfully improve the effectiveness of treatment. Similarly to VEGR, the MET and AXL tyrosine kinase receptors are induced by tumour hypoxia and play an important role in tumour biology. The dysregulation of HGF/cMET pathway receptors is crucial for hepatocyte regeneration after liver injury. Both kinases are also involved in the development of resistance to anti-angiogenic therapies. High MET and

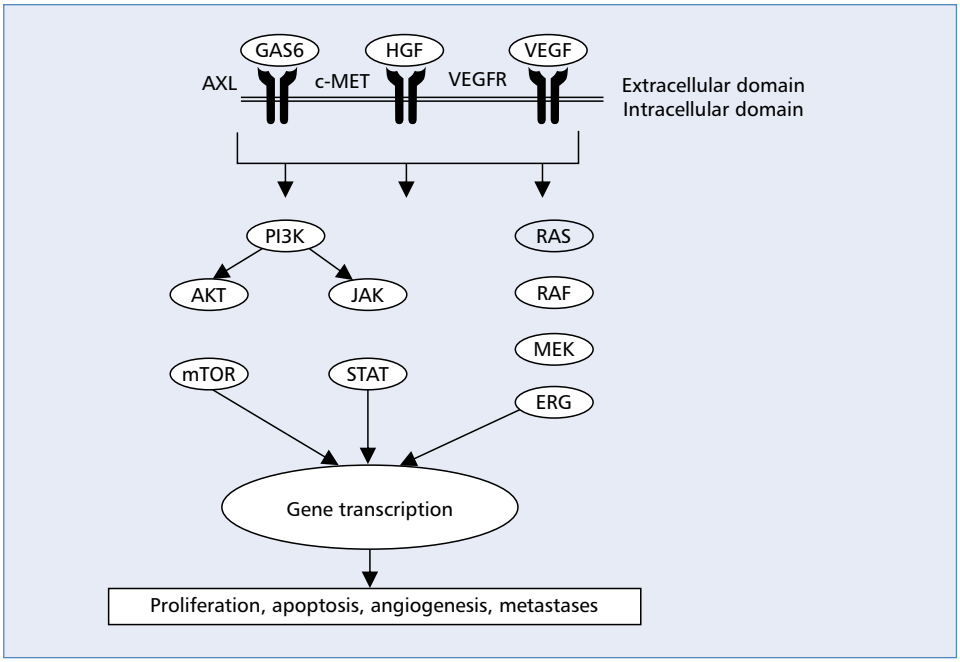

Figure 1. Mechanism of action of cabozantinib

AXL expression may be associated with poor prognosis in HCC patients.

In a phase II randomised clinical trial, cabozantinib showed clinical activity in patients with advanced HCC, and the results were independent of previous treatment (prior sorafenib use — yes or no). The median OS was 11.5 months, and the median progression-free survival (PFS) reached 5.2 months.

Based on the aforementioned results, a phase III double-blind, randomised, placebo-controlled study (CELESTIAL) was performed. Recruitment for the study was conducted in 19 countries from September 2013 to September 2017. The study included 707 patients with advanced HCC, who were ineligible for radical treatment and had previously received sorafenib in first-line treatment. Inclusion criteria were as follows: age over 18 years, ECOG performance status 0–1, Child-Pugh class A, normal kidney function, and absence of abnormalities in haematopoietic function. Patients were allowed to receive one previous treatment line — apart from sorafenib — due to advanced disease. Patients were randomly assigned (2: 1) to a group receiving cabozantinib (n = 470) or a group receiving placebo (n = 237). Randomisation was stratified according to the aetiological factor (HBV with or without HCV, HCV — without HBV, or other), geographical region (Asia or other region), and the presence of extrahepatic metastases and infiltration of large blood vessels. Cabozantinib was administered orally at a daily dose of 60 mg. A treatment disruption or dose reduction to 40 mg and 20 mg was used to control side effects. Treatment was continued until patients had clinical benefit or until unacceptable toxicity occurred. OS was a primary endpoint, and the secondary endpoints included PFS and overall response rate (ORR). The response was assessed based on CT according to RECIST 1.1 criteria every eight weeks, and patients were allowed to continue blinded treatment after radiological disease progression as long as they had clinical benefit. Based on the data analysis, it was found that the median OS in the cabozantinib group was 10.2 months (95% CI [confidence interval]: 9.1–12.0 months) and 8.0 months in the placebo group (95% CI: 6.8–9.4 months). The risk of death decreased by 24% (hazard ratio [HR] = 0.76; 95% CI: 0.63–0.92; p = 0.005). The median PFS in cabozantinib group was 5.2 months (95% CI: 4.0–5.5 months) and 1.9 months in the placebo group (95% CI: 1.9 months). The risk of disease progression decreased by 56% (HR = 0.44, 95% CI: 0.36–0.52, p < 0.001). Objective response rate according to RECIST 1.1 criteria was 4% in the cabozantinib group (18 out of 470 patients achieved PR) and less than 1% in the placebo group (one out of 237 patients). Disease control (PR and SD) was achieved in 64% of patients treated with cabozantinib (n = 300) compared with 33% (n = 79) in the placebo group. In the CELESTIAL clinical trial, the mean treatment duration was 3.8 months in the cabozantinib group and two months in the placebo group. The dose was reduced in 62% of patients receiving cabozantinib (n = 291) and in 13% in the placebo group (n = 30). The average daily dose of cabozantinib was 35.8 mg, and in the placebo group it was 58.9 mg, with median time to

first dose reduction of 38 days, and to first disruption of cabozantinib treatment — 28 days. The majority of complications observed with cabozantinib were analogous to the adverse effects profile observed during treatment with other tyrosine kinase inhibitors with anti-VEGFR activity. The incidence of adverse events (AEs) of any degree was high, e.g. 99% *vs.* 92%, of which there were 68% and 36% grade 3 and 4 AEs, respectively. The most common grade 3 and 4 adverse events in the cabozantinib group were: hand-foot syndrome (palmar-plantar erythrodysesthesia [PPE]) — 17% *vs.* 0%, hypertension — 16% *vs.* 2%, increased transaminases activity — 12% *vs.* 7%, fatigue — 10% *vs.* 4%, diarrhoea — 10% *vs.* 2% [34]. The most frequent cause of dose reduction in patients receiving cabozantinib was PPE (22%), diarrhoea (10%), fatigue (7%), hypertension (7%), and elevated transaminases (6%).

In conclusion, cabozantinib therapy in patients previously treated systemically due to advanced HCC resulted in statistically and clinically significantly longer OS and PFS, compared with patients receiving placebo.

Conclusions

Significant evolution in understanding the molecular pathology of HCC has contributed to the development of drugs targeted on signalling pathways [18, 35]. Pre-clinical and clinical trials are underway to test other options in HCC therapy. Recently, high hopes are associated with immunotherapy, used in various types of cancer. There are currently many clinical trials evaluating the safety and efficacy of new therapies for the treatment of HCC, including nivolumab, pembrolizumab, tremelimumab, and lenvatinib [36–39]. It seems that in the near future this may translate into an improvement in the treatment outcomes in patients with advanced HCC.

References

1. Höpfner M, Schuppan D, Scherübl H. Growth factor receptors and related signalling pathways as targets for novel treatment strategies of hepatocellular cancer. World J Gastroenterol. 2008; 14(1): 1–14, indexed in Pubmed: 18176955.
2. Torre L, et al. Global cancer statistics 2012. Global cancer statistics 2012, CA Cancer J Clin. 2015; 65: 87–108.
3. Galle P, Forner A, Llovet J, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. Journal of Hepatology. 2018; 69(1): 182–236, doi: 10.1016/j.jhep.2018.03.019.
4. Vogel A, Cervantes A, Chau I, et al. Hepatocelular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annalos of Oncology. 2018; 29(supl 4): 238–255.
5. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136(5): E359–E386, doi: 10.1002/ijc.29210, indexed in Pubmed: 25220842.
6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018; 68(1): 7–30, doi: 10.3322/caac.21442, indexed in Pubmed: 29313949.
7. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology. 2007; 132(7): 2557–2576, doi: 10.1053/j.gastro.2007.04.061, indexed in Pubmed: 17570226.
8. Kudo M. Signaling pathway/molecular targets and new targeted agents under development in hepatocellular carcinoma. World J Gastroenterol. 2012; 18(42): 6005–6017, doi: 10.3748/wjg.v18.i42.6005, indexed in Pubmed: 23155330.
9. Kojiro M, Roskams T. Early hepatocellular carcinoma and dysplastic nodules. Semin Liver Dis. 2005; 25(2): 133–142, doi: 10.1055/s-2005-871193, indexed in Pubmed: 15918142.
10. Simon K. Etiopatogeneza raka wątrobowokomórkowego 2012. Kompendium postępowania w nowotworach wątroby. 2012: 12–18.
11. Górnicka B, Nasierowska-Guttmejer A. Rak wątrobowokomórkowy — podstawy diagnostyki morfologicznej. 2014; 18(1): 9–13.
12. Pazgan-Simon M, Zuwała-Jagiello J. Kompendium postępowania w nowotworach wątroby. 2012: 19–21.
13. Krawczyk M, Wasilewicz M, Hartleb M, et al. Rozpoznanie i leczenie raka wątrobowo komórkowego. Rekomendacje sekcji hepatologicznej PTG. Gastroenterologia Praktyczna. 2016.
14. Krzakowski M, Zieniewicz A, Habior A, et al. Rak wątrobowokomórkowy — rozpoznanie i leczenie. Med Prakt Onkol. 2009; 6: 73.
15. Ayuso C, Rimola J, García-Criado A. Imaging of HCC. Abdom Imaging. 2012; 37(2): 215–230, doi: 10.1007/s00261-011-9794-x, indexed in Pubmed: 21909721.
16. National Comprehensive Cancer network. NCCN clinical practice guidelines in oncology: hepatobiliary cancers, vers. 2017; 4.
17. Bruix J, Sherman M, Llovet JM, et al. EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona — 2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001; 35(3): 421–430, indexed in Pubmed: 11592607.
18. Akoad ME, Pomfret EA. Surgical resection and liver transplantation for hepatocellular carcinoma. Clin Liver Dis. 2015; 19(2): 381–399, doi: 10.1016/j.cld.2015.01.007, indexed in Pubmed: 25921669.
19. Marín-Hargreaves G, Azoulay D, Bismuth H. Hepatocellular carcinoma: surgical indications and results. Crit Rev Oncol Hematol. 2003; 47(1): 13–27, indexed in Pubmed: 12853096.
20. Małkowski P, Chmura A, Pacholczyk M, et al. Przeszczepienie wątroby — metody klasyczne i warianty. Med Sci Rev Hepatol. 2005: 119–126.
21. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis. 2005; 25(2): 181–200, doi: 10.1055/s-2005-871198, indexed in Pubmed: 15918147.
22. Mazzaferro V, Battiston C, Perrone S, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. Ann Surg. 2004; 240(5): 900–909, indexed in Pubmed: 15492574.
23. Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. Gastroenterology. 2004; 127: S179–88.
24. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology. 2003; 37(2): 429–442, doi: 10.1053/jhep.2003.50047, indexed in Pubmed: 12540794.
25. Llovet JM, Ricci S, Mazzaferro V, et al. SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359(4): 378–390, doi: 10.1056/NEJMoa0708857, indexed in Pubmed: 18650514.
26. Rimassa L, Santoro A. Sorafenib therapy in advanced hepatocellular carcinoma: the SHARP trial. Expert Rev Anticancer Ther. 2009; 9(6): 739–745, doi: 10.1586/era.09.41, indexed in Pubmed: 19496710.
27. 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(1): 25–34, doi: 10.1016/S1470-2045(08)70285-7, indexed in Pubmed: 19095497.
28. Tokajuk P, Uścinowicz A, Wojtukiewicz MZ. Sorafenib w leczeniu chorych na zaawansowanego raka wątrobowokomórkowego. Contemp Oncol. 2014; 18(1): 41–46.
29. Bruix J, Qin S. Merle Ph., Granito A . Regorafenb for patiens with hepatocellular carcinoma who progresse on sorafenib treatment (RESORCE): a randomised, double- blind, placebo- controlled, phase 3 trial. Lancet. 2017; 389: 56–66.
30. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med. 2018; 379(1): 54–63, doi: 10.1056/NEJMoa1717002, indexed in Pubmed: 29972759.
31. Kelley RK, Verslype C, Cohn AL, et al. Cabozantinib in hepatocellular carcinoma: results of a phase 2 placebo-controlled randomized dis-

continuation study. Ann Oncol. 2017; 28(3): 528–534, doi: 10.1093/annonc/mdw651, indexed in Pubmed: 28426123.
32. Xiang Q, Chen W, Ren M, et al. Cabozantinib suppresses tumor growth and metastasis in hepatocellular carcinoma by a dual blockade of VEGFR2 and MET. Clin Cancer Res. 2014; 20(11): 2959–2970, doi: 10.1158/1078-0432.CCR-13-2620, indexed in Pubmed: 24700742.
33. Rankin EB, Giaccia AJ. The receptor tyrosine kinase AXL in cancer progression. Cancers (Basel). 2016; 8(11): E103, doi: 10.3390/cancers8110103, indexed in Pubmed: 27834845.
34. Gerendassh BS, Creel PA. Praktyczne postępowanie w przypadku działań niepożądanych związanych z leczeniem kabozantynibem chorych z rakiem nerkowokomórkowym. Onco Targets and Therapy. 2017; 10: 5053–5064.
35. Heinrich B, Czauderna C, Marquardt JU. Immunotherapy of Hepatocellular Carcinoma. Oncol Res Treat. 2018; 41(5): 292–297, doi: 10.1159/000488916, indexed in Pubmed: 29705790.
36. El-Khoueiry A, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. The Lancet. 2017; 389(10088): 2492–2502, doi: 10.1016/s0140-6736(17)31046-2.
37. Zhu AX, Finn RS, Edeline J, et al. KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018; 19(7): 940–952, doi: 10.1016/S1470-2045(18)30351-6, indexed in Pubmed: 29875066.
38. Sangro B, Gomez-Martin C, de la Mata M, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol. 2013; 59(1): 81–88, doi: 10.1016/j.jhep.2013.02.022, indexed in Pubmed: 23466307.
39. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018; 391(10126): 1163–1173, doi: 10.1016/S0140-6736(18)30207-1, indexed in Pubmed: 29433850.
40. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology. 2003; 228(1): 235–240, doi: 10.1148/radiol.2281020718, indexed in Pubmed: 12759473.
41. Fabregat I. Dysregulation of apoptosis in hepatocellular carcinoma cells. World J Gastroenterol. 2009; 15(5): 513–520, indexed in Pubmed: 19195051.
42. Vogel A., Cervantes A., Chaul et al. Hepatocelular carcinoma : ESMO Clinical Practice Guidelines for diagnossis, treatment and follow-up. Annals of Oncology 2018; 29(supl 4): iv238–iv255.
43. Pazgan-Simon M, Simon K. Problemy diagnostyczne w rozpoznaniu raka pierwotnego wątroby. Hepatologia. 2011.
44. Di Bisceglie AM, Bolondi L, Cheng AL. Cheng A-L. Rak wątrobowokomórkowy. Via Medica. 2010.
45. Forner A, Llovet J, Bruix J. Hepatocellular carcinoma. The Lancet. 2012; 379(9822): 1245–1255, doi: 10.1016/s0140-6736(11)61347-0.
46. Grandhi MS, Kim AK, Ronnekleiv-Kelly SM, et al. Hepatocellular carcinoma: From diagnosis to treatment. Surg Oncol. 2016; 25(2): 74–85, doi: 10.1016/j.suronc.2016.03.002, indexed in Pubmed: 27312032.
47. Knox JJ, Cleary SP, Dawson LA. Localized and systemic approaches to treating hepatocellular carcinoma. J Clin Oncol. 2015; 33(16): 1835–1844, doi: 10.1200/JCO.2014.60.1153, indexed in Pubmed: 25918289.
48. Bupathi M, Kaseb A, Meric-Bernstam F, et al. Hepatocellular carcinoma: Where there is unmet need. Mol Oncol. 2015; 9(8): 1501–1509, doi: 10.1016/j.molonc.2015.06.005, indexed in Pubmed: 26160430.
49. 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. Oncologist. 2010; 15(11): 1198–1204, doi: 10.1634/theoncologist.2010-0180, indexed in Pubmed: 21036880.
50. Yada M, Masumoto A, Motomura K, et al. Indicators of sorafenib efficacy in patients with advanced hepatocellular carcinoma. World J Gastroenterol. 2014; 20(35): 12581–12587, doi: 10.3748/wjg.v20.i35.12581, indexed in Pubmed: 25253961.
51. Shao YY, Shau WY, Chan SY, et al. Treatment efficacy differences of sorafenib for advanced hepatocellular carcinoma: a meta-analysis of randomized clinical trials. Oncology. 2015; 88(6): 345–352, doi: 10.1159/000369559, indexed in Pubmed: 25572912.
52. Gbolahan OB, Schacht MA, Beckley EW, et al. Locoregional and systemic therapy for hepatocellular carcinoma. J Gastrointest Oncol. 2017; 8(2): 215–228, doi: 10.21037/jgo.2017.03.13, indexed in Pubmed: 28480062.
53. Murata S, Mine T, Sugihara F, et al. Interventional treatment for unresectable hepatocellular carcinoma. World J Gastroenterol. 2014; 20(37): 13453–13465, doi: 10.3748/wjg.v20.i37.13453, indexed in Pubmed: 25309076.
54. Siu EHL, Chan AWH, Chong CCN, et al. Treatment of advanced hepatocellular carcinoma: immunotherapy from checkpoint blockade to potential of cellular treatment. Transl Gastroenterol Hepatol. 2018; 3: 89, doi: 10.21037/tgh.2018.10.16, indexed in Pubmed: 30603725.
55. Greten T, Sangro B. Targets for immunotherapy of liver cancer. Journal of Hepatology. 2018; 68(1): 157–166, doi: 10.1016/j.jhep.2017.09.007.
56. Llovet J, Zucman-Rossi J, Pikarsky E, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2016; 2: 16018, doi: 10.1038/nrdp.2016.18.
57. Prieto J, Melero I, Sangro B. Immunological landscape and immunotherapy of hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2015; 12(12): 681–700, doi: 10.1038/nrgastro.2015.173, indexed in Pubmed: 26484443.
58. Greten TF, Ormandy LA, Fikuart A, et al. Immunotherapy of HCC. Rev Recent Clin Trials. 2008; 3(1): 31–39, indexed in Pubmed: 18474013.
59. Brar G, Greten TF, Brown ZJ. Current frontline approaches in the management of hepatocellular carcinoma: the evolving role of immunotherapy. Therap Adv Gastroenterol. 2018; 11: 1–12, doi: 10.1177/1756284818808086, indexed in Pubmed: 30377451.
60. Ikeda M, Morizane C, Ueno M, et al. Chemotherapy for hepatocellular carcinoma: current status and future perspectives. Jpn J Clin Oncol. 2018; 48(2): 103–114, doi: 10.1093/jjco/hyx180, indexed in Pubmed: 29253194.
61. Friedman LS, Keeffe EB. Handbook of liver diseases. 3th Ed. Churchill Livingstone, New York. 2012.