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*Review*

# Improved Chemotherapy for Hepatocellular Carcinoma

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**Abstract.** *Hepatocellular carcinoma (HCC) is the fifth most common cancer and it is the third leading cause of cancer-related deaths worldwide. Once diagnosed with the disease, only 30-40% of patients are deemed eligible for curative intention with treatment modalities including surgical resection, liver transplantation, and chemoembolization. Eventually, most patients will receive some forms of chemotherapy in hope of prolonging life. Sorafenib is the first molecular inhibitor to be approved by the FDA for the treatment of advanced HCC. It is a tyrosine kinase inhibitor, targeting multiple molecular pathways. Prior to the arrival of sorafenib, doxorubicin was routinely used as a single drug for advanced HCC, but has shown inefficacy, with a response rate of about 15-20%. Other chemotherapy agents, such as epirubicin, cisplatin, 5-fluorouracil, etoposide and their combinations, demonstrate even lower efficacy. While being considered an advance over conventional chemotherapy, sorafenib only improves life expectancy approximately by 3 months over placebo. With that in mind, continuous efforts have been put into finding new targets and molecular pathways for possible new drug development. In this article, we summarize the current literature over the past year on chemotherapy treatment of advanced HCC.*

Hepatocellular carcinoma (HCC) is the fifth most common type of cancer and with an estimated 748,000 newly diagnosed cases per year it is the third leading cause of cancer-related deaths worldwide (1). Despite advancement in technologies and research, only fewer than 30-40% of HCC patients are eligible for potentially curative therapies including surgical resection, transplantation or percutaneous ablation because of the advanced stage of the disease at the time of diagnosis (2). Consequently, most patients with advanced HCC will receive systemic chemotherapies. In the past, doxorubicin was used routinely as a single drug for advanced HCC, and has shown inefficacy with a response rate of about 15-20% (3). Other chemotherapy agents such as epirubicin, cisplatin, 5-fluorouracil, etoposide and their combinations demonstrate even lower efficacy. Sorafenib is the first molecular inhibitor to be approved by the FDA for the treatment of advanced HCC. It simultaneously inhibits molecular components of the mitogen-activated protein kinase/extracellular-signal-regulated kinase (RAF/MEK/ERK) signaling pathway, abrogating tumor growth, and vascular endothelial growth factor receptor (VEGFR)/platelet-derived growth factor receptor-β, thus inhibiting angiogenesis (4). Single-agent therapy with sorafenib reduced the risk of death during one year by 31%, and prolonged median survival and the time to progression by nearly three months (5). This advancement in the treatment of HCC has brought excitement to the field of systemic therapy and has helped to push for further studies for potential molecular targets. In this review article, we performed a comprehensive Medline search for all studies from January 2011 to the present on the systemic treatment of HCC. We focus on three different components: Monotherapy (clinical trials and experimental drugs that have been tested on humans; combined chemotherapy (combination of two or more medications tested *in vitro* and *in vivo*; and possible new molecular targets tested isolated on rats or human cells.

## Monotherapy

HCC is a heterogenous disease, and many molecular pathways contribute to hepatocarcinogenesis. However, in the past few years since the approval of sorafenib, several pathways have been elucidated and this led to the

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Table I. *Existing agents and their respective molecular targets (6).*

| Agent | Target | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | VEGF | VEGFR | PDGFR | FGF | FGFR | EGFR | Raf | MEK | mTOR | IGF1R | TRAILR1 | Heparanase |
| Sorafenib | | x | x | | | | x | | | | | |
| Sunitinib | | x | x | | | | | | | | | |
| Brivanib | | x | | | x | | | | | | | |
| Linifanib | | x | x | | | | | | | | | |
| TSU-68 | | x | x | | x | | | | | | | |
| Bevacizumab | x | | | | | | | | | | | |
| Erlotinib | | | | | | x | | | | | | |
| Gefitinib | | | | | | x | | | | | | |
| Lapatinib | | | | | | x | | | | | | |
| Cetuximab | | | | | | x | | | | | | |
| AZD6244 | | | | | | | | x | | | | |
| BAY86-9766 | | | | | | | | x | | | | |
| PI-88 | x | | | x | | | | | | | | x |
| Mapatumumab | | | | | | | | | | | x | |
| Everolimus | | | | | | | | | x | x | | |

Abbreviations: VEGF=vascular endothelial growth factor; VEGFR=vascular endothelial growth factor receptor; PDGFR=platelet derived growth factor receptor; FGF=fibroblast growth factor; FGFR=fibroblast growth factor receptor; EGFR=epithelial growth factor receptor; MEK=mitogen-activated protein kinase; mTOR=mammalian target of rapamycin; IGF1R=insulin-like growth factor 1 receptor; TRAILR1=tumor necrosis factor-related apoptosis-inducing ligand receptor.

development of new targeted agents. In their review article, Kim and Park summarized molecular targeted agents for HCC with active trials shown in Table I (6). Among those targets, VEGF represents an important target and its signaling pathways have been investigated extensively. HCC is one of the most vascularized tumors; therefore, it is easily understandable why VEGF is central to HCC tumorgenesis. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature; therefore, its expression reduces the barrier to tumor cell migration during metastasis. Bevacizumab, a recombinant humanized monoclonal antibody directed against VEGF-A, is a representative drug of those under active trials. In a multicenter phase II study of bevacizumab, 65% of patients had a 6-month progression-free survival period, and 13% had partial responses out of 46 patients (7). Bleeding is a major complication of bevacizumab therapy, however.

VEGF represents only one of the many available targets for drug development. We conducted a comprehensive Medline search for ongoing trials since January 2011 and focused on trials that are being and were conducted with single-agent therapy. Four trials with published data were found. Cediranib (AZD2171), a potent tyrosine kinase receptor inhibitor affecting VEGF-A or VEGF, was recently tested in a phase II trial on 28 patients with unresectable or metastatic HCC. Patients received 45 mg of cediranib orally once daily for 28-day cycles. Twelve patients (42.9%) survived 6 months, 15 (53.6%) died within 6 months, and one (3.6%) was lost to follow up. The median overall survival was 5.8 months and the median time to progression was 2.8 months. The majority of patients (93%) suffered adverse side-effects, with most common events being fatigue, anorexia, hypertension, and elevated alanine aminotransferase. Due to the multiple adverse events experienced with the current recommended dose from the phase I trial and its lack of efficacy compared to soratinib (stable disease 25% *vs*. 71%), the authors of this study advised against monotherapy use of cediranib (8).

In a phase II study of the mitogen-activated protein kinase 1/2 (MEK) inhibitor, selumetinib was used for patients with advanced HCC. In previous studies, it was noted that the RAF/MEK/ERK signaling pathways play a pivotal role in the regulation of many cellular processes, including proliferation, survival, differentiation, apoptosis, motility, and metabolism (9). Through phosphorylation, MEK is activated, which subsequently phosphorylates ERK1 and ERK2. Activated ERK then dimerizes and translocates to the nucleus, where it is involved in important cellular functions (10). Patients enrolled in this study had not been treated with prior systemic therapy. Out of the 19 patients enrolled, 17 were evaluated for response (two did not complete the full cycle of therapy). Among these 17 patients, there was no partial response or complete response based on radiographic criteria. The median progression free survival (PFS) was 1.4 months and the median overall survival (OS) was 4.2 months. Inhibition of ERK phosphorylation was demonstrated by western blotting. Based on this result, the authors of the study concluded that selumetinib is ineffective

as a single-agent therapy for advanced HCC despite evidence of suppression of target activation (11).

Another target recently tested in a trial is the phosphoinositide 3-kinase/AKT/mammalian target of rapamycin (mTOR) pathway. Inhibition of the mTOR pathway might prevent angiogenic activity in HCC since it is involved in production of many angiogenic factors, including VEGF (12). Everolimus, an oral small-molecule serine-threonine kinase inhibitor of mTOR, was used for the phase 1 and 2 study in patients with advanced hepatocellular carcinoma. From phase I of the study, it was determined that 10 mg daily dose was safe with no significant side effects. A total of 25 patients were enrolled in the phase II of the study where each of them received 10 mg daily dose. Of note, one patient had a partial response. The median PFS and OS were 3.8 months and 8.4 months, respectively. The authors concluded that preliminary antitumor activity was observed with everolimus in patients with advanced HCC. However, the study is weakened by fact that the majority of patients (71%) had received prior systemic therapy, including 11 (39%) patients who had received prior sorafenib therapy and nine (32%) patients who had received other systemic regimens (13).

Another study was carried out by using deferoxamine on patients who had advanced HCC and did not respond to hepatic arterial infusion chemotherapy with anticancer drugs. On a previous study, deferoxamine was found to arrest the cell cycle and induce apoptosis (14). A total of 10 patients were enrolled in the study and they received an arterial infusion of deferoxamine (at a dose of 10 to 80 mg/kg of body weight) over 24 hours on alternate days. Of note, five patients had Child-Pugh class B and two patients had Child-Pugh class C. One patient with lung metastasis responded to deferoxamine and his hepatocellular mass disappeared after two months of treatment. The one-year cumulative survival rate was 20%. Side-effects at the recommended were tolerable in most patients (four patients with grade 2 or 3 interstitial pneumonia and one patient with grade 2 renal dysfunction). The authors suggested deferoxamine be used and tested on HCC patients with Child-Pugh class B or C as an alternative to sorafenib (15).

Another effort was focused on the prevention of recurrence after curative treatment. The study was a phase I trial on acyclic retinoid NIK-333, a synthetic polyprenoic acid that exhibits retinoid-like activities by binding to cellular retinoic acid-binding protein (16). It was previously found that oral administration of NIK-333 for one year in patients with treated HCC prevented the development of a second primary hepatoma and improved survival (17). The purpose of this study was to establish the maximum tolerated dose and dose-limiting toxicities (DLT). The medication was administered at doses ranging from 300 to 900 mg/day as a single dose and two equally divided doses. At the dose level of 900 mg/day, hypertension developed in three out of nine patients; therefore, the authors recommended phase II/III to be carried out with 300-600 mg/day dose (18).

## Combined Therapy

Sorafenib is an oral multi-targeted tyrosine kinase inhibitor and the first agent shown to improve the OS in advanced HCC. At present, we have no standardized second-line regimen for HCC patients after progression on first-line sorafenib. We reviewed some promising combined therapies which might enhance the effect of soratinib.

Bufalin, a component of the traditional Chinese medicine chan'su, enhances the anti-cancer effects of sorafinib on different HCC cell lines, PCL/PRF/5 and Hep G-2, by contributing to the downregulation of ERK. Apoptosis occurred in PLC/PRF/5 and Hep G-2 cells treated with sorafenib or bufalin alone, or in combination for 24 hours. Compared with untreated cells, various degrees of damage to mitochondria were present upon drug treatment for both cell lines. Synchronous exposure to sorafenib and bufalin resulted in the most severe damage. More apoptosis was detected in the PCL/PRF/5 cell line compared with the Hep G-2 cell line (19).

Everolimus augments the effects of sorafenib in a syngeneic orthotopic model of HCC. Everolimus inhibits the mTOR, a kinase overactive in HCC (20). Combined treatment with everolimus and sorafenib exerts a stronger antitumoral effect on Morris hepatoma cells than monotherapy. On day 35 of treatment, when compared with untreated tumors, the tumor volumes had decreased by 29% after sorafenib treatment, 55% after sequential of sorafenib then everolimus, 50% after everolimus, and 85% after combined treatment ($p<0.001$ in comparison with control). The median survival was 57 days in the control group (n=7), 63.5 days when treated with sorafenib (n=6), and 70 days when treated with the combination sorafenib-everolimus (n=5) (20).

The hepatoma up-regulated protein (*HURP*) represents a putative oncogene that is overexpressed in many types of human cancer, especially HCC. HURP plays an important role during mitotic spindle formation, a process that is targeted by various anticancer agents such as Taxol (paclitaxel). In a study of Kuo and Lu, it was observed that HURP promoted taxol resistance in both non-tumorigenic and hepatoma cells. By using real-time polymerase chain reaction (PCR) and chromatin immunoprecipitation assays, they observed that the nuclear factor kappa beta (NF-KB) family member c-REL represents a putative transcription factor that activates *HURP* gene expression. In addition, the inhibitory effect of sorafenib on HURP expression was attributed to reduced translation and nuclear translocation of c-REL. Accordingly, down-regulation of c-REL was shown

to reduce the *HURP* levels and enhance taxol-induced cell death. The number of apoptotic cells increased following combined treatment with sorafenib and taxol when compared to both sorafenib and taxol alone ($p<0.01$) (21).

There are agents other than sorafenib which also showed promise for the treatment of HCC. Interferon α/β and anti-fibroblast growth factor receptor 1 (FGFR1) monoclonal antibody suppresses HCC *in vitro* and *in vivo* (22). By using western blot and flow cytometric and immunocytochemical analyses, a group scientists of Sapporo Medical University, Japan, found that interferon α/β induces expression of FGFR1 in human HCC cell lines, and that an anti-FGFR1 monoclonal antibody (mAb) can effectively inhibit growth and survival of HCC cells *in vitro* and *in vivo*. Moreover, the combination of interferon-α, anti FGFR1 mAb and peripheral blood mononuclear cells exerted a significant antitumor effect *in vitro*.

Arsenic trioxide has already been used in the clinic for hematologic malignancies by inducing differentiation of cancer stem cells (CSCs) into non-tumorigenic cells, which are more sensitive to conventional therapy. The failure of existing treatments for liver cancer has recently been attributed to the existence of CSCs, which are difficult to kill using current drugs due to their chemoresistant properties, as well as their ability to stimulate neoangiogenesis. Tomuleasa *et al*. have shown that low concentrations of arsenic trioxide lead to morphologic differentiation and differentiation-assosiated cytochemical features, such as increased sensitivity to cytostatic drugs. When adding arsenic trioxide prior to treatment with cisplatin, doxorubicin, 5-fluorouracil and interferon α-2b (PIAF), the results show a reduced survival of tumor cells in a dose- dependent manner at 24, 48, 72 hours and that the arsenic trioxide plus PIAF regimen is the best combination chemotherapy for HCC, superior to both tyrosine kinase inhibitor and PIAF regimens alone ($p<0.05$) (23). Further studies on animal models will be needed before these ideas can be implemented in human clinical trials.

Several phase I trials suggest promising activity of a combination of gemcitabine and docetaxel. In a phase II clinical trial, 25 patients with advanced HCC were enrolled for this treatment with 26 months follow-up. Although this combination seemed to have a potential benefit, with median survival of 12.8 months (95% confidence interval=5.26-28.00), its toxicity and the recent introduction of sorafenib have further limited its use. In this trial, twenty patients (81%) experienced grade 3+ adverse events, including 11 with grade 4+ adverse events, primarily neutropenia, thrombocytopenia, diarrhea, and fatigue (24). The better toxicological profile of bevacizumab, capecitabine and oxaliplatin is an attractive option for further study as first- or second-line therapy for advanced and metastatic HCC. A phase II study of 40 patients was designed to determine the efficacy and the toxicity of this combination in patients with advanced unresectable and untransplantable HCC. This trial showed good tolerability for this combination, with mild to moderate grade 3/4 toxicity (<10% hematologic grade 3/4 toxicities), which is less than that with other combination regimens with relatively newer chemotherapy agents (25).

Another phase I trial of S-1, a fourth-generation oral fluoropyrimidine, in combination with sorafenib showed a tolerable toxicity profile and a modest clinical efficacy in patients with advanced HCC. The most common drug-related adverse effect was hand and foot syndrome (65%), but a severe toxic effect developed in only one patient (5%); the median PFS was 3.9 months (95% CI=0.8-7.0) and median OS was 10.4 months (95% CI=0.0-22.4) (26). Given the convenient administration of two oral drugs, excellent tolerability and no significant drug interaction, S-1 and combination of sorafenib may be a novel therapeutic option for advanced HCC.

## New Molecular Targets, Pathways and Agents

Sorafenib is the only FDA-approved chemotherapy for the treatment of HCC. While it shows effectiveness for patients with advanced HCC, it only prolongs life expectancy for approximately three months. Many clinical trials, both monotherapy and combination therapy, are underway; however, few of them show definitive results. What is needed is an agent or a combination of agents that can target multiple pathways that are central to the development of HCC. Due to the vast amount of research and literature available, here we only discuss selected articles on possible new molecular targets that might be the basis for new drug development. Other studies are summarized in Table II.

Several studies have focused on mesenchymal epithelial transition factor (c-MET), a type of receptor tyrosine kinase that might play a critical role in cancer growth, invasion and metastasis. Upon ligand binding, c-MET is activated by autophosphorylation. This then signals multiple downstream pathways including PI3K/AKT and MAPK/ERK, which control cell proliferation, resistance to apoptosis, and cytoskeletal re-arrangement (27). Based on this information, a c-MET inhibitor seems to be an attractive target for HCC treatment. SU11274, a c-MET inhibitor, was found to suppress HCC cell growth. By adding SU11274 to HCC cells incubated with des-gamma-carboxyprothrombin (DCP) (a protein that interacts with c-MET and activates HCC cell growth), the activation of HCC cell growth was neutralized (28). You and colleagues took a step further by studying the effect of PHA665752, a c-MET tyrosine kinase inhibitor, on c-MET positive HCC cells and c-MET-negative HCC cells. They found that PHA665752 significantly inhibited growth on c-Met-positive HCC cells while it had no effect on c-Met negative HCC cells. The authors logically concluded that c-

Table II. *Summary of possible new molecular targets and pathways.*

| Authors (ref) | Target(s) | Comment |
|---|---|---|
| Xiao *et al*. (37) | ERK, JNK | Using isomalto-oligosaccharide sulfate as a substrate to test for HCC proliferation, apoptosis, adhesion, migration, and invasiveness |
| Amin *et al*. (38) | TNF alpha, NF-KB | Using saffron as a substrate to test for inhibition of HCC cell proliferation and induction of apoptosis |
| Liu *et al*. (39) | Osteopontin | Osteopontin is required for vascular mimicry in HCC cells |
| Lai *et al*. (40) | c-FLIP/VEGF | Pigment epithelial-derived factor inhibits c-FLIP expression |
| Maazocca *et al*. (41) | LPA | LPA accelerates HCC progression by recruiting peritumoral tissue fibroblasts |
| Huang *et al*. (42) | Smoothened, microRNAs | Smoothened is a receptor important in Hedgehog signaling pathway |
| Zheng *et al*. (43) | microRNA-124 | Low-level expression of miR-124 is correlated with an aggressive HCC |
| Cohen *et al*. (44) | Adenosine receptor | CF102, adenosine receptor agonist, induces HCC cell apoptosis *via* the PI3K-NF-KB pathway |
| Zhang *et al*. (45) | Mitochondria path, BCL-2 | Chelerythrine chloride induces HCC apoptosis *via* the mitochondria pathway and BCL-2 |
| Liu *et al*. (46) | TGIF | Blockage of the PI3K/AKT pathway or TGIF expression combined with ATO treatment may be a promising strategy for HCC therapy |
| Xu *et al*. (47) | Cell cycle arrest | miR-122 in combination with adriamycin and vincristine induce G2/M arrest |
| Song *et al*. (48) | Mitochondrial potential | Astaxanthin induces cell apoptosis through regulation of mitochrondial-dependent manner |
| Yang *et al*. (49) | Mitochondria/ MAPKs | ZL11n induces apoptosis through the mitochondrial pathway and the MAPK pathway |
| Sun *et al*. (50) | p53-dependent | Coumarin induces p53-dependent apoptosis |
| Carlisi *et al*. (51) | TRAIL/STAT3 | Parthenolide sensitizes HCC to TRAIL |
| Wolfe *et al*. (52) | FXR | FXR-KO mice exhibit increased activation of Wnt/ β-catenin, leading to spontaneous HCC |
| Choi *et al*. (53) | Cell cycle arrest | HS-113 causes cell cycle arrest, decreased expression of HIF-1alpha and VEGF |
| Yin *et al*. (54) | Mitochondrial pathway | Combination of IFN alpha/5-FU induces apoptosis through mitochondrial pathway |
| Chen *et al*. (55) | Telomerase / capspase-3 | Combination of AZT and arsenic trioxide has synergistic effect. |
| Cho *et al*. (56) | Cyclin-dependent kinases | Ibulocydine, a CDK inhibitor, induces apoptosis in HCC cells |
| Liu *et al*. (57) | IL-6/STAT 3 | Celecoxib blocks the IL-6/STAT 3 pathway |
| Vara *et al*. (58) | AMPK | Cannabinoid induces AMPK-dependent activation of autophagy |
| Chiu *et al*. (59) | MMP/MAPK | Baicalein prevents tumor through inhibition of adhesion, invasion, migration |
| Zhao *et al*. (60) | BCL-2 / survivin | ABT-263 and YM-155 combination induce apoptosis through BCL-2/survivin inhibition |
| Sasaki *et al*. (61) | FGFR | Interferon enhances accumulation of anti-FGFR antibody in tumors |
| Zheng *et al*. (62) | Topoisomerase | 9NC-LP inhibit HCC growth |
| Rajendran *et al*. (63) | STAT 3 | Honokiol potentiates the apoptotic effects of paclitaxel and doxorubicin in HCC cells |
| Chen *et al*. (64) | AKT | rVP1, an AKT inhibitor, induces apoptosis in HCC cells |
| Liu *et al*. (65) | ROS/AKT | Tetrandrine induces HCC cell apoptosis as a regulator of ROS/AKT pathway |

Abbreviation: ERK=extracellular-signal-regulated kinase; JNK=Jun n-terminal kinase; TNF=tissue necrosis factor; NF-KB=nuclear factor kappa beta; c-FLIP=caspase-8-inhibitory protein; VEGF=vascular endothelial growth factor; LPA=lysophostatidic acid; TGIF=TG-interacting factor; MAPK=mitogen-activated protein kinase; TRAIL=tumor necrosis factor-related apoptosis-inducing ligand; FXR=farnesoid X receptor; ATO=arsenic trioxide; PI3K=phosphoinositide 3-kinase; IL-6=interleukin-6; ROS=reactive oxygen species; AKT=serine–threonine kinase AKT; AMPK=adenosine monophosphate-activated kinase; NC-LP=Nitrocamptothecin-loaded liposomes; rVP1=recombinant VP1; FGFR=fibroblast growth factor receptor; CDK=cyclin-dependent kinases; MMP=matrix metalloproteinase.

MET inhibitor might be tailored to patients with tumors with strong c-MET expression (29).

Other studies focused on transforming growth factor beta (TGF-β). TGF-β is a tumor suppressor which acts by inhibiting cell cycle progression and arresting cells in early G1 phase. However, during early cancer progression, TGF-β switches from being a tumor suppressor to a tumor promoter (30). It triggers the epithelial-mesenchymal transition (EMT), important in cancer progression, through the Smad-dependent signaling pathway in cooperation with other Smad-independent oncogenic pathways to maintain the mesenchymal phenotype of invasive cells (31). In turn, Smad activity is negatively regulated by cyclin dependent kinase 4 (CDK4) and CDK2. Baek HJ and colleagues found that by increasing expression of B2SP (a crucial Smad adaptor) CDK4 level was suppressed leading to cell cycle arrest in G1 (32). Another study that was related to the TGF-B pathway was on CD147, an extracellular matrix metalloproteinase (MMP) inducer capable of inducing tumor cells to produce MMPs to promote tumor invasion and metastasis. The authors found that CD147 was up-regulated by TGF-B and mediated EMT in tumor formation, making it an attractive target for the treatment and prevention of HCC (33).

We found studies that focused on inhibitors related to the NF-KB pathway. NF-KB is a key regulator of inflammation and has been reported to be activated constitutively in human HCC (34). It also regulates angiogenesis and mediates inhibition of apoptosis. In their article, Freise and colleagues

treated different HCC cells with *Lindera obtusiloba* extract (derived from wood and bark of the Japanese spice bush) and the result was encouraging. The extract reduced basal and insulin-like growth factor 1 (IGF-1)-induced activation of the insulin-like growth factor 1 receptor (IGF-1R) signaling cascade, it reduced the protein expression of cyclooxygenase 2 (COX-2) and of inducible nitric oxide synthase (iNOS), it blocked the expression of VEGF and reduced the transcriptional activity of NF-KB. All these mechanisms resulted in apoptosis and blockage of HCC cell invasion (35). Therefore, IGF-1 and NF-KB signaling pathway might represent potential targets for drug development. In a separate study, Khan and colleagues confirmed the important of the NF-KB pathway in preneoplastic hepatic lesions. They treated rats with induced preneoplastic hepatic lesions with dimethoxy flavone (DMF), a methylated flavone derived from chrysin, which resulted in the suppression of the lesions. In a follow-up study, they found that DMF suppressed the activation of the NF-KB pathway as shown by the decrease in end point protein expression (36).

## Conclusion

Cancer is one of the most dreadful diagnoses a patient can receive and will continue to be so in the future. We have gained so much ground on the fight against cancer, yet we are still not where we want to be. With increased public awareness, early detection through effective screening and effective treatment modalities, many types of cancer are now considered curable. However, many other forms still cause great concern because of their aggressiveness and early metastasis; one of these is HCC.

Based on our literature review, we feel that combination chemotherapy, in which drugs enhancing the known effect of sorafenib and targeting multiple molecular pathways, will be superior to monotherapy for the treatment of patients with advanced HCC. Finally, we also recognize that with so much advancement in technology, specific gene therapy might be a possibility in the near future.

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