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Amber Sani [a] | M. Khalil-ur-Rehman [b] | Aqsa Saleem Raza [c]

Muhammad Khalid Tipu [d]

Hepatocellular Carcinoma: From Epidemiology to Advancement in Treatment

Abstract *Hepatocellular carcinoma is a heterogenous malignant tumor that is known as the deadliest cancer worldwide due to its complexities. Most of the time, it occurs with underlying liver complications, including cirrhosis. The most predominant risk factors in HCC development are cirrhosis and chronic Hepatitis B virus (HBV) infection. Its complexities pose multiple challenges in diagnostic and therapeutic measures. In recent years, a huge rise in cases is seen in non-traditional countries such as North America and European regions rather than Japan and China. Herein, our aim is to give an overview of the latest information about hepatocellular carcinoma regarding its epidemiology, risk factors, biomarkers, staging, diagnosis, and treatment.*

Key Words: Hepatocellular Carcinoma, Epidemiology, Risks, Staging Systems, Treatment

Introduction

Hepatocellular carcinoma (HCC) is a hostile malignant tumor that is the primary cause of cancer-related mortalities worldwide. It is a complex type of tumor also known as hepatoma, including complexities such as hepatocyte necrosis, fibrotic disposition, regeneration, genetic mutations and intratumoral heterogeneity. It illustrates a paramount international health issue and attributes to 90% of all hepatic malignancies. Incidence and mortality of HCC are increasing and are anticipated to continue to rise owing to the prevalence of obesity worldwide. Some of the important causes are hepatitis C, hepatitis B, alcohol abuse, diabetes, and possibly non-alcoholic fatty liver disease (NALFD).

Epidemiology

Hepatocellular carcinoma is the seventh most widespread and deadliest cancer worldwide. Globally, HCC accounts for 75% of the cancer cases and the highest incidence rates were recorded in Asia and Africa in time period of 1978 to 2012 (Petrick JL, et al., 2019). Traditionally, China having the largest population, had the greatest number of cases with an uplifted incidence rate of 18.3 per 100,000 *(IARC, 2012).* Mongolia had the greatest incidence rate of about 93.7 per 100,000 *(Bray F et.al., 2018).*

In recent years, a decline in incidence is observed in Asian countries. On the contrary, an increasing incidence order is spotted in North America, India, Oceania and some European regions (Valery PC, et.al., 2018). A possible explanation for the decline in incidence rate in traditional countries (high rate of hepatitis B infections) includes the influence of hepatitis B vaccination and depletion of aflatoxins exposure. However, incidence and mortality of HCC is approximately analogous as the prognosis is exceptionally variable with multiple determining factors.

Sex

Globally, men are more likely to develop HCC as

[a] Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan.
[b] Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan.
[c] Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan.
[d] Assistant Professor, Department of Pharmacy, Faculty of Biological Sciences, Quaid I Azam University, Islamabad, Pakistan. Email: mktipu@qau.edu.pk

compared to women. Major sex differences were observed in European regions. On the contrary, in some other countries the ratios were similar (Petrick JL, et al., 2019).

Table 1

Countries	Ration (M/F)
France	5: 0
Malta	1: 2
Uganda	1: 1
Costa Rica	1: 6
Ecuador	1: 0
Colombia	1: 6

Age

HCC is also predominant in older patients. Mostly, incidence rates of HCC seem to be directly correlated with the age (mean age at diagnosis ranges from 50 – 60 years) (Petrick JL, et al., 2019). In 2018, highest age-standardized incidence rate (ASIR) was estimated in Eastern and Southeastern Asia, Northern Africa and Micronesia. While the lowest ASIR was recorded in Western Asia and Central and Eastern Europe (Ferlay J, et al., 2018).

Ethnicity

There is a wide variability in incidence of different geographic regions. Although initially, in US the incidence was highest in Asians/pacific Islanders but thereafter the incidence rate began declining in these races. However, an increasing incidence order was observed in Asian Indians, Hispanics etc.

Risk Factors

The risk of HCC depends on three types of factors; Host factors (age, gender, ethnicity etc.), Environmental or lifestyle factors (exposure to aflatoxins, alcohol or tobacco use, metabolic diseases) and Viral factors (HBV and HCV variants, genotype and viral load, Hepatitis D and HIV etc.).

Worldwide, HBV infects millions of people chronically, which is a predominant risk factor in development of HCC. In traditionally high incidence areas (Sub-Saharan Africa and East Asia) it attributes to almost all of the cases. HbsAg positivity accounts for 10-times the risk of HCC development as compared to HbsAg. Additionally, HbeAg positivity accounts for 60-times the risk of HCC (Yang HI, et al., 2002). On the other hand, chronic HCV accounts for 25% risk of HCC development. Hepatitis C antibody positivity accounts for 20-times the risk of HCC as compared to hepatitis-C antibody negative (Sun CA, et al., 2003). The risk of HCC development in both chronic HBV and HCV patients depends on the viral, environmental and lifestyle related determinants.

Co-infections among HBV, HCV, HDV, and HIV frequently leads to HCC. With the influence of HBV vaccinations worldwide the co-infections HBV/HCV are minimized. According to a study in Swedish series, the HCC risk increased 60-fold in HBV/HDV co-infection patients as compared to the patients infected with HBV alone (Ji J, et.al. , 2012). In HIV patients co-infected with viral hepatitis (HBV and HCV), accelerated hepatocarcinogenesis is observed due to inflammatory and immunosuppressive effects (Gelu-Simeon M, et al., 2014).

Chronic alcohol intake may lead to liver injury, cirrhosis and ultimately HCC and end-stage liver disease. Alcohol use, obesity and smoking has a compound effect on HCC risk. The combination of chronic alcohol consumption and diabetes mellitus leads to exceptional increase in the risk of HCC (Yuan JM, et al., 2004). Non-alcoholic fatty liver disease (NAFLD) contribution to HCC development is likely to become significant. Although, majorly the risk is attached to cirrhotic NAFLD but cases in non-cirrhotic patients are also reported *(White DL, et.al., 2012).* Notably, HCC occurs in alpha-1 antitrypsin deficiency with or without cirrhosis

Aflatoxins are family of toxins produced by fungi (Aspergillus parasiticus or Aspergillus flavus), found on agricultural crops. Aflatoxins increase the risk of HCC independently and collaborate with HBV to increase the HCC risk by 60-folds (Ross RK, et al., 1992).

Biomarkers

It is very important to detect HCC development at an emerging stage whether in cirrhotic or non-cirrhotic patients. However, given its asymptomatic nature

most of the times it is detected at an advanced stage progressing to an incurable disease stage.

HCC cells appear to be related to genetic and epigenetic alterations and abnormal micro-RNAs expression. There are various atypical genes encoding for proteins (P16, P53, P73, PTEN, APC, SMAD2, BRCA2, SOCS, IGF-2, retinoblastoma proteins, beta-catenin, cyclin D1 and c-myc proteins etc.) that are observed in HCC development (Shearn CT, Petersen DR, 2015). P-53 is contemplated to be the major altered gene expressed in HCC. Other than this, there are specific signaling pathways observed in HCC development like growth and vascular factors, oncogene receptors etc. HCC is marked with high angiogenetic activity in the vascular tissues (tumor is highly vascularized) resulting in increased vascular-endothelial growth factor (VEGF) which can be used for targeted treatment of HCC (Villanueva A, Llovet JM, 2011).

Epigenetic alterations in HCC includes; hypermethylation or hypomethylation of DNA, non-coding RNAs (due to expression of abnormal micro-RNAs) or histone protein depletion and disruption. Liver specific epigenetic changes can be an early guide in HCC screening and diagnosis *(Anwar SL, Lehmann U., 2014)*

Most used biomarker for HCC detection is alpha-fetoprotein (AFP). It is a glycoprotein produced by the liver of a maturing fetus. It is structurally very similar to albumin protein. Although, it is a useful biomarker its specificity is diminished as its level is elevated in other complications such as acute and chronic hepatitis, intra-hepatic carcinoma and embryogenic tumors. Recently, lack of AFP reduction with DAAs (Direct Acting Anti-virals) treatment during Hepatitis-C is marked as an independent risk determinant for HCC development (Masetti C et al., 2018).

Novel Biomarkers and their Applications

Other novel biomarkers include; Lens culinaris agglutinin-reactive glycoform of AFP (AFP-L3), osteopontin (OPN), Fibroblast growth factor (FGF), insulin growth factor-1 (IGF-1), angiopoietin 2 (ANG-2), des-gamma-carboxyprothrombin (DCP), Golgi protein 73 (Gp-73), hepatic growth factor (HGF), single nucleotide polymorphism (SNP), c-MET and Glypican-3 etc. (Chaiteerakij R, et.al., 2015)

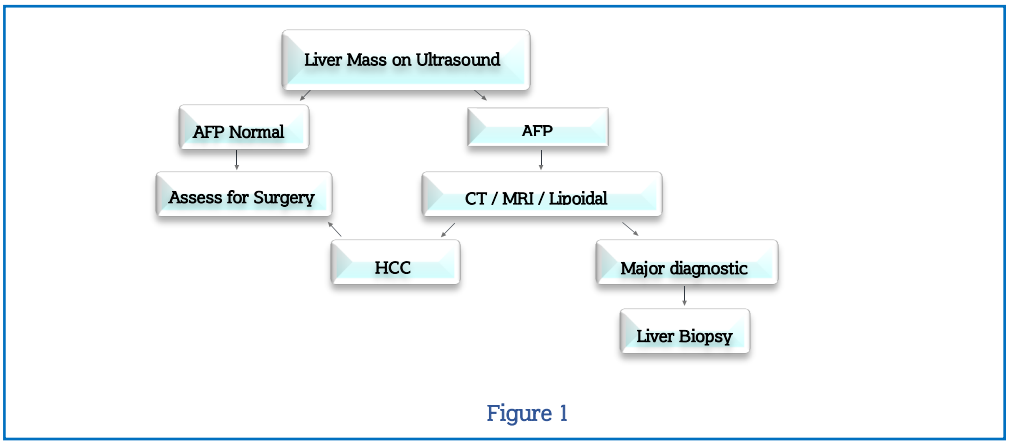

Figure 1

Table 2

Use	Biomarkers
Identifying at-risk population	AFP, DCP, AFP-L3%, SNPs
Screening for early detection	AFP, DCP, AFP-L3%
HCC diagnosis	AFP, DCP, AFP-L3%, GPC, Osteopontin, GP73

Table 3

Use (HCC Diagnosis)	Biomarkers
Prediction of patient survival	AFP, Osteopontin
Prediction of HCC reoccurrence	AFP
Patient stratification for targeted therapy	AFP, FGF3/FGF4, high MET expression
Prediction of response to therapy	AFP

Challenges to use these Biomarkers

There is not a specific biomarker that is present in all cancer patients. Furthermore, the heterogeneity of individual person as well as heterogeneity of cancers makes it even more difficult. In order to optimize the use of biomarkers, a combination of biomarkers can be utilized to reach the maximum diagnostic results.

Diagnosis

Diagnosis of HCC includes following tests;

1. Imaging tests (CT scan and MRI)
2. Blood tests (for examining liver function)
3. In some cases, liver biopsy (for laboratory testing).

In recent years, there have been major improvements in imaging techniques which was helpful in providing functional information; usage of hepatobiliary contrast media for MRI and introduction of new radio-tracers for PET (positron emission tomography). (Bartolozzi C, et.al., 1996)

Staging

Globally, various staging systems are designed to in accordance with the parameters of the disease in order to propose a proper treatment method. According to consensus conference held in 2010 there are 18 HCC staging systems (Vauthey JN, et al., 2010). Among these, OKUDA, MESIAH, CLIP, ITA.LI.CA are used to foretell survival. On the other hand, Alberta, BCLC and HKLC are used to guide in decision making during treatment. Other staging systems include; TNM, GRETCH and CUPI.

In order to evaluate HCC prognosis, the staging system should be able to account for physical state, tumor stage and liver functioning. The CLIP and BCLC systems are excessively utilized in European regions. The BCLC system is preferred as it is the only system that relates prognosis with treatment interpretations, and it has been really helpful in patient stratification into different HCC classes. TNM system is usually utilized for prognostic determination after surgery or liver transplant. It is really important in determining post-transplantation survival rate of patients

Table 4

Systems for Staging	Stages Of Tumor	Liver Functioning	Stages
OKUDA System	Tumor complicity is greater than 50%	Albumin, Bilirubin and Ascites	I - III
CLIP System	AFP, Hepatic Portal vein thrombosis and tumor morphology	Child-Turcotte-Pugh state	0 - 6
GRETCH System	AFP, Hepatic Portal vein invasion	Bilirubin and Alkaline Phosphate	A - C
BCLC System	Tumor size, Number of nodules, Hepatic Portal vein thrombosis and tumor morphology, metastasis	Portal Hypertension and Child-Turcotte-Pugh state	0 and A-D
CUPI System	TNM and AFP	Alkaline Phosphate, Bilirubin and Ascites	3 risk groups and 0 - 12 score
AJCC TNM System	Tumor size, Number of nodules, Hepatic Portal vein thrombosis and metastasis	-	I - IV
Tokyo Score System	Tumor size and Number of nodules	Albumin and Bilirubin	0 - 8
Taipei Integrated Scoring System	AFP and Total tumor mass volume	Child-Turcotte-Pugh state	0 - 6

(Olthoff K.M et.al., 2011)

Terminologies

ITA.LI.CA (Italian Liver Cancer), HKLC (Hong Kong Liver Classification), BCLC (Barcelona Clinic Liver Cancer), MESIAH (Model to Estimate Survival in Ambulatory HCC patients), GRETCH (Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire), CLIP (Cancer of the Liver Italian Program score), CUPI (Chinese University Prognostic Index), TNM (Tumor/ node/ metastasis).

Treatment of Hepatocellular Carcinoma (Hcc)

The 2nd deadliest cancer around the globe with minimum survival rate causing millions of deaths per annum is the liver cancer or hepatocellular cancer (HCC). It is classified into different stages (stage 0, A, B, C and D) according to the Barcelona-Clinic Liver Cancer (BCLC) system which is valid and is recommended for the prognosis and treatment strategies. The decision for a particular therapy against HCC treatment depends on the stage of the liver cancer, carcinoma burden, functioning (Child-Pugh's system: Stage A, B, and C) and performance status of the liver. (EASL Clinical Practice Guidelines, 2018).

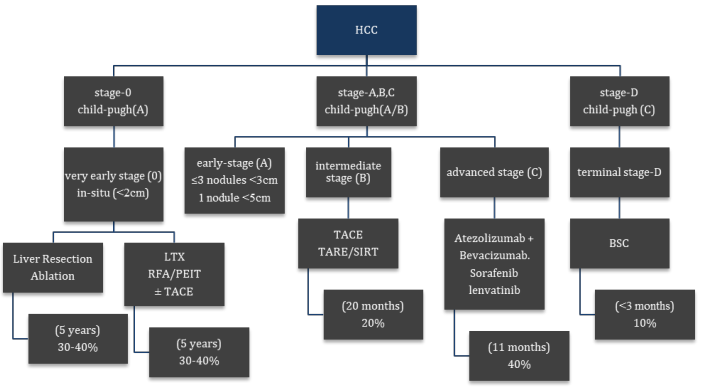

Figure 2

Today, we have the following treatment alternatives in contrast to the distinctive stages of the HCC e.g., the curative and the palliative treatments. The curative treatments are recommended for the BCLC stage 0 and A whereas the palliative treatments are most of the time recommended for those patients belonging to the BCLC stage B, C and D (intermediate, advanced and end stage liver function). (Kumari, Sahu, et al, 2018)

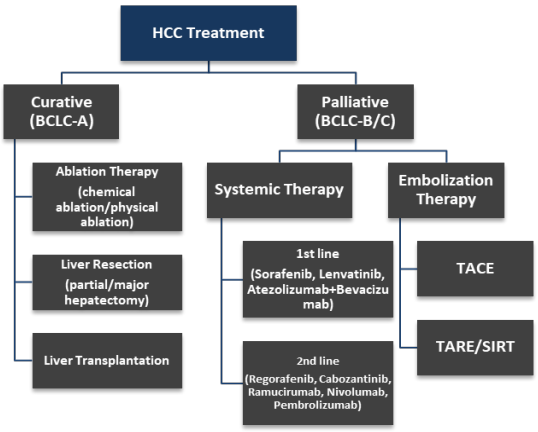

Figure 3: (Kumari, Sahu, et al, 2018)

Hepatectomy

Surgical resection/ablation is considered as treatment of choice for the patients of non-cirrhotic liver with early-stage HCC while for cirrhotic liver patients and HCC of 2-3 nodules within Milan criteria (gold standard for selecting HCC patients for possible therapies), it is indicated after assessing adequate liver functioning, portal hypertension (PT), and co-morbidities in patients. (EASL Clinical Practice Guidelines, 2018) For large size tumor growth, major whereas for small size tumor, partial liver resection is done. (Kumari, Sahu, et al, 2018) Hepatectomy is the maintop of HCC cure with excellent consequences of greater than 5 years survival rate in patients with prominent PT (25%) and in patients without PT (>79%). In non-cirrhotic patients, liver resection is indicated for HCC caused by NAFLD (non-alcoholic fatty acid disease) or Metabolic syndrome. Using diagnostic techniques (MRI, CT scan), it is essential to measure (using 3D Multidetector Computed Tomography) the volume of liver to be removed. Hepatectomy is associated with high recurrence rate (presence of satellite nodules) and postoperative death. While performing liver resection, a minimal liver residual volume of 40% should be kept accommodating liver performance/functioning. That's why future liver remnant (FLR) prediction is necessary for the postoperative mortality and morbidity in treated patients. (Graf D. et al, 2014).

Liver Transplantation (LTX)

Another distinctive treatment for treating both the underlying liver insufficiency and the HCC thereby minimizing the tumor generating environment for cirrhosis is the hepatic transplantation. It provides a mean four-year survival rate (>74%) in early stage (BCLC stage A) HCC patients who are acceptable according to the Milan criteria (MiC). Generally, LTX is performed for a tumor ranging in size of approx. 65mm or ≤3 nodules of 45mm or a single tumor growth with an average size of ≤80mm. The chances of recurrence are there after transplantation has been done in HCC patients. It was first done back in 1963. Although, it promotes beneficial effects in early-stage patients, yet it can't be done on a larger scale due to the fact that acute organ shortage (demand>supply), donor's liver crossmatch is a barrier and subsequent autoimmune response to the transplanted organ minimizes the chances of survival in these patients. (Daher S. et al, 2017). Using neoadjuvant therapies to downstage tumors prior to LTX is recommended for those who are possible candidates of LTX and can enjoy post-transplantation merits just like those of LTX within MiC as they can decrease the post-LTX recurrence. (Kumari, Sahu, et al, 2018)

Neoadjuvant/Local Ablative Therapy (pei/rfa/mwa)

Radiofrequency Ablation (rfa)

The most widely implemented minimally invasive therapy for the advanced HCC treatment approved (2001) by the Food and Drug Regulatory Authority (FDA) is the radio frequency (physical) ablation. (Daher S. et al, 2017) Percutaneous RFA works by delivering a quick electromagnetic (EM) pulse of current usually of 375-500 KHz using an electrode placed into the cancerous mass that causes heat-based damage (that is dependent on both the temperature (60-100 °C) and time of heating) in the carcinoma leading to the coagulative necrosis. (Nault, J.C. 2017) The produced heat radiates centrifugally from the electrode to the peripheral tissue which causes decrease in the temperature. This effect shows its limitations for targeting the tumors only of the size range of 20-30mm in BCLC stage 0 and A (100% response: complete removal promising +3 years survival rate). (Kumari, Sahu, et al, 2018) For the tumors larger in size or greater in numbers, the recommended therapy for that case is liver resection which provides better survival compared to RFA. The chances of recurrence are there after RFA therapy compared to surgical resection. It is recommended only in those who are not the suitable candidates of the hepatic surgical resection. It possesses excellent safety profile (minimum pain, short in-hospital stay, less complications) (Graf D. et al, 2014). and can be used as a mean to stop the spread of HCC until the liver transplantation. Some systemic adverse events reported are abscess and hemorrhage in liver and perforation of intestines. (Daher S. et al, 2017)

Percutaneous Ethanol Injection Therapy (PEIT)

A chemical ablation therapy (ultrasound guided) for the carcinoma patients *(*who are non-recommended for the liver resection (LR)*)* having tumors <20mm in size (BCLC stage 0, A), and also for cancerous growth closer to blood vessels, it is implemented. (Kumari, Sahu, et al, 2018) Ethanol possesses cytotoxic properties, can cause cancerous tissue necrosis

through dehydration of cells, denaturation of protein molecules (Graf D. et al, 2014). and by generating ischemic environment. As it can diffuse easily through the HCC owing to its vascularity/loose consistency, in this way, it shows destructive effects at the cancerous site. The multiple recommended dose on alternate days of ethanol is required so as to maintain effective concentration at the target site to achieve desired outcomes. The survival rate of 1-year is reported (64-100%) and of 5-years (32-59$%) respectively. (Daher S. et al, 2017).

Microwave Ablation

Usage of electromagnetic radiations (1-300GHz) with the help of an antenna through the routes (intraoperative, laparoscopic, percutaneous) to target the cancerous tissue causing thermal degradation of tissue. Promoting an overall survival of 5-years (51%) in treating tumors of size between 30-50mm. (Graf D. et al, 2014). It has some merits superior to RFA and included in these are: it delivers high temperature to the cancer target, has short duration of therapy and minimal or no skin burning risks compared to RFA therapy. But RFA relatively possesses localized cancer control and low complications with respect to MWA. (Daher S. et al, 2017). Most studies show that both the RFA and the MWA are almost equally effective. (EASL Clinical Practice Guidelines, 2018)

High Intensity Focused Ultrasound Ablation (hifu)

HIFU technique utilizes energetic ultrasound waves using a extracorporeal transducer to target tumors results in breakdown/removal of cancerous mass by heat waves. It has shown promising outcomes in treating prostate tumor and BPH (benign prostatic hypertrophy). (Daher S. et al, 2017).Here, the transverse/longitudinal ultrasounds promote vibrational particles movement towards the tumor. At high acoustic density (≤3.5MHz), the temperature rises to about 56 °C, which results in tissue necrosis by heat shock within no time. In general, a particular transducer can produce a focus of 10mm long and 1.5mm wide along the waves and there is a significant temperature drop surrounding the focus which leads to distinguishable tissue coagulation. The limitations included are the deliverance of minute focus volume size and the production of microbubbles during the procedure which then interfere with the field in generating the ultrasound beam. (Graf D. et al, 2014).

Irreversible Electropolation (IRE)

This therapy is recommended for hepatic carcinoma treatment which can't be treated by heat-based therapies (RFA/MWA). The method includes generation and deliverance of short pulses (↑ power, ↑intensity) of electric current between the electrodes (collective centripetal technique) which results in producing holes/pores across the biological lipid bilayer membrane thereby disturbing cell potential (loss of homeostasis) leading to programmed death of the cancerous cells (apoptosis) and necrosis. *(Daher S. et al, 2017)* The non-thermal treatment minimizes the chances of damage to the adjacent tissue, and preserve the integrity of hepatic overall skeleton (results in less frequent hepatic failure than thermal ablation) This method of treatment is contraindicated/non-recommended in patients with underlying cardiac arrhythmia. (Nault, J.C. 2017)

Selective Internal Radiation Therapy (sirt)/Transarterial Radioembolization (tare)

SIRT is indicated in patients where the desired consequences from TACE are no longer achievable, for multifocal HCC tumors having diameter of >70mm and HCC with portal-vein thrombosis. In this method, radioactive nucleotides (Yttrium90, a β-particle emitting radioisotope half-life: 60 hours, I2 or Re labelled lipiodol) in combination with insoluble glass microspheres (Thera-spheres, 25um approx.) and resin containing microspheres (SIR-spheres, 40um approx.) are infused into the liver artery (hepatic artery angiography) using a microcatheter to allow radiations reach the target tumor. (Graf D. et al, 2014). Results are achieved like partial responses (37%), complete responses (3%) and stable disease (53%) in patients treated with SIRT. The average survival of 17 months (in comparison with TACE) is reported. SIRT is done in lobar/sectorial/segmental approach keeping in view the size/location of the carcinoma. (EASL Clinical Practice Guidelines, 2018). The improper liver functioning limits the applications of SIRT in HCC patients. The adverse effects commonly reported after this therapy are pulmonary fibrosis, Gastrointestinal ulcers, pneumonitis, post-radioembolization syndrome (fever, nausea, fatigue, abdominal pain). (Daher S. et al, 2017).

Cryoablation

In this curative treatment method, a device (containing Argon/Helium gas) capable of producing Joule Thomson Effect when the needle is inserted

causing temperature drop with subsequent tissue freezing/vascular injury. The corresponding icy tissue is detected with the help of MRI, CT, or US techniques which also allow in monitoring the treatment. Initially, cryo-shock was reported with multi-organ damage/failure with devices that were using liq. Nitrogen gas that caused a mix-up of HCC & metastasis, and laparoscopic ablation was mixed with percutaneous ablation. Latest studies revealed that cryoablation is safe/efficacious for treating HCC. (Nault, J.C. 2017)

Transarterial Therapy

In patients with BCLC stage B or C (intermediate/advanced), with stage 2 cirrhosis (compensated hepatic functioning) having unresectable HCC, this therapy is recommended selectively. It provides a bridge for those patients who are waiting for the hepatic transplantation. The basis of the therapy relies on catheter-guided infusion of cytotoxic chemotherapeutic medicine intra-arterially followed by the particle embolization of cancer-feeding blood vessels resulting in cytotoxicity and ischemic condition in the targeted tumor. It has been observed that combination (drug/lipiodol) emulsion plus particles express better extended survival as compared to the injectable emulsion (drug/lipiodol) lacking particles. (EASL Clinical Practice Guidelines, 2018) Interestingly, two kinds of embolizing agents are available, one that gives temporary embolism (Sponge Gelatin; mostly used) and the other which gives permanent embolism (microspheres/steel-oils/polyvinyl alcohol). (Kumari, Sahu, et al, 2018) This technique is classified into conventional-TACE (cTACE), drug eluting bead TACE (DEB-TACE), trans-arterial embolization. (Greten et al, 2018) In conventional trans-arterial chemo-embolization, chemotherapeutic agent, in lipiodol emulsion formulation, is injected into the artery which follows the embolization of the particle. DEB-TACE is used to administer a chemotherapeutic/cytotoxic agent (mainly doxorubicin/cisplatin/). When no drug is loaded, and simple arterial perfusion obstruction is done using Gel-foam which results in ischemic environment around the tumor and tissue necrosis, this method is termed as trans-arterial embolization. The limitations of TACE include decompensated (stage 3 cirrhotic) liver, jaundice, ascites, clinical encephalopathy. The optimal survival from TACE is approx. 2 years (4 years in some studies). (Graf D. et al, 2014). The possible side effects encountered by the patients include hepatic abscess, post-embolization syndrome (↑temp/↑hepatic enzymes/pain in abdomen), cholecystitis, bile-duct injury. (Daher S. et al, 2017).Studies revealed that TACE can be better tolerated only when HCC cases have less complications (<5%). (Kumari, Sahu, et al, 2018)

Systemic Therapy

Table 5. SORAFENIB: (FDA Approval: 2008)

Drug Molecule	MOA: Target Receptors	HCC TYPE	FDA/EMA Approval	Clinical Trials Study	Optimal Survival Rate	Adverse Effects
SORAFENIB (1st line oral Tyrosine multi-kinase inhibitor**)**	Prevent tumor growth by blocking VEGFR 1-3, PDGFR, Serine/Threonine kinase RAF/RAS, BRAF protein.	aHCC BCLC stage C, Child-Pugh-A, ECOG PS 0-2.	Yes	SHARP. CheckMate-459. Asia-Pacific.	10.7-14.7 months	Palmar-Plantar Erythrodysesthesia (Hand-Foot syndrome), HTN, Diarrhea Abdominal pain.

(koulouris et al, 2021)

Table 6. LENVATINIB: (FDA Approval: 2018)

Drug Molecule	MOA: Target Receptors	HCC TYPE	FDA/EMA Approval	Clinical Trials Study	Optimal Survival Rate	Adverse Effects
LENVATINIB (1st line oral Tyrosine multi-kinase inhibitor**)**	VEGFR 1-3, PDGFRα, FGFR 1-4, RET, KIT.	Un-respectable HCC Child-Pugh-A	Yes	REFLECT (phase 3, 2018)	13.6 months	Anemia, kidney failure, liver encephalopathy, HTN, thrombocytopenia, hand-foot syndrome, weight loss, diarrhea, thyroiditis.

(koulouris et al, 2021) (Huang et al, 2020)

Table 7. ATEZOLIZUMAB+BEVACIZUMAB: (FDA Approval: 2020)

Drug Molecule	MOA: Target Receptors	HCC TYPE	FDA/EMA Approval	Clinical Trials Study	Optimal Survival Rate	Adverse Effects
ATEZOLIZUMAB + BEVACIZUMAB (1st line Ref. Std. combination therapy**)**	PD-L1 VEGFRα	Un-resectable HCC Child-Pugh-A	Yes	IMbrave 150 (phase 3, 2020)	6-12 months	Hypertension (HTN)

(koulouris et al, 2021)

Table 8. REGORAFENIB: (FDA Approval: 2017)

Drug Molecule	MOA: Target Receptors	HCC TYPE	FDA/EMA Approval	Clinical Trials Study	Optimal Survival Rate	Adverse Effects
REGORAFENIB (2nd line Tyrosine multi-kinase inhibitor, similar to sorafenib differ by 1-fluorine on C-atom**)**	PDGFR, VEGFR 2-3, RET, BRAF, c-KIT, RAF-1, Tie2, FGFR	BCLC (B-C) HCC, Child Pugh A, ECOG PS 0-1	Yes	RESORCE (phase 3, 2016)	10.6 months	Hypertension (HTN), hand-foot syndrome, fatigue, diarrhea.

(koulouris et al, 2021)

Table 9. CABOZANTINIB: (FDA Approval: 2019)

Drug Molecule	MOA: Target Receptors	HCC TYPE	FDA/EMA Approval	Clinical Trials Study	Optimal Survival Rate	Adverse Effects
CABOZANTINIB (2nd/3rd line Tyrosine Kinase Inhibitor**)**	VEGFR 2, MET, AXL, c-MET, RET.	BCLC (B-C) HCC, Child Pugh A, ECOG PS 0-1	Yes	CELESTIAL (phase 3, 2018)	10.2 months.	AST increment, HTN, weakness, hand-foot syndrome, diarrhea.

(koulouris et al, 2021) (Huang et al, 2020)

Table 10. RAMUCIRUMAB: (FDA Approval: 2019)

Drug Molecule	MOA: Target Receptors	HCC TYPE	FDA/EMA Approval	Clinical Trials Study	Optimal Survival Rate	Adverse Effects
RAMUCIRUMAB (2nd line humanized monoclonal antibody**)**	VEGFR-2	Advanced HCC	Yes	REACH (phase-3, 2015). REACH-2 (phase-3, 2018).	9.2 months. 8.5 months.	Hyponatremia, HTN.

(koulouris et al, 2021)

Table 11. NIVOLUMAB: (FDA Approval: 2017)

Drug Molecule	MOA: Target Receptors	HCC TYPE	FDA/EMA Approval	Clinical Trials Study	Optimal Survival Rate	Adverse Effects
NIVOLUMAB (2nd line immune	Programmed cell death protein-1	Advanced HCC with HBV/HCV hepatitis	FDA (Yes). EMA (No)	Checkmate -459 (P-3, 2019) Checkmate -040(P1-2, 2017)	16.4 months. 15.6 months. 1-2 years.	Pruritis, rash, diarrhea.

Drug Molecule	MOA: Target Receptors	HCC TYPE	FDA/EMA Approval	Clinical Trials Study	Optimal Survival Rate	Adverse Effects
checkpoints inhibitor)				Checkmate -040 (P-2, 2020)		

(koulouris et al, 2021)

Table 12. PEMBROLIZUMAB: (FDA Approval: 2018)

Drug Molecule	MOA: Target Receptors	HCC TYPE	FDA/EMA Approval	Clinical Trials Study	Optimal Survival Rate	Adverse Effects
PEMBROLIZUMAB (2nd/3rd line immune checkpoints inhibitor)	Programmed cell death protein-1	Advanced HCC (aHCC).	FDA (Yes). EMA (No)	KEYNOTE-224 (phase-2, ongoing) KEYNOTE-240 (phase-3, ongoing)	12 months. 13.9 months.	N-A

(koulouris et al, 2021)

Terminologies

PDGFR (platelet derived growth factor receptor) , VEGFR 2-3(vascular endothelial growth factor receptor), RET/c-KIT(receptor tyrosine kinase), Tie2(tyrosine kinase receptor), FGFR(fibroblast growth factor receptors), Serine/Threonine kinase RAF/RAS, BRAF protein, , EMA(European medicine agency), c-MET(tyrosine protein kinase met).

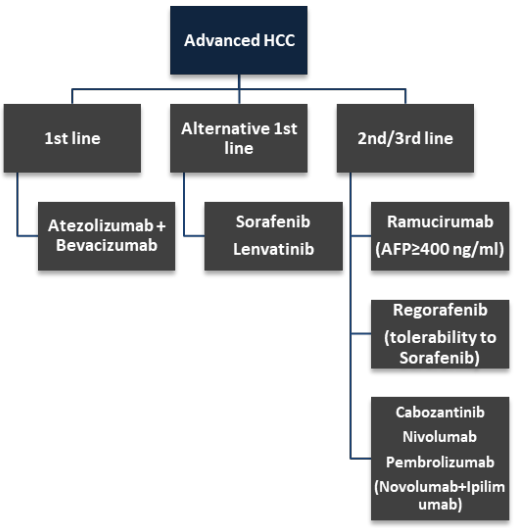

Figure 4: (Aitcheson et al, 2021)

Non-Immune Based Cytotoxic Agents

TRC105

it is a monoclonal antibody that works by interfering with Endoglin part of TGFβ (transforming growth factor-β) which shows overexpression in the cancer cells (esp. endothelial cells) and its function is angiogenesis. TRC105 binds with endoglin and hinders angiogenesis thereby slowing down its

growth resulting in cytotoxicity (antibody dependent cell mediated) and apoptosis. The average survival is of 15.5 months. The side effects included are headache, anemia, fatigue, and epistaxis. (Greten et al, 2018)

Immunotherapy

Tremelimumab

It is included in immune-checkpoint inhibitors show working preference by binding to the CTL-4(cytotoxic T-lymphocyte associated protein-4). It is recommended in advanced HCC, HCV-associated HCC, and biliary tract carcinoma (BTC). The clinical trial HIMALAYA study is ongoing (phase-3, 2021), have anti-VEGF activity, evaluating the results (well tolerated) from the combination therapy of Tremelimumab plus Durvalumab (anti programmed cell death ligand-1). (koulouris et al, 2021) Another study of Tremelimumab in patients with HCV (hepatitis C virus) in combination with TACE/RFA witness its safety profile with only pruritis side effect reported. (Greten et al, 2018)

Adjuvant Therapy

In HCV patients, IFN-γ (interferon gamma) is well tolerated therapy results in declining the HCC occurrence incidents owing to the clearance of viremia. Pegylated-interferon in combination with Ribavirin show the same efficacy in minimizing the chances of HCC. Lamivudine, Telaprevir, Boceprevir have shown excellent results in decreasing the risks of HCC in patients with HCV. (Dutta et al, 2017) Anti-viral therapy based on NAs (nucleotide analogues) e.g. lamivudine is effective in treating HBV-linked HCC. Similarly, DAAs (direct acting antiviral drugs) are treatment of choice (prophylaxis) for the HCV-associated HCC in patients with underlying cirrhosis. In-vivo PHT (primary hepatocyte transplantation), BSC (best supportive care) KEYNOTE-394 ongoing phase-3 trial, BAL (bio-artificial liver) are also considered as cell-based therapies for the treatment of HCC. (Kumari, Sahu, et al, 2018) Moving towards the biomarkers (intratumoral/extratumoral) which are possible targets of HCC-based immunotherapy, trial-based research is going on in bringing the optimal consequences from the therapeutic regimen of anti-tumor agents. (koulouris et al, 2021) Use of oncolytic virus, (JX-594 (PexaVec), a vaccinia poxvirus genetically engineered strain along with Sorafenib) for aHCC is undergoing trial-based studies. (Greten et al, 2018)

Similarly, tumor eating HSV-1 (2nd generation herpes simplex virus) in combination with GMC-SF (granulocyte macrophage colony stimulating factor) is effective in treatment of MM (malignant melanoma). (Daher S. et al, 2017).

Peptide-Based Targeting Therapy

Various peptides/proteins which are over-expressed in HCC patients can be considered as possible targets in eradicating the tumorous mass from the body. Pegylated liposomes plus SP94 (synthetic peptide) in combination with Doxorubicin has shown remarkable targeted deliverance of therapy for HCC. GPC3 (Glypican-3), an antigen/novel HCC marker, coupled with liposome (pGPC-3liposome) vaccine, MRP-3 (multidrug resistance associated protein-3) derived peptide vaccine through HAIC (hepatic artery infusion chemotherapy), microRNAs/small interfering RNAs (either upregulated or downregulated), LCN (liquid crystal nanoparticles), drug combination for the integrins/transferrin receptors have shown promising effectiveness in patients of HCC(Dutta et al, 2017)

Conclusion

Hepatocellular carcinoma is an asymptomatic cancer chiefly detected at the advanced stage with results of unrecoverable clinical consequences. Prior as well as current or futuristic treatment regimens can only increase the optimal survival rate in HCC patients. If it is diagnosed at earlier stage, better results will be obtained by performing liver transplantation. Various ongoing research-based studies are looking for the tremendous therapeutic multi-modal regimen approach that can reduce HCC-based mortality, improve patients' survival and quality of life. It is recommended to choose individualized therapy after considering the HCC complication stage and possible underlying abnormalities /dysfunctions. Currently, the Bevacizumab-Atezolizumab combination (IMbrave150 trial) is considered as the 1st line reference standard systemic therapy for the treatment of HCC.

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