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Overview

Contrasting Some Differences in Managing Advanced Unresectable Hepatocellular Carcinoma Between the East and the West

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Abstract

Hepatocellular carcinoma (HCC) is a common malignancy worldwide, although its aetiologies vary significantly between the East and the West. About a half of HCC cases present with advanced unresectable HCC at the time of diagnosis, leading to a worse prognosis. Over the past 20 years, the treatment paradigm for advanced unresectable HCC has shifted from an entirely palliative approach to a multidisciplinary treatment, with continuous reassessment and possible repeat treatment attributed to the advent of novel and improved local, regional and systemic therapeutic options, contributed by both the East and the West. An individualised treatment plan should be determined for each patient, as there can be substantial differences in the decision-making and treatment response to the same treatment for different patients and different patient populations. This review provides a summary of the recent advances in management and compares Eastern and Western strategies for HCC.
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Keywords: Bridging therapy; hepatocellular carcinoma; targeted therapy; transarterial chemoembolisation; transarterial radioembolisation

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the fourth leading cause of cancer death worldwide [1–4]. Incidence and mortality rates are two-to three-fold higher in men in most of the world. Of interest, it is the most common cancer in men in Mongolia and Southeast Asia, Egypt and some other African countries, probably related to the relatively high incidence of prior hepatitis B virus (HBV) infection and aflatoxin exposure [3]. Alcohol abuse and the increasing obesity prevalence leading to non-alcoholic fatty liver disease (NAFLD) are contributory factors in Western countries, with NAFLD and NAFLD-related HCC on the rise [4]. The primary prevention of HBV-related HCC in endemic regions heavily relies on successful implementation of vaccination programmes against hepatitis B infection that were initially implemented in 1982. The World Health Organization recommends inclusion of hepatitis B vaccine in the routine infant vaccination programme, and 186 countries have agreed to introduce it into their national immunisation schedules [5]. However, there are no vaccines to prevent hepatitis C virus (HCV) infection. The rates of HCV transmission in developed countries, the practices of needle

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sharing and contamination and unsafe blood transfusion still continue to contribute to the spread of HCV in some low-income countries. The recent development of improved antiviral treatment against HBV and HCV will probably prevent a substantial number of HCC cases and mortality in the future, despite the almost unaffordable costs at this time, especially in developing and low–middle income countries, where HCC is often endemic [4,6]. Screening for HCC in high-risk patients has been accepted in both the East and the West, although compliance with screening in high-risk patients is not 100%, especially in the West, where there is a need for improved public advocacy [7,8]. A large Chinese study of almost 20 000 patients proved a reduction in mortality by 37% with ultrasonography and serum alpha-fetoprotein (AFP) screening biannually [9]. In the West, in high-risk patients, ultrasonography screening every 6 months is recommended and has been shown to be cost-effective [10,11].

Despite these active preventative and screening measures, about a half of HCC patients present with advanced unresectable disease. Treatment is usually based on the stage of the disease, and depends on the degree of underlying liver function impairment and patient performance status. The Barcelona Clinic Liver Cancer (BCLC) classification system has been widely used to aid in treatment decision making, as it includes liver function and performance status in addition to transitional tumour staging (Table 1) [12]. The Hong Kong Liver Cancer Staging System may be more appropriate and predictive of survival compared with the BCLC staging system for the Asian population, where HBV coinfection is prevalent [13]. Substantial survival improvement has been achieved in the recent two decades due to the development of locoregional treatment, systemic therapy including targeted therapies and, more recently, immune checkpoint inhibitors. Although Western countries are pioneering the use of novel therapies, Eastern counterparts have confirmed and substantiated their efficacy and safety in their large study population with different HCC aetiologies and clinicopathological behaviour. Here we provide an overview of the recent treatment advances and a comparison of the management paradigm between the East and the West for advanced unresectable HCC.

Transarterial Chemoembolisation

Transarterial chemoembolisation (TACE) is the most commonly recommended treatment for BCLC stage B disease [14]. Some three decades ago, three randomised controlled trials in the West failed to show a survival benefit with TACE compared with conservative management for patients with unresectable HCC, three-quarters of whom had alcoholic liver disease [15–17]. The studies were probably underpowered because of the small numbers of patients (42–79 patients only) recruited in each study and a mixture of TACE (chemoembolisation versus embolisation alone) within these studies was used. The Hong Kong randomised controlled trial of 80 patients, with 80% being hepatitis B carriers, produced a survival benefit with TACE (3-year rates 26% versus 3%, hazard ratio 0.49, $P = 0.006$) [18]. In the same year, a Western randomised controlled trial showed an overall survival benefit (2 years 63% versus 27%, $P = 0.009$) [19]. A subsequent systematic review confirmed the survival benefits with TACE over symptomatic treatment (2-year overall survival rates 41% versus 27%, hazard ratio 0.53, $P = 0.017$) [20]. The confirmed survival advantage with TACE in this meta-analysis was essentially attributed to the positive results of the latest two high-quality trials, which treated patients with chemoembolisation rather than embolisation alone [18,19].

More and more centres now use drug-eluting beads TACE (DEB-TACE) rather than conventional TACE (cTACE). The DEBs are deposited into the feeding tributaries of the hepatic arteries and the drugs are slowly released to increase their concentrations inside the tumours, leading to fewer side-effects. An investigator-initiated single-arm phase II trial of 192 patients having intermediate stage unresectable HCC treated with DEB-TACE and interrupted dosing of sorafenib in Taiwan showed a promising 3-year overall survival rate of 86.1%, at the expense of 27.1% serious adverse events [21]. The European Precision V phase II randomised trial of 212 patients showed a similar response rate but a significant reduced drug- and liver-related toxicities with DEB-TACE [22]. TACE in combination with targeted therapy has also been evaluated in randomised trials. With disappointment, the addition of targeted therapies, such as sorafenib, and more recently orantinib, in the West and the East, respectively, did not improve survival over TACE alone [23,24].

Hepatocellular Carcinoma with Portal Vein Thrombosis

Advanced HCC with portal vein thrombosis deserves special attention and further discussion as a separate entity here because it presents as an extremely challenging scenario that usually precludes surgical resectability and various types of locoregional treatment, including radiofrequency ablation (RFA) and TACE, due in part to its strong negative prognostic significance. Tumour propagation along the main portal vein can also reduce blood supply to the liver, leading to a rapid decline in liver function and a rise in portal hypertensive sequelae, leading to liver failure. Sorafenib and lenvatinib are the only approved treatments in most guidelines for these patients. However, a pooled analysis of two phase III sorafenib trials suggested that sorafenib prolongs the median survival of these patients by 47 days only, compared with placebo [25–27].

The development of contemporary novel treatment modalities including external and internal radiation therapy, like stereotactic body radiation therapy (SBRT) and transarterial radioembolisation (TARE), may reverse unresectability to curative resection or liver transplantation as further elaborated below. With the advancement of advanced radiation technologies, early studies have suggested that conformal radiation therapy can be safely administered to these patients, resulting in sustained

Table 1
Description of the Barcelona Clinic Liver Cancer (BCLC) classification system and the Hong Kong Liver Cancer Staging System (HKLCSS)

BCLC stage	Description
0	PST 0, Child-Pugh A, single <2 cm, carcinoma *in situ*
A	PST 0–2, Child-Pugh A-B, single or 3 nodules ≤2 cm, PS 0
B	PST 0–2, Child-Pugh A-B, multinodular, PS 0
C	PST 0–2, Child-Pugh A-B, portal vein invasion, N1, M1, PS 1–2
D	PST >2, Child-Pugh C
HKLCSS stage	**Description**
I	ECOG 0, Child A, early tumour, no EVM
IIa	ECOG 1, Child B, early tumour, no EVM
IIb	ECOG 0–1, Child A, intermediate tumour, no EVM
IIIa	ECOG 0–1, Child B, intermediate tumour, no EVM
IIIb	ECOG 0–1, Child A-B, locally advanced tumour, no EVM
IVa	ECOG 0–1, Child A, EVM
IVb	ECOG 0–1, Child B, EVM
Va	ECOG 2–4, Child C, early tumour, no EVM
Vb	ECOG 2–4, Child C, other tumours, EVM

Early tumour is defined as ≤5 cm, ≤3 tumour nodules and no intrahepatic venous invasion.
Intermediate tumour is defined as (i) ≤5 cm, either >3 tumour nodules or with intrahepatic venous invasion or (ii) >5 cm, ≤3 tumour nodules and no intrahepatic venous invasion.
Locally advanced tumour is defined as (i) ≤5 cm, >3 tumour nodules and with intrahepatic venous invasion or (ii) >5 cm, >3 tumour nodules or/and with intrahepatic venous invasion or (iii) diffuse tumour.
ECOG, Eastern Cooperative Oncology Group; EVM, extrahepatic vascular invasion/metastasis; PST, performance status.

locoregional control, recanalisation and longer than expected survival in a subset of patients. There is a rationale for combining radiation therapy with regional or systemic therapies. The West has investigated the combination of radiation therapy and TACE and has shown better control of intravascular tumour growth and restoration of portal venous flow with radiation therapy, which may allow further TACE delivery to be more effective. A recent randomised controlled trial of 90 patients conducted in South Korea showed that TACE followed by three-dimensional conformal radiation therapy with 45 Gy in 15–18 fractions over 3–3.5 weeks produced a higher radiological response, a longer time-to-progression and, more importantly, a significant improvement in overall survival compared with sorafenib alone (55.0 versus 43.0 weeks, $P = 0.04$) [28]. Interestingly, five (11.1%) patients received curative surgical resection following downstaging by TACE plus radiation therapy; these patients had a survival time between 119 and 149 weeks.

Bridging Therapy before Surgical Resection or Liver Transplantation

With the advent of new therapeutics, some initially locally advanced unresectable diseases can be amenable to radical surgery or liver transplantation following significant downstaging bridging therapy. A systematic review of 13 studies with 950 patients revealed that the recurrence rate after various downstaging modalities was 16% [29]. The Milan criteria (presence of a tumour ≤5 cm in diameter in patients with single HCC or ≤3 HCCs each ≤3cm in diameter in patients with multiple tumours) have been the standard eligibility criteria for liver transplantation [30]. Various extended criteria have also been recently adopted in some tertiary centres in the last decade with encouraging outcomes, which makes evaluation of the efficacy of downstaging techniques difficult [31]. In general, percutaneous ethanol injection, RFA, TACE, radiation therapy, including SBRT, and TARE have been used to downstage the tumours with various inclusion and transplantation criteria in both the East and the West, with results comparable with those who received transplantation without prior downstaging treatment [32–35]. A prospective randomised trial would be needed to better understand the benefits of bridging therapies and which is best for such patients [36].

Transarterial Radioembolisation

Patients with major vascular invasion are also candidates for TARE, through injection of yttrium-90 glass or resin microspheres into the feeding arteries supplying the tumours. The microspheres are trapped at the precapillary level and emit pure β-emission with an 11 mm maximum penetration length. A meta-analysis of 17 Eastern and Western studies with 722 HCC patients with portal vein invasion showed that the response rate, median time-to-progression and median survival after TARE was 47.8%, 5.6 months and 9.7 months, respectively [37]. When compared with TACE, TARE showed at least comparable results with TACE but with a more favourable treatment-related toxicity profile and post-procedure pain, as reported in a meta-analysis of five Western studies [38]. Another meta-analysis of 14 Western studies comparing TARE with DEB-TACE found that DEB-TACE had a better 1-year overall survival that became imperceptible after 2 and 3 years [39].

TARE has been extensively used in Western populations, mainly for metastatic colorectal cancer with liver-limited metastases and advanced unresectable HCC. For HCC, TARE was first studied in Asian populations, in particular in Singapore and Hong Kong, where a strong multidisciplinary team of surgeons and interventional radiologists have led several studies [40–42]. TARE has been compared with sorafenib in SIRveNIB and SARAH trials in Asia Pacific and France [43,44]. Both were phase III randomised controlled trials, with a similar study design. To our disappointment, neither study failed to meet the primary study end point compared with sorafenib (median overall survival 8.8 [TARE] versus 10.0 [sorafenib] months in SIRveNIB and 8.0 [TARE] versus 9.9 [sorafenib] months in SARAH).

Stereotactic Body Radiation Therapy

Radiotherapy has gained popularity in both the East and the West for treating advanced unresectable HCC with macroscopic vascular invasion, showing encouraging response rates ranging from 39 to 62% [45–54]. Highly conformal and precise radiotherapy, including SBRT, in which a high dose of radiation focused to the tumours while sparing the adjacent organs from unnecessary radiation, can be delivered in a few fractions (generally less than six). This is achieved through accurate image guidance, motion management and computer controlled radiation planning and delivery. Indeed, SBRT seems to be an acceptable treatment option for advanced HCC with invasion into major vessels, in which surgical resection and other ablative treatments are precluded.

A recent systematic review and meta-analysis conducted in South Korea that included 32 retrospective or prospective trials of 1950 patients with various aetiologies and stages of HCC showed that SBRT (in less than 10 fractions) is feasible with few liver-related toxicities [55]. Most of the trials in this meta-analysis contained a mixture of early and advanced HCC, making the survival analysis for advanced disease difficult. Randomised controlled trials comparing SBRT with other standard treatment are ongoing but not yet published. There is increasing evidence supporting SBRT for advanced unresectable HCC, but this is limited by the non-randomised nature of the studies. In a sequential phase I/II study conducted in Canada, a local control rate of 87% and a median survival of 17 months were achieved with SBRT for 102 patients [54]. Of them, 55% had tumour vascular thrombosis and 61% had multiple tumours with a median sum of the largest diameter of almost 10 cm and a median diameter of 7.2 cm for the largest lesion. There were conflicting results when SBRT was compared with RFA for early stage I/II HCC in three meta-analyses conducted in the East and the West, probably because of selection bias, patient preference and retrospective comparison [56–58]. Overall, outcomes following SBRT or RFA for early stage HCC seem to be similar and both should be considered in the East and the West, with SBRT preferred for HCC >4 cm and adjacent to large vessels and RFA preferred for easily accessible HCC <3 cm.

The utility of SBRT has not yet been addressed in the European Association for the Study of the Liver guidelines [59]. The National Comprehensive Cancer Network guidelines has included SBRT as a feasible locoregional treatment with level 2A recommendation [60]. The Asia-Pacific Primary Liver Cancer Expert Meeting, an international association of liver cancer experts in Asia Pacific, has recommended SBRT for early HCC, defined as a solitary tumour ≤5 cm in maximum diameter or multiple tumours (three in total) and 3 cm in maximum diameters, without vascular invasion/extrahepatic metastases and with Child-Pugh A/B, for which RFA or liver transplantation is not feasible [61]. SBRT is now being evaluated with other systemic treatment (NCT02906397, NCT02989870, NCT02794337, NCT01730937) and immunotherapy (NCT03817736 and NCT03203304) for advanced HCC in both Western and Eastern populations.

Targeted Therapy

Sorafenib

Sorafenib is the first approved targeted therapy for advanced HCC. It is also the first targeted therapy that showed an improvement in overall survival in both Western and Eastern populations [25,26]. In the 'Western' SHARP trial, sorafenib conferred an overall survival advantage from 7.9 to 10.7 months (hazard ratio 0.69, $P < 0.001$) when compared with placebo [25]. One year later, the Asia-Pacific trial confirmed the same result with almost the same magnitude of overall survival benefit in the 'Eastern' population (hazard ratio 0.68, $P = 0.014$) [26]. That said, the median overall survival of the 'Eastern' population was still shorter (6.5 months versus 10.9 months in the Asia-Pacific and SHARP trials, respectively), which might be attributed to the fact that there was a higher percentage of patients with HBV in the Asia-Pacific study. A subsequent exploratory pooled analysis of these two studies revealed that the overall survival benefit with sorafenib was seen across all subgroups, including ethnicity and presence of macrovascular invasion, and the benefit was even greater than in those without extrahepatic spread (hazard ratio 0.55 versus 0.84), with HCV (hazard ratio 0.47 versus 0.81) and a low neutrophil-to-lymphocyte ratio (hazard ratio 0.59 versus 0.84) [27].

As described previously, sorafenib did not add further survival advantage to DEB-TACE in both the East and the West, as confirmed by the British TACE2 phase III randomised controlled study and a Taiwan phase II single-arm trial in which an interrupted dosing of sorafenib was given [21,23]. The East and the West joined hands to investigate if erlotinib could bring further benefits in addition to sorafenib [62]. Unfortunately, the SEARCH study, which compared sorafenib plus erlotinib to sorafenib plus placebo failed to improve overall survival (9.5 versus 8.5 months, $P = 0.408$). Further subgroup analysis did not confirm any benefits among all ethnic groups.

Sorafenib was also evaluated as adjuvant treatment following resection or ablation. In this setting, the STORM phase III trial was conducted throughout the Americas, Asia-Pacific and Europe across 202 sites and 28 countries [63]. The Asian population contributed about two-thirds of subjects. The geographical region was in fact a stratification factor of randomisation in this study. Unfortunately, none of the ethnic groups found a recurrence-free survival benefit for adjuvant sorafenib (8.5 versus 8.4 months in the sorafenib and placebo arms, respectively).

Lenvatinib

In contrast to many other targeted agents investigated, lenvatinib has recently been found to be non-inferior to sorafenib in the first-line setting. The REFLECT randomised controlled trial is a joint effort between the East and the West comparing lenvatinib with sorafenib, with geographical region (Asia-Pacific or Western) as one of the stratification factors during randomisation [64]. The median overall survival was 13.6 months on lenvatinib versus 12.3 months on sorafenib, with a hazard ratio of 0.92 (95% confidence interval 0.79–1.06), reaching the primary study point of non-inferiority. In addition, progression-free survival, time to progression and objective response rates as secondary study end points were in favour of lenvatinib, based on masked independent imaging review with mRECIST and RECIST 1.1. Intriguingly, Asia-Pacific patients, in the pre-planned subgroup analyses, had longer progression-free survival and overall survival with lenvatinib against sorafenib, which may be due to the relatively lower efficacy of sorafenib in HBV-related HCC. Another important point to note in this study is that patients with more than 50% tumour involvement in their liver or main portal vein invasion were excluded, as this exclusion criterion was adopted in the previous phase II proof-of-concept study in Japan, mandated by the Liver Cancer Study Group of Japan [65]. Thus, the role of lenvatinib in those with diffuse tumours, clear invasion of the bile duct and main portal vein invasion is still uncertain. Nevertheless, a further cost-effectiveness analysis in Japan showed an incremental 0.27 and 0.23 life years and quality-adjusted life years, respectively, but at a negative incremental cost for lenvatinib compared with sorafenib [66]. Lenvatinib, based on REFLECT, has been approved in Japan and by the Food and Drug Administration in the USA and the European Medicines Agency as an alternative first-line systemic treatment for advanced or unresectable HCC. The difference in patterns of post-study treatment between the East and the West after progression to lenvatinib also deserves attention. There were more Asia-Pacific patients who received post-lenvatinib treatment compared with Western counterparts. It is still unknown if this preference of care would have an effect on overall survival.

Following sorafenib in the SHARP and the Asia-Pacific trials, other targeted therapies (sunitinib, brivanib, linifanib) have not been shown to offer survival benefit or similar safety profiles compared with sorafenib in the first-line setting [67–69]. Overall, the use of targeted therapies should be an individualised decision, preferred for patients with intact liver function (e.g. Child-Pugh A) and a one-size-fits-all strategy is not appropriate for all HCC patients. Factors including HBV status (lenvatinib favoured), HCV status (sorafenib favoured), AFP response, pre-treatment AFP levels and patterns of disease progression should all be considered when choosing the right targeted therapy [70–72].

Second-line Targeted Therapy

In the second-line setting, after prior failure with or intolerance to sorafenib, a number of targeted therapies (brivanib, everolimus, ramucirumab, tivantinib, ADI-PEG 20) failed to show an overall survival benefit compared with placebo, as shown in phase III trials conducted in either Eastern or Western continents alone or among different regions [73–78]. So far, three phase III randomised controlled trials have proven the benefits of additional targeted therapy following failure with sorafenib. The RESORCE study showed an overall survival gain in patients who received regorafenib compared with placebo on progression with sorafenib (10.6 versus 7.8 months, hazard ratio 0.63, $P < 0.0001$) [79]. Similarly, the CELESTIAL study produced a better overall survival (10.2 versus 8.0 months, hazard ratio 0.76, $P = 0.005$) and progression-free survival (5.2 versus 1.9 months, hazard ratio 0.44, $P < 0.001$) with cabozantinib after progression with up to two previous systemic treatments, including sorafenib for advanced HCC [80]. Those who received sorafenib as the only prior systemic treatment had a more favourable survival with cabozantinib compared with placebo (11.3 versus 7.2 months, hazard ratio 0.74). Finally, the REACH-2 study, which randomised patients with baseline AFP $\geq$400ng/ml to either ramucirumab or placebo as second-line treatment, also showed a benefit [81]. This inclusion criterion was based on the results of a subgroup analysis of the previous REACH study [75]. The REACH-2 study met its primary study end point and showed an improved overall survival with ramucirumab (8.5 versus 7.3 months, hazard ratio 0.71, $P = 0.0199$). All of these trials were conducted throughout the East and the West, and their joint efforts and close collaborations on these positive studies should be commended.

Despite the evidence and the subsequent approval of these targeted therapies, financial affordability is also a serious concern to governments, oncologists and patients. One of the solutions to cut drug costs is to introduce biosimilars or generic biologics [82]. Impending expiration of patented drugs provides the opportunity to introduce biosimilars, which provide alternative options to various stakeholders, including patients, regulators, policy makers and drug manufacturers. Some countries and regions have already provided expedited pathways to approve biosimilars, based on pharmacokinetics, efficacy, immunogenicity and safety [83–85]. Nevertheless, challenges such as appropriate clinical trial design to assess biosimilarity, extrapolation of indications, immunogenicity,

Table 2
Selected ongoing clinical trials evaluating immunotherapy for hepatocellular carcinoma

Drug	End year	Mechanism	Phase	Setting	Design	ClinicalTrials.gov identifier
Nivolumab	2017	Immune checkpoint inhibitor against PD-1	III	First	RCT	NCT02576509
Tremelimumab ± durvalumab	2018	Monoclonal antibody against CTLA-4 and PD-L1	II	First or second	RCT	NCT102519348
Pembrolizumab + tumour-infiltrating lymphocytes + aldesleukin + cyclophosphamide + fludarabine	2019	Immune checkpoint inhibitor against PD-1	II	Second	Non-randomised	NCT01174121
Pexastimogene devacirepvec + sarafenib	2019	Vaccinia virus-based immunotherapy	III	First	RCT	NCT02562755
Pembrolizumab	2019	Immune checkpoint inhibitor against PD-1	III	Second	RCT	NCT02702401
Pembrolizumab (Asian)	2022	Immune checkpoint inhibitor against PD-1	III	Second	RCT	NCT03062358
Pembrolizumab and SBRT	2022	Immune checkpoint inhibitor against PD-1	II	Second	Non-randomised	NCT03316872

CTLA-4, cytotoxic T-cell lymphocyte-4; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; RCT, randomised controlled trial; SBRT, stereotactic body radiation therapy.

interchangeability with the reference drugs, lack of public awareness and acceptance among oncologists may limit their effective usage and popularity. In fact, because of poor quality and propaganda, biosimilars may produce a counter effect, encouraging patients to resort back to brandname drugs.

Table 3
Differences in aetiologies and clinical practice for hepatocellular carcinoma between the East and the West

	East	West
Aetiology	Hepatitis B infection constitutes the majority (about 80%) The rest are hepatitis C infection, aflatoxin exposure, alcoholism and non-alcoholic fatty liver disease	Alcoholism and non-alcoholic fatty disease constitute the majority The rest are hepatitis C, hepatitis B and aflatoxin exposure
Screening	National screening programmes only available in certain countries	National screening programmes available in most countries
Management of advanced unresectable disease		
TACE	Routinely available Can be considered as bridging therapy before surgery or transplantation in highly selected patients	Routinely available Can be considered as bridging therapy before surgery or transplantation in highly selected patients
TARE	Only available in specialised tertiary oncology centres Can be considered as definitive treatment or bridging therapy before surgery or transplantation in highly selected patients	Only available in specialised tertiary oncology centres Can be considered as definitive treatment or bridging therapy before surgery or transplantation in highly selected patients
SBRT	Only available in specialised tertiary oncology centres Can be considered as definitive treatment or bridging therapy before surgery or transplantation in highly selected patients	Only available in specialised tertiary oncology centres Can be considered as definitive treatment or bridging therapy before surgery or transplantation in highly selected patients
Targeted therapy	Sorafenib approved and available Lenvatinib approved in some Asian countries	Sorafenib and lenvatinib approved and available
Immune checkpoint inhibitors	Nivolumab is only available and approved in some Asian countries Can be considered as first-line or subsequent lines of treatment after prior failure with sorafenib or other targeted therapy Other immune checkpoint inhibitors are not approved	Nivolumab is available and approved as first-line treatment Other immune checkpoint inhibitors are not approved

SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation.

Immunotherapy

Immunotherapy in the form of immune checkpoint inhibitors has brought a new treatment paradigm for HCC patients from both the East and the West. A small phase II study showed the feasibility and safety of tremelimumab against cytotoxic T lymphocyte-associated antigen in HCV-infected HCC [86]. Extensive research has also recently focused on the inhibition of programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1). The pivotal CheckMate-040 phase Ib/II dose escalation and expansion trial, which has almost equal participation from the East and the West, showed an objective response rate of 20% in the dose-expansion phase [87]. However, the response was more readily observed in uninfected (23%) and HCV-infected (20%) HCC, which implied that most of the HBV-infected Asian population derived less benefit from it. Pembrolizumab as second-line treatment after sorafenib was also evaluated in the KEYNOTE-224 non-randomised phase II study [88]. The overall objective response rate was 17%, more commonly observed in Americans (26%) and uninfected HCC (20%). More recently, the drug company made an announcement that pembrolizumab failed to meet its study end points of progression-free survival and overall survival improvement as second-line treatment compared with placebo [89].

Immune checkpoint inhibitors are now being tested as first-line treatment compared with sorafenib. The CheckMate-459 study, comparing nivolumab with sorafenib, with a significant Asian participation, has completed patient accrual and the first results are soon to be released. Other studies on immune checkpoint inhibitors alone, or in combination with other treatments, are on the way (Table 2).

Multidisciplinary Management

The management of advanced unresectable HCC has been increasingly difficult and complex in view of the numerous emerging novel promising treatment modalities operated by different specialties. It is evident that multidisciplinary management improves detection rates, leading to more duly management with higher rates of both radical and palliative treatment and improved survival. An American prospective study revealed that multidisciplinary management doubled patient referrals, resulting in more patients evaluated at earlier stages of disease [90]. The overall survival and duration of follow-up also significantly improved after the implementation of multidisciplinary care. In addition, stage-by-stage comparisons showed that aggressive multidisciplinary care conferred a survival advantage for intermediate or advanced disease [90]. Another similar study by Yopp *et al.* [91] also echoed the same findings, with earlier detection, shorter time to treatment after diagnosis and better survival after adjusting BCLC stage and recipient of curative treatment. This is certainly the gold standard treatment paradigm in both the East and the West, as clearly shown in the treatment guidelines in these regions.

Conclusion

The survival of advanced unresectable HCC has dramatically improved over the past few decades, since the advent of various novel therapeutics and interventions. The availability of expertise and infrastructure for SBRT and TARE is also a crucial factor. Currently there are similarities and differences in terms of aetiologies and clinical practices between the East and the West (Table 3). In view of the inherent ethnical and aetiological differences, these two factors should be considered as stratification factors when designing future international multicentre randomised controlled trials. As a result, the decision-making strategy must be individualised after taking into account these factors, apart from patient and disease factors. In both the East and the West, a multidisciplinary management approach is highly recommended and should be regarded as the current and future standard of care.

Conflicts of Interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.06.002.

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