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Management of Hepatocellular Carcinoma: An Update at the Start of 2014

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Abstract

Background: Over the past 15 years, the incidence of hepatocellular carcinoma [HCC] has more than doubled.

Materials and methods: A search of the literature was made using cancer literature and the PubMed, Scopus, and Web of Science [WOS] database for the following keywords: “hepatocellular carcinoma”, “molecular hepatocarcinogenesis”, “RFA”, “TACE”, “TABE”, “OLTx”, “targeted therapy”, “sorafenib”, “sunitinib”, “tivantinib”, “antiangiogenic” “drugs”, “immunotherapy”.

Discussion and conclusion: For a correct and effective treatment strategy in patients with cirrhosis, it is necessary to perform a liver ultrasound twice a year. With the recent dramatic advances in diagnostic modalities, the diagnosis of HCC is primarily based on imaging. Ultrasound plays a crucial role in HCC surveillance, dynamic multiphasic multidetector-row CT [MDCT] and magnetic resonance imaging [MRI] are the standard diagnostic methods for the noninvasive diagnosis of HCC. Treatment decisions are complex and dependent upon tumor staging, presence of portal hypertension and the underlying degree of liver dysfunction, as well as local expertise, as indicated by the NCCN, APASL, AASLD, BCLC,EASL. Unfortunately, HCC is diagnosed at an advanced stage. In this case the therapeutic option is the systemic therapy. The knowledge of molecular hepatocarcinogenesis broadened the horizon for patients with advanced HCC. During the last years several molecular targeted agents have been evaluated in clinical trials in advanced HCC. In the future new therapeutic options will be represented by a blend of immunotherapy-like vaccines and T-cell modulators, supplemented by molecularly targeted inhibitors of tumor signaling pathways. Thus, it will be necessary in the future to classify HCCs into subgroups according to their genomic and proteomic profiling. The identification of the key molecules/receptors/signaling pathways and the assessment of their relevance as potential targets will be the main future challenge. Defining molecular targeted agentseffecttive for a specific subgroup will hopefully lead to personalized therapy.

Keywords: Hepatocellular carcinoma; Molecular hepatocarcinogenesis; RFA; TACE; TABE; OLTx; Targeted therapy; Sorafenib; Sunitinib; Tivantinib; Antiangiogenic drugs; Immunotherapy

Introduction

Over the past 15 years the incidence of hepatocellular carcinoma [HCC] has more than doubled. Every year there are 500,000 new cases in the Asia–Pacific region, often due to chronic hepatitis B virus [HBV] infection [1]. More than 60% of the total number of HCC cases occurs in China alone and an estimated 360,000 patients residing in Far East countries, including China, Japan, Korea and Taiwan, die from this disease each year. In Japan hepatitis C virus [HCV]-related HCC represents 70% of all cases [2]. In addition, in the USA and Europe, an increased incidence of HCV has led to an increased incidence of HCC [3]. A relevant risk factor for the high incidence of nonalcoholic fatty liver disease is obesity and diabetes, which can promote the development of liver cancer [4]. This involves a poor diagnosis and a low level of survival [5] year survival rate: less than 5%] in patients with advanced HCC at diagnosis. For a correct and effective treatment strategy in patients with cirrhosis, it is necessary to perform a liver ultrasound twice a year. Recently, the role of AFP serum levels has been discussed to be less useful than previously assumed [5,6]. Furthermore, in addition to AFP there are other biomarkers [7-9]: Lens culinaris agglutinin-reactive AFP [AFP-L3], des-carboxyprothrombin [DCP], glypican-3 [GPC-3], osteopontin[OPN] and several other biomarkers [such as squamous cell carcinoma antigen-immunoglobulin M complexes, alpha-1-fucosidase [AFU], chromogranin A [CgA], human hepatocyte growth factor, and insulin-like growth factor [IGF]] have been proposed as markers for the early detection of HCC [7-11]. None of them is optimal; however, when used together, their sensitivity in detecting HCC is increased. Recent developments in gene-expressing microarrays and proteomics promise even more potential diagnostic options [7-12].

More recent research has demonstrated that some of these tumor markers [such as DCP, GPC-3, OPN], in addition to diagnostic and prognostic role in HCC, stimulate HUVEC growth and migration; growth of HCC cells by upregulatingautocrine/paracrine canonical Wnt signaling; Met-Janus kinase 1-signal transducer and activator of transcription 3 [Met-JAK1-STAT3] signaling pathway, which results in HCC cell proliferation [7,9,13]. Therefore, these tumor markers have an important role in hepatocarcinogenesis and this represents a great opportunity in HCC treatment [7,13].

While the endpoint of an early diagnosis is achieved quite easily in most patients with >1 cm HCC by computed tomography [CT] or

magnetic resonance imaging [MRI], demonstrating the specific pattern of an intense contrast uptake during the arterial phase [wash-in] and contrast wash-out during the venous/delayed phase, nodules <1 cm in size are more difficult to diagnose, almost invariably requiring an enhanced follow up with three monthly examinations with US until they grow in size or change their echo pattern. Owing to the lack of robust controlled evidence demonstrating a clinical benefit of surveillance, the real support for screening for liver cancer comes from the striking differences in response to therapy between screened populations in whom HCC is diagnosed and treated at early stages and patients with more advanced, incidentally detected tumors [14].

With the recent dramatic advances in diagnostic modalities, the diagnosis of HCC is primarily based on imaging. Ultrasound plays a crucial role in HCC surveillance. Dynamic multiphasic multidetector-row CT [MDCT] and magnetic resonance imaging [MRI] are the standard diagnostic methods for the noninvasive diagnosis of HCC, which can be made based on hemodynamic features [arterial enhancement and delayed washout]. The technical development of MDCT and MRI has made possible the fast scanning with better image quality and resolution, which enables an accurate CT hemodynamic evaluation of hepatocellular tumor, as well as the application of perfusion CT and MRI in clinical practice. Perfusion CT and MRI can measure perfusion parameters of tumor quantitatively and can be used for treatment response assessment to anti-vascular agents. Besides assessing the hemodynamic or perfusion features of HCC, new advances in MRI can provide cellular information of HCC. Liver-specific hepatobiliary contrast agents, such as gadoxetic acid, give information regarding hepatocellular function or defect of the lesion, which improves lesion detection and characterization. Diffusion-weighted imaging [DWI] of the liver provides cellular information of HCC and also has broadened its role in lesion detection, lesion characterization and treatment response assessment to chemotherapeutic agents [15].

Treatment decisions are complex and dependent upon tumor staging, presence of portal hypertension, and the underlying degree of liver dysfunction, as well as local expertise, as indicated by the National Comprehensive Cancer Network [NCCN], Asian Pacific Association for the Study of the Liver [APASL], American Association for the Study of Liver [AASLD], Barcelona-Clinic Liver Cancer [BCLC], European Association for the Study of the Liver [EASL] and Italian Association of Study of the Liver [AISF] guidelines.

Only 30-40% of HCC patients at initial diagnosis are early stage [0 or A] according to the BCLC classification, which defines patients who may be treated with local ablation [particularly radiofrequency ablation: RFA], resection or orthotopic liver transplantation [16]. Orthotopic liver transplantation provides 5-year survival rates of 70%, whereas radiofrequency, transcatheter arterial chemoembolization [TACE] or resection show lower rates [50-60%] due to the high rate of tumor recurrence [up to 70% within 5 years]. Unfortunately, most patients will not be candidates for either surgery or transplant. For patients in the intermediate stage [asymptomatic HCC multifocal without vascular localization or metastasis: BCLC stage B], TACE is considered the standard of care, achieving partial response [PR] in 20-50% of patients and an expansion of median survival for up to 20 months throughout the development of new vector systems [polymers] and more accurate patient selection methods [17]. Unfortunately, HCC is diagnosed at an advanced stage. In this case the therapeutic option is the systemic therapy. In the last decade, no effective conventional cytotoxic systemic therapy was available [18,19], which has contributed to the dismal prognosis in patients with HCC [16]. In the pivotal phase III studysorafenib, a small molecule multikinase inhibitor, was shown to extend overall survival by almost three months [20]. Thus, current guidelines suggest its use in patients with advanced HCC [BCLC C] [21].

In fact, HCC is highly refractory to cytotoxic chemotherapy and, until now, no conventional systemic chemotherapy has provided response rates >25% and prolonged survival in patients with advanced HCC [22]. Patients with HCC have been observed to need high rates of chemotherapy sessions due to tumor drug resistance mechanisms. The intrinsic drug resistance of tumor cells is mediated by enhanced cellular drug efflux mechanisms in association with an increase in a drug transporter family [ATP-binding cassette proteins containing MDR1 and P-gp] [23]. Furthermore, resistance is also determined by p53 mutations and overexpression of DNA topoisomerase IIa. In addition, we must consider that the liver cirrhosis and hepatic dysfunction complicate administration of systemic therapy due to pharmacokinetic properties [24–26]. Altogether, no systemic therapy could be considered as a standard of care for patients with advanced HCC in the pre-era of targeted therapy [21].

However, a better knowledge of molecular hepatocarcinogenesis today provides the opportunity for targeted therapy [27].

Mechanism of Hepatocarcinogenesis

The knowledge of the mechanisms of hepatocarcinogenesis in HCC is crucial.

Hepatocarcinogenesis is known to be a highly complex multistep process and nearly every pathway involved in carcinogenesis is altered to some degree in HCC [28,29]. Therefore, no single dominant or pathognomonic molecular mechanism exists in HCC.

Hepatocarcinogenesis is considered to be a process originating from hepatic stem cells [however, the role of liver stem cells as HCC cells of origin is under debate] [22] or mature hepatocytes and evolving from chronic liver disease driven by oxidative stress, chronic inflammation and cell death followed by unrestricted proliferation/restricted regeneration and permanent liver remodeling. Chronic liver injury caused by HBV, HCV, chronic alcohol consumption, nonalcoholic steatohepatitis, hereditary hemochromatosis, primary biliary cirrhosis and a-1 antitrypsin deficiency leads to permanent hepatocyte damage followed by a massive compensatory cell proliferation and regeneration in response to cytokine stimulation. Finally, fibrosis and cirrhosis develop in this setting of permanent liver remodeling, particularly driven by the synthesis of extracellular matrix components from hepatic stellate cells. In this carcinogenic environment, the development of hyperplastic and dysplastic nodules as pre-neoplastic conditions is only a question of time. However, the suspected sequential accumulation of molecular events at different stages of liver disease [normal liver tissue, chronic hepatitis, cirrhosis, hyperplastic and dysplastic nodules and cancer] is only partially understood. The molecular pathogenesis of HCC involves different genetic/epigenetic aberrations and alterations in multiple signaling pathways leading to the known heterogeneity of the disease in terms of its biologic and clinical behavior. Current evidence indicates that in hepatocarcinogenesis, two main mechanisms seem to be involved: cirrhosis and the association with hepatic regeneration after chronic liver damage caused by several factors [hepatitis infection, toxins or metabolic impairments] and the collection of DNA mutations with impairment of the cellular oncogenesis-oncosuppression equilibrium

leading to the development of neoplastic cells. Finally, the accumulation of genetic and epigenetic alterations leads to an activation of oncogenes and inhibition of tumor suppressor genes accompanied by an escalation of genetic instability and the disruption of signaling pathways related to the main promoters of hepatocarcinogenesis, namely cell proliferation and [neo]-angiogenesis. However, as known from gene expression studies [microarray analyses], there exists no single dominant or pathognomonic receptor or signaling pathway in HCC and the concept of a multistep process explains why single-targeted agents will not achieve complete response [CR] in HCC [30,31].

Although HCCs are phenotypically and genetically heterogeneous tumors, several signaling pathways such as the Ras/Raf/MEK/ERK [MAPK] pathway, the phosphoinositol 3-kinase [PI3k]/Akt/mammalian target of ramamycin [mTOR] pathway and the Wnt/beta catenin pathway have been repeatedly identified as important for HCC cell proliferation and angiogenesis. In addition, the relevance of growth and angiogenic factors/receptors such as vascular endothelial growth factor [VEGF], platelet-derived growth factor [PDGF] and particularly epidermal growth factor[EGF] receptor was recognized [27].

The MAPK pathway, frequently upregulated in HCC [32], includes a cascade of phosphorylation of four major cellular kinases, ras, raf, mitogen-activated protein extracellular kinase [MEK] and extracellular signal-regulated kinase [ERK] [33].

Several members of the EGF family, in particular EGF, and transforming growth factor-alpha have been shown to play a crucial role in HCC proliferation. EGF receptor [EGFR] is frequently expressed in HCC and its overexpression has shown to be an independent negative prognostic factor for early tumor recurrence and extrahepatic metastasis. EGFR can be targeted either by the use of the monoclonal antibody cetuximab or by small molecules that inhibit the intracellular tyrosine kinase [erlotinib, gefitinib, lapatinib]. The ligands EGF, hepatocytes growth factor [HGF], VEGF and PDGF among others activate this pathway and induce transcription of genes of the AP-1 family, such as c-fos and c-jun involved in HCC proliferation and differentiation. The currently most promising molecular targeted agent within this pathway is the raf kinase inhibitor sorafenib that additionally targets the tyrosine kinases of VEGFR and PDGFR. HCC is a hypervascularized tumor depending by neoangiogenesis and both cell proliferation and also neoangiogenesis contribute to initiation and progression of HCC. Neoangiogenesis play a crucial role in each step of hepatocarcinogenesis [34], providing the rationale for angiogenic inhibitors as a new class of relevant therapeutics in this malignancy.

Hence, targeted therapy of HCC has to include both aspects and hence, VEGF/EGFR receptor signaling and the MAPK pathway have been addressed in clinical settings. VEGF as central mediator of angiogenesis is frequently expressed in HCC [34] and VEGF levels correlate with angiogenic activity, tumor progression and poor prognosis [35-37]. Its effects are mediated via its interaction with tyrosine kinase receptors, namely VEGFR-1 [Flt-1], VEGFR-2 [Flk-1/Kdr] and VEGFR-3 [Flt-4], which are located on endothelial cells [37]. Angiogenesis and particularly VEGFR signaling can be targeted either by the monoclonal antibody bevacizumab or by inhibiting downstream intracellular tyrosine kinases by small molecules such as sorafenib or sunitinib. Other relevant factors for angiogenesis are platelet-derived growth factor [PDGF], basic fibroblast growth factor [bFGF], HGF and angiopoietins. The PI3k/Akt/mTOR pathway which is located downstream of various tyrosine kinase receptors such as EGFR is upregulated in a subset of HCC patients and controls cell proliferation, cell cycle progression and apoptosis [38]. Have been identified other signaling pathways potentially responsible for hepatocarcinogenesis: c-mesenchymal-epithelial transition factor [Met]/HGF signaling, insulin-like growth factor signaling, nuclear factor-KB, and the extrinsic /intrinsic apoptotic pathways [39].

Molecular Targeted Therapy

The knowledge of molecular hepatocarcinogenesis broadened the horizon for patients with advanced HCC. During the last years, several molecular targeted agents have been evaluated in clinical trials in advanced HCC. Despite of only modest objective response rates according to the Response Evaluation Criteria in Solid Tumors [RECIST] [39], several studies showed encouraging results in terms of prolongation of the time to progression [TTP], disease stabilization [DS] and survival.

Sorafenib [BAY43-9006] is currently the only approved systemic treatment for HCC. It has been approved for the therapy of asymptomatic HCC patients with well-preserved liver function who are not candidates for potentially curative treatments, such as surgical resection or liver transplantation and it is the first FDA approved systemic therapy for patients with advanced HCC. In clinical practice, the failure of locoregional therapy, such as TACE, led to the use of sorafenib. Its efficacy and safety in HCC patients was demonstrated by the SHARP trial in western patients [40].

In a study by Di Costanzo et al., a single center's experience in treating 116 patients with advanced HCC with sorafenib was reported on [41]. The study evaluated the response of HCC to and safety of sorafenib. The efficacy of sorafenib was evaluated considering the time to radiographical progression, DCR, OS and survival by grade of radiological response. The TTP was measured every 3 months with the modified RECIST [mRECIST] for HCC. With regards to the appearance of adverse events [AEs], patients were monitored every month using the common toxicity criteria version 3.0. The 3-month overall DCR was 71%: stable disease was observed in 37%, PR in 31% and complete response in 2-5% of patients. The 3-month radiological response is in relation to OS. In the study the authors emphasize that it is very important to evaluate tumor response after 3 months of therapy. In fact the therapeutic response correlates with the prediction of survival. The OS rate at 12 months increased from 10% in complete responder patients to 100% in patients with disease progression. In both the SHARP trial and Asia–Pacific study, 71 and 54% of patients achieved stable disease, while only 2 and 3.3% achieved a PR, respectively, and no patients with a complete response were observed [22,42,43]. The authors explain that the difference is due to the different criteria used to establish the response [RECIST was conventional in the SHARP and Asia–Pacific trials, whereas mRECIST was used in the authors studies] and early termination of the study may have underestimated the SHARP response assessment. These facts can also explain the most significant radiological TTP in this study compared with the SHARP study [12 vs. 5.5 months]. The AEs were moderate [grade 1 or 2] and symptom treatment and dose adjustments were usually enough tomanage AEs [40,44]. Xie et al. demonstrated that sorafenib treatment is significant from the statistical point of view, but clinically only modest improvements in OS, TTP and DCR have been demonstrated [45].

Other Agents

Several pathways are now implicated in hepatocarcinogenesis and agents that target these pathways continue to be developed and effective drugs can be synthesized and used to target a specific HCC subgroup.

Sunitinib malate [SU11248, Sutent®; Pfizer, NY, USA] is an oral multikinase inhibitor that targets several tyrosine kinases receptors, such as VEGF-1/2 and PDGFR-a/b [46] and is implicated in HCC proliferation and angiogenesis. In addition, it was defined as an inhibitor of c-kit, Fit-3 and RET [47].

Linifanib[ABT-869] is a multitargeted tyrosine kinase inhibitor that inhibits multiple members of the VEGFR and PDGFR families [48]. In a xenograft model of HCC, ABT-869 significantly reduced tumor burden. Interim Phase II results in patients with advanced HCC showed a median TTP of 3.7 months with ABT-869 treatment and a safety profile consistent with angiogenesis inhibition. In the Toh et al. study, the authors demonstrate that linifanib as a single agent was found to be clinically active in patients with advanced HCC, with an acceptable safety profile [48].

Tivantinib [ARQ 197] is a new oral selective MET inhibitor that acts by blocking growth and inducing apoptosis in human tumor cell lines that express MET. MET is a tyrosine kinase receptor involved in tumor development and metastatic progression, which is encoded by a MET proto-oncogene. When binding to HGF, MET activates the RAS–MAPK and PI3K–AKT signaling pathways [49,50]. Tivantinib anti-tumor activity was demonstrated in murine xenograft models and its efficacy was confirmed in a panel of HCC cell lines [51].

Tivantinib may provide an option for second-line treatment in patients affected by advanced HCC with well-compensated cirrhosis, especially if they have MET high tumors. MET can represent an important prognostic and predictive biomarker in this type of patient. Tivantinib demonstrated a manageable safetyprofile and preliminary anti-tumor activity in patients with HCC and Child's A or B cirrhosis. Further studies of tivantinib in a biomarker-selected patient population are warranted [52].

New Antiangiogenic Agents

In addition to these drugs have been studied new antiangiogenic agents: bevacizumab, brivanib, ramucirumab.

Bevacizumab[Avastin®; Genentech, CA, USA], a recombinant, humanized monoclonal antibody that targets VEGF, is one of the central drugs of colorectal tumor treatment [53]. In addition to inhibiting tumor growth, growth factor release and metastasis, it can enhance chemotherapeutic agent delivery by normalizing tumor vasculature [54]. Many Phase I–II studies in advanced HCC examined bevacizumab either as a single agent [55] or combined with conventional chemotherapy, such as gemcitabine/oxaliplatin[56] or with capecitabine and oxaliplatin [57,58]. As a single agent it reached objective response rates in up to 13% of patients [55]. In combination with gemcitabine/oxaliplatin it showed a response rate of 20%, with an additional 27% of patients having DS [56]. Good results were also achieved with capecitabine and oxaliplatin[PR: 11%; DS: 78%] [57,58]. A recent study by Kaseb et al. evaluated the use of bevacizumab in combination with erlotinib in patients with advanced HCC and achieved encouraging results [59]. However, apart from more contraindications [cardiovascular and renal impairment] compared with other targetedagents, the risk of hemorrhagic and thromboembolic events needs further evaluation [55,59]. In addition, due to the small sample size, the non-randomized nature and the single-arm setting in these studies, the relative contribution from the chemotherapy regimen remains unknown and no recommendation for routine clinical use of bevacizumab can be recommended. Studies are necessary to further characterize the efficacy and safety profile of bevacizumab, to determine which patients are most likely to benefit from treatment and how bevacizumab can be optimally incorporated into HCC treatment strategies [60].

Brivanib, a selective dual inhibitor of FGF and VEGF signaling, has recently been shown to have activity as a first-line treatment for patients with advanced HCC [61]. In the Phase II open-label study by Finn et al., brivanib was assessed as a second-line therapy in patients with advanced HCC who had not been successfully treated with prior antiangiogenic treatment [47,62]. The authors conclude that brivanib had a manageable safety profile and is one of the first agents to show promising anti-tumor activity in advanced HCC patients treated with prior sorafenib. Nevertheless, recent data showed that patients administrated with brivanib did not reach the primary end point [OS] both in first-and second-line therapy [62].

The monoclonal antibody ramucirumab is a specific inhibitor of VEGFR-2. A Phase II study of 42 patients with advanced HCC and primarily well-preserved liver function (75% Child–Pugh A status) showed that first-line ramucirumabmonotherapy produced a DCR of 50% and a median PFS of 4.3 months [63]. This positive study prompted the initiation of the Phase III REACH trial in HCC, which compares ramucirumab/supportive care with placebo/supportive care for second-line treatment after sorafenib. REACH Phase III trial enrollment has been completed but no results are available yet. It will be very interesting to see the results and the final end points.

In addition to these drugs, cabozantinib acts as a dual c-Met/VEGFR2 inhibitor, inhibiting the tyrosine kinase activity of RET, MET, VEGFR-1, -2 and -3, KIT, TRKB, FLT-3, AXL and TIE-2. The Verslypeet al. study also demonstrated early evidence of anti-tumor activity in a randomized discontinuation Phase II study. Interestingly, the clinical benefits were observed regardless of whether patients had received prior sorafenib treatment. Cabozantinib is undergoing additional evaluation in HCC to better assess its efficacy and safety profile in several ongoing clinical trials [64]. Phase III studies should evaluate the effectiveness of cabozantinib versus placebo, and OS in patients with advanced HCC who have already been treated. OS was the primary end point, and the objective response rate and PFS for RECIST 1.1 were the secondary end points. Additional end points were: safety and tolerability of cabozantinib; pharmacokinetics [PK]; change from baseline tumor biomarker levels in the serum; and health-related quality of life as assessed by the EuroQol Health questionnaire.

Immunotherapy

The human immune system against tumors is mainly dependent on cellular immunity. Patients with HCC are found to have a functional deficiency in a variety of immunocytes [65]. Thus, cellular immunotherapy would improve the immune state and has potential in enhancing the therapeutic outcome for HCC patients.

In HCC, there is a reduction in cell-mediated immunity, including cytotoxic CD8 and CD4 Th1 T cells, natural killer cells, tumor associated macrophages and myeloid-derived suppressive cells. In HCC, there is chronic hepatitis B virus and hepatitis C virus-mediated

immunosuppression. Dysfunctional T-cell responses to both virus-specific and unrelated antigens, characterized by impaired proliferation and IL-2 production, are observed in chronic hepatitis B virus-infected patients. Chronic infection with hepatitis C virus negatively regulates both the innate and adaptive arms of the immune system. There are many mechanisms of HCC immune escape; the peripheral blood of HCC patients shows impaired IL-12 production and reduced all ostimulatory activity. In HCC numerous regulatory mechanisms involving nearly all cellular subsets of the immune system contribute to tumor development and progression.

Chronic HBV or HCV infections are well known to induce a chronic proinflammatory hepatic and systemic state associated with immunosuppressive and immunomodulatory effects [66-71].

In addition, it should be noted that there are many mechanisms of HCC immune escape. The peripheral blood of patients with HCC shows impaired IL-12 production and reduced allostimulatory activity [72]. An impairment of natural killer cell production and activity has also been described in HCC patients [73].

Immune-based therapy can represent an improvement in outcomes for patients with HCC9(102), as many clinical trials demonstrate.

Immunotherapy can be combined with vaccines and T-cell immunomodulators supplemented with molecularly targeted inhibitors of tumor signaling pathways to target HCC [74,75].

Discussion and Conclusion

HCC treatment decisions are complex and dependent upon tumor staging. When HCC is confined to the liver with preserved hepatic reserve and no or minimal portal hypertension, a partial hepatectomy can be curative; however, recurrence, or de novo HCC is common. In patients with unresectable disease and tumor staging that falls within criteria, liver transplantation can be curative in a great majority of patients. Unfortunately, most patients will not be candidates for either surgery or transplant [76-78].

Cytotoxic chemotherapy, hormonal agents and immunotherapy have been tested in HCC with marginal efficacy to date. Recent insights into the molecular pathogenesis of HCC have identified several aberrant signaling pathways that have served as targets for novel therapeutic agents. Several pathways are now implicated in hepatocarcinogenesis, and agents that target these pathways continue to be developed. Thus, in the future, new therapeutic options will be represented by a blend of immunotherapy-like vaccines and T-cell modulators, supplemented by molecularly targeted inhibitors of tumor signaling pathways [79,80].

Molecular alterations may differ depending on the underlying risk factors and etiologies, potentially influencing patient responses to therapy. Thus, it will be necessary in the future to classify HCCs into subgroups according to their genomic and proteomic profiling. The identification of the key molecules/receptors/signaling pathways and the assessment of their relevance as potential targets will be the main future challenge. Defining molecular targeted agents effective for a specific subgroup will hopefully lead to personalized therapy [81].

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