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Current role of chemoembolization in the treatment of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) accounts for 75% to 85% of primary liver cancers. Recent years have shown a significant increase in the incidence of HCC in Europe and the United States. The algorithm used most commonly in the treatment of HCC is the one developed in 1999 by Barcelona Clinic Liver Cancer (BCLC), updated from clinical trials. The last update is from 2022. Among the available treatments, depending on the stage of HCC, are liver transplantation, resection, thermal ablation, transarterial embolization (TAE), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), stereotactic body radiation therapy (SBRT) as well as systemic treatment. The use of irreversible electroporation (IRE), a method involving disruption of cell membrane integrity is currently undergoing research. According to the BCLC, TACE is recommended for patients with BCLC stage-B (more than three lesions, preserved portal vein flow, preserved Child–Pugh A–B liver function and no extrahepatic lesions) and with BCLC stage 0 and stage 1 as an option after failure or not feasible for the first treatment option. In this article, we will try to explain in more detail what the chemoembolization method is and what the indications for its implementation are.

Key words: liver, embolization, chemoembolization, transarterial chemoembolization, Barcelona Clinic Liver Cancer

Introduction

Hepatocellular carcinoma (HCC) accounts for 75% to 85% of primary liver cancers [1]. In Poland, there are between 2,000 and 3,000 new cases per year, while globally in 2020, HCC will account for around 900,000 new cases and around 830,000 deaths [2, 3]. HCC is the sixth most common cancer and third/fourth most common cause of death among cancers [4, 5].

It is three times more frequent in men. Recent years have shown a significant increase in the incidence of HCC in Europe and the United States. Between 2000 and 2016, mortality from HCC in the United States increased by 43% [6]. HCC is associated with chronic liver disease and cirrhosis in 80–90% of cases. Major risk factors include hepatitis B and C, alcohol abuse, non-alcoholic steatohepatitis (NASH), as well as diabetes, obesity and aflatoxin B1. It is estimated that approximately one-third of patients with cirrhosis may develop HCC with a one-year rate of 1–8% [7]. Elevated α-fetoprotein levels are found in 70–80% of patients with HCC.

There is also a variant of HCC – fibrolamellar carcinoma (FLC) – unrelated to cirrhosis, occurring mainly in young people with a slight predominance in women. This form has a different pathology and histopathology, and also a different prognosis. α-fetoprotein levels remain normal.

The algorithm used most commonly in the treatment of HCC is one developed in 1999 by The Barcelona Clinic of Liver Cancer (BCLC), updated from clinical trials. The last update from 2022 is presented in figure 1 [8]. Among the available treatments, depending on the stage of HCC, are liver

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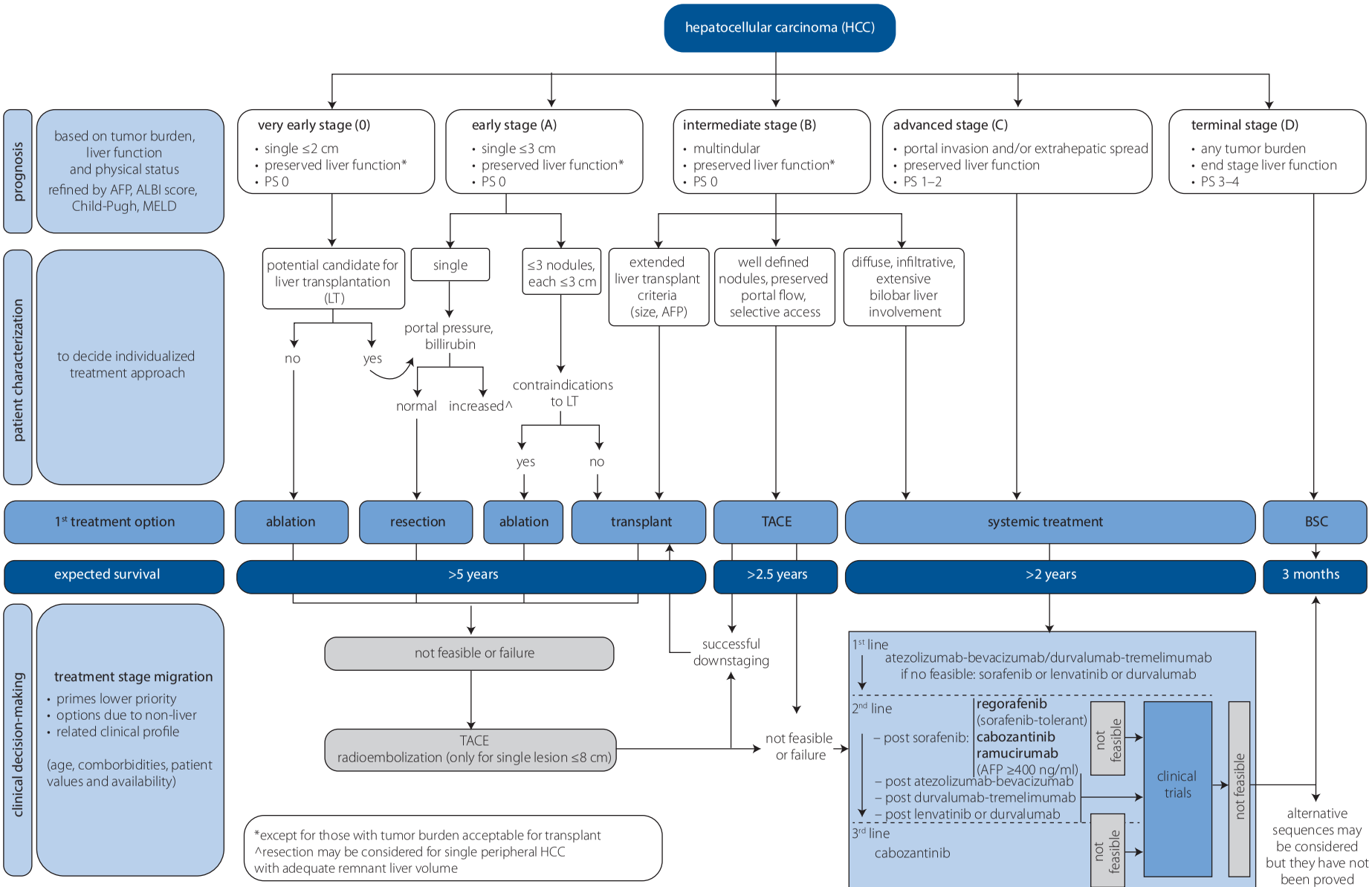

Figure 1. Barcelona Clinic Liver Cancer (BCLC) – updated from clinical trials (2022)

transplantation, resection, thermal ablation (microwave [MWA], radiofrequency [RFA] and laser ablation), transarterial embolization (TAE), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), stereotactic body radiation therapy (SBRT) as well as systemic treatment. The use of irreversible electroporation (IRE), a method involving disruption of cell membrane integrity [9, 10], is currently undergoing research. According to the BCLC, TACE (transarterial chemoembolization) is recommended for patients with BCLC stage-B (more than three lesions, preserved portal vein flow, preserved Child-Pugh A–B liver function and no extrahepatic lesions) [11–15], and with BCLC stage 0 and stage 1 as a option after failure or not feasible for the first treatment option [8].

Treatment strategy for HCC

An understanding of the liver's vascularity and HCC is necessary for the correct choice of treatment strategy for HCC. Healthy liver parenchyma is nourished approximately 75% from the portal vein branch, with only the remainder coming from the hepatic artery branch [16]. The terminal branches of the hepatic artery are divided into two sections. The first section accompanies the portal vessels and supplies the peribiliary vascular plexus (PBP), the interstitial tissue of the portal system and the walls of the portal vessels. The second section, named the isolated artery, penetrates the liver parenchyma independently of the portal vein branch. In the cirrhotic liver, PBPs are more developed which provides a link between the arterial and portal systems, and favors tumour survival in the event of arterial occlusion. The development of HCC in a cirrhotic liver progresses in several stages from a regenerative nodule undergoing transformation initially to a dysplastic nodule with a low and then high degree of dysplasia. In subsequent stages, a foci of HCC, known as nodule-in-nodule, appears within the dysplastic nodule to eventually progress to a large HCC. With this process, the proportions of vascularization change – the role of the portal system gradually declines in favor of the arterial system. In poorly and moderately differentiated HCC, portal vascularization almost completely disappears [17]. HCC can grow in an expanding, infiltrating or mixed form. The first form is encapsulated and compresses the surrounding parenchyma, while the second form is poorly differentiated without a capsule with blurred outlines. This differentiation makes some HCCs, especially encapsulated, well-differentiated and extracapsular infiltrating HCCs having partially preserved portal vascularization.

The mode of enhancement has an obvious impact on HCC characteristics in imaging studies. In patients at risk, LI-RADS criteria are used in the assessment of liver lesions. These take into account lesion size, non-rim arterial phase hyperenhancement (APHE), non-peripheral washout, enhancing capsule and threshold growth. Using the above as a basis, the lesion can be assigned to one of the groups from LI-RADS 1, defined as definitely benign, to LI-RADS 5, defined as definitely HCC [18].

The first reports of hepatic artery embolization in the treatment of hepatic cancers date back to 1974. In the 1970s, the first doses of chemotherapeutic agents were administered *via* the hepatic artery, and results showed that even single procedures gave better results than multiple cycles of systemic therapy [19–22]. There are currently two types of TACE procedures resulting from the embolization material used. Conventional TACE (cTACE) in which the chemotherapeutic agent is mixed with Lipiodol – an oily, thick contrast agent to act as a drug carrier.

Drug eluting bead TACE (DEB TACE) – drug-soaked microspheres which, when injected into the vasculature, close the vasculature and then release the chemotherapeutic agent into the tumour in a controlled manner. The microspheres require the addition of a contrast agent to visualize the mixture.

Both procedures can be performed using a standard microcatheter or with a balloon-tipped microcatheter that, when inflated, changes regional hemodynamic conditions in the catheterized vessel or can be used as a safeguard against reflux. This method is called ballon occluded TACE (b-TACE). There is a difference in the distribution of embolization material in cTACE and DEB-TACE. In cTACE, the emulsion, formed at a ratio of one part chemotherapeutic agent to two parts Lipiodol, selectively injected into the arteries is initially deposited in the tumor's sinusoids and then passes into the tumor's draining vessels on the side of the portal system and, *via* PBP, enters the portal system of healthy liver tissue in the tumor's immediate vicinity and into the arterial anastomoses [23–25]. This results in the prevention of flow reversal in the outflow pathway, the tumors necrosis and the increased margin of healthy liver surrounding the tumour. There is also an opportunity to potentially identify other tumour feeding routes that were not originally visible [26]. In the case of richly vascularized lesions, where the mixture's full dose is not sufficient to close the tumor's vascular bed, embolization can be completed using particles or Spongostan. As this mechanism also causes necrosis of healthy hepatocytes surrounding the tumour, ultra-selective embolization of the feeding vessels to minimize liver damage is very important [27].

DEB-TACE involves injecting embolization material saturated with a chemotherapeutic agent (usually doxorubicin but also epirubicin, mitomycin, cisplatin) through a catheter directly into the branch of the hepatic artery feeding the tumour. In DEB-TACE, it is possible to select the size of microspheres (from 40 µm to 900 µm). Smaller microspheres result in more peripheral vascular closure (i.e. closer to the tumor's centre) resulting in better deposition of the chemotherapeutic agent, but also significantly more necrosis of the liver parenchyma compared to the procedure performed with larger particles [28]. With smaller microspheres, there may also be an increased risk of biliary necrosis and blockages outside the liver. At the same time, microspheres are unable to block outflow from the tumour in DEB-TACE. Closing only the arterial vessels

enables reverse flow to be generated from the surrounding hepatic sinuses and portal veins to the tumor's peripheral part. Arterial micro-anastomoses can also be difficult to block. Peripheral tumour tissues can therefore survive due to retained vascularization. Admittedly, the chemotherapeutics released from the microspheres in DEB-TACE can induce necrosis of surviving tumour cells, but this requires depositing them close to the living part of the tumour. DEB TACE also causes more arterial damage than cTACE and a higher risk of arteriovenous fistulae [29–31].

The procedure is performed under local anaesthesia with fluoroscopy guidance. After a percutaneous puncture of the femoral or radial artery, the interventional radiologist inserts a vascular sheath 5 Fr (2 mm in diameter) to prevent blood loss while providing access for subsequent instruments. A guidewire and catheter of appropriate curvature are inserted through the sheath, with fluoroscopy guidance, obtained with an angiographic apparatus. As an a-traumatic tool, the guidewire allows for safe navigation through the vascular system while providing guidance for the catheter, through which the contrast agent is administered. Aortic nephrography is performed first to assess possible routes for feeding the lesion. The visceral trunk is catheterized first, followed by the common hepatic artery. Angiography is performed by administering 25 ml of contrast for 5 seconds. This allows for an accurate assessment of the liver's vascular bed and the tumor's vascularization. If the vascularization is not complete, arteriography of the superior mesenteric artery is also performed in search of the right hepatic artery. This is the most common anatomical variation. Once the vessels feeding the HCC have been identified, the catheter tip is inserted as close to the tumour as possible using a micro-catheter, while avoiding the vessels feeding the healthy liver parenchyma. Once the micro-catheter's correct location is confirmed, a slow infusion of embolization material (beads soaked in a cytostatic agent) mixed with contrast begins, thereby enabling observation of the material's distribution. Chemoembolization using slow-release drug particles produces a synergistic effect: it closes or reduces the arterial blood supply to the tumour with simultaneous deposition of the chemotherapeutic agent in the tumour area and reduced washout.

Depending on the number, size and degree of vascularization of the lesions, the authors perform 1 to 3 procedures at intervals of 4–6 weeks per TACE cycle. A follow-up examination is performed after the last procedure, preferably using the same technique as the eligibility examination. MRI is the preferred method. If there is no enhancement after embolization and the tumour regresses, a follow-up examination is performed after another 3 months.

If enhancement of the residual tumour tissue is visualized, thermal ablation is used or further TACE sessions are performed, depending on the tissue's extent and availability. Two thermal ablation systems can be used: Emprint Medtronic (tMVA) and Echo Laser Elesta. In BCLC stage A patients, a complementary TACE procedure, after thermal ablation of lesions with borderline indications, is used. The efficacy of such combination therapy is confirmed in the available literature [32–37].

The causes of TACE failure and incomplete tumor necrosis can be divided into two groups. The first group includes reasons related to the technical side of the procedure. These include: incomplete, overly rapid embolization which results in compaction of the embolization material and blood supply into the vessels proximally feeding the lesion. Another reason may be the catheterization of the abnormal vessel (this occurs when tumors have a poor vascularization) or embolization of not all the vessels feeding the lesion, particularly marginal, subcostal lesions, where additional feeding may come from arterial anastomoses or from extrahepatic arteries, e.g. from the internal thoracic or diaphragmatic artery, which is usually given off directly from the aorta.

The second group can be described as dependent on the form of HCC. A proportion of HCCs, especially encapsulated, well-differentiated and extracapsular infiltrating HHCs have partially preserved portal vascularization.

In other cases, arterial inflow closure may result in portal vascularization of the tumour due to reversed flow in the small vessels on the portal system side and in the surrounding hepatic sinusoids [38–40]. Although TACE enables obtaining high concentrations of chemotherapeutic agents in the tumor not achievable with systemic treatment and relatively low concentrations outside the tumour area, it is the ischaemia caused by embolization that contributes significantly to HCC necrosis [41].

The mRECIST criteria, in which areas undergoing contrast enhancement are considered as a viable tumour, are adopted to assess the response to treatment [42]. This is of great importance, as necrosis caused by TACE often leads to tumour swelling and an increase in tumour size which can be incorrectly treated as progression. Unintentional chemoembolization of a healthy part of the liver, and a concentrated dose of the cytostatic agent can lead to local liver damage and the formation of perfusion lesions in the healthy part of the liver, or lesions that mimic new foci.

Hence, it is extremely important that imaging examinations are evaluated by radiologists who are familiar with the specifics of the procedures and are members of multidisciplinary teams.

The efficacy of both TACE and also TAE methods has been evaluated in a number of studies.

In a five-year follow-up of 173 patients treated with DEB--TACE with Child-Pugh class A/B (102/71 [59/41%]), and mean lesion diameter 7.6 ± 2.1 cm, Malagari and her team obtained the following results: Overall survival at 1, 2, 3, 4, and 5 years was 93.6, 83.8, 62, 41.04, and 22.5 %, with higher rates achieved in Child class A compared with Child class B patients. Mean overall survival was 43.8 months (range 1.2–64.8). Cumulative survival was better for Child class A compared to Child class B patients ($p = 0.029$). For patients with dominant lesions

≤5 cm 1-, 2-, 3-, 4-, and 5-year survival rates were 100, 95.2, 71.4, 66.6, and 47.6 % for Child class A and 94.1, 88.2, 58.8, 41.2, 29.4, and 23.5% for Child class B patients. Regarding DEB-DOX treatment, multivariate analysis identified a number of lesions ($p = 0.033$), lesion vascularity ($p < 0.0001$), initially achieved complete response ($p < 0.0001$), and objective response ($p = 0.046$) as significant and independent determinants of 5-year survival (43).

The PRECISION V study compared cTACE with DEB-TACE. The microsphere treated group showed higher rates of complete response (27% *vs.* 22%), objective response (52% *vs.* 44%) and disease control (63% *vs.* 52%) compared to the cTACE treated group. The hypothesis of a DEB TACE advantage was not confirmed (unilateral $p = 0.11$). Nevertheless, patients with cirrhosis and Child-Pugh class B, ECOG 1 performance, lesions in both lobes of the liver and disease recurrence showed a significant increase in objective response ($p = 0.038$) compared to cTACE. The use of microspheres was associated with improved tolerability, a significant reduction in severe liver toxicity ($p < 0.001$) and a significantly lower rate of doxorubicin-related side effects ($p = 0.0001$) [44].

In a randomized controlled trial (RCT) conducted between 1996 and 2000, Llovet and his team compared the efficacy of TAE, TACE and conservative treatment. Of the 903 patients, 112 were eligible for the study. Survival probabilities at 1 year and 2 years were 75% and 50% for embolization; 82% and 63% for chemoembolization, and 63% and 27% for control (chemoembolization *vs* control $p = 0.009$). chemoembolization induced objective responses sustained for at least 6 months in 35% [14] of cases, and was associated with a significantly lower rate of portal-vein invasion than conservative treatment [45].

The systematic review and meta-analysis presented by Bzeizi and co-authors included 34 studies involving 4,841 patients with HCC, and an average follow-up period of 1.5 to 18 months. There were no significant differences between DEB-TACE and cTACE in terms of complete response, partial response and disease stability. However, disease control (OR: 1.42, 95% CI: 1.03, 1.96) and objective response (odds ratio [OR]: 1.33, 95% confidence interval [CI]: 0.99, 1.79) were significantly more successful with DEB-TACE treatment with fewer major complications and overall mortality. A pooled analysis showed no superiority of DEB-TACE in terms of complete or partial response, disease stability, disease progression control or mortality at 30 days or at the end of the study [46].

However, the results showed that DEB-TACE was associated with better objective response, disease control and lower overall mortality compared to C-TACE treatment with fewer major complications. DEB-TACE shows less systemic exposure to the chemotherapeutic agent. Furthermore, it shows a standardized release of the chemotherapeutic agent from microspheres, resulting in prolonged retention in the tumor as well as lower liver toxicity. An important aspect is the ability to select the size of the microspheres.

Our extensive experience also shows the advantage of DEB-TACE in terms of controlling the rate and volume of microspheres administered [44].

In vivo studies performed on pigs have shown the spread of doxorubicin to a distance of 600 µm from the edge of the microsphere, with a very rapid decrease in the first 100–200 µm around the particle, and a very slow decrease in the next 400 µm. A sudden drop in drug concentration suggests the presence of barriers to drug diffusion [47]. Particles released 43% of the initial doxorubicin load within the first month and 89% within 3 months of the procedure, consistent with *in vitro* tests predicting a 50% release within 2–3 months [48, 49].

However, it should be noted that the above study took place on healthy pig livers without a tumor. HCC occurring in a cirrhotic liver has a different vascularization from healthy tissue, and the permeability and sensitivity of tumor cells to doxorubicin is also different [50–52]. The above work suggests that when deciding on the type of TACE (cTACE *vs.* DEB-TACE), an in-depth analysis of imaging examinations, in particular, is required to optimally select the procedure technique due to the heterogeneity of the BCLC B group. Despite the clear advantages of DEB-TACE, some authors identify groups of patients in whom they prioritize cTACE.

Adverse effects associated with TACE include post-embolism syndrome, which is the body's natural response to tumor embolization. It can manifest in a number of ways: abdominal pain, raised body temperature, vomiting or temporary deterioration of liver function. The duration of symptoms is highly individual, ranging from 2–3 days to 2 weeks. The incidence ranges from 5 to about 22% [53]. It is important to adequately provide patients with painkillers. More serious complications include liver abscesses requiring drainage, acute pancreatitis or acute cholecystitis, liver failure, kidney failure. Their incidence ranges from 2% to 4% [53]. Vascular dissection and punctures are even rarer.

Monier et al. in their study assess adverse effects of forming biloma, portal vein trombosis, portal vein branch narrowing, and bile duct dilatation. They assess incidence range up to 5% and for global hepatic damages up to 15% [54]. In order to detect potential side effects quickly, patients require regular monitoring after TACE, especially of liver parameters. Due to the contrast agent used during the procedure, contrast-induced nephropathy should be excluded in patients at risk. It is defined as an increase in creatinine concentration by ≤0.5 mg/dl or more than 25% from the baseline within 2–3 days of contrast agent administration. The evaluation of liver function is done according to the Child-Pugh scale correlated with the pre-treatment results. The ALBI score also shows great usefulness in post-treatment evaluation [55].

Conclusions

In case of TACE failure and disease progression at BCLC stage C and Child-Pugh liver stage A–B, the patient receives systemic treatment. Systemic therapy should be considered as a first line over TACE in patients where: HCC exceeds "up to seven" criteria, tumor(s) is/are larger then 5 cm, contiguous multinodular tumors, poorly differentiated or undifferentiated HCC and if there is no objective response after two consecutive TACE treatments [56].

Sorafenib was initially used, being the first multi-kinase inhibitor available for the treatment of advanced HCC. Currently, a atezolizumab and bevacizumab combination is the preferred treatment method, superior to Sorafenib, and demonstrating prolonged overall survival. On the other hand, in the presence of sorafenib contraindications, lenvatinib remains the preferred drug of choice. Second-line treatment includes using regorafenib, cabozantinib, nivolumab, pembrolizumab, ramucirumab and combination therapies [57].

Article information and declarations

Author contributions

Rafał Kidziński – writing – original draft preparation, writing – review and editing.

Grzegorz Kade – writing – original draft preparation, writing – review and editing.

Krzysztof Pyra – conceptualization, writing – original draft preparation, writing – review and editing.

Conflict of interest

None declared

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