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HEPATOCELLULAR CARCINOMA TREATMENT BY USING TACE: A LITERATURE REVIEW

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Abstract: *Hepatocellular Carcinoma (HCC) is the most prevalent liver malignancy. Trans arterial chemoembolization (TACE) is the gold standard treatment for Barcelona Clinic Liver Cancer (BCLC) stage B patients, who are considered to have unresectable HCC. In the following review it is shown that BCLC stage B group is too heterogenous, at the same time some patient may present a better outcome by receiving a more aggressive procedure, while others may benefit from systemic therapy. Those methods suggest which is the optimal treatment for BCLC stage B patients and when to apply it. Apart from alternatives to TACE, this review has highlighted other situations when TACE may be used – BCLC stage A or C.*

Key words: *HCC, TACE indications, BCLC stage B*

1. Introduction

Among the primary neoplasms of the liver is the Hepatocellular Carcinoma (HCC). This is the archetypal primary malignant tumour of the liver according to WHO (approximatively 85-90% of liver cancers) [1]. Regarding the epidemiology, HCC is the sixth most typical type of cancer around the world. The incidence varies between the geographical areas of the globe, being higher in Eastern Asia and sub-Saharan Africa (Eastern and Western Africa) [2]. The HCC BRIDGE study identifies the mean age of diagnosis according to the geographical area as follows: 52-59 years old in China, respectively South Korea and 62-69 in Europe, North America and Japan [3].

Concerning the risk factors, the HCC carcinogenesis is associated in most cases with liver cirrhosis (as a result of chronic liver disease), Hepatitis B Virus (HBV)/ Hepatitis C Virus (HCV) and autoimmune disease. [4] A study based on more than 11.000 people from Taiwan has noted that the most common factors influencing HCC development have been the infection with HBV (55.7%), HCV (15.3%) and independent use of alcohol (2.1%) [5]. HBV carriers are in danger of developing HCC of about 10-25% during their lifetime,

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most important feature of this infection being the possibility of carcinogenesis without evidence of cirrhosis [6]. HBV infection is more predominant in Africa, while HCV is more common among people in the Eastern Mediterranean Region and the European Region. The risk of developing HCC significantly grows, if the coinfection of HBV and HBC it's present (dual infection odds ratio (OR) of 165 compared to 17 for hepatitis C and 23 for hepatitis B alone) [7]. Other important risk factors consist of excessive alcohol consumption, non-alcoholic steato-hepatitis (NASH), diabetes mellitus, aflatoxin, non-alcoholic fatty liver disease (NAFL), tobacco etc. [8]. So far, several studies have observed the fact that women have less malignant tumours than men. It is believed that oestrogens play a particularly important role. A study based on 44.000 people from the USA has concluded that sex ratio (male to female) is lower than 2 at an age below than 25. Moreover, the same meta-analysis states that the peak male-to-female sex ratio for HCC incidence is at the age 50-54 with a value of 5.4 [9], [10].

The HCC incidence can be lowered by screening. A priority is to identify the specific population that will benefit from surveillance. The screening guidelines suggest to observe all the patients with cirrhosis, HBV positive (HBsAg positive), family history, chronic hepatitis C etc. [5], [11]. On the subject of screening, the difficulties in identifying a reliable biomarker are reported by several studies and reviews. Alpha-fetoprotein (AFP) is the archetypal serological test used worldwide, but unfortunately the specificity is 82-93% and sensitivity 21-64% [5]. Because of this, other biomarkers have been tested, such as GPC3 (Glypican-3), VEGF gene (Vascular Endothelial Growth Factor), GP73 (Golgi Protein 73) etc. Although some of them can be more specific and sensitive, the cost of testing is too high to be feasible for screening [8]. The most used imaging screening test is ultrasonography (US) which unfortunately depends with a high degree on the tumour stage. Moreover, US relies on the ability of the specialist. Concluding, its sensitivity ranges from 58 to 89%, while specificity is greater than 90% [11].

For diagnosis, the European Association for the Study of the Liver (EASL) strongly recommends with high evidence the diagnosis of HCC in cirrhotic patients by non-invasive (imaging studies) criteria or by pathology. On the same level of recommendation, for the non-cirrhotic patient, HCC is identified by pathology. The imaging studies that are highly suggested to be used are multiphase CT, contrast-enhanced US (CEUS) or dynamic contrast-enhanced MRI [11]. Hallmarks in imaging identification are represented by hypervascularity in late arterial phase – defined as arterial phase hyper-enhancement (APHE) – and washout on portal venous and/or delayed phases [12]. As underlined in the previous paragraph, the surveillance and diagnosis techniques have some limitations. HCC lesions under 2 cm are hardly identified and may be missed. The golden standard is pathohistological diagnosis which is built on the strength of criteria of the World Health Organization (WHO).

The patient should be classified based on the serological tests, biomarkers, history, physical examination etc. The best treatment should not be selected by a single doctor, but by - as EASL recommends - a board of doctors: surgeon, oncology, radiology, hepatology specialist etc. [11].

2. Staging and indications for HCC patients

Specialists all over the world are working on finding the greatest staging system and treatment allocation. At this moment there are 5 different staging systems that are commonly used: American Association for the Study of Liver Diseases (AASLD); Asian Pacific Association for the Study of the Liver (APASL); Barcelona Clinic Liver Cancer (BCLC); Japan Society of Hepatology (JSH); Korean Liver Cancer Study Group (KLCSG) [13]. Out of those, BCLC is the most used and EASL highly recommends it to be taken into consideration by specialists who treat HCC.

In order to decide about the best treatment of HCC, at least the following information should be obtained: tumour burden, performance status and liver function. In BCLC classification the tumour burden may be the surface of the malign tissue – less than 2cm or less than 3cm – or the number of the tumours – single tumour or multiple. The performance status is calculated using Eastern Cooperative Oncology Group (ECOG) Performance Status grades – 0 being completely active people, while 5 represents death. To asses the function of the liver, the Child Pugh score is recommended in chronic liver disease, primary cirrhosis etc. – class A being good liver function, while C meaning impairment. The Child Pugh score is calculated using the total bilirubin, ascites, prothrombin time or INR, albumin levels and hepatic encephalopathy [14]. Another liver function score is the Model of End-stage Liver Disease (MELD score) used for evaluating relative disease gravity and odds-on survival of patients eager to receive liver transplantation. MELD score is based on creatinine levels, bilirubin levels, INR and Haemodialysis [14].

BCLC is subdivided in five stages based on the above-mentioned points: 0 (or very early), A (early stage), B (intermediate), C (advanced), D (terminal).

Using the BCLC staging, patients are designated to receive a specific treatment.

Trans arterial chemoembolization (TACE) is the gold standard for stage B – intermediate liver disease [11], [13].

While EASL recommends TACE for intermediate stage – according to BCLC classification – the other eastern and western guidelines plead to use TACE in more or less similar situations (Table 1) [15], [16], [17].

Recommendation of different guidelines to use TACE Table 1

Guidelines	Recommendation
Asian Pacific Association for the Study of the Liver (APASL)	Unresectable without vascular invasion and extrahepatic spread
Europeam Association for the Study of the Liver (EASL)	BCLC stage B Not recommended for decompensated liver disease advanced liver and/or kidney dysfunction
Korean Liver Cancer Association-National Center Korea	Ineligible for surgical resection, liver transplantation, RFA and PEIT
Japan Society of Hepatology (JSH)	Unresectable Child-Pugh A and B 1-3 nodules(≥3cm) and more than four nodules

Chemotherapy and synthetic materials named embolic agents, are placed by TACE into blood vessel, who are feeding the carcinoma, to cut off the blood supply

and the chemotherapy will be trapped inside the neoplasm. Principally the role of the TACE it is most often used to treat liver carcinoma, but can be used in the cases of patients whose cancer disseminated in new areas of the body, from the liver.

It is used mostly for HCC, as its vascularization is mostly dependent on the hepatic artery [18]. Other diseases or situations for which TACE may be used include liver metastases of medullary thyroid carcinoma [19], cholangiocarcinoma, bridging for liver transplantation, downsizing the tumour 4 etc. The counterindications of TACE reported by all staging systems are lack of portal blood flow, decompensated liver disease and extensive tumour with massive replacement of both entire lobes [18]. Inclusion criteria for TACE are focal or multinodular HCC under 3 cm, with preserved liver function (Child Pugh A) and performance status 0. The most important principle is that the tumour is unresectable [8], [11], [13].

TACE as a bridge to transplant is used depending on the medical centre's choice. It has a 48% rate of success as shown in a systematic review [20]. There are other locoregional therapies for prolonging the patient's life – with similar outcomes as TACE – and preserving the liver function while wating for transplant, such as TACE with Y-90 or Stereotactic body radiotherapy, but those will not be the subject of this review [21]. Conventional TACE (cTACE) uses Lipiodol, an iodised oil, which has the characteristics necessary to embolize small blood vessels as well as take and concentrate chemotherapeutic agent inside the malignant tissue. Another way to perform this technique is by using drug-eluting beads TACE (DEB-TACE) which can enter thinner vessels and release chemotherapeutic medication just inside the tumour. In this way it is diminished the systemic dose exposure – important for patients who have been treated in the past for other cancers with doxorubicin. Moreover, DEB-TACE may reduce the systemic adverse events and it increases the local ischaemia intensity and duration [22], [23].

Decomposable starch microspheres trans arterial chemoembolization (DSM-TACE) has been demonstrated to have great end-points – overall survival (OS) – in a 163 single-centre cohort study. Orlacchio et al. has provided some further data in favour of DSM-TACE [24]. TACE can be combined with radiotherapy, surgery – liver resection surgery –, liver transplant, radiofrequency ablation (RFA) etc. and those will be discussed later when we will describe the survival rate.

Regarding staging and indication for TACE, multiple publications have advised that BCLC stage B is heterogenous, consisting of a wide variety of patients. Those being said, there have been proposed substages of BCLC stage B. In 2012 Bolondi L. et al. proposed 4 subgroups of stage B [25] (Table 1). In 2016, ITA.LI.CA. group confirmed the prognostic value of this subclassification with a study which enrolled 269 patient and observed them for 25 years [26]. In order to be validated, the subclassification proposed by Bolondi L. et al. has been tested in more countries.

Several studies (two eastern cohorts and two European) have identified that B1 is a well-defined group with clear survival rate and outcomes. The same results for quasi-C. On the other hand, they have underlined that B2, B3, B4 present slightly different outcomes and the end points

have been too close to each other to discriminate between them [27], [28], [29], [30]. In order to overtake this shortage, the Taiwan study group has proposed introduction of alpha fetoprotein to the classification [29], the Korean study has proposed to merge the B3 with B4 [29], while the German and Italian studies have supported the idea of introducing MELD score for a better prediction [27], [30]. Furthermore, ITA.LI.CA. group has concluded that MELD score may be incorporated and should be observed in more studies if it brings a more precise prognosis of the treated patients [26]. In multivariate analysis has been observed the fact that Child-Pugh score and alpha fetoprotein are independent variables. Based on those studies, they can be used as independent predictors of survival and for choosing the best therapy [31]. Nonetheless, in a French cohort of 167 patients has been identified that the liver function is not an independent prediction factor [32].

In another research, Kudo et al. proposed a way to classify the patients selected for BCLC stage B so that they will receive the best treatment. Kinki criteria (Table 2), which is based on the up-to-seven criterion and Child Pugh score. They have concluded that these norms would stratify the heterogeneous population of BCLC B group patient adequately.

BCLC B stage subclassification Table 2

	B1	**B2**	**B3**	**B4**	**Quasi-C**
Child Pugh score [5], [16]	5-7	5-6	7	8-9	5-6
Up-to-seven criterion [5], [16]	in	out	out	any	any
Performance status [5], [16]	0	0	0	0-1	0
Portal vein thrombosis [5], [16]	No	No	No	No	Yes

Furthermore, Kinki criteria will give the treatment indication according to all of the substage (B1, B2, B3) [33]. Kinki criteria has been validated by a study from Japan, based on 1633 participants. Tadaaki Arizumi et al. have demonstrated statistically compelling variations in survival, indicating the performance of Kinki criteria. [34] The up-to-seven criteria is the update to Milan criteria which has been brought by Mazzaferro et al. in 2009. This criterion is built on the sum of tumour number and size of the largest tumour without microvascular invasion and is used mainly for categorizing patients as suitable or unsuitable for liver transplant (LT) [35]. Using this classification for generating BCLC stage B subgroups suggests that the group is diverse and recommending only one treatment may be inappropriate. Supposing both tumour burden and tumour number are linear predictors, in 2019 a new predictor score has been developed – being demonstrated that they are independent variables. Using a group of 1604 patients, the “six and twelve score” has been created and tested. The patients are divided in 3 strata: sum of surface of malignant tissue plus number of tumours below 6, between 6 and 12, greater than 12. [36] The “six and twelve score” has been validated on a French cohort of 167 patients, a retrospective study [32].

The stage migration strategy, as it is described in EASL`s 2018 guide, implies usually that a treatment hypothetically

recommended for a different stage is selected as preferred 1st line treatment choice. Mostly it is used when a patient`s first line is not available, and the stage moves upward to the next step. Although specialists usually select the next stage way of treatment, in some particular cases they can opt for downstaging the treatment if the patient is at the borderline with the previous stage [11].

Table 3

Kinki criteria to divide BCLC stage B

	B1	**B2**	**B3**
Child Pugh score	5-7	5-7	8-9
Up-to-seven criterion	in	out	any

BCLC B stage group`s heterogeneity is reflected also in the clinical practice, as doctors prescribe TACE in different situations than the guides. A. Fohlen et al. has asked 64 French interventional radiologists (IR) about the way they perform TACE. Only 4 (6%) of the responders have confirmed that they have used TACE only for BCLC stage B, while 52 IR (81%) have treated also BCLC stage A [37]. In an prospective Bern HCC cohort with 223 patients the BCLC algorithm has been tested. In order to reduce the heterogeneity of BCLC B stage they have used the Bolondi L et al. subclassification [25]. The outcome has underlined that in the intermediate and advanced stage groups the treatment options have varied and have not been in accordance with the BCLC algorithm. Only 29% of the BCLC stage B patients have been managed as the BCLC system recommends. This means 23 out of 77 patients have been treated using TACE, while the others have received TARE (trans arterial radio embolization), Sorafenib, resection, ablation or best supportive care [38].

3. Overall Survival for TACE – various indications

In order to evaluate alternatives to TACE every study needs a well-chosen end point, which may be the Overall Survival (OS), Time To Progression (TTP), Disease-Free Survival (DFS) etc. Those end points can be useful to evaluate the strata of BCLC stage B patients discussed above. Furthermore, based on those strata we can classify patients in a clearer manner, bringing them closer to stage A or stage C, which may result in the optimal treatment choice – by using stage migration strategy. As EASL has stated in the latest guide available (2018), the median OS for stage A is considered to be more than 5 years, stage B more than 2.5 years, stage C more than 10 months and stage D more than 3 months [11].

3.1. Stage A

TACE has been observed in every stage with different outcomes. Regarding stage A patients, liver resection surgery (RS) is the gold standard. For resectable HCC, TACE has been tried to precede RS. In a meta-analysis with 1347 patient enrolled, TACE has been tested as a preoperative option before RS, the control group being RS without TACE. The end point has been DFS: the combined group has better 5-year DFS and, furthermore, better 5-year OS. [39] Despite this, some patients are not desirable candidates for RS, so they are referred for RFA. More studies have supported the fact that RFA combined with TACE has better outcomes. Jong Woo Kim et al. has compared, in a cohort of 314 patients, RFA with RFA plus TACE. OS at 1, 3 and 5 years have been: 93%, 73%, and 53% for RFA, respectively 93%, 72%, and 63% for TACE with RFA [40]. A Korean

meta-analysis, based on 534 patients in 9 RCTs, has concluded that combined therapy has a significantly longer OS than single RFA in HCC. [41] Combined therapy has been compared to RS in order to observe if there is any difference regarding OS, DFS and TTP. Jin Woong Kim et al. has compared the two therapies by enrolling 47 patients for RS and 37 for TACE+RFA. Regarding OS at 1, 2, 3 and 4 years they have noted: 95.7%, 89.4%, 84.3% and 80.3% for RS, respectively 97.3%, 86.5%, 78.4% and 78.4% for combined therapy. The results are similar between the groups, concluding there is not a remarkable difference [42]. On the contrary, a meta-analysis published in 2018, based on 1502 patient, has observed that OS at 1 year is better in the combined therapy group. Even with this contrast, the 3 and 5 years OS rates have presented no significant differences between groups [43]. For some very well selected patients with BCLC stage A HCC, who cannot endure RFA, may profit from DEB-TACE. The OS has been reported to be as much as 54.2 months for a group of 41 BCLC stage A patients out of which: 35 could not receive ablation, and 6 have had post-treatment recurrences [44]. Moreover, TACE is used in treatment for BCLC stage A as bridge to transplant. For some very well selected patients, ultra-selective TACE can be used with better prognosis than other treatment for BCLC stages 0 or A. [45] Recently a combination has been tested between hepatectomy and TACE with radioactive iodine (^{131}I) labelled metuximab. In a phase 2 RCT with 156 patients enrolled, it has been observed that adjuvant ^{131}I-metuximab treatment undoubtedly enhanced the 5-year recurrence free survival of patients after RS for HCC tumours expressing CD147 – a good end point after a curative treatment [46].

3.2. Stage B

While justifying Bolondi et. al. classification, Giannini et. al. has assessed the prognosis of 269 patients enrolled in the ITA.LI.CA. group cohort and has noted the survival rates: B1 (24.2% out of 269 patients) : 25 months; B2 (39.0%): 16 months; B3 (8.2%): 9 months; B4 (28.6%): 5 months; P<0.0001 [26].

On the contrary, Biolato et al. has observed that the results (OS) for the 289 cohort have been: 33.0 months for stage B1 (28% out of 289 patients); 20.8 months: stage B2 (36.68%), 16.1 months: stage B3 (8.3%), 22.2 months: stage B4 (14.53%) and 15.0 months: quasi-C stage (12.46%) [27]. It has been highlighted that B3 and B4 are close to each other and may be combined or introduce another score for an accurate prognosis [27], [29], [30].

In another sub staging system, the Kinki criteria, the OS of 1633 patients with HCC and TACE as treatment has been: B1 4.3 years (3.7-4.9), B2 2.9 years (2.2-3.4) and B3 1.1 years (0.5-1.80) [47].

TACE is the gold standard for BCLC stage B, but as we have underlined before, OS in this group varies significantly, so much that the extremes can benefit more from stage migration strategy, B1 to BCLC stage A and B3, quasi-C to BCLC stage C indications. It is worth to remember at this stage the fact that cTACE and DEB-TACE have comparable OS and number of procedures [11].

A meta-analysis based on 673 patients has concluded that OS is similar, but the number of procedures have been 2.9 ± 1.8 in the DEB-TACE group compared to 4 ± 3.1 in the cTACE, stating that cTACE may need more interventions than DEB-TACE

[48]. On the other hand, a retrospective cohort study on 81 patients has obtained median values of OS in the cTACE group of 23.0 months while for DEB-TACE lot: 29.8 months. [49] Patients within stage B1 group may be suitable to receive ultra-selective TACE and in this way any arterial damage will be prevented – arteritis is present usually after TACE [27]. After TACE, another side effect has been observed: Vascular endothelial growth factor (VEGF) rises within the tumour. Pointing out the tumour growth, VEGF has been exposed to play a substantial role. The most used drug to inhibit the VEGF receptors has been sorafenib [11]. It has been thoroughly tested in order to observe its efficacy in combination with TACE. TACTICS Trial, 156 patients enrolled, has identified that combination therapy has a better progression free survival rate than TACE in monotherapy [33]. As TACTICS Trial has stated, another study based on 307 patients has confirmed that OS for TACE in monotherapy has been 14.9 ± 1.5 months, while in combination group has been 29.0 ± 7.2 months, p=0.018 [50]. Although some trials have proven the effectiveness of combination therapy, other trials, such as SPACE Trial, with 307 patients, have come to a different result. They have compared DEB-TACE with TACE plus sorafenib, but there has been no meaningful improvement in the combination group [7]. Several combination therapies have been tested with TACE: percutaneous ethanol injection (PEI), three-dimensional conformal radiotherapy (3DCRT), percutaneous microwave coagulation therapy, percutaneous acetic acid injection (PAI), and sorafenib. A meta-analysis consisting of 5627 patients has assessed all those combinations. The outcomes have been evaluated by comparing 6 months to 3 years OS. At 6 months and 1-year, TACE-3DCRT has performed the best survival rate, while most of the others have been insignificant statistically. For 2-years OS, the best result has been obtained by using TACE with PAI, while half of the others have not reached significance. OS at 3-year has been the best improved by TACE+PAI, secondly being TACE+RFA. [51]

3.3. Stage C

Moving on to BCLC stage C patients, the gold standard is represented by Sorafenib. Lenvatinib has been demonstrated to have the same efficacy like sorafenib, so it has also been introduced as a first line therapy for BCLC stage C or for patients who are not suitable for previous treatments [11]. Built on the Cancer of the Liver Italian Program (CLIP) scores, stage C patients can be split into subgroups. Li et. al. has noticed in a study with 295 enrolled stage C patients that OS for TACE group has been 9 months, respectively 4 months for sorafenib alone [52]. TACE has been compared with other therapies for advanced stage patients. A study based on 326 patients compared SR to TACE for this stage of treatment. The OS has been considerably elongated in the SR group than in the TACE group [53].

Because stage C group has also been observed as heterogenous during practice, it has been proposed to be subdivided. Some treatments from previous stages have been tried for both stage B and C patients. A meta-analysis has investigated the fusion among TACE and sorafenib for both intermediate HCC and advanced HCC groups. After comparing 27 studies, Lin Li et. al. have concluded that combination therapy has improved the TTP and disease

control rate, but they have failed to provide significant data about OS [54].

For stage C, TACE and radiotherapy can be used for downstaging, so that a patient can receive an invasive or even curative treatment. An RCT with 90 patients enrolled has shown that the combination between TACE and external beam radiotherapy has been well tolerated by patients. Furthermore, combination therapy has provided an enhanced OS, DFS and TTP than sorafenib alone [55].

4. Discussion –TACE refractoriness

Patients who are treated for HCC usually do not receive only one TACE procedure. They are schechuled for several procedures, during which other substances may be used or another feeder artery may be chosen. Stage migration strategies - when to stop and choose another therapy – have been a subject of discussion for a long time. Two major negative outcomes have been identified after TACE: post embolization syndrome and refractoriness, respectively.

Post embolization syndrome is a common adverse event. Clinical manifestation is represented by nausea and vomiting, fever (without infection) associated with pain in the right upper quadrant. The most effective treatment is represented by steroids, serotonin antagonist (5-HT3 receptor) and/or intraarterial lidocaine [56].

The definition of failure to TACE has been given by the Liver Cancer Study Group of Japan (LC-SGJ). First and most important is the number of procedures: more than 2 with ineffective response (reduction of less than 50% of the tumour) or more than 2 with increasing number of tumour nodules or mass. The first criterion is considered despite the changing of chemotherapeutic agent or selection of the feeding artery. Secondly, an elevation of the tomours markers is also considered. The last criterion underlines that any new point of vascular invasion or any new extrahepatic metastasis must be considered [57]. The effectiveness of TACE is evaluated by modified Response Evaluation Criteria in Solid Tumors (mRECIST) – uptake of contrast agent during the arterial phase in dynamic studies [58]. The second intervention must not be too soon, nor too late as a study from 2018 has discovered. By dividing 476 patients in two groups, short interval (less than 48 days) and long interval (more than 48 and less than 90 days) between two embolization procedures, it has been studied which group has an improved OS. The short interval group has presented lower OS than the long interval cohort, a clear fact in BCLC stage C patients [59]. Somewhere between 48 days and 90 days is the perfect interval to perform the second TACE, as less than 48 days may be excessive and tiring for the patient, while more than 90 days may imply a lower adhesion of the patient to the treatment.

As stated previously, if one treatment is not suitable or fails, the stage migration strategy is applied [11]. In order to overcome the refractoriness, different theories have been tried around the world.

A meta-analysis from 2014 has enrolled 1234 patients to study the OS difference between TACE in combination with sorafenib and TACE alone. The end point has shown a reduction by 35% of death risk for patients in the combination group. Despite the good results regarding the OS, the meta-analysis has concluded that TACE with sorafenib may have more

adverse reactions [60]. Based on more research, doctors have started and have tried to switch therapies, from TACE to systemic therapy – sorafenib – when the first one fails to obtain the desired outcome.

A small retrospective study on 61 patients has observed that TACE followed by sorafenib therapy has a better outcome than TACE alone. Concerning the OS, it has been noted that the combination group has had median OS of 17.9 months while the control group (TACE only) has had 7.1 months [61].

Another study has been conducted on the efficacy of sorafenib versus continuation of TACE. The study has been carried on 497 patients diagnosed with HCC, out of which 56 have been considered as refractory to TACE. The group treated with sorafenib has had an OS of 24.7 months, while the TACE group has had a median OS of 10.27 months [62].

There have been several studies in support to the combination therapy. All of them have shown an improved OS comparing to the control group. The drawback of those studies is the lack of clear information regarding the best moment to switch from locoregional therapy to systemic one. It is considered the proper time to converse when the treatment is not working as expected – definition given above – or whenever the general status of the patient deteriorates. [63] Even though it seems clear in theory, it appears that during the clinical practice there may be a lot of other factors influencing the choice of the perfect timing.

Apart from sorafenib, some other molecules have been tested. One of those is apatinib. A cohort of 125 patients has been divided into a group of TACE with apatinib therapy and a control group – TACE only. The median OS for the first group has been 17.0 months, respectively 8.5 months for single therapy [64].

Another drug to add for the combination therapy is being searched as there have been reported cases who have developed resistance to sorafenib. Nowadays there are laboratory tests to assess different pathways that may be inhibited in order to obtain better control. So far, the sorafenib/MEK combination has produced good results in the xenograft models – the treatment has inhibited the tumour growth even in sorafenib refractory malignancy [65]. An alternative to the MEK inhibitor is thought to be capsaicin. In a laboratory test on cell cultures, it has been observed that capsaicin inhibits the phosphoinositide 3 kinase/Akt/mTOR pathway. This signalling path is believed to have an important relationship with HCC cell growth. The results are promising as sorafenib and capsaicin have managed to block HCC growth [66].

5. Conclusion

Transarterial chemoembolization is the gold standard for HCC treatment, for patients classified as Barcelona Clinic Liver Cancer Stage B. Although it may look simple and straight forward, there have been several discussions about this subject. Stage B patients are vastly different from each other, making almost impossible to fit one treatment for all. One important issue to think about is represented by the performance status criterion. PS 1 automatically pushes the patient into BCLC stage C, even though the other criteria makes him suitable for a more aggressive therapy [67]. In order to overcome this trouble, many specialists

have proposed multiple ways to divide the heterogenous population of BCLC stage B. Soon we are going to observe whether those subclassifications have led to clearer guidelines. Until that moment, we can observe that TACE is used in a much bigger range than the one it has been designated for. TACE has been reported to be utilized alone or in different combinations in patients classified as stage A or C, not only B. Patients with an early stage disease have great results by using TACE before RS or transplant, but this does not apply to the whole group. Patients from an advanced stage who receive TACE in combination with sorafenib have been shown to survive more. This is meaningful information not only for stage C patients, but also for those who are stage B and become unresponsive to TACE. Fortunately, the results of combination therapies have been positive, OS rising comparatively to the classic treatment. On the other hand, this has brought to light improvements in the guidelines, as some specific patients may benefit from better treatments, improving their survival. OS has been shown to be a good end point of the studies. By observing the definition criteria for each group and identifying their specific OS, specialists can appreciate the suitable management going forward.

The most important idea that should be accentuated is regarding the aetiology. It has been proven that different aetiologies may change extensively the therapy and the outcomes of the treatment. While in Asia or Africa HBV infection and smoking prevail as risk factors, in Europe or the USA there is a greater incidence of HCV infections and HCC related to obesity, diabetes mellitus and alcohol consumption. [68] Regrettably, this review has not taken this into consideration and has presented data from western and eastern countries trying to give a general view. Not only the aetiology is different on those two sides of the globe, but also the guidelines. Fortunately, they are not so different, and the specialists encounter the same difficulties while dividing the patients into subgroups. It may be a source of bias that both sides have been presented together.

In conclusion, it is not possible to say exactly whether to use or not TACE, when to use it or until when. There are several factors that should be observed and followed, so that a higher Overall Survival rate will be obtained. Until more comprehensive guidelines are presented, there is enough space for future research and discoveries.

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