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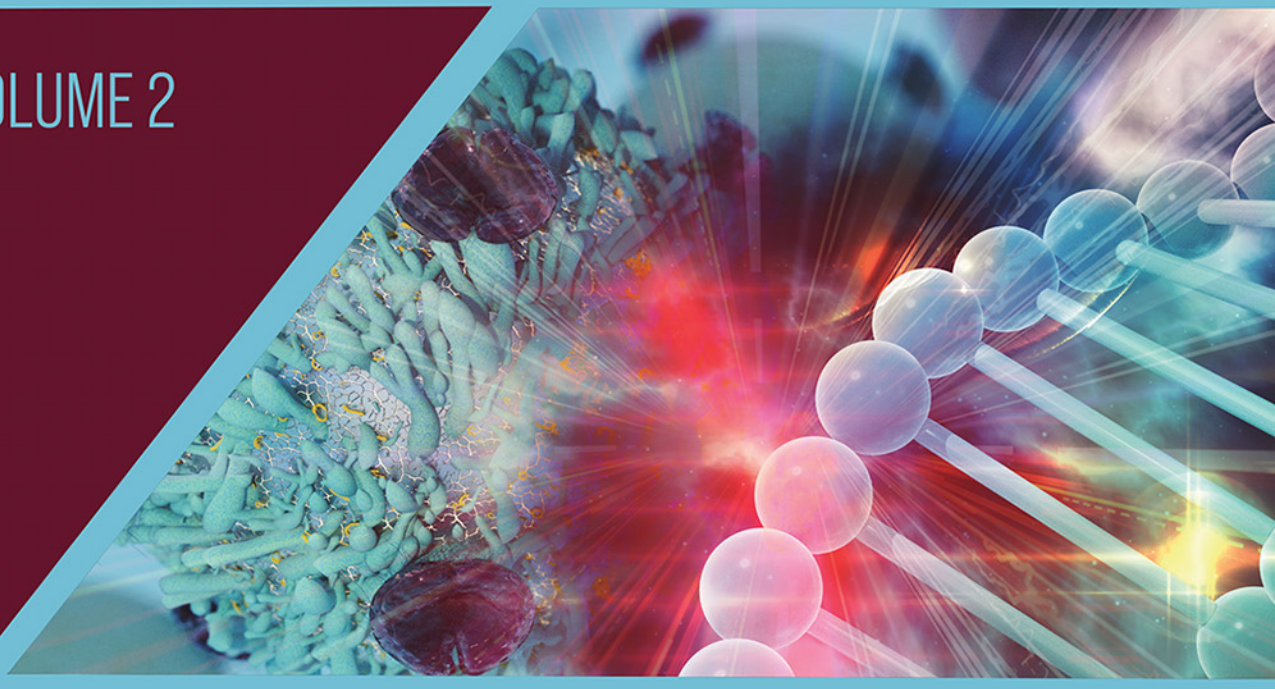

Theranostics and Precision Medicine for the Management of Hepatocellular Carcinoma

Diagnosis, Therapeutic Targets, and Molecular Mechanisms

Editors
Ganji Purnachandra Nagaraju and Ramakrishna Vadde

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THERANOSTICS AND PRECISION MEDICINE FOR THE MANAGEMENT OF HEPATOCELLULAR CARCINOMA VOLUME 2

Diagnosis, Therapeutic Targets, and Molecular Mechanisms

Edited by

GANJI PURNACHANDRA NAGARAJU, PhD, DSc, FAACC
School of Medicine, Division of Hematology and Oncology, University of Alabama, Birmingham, AL, United States

RAMAKRISHNA VADDE, PhD
Department of Biotechnology and Bioinformatics, Yogi Vemana University, Kadapa, India

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CHAPTER

15

Multidrug resistance, a major obstacle in hepatocellular carcinoma treatment: challenges and future perspectives

Tarun Sahu[1], *Arundhati Mehta*[2], *Henu Kumar Verma*[3] and *L.V.K.S. Bhaskar*[4]

[1]Department of Physiology, All India Institute of Medical Science, Raipur, India [2]Department of Biotechnology, Guru Ghasidas Vishwavidyalaya, Bilaspur, India [3]Department of Immunopathology, Institute of Lungs Biology and Disease, Comprehensive Pneumology Center, Munich, Germany [4]Department of Zoology, Guru Ghasidas Vishwavidyalaya, Bilaspur, India

Abstract

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and the third leading cause of cancer-related death and therefore a serious challenge to public health. Liver cirrhosis, especially following chronic hepatitis B and hepatitis C infections, is the leading risk factor for HCC worldwide. Global data suggest that metastatic or unresectable HCC has a poor prognosis, and early detection and chemotherapy drugs provide marginal benefit and improve patients' life expectancy. In addition, despite significant progress in diagnostic and therapeutic epidemiological studies, it was noted that there was less than 1 year of median survival after resection and that only approximately 5% of patients remained alive 3 years after resection. At 2 years, the recurrence rate could be as high as 50%. The complex pathogenesis and the high metastatic nature of the disease constitute significant obstacles in treating HCC. Another hindrance is a higher rate of recurrence due to resistance to conventional chemotherapy resulting in a relapse. Understanding the molecular factors associated with the development of resistance can help us to develop new therapeutic strategies based on the molecular target and reduce the relapse rate. This chapter focuses on the various existing therapeutic approaches and molecular mechanisms that underlie chemoresistance in HCC. We also intend to provide a comprehensive summary of the different drug-induced chemoresistance treatments for HCC and the updated targeted therapies for this carcinoma.

Keywords: Hepatocellular carcinoma; multidrug resistance; pathways; chemoresistance molecularly targeted agents; therapeutics

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Abbreviations

ABC	ATP-binding cassette
ATP	adenosine triphosphate
BER	base excision repair
CAR	chimeric antigen receptor
Cas9	CRISPR-associated endonuclease
CRISPR	clustered regularly interspaced short palindromic repeats
CSCs	cancer stem cells
EBRT	external beam radiation therapy
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EpCAM	epithelial cell adhesion molecule
ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FLT3	FMS-like tyrosine kinase 3
HCC	hepatocellular carcinoma
HER	human epidermal growth factor receptor
HR	homologous recombination
IGF	insulin-like growth factor
IGFR	insulin-like growth factor receptor
IL-2	interleukin 2
MAPK	mitogen-activated protein kinase
MDR	multidrug resistance
MGMT	O6-methylguanine DNA methyltransferase
MMR	DNA mismatch repair
MOC	chemoresistance mechanisms
mTOR	mammalian target of rapamycin
NER	nuclear excision repair
NHEJ	nonhomologous end joining
OS	overall survival
OV6	oval cell marker
PBT	proton beam therapy
PCD	programmed cell death
PD-1	antiprogrammed death 1
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
PTEN	phosphatase and tensin homolog
RET	rearranged during transfection
RFA	radiofrequency ablation
RFA	radiofrequency ablation
ROS	reactive oxygen species
RTK	receptor tyrosine kinase
SBRT	stereotactic body radiation therapy
SEARCH	Sorafenib and Erlotinib, a Randomized Trial Protocol for the Treatment of Patients with Hepatocellular Carcinoma
SHARP	Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol
siRNA	small interfering RNA
TACE	transarterial chemoembolization

TIC	tumor-initiating cells
TKI	tyrosine kinase inhibitor
TME	tumor microenvironment
TMZ	temozolomide
TNF	tumor necrosis factor
USP22	deubiquitin-specific protease 22
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. It is heterogeneous in nature, affecting mainly hepatocytes under carcinogenic conditions such as cirrhosis of the liver. GLOBOCAN 2018 data show that the incidence of HCC is widely heterogeneous by region and is frequently seen in developing countries. It is the sixth most common and fourth most deadly type of cancer [1]. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program has reported that the overall 5-year survival rate of HCC remains very low at 20% [2].

The prevalence of HCC is linked with its most common etiological factor, which reflects the geographic distribution of HCC. The highest incidence of HCC was observed in Asian and African countries, owing to major causative factors, such as chronic alcohol abuse, infection with the hepatitis B virus, and food contamination. A metaanalysis demonstrated that tumor necrosis factor alpha (TNF-α) gene promoter polymorphisms increase the risk of HCC in Asians [3]. On the other hand, chronic hepatitis C virus infection is the highest risk factor in Western countries and Japan [4,5].

Patients with HCC may be treated with chemotherapy and surgery. Trends in the burden of HCC have undergone significant changes worldwide, owing to the development of advanced cancer screening, with broad guidelines for colonoscopy at the end of the 1990s [6]. In the current scenario, radiation therapy combined with immunotherapy and surgery is a promising clinical solution for HCC. However, these remedies are not beneficial for some patients because of resistance to chemotherapeutic agents and immunotherapy based on tyrosine kinase inhibitors (TKIs), which is still poorly understood [7]. Despite advances in early detection, nearly 80% of HCC patients are diagnosed at a late stage of the disease, and they are not suitable for surgical resection of the tumor. Intensive and acquired drug resistance mechanisms are a major obstacle to developing effective cancer treatments in tumors.

Recently, the tumor microenvironment (TME) has attracted more attention in drug resistance mechanisms regulated by microRNA in HCC [8,9]. Several reports suggest that TME and signaling molecules are involved in different drug resistance processes in many cancers, including HCC [10–13]. Furthermore, more than 100 genes have been identified as playing a role in interlinked drug resistance mechanisms. HCC development is a multistep process characterized by genetic and epigenetic changes that trigger oncogenes, deregulate tumor suppressor genes, and deregulate various cell signaling pathways. Therefore more emphasis should be placed on understanding the molecular processes underlying chemoresistance, particularly multidrug resistance (MDR), to identify new drug strategies and diagnostic biomarkers.

It is essential to adopt new approaches and screening methods to identify novel therapeutic targets to achieve improved treatment and survival of HCC patients. To achieve

this, we examine the available data on the most recent pharmacological choices for HCC, including the molecular signaling pathways that are associated with drug resistance in HCC, and we discuss potential therapeutic strategies to provide novel insights and overcome drug resistance.

Current therapy for hepatocellular carcinoma

Small, clustered tumors may be treatable by surgical procedures (resection and liver transplantation). Regrettably, fewer than 20% of patients with HCC are appropriate for surgical measures. Most patients are diagnosed with a progressive liver dysfunction that prevents intensive surgery or with a recurring disease [14]. Local treatment is primarily symptomatic and includes radiofrequency ablation (RFA), cryoablation, and transarterial embolization, in which a hepatic artery block leads to tumor necrosis [15].

Chemotherapy

Among the clinical treatments for HCC, chemotherapy is the most commonly used treatment for advanced HCC. It is used to treat patients who are deemed unsuitable for the surgical procedure transarterial chemoembolization (TACE), such as those with extrahepatic malignancies, signs of vascular invasion, or resistance to TACE [16].

HCCs are known to be characteristically chemotherapy-resistant tumors as a result of the overexpression of the multidrug-resistant gene MDR-1. HCC typically emerges in the course of a malignant cirrhotic liver, and limited hepatocellular deposit sometimes prevents or restricts systemic chemotherapy. Chemotherapy, the use of chemical agents to cure cancer, is typically an adjuvant of metastatic disease where alternative treatment choices are minimal. Though there are many clinical trials of most types of chemotherapeutic agents that have been conducted, none of the approaches, either in single or in combination therapy, have shown to be beneficial in HCC. Several trials of chemotherapy agents have demonstrated that they have minimal HCC activity, as their response rates are poor, and the duration of response is generally short [17,18].

Immunotherapy

Immune checkpoint receptors are upregulated in tumor cells and facilitate immune surveillance of the host by the tumor. Immunotherapy is a favorable, innovative therapeutic technique for HCC, especially as a second-line treatment to avoid recurrence. It is an enticing alternative method that is focused on sensitivity, tumor cell specificity, the immune system's ability to regenerate itself, and the capacity to remove remaining tumors after traditional therapy. Outcomes from many clinical trials have demonstrated that immunotherapy can enhance results in HCC patients [19].

Immune tolerance in HCC arbitrated by reduced costimulation leads to immune suppression. Numerous immunotherapy agents, such as anticytotoxic T lymphocyte antigen 4 antibody and antiprogrammed death 1 (PD-1) monotherapy/programmed death ligand 1

antibody have been employed in the treatment of HCC. But success rates have been limited. Another rapidly evolving immunotherapy method was is antigen receptor (CAR) engineered T cell therapy, which had previously shown confirmed efficiency against hematological malignancies. CAR T cell therapy implements the anticancer activity of "domesticated" T cells that have been engineered to produce cancer-specific antigen-targeted receptors to treat malignant tumors. Randomized clinical trials showed increases in recurrence time and recurrence-free survival with IL-2 and anti-CD3 triggered peripheral blood mononuclear cells in patients with HCC undergoing surgical resection [20,21]. In patients with chronic HCC, recombinant interferon alpha (IFN-α) is advantageous compared to doxorubicin in terms of survival, tumor response, and toxicity [22].

Radiotherapy

Radiotherapy was previously not considered a feasible choice as a harmless treatment option for HCC because the liver's cancerous and noncancerous tissues are radiosensitive. With technological advancements and the introduction of stereotactic body radiation therapy (SBRT) and external beam radiation therapy (EBRT), cancerous tissues can be treated with high accuracy and intensity while saving adjacent tissue by administering high-dose radiation to small treatment areas. A wide variety of retrospective and prospective studies recently showed that SBRT has been used for early-stage inoperable HCC using a variable dose of approximately 600 cGy. Post SBRT liver explant showed a complete response rate of 27%, a partial response rate of 54%, and a stable response rate of 18% [23]. SBRT was compared with RFA in a retrospective study of HCC patients, in which SBRT provides 2 years longer survival than RFA in terms of local progression. In addition, the overall survival rate for SBRT for 2 years was 46% compared to RFA, which had a 53% overall survival rate [24]. Another promising category of radiation therapy is charged particle therapy, including proton beam therapy (PBT) or carbon ion therapy, which has possible dose benefits over traditional EBRT therapies. PBT utilizes protons instead of photons and allows correct energy deposition inside tumors and safe dosage elevation due to lack of an exit dose. A phase II trial of PBT in patients with HCC attained a controlled rate of 94.8% and a survival rate of 63.2% 2 years after treatment initiation [25]. The latest PBT review for HCC documented 3 years of local control rates ranging from 70% to 79% and 3 years of overall survival rates ranging from 45% to 65% [26]. Qi et al. did a systematic review comparing charged particles with photon therapy. In patients with HCC, they found that survival rates for charged particle therapy are higher than those for conventional radiation therapy but similar those for to SBRT [27]. However, charged particle therapy offers some possible benefits over traditional EBRT approaches, but further study is needed.

Surgical therapy

At present, surgical resection is the only long-lasting treatment option available for patients with HCC. Still, it is limited to patients who do not have any issues related to the liver. Therefore it is an option only for a tiny proportion of patients, perhaps fewer than 18%, because 85%–90% of HCC patients have chronic liver disease or liver cirrhosis.

For patients with cirrhosis, surgical abscission raises the risk of liver decompensation [28,29]. Under the recommendations of the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases, portal hypertension is considered a relative contraindication for surgical abscission in cirrhotic patients. The occurrence of portal hypertension, based on a gradient of hepatic venous pressure (HVPG) of 10 mmHg or more, was reported to be the best indicator of liver decompensation after surgery and poor long-term consequences in Child-Pugh class A cirrhotic patients who undergo hepatic abscission [30,31]. Therefore liver function and the size of a tumor should be assessed before surgery to prevent liver dysfunction after abscission. Typically, HCC is a fatal disease that could require an immediate liver transplant. After adequate HCC resection, recurrence of tumors in the cirrhotic liver is a significant clinical concern in around 70% of patients over 5 years of age. The recurrence rate corresponds to an occurrence of microscopic vascular invasion, which is present without any indication of macroscopic vascular invasion in more than 30% of HCC patients [19,32].

Molecular drug targets

Study of HCC's molecular pathology has revealed various molecules that crucial to the onset and persistence of this disease in recent decades. Many molecular pathways are involved in the development of HCC, including epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), mitogen-activated protein kinase (MAPK), insulin-like growth factor (IGF), c-Met, mammalian target of rapamycin (mTOR), and Wnt/beta-catenin pathways. In this chapter we discuss the current status of various drug targets that have been identified for targeting the family of these signaling pathways that are critical for the development of HCC [33,34].

Antiangiogenic factors

HCC is a vascular tumor that depends on angiogenesis for its development. Fibroblast growth factors (FGFs), VEGFs, and platelet-derived growth factors (PDGFs) are essential angiogenic factors that are implicated in HCC pathogenesis. Overexpression of VEGF and VEGF receptors (VEGFRs) has been observed both in vitro and in HCC patients' serum. Therefore for the production of antiangiogenic cancer drugs, the primary targets are the pathways associated with VEGF and VEGFRs and PDGF and PDGF receptors (PDGFRs) [21,35–38]. To date, sorafenib is the only drug that has been used successfully in treating patients suffering from HCC [39].

Sorafenib

Sorafenib is a multikinase inhibitor that is taken orally. It confers its activity by interfering with some tyrosine kinase receptors on cancer cells and vasculature cells plus the VEGF R1–R3, the PDGFRs, and the c-KIT RET, and FMS-like tyrosine kinase 3 (FLT3).

Sorafenib is oral biaryl urea that induces apoptosis and autophagy in human hepatocarcinoma cells [40]. Sorafenib also inhibits cell proliferation via the Raf/MAPK/ERK signaling pathway [41]. Its primary action mechanism is that it prevents adenosine triphosphate (ATP) from binding to the catalytic sites of these kinases.

Abou-Alfa et al. reported a median overall survival (OS) of 9.2 months in a phase II clinical study of sorafenib in 137 patients with advanced HCC [42], which was quite satisfactory in comparison to other single-arm studies that evaluated the use of combination therapy for HCC patients, with a median OS of 8.9 months and 7.3 months, respectively [18,43].

Improved overall survival with sorafenib was reported in two large phases III randomized, placebo-controlled trials performed in Western countries (SHARP) [44] and Asia-Pacific [45]. In the SHARP trial, the OS was 10.7 (7.9 months for the placebo group), while in the Asia-Pacific trial, the OS was 6.5 months (4.2 months for the placebo group). Although the role of sorafenib in moderate HCC is less well understood, these two phase III studies validated sorafenib as the preferred first-line systemic therapy for advanced HCC. Furthermore, a limited number of patients in Child-Pugh class B were involved in these studies, so it is impossible to determine the effectiveness and safety of sorafenib in this patient group. Therefore the need for rapid production of newer and more efficient agents for advanced HCC remains crucial and unfulfilled.

Following the establishment of sorafenib as the standard first-line therapeutic regimen for advanced HCC, a significant number of phase III studies comparing sorafenib to various other molecular-targeted regimens were conducted, either alone or in combination, to determine whether novel selective molecular therapies would improve sorafenib's antitumor efficiency. For example, in patients with advanced HCC, linifanib was compared with sorafenib. Linifanib favored progression time and overall response rate, while sorafenib favored safety results, resulting in similar OS (9.1 and 9.8 months, respectively) [46]. Another phase III SEARCH trial showed less advantage with the addition of erlotinib over sorafenib to sorafenib alone with OS of 9.5 months with combined sorafenib and erlotinib and 8.5 months with sorafenib alone [47]. Sorafenib is also used in combination with other molecular targeted drugs such as sunitinib and brivanib [48,49]. Sorafenib plus doxorubicin (a mixture of molecularly targeted drugs and cytotoxic drugs) [50] has been used as first-line therapy for patients with advanced HCC. So far, none of these agents has shown a significant benefit over sorafenib. However, a recent phase III study of lenvatinib versus sorafenib showed that lenvatinib was not inferior to sorafenib in treating advanced HCC patients [51].

Bevacizumab

Bevacizumab is a humanized monoclonal IgG antibody that inhibits angiogenesis by binding and neutralizing the VEGF-A receptor. It also works in conjunction with chemotherapy and selective agents such as erlotinib to treat advanced breast cancer and nonsquamous lung and colorectal cancers. Siegel et al. phase II trial showed that bevacizumab is quite effective alone, showing a median OS of 12.4 months in patients of HCC [52]. Zhu et al. reported that bevacizumab, when used in combination with gemcitabine and

oxaliplatin, gives rise to a 20% overall response rate and OS of 9.6 months [53]. A Phase II study was also conducted to test the combination of capecitabine and oxaliplatin, with a median OS of 10.3 months reported [54]. Administering these drugs has also resulted in significant treatment-related toxicity, resulting in leukopenia, transaminitis, hypertension, and fatigue. Previous trials have shown that bevacizumab is moderately effective in HCC, but further studies are needed to explain its effectiveness and safety.

Sunitinib

Sunitinib is an oxindole-based multitargeted kinase inhibitor that inhibits specific receptor tyrosine kinases (RTKs), such as VEGFRs (1, 2, and 3), PDGFRs (α and β), c-kit, FLT3, and a variety of other associated tyrosine kinases with antitumor and antiangiogenic activity. Sunitib has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of gastrointestinal stromal tumors and kidney cancer. In a phase II trial of sunitinib, patients received the drug 37.5 mg/day for 4 weeks followed by 2 weeks of rest per cycle; the median progression-free survival (PFS) was 3.9 months, and the time to progression was 4.1 months. The median PFS was 3.7 months and the median OS was 8 months when patients were treated with repeated cycles of oral sunitinib (50 mg/day for 4 weeks followed by 2 weeks off treatment) in the second phase II trial. However, these trials were terminated prematurely, owing to low response rates, inability to meet the target endpoint, and a high number of grade 3 and 4 adverse effects, such as leukopenia, neutropenia, thrombocytopenia, hand-foot syndrome, anemia, aminotransferase elevation, and fatigue [55,56]. A phase III trial comparing sorafenib to sunitinib was prematurely terminated because of a higher recurrence of negative effects in the sunitinib arm than in the sorafenib arm [48].

Pazopanib

Pazopanib is an angiogenesis inhibitor that is synthesized from indazolyl-pyrimidines. The FDA recently approved pazopanib for the treatment of renal cancer. This is a newer multitargeted TKI that inhibits several VEGFRs (1, 2, and 3), PDGFRs (α and β), and c-Kit. Phase I clinical trials have demonstrated that while pazopanib's toxicity level is appropriate, there could be an opportunity for advanced HCC therapy [17,57].

Brivanib

Brivanib is a selective inhibitor of VEGFR and FGFR tyrosine kinases. Phase II open-label first-line and second-line treatment trials in patients with unresectable, locally advanced, or metastatic HCC demonstrated a median average survival of 10 and 9.5 months, respectively [58,59]. Brivanib did not show any benefits in terms of OS when given orally to patients who had previously undergone sorafenib therapy. Treatment-related adverse effects were induced in 23% of patients [60]. Another phase III study found that there were no statistically significant results in first-line therapy in HCC when brivanib was compared to sorafenib. The median OS in the brivanib arm was 9.5 months versus 9.9 months in the sorafenib arm [49].

Axitinib

Axitinib is a derivative of the small molecule indazole. It is an orally administered multi-TKI that inhibits VEGFRs 1, 2, and 3. Axitinib has demonstrated beneficial effects on kidney cell cancer and thyroid cancer. Phase II and III clinical trials are planned to test this drug's efficacy for use in treating HCC [61,62].

Linifanib

Linifanib is also known as ABT-869. It is an inhibitor of VEGF and PDGF RTKs, and it competes with ATP for binding to the receptors. A phase II clinical trial for advanced HCC has demonstrated that linifanib is clinically successful with an appropriate safety profile, and median OS was 9.7 months for nonresectable HCC [63]. In a phase III trial of linifanib versus sorafenib, linifanib demonstrated high overall survival and a slightly better progression period than the sorafenib arm; however, the predefined margin of noninferiority overall survival was not reached [46].

Foretinib

Foretinib is a new TKI receptor inhibitor targeted at VEGFR 2 and c-Met. Huynh et al. performed a study using human HCC mouse models to test the antitumor and antiangiogenic actions of foretinib and found that foretinib exhibited significant antitumor efficacy in patient-derived HCC xenograft models. This research offers a strong basis for clinical investigation in patients with advanced HCC [64].

Dovitinib

Dovitinib is an inhibitor of RTKs targeting VEGFRs 1 and 2; FGFR 1, 2, and 3; and PDGFR β. Several phase I and II trials have been conducted to evaluate this medication's pharmacokinetics, pharmacodynamics, and safety profile. According to a study, dovitinib preferentially prevents HCC growth and metastasis via an antiangiogenic mechanism that does not directly target HCC cells [23]. This compound has been reported to decrease angiogenesis and cell proliferation, inducing tumor cell apoptosis in xenograft models of human HCC [65].

Anti-epidermal growth factor receptor inhibitors

Ramucirumab

Ramucirumab is an injectable monclonal antibody that precisely and potently inhibits VEGFR 2. It interacts with the VEGF-binding domain of VEGFR 2, blocking VEGF−VEGFR 2 interaction. Although ramucirumab did not achieve its primary endpoint for second-line therapy in the REACH trial [66], the PFS and OS were extended in the subcategory of patients with baseline serum alpha-fetoprotein levels of 400 ng/mL or more [67−70]. This was confirmed later in the REACH-2 trial, which led to the endorsement of

ramucirumab as second-line therapy for advanced HCC [71]. REACH-2 is the first promising phase III trial in HCC patients conducted in a biomarker-selected patient cohort. More recent studies have shown that AFP-enriched HCCs have shown substantial activation of VEGF, which indicates the underlying mechanism of action and reinforces the possible importance of biomarker-driven clinical trials [25].

Erlotinib

Erlotinib is an oral TKI-associated with the EGF receptor (EGFR, HER-1). Erlotinib inhibits EGF-dependent tumor cell growth at submicromolar concentrations and prevents the cell cycle's progression in the G1 stage. Phase II analysis of standard erlotinib in HCC patients showed that resistance to this medication was strong, but it had a slight advantage in regulating HCC, which was seen to extend overall survival for 13 months discretely [72]. Zhu et al. conducted a phase III clinical trial (SEARCH trial) to compare the clinical outcomes of sorafenib versus erlotinib or placebo in patients with advanced HCC. The results showed that the use of erlotinib compared to sorafenib did not increase survival in patients with advanced HCC [47].

Lapatinib

Lapatinib ditosylate, a quinazoline family member with a 4-anilinoquinazoline core, is a reversible, small molecule tyrosine kinase dual inhibitor of EGFR and HER2. Lapatinib works in the extracellular environment by competing with ATP for the ATP-binding domain of the TKIs' cytoplasmic tail. Its primary mechanism of action is the inhibition of tyrosine kinase phosphorylation, which reduces and replaces signal transduction along with the PI3K/Akt and Ras/Raf/MAPK pathways. Studies have shown that this drug is well tolerated at doses of 500−1600 mg daily and has antitumor activity in extensively pretreated patients who have many solid tumors [73]. The FDA has approved lapatinib for metastatic BC [74]. A phase II analysis of lapatinib in advanced HCC patients found that the drug was well tolerated but had modest antitumor efficacy based on a lack of objective response and 12.6-month OS [75]. Another phase II study showed a lower median OS of 6.2 months. This lower survival rate could be attributed to the small sample size [76].

Mammalian target of rapamycin pathway inhibitor

The EGF and IGF signaling pathways stimulate intracellular downstream proteins such as phosphoinositide 3-kinase (PI3K), protein kinase B (AKT), and mTOR. These are the most critical intracellular pathways, regulating cell growth, motility, survival, metabolism, and angiogenesis. Both EGF and IGF receptors are upregulated in HCC, leading to PI3K/AKT/mTOR pathway activation, which causes tumor growth and susceptibility to anticancer therapy [77]. The blocking of the mTOR pathway thus exerts anticancer, antiangiogenic, and immunosuppressive effects. Preclinical results showed that mTOR inhibitors

have been beneficial for cell and tumor suppression growth in cell lines and tumor models of HCC [78].

Rapamycin

Rapamycin is a natural antibiotic that tends to work as an mTOR inhibitor. Three rapamycin analogs were recently developed and found to have excellent pharmacokinetic and biological properties. They hinder the development of cell lines originating in vitro from many forms of tumors and in vivo models. Sirolimus, also known as rapamycin, is a macrolide substance with immunosuppressive activity in humans and is particularly useful in preventing the rejection of kidney transplants. It is an mTOR inhibitor with immunosuppressive properties and has been used in the posttransplantation setting. Sirolimus can also suppress the rejection of liver transplantation in patients and prevent HCC recurrence [79]. Rizell et al. conducted a small pilot study to investigate the effects of the mTOR inhibitor sirolimus in hepatocellular and cholangiocellular cancer patients. They found that the treatment of HCC and CCC with sirolimus can induce temporary stable disease. The authors suggest that sirolimus could be a potential drug for this treatment, but more clinical trials on biological effects are needed [80].

Everolimus

Everolimus acts as a PI3K/Akt/mTOR inhibitor, which regulates cell development, proliferation, and angiogenesis. Phase I and II trials of everolimus in patients with unresectable or metastatic HCC demonstrated moderate antitumor activity with a median OS of 8.4 months and a disease control rate of 44%. The authors concluded that in patients with advanced HCC, everolimus was well tolerated, and 10 mg/day was specified as the phase II dosage [81]. In a phase III study of everolimus versus placebo in HCC patients in Child-Pugh class A (in whom the disease worsened before or after sorafenib therapy or who were intolerant to sorafenib), everolimus had no beneficial effect on overall survival or time of development [22] (Table 15.1).

Pathway associated with multidrug resistance

Resistance to chemotherapy in cancer patients is a major concern. Clinical drug resistance may be complex and multifaceted. At present, MDR is a significant clinical challenge, leading to poor prognosis for some patients despite vital advances in treatment. MDR is a cross-resistance event for various structurally and functionally disseminated agents in cancer cells that are exposed to cancer drugs [88,89]. Previous research has shown a wide range of pathways involved in the regulation of MDR. The ATP-binding cassette (ABCB1, ABCC1, ABCG2) is the most identifiable gene associated with MDR [89–91]. Such resistance processes can be categorized in various waved forms. The most distinguished ones have improved viability or cell death, drug target changes, transformed DNA repairs, and cellular drug transport modifications [92,93] (Fig. 15.1).

TABLE 15.1 List of drugs with their mechanism, targets, and limitations.

Type	Drug	Subtype	Mechanism	Target	Pathways inhibited	Limitations	References
	Sorafenib	Multikinase inhibitor	Inhibits tumor growth by preventing the activation of the tyrosine kinase receptor	Raf, VEGFR 1, 2, 3, PDGFRs, flt-3, FGFR-1, RET, c-KIT, FMS	Ras (Raf-1 (C-Raf) and B-Raf) /MAPK/ ERK signaling pathway	Hypertension, diarrhea, proteinuria, skin-related toxicities	[47,50–52,55,56]
	Bevacizumab	Moab	Blocks VEGF binding to its receptor	VEGFR members	VEGFR Pathway	Low rate of response, gastrointestinal bleeding, including variceal bleeding	[52–54]
	Sunitinib	Multikinase inhibitor	Inhibits tumor growth by preventing the activation of the tyrosine kinase receptor	VEGFR1,2&3, P.D.G.F.R.s, c-KIT, RET, and FLT3	Tyrosine kinase	Low response rates, failure to meet the primary endpoint neutropenia, thrombocytopenia, hand-foot syndrome, anemia, the elevation of aminotransferases, and fatigue	[55,56]
	Pazopanib	VEGFR inhibitor	Blocks VEGF binding to its receptor	VEGFR members, PDGFR α, PDGFR β, c-Kit	VEGFR Pathway	Hypertension, dizziness, nausea and vomiting	[17,57]
	Brivanib	FGFR and VEGFR tyrosine kinase inhibitor	Inhibits tumor growth by preventing the activation of FGFR and VEGFR tyrosine kinase receptor	VEGFR, PDGFR	VEGF and FGF signaling pathway	Did not show any benefits in terms of OS	[60]

	Axitinib	VEGF, PDGFR inhibitor	Blocks VEGF and PDGF binding to its receptor	VEGFR members, PDGFR α, PDGFR β, c-Kit	VEGF signaling pathway	Diarrhea, hypertension, fatigue	[61,62]
Antiangiogenic factor	Linifanib	ATP-competitive inhibitor of all VEGF and PDGF receptor tyrosine kinases	Blocks VEGF and PDGF binding to its receptor	VEGF	VEGF and PDGF signaling pathway	Overall survival was not reached	[46]
	TSU-68	VEGF, PDGFR inhibitor	Blocks VEGF and PDGF binding to its receptor	VEGFR 2, PDGFR α, PDGFR β, c-Kit, Flk-1	VEGF signaling pathway	—	[82]
	Foretinib	VEGF inhibitors	Blocks VEGF binding to its receptor	VEGFR 2, c-Met	VEGF signaling pathway	—	[64]
	Dovitinib	VEGF, PDGFR inhibitor	Blocks VEGF and PDGF binding to its receptor	VEGFR members, PDGFR β FGFR members Flt-3 c-Kit	VEGF and PDGF signaling pathway	—	[23,65]
Anti-EGFR Inhibitor	Ramucirumab	Humanized anti-VEGFR-2 MoAB	Binds specifically to VEGFR 2, thus blocking binding of its ligands	VEGFR	VEGF pathway	Did not achieve its primary endpoint for second-line therapy in the REACH trial	[66−69]
	Erlotinib	Small molecule inhibitors	Targets EGFR	EGFR/HER-1	EGF pathway	Small benefit in regulating HCC	[72]
	Lapatinib	Small molecule inhibitors	Targets EGFR	EGFR/HER-1/HER-2/NEU	EGF pathway	Limited antitumor activity	[75]

(*Continued*)

TABLE 15.1 (Continued)

Type	Drug	Subtype	Mechanism	Target	Pathways inhibited	Limitations	References
	Gefitinib	Adenosine triphosphate mimetic anilinoquinazoline EGFR-TKI	Targets EGFR	EGFR/HER-1	EGF pathway	—	[83–85]
	Cetuximab	Chimeric (human and mouse) monoclonal antibody against EGFR	Targets EGFR	EGFR/HER-1	EGF pathway	Shows moderate activity	[86,87]
mTOR pathway Inhibitor	Rapamycin	mTORC1 blocker	Targets mTOR pathway	PI3K/Akt/mTOR	PI3K/Akt/mTOR pathway	—	[79,80]
	Everolimus	Small molecule inhibitors	Targets mTOR pathway	PI3K/Akt/mTOR	PI3K/Akt/mTOR pathway	Little positive impact on overall survival	[22]

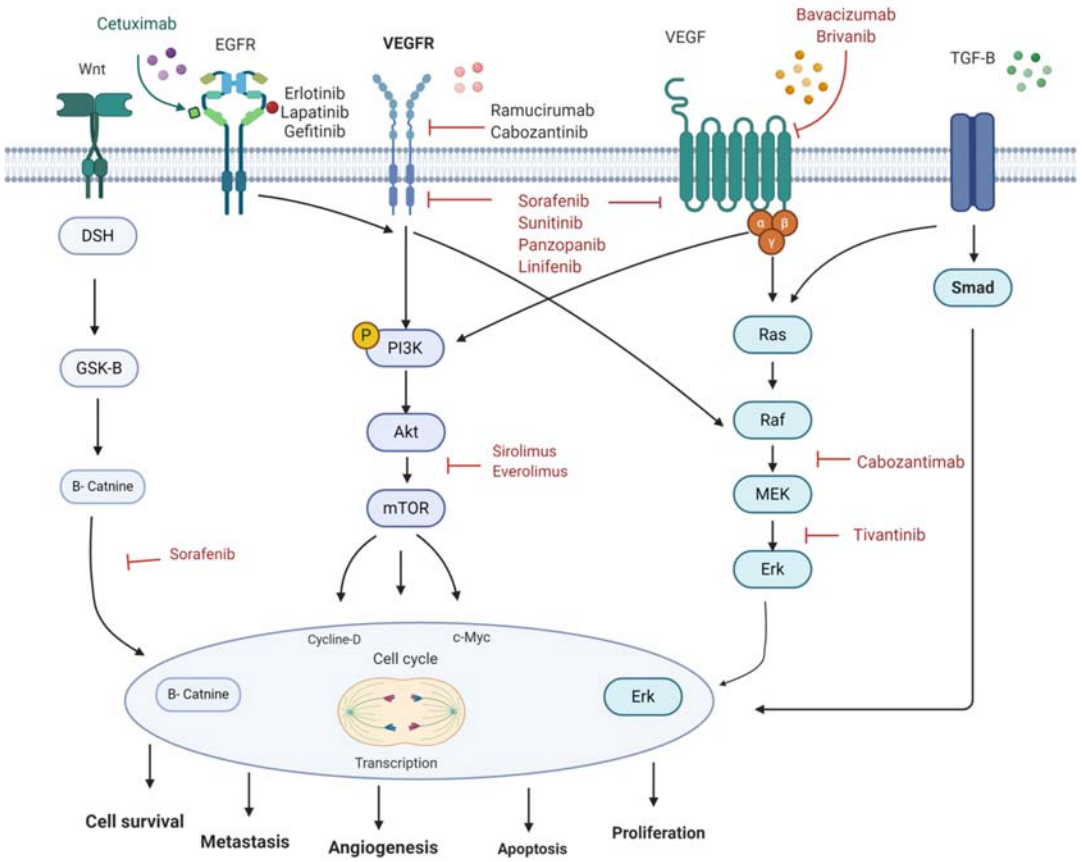

FIGURE 15.1 Molecular signaling pathway and drug target involvements in HCC cancer. *HCC,* Hepatocellular carcinoma.

DNA repair pathway

Humans are frequently subjected to several physical and chemical factors that can damage DNA, such as reactive oxygen species (ROS), reactive nitrogen species, ionizing radiation, ultraviolet light, and a wide range of ecological, nutritional, and polluting chemicals. The specificity and viability of the cell depend on the genome's integrity, and the cells have many ways to repair DNA abrasion. These are complex processes that are aimed at different types of injury [94,95]. Enhanced developmental retention of alterations that could potentially contribute to increased drug resistance could increase the existence of a "mutate phenotype" [96]. Chemotherapy, which is widely used in cancer treatment, causes a large number of abnormalities and can thus be a target site for cell reactions such as anthracyclines, ionizing radiation, induced double-stranded DNA breaks, and single-strand breaks [97,98].

The DNA repair route to repair these damages encompasses direct repair by O6-alkylguanine DNA alkyltransferase on alkyl additives; restitution via base excision repair

(BER) of single-strand breaks and base damage; nuclear excision repair (NER) of massive DNA inducts; double-strand break repair by HR (homologous recombination) and NHEJ (nonhomologous end joining); repairing DNA crosslink connections and mismatches, deletions, and insertions by interstrand DNA crosslink repair and DNA mismatch repair (MMR) [94,99–102]. Alkylating models are frequently used in cancer treatment, which can cause DNA breakage and cell death as one of the vital DNA lesions caused by alkylating DNA at the O6 guanine site. Cancer methylating DNA chemotherapy includes temozolomide (TMZ), streptozotocin, procarbazine, and dacarbazine. By transferring the alkyl residue directly to its active site, where the alkyl group is covalently bound together, the O6-methylguanine DNA methyltransferase (MGMT) protein extracts alkyl from O6-alkyguanine, resulting in protein inactivation [103]. Many studies have found that MGMT activity is strongly linked to chemoresistance in primary tumors and human tumor cell lines [104,105], directly linking protein overexpression and resistance pattern [106].

During DNA replication, MMR identifies and fixes base-base mispairs and small-scale insertion and deletion mutations in repetitive microsatellite regions and controls HR remediation of DNA damage caused by ROS, and alkylating agents are also involved in MMR proteins. In the event of DNA damage, these proteins interact with components in other repair systems, including NER, BER, and HR [107], and their deficiency contributes to an array of cancer, including hereditary nonpolyposis colorectal cancer (Lynch syndrome) [108,109]. The silencing of MMR in cancer cells results in tolerance to alkylating agents such as TMZ and procarbazine. MMR-deficient cells are relatively resilient to methylates (up to 100-fold). In contrast, cells with a functioning MMR system undergo G2 halting or programmed cell death based on the magnitude of the DNA defect.

Resistance to clinically relevant drugs such as epipodophyllotoxins, alkylating agents, antimetabolites, platinum-containing compounds, and anthracyclines is associated with MMR protein pathway downregulation [110].

BER provides the main route for eliminating minor base lesions from the genome that are non-helix-distorting. BER mainly targets base lesions through oxidative damage, alkylating, deaminating, and deburring and depyrimidization. BER-targeted chemical therapeutic agents include streptozotocin, dacarbazine, melphalan, TMZ, and ROS generation by-product anthracyclines (doxorubicin, epirubicin, daunorubicin), paclitaxel, and Pt-based drugs (cisplatin and oxaliplatin) [102]. Once the specific DNA glycosylase identifies the damaged base, the dissociation of the N-glycosidic bond is catalyzed by removing the damaged base and forming an AP site, which is further processed by DNA AP endonuclease or lyase [111]. A spike in BER expression in imatinib K562 leukemia-resistant cells MDB4 and NTHL1 was observed with decreased resistance expression levels of cells with small interfering RNA (siRNA) cell survival after doxorubicin dosing [112].

Apoptotic pathway

Programmed cell death (PCD) is involved in several pathological and physiological pathways [113]. Apart from proliferating and resisting growth suppression, aversion to cell death or apoptotic signal disruption is one of the critical drivers of carcinogenesis [114]. For both tumor generation and drug resistance to be effective, PCD is caused by

several external and covert stress signals that must be resolved. Apoptosis operates mainly through two mechanisms: the cyt c–releasing mitochondrial pathway that binds to the caspase effector protease level and the extrinsic signaling pathway of the death receptor. The beginning of such frameworks corresponds to the stimulation of caspases, which facilitates the division of cell substrates and lead to phenotypic and biochemical modifications before apoptosis [115].

Damage to DNA and instigation of oncogenes may lead to an accumulation of p53, which results in the G1 phase of cell cycle arrest or stimulates apoptotic death. Based on the degree of DNA damage, the cancer resistance of chemotherapy may be caused by mutation or inactivation of p53 [116]. Further, research has shown that cisplatin resistance to apoptosis-inducing ligand (TRAIL) has been overturned in HCC-related TNF cells, depending on p53 status [117]. The absolute stimulus for caspase induction in the endogenous system is release by mitochondrial outer membrane permeability under tight regulation of the BCL2 protein family—proapoptotic and antiapoptotic [118] and BH3 proteins (Bim, Noxa, Bid, Puma, and Bad)—to liberate factors including cytochrome C. The TP53 tumor suppressor gene, best known for its monitoring activity concerning DNA defects, promotes the expression of various integral pathway control genes, particularly Bax and PUMA, which eventually lead to the stimulation of caspases [119].

Autophagy

Autophagy is an extensively conserved, autoplastic evolutionary cellular mechanism that erodes and regenerates cytoplasmic components (long-lived or misfolded proteins, protein collates, and impaired organelles) to preserve homeostasis [119,120]. Basal autophagy is a physiologically focused energy recycling mechanism that responds more and more to protein-lipid turnover, including starvation. It can therefore be interpreted as a prosurvival mechanism for any normal or cancer cell. A regulated PCD mechanism called autophagic cell death is observed during long starvation periods [121].

Autophagy typically plays a binary role in MDR cancer. It corresponds not only to the growth of MDR but also to the destruction of MDR cancer cells in which the pathways of apoptosis are inactive [122,123]. In carcinoma cases, autophagy plays an active role by regulating several pathways, including class III and class I PI3K (PI3K-I and PI3K-III), TP53, mTORC 1/2 AKT, and BCL2, that regulate cell life and death [124]. Autophagy initiation and boosted signaling pathways of PI3K-AKT-mTOR and MAPK are often linked to susceptibility to a broad range of drugs in different types of cancer, further demonstrating their significance during carcinogenesis [119].

Cancer stem cells

Cancer stem cells (CSCs) or tumor-initiating cells (TICs) are cancer cells that are capable of self-renewing and distinguishing between heterogeneous tumor cell lines [125–127]. Published studies show that these stem cells respond to standard chemotherapy because a small group of tumor tissue cells, defined as CSCs, can thrive and develop. In contrast,

most chemotherapy agents destroy most cancer cells [128]. The HCC CSC markers include CD133, deubiquitin-specific protease 22 (USP22), oval cell marker (OV6), epithelial cell adhesion molecule (EpCAM), CD13, CD44, CD24, and CD90. Several biomarkers that confer drug resistance to HCC have been identified [115,129]. Activation of the signaling pathway of Wnt/beta-catenin, Hh, and Notch 1 has been shown to strengthen chemoresistance in combination therapy to IFN-α/5-FU, SHH, GSIs, and NICD1, respectively [126].

Researchers have suggested that higher levels of ABC protein expression may be the primary survival response for CSCs in therapeutic drug reactions [130]. Reduced expression profile of USP22 significantly censored ABCC1 (MRP1) expression signals in the HCC cell line by confirming the USP22-ABCC1 alliance in the HCC cell tissue clinical sample. These findings show that USP22 is related to the BEL-7402/FU MDR phenotype [115]. The TICs also show a reduced level of ROS, owing to the upregulated expression of free radical scavenging systems, leading to higher ROS defense lines and radiation resilience [126].

Tumor microenvironment

In epithelial mesenchymal transformation and MDR, the connection of tumor cells to the TME is essential [131]. The tumor's microenvironment constitutes an extracellular matrix, aided by anomalous vasculature, cancer stromal cells, low pH, inadequate nutrition, high interstitial pressure, tumor hypoperfusion, and low oxygen; the anoxic condition can cause chemoresistance [115,132,133]. Cancer cells display higher glucose metabolism levels in comparison to healthy cells and under hypoxic conditions, indicating the Warburg effect favoring glycolysis to oxidative phosphorylation. This inevitably produces lactic acid, which results in acidification [134]. The structure and arrangement of the ECM and stromal components lead to defined drug concentration gradients, intensified interstitial pressures, and metabolism changes that can all significantly increase tumor cell resistance to the therapeutic agent [135].

Therapeutic aspects (overcoming multidrug resistance)

A significant therapeutic payoff for cancer requires that malignant cells lose their MRP or MDR-1 driven chemical defense properties, boosting the apoptotic frequency for those cells. Several variables may affect chemicals' ability to destroy tumor cells. These include, but are not limited to, metabolism and drug pharmacokinetics, microenvironmental changes, genetic or epigenetic variations; genes restoring DNA, tumor suppressor genes, MDR genes, genes with an apoptotic relationship, and various growth factors [136]. Therefore it is the first step toward addressing this obstacle to grass-roots awareness of the possible etiology of resistance.

As has been noted, MDR is handled by extrusion pumps, which are an array of ABC drug carriers, including P-glycoprotein (P-gp). The exorbitant expression of P-gp is a therapeutic aim to bypass MDR in cancer cells, one way of coping with MDR by encapsulating P-gp substratum drugs into liposome nanoparticles has already been shown to be possible in clinical environments [137,138]. It is developing drugs that are not prone to P-gp

extrusion that elevates the expression profile of cancer cells that are not P-gp substrates. Taxane, tesetaxel (DJ-927), and milataxel data (MAC-321) are weak P-gp strata and have exhibited improved antitumor performance as correlated with in vitro or in vivo docetaxel [139]. Molecules that block the action of P-gp and the transporter for outflows, such as telatinib or silibinin, can overcome resistance. These are natural molecules extracted from milk thistle seeds that inject ABCG2 efflux and enhance the efficacy of drugs in tumor cells [140]. Chemotherapy induces cell apoptosis, but this strategy is prevented in cancerous cells because of escalated expression of antiapoptotic protein such as Bcl-2 or a reduction in the proapoptotic proteins along with the expression of Fas, Bax, or cysteine proteases (caspase proteins) [141,142].

Increased levels of protein-tyrosine kinases (PTKs), such as EGFR, HER2, and IGFR, trigger potential mechanisms in cell signals, including PI3/AKT, NIF, STAT3, and ERK1/2, which are also the key causes of chemotherapy resistance in tumor cells' aberrant affirmation. Consequently, the targeted therapy can resolve such opposition against particular PTKs [142]. Over the years, objective treatments in the medical field have evolved and proved promising. Trastuzumab is an antibody that targets and links positively related HER2 receptors to the cell surface and precludes stimulation of a receptor [143]. By comparison, the blockage of EGFR, an antibody that binds EGFR by cetuximab selectively, demonstrated improvement in a response rate of 5-Fu in patients with neoplastic colon cancer and liver cancer who initially failed 5-FU medication [144,145]. DNA methylation is a significant process for deranging the expression of genes linked to apoptotic cell death. Chemotherapy combined with methylation-reversing agents aims to resolve resistance to medications [146].

Combinatorial immunotherapy, which includes monoclonal antibodies, cancer vaccines, and immune-control inhibitors such as PD-1/PDL-1, has the potential to transform cancer care by inducing, growing, or suppressing inflammatory immune responses against various cancerous cell etiologies [147,148]. Knockout genes with antisense molecules and the editing of genes by CRISPR/Cas9 have proven to be successful for suppressing genes with drug resistance [147]. Advances in siRNA technology will establish a new treatment approach in gene-specific silencing that substantially represses mRNA expression and prevents protein synthesis. MiR-125a-5p overexpression boosts drug sensitivity, while miR-15−5p overexpression is correlated with tolerance to medications [149]. The production of small molecule target histonic modifiers such as KDM4B will improve the effectiveness or overcome drug impedance in standard chemotherapy [150−152]. Furthermore, the ancient method of treatment of bacterial-mediated cancer therapy has been reinvigorated in synthetic biology. It is innovative in confronting dynamics of primary resistance to conventional treatments [145,153].

Conclusion and future perspectives

Despite recent developments in both pathophysiology and treatment, HCC is still a disease with a poor prognosis. MDR seems to be a significant barrier that seriously reduces the successful treatment of cancer via medical chemotherapy. Experimental models of drug-resistant cancer helped to identify many of the principles that govern MDR growth.

The evolution in molecular science and computational biology has enabled us to develop "molecular autographs" for cancer patients and to distinguish patients who will benefit from specific treatments. The MDR protein expression level can differ as a result of MDR. Adaptation to therapeutic interventions alone can be explained by the context of particular markers or tumor forms, making it hard to forecast resistance modalities. More complex prediction methods are needed to enhance the response rate to targeted therapies. Advancing molecular diagnostic techniques, chemotherapy-immunotherapy combination therapy, or combinatorial inhibition strategies will have pharmaceutical and therapeutic roles in overcoming the resistance battle. Further research is expected to reveal the use of novel practices such as viral vector, nanoparticle-based approaches, the functionality of autophagy in a tumor microenvironment, and the association with other pathways of signaling associated with the tumor drug resistance. The emergence of appropriate laboratory tests, such as liquid biopsy through the estimation of cell-free RNA or cell-free DNA and the sequence of tumor genomes of FFPE or plasma, would improve the ability to choose the best drugs and prevent incompetent therapy for optimal clinical outcomes.

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VOLUME 2

Theranostics and Precision Medicine for the Management of Hepatocellular Carcinoma

Diagnosis, Therapeutic Targets, and Molecular Mechanisms

Edited by

Ganji Purnachandra Nagaraju, School of Medicine, Division of Hematology and Oncology, University of Alabama, Birmingham, AL, United States

Ramakrishna Vadde, Department of Biotechnology & Bioinformatics, Yogi Vemana University, Kadapa, AP, India

Theranostics and Precision Medicine for the Management of Hepatocellular Carcinoma provides comprehensive information about ongoing research as well as clinical data about liver cancer. It presents detailed descriptions about diagnostics and therapeutic options for easy understanding, with a focus on precision medicine approaches to improve treatment outcomes.

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Key features

- Provides detailed information on traditional and novel diagnostic tools for HCC
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