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REVIEW

The management of hepatocellular carcinoma. Current expert opinion and recommendations derived from the 24th ESMO/World Congress on Gastrointestinal Cancer, Barcelona, 2022

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This article summarises expert discussion on the management of patients with hepatocellular carcinoma (HCC), which took place during the 24th World Gastrointestinal Cancer Congress (WGICC) in Barcelona, July 2022. A multidisciplinary approach is mandatory to ensure an optimal diagnosis and staging of HCC, planning of curative and therapeutic options, including surgical, embolisation, ablative strategies, or systemic therapy. Furthermore, in many patients with HCC, underlying liver cirrhosis represents a challenge and influences the therapeutic options.
Key words: hepatocellular carcinoma, liver transplantation, chemoembolisation, immunotherapy, radioembolisation

INTRODUCTION

With 905 700 new cases in 2020 (just under 5% of all cancers) and 830 200 deaths, liver cancer is the third leading cause of cancer deaths worldwide after lung and colorectal cancer.[1] With a mortality/incidence ratio of 0.92, liver cancer is a major cancer burden with a very poor prognosis. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and it comprises 75%-85% of primary liver cancer cases.[2]

The most common risk factors and aetiologies for HCC are chronic infection by hepatitis B virus or hepatitis C virus, nonalcoholic fatty liver disease in the setting of obesity with/without associated diabetes mellitus type 2, and heavy alcohol consumption.[3,4] Other reported aetiologies are metabolic disorders, including α1-antitrypsin deficiency, hemochromatosis, and autoimmune diseases. Contributory environmental factors include aflatoxin-contaminated food and tobacco. There is a wide variation in exposure to these different risk factors depending on geographical and sociocultural factors. Significant improvements in the knowledge and management of HCC have been seen in the past two decades. The advent of powerful antiviral treatments and lifestyle changes mostly explain the important

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epidemiological changes. Several clinical guidelines are available, which are endorsed by societies involved in clinical care and research in HCC. To master this rapidly evolving field, clinicians need more than streamlined guidelines. This article summarises an expert discussion on the management of HCC, which was organised during the 24th European Society for Medical Oncology (ESMO)/World Congress Gastrointestinal Cancer Congress (WCGICC) in July 2022 in Barcelona, Spain. In view of the rapid progress of knowledge in the field of HCC, it was decided in agreement with all the experts to include in this text presentations or publications that occurred after the congress.

METHODS

At the 24th ESMO/WCGICC held in Barcelona in July 2022, a panel of invited experts involved in the basic science, clinical care, and clinical research for patients with HCC conducted a structured discussion on different aspects of HCC management. The included experts represented multiple disciplines involved in the care of HCC: hepatologists, medical oncologists, gastrointestinal oncologists, interventional radiologists, radiation oncologists, pathologists, and surgical oncologists. Experts were selected based on their scientific merits and their recognition as international opinion leaders. The panel was presented with a detailed questionnaire prior to the meeting. Answers were summarised and then discussed in an extended forum. Conclusions of the recommendations and expert opinions are based on published data and on clinical experience. The experts' opinions/recommendations do not therefore represent an official guideline or true consensus statements. This publication aims to guide clinicians in the hands-on decisions encountered in the management of HCC, especially in fields where scientific evidence remains limited.

EPIDEMIOLOGY

In 2020, age-standardised incidence and mortality rates for liver cancer were 9.5 and 8.7 per 100 000, respectively. Age-standardised incidence and mortality rates were highest in Eastern Asia (17.8 new cases, 16.1 deaths), Northern Africa (15.2 new cases, 14.5 deaths), and South-Eastern Asia (13.7 new cases, 13.2 deaths).[1] The major risks of HCC vary by geographic region, resulting in marked differences in the burden of HCC across regions.[2] In the United States, the incidence of HCC has tripled since the 1980s, with >40 000 new cases in 2020.[5] It should be noted that this incidence has continued to increase in recent years despite the implementation of screening for HCC in patients with liver cirrhosis. The number of new cases of HCC is predicted to increase globally by 55% between 2020 and 2040, with 1.4 million new diagnoses forecast for 2040.[1] The experts considered that HCC would undoubtedly remain a global public health problem in the coming years.

In the future, it is anticipated that there will be a change in the spectrum of chronic liver disease preceding the occurrence of HCC with a decrease in viral causes related

to both vaccination for hepatitis B and the implementation of curative therapy for hepatitis C, albeit a total disappearance is unlikely due to the lack of a universal vaccination and treatment strategies particularly in lower-resource settings.[3,6]

In summary, the experts anticipate that the observed decrease in HCC related to chronic viral liver disease will be compensated by an increase in liver disease related to nonalcoholic fatty liver disease linked to an overall increase in the incidence of obesity, as already observed in patients transplanted for HCC,[7] while alcohol-related liver disease will have a stable incidence.

HCC SCREENING

Screening of patients with liver cirrhosis to detect small and potentially curable HCCs started >35 years ago. Ultrasound examination of the liver remains the reference for screening of HCC.[8] Alpha-fetoprotein (AFP) measurement was added to ultrasound examination, but its value has been debated in terms of cost-effectiveness and removed from recommendations in some countries. However, a recent meta-analysis showed that ultrasound alone detected only 45% of HCC, whereas the detection rate rose to 63% when the AFP assay was used in addition to ultrasound.[9] In patients with a liver that is very difficult to examine by ultrasound, it has been proposed to use computed tomography (CT) or even magnetic resonance imaging (MRI),[10] but this raises additional questions in terms of the cost of screening and the availability of equipment, as well as in terms of cost-effectiveness. Surveillance examinations are recommended every 6 months.[11] On a country scale, the effect of this screening in terms of mortality reduction remains limited and debated.[12] However, experts recommend the use of ultrasound and AFP testing every 6 months in patients with cirrhosis.

HCC SCORING AND STAGING SYSTEMS

The Child—Pugh score[13,14] remains the most widely used score in evaluating liver functional reserve in patients with liver cirrhosis. Despite its age (or perhaps because of its age, which makes it universally known), it is systematically calculated before a therapeutic decision is made. The albumin—bilirubin (ALBI) score developed more recently in the specific context of HCC is gaining ground in hepatology circles.[15] This growing interest derives from the fact that it is a continuous score that is more objective in its application because it is based solely on biological data, lacks ground or ceiling effects, and makes it possible to differentiate prognosis within Child—Pugh A5 score and Child—Pugh A6 score. The ALBI score is not yet used to select or stratify patients even in the most recently reported trials with a stratification that continues to use the Child—Pugh score. However, real-life studies or *post hoc* analyses have confirmed the prognostic value of this score, including in patients receiving recent combination therapies such as atezolizumab bevacizumab[16] or durvalumab tremelimumab,[17] confirming that the ALBI score may be

incorporated as a stratification factor in future studies. *Post hoc* studies on, for example, the evolution of the ALBI score during modern HCC treatment such as ramucirumab, have been published.[18] The ALBI score was difficult to use in the past but is now accessible via a specific website.[19] However, it is still criticised because the mechanical basis of its calculation are not accepted by all. As a result, a simplified version has recently been developed; however, its validation is needed in large-scale studies.[20]

The Model for End-Stage Liver Disease (MELD) score is less used at this stage for the assessment of hepatocellular function outside the special cases of patients for whom liver transplantation is being considered, where it is widely used to manage the waiting list.[21,22]

The Barcelona Clinic Liver Cancer (BCLC) prognosis and treatment strategy score is widely accepted, especially as it was updated in 2022 to reflect recent changes in the management of HCC.[23] The interest of this classification system lies in its prognostic value linked to a definition of the therapeutic strategy. In addition, since its first publication in 1999,[24] the BCLC score has undergone many iterations to adapt to the evolution of knowledge and treatment advances of HCC, which are led by experts beyond the original Barcelona group.[23] As the versions evolved, some categories saw their heterogeneity better taken into account. Changes include category B, which was previously recommended to be treated by transarterial chemo-embolisation (TACE)[24] and which in the latest version is subdivided into three different groups with indications ranging from liver transplantation to systemic treatment and TACE.[23] Therefore although the experts unanimously accept this score regarding prognostic use, this is not always the case in terms of therapeutic choice.

The Japanese HCC score (Japan Integrated Staging Score) has not been adopted beyond its country of origin, although it accurately defines potential treatment indications.[25]

In summary, the experts recommend the use of the BCLC score to assist in the management of HCC. They also recommend the use of the Child—Pugh score to assess liver function but suggest that the ALBI score should be given more prominence in future studies.

DIAGNOSIS

Biopsy should be carried out routinely if the patient is not known to have and does not show signs of chronic liver disease. Several organisations have published guidelines for the noninvasive diagnosis of HCC in patients with defined risk, including the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver-European Organisation for Research and Treatment of Cancer (EASL-EORTC), and the Asian-Pacific Association for the Study of the Liver (APASL).[26] In addition, radiologists have been working to standardise the elements of HCC diagnosis.[27] These guidelines essentially use the vascular pattern of HCC: contrast uptake during the arterial phase combined with the washout of contrast media during the portal venous or the delayed phases on

dynamic CT or MRI. However, biopsy is increasingly being carried out for many reasons particularly when there is no curative approach. The first is purely clinical and diagnostic: there are mixed tumours of the combined hepatocellular plus intrahepatic cholangiocarcinoma type that must be diagnosed because they require specific treatments. However, their incidence is rare [comprising 1.3% of liver tumours from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (SEER) database in 2008].[28,29] In addition, the interest of the biopsy lies in the possibility of sequencing the tumour DNA and RNA and specifying its biological subtype,[4] even in the absence of trials specifically dedicated to biological subgroups in this disease, despite suggested targets.[30] Biopsy is also of scientific interest as it allows a better characterisation of the disease and the identification of predictive biomarkers. The experts therefore recommend the widespread use of biopsy in the diagnosis of HCC, even though radiological diagnosis has become much more effective and should be preferred for localised forms.

STAGING

Baseline imaging of localised HCC should include contrast-enhanced CT and MRI scans. Diagnostic evaluation (but also imaging in response to locoregional therapy) in HCC is currently evaluated using Liver Imaging Reporting and Data Systems version 2018, which offers a comprehensive approach for a lesion-by-lesion assessment of cirrhotic nodules.[31] Liver MRI is not necessary if the cancer is extensive on CT scan and if no curative or locoregional treatment can be considered, and in these cases the CT scan is usually sufficient to assess the effectiveness of systemic treatments. The role of fluorodeoxyglucose-positron emission tomography is extremely limited in this disease, due to its lack of sensitivity[32] and is not recommended. Choline PET is exceptionally used in the extension assessment of these tumours. Although it has produced some interesting results, its diffusion remains limited[33] and therefore does not apply to clinical practice. Contrast-enhanced ultrasound can play a role in certain situations where CT and MRI have failed.[34]

A serum AFP assay should be carried out in all cases prior to treatment. In the event the AFP level is normal, carcinoembryonic antigen (CEA) and carbohydrate antigen 19 19-9 (CA19-9) assays can be carried out if the tumour has a mixed component.[28] The practice of measuring other markers such as decarboxyprothrombin has not become established and is not recommended by the experts.[35]

TREATMENT OF LOCALISED FORMS

Liver resection

Indications for liver resection may follow the EASL recommendations[8] or other validated ones. Surgical resection is recommended as the treatment of choice in patients with HCC arising in a noncirrhotic liver or limited cirrhosis with preserved liver function. Measurement of liver function particularly in patients with underlying liver disease before

an intended liver resection is of critical importance; further, a European guideline summarising essential tools in its assessment is being developed. Liver resection is recommended for single HCC of any size and in particular for tumours >2 cm, when hepatic function is preserved, and sufficient remnant liver volume is maintained, and when there is no portal hypertension. HCC presenting with two or three nodules within Milan criteria may be eligible for liver resection according to patient performance status, comorbidities, and the aforementioned criteria. Minimal invasive resection has become the therapy of choice in experienced hands with the main benefit of less postoperative morbidity, reduced postoperative stay, and improved long-term outcome.[36]

Liver transplantation

The Milan criteria (one nodule <5 cm or up to three nodules each <3 cm) remain the reference in most countries for defining the indications for liver transplantation.[37] However, some prefer the somewhat broader criteria that were described later: University of San Francisco criteria[38] or up-to-seven criteria.[39] Recently, it has been reported that the addition of AFP to the Milan criteria improved their performance.[40] This 'AFP-score' is used in France and in Latin America[41] to prioritise transplants; in the United States, the United Network for Organ Sharing (UNOS) criteria are recognised at the national level and in many European countries the Eurotransplant criteria help in prioritisation for transplantation.

Given the difficulty of access to transplantations, most offer their patients a bridging treatment approach, in particular if the expected waiting time exceeds 6 months. Bridging treatments vary; the most commonly used are TACE, radiofrequency (or microwave) ablation (RFA/MWA), or more recently trans-arterial radioembolisation (TARE).[42] For the experts, RFA or MWA techniques are on a downward trend in favour of TARE, which is gaining popularity.

The type of procedure to be selected is the one that offers the best local control-to-adverse effects ratio depending on the size and location of the tumour. This is typically a decision that should be made in a multidisciplinary setting. A recent meta-analysis evaluated these bridging techniques through 3106 records in six articles (1043 patients) that met the inclusion criteria.[43] Patients with HCC listed for liver transplantation and undergoing bridging techniques had a longer waiting time to liver transplantation [mean difference = 3.77 months, 95% confidence interval (CI) 2.07-5.48] compared with the non-interventional group. However, they had higher survival rates after liver transplantation at 1 year [odds ratio (OR) = 2.00, 95% CI 1.18-3.41], 3 years (OR = 1.47, 95% CI 1.01-2.15), and 5 years (OR = 1.50, 95% CI 1.06-2.13).[43]

Local ablation

Ablation is used in BCLC 0 patients (i.e. with preserved hepatocellular function, good general condition, and a single tumour ≤2 cm) because there is a high level of evidence

that this treatment is equivalent to surgery in terms of overall survival but the duration of the procedure and hospitalisation are shorter.[44] In this situation, MWA is more frequently used because a recent meta-analysis reported that MWA resulted in a higher complete ablation rate and lower local tumour progression than RFA in treating HCC nodules.[45] There was no significant difference in overall survival between the two therapeutic procedures. It is also recommended in case of three nodules <3 cm not suitable for surgical procedures. Recent evidence suggests that TARE may also play a role in this indication.[46]

Radiotherapy

Recent comparative studies have reported that the local control rate of stereotactic body radiotherapy (SBRT) for intrahepatic malignancies is comparable with that of RFA.[47] Furthermore, a recent meta-analysis has shown that SBRT/ablative RT can yield oncologic outcomes similar to RFA, and suggested that it can be more effective for the treatment of tumours in locations where RFA is difficult to carry out or for large-sized tumours (>3 cm).[48] However, it is rarely used. The experts considered that SBRT should be discussed as an option on a routine basis during a multidisciplinary board for localised tumours and especially when no other treatment can be offered, particularly when there is a vascular contact but not only in these cases.

In summary, in this situation, the experts follow the recommendations of the ESMO clinical guidelines published in 2018[49] and updated in 2021,[50] and more closely the BCLC recommendations updated in 2022.[23] A particular recommendation lies in the interest of TARE in bridging situations before liver transplantation, the results of which seem to be very interesting.

TREATMENT OF INTERMEDIATE DISEASE (STAGE B BCLC)

TACE and TARE

TACE using conventional TACE with lipiodol or TACE with drug-eluting beads is the standard treatment for intermediate BCLC cases [i.e. tumour >3 cm, multinodular (≥4 nodules)] without vascular invasion, or extrahepatic disease, Eastern Cooperative Oncology Group performance status 0, Child—Pugh A, and without portal thrombosis.[51] There is no substantial benefit from choosing one specific embolising procedure versus the other based on results from several randomised trials. A randomised trial has even shown that embolisation with microspheres alone was as active as the same treatment with doxorubicin-loaded microspheres.[52] The use of TACE varies across centres and typically this technique applies to HCCs with two to seven nodules, the largest of which is <7 cm in size and which can be treated supra-selectively.

TARE, in particular because it has been demonstrated that real dosimetry can be carried out to improve the efficacy-to-adverse effects ratio,[53] is increasingly being used in this indication. Undoubtedly, the cost of TARE treatment remains an obstacle in some countries. However, it should

be noted that no cost-effectiveness study of the various treatments has been carried out.

A meta-analysis conducted on individual patient data included 17 studies comparing TACE and TARE.[54] This meta-analysis was inconclusive and reported no difference in overall survival but a longer time to progression with TARE relative to TACE (mean time to progression 17.5 versus 9.8 months).[54] In addition, a recent randomised phase II study comparing drug-eluting TACE (34 patients) with TARE (38 patients) found a benefit in terms of local control and overall survival in favour of TARE: 30.2 versus 15.6 months (hazard ratio = 0.46; $P = 0.006$).[55]

Intra-arterial hepatic chemotherapy

The results from one phase III trial showed that compared with TACE, hepatic arterial infusion of chemotherapy with oxaliplatin plus intravenous 5-fluorouracil (5-FU) and folinic acid significantly improved the overall survival with a significantly lower incidence of grade 3-4 adverse events for large and unresectable HCC.[56] Despite these results, hepatic intra-arterial chemotherapy is not considered by experts as a treatment option that they would be likely to use.

Combination of locoregional treatments

Combination of sorafenib to TACE in the TACTICS trial did not show any overall survival advantage (median: 36.2 months with TACE plus sorafenib and 30.8 months with TACE alone, not significant).[57] The combination of locoregional treatments is limited to clinical trials, some of which evaluate, for example, SBRT combined with TACE[58] or immunotherapy and TACE. Some centres are already combining TACE and RFA to try to downstage tumours to make them accessible for curative treatment. This is particularly true for tumours between sizes 3 and 5 cm, as in this population a randomised trial[59] and a meta-analysis[60] showed that trying to reduce the tumour size to allow access to curative treatment was beneficial. Another trial, which was prematurely closed due to slow accrual after inclusion of 40 patients, suggested that the use of SBRT could result in superior local control as compared with TAE/TACE rechallenge (median duration of local control not reached versus 8 months; $P = 0.0002$).[61]

The role of systemic treatment

Systemic treatment is considered for patients who have recurrence of disease after a curative intent, or progress after locoregional therapy. Individualisation of decisions plays an important role in this type of treatment strategy. It was particularly emphasised that the transition to systemic therapy should not be too late, given the improved outcome of systemic treatment. Artificial intelligence could in the future help define the optimal moment for this switch.[62] A study including 237 patients evaluated the value of adding RFA or SBRT after TACE, using an artificial intelligence system that recommended it in about half of the patients. In these patients the mean progression-free survival was 5.3 months compared to 1.8 years in untreated patients, and overall survival was also increased to 7.5 versus 5.3 years. Furthermore, the experts agree with the proposal of the new BCLC guidelines that infiltrative forms are better treated early or exclusively with new systemic combinations.[23]

Again, the experts follow the ESMO 2018 recommendations updated in 2021,[49,50] but also especially the latest BCLC update.[23] This is true in particular with regard to the subdivision of the intermediate group into three categories. The experts also emphasise the importance of (i) ensuring that systemic treatment is rapidly introduced if TACE shows initial signs of ineffectiveness, (ii) considering a global strategy involving combined systemic treatment first in the event of a borderline indication for TACE, and (iii) giving TARE an increasingly important role in this indication. By contrast, the role of intra-arterial hepatic chemotherapy remains marginal.

TREATMENT OF ADVANCED DISEASE

The combination of atezolizumab and bevacizumab demonstrated superior efficacy to sorafenib in terms of response rate (30% versus 11%), progression-free survival (median: 6.8 months versus 4.3 months), and overall survival (median: 19.2 versus 13.4 months).[63] More recently, the combination of durvalumab and tremelimumab has also been shown to be more active than sorafenib in terms of response rate (20% versus 6%) and overall survival (median: 16.4 months versus 13.8 months) but without effect on progression-free survival (median: 3.78 versus 4.07).[64] There is no direct head-to-head comparison of these two new standards of treatment, which are therefore valid first-line option. The combination of atezolizumab + bevacizumab is widely used and oncologists and hepatologists have learned to manage its toxicity. The combination of durvalumab and tremelimumab is easier to use in patients potentially at risk of gastrointestinal bleeding, and the potential toxicity of the addition of anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) has been reduced using a single injection regimen of tremelimumab at the initiation of therapy (Figure 1).

Despite the evidence of the superiority of these two combinations with immunotherapy, there will still be ∼15%-20% of patients who will only receive tyrosine kinase inhibitors (sorafenib or lenvatinib), in particular because of underlying autoimmune diseases.[65] The question was also raised for treating a recurrence of HCC after transplantation in patients receiving immune suppressors. The use of immunotherapy in this context remains contraindicated. However, the situation may change in the future, as a recent trial in kidney transplant recipients found no transplant rejection and no net decrease in the efficacy of immunotherapy, which was administered (median number of cycles = 3) in 22 kidney transplant patients while immune-suppressive therapy was maintained.[66]

The use of immunotherapy beyond the first line is anecdotal, partly for scientific reasons, as randomised trials in patients who have not received immunotherapy in the
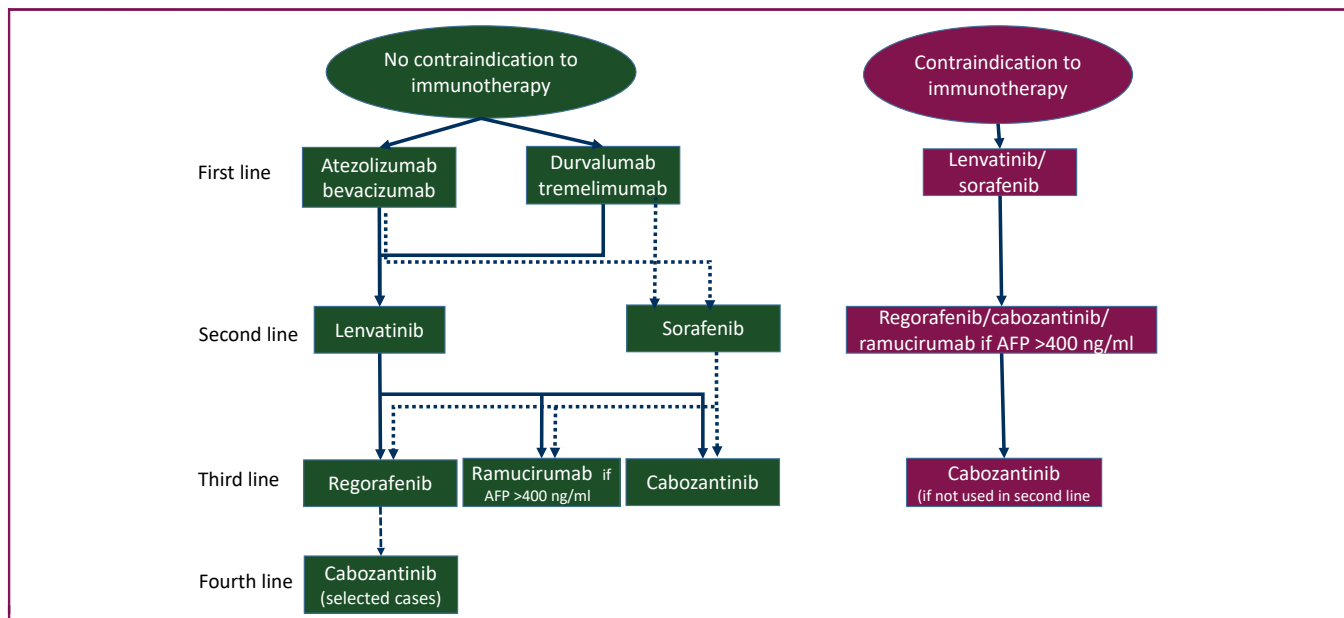
Figure 1. Treatment of advanced disease.

first line gave somewhat discordant results, with the KEY-NOTE 240 study being totally negative[67] and the KEYNOTE 394 study including only Asian population and[68] finding an improvement in median survival from 13 to 14.6 months, an improvement in median progression-free survival from 2.3 to 2.6 months.[69] In addition, in many countries there is a problem of access to the drug due to a lack of funding. When used in the second line, a programmed cell death protein 1 (PD-1) inhibitor alone is most often chosen. In the United States, it is possible to administer the combination nivolumab and ipilimumab to these patients. This combination has shown significant efficacy in early-phase trials[70] and pending validation from an already completed phase III clinical trial (CheckMate-9DW trial (NCT04039607).

In case of progression or intolerance of the chosen immunotherapy-based combination, the choice of second-line treatment is usually a targeted therapy previously used in the first line (i.e. sorafenib or lenvatinib). Lenvatinib, which has been shown to be noninferior to sorafenib and with a higher objective response rate,[67] is gaining acceptance in this situation. In some countries, restrictions on use, such as funded access to regorafenib in the event of proven progression on sorafenib, have led to the prescription of sorafenib after failure to immunotherapy.

After the failure of first-line targeted therapy, experts in countries with access to all the molecules give either regorafenib[71] or cabozantinib,[68] reserving ramucirumab for patients with AFP levels >400 ng/ml.[72]

In the event of progression under second-line tyrosine kinase inhibitor treatment, the approach is not uniform, with some experts trying to give the most suitable patients all the available molecules (switching to cabozantinib, for example, if regorafenib fails),[73] while others limiting treatment only to the second line. The lack of third-line treatment seems to be more related to the issue of financial

support for expensive treatments in some countries as the pivotal study validating the use of cabozantinib included patients in third line.[68] There is even some published data confirming the efficacy of cabozantinib in patients who received immunotherapy.[74]

BCLC staging defines patients with portal vein invasion as advanced stage (C) and recommends systemic therapy. However, SBRT has been reported to be an effective treatment for this type of situation, particularly in a series of 70 patients, resulting in repermeabilisation of the portal vein and subsequent TACE.[75] In another recent study, adding hepatic intra-arterial chemotherapy with 5-FU and oxaliplatin to sorafenib improved median overall survival (13.4 months versus 7.1 months).[76] Despite these results, experts consider that adequate systemic treatment should remain the rule in these patients, especially as they show major improved outcomes, for example, in the phase III IMbrave150 study that proved the efficacy of the combination of atezolizumab and bevacizumab.[63] However, these patients with main portal vein thrombosis were not eligible for inclusion in the HIMALAYA trial, so there are no data on the combination of durvalumab and tremelimumab in this situation.[64]

In summary, again, the experts' position is closer to the position of the recent BCLC update than to the ESMO guidelines published in 2018 and updated in 2021, as it obviously incorporates the possibility to choose between the two first-line combination treatment options.

TERMINAL STAGE (BCLC D)

The proportion of patients diagnosed at this stage remains high, in the order of 20%-30% in different countries around the world. At this stage, no anticancer treatment can be proposed. However, the most effective comprehensive

management of the symptoms and patients' needs should be provided. A specialised palliative and supportive care team should be involved whenever possible.

THE FUTURE

The future of HCC treatment is exciting but also full of new challenges and opportunities. Better prevention could significantly reduce the burden of disease and better surveillance could increase the chances of curing more patients. In the treatment of localised disease, the role of each of the techniques that can be used to challenge surgery remains to be defined. The very recently reported IMbrave050 trial included 668 patients with HCC who had undergone a curative resection or ablation. They were randomly assigned to receive atezolizumab plus bevacizumab ($n = 334$) or to undergo active surveillance ($n = 334$) until disease recurrence or unacceptable toxicity. The primary endpoint was recurrence-free survival (RFS). The median RFS was not reached in either arm at a median follow-up of 17.4 months. However, the 12-month RFS rate was significantly higher in the atezolizumab—bevacizumab arm than in the active surveillance arm: 78% and 65%, respectively (hazard ratio = 0.72; 95% CI 0.56-0.93; $P = 0.012$). The overall survival data were immature.[77] The adjuvant use of the combination of atezolizumab and bevacizumab could change the overall management of these patients. In case of early recurrence, patients should be considered resistant to this combination, which would make them potential candidates for durvalumab + tremelimumab. However, we have no data on the efficacy of this combination after failure of a combination of antiangiogenic and anti-programmed death-ligand 1 (anti-PD-L1). In patients who are going to be treated by liver transplantation, the indications of the different bridging techniques including newcomers such as TARE will have to be clarified. In intermediate forms, TARE is becoming increasingly important, but its precise indications should be better defined. The combination of new, more powerful systemic therapies with local treatment techniques (TACE or TARE) is the subject of numerous therapeutic trials. The LAUNCH trial has already tested a combination of systemic therapy and TACE, but it actually tested the value of adding TACE to lenvatinib and not vice versa. Nevertheless, this trial showed in 338 patients with advanced HCC that the addition of TACE to lenvatinib improved overall survival, 17.8 versus 11.5 months ($P < 0.001$), and progression-free survival, 10.6 versus 6.4 months ($P < 0.001$).[78] On the contrary, the combination of sorafenib with SBRT did not improve the results of irradiation in a randomised phase III trial including 193 patients.[79] Much remains to be done in this area of combining systemic and locoregional treatments, particularly with those combination therapies that have shown the best results in the treatment of advanced forms. A new anti-PD-1, tislelizumab, has recently shown its efficacy as first-line monotherapy in advanced forms (RATIONALE-301 trial),[80] as has the combination of camrelizumab (another anti-PD-1) plus rivoceranib (a VEGF inhibitor tyrosine kinase).[81] The respective positioning of these new treatments will have to be determined in clinical practice, even if the first line of treatment for HCC is beginning to be busy. With the abundance of systemic treatment options, the time has come in advanced forms for sequence trials and also for attempts to personalise these treatments with the search for predictive and prognostic biomarkers. The role of even more innovative therapies such as chimeric antigen receptor-T cells will also need to be clarified.

DISCLOSURE

MD reports participation in the advisory boards of Roche, Merck Serono, Amgen, Bayer, Servier, Pierre Fabre, BeiGene, Astra Zeneca, Daiichi Sankyo, Merck-Sharp-Dohme, Boehringer Ingelheim; served as a speaker in symposium sponsored by Roche, Merck Serono, Bayer, Merck-Sharp-Dohme, Servier, Pierre Fabre, and Daiichi Sankyo; reports institutional research funding from Roche, Merck Serono, Esteve: Roche, and PanCAN. His wife is the head of the oncology business unit at Sandoz France. GKAA reports research support to the institution from Arcus, Agios, AstraZeneca, Bayer, BioNTech, BMS, Celgene, Flatiron, Genentech Ltd./F. Hoffmann-La Roche Ltd., Genoscience, Incyte, Polaris, Puma, QED, SillaJen, and Yiviva; and receives consulting support from Agios, Alnylam, AstraZeneca, Autem, Bayer, BeiGene, Ltd., Berry Genomics, Eisai, Eli Lilly, Exelixis, Flatiron, Genentech Ltd./F. Hoffmann-La Roche Ltd., Genoscience, Helio, Incyte, Ipsen, Legend Biotech, Merck, MINA, QED, Redhill, SillaJen, Surface Oncology, TheraBionic, twoXAR, Vector, and Yiviva. TBS reports research funding (to institution) from Agios, Arys, Arcus, Atreca, Boston Biomedical, Bayer, Eisai, Celgene, Lilly, Ipsen, Clovis, Seattle Genetics, Genentech, Novartis, Mirati, Merus, AbGenomics, Incyte, Pfizer, BMS; consulting (to institution) for Ipsen, Arcus, Pfizer, Seattle Genetics, Bayer, Genentech, Incyte, Eisai, Merus, Merck KGA, and Merck; consulting (to self) for Stemline, AbbVie, Blueprint Medicines, Boehringer Ingelheim, Janssen, Daiichi Sankyo, Natera, Treos Bio, Celularity, Caladrius Biosciences, Exact Science, Sobi, BeiGene, Kanaph, Astra Zeneca, Deciphera, Zai Labs, Exelixis, MJH Life Sciences, Aptitude Health, Illumina, Foundation Medicine, and Sanofi. Independent Data safety Monitoring Committee/ Data Safety Monitoring Board: The Valley Hospital, FibroGen, Suzhou Kintor, Astra Zeneca, Exelixis, Merck/Eisai, PanCAN, and 1Globe; serves on the Scientific Advisory Board of Imugene, Immuneering, Xilis, Replimune, Artiva, and Sun Biopharma. JB reports participation in the advisory boards of Mirati, Insmed, Oxford BioTherapeutics, BioSapien, EMD Serono, Ipsen, Merck-Sharp-Dohme, Merus, BMS, Bexion; research funding (to institution) from AbbVie, Astellas, Atreca, Bayer, Dragonfly, I-Mab, Lilly, Incyte, EMD Serono, Pfizer, BMS, Transcenta Therapeutics, Tyra, Totus, Sumitomo Dainippon Pharma Oncology, 23 and me,

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