Chapter 5

Past, Present, and Future Perspectives on the Systemic Therapy for Advanced Hepatocellular Carcinoma (HCC) — A Comprehensive Review

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Abstract

Hepatocellular carcinoma (HCC) is the fifth most frequent cancer, the third leading cause of cancer-related mortality, and the first leading cause of death in patients with cirrhosis. Management of primary locally advanced, inoperable, recurrent or metastatic HCC is very challenging and continues to be a topic of controversy. Herein, we shed light on the past, present, and future perspectives on the systemic therapy (hormonal therapy, cytotoxic chemotherapy, and novel molecularly targeted therapy) for management of patients with advanced HCC.

Keywords: Hepatocellular Carcinoma

1. Introduction

Globally, hepatocellular carcinoma (HCC) is the fifth most frequent cancer, the third leading cause of cancer-related mortality, and the first leading cause of death in patients with cirrhosis. The incidence of HCC has doubled in developing and developed countries over the recent decades [3]. HCC generally takes place in the setting of variable underlying hepatic conditions,

such as autoimmune hepatitis, nonalcoholic steatohepatitis (NASH), hepatitis B, hepatitis C, alcohol-associated liver disease, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), and other liver diseases [4]. Therefore, the patient population is varied, accounting for the intricacy of studying this neoplasm, and how to effectively manage it.

Therapeutic modalities for management of HCC can be largely categorized into three main types: surgical and nonsurgical therapies [5, 6]. Surgical therapies include surgical resection, cryosurgery, and living/deceased donor liver transplantation. Nonsurgical therapies can be divided into liver-directed and systemic. Liver-directed therapies include percutaneous ethanol/acetic acid injection, percutaneous microwave coagulation therapy, radiofrequency ablation, microwave coagulation therapy, interstitial laser photo-coagulation, targeted cryoablation therapy, high-intensity focused ultrasound, transcatheter arterial therapy, and radiation therapy. Systemic therapy includes hormonal therapy, cytotoxic chemotherapy, and novel molecularly targeted therapy.

At the time of clinical diagnosis, roughly 60%-70% of HCC patients present with primary advanced, inoperable, recurrent, or metastatic disease [7]. Moreover, tumor relapse (recurrence) following curative surgical management continues to be a substantial dilemma and is documented as high as approximately 70% at 5 years postoperatively [8]. The standard of care management for recurrent HCC remains undefined [8].

The management of primary locally advanced, inoperable, recurrent, or metastatic HCC is very challenging and continues to be a topic of controversy. Herein, we shed light on the past, present, and future perspectives on the systemic therapy (hormonal therapy, cytotoxic chemotherapy, and novel molecularly targeted therapy) for the management of patients with advanced HCC.

2. Hormonal therapy

Several HCCs express sex-hormone receptors such as estrogen (ER), progesterone (PR), and androgen receptors [9] as well as somatostatin receptors [10, 11]. Hence, hormonal therapies (hormone receptor blockers) can be initiated as practical therapeutic choices in patients with hormone receptor-positive HCC [5]. The most frequently employed hormonal agents for the management of HCC include tamoxifen, megestrol, octreotide, and lanreotide.

2.1. Tamoxifen

Multiple studies including single-center and multicenter prospective randomized controlled trials, systematic reviews, and meta-analyses investigated the role of tamoxifen for the management of patients with advanced unresectable HCC [12-16]. These studies were unsatisfactory and failed to demonstrate improved survival advantages (disease-free survival [DFS] and overall survival [OS] rates) or enhanced quality of life (functional status).

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One plausible explanation for absence of survival efficacy could be attributed to the existence of variant estrogen receptors (ERs) in a subset of these HCC lesions leading to more hostile biological behavior and insensitivity to tamoxifen therapy [17, 18].

Tamoxifen has been shown to function as a potential multidrug resistance (MDR)-reversing remedy in the chemoresistant HCC [19]. Subsequently, several clinical trials have been conducted exploring the clinical benefits of combining tamoxifen with diverse cytotoxic chemotherapeutics.

The cellular (molecular) potentiation of doxorubicin-induced apoptosis of HCC cells by tamoxifen has been confirmed in a bench laboratory work by Cheng et al. [20]. Subsequently, in 1998, a prospective phase II study by the same authors [21] enrolled 36 patients with advanced HCC. Patients received high-dose tamoxifen (120 mg/m^2 per day) plus doxorubicin. Only 12 patients (33.3%) attained partial remission with a median PFS of roughly 7 months.

Another randomized controlled study by Melia et al. [22] enrolled around 60 advanced inoperable HCC patients who were then randomized to two groups: (1) doxorubicin alone (60 mg/m^2 at 3-week intervals) and (2) combined doxorubicin plus tamoxifen (10 mg twice daily). Drug response happened only in 3 (11%) and 4 (16%) patients of the above-mentioned groups, respectively, without statistical significant difference.

Moreover, Lu et al. [23] studied the combination therapy of high-dose tamoxifen, doxorubicin, and interferon alpha [IFNα] in 25 patients with advanced unresectable HCC. Partial remission was achieved in five patients (20%) with median PFS of 7 months. Overall, median OS was 6 months, whereas the 1-year survival rate was roughly 16%. The study concluded that this triple combination (high-dose tamoxifen, doxorubicin plus IFNα) is effective but not superior to the double therapy (high-dose tamoxifen plus doxorubicin).

Furthermore, the combination of tamoxifen with oral etoposide [24] and epirubicin [25] have been conducted with only modest antitumor outcomes.

2.2. Megestrol

In 1997, Chao et al. [26] (phase II study) explored the role of megestrol acetate (160 mg/day, orally) in 46 patients with advanced unresectable HCC. Thirty-two patients were included in the analysis. No single patient attained partial or complete response. Twenty patients (62%) experienced disease progression, and a similar percentage (62%) experienced improved symptoms/functional status. Twelve patients (38%) attained stable disease. Glucocorticoid receptor-positive HCC (n = 4/5) experienced stable disease, whereas glucocorticoid receptor-negative HCC (n = 5/5) experienced disease progression. The study concluded that while megestrol acetate does not exhibit noteworthy anticancer activities against HCC, it is very beneficial as palliative treatment to improve quality of life. Also, the stable disease status may be attributed to glucocorticoid receptor-positive HCC. Further research is needed.

In 2001, Villa et al. [18] studied 45 patients with variant ER HCC. Twenty-one (n = 21) and twenty-four (n = 24) patients were randomized to receive megestrol 160 mg daily and only best supportive care (BSC), respectively. In comparison with the BSC group, the megestrol-treated

group achieved higher statistically significant median survival (18 vs. 7 months; $P = 0.0090$) and decelerated tumor growth ($P = 0.0212$).

More recently in 2011, Chow et al. [27] studied 204 patients with therapy-naive advanced HCC across six Asia-Pacific countries. Patients were randomized to two groups: (1) treated group with megestrol acetate (320 mg daily) and (2) placebo group. Placebo group had higher (statistically insignificant) OS than the treated group (2.14 vs. 1.88 months, respectively). The treated group had lower frequencies of nausea, vomiting, and anorexia but experienced a worse (statistically insignificant) global health status. The study concluded that megestrol acetate does not extend OS in patients with advanced treatment-naive HCC.

Most importantly, the noticeably dissimilar OS intervals in the Chow et al. [27] placebo group versus the supportive care group in the Villa et al. [18] study (2.14 vs. 7 months, respectively) propose that therapeutic results may be largely dependent on different aspects, for example, baseline liver function (Child-Pugh score [CPS]) and performance status (Eastern Cooperative Oncology Group performance status).

2.3. Octreotide

In 1998, Kouroumalis et al. [11] studied the role of octreotide in 58 patients with advanced unresectable HCC. Patients were randomized to two groups: (1) treated group with somatostatin analog, i.e., octreotide (250 mg twice daily subcutaneously) and (2) placebo-controlled group. Numerous quantities of somatostatin receptors were recognized in the liver tissue of all patients with HCC. The treated group achieved higher statistically significant median OS rates than the control group (13 vs. 4 months, respectively; $P = 0.002$), but without objective responses rates (ORR). Moreover, the treated group achieved higher cumulative survival rates than the placebo-controlled group at 6 and 12 months (75% vs. 37% and 56% vs. 13%, respectively). At 6 months post octreotide administration, the treated group had significantly decreased alpha-fetoprotein (AFP) levels. The study concluded that octreotide administration substantially offers survival advantages and is a plausible substitute in the management of advanced unresectable HCC.

However, the above-mentioned findings [11] could not be validated and reproduced in 2 successive randomized placebo-controlled trials employing sandostatin—a long-acting analog of octreotide [28, 29]. The two studies were conducted in 2002 and 2007.

In 2011, Ji et al. [30] conducted an updated systematic review and meta-analysis of 11 randomized controlled trials (total of 802 patients) exploring the role of somatostatin analogs in advanced HCC. Only nine studies were incorporated into the meta-analysis and revealed higher statistically significant 6-month and 12-month survival rates in the treated octreotide group versus the control/placebo group. This meta-analysis concluded that octreotide administration could provide survival benefits in patients with advanced HCC.

2.4. Lanreotide

Previous nonrandomized studies have shown inadequate antineoplastic effects of lanreotide for the management of patients with advanced inoperable HCC [10, 31].

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In 2000, Raderer et al. [31] administered lanereotide (30 mg once intramuscularly every 2-week period) in 21 treatment-naive patients with advanced HCC. The object response rate (ORR) and the stable disease rates were 5% and 38%, respectively, whereas the median OS and the time to progression (TTP) were 4.2 months and 2.5 months, respectively.

In 2006, Cebon et al. [10] administered lanereotide (20 mg once intramuscularly every 4-week period) in 63 patients with advanced HCC. Only one patient (2%) experienced partial objective response and median OS was 8 months.

In 2009, Barbare et al. [32] conducted a multicenter, phase III, randomized, double-blind placebo-controlled study investigating the role of lanreotide in 272 patients with primary advanced or recurrent HCC. Patients were randomized to two groups: (1) treated group with lanreotide (intramuscular injection of 30 mg once every 4 weeks for up to 2-year interval) and (2) placebo-controlled group. The median OS and the disease-free survival (DFS) were comparable and did not differ significantly between both groups. Four and zero objective responses were achieved in the placebo and treated groups, respectively. Objective response and disease stabilization were achieved in 0% and 33% of the lanreotide-treated group, respectively. The treated group had faster global heath deterioration that the control group. The study concluded that lanreotide has fairly a well-tolerated toxicity profile, negative influence on functional status, and nonbeneficial OS outcomes.

2.5. Conclusion

All studies examining the role of single-agent tamoxifen or in combination with diverse chemotherapeutic drugs were unsatisfactory and failed to yield substantial worthy survival advantages. Similar discouraging results occurred with megestrol administration as well as somatostatin analogs (octreotide and lanreotide). It can be concluded that the use of hormonal therapy for the management of advanced inoperable HCC is not recommended. Its use may be only recommended within the context of clinical trials. Further research is needed.

3. Systemic cytotoxic chemotherapy

Several nonrandomized and phase I, II, and III clinical trials have been conducted to investigate the role of systemic cytotoxic chemotherapy (monotherapy or combination therapy) for the management of advanced inoperable HCC.

3.1. Monotherapy (single-agent) systemic chemotherapy

Several single-agent systemic chemotherapies have been tested in patients with advanced HCC, such as: doxorubicin, pegylated liposomal doxorubicin (PLD), epirubicin, mitoxantrone, 5-fluorouracil (5-FU), etoposide, capecitabine, gemcitabine, irinotecan, and thalidomide.

3.1.1. Doxorubicin

Single-agent doxorubicin is the most frequently investigated systemic chemotherapeutic agent in patients with locally advanced unresectable HCC [33].

In 1975, Olweny et al. [34] (phase II clinical trial) studied the role of doxorubicin (75 mg/m^2 intravenously once every 3 weeks) in 14 patients with primary advanced inoperable HCC. Eleven patients (78.5%) achieved objective responses (78.5%). However, successive studies (from 1977 to 2005) failed to validate Olweny et al. [34] study and rather exhibited that the actual objective response rate with single-agent doxorubicin (dose: 75 mg/m^2) was roughly equal to or less than 20% [35-40]. Additional large-sized subsequent randomized trials employing lower doses of single-agent doxorubicin (dose: equals to or less than 60 mg/m^2 per schedule) were shown to yield even lower objective response rates ranging from 4% to 10.1% [41-42].

In 1988, Lai et al. [39] (prospective randomized trial) studied the efficacy of doxorubicin (60-75 mg/m^2) versus the best supportive care (no chemotherapy) in 60 and 46 patients, respectively. The doxorubicin-treated group achieved higher statistically significant median OS than the no chemotherapy group (10.6 vs. 7.6 weeks; P = 0.036). However, life-threatening toxicities (cardiotoxicity and septicemia) occurred in the doxorubicin-treated group (25%). The study concluded that despite the minimal survival advantages of doxorubicin, it was associated with serious complications and should not be recommended for the management of inoperable HCC.

In 2007, Gish et al. [42] (phase III randomized controlled trial) examined the efficacy of doxorubicin versus nolatrexed in 445 patients. The doxorubicin-treated group achieved a higher statistically significant OS than nolatrexed-treated group (32.3 vs. 22.3 weeks; P = 0.0068). The objective response rates for doxorubicin-treated and nolatrexed-treated groups were 4% and 1.4%, respectively. The most frequently observed toxicities for doxorubicin-treated and nolatrexed-treated groups were alopecia and grade 3/4 (thrombocytopenia, vomiting, diarrhea, and stomatitis), respectively.

In conclusion, single-agent doxorubicin can be effective in 20% of patients; however, OS advantages are uncertain. Moreover, its cardiotoxicity is a major limiting adverse event. Combination therapy with other systemic cytotoxic chemotherapeutics and novel molecularly targeted therapies are in progress.

3.1.2. Pegylated liposomal doxorubicin (PLD)

The efficacy of single-agent PLD has been studied in a pilot study [43] and two phase II trials [44, 45] as an initial therapy in patients with advanced inoperable HCC. The research outcomes were discouraging. Combination chemotherapeutic remedies containing PLD are elaborated below.

3.1.3. Epirubicin and mitoxantrone

In comparison with doxorubicin, previous retrospective studies and phase II trials demonstrated that single-agent epirubicin [46, 47] and mitoxantrone [48, 49] share relatively comparable antineoplastic activity as well as relatively equal or slightly higher objective response rates (epirubicin, range: 9.1%-23%; mitoxantrone, range: 23.7%-27.2%). Cardiotoxicity is a major limiting adverse event. Both chemotherapeutics are not commonly used.

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3.1.4. 5-Fluorouracil (5-FU)

In one prospective randomized controlled trial by Choi et al. [37], there were higher objective response rates and median OS in HCC patients receiving doxorubicin versus those patients receiving 5-fluorouracil-containg quadruple therapy (5-fluorouracil, methotrexate, cyclophosphamide, and vincristin) therapy (24% vs. 0%, respectively; 14.4 vs. 6.5 weeks, respectively).

In 1995, Porta et al. [50] (preliminary results of a phase II study) explored the role of 5-FU (370 mg/m^2) plus racemic leucovorin (200 mg/m^2) for 5 successive days in 25 patients with advanced inoperable HCC. The regimen cycle was continual every 28 days until disease progression took place. Seven objective responses (28%) were achieved as follows: 6 partial (24%) and 1 complete (4%) responses. Only 5 patients (20%) displayed stable disease, whereas 13 patients exhibited disease progression. Regimen-related adverse events were mild and no grade 4 toxicity occurred. Specifically, 1 patient (4%) experienced grade 1 skin toxicity, 2 patients (8%) grade 3 granulocytopenia, 7 patients (28%) grade 2 nausea, 10 patients (40%) grade 2 diarrhea, and 11 patients (44%) grade 2/3 mucositis. The study concluded that (5-FU plus racemic leucovorin) chemotherapeutic schedule could provide objective responses in patients with advanced unresectable HCCs, which are frequently regarded as chemoresistant neoplasms.

In 1995, Tetef et al. [51] (phase II trial) examined the role of 5-FU (250-450 mg/m^2/day for 5 days by means of an intravenous [IV] bolus) in combination with calcium leucovorin (500 mg/m^2/day for 5 days by means of continuous IV infusion) in 15 patients with advanced unresectable HCC. The regimen was given on a 28-day schedule. Overall, 8 (53%), 6 (40%), and 1 (7%) patients experienced stable disease, disease progression, and partial response, respectively. The median duration of stable disease was 5.7 months, whereas the median TTP was 2.7 months and the partial response persisted only for 2.4 months. Overall, the median OS was roughly 4 months. Regarding regimen-related adverse events, only 9% and 10% of chemotherapeutic schedules were impacted negatively by grade 3/4 hematological toxicity and grade 3/4 gastrointestinal toxicity, respectively. The study concluded that (5-FU plus calcium leucovorin) chemotherapeutic schedule is ineffective highlighting the chemoresistant characteristic of HCC to the modulated 5-FU.

In conclusion, objective response rates with single-agent 5-FU have been frequently low despite the addition of modulating agents such as leucovorin. Advantageously, despite the widespread hepatic metabolism, satisfactory doses of 5-FU can be often administered in HCC patients with hepatic insufficiency or jaundice.

3.1.5. Etoposide

An early prospective randomized controlled trial demonstrated higher ORR (however no survival advantages) when single-agent doxorubicin was contrasted to single-agent etoposide (28% vs. 18%, respectively)[52].

Further trials are underway to test its true efficacy both singly and in combination with other drugs in the management of HCC.

3.1.6. Capecitabine

In 2004, Patt et al. [53] (retrospective analysis) studied the role of single-agent oral capecitabine (1000 mg/m^2 twice daily for 2 weeks; treatment was repeated every 3 weeks) in 37 patients with advanced inoperable HCC. Of the 37 patients, 22 patients had not received any previous treatment. Objective responses were attained in 9 patients (24.3%), comprising 1 complete response. The median OS was 10.1 months. Grade 3 thrombocytopenia happened in 3 patients. The study concluded that capecitabine is well tolerated and offers only minimal antitumor activities against HCC.

In 2013, Brandi et al. [54] (single-center phase II study) examined the role of single-agent metronomic capecitabine (500 mg twice daily) in 90 patients with advanced HCC. The patients were divided into two groups. The first group consisted of 59 patients who had received no prior therapy. Three objective responses (1 partial and 2 complete) were attained whereas 30 patients experienced stable disease. The median PFS and OS were 6.03 and 14.47 months, respectively. The second group consisted of 31 patients who received prior therapy with sorafenib. No objective responses (neither partial nor complete) were attained whereas 10 patients experienced stable disease. The median PFS and OS were 3.27 and 9.77 months, respectively. The first group (capecitabine-treated) was matched to untreated HCC patients from the Italian Liver Cancer group. The capecitabine-treated group achieved a higher statistically significant median OS than the matched untreated patients (15.6 months vs. 8.0 months; $P = 0.043$). The study concluded that metronomic capecitabine seems to offer anti-neoplastic activities in therapy-naive and sorafenib-treated patients.

The superiority of single-agent sorafenib over capecitabine was confirmed in a single-center, open-label, phase II trial by Abdel-Rahman et al. [55]. The study enrolled 52 treatment-naive HCC patients who were randomized to get administered sorafenib (400 mg twice daily) or capecitabine (100 mg mg/m^2 twice daily). In comparison with the capecitabine-treated group, the sorafenib-treated group achieved higher statistically significant median PFS (6 months vs. 4 months; $P < 0.005$) and OS (7.05 vs. 5.07 months; $P < 0.016$). Four objective responses (3 partial and 1 complete) were achieved in sorafenib-treated group; only 1 partial response was achieved in capecitabine-treated group. The most commonly observed toxicities in sorafenib-treated and capecitabine-treated groups were hand-foot skin reaction and hyperbilirubinemia, respectively. The study concluded that (1) sorafenib is superior to capecitabine in patients with HCC and (2) capecitabine should not be employed as a single-agent therapy; instead, combination regimens with sorafenib should be attempted.

In conclusion, the DFS and OS advantages of single-agent fluoropyrimidines (5-FU and capecitabine) are uncertain, partly due to inconsistent study participants (treatment naive and previously treated). Combination regimens with other chemotherapeutic agents should be examined in phase II/III clinical trials.

3.1.7. Gemcitabine

Single-agent gemcitabine chemotherapy has showed varied modest results in 3 phase II clinical trials [56-58].

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In 2000, Yang et al. [56] studied the role of gemcitabine (intravenous 1250 mg/m^2 once weekly for 3 weeks followed by a 1-week rest) in 28 chemotherapy-naive patients with inoperable, nonembolizable, locally advanced or metastatic HCC. All study patients received 6 cycles of gemcitabine, as follows: 1250 mg/m^2 once weekly for 3 weeks followed by a 1-week rest. Partial response was attained in 5 of 28 patients (overall response rate: 17.8%). Stable disease was attained in 7 patients (25%). Disease progression occurred in 16 patients (57.2%). The median OS in all the 28 patients and those 5 patients who had partial response was 18.7 and 34.7 weeks, respectively. The median TTP was roughly 12 weeks. Grade 3/4 adverse events mainly comprised equally thrombocytopenia and leucopenia (10.7%) as well as equally anemia and hepatotoxicity (14.3%).

In 2001, Kubicka et al. [57] studied the role of gemcitabine in 20 patients with advanced unresectable HCC. The median number of gemcitabine administration was 7.6 (range: 3-21). The overall response rate was attained in 1 patient (5%), and gemcitabine did not ameliorate the cancer-related symptoms. Grade 3/4 thrombocytopenia was the most commonly observed adverse event (30%).

In 2002, Fuchs et al. [58] studied the role of gemcitabine (intravenous 1000 mg/m^2 once weekly for 3 weeks followed by 1 resting week) in 30 patients with advanced unresectable metastatic HCC. The enrolled patients had received at least one prior modality of systemic therapy in the past. The median number of gemcitabine administration was 2 (range: 1-8). Neither complete nor partial responses were attained. Only 9 patients (30%) attained stable disease (median interval: 7.4 months). The median OS was 6.9 months, whereas the overall 1-year survival was 40%. One patient (3%) suffered grade 3 thrombocytopenia whereas another one patient (3%) suffered hemolytic-uremic syndrome. Additionally, 2 patients (7%) developed grade 4 neutropenia.

In conclusion, although gemcitabine is largely well tolerated, phase II clinical trials of gemcitabine exhibited minimal effects in patients with advanced unresectable HCC and therefore is not recommended. Gemcitabine-based combination therapies are interesting therapeutic targets.

3.1.8. Thalidomide

Single-agent thalidomide chemotherapy has been investigated in 3 early phase II clinical trials -61]. Thalidomide showed lower rates of antineoplastic effects; however, disease stabilization was achieved in up to 33% of patients.

In 2003, Hsu et al. studied the role of low-dose thalidomide (starting dose of 200 mg per day; the dose was gradually upgraded in 100-mg phases up to maximum tolerated dose or 600 mg per day) in 68 patients with advanced unresectable HCC. Four patients (6.3%) attained chemotherapy responses (1 complete and 3 partial), and their AFP levels fell greatly. Moreover, an additional 6 patients experienced more than 50% reduction in their AFP levels post treatment with thalidomide. In total, 10 patients achieved objective response to thalidomide with a median OS of 62.4 weeks (range: 31.2-93.6). For all patients, the median OS was 18.7

weeks, whereas the overall 1-year survival was 27.6%. Only 6 and none patients developed grade 3 and grade 4 thalidomide-related adverse events, respectively.

In 2005, Lin et al. studied the role of thalidomide (starting dose of 200 mg per day; the dose was gradually upgraded in 100-mg phases up to maximum tolerated dose or 800 mg per day) in 27 patients with advanced unresectable HCC. The median daily dose was 300 mg. Only 1 patient achieved near-complete drug response (expressed as reduced AFP level) as well as partial radiological response on computed tomography (CT) imaging. Stable disease of 16-week interval was attained in 2 patients. The median DFS was 6 weeks, whereas the overall OS was 17.6 weeks. Fatigue (81%) and somnolence (62%) were the two most frequent thalidomide-related adverse events. Three patients suffered grade 4 hyperbilirubinemia.

In 2005, Patt et al. [61] studied the role of thalidomide (starting dose of 200 mg per day; the dose was gradually upgraded from 400 mg during the first week to 1000 mg during the fifth week) in 37 patients with advanced unresectable HCC. Overall, 1 (5%), 1 (5%), and 10 (31.3%) patients attained partial response, minor response, and stable disease, respectively. Twenty patients (62.5%) experienced disease progression. The overall OS was roughly 6.8 months. The most frequently observed drug-related adverse events were grade 2/3/4 somnolence in 65% whereas grade 3/4 reactions occurred in 20% of patients.

In conclusion, with gradual dose escalation, thalidomide exhibited well-tolerated toxicity profile. While thalidomide demonstrated lower response rates, it offered disease stabilization in one-third of patients. Future studies should be targeted toward exploring different thalidomide analogs and doses as well as trial of combination therapy with other systemic management modalities. As of now, thalidomide use in the management of advanced HCC is not recommended.

3.1.9. Irinotecan

Single-agent irinotecan chemotherapy has been investigated in two phase II clinical trials for the management of patients with advanced unresectable HCC [62,.

In 2001, O'Reilly et al. (phase II) studied the role of irinotecan (starting dose of 125 mg once weekly for 4 weeks followed by a 2-week rest) in 14 patients with advanced unresectable HCC. The median number of irinotecan cycle administration was 1 (range: 1-6). Partial response was attained in only 1 patient (7%), which lasted for 7 weeks. Transient stable disease was attained in 1 patient (7%). Disease progression occurred in all the 12 remaining patients (86%). Significant irinotecan-related adverse events were noted, mainly nausea, vomiting, diarrhea, fatigue, and neutropenia.

In 2006, Boige et al. (multicenter phase II study) studied the role of irinotecan (dose was adjusted according to total bilirubin level) in 29 patients with advanced unresectable HCC. In total, 0, 1, and 12 patients experienced objective response, minor response, and disease stabilization, respectively. Median TTP was 3.1 months whereas the OS was 7.4 months. Grade 3/4 toxicities primarily compromised diarrhea (17%), anemia (24%), and neutropenia (47%).

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In conclusion, irinotecan had considerable drug-related toxicities (adverse events) and very minimal antitumor effects against advanced unresectable HCC. Single-agent irinotecan chemotherapy is not recommended.

3.2. Combination systemic cytotoxic chemotherapy

Various combinations of systemic cytotoxic chemotherapeutics have been investigated in patients with advanced HCC, such as cisplatin-based, gemcitabine-based, and oxaliplatin-based regimens.

Table 1 exhibits a summary of major phase I to II studies on combination systemic cytotoxic chemotherapy in patients with advanced inoperable HCC.

Overall, cisplatin-based combination chemotherapeutic schedules seem to yield greater objective response rates than non-cisplatin-based combination chemotherapeutic schedules. However, no single combination systemic chemotherapy regimen definitely appeared to offer superior or valuable survival advantages such as TTP, PFS, OS, and disease stabilization.

Regimens containing oxaliplatin plus short-term infusional 5-FU and leucovorin are most frequently utilized in the management of advanced colorectal cancer with hepatic metastases.

In 2013, Qin et al. (multicenter open-label, phase III randomized trial) examined the efficacy of single-agent doxorubicin (50 mg/m^2 once every three weeks) versus modified FOLFOX4 regimen (infusional 5-fluorouracil, leucovorin, and oxaliplatin) in 371 Asian patients with primary locally advanced, inoperable, or metastatic HCC. Of note, 90 of all enrolled 371 patients (24.3%) had cirrhosis secondary to hepatitis B virus infection. In comparison with the doxorubicin group, the modified FOLFOX4 achieved slightly higher PFS (2.93 vs. 1.77 months, respectively), median OS (6.40 vs. 4.97 months, respectively), ORR (8.15%, vs. 2.67%, respectively), and DCR (52% vs. 32%, respectively). On continual follow-up, there was a statistically significant sustainable tendency toward improved OS with FOLFOX4 regimen versus doxorubicin ($P = 0.04$). Modified FOLFOX4-related adverse events were comparable to earlier studies. Both treated groups experienced similar grade 3/4 drug-related toxicities. The study concluded that the propensity toward enhanced OS, PFS, and ORR with modified FOLFOX4 regimen may offer some palliative advantages to the Asian HCC patients; however, a definite OS advantage cannot be deduced from their study, and further research was suggested.

3.3. Interferon alpha (IFNα)

Interferon alpha (IFNα) is an immunomodulatory cytokine (immunotherapy/biotherapy) that has exhibited antineoplastic effects against many neoplasms counting HCC.

3.3.1. IFNα monotherapy

As a minimum, three controlled trials have examined single-agent IFNα therapy in patients with far-advanced unresectable HCC; however, research outcomes were contradictory.

Regimen	Reference	Authors	Year	Combination systemic chemotherapy	*n*	RR (%)	DS (%)	TTP (mon)	PFS (mon)	OS (mon)
Cisplatin-based regimen	[134]	Lee et al.	2004	Cisplatin plus doxorubicin	42	18.9	16.2	6.6	NR	7.3
		Yang et al.	2004	Cisplatin, mitoxantrone, plus continuous infusion 5-FU	63	23.8	NR	2.5	NR	4.9
		Ikeda et al.	2005	Cisplatin, mitoxantrone, plus continuous infusion 5-FU	51	27	NR	NR	4	11.6
	[137]	Boucher et al.	2002	Cisplatin, epirubicin plus infusional 5-FU	21	14.5	NR	5.9	NR	10
	[138]	Park et al.	2006	Cisplatin, doxorubicin plus capecitabine	29	24	20.7	3.7	NR	7.7
	[139]	Shim et al.	2009	Cisplatin plus capecitabine	178	19.7	45	NR	2.8	10.5
	[140]	Lee et al.	2009	Cisplatin plus capecitabine	32	6.3	34.3	2	NR	12.2
Gemcitabine-based regimen	[141]	Parikh et al.	2005	Gemcitabine and cisplatin	30	20	43	4.5	NR	5.3
	[142]	Chia et al.	2008	Gemcitabine and cisplatin	15	6.7	20	NR	1.5	4.5
	[143]	Lombardi et al.	2011	Gemcitabine plus pegylated liposomal doxorubicin	41	NR	24	NR	5.8	22.5
Oxaliplatin-based regimen	[144]	Louafi et al.	2007	Gemcitabine plus oxaliplatin (GEMOX)	34	18	58	NR	6.3	11.5
	[145]	Mir et al.	2012	Gemcitabine plus oxaliplatin (GEMOX)	18	18.8	18.8	NR	3.2	4.7
	[146]	Zaanan et al.	2013	Gemcitabine plus oxaliplatin (GEMOX)	204	22	66	NR	4.5	11
	[147]	Boige et al.	2007	Gapecitabine plus oxaliplatin (XELOX)	50	6	72	NR	4.1	9.3

n: sample size; RR: response rate; DS: disease stabilization; TTP: time to progression; PFS: progression-free survival; OS: overall survival; NR: not reported; mon: months

Table 1. Summary of major phases I and II studies on combination systemic chemotherapy in patients with advanced inoperable HCC

In 1989, Lai et al. (Chinese prospective randomized trial) explored the efficacy of single-agent IFNα versus single-agent doxorubicin in 75 patients with advanced unresectable HCC. The IFNα group achieved a higher median OS than the doxorubicin group (8.3 months vs. 4.8 months), although it was not statistically significant. Doxorubicin-related adverse events included neutropenia and cardiotoxicity in approximately 25% of patients. Conversely, IFNα-related adverse events included adrenal gland failure and dementia in roughly 3.8% of patients. Overall, IFNα achieved statistically significant robust cancer regression ($P = 0.00199$),

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less worsening cancers ($P = 0.00017$), less life-threatening long-lasting bone marrow suppression ($P = 0.01217$), and less severe drug-related adverse events ($P = 0.01383$) when compared to doxorubicin group. The study concluded that IFNα was superior to doxorubicin in terms of cancer control as well as less lethal bone marrow suppression and adverse events.

In 1993, Lai et al. [66] (randomized controlled trial) examined the efficacy of IFNα (intramuscular 50×10^6 IU/m^2 3 times weekly) and no anticancer treatment in 35 and 36 advanced unresectable HCC Chinese patients, respectively. The IFNα group achieved a higher median OS than no anticancer group (14.5 vs. 7.5 months; $P = 0.0471$), as well as significant robust cancer regression ($P < 0.0001$) and less worsening (progressive) cancers ($P = 0.001$). Despite the IFNα dose was comparatively high, it was well tolerated; roughly 34% of patients had one-third to one-half dosage decreases as a result of continuous generalized weakness. Moreover, type 2 diabetes mellitus patients experienced mental worsening that could be related to IFNα treatment. The study concluded that IFNα was beneficial in a subset of Chinese patients with advanced unresectable HCC, in terms of cancer control (tumor regression) and extended disease-related survival expectancy.

However, the above-mentioned results of Lia et al. [66] were not validated and reciprocated in a second randomized clinical trial by Llovet et al. in 58 advanced HCC patients with ineligibility to undergo surgery, transplantation, or other treatment modalities. The study took place in year 2000 and randomized patients to receive either IFNα ($n = 30$) or BSC ($n = 28$). Of the 30 IFNα-treated patients, only 2 patients (6.6%) achieved objective partial responses. Although the 1-year and 2-year survival rates were higher in IFNα-treated vs. BSC groups (58% vs. 38% and 36% vs. 12%, respectively), there were no statistical significant differences. Although IFNα dose was greatly decreased, 23 (76.7%) of 30 patients experienced severe unbearable drug-related adverse events (toxicities) resulting in drug suspension in exactly 13 patients. The study concluded that IFNα was not appropriately endured by advanced HCC patients, and its administration did not yield beneficial advantages in the context of cancer progression and OS rates.

In conclusion, studies on single-agent IFNα therapy showed conflicting outcomes. Additionally, dose-related toxicities were frequent despite lower doses were administered. Clear-cut clinical benefits are uncertain and further research is needed.

3.3.2. IFNα-based combination therapy

There are two major IFN-based combination chemotherapeutic regimens: PIAF regimen and (5-FU plus IFNα) regimen.

3.3.2.1. PIAF regimen

PIAF regimen is composed of cisplatin, IFNα, doxorubicin, and infusional 5-FU. PIAF regimen has been shown to exhibit active antitumor effects despite its significantly lethal drug-related toxic adverse events in patients with advanced HCC 8-. For example, in 1999, Leung et al. administered PIAF regimen in 50 patients. Around 13 patients (26%) experienced a partial response. The median OS was 8.9 months. The most frequent toxicities were mucositis and

myelosuppression. There were two events of drug-related mortality as a result of neutropenic sepsis.

In 2005, Yeo et al. (multinational randomized phase III study) examined the efficacy of single-agent doxorubicin (60 mg/m^2 every three weeks) versus PIAF regimen (cisplatin: 20 mg/m^2 on days 1-4; IFNα: 5 MU/m^2 subcutaneously on days 1-4; doxorubicin: 40 mg/m^2 on day 1; and 5-FU 400 mg/m^2 on days 1-4) in 188 chemotherapy-naive patients with inoperable HCC. Although not statistically significant, the PIAF-treated group achieved higher ORR and median OS than the single-agent doxorubicin group (20.9% vs. 10.5% and 8.7 months vs. 6.8 months, respectively). However, as expected, drug-related adverse events were more noticeable and statistically significant in the PIAF-treated group than in doxorubicin-treated group, as follows: grade 3/4 hypokalemia (7% vs. 0%, respectively), grade 3/4 neutropenia (82% vs. 63%, respectively), and grade 3/4 thrombocytopenia (57% vs. 24%, respectively). The study concluded that although the PIAF-treated group achieved higher overall ORR and beneficial survival outcomes, the difference was statistically insignificant and not worthwhile. Additionally, PIAF regimen incurred far greater statistically significant drug-related adverse events.

One potential clarification for the Yeo et al. study's failure to demonstrate a survival advantage may be attributed to the improper patient selection. Subsequently, the correlation significance between results of PIAF regimen and baseline liver function was exhibited in a retrospective analysis by Leung et al.. The study analyzed a series of roughly 150 patients with advanced inoperable HCC who received prior therapy with PIAF regimen. The study concluded that good risk patients (normal baseline total bilirubin levels and noncirrhotic liver) achieved higher statistically significant objective responses (50% vs. 6%) and prolonged survival rates than bad risk patients (total serum bilirubin level >0.6 mg/dL and cirrhotic liver) when medicated with systemic PIAF regimen.

In short, the role of PIAF chemotherapeutic schedule in the management of advanced inoperable HCC remains unclear. Bearing in mind the lethal drug-related toxicity profile, it should be indicated only for physically and biochemically fit patients who possess appropriate performance status and minimal hepatic insufficiency.

3.3.2.2. 5-FU plus IFNα

Stuart et al. and Patt et al. had conflicting results. In 1996, Stuart et al. administered 5-FU (750 mg/m^2 weekly) plus IFNα (9 MU three times weekly) in 10 patients with advanced HCC. The ORR and the OS were 0% and 10 months, respectively. It was concluded that the 5-FU plus IFNα regimen was not effective and drug-related toxicities were highly significant.

Moreover, in 2003, Patt et al. (phase II) administered 5-FU (200 mg/m^2/day for 3 weeks every 4-week interval) plus IFNα2b (4 million U/m^2 for three times weekly) in 43 patients with advanced HCC. Liver cirrhosis was present among 71% of HCC. ORR was evaluable in only 28 patients, and it was 14% (all were partial responses). For all patients, the OS was 15.5 months. The study concluded that 5-FU plus IFNα is effective and can be tolerated by cirrhotic patients.

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Of note, several studies by Sakon et al., Ota et al., and Nagano et al. have examined the combination of systemic IFNα with intrahepatic arterial 5-FU in patients with primary advanced inoperable HCC complicated by major portal vein thrombosis. Interestingly, ORRs ranging from 33% to 73% were achieved. More specifically, chemotherapy responsiveness, TTP, and OS rates were higher in IFN-alpha type 2 receptor (IFNAR2)-positive HCC versus IFNAR2-negative HCC. It was concluded that chemotherapy responsiveness, TTP, and OS are significantly linked to expression of IFNAR2 in HCC patients receiving 5-FU plus IFNα combined chemotherapeutic regimen.

In conclusion, combinations of chemotherapeutics with interferon alpha (IFNα) seem to be active. However, definitive survival benefits are not clear.

3.4. Conclusion

The employment of systemic chemotherapy has been accompanied by low ORRs, no survival advantages, and high incidences of drug-related toxicities and adverse events. Moreover, there are no adequate data to endorse or approve any single-agent or combined chemotherapeutic regimens for the management of patients with advanced inoperable HCC [76].

Recently, chemotherapy is not being employed routinely for patients with advanced inoperable HCC. This tendency can be attributed to three major rationales:

1. First, HCC is largely a chemoresistant neoplasm. This may be related to expression of several drug resistance genes, such as heat shock proteins, p53 mutations, glutathione-S-transferase, p-glycoprotein, and multidrug resistance gene (MDR-1) -81].

2. Second, the status of underlying liver cirrhosis and its associated complications (for example, hepatic encephalopathy, portal hypertension, hypoalbuminemia, coagulopathies, portal venous thrombosis, ascites, hypersplenism, platelet sequestration, varices and gastrointestinal bleeding, discrepant drug binding, altered biochemical distribution, and disrupted pharmacokinetics) in the vast majority of patients precludes the choice and effective dosing administration of substantial proportions of anticancer chemotherapeutics. Systemic chemotherapeutics are generally not well tolerated by patients with substantial underlying hepatic insufficiencies, and this is a major limitation. In one study by Nagahama et al. [82], there were no objective responses among HCC patients with bilateral disease (2 hepatic lobes), 50% or more of hepatic involvement, ascites, total serum bilirubin >2.0 mg/dL, portal venous thrombosis, and poor functional status of 2-3.

3. Third, the vast majority of studies have been conducted in diverse patient populations with various clinicopathological factors such as old vs. young, cirrhosis due to hepatitis B or C virus vs. cirrhosis due to alcoholism, chemotherapy-naive patients vs. previously chemotherapy-treated patients, etc. Such population diversity is expected to result in inconsistent enrolling criteria and study outcomes among the various controlled trials. Moreover, almost all controlled clinical trials are negatively impacted by insufficient sample size, improper study controls, and inappropriate study primary/secondary end points.

The arrival of novel molecularly targeted therapy (specifically sorafenib) is rapidly emerging as the standard of care in patients with advanced inoperable HCC.

That being said, systemic chemotherapy may still be regarded in patients whom their HCC get worse while on sorafenib and whom baseline liver function and performance status are adequate enough to endure it.

The chemotherapy-related adverse events of any single-agent or combined regimen should be deliberated cautiously in patients with progressive inoperable HCC, multiple comorbidities, and very short life expectancy. Generally speaking, systemic chemotherapy should be selectively administered to physically and medically fit patients who possess appropriate hepatic functional reserve. Moreover, such administration should be ideally considered only within the context of phase II and III clinical trials.

The choice of systemic chemotherapy should be guided by patients' functional hepatic reserve, physical fitness, prognosis, life expectancy, and most importantly availability of the best evidence-based medicine (randomized controlled phase III clinical trials).

Lastly, the reactivation of viral hepatitis may take place in HCC patients receiving aggressively exhaustive systemic chemotherapeutic regimens. Accordingly, it is crucial and greatly recommended to maintain antiviral therapies, whenever deemed necessarily.

4. Novel molecularly targeted therapy

These therapies are targeted against specific molecular signaling pathways involved in HCC carcinogenesis. Several nonrandomized and phase I, II, and III clinical trials have been conducted to examine the role of novel molecularly targeted therapy (monotherapy or combination therapy) for the management of advanced inoperable HCC.

4.1. Sorafenib

Sorafenib is the official first Food and Drug Administration (FDA)-approved monotherapy drug for the management of patients with advanced unresectable HCC, ineligible for surgical resection, liver transplantation, and loco-regional therapies. Several prospective studies have evaluated the efficacy of sorafenib as single-agent (monotherapy) and combination therapy with systemic cytotoxic chemotherapy and loco-regional therapy.

4.1.1. Sorafenib monotherapy

A total of 7 studies have been conducted on single-agent sorafenib with a sum of 1072 patients.

Table 2 exhibits a summary of major phase I and III studies on single-agent sorafenib for the management of patients with advanced inoperable HCC.

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Ref.	Authors	Year	Phase	*n*	Age (yr)	Gender (%)		CPS (%)			Hepatitis		DCR (%)	TTP (mon)	OS (mon)	Toxicities		
						Male	Female	A	B	C	HBV	HCV				Diarrhea	Fatigue	HFS
[88]	Furuse et al.	2008	I	27	70	93	17	48	52	0	15	74	83	4.9	15.6	0	0	27
[148]	Castroagudin et al.	2008	I	13	64	100	0	92	NR	NR	0	23	62	NR	2	82	91	18
[149]	Abou-Alfa et al.	2006	II	137	69	88	12	72	28	0	17	48	36	4.2	9.2	8	10	5
[150]	Massa et al.	2008	II	16	72	88	12	NR	NR	NR	NR	NR	64	3	15	6	6	6
[87]	Yau et al.	2008	II	51	56	93	7	71	26	3	90	6	26	3	5	16	20	8
[84]	Llovet et al.	2008	III (sorafenib)	299	65	87	13	95	5	0	19	29	43	5.6	10.7	1	3	3
			III (placebo)	303	66	87	13	98	2	0	18	27	32	2.8	7.9	1	0.6	0.3
[85]	Cheng et al.	2009	III (sorafenib)	150	51	85	15	97	3	0	71	11	35	2.8	6.5	6	3	11
			III (placebo)	76	52	87	13	97	3	0	78	4	16	1-4	4.2	1	0	0

n: sample size; yr: year; CPS: Child-Pugh score; HBV: hepatitis B virus; HCV: hepatitis C virus; DCR: disease control rate; TTP: time to progression; OS: overall survival; HFS: hand-foot syndrome; NR: not reported; mon: months.

Table 2. Summary of major phases I-III studies on single-agent sorafenib for the management of patients with advanced inoperable HCC

The numbers of phase I, II, and III studies were 2, 3, and 2, respectively. Overall, the vast majority of patients were elderly (above 50 years), males, CPS-A/CPS-B, and HBV/HCV positive. The DCR ranged from as low as 26% to as high as 82%. TTP ranged from 3 to 5.5 months, whereas OS ranged from 3 to 15.6 months. The most frequent sorafenib-related toxicities were fatigue (range: 0-91%), diarrhea (range: 0-82%), and hand-foot syndrome [HFS] (range: 3-27%).

The two high-quality, large-sized, randomized placebo-controlled phase III trials were the SHARP and Asia-Pacific reports. In both reports, the greater proportions of patients had CPS-A cirrhosis, and these proportions were almost similar (95% and 97%, respectively). However, the occurrence of hepatitis B infection (HBV) was different (19% vs. 71%, respectively). In the SHARP report, in comparison with placebo groups, the sorafenib group achieved higher statistically significant median TTP (5.5 vs. 2.8 months, respectively; $P < 0.05$) and OS (10.7 vs. 7.9 months, respectively; $P < 0.05$). Conversely, in the Asia-Pacific report, in comparison with the placebo groups, the sorafenib group achieved higher statistically significant median TTP (2.8 vs. 1.4 months, respectively; $P < 0.05$) and OS (6.5 vs. 4.2 months, respectively; $P < 0.05$).

The noted differences between TTP and OS between SHARP and Asia-Pacific trials were contemplated, and a question was raised as whether etiology of cirrhosis (HBV vs. HCV) influences the therapeutic response to sorafenib. Subsequently, Bruix et al. conducted sub-analyses of SHARP study and showed that the median OS (sorafenib vs. placebo) was highest in patients with HCV cirrhosis (14 vs. 7.4 months; difference: 6.6 months), followed by patients with HBV cirrhosis (9.7 vs. 6.1 months; difference: 3.6 months), and then by patients with underlying alcohol-related liver disease (10.3 vs. 8 months; difference: 2.3 months). The study concluded that HCV (as opposed to HBV) positively influences therapeutic response to sorafenib. Similar conclusions were attained elsewhere in other studies in Korea and Japan.

Exploring prognostic biomarkers of therapeutic responses is necessary. Several molecular (for example, FGF3/FGF4, MET, VEGF/VEGFR, pERK), biochemical (for example, elevated AST) -, and clinical (for example, diarrhea, high blood pressure) [94, 95] factors have been proposed to forecast therapeutic response; however, none has been confirmed and definitely established for employment in clinical practice.

In summary, based on the findings of SHARP and Asia-Pacific phase III trials, sorafenib is the official first Food and Drug Administration (FDA)-approved monotherapy drug for the management of patients with advanced unresectable HCC, ineligible for surgical resection, liver transplantation, and loco-regional therapies [83]. Table 2 exhibits that single-agent sorafenib therapy yields statistically significant, although moderate, clinical improvements in the contexts of DCR, TTP, and OS in males younger than 70 years and have CPS-A cirrhosis. Not much information are existing regarding the effects of single-agent sorafenib therapy in females and in patient populations older than 70 years of age and having advanced CPS-B/CPS-C cirrhosis. Patients with HCV-related cirrhosis have longer OS and higher DCR rates, whereas patients with HBV-related cirrhosis have shorter OS and lower DCR rates in patients receiving sorafenib. The most frequent sorafenib-related adverse events include fatigue, diarrhea, and HFS.

4.1.2. Sorafenib-based combination therapy

Several studies have combined sorafenib with loco-regional and systemic therapies in patients with advanced unresectable HCC. Loco-regional therapies mainly include transarterial chemoembolization (TACE), transarterial radioemobolization (TARE), radiation, and others. Systemic therapies mainly include cytotoxic chemotherapeutics, hormonal (somatostatin analog) therapies, and others.

The most frequently studied sorafenib-based combination regimen is sorafenib plus TACE. A recently published meta-analysis in 2014 by Zhang et al. [96] examined six studies published from 2011 to 2013 (n = 1254 patients) about the efficacy and safety of sorafenib plus TACE versus TACE alone in patients with intermediate to advanced unresectable HCC. The meta-analysis concluded that the combination therapy of sorafenib plus TACE was associated with higher statistically significant ORR (P = 0.021), TTP (P = 0.003), and OS (P = 0.007); however, greater frequency of grade 3/4 adverse events than in the TACE group.

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Prete et al. [97] examined the safety and efficacy of sorafenib plus octreotide in 50 patients with advanced HCC; 16 patients (n = 16) were treatment naive (34%), whereas the rest underwent prior local and/or systemic management. Partial response, stable disease, and disease progression occurred in 10%, 66%, and 24% of patients, respectively. The median TTP and OS were 7 months and 12 months, respectively. Regimen therapy was generally well endured, and hypertension (4%) and diarrhea (6%) were the most common grade 3/4 drug-related adverse side effects. The study concluded that sorafenib plus octreotide regimen is active and well tolerated and signifies a potential therapeutic choice in such patient population with advanced HCC.

Hsu et al. [98] examined the safety and efficacy of sorafenib plus metronomic tegafur/uracil in 53 patients with advanced HCC, all of which (100%) and 72% were CPS-A and Hepatitis B surface antigen positive. Partial response and stable disease occurred in 8% and 49% of patients, respectively. The median TTP and OS were 3.7 months and 7.4 months, respectively. The most common grade 3/4 drug-related adverse side effects included bleeding (8%), HFS (9%), elevated serum lipase enzyme (10%), deranged liver function tests (13%), and generalized weakness (15%).

Petrini et al. [99] investigated the safety and efficacy of sorafenib plus 5-FU in 38 patients with advanced HCC. DCR was 48%, whereas the median TTP and OS were 7.6 months and 12.2 months, respectively. The most common drug-related adverse side effects were HFS (55%) and diarrhea (13%).

Yau et al. [100] investigated the safety and efficacy of sorafenib plus capecitabine plus oxaliplatin in 51 patients with advanced or metastatic HCC (phase II trial). The vast majority of patients had CPS-A (98%) and HBV infection (84%). DCR was 75%, whereas the median TTP and OS were 7.1 months and 10.2 months, respectively. The most common drug-related adverse side effects were HFS (73%) and diarrhea (69%).

Richly et al. [101] investigated the safety and efficacy of sorafenib plus doxorubicin in 47 patients with advanced or metastatic HCC (phase II trial). All patients had CPS-A (100%). DCR was 62%, whereas the median TTP and OS were 6.4 months and 13.7 months, respectively. The most common drug-related adverse side effects were HFS (6%), diarrhea (11%), and generalized weakness (6%).

There was only one randomized, placebo-controlled, phase III trial that examined the efficacy of doxorubicin plus sorafenib (n = 47) versus doxorubicin plus placebo (n = 49) in patients with advanced unresectable HCC [102]. In contrast to the doxorubicin plus placebo group, the doxorubicin plus sorafenib group achieved higher statistically significant DCR (62% vs. 29%, respectively), TTP (6.4 vs. 2.8 months, respectively), and OS (13.7 vs. 6.5 months, respectively). The frequencies of drug-related adverse events were comparable to those for monotherapies. Despite the survival benefits associated with doxorubicin plus sorafenib, the combination of doxorubicin plus sorafenib is not yet indicated for routine clinical use.

In summary, studies of sorafenib-based combination therapy report better DCR, TTP, and OS benefits when compared to single-agent sorafenib therapy, without increased frequencies of excessive treatment-related toxicities and adverse events. However, the vast majority of the

conducted sorafenib-based combination therapy studies were quite small-sized case series reporting preliminary findings, and comprehensive data about patient characteristics and clinical outcomes were not often provided. Thus, it is improper to compare such studies. Moreover, in the only phase III trial by Abou-Alfa et al. [102], it was demonstrated that sorafenib plus doxorubicin regimen is more efficacious than doxorubicin alone but does not automatically deliberate that combination therapy (doxorubicin plus sorafenib) is better than single-agent doxorubicin alone. Further research is needed.

4.1.3. Safety and efficacy of sorafenib in hepatic dysfunction

The safety of sorafenib in patients with hepatic dysfunction, as determined by Child-Pugh score (CPS), has been explored.

In 2011, Abou-Alfa et al. [103] explored the efficacy and safety of sorafenib in HCC patients with CPS-A (n = 98) and CPS-B (n = 38). In comparison with CPS-A patients, CPS-B patients achieved lower statistically significant median duration of therapy (1.8 vs. 4 months, respectively) and OS (3.2 vs. 9.5 months, respectively). Moreover, grade 3/4 adverse events took place in both CPS-A and CPS-B patients and encompassed encephalopathy (3% vs. 13%, respectively), ascites (3% vs. 5%, respectively), and hyperbilirubinemia (14% vs. 53%, respectively).

Moreover, Pinter et al. [104] examined the efficacy and safety of sorafenib in HCC patients with CPS-A (n = 26), CPS-B (n = 23), and CPS-C (n = 10). Respectively, the median OS was 8.3, 4.3, and 1.5 months. It was concluded that sorafenib is questionable to offer survival advantages in patients with CPS-C cirrhosis.

Furthermore, Lencioni et al. [105] examined the safety and efficacy of sorafenib in 1586 patients with liver dysfunction in their first interim analysis of the Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib (GIDEON). CPS-B patients experienced more serious adverse events than CPS-A patients (60% vs. 3%, respectively), higher rates of treatment termination (40% vs. 25%, respectively), and higher frequencies of mortality during treatment up to 1 month from the latest sorafenib dose administration (37% vs. 18%, respectively).

However, Raoul et al. [106] in a subanalysis of SHARP trial concluded that sorafenib was safe and effective in patients with mild to moderate liver dysfunction (equal to or greater than 1.8 times the upper limit of normal) without events of increased hepatic toxicities.

In conclusion, sorafenib has better efficacy and safety profiles in HCC patients with CPS-A than CPS-B and CPS-C. For HCC patients with CPS-B, standard dosing should be initiated and then doses can be adjusted accordingly, whenever deemed necessary. Sorafenib is not recommended for HCC patients with CPS-C. Further research is needed.

4.1.4. Safety and efficacy of sorafenib post liver transplantation

There are minimal data regarding the safety and efficacy of sorafenib plus immunosuppressive therapies (such as mammalian target of rapamycin [mTOR] or calcineurin inhibitors) in patients with recurrent HCC post orthotopic liver transplantation (OLT).

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The largest experienced was reported by Gomez-Martin et al. [107]. Twenty-six patients had recurrent HCC post OLT. Ten and sixteen patients received sorafenib doses at 800 mg and 400 mg daily, respectively, in addition to anti-mTOR as an immunosuppresive therapy post OLT. The overall DCR was 54%, whereas the overall TTP and OS were 6.8 and 19.3 months, respectively. Diarrhea (13%, probably due to sorafenib treatment) and mucositis (8%, probably due to anti-mTOR treatment) were the most frequent adverse events.

However, higher frequencies of therapy-related toxicities and adverse events were documented in other studies combining sorafenib and anti-mTOR [108-110]. For instance, Staufer et al. [109] reported grade 3/4 adverse events in 92% of patients, 77% of whom terminated sorafenib therapy. However, partial response and stable disease were attained in 1 and 4 patients, respectively.

In summary, the combination of sorafenib plus anti-mTOR is feasible in recurrent HCC patients following OLT. However, therapy should be carefully checked due to the probability of severe adverse events. Dose modification may be needed.

4.2. Antiangiogenic agents

HCCs are largely vascular neoplasms as increased expressions of micro-vessel concentration and vascular endothelial growth factor (VEGF) have been identified [111-114]. The increased expression of VEGF has been linked to poorer survival outcomes [115-117]. Thus, the inhibition of angiogenesis denotes a highly desired therapeutic target in patients with advanced inoperable HCC. Numerous antiangiogenic drugs have already been introduced in clinical studies in monotherapies and combined therapies. Such drugs include bevacizumab, sunitinib, brivanib, pazopanib, inifanib (ABT-869), cediranib (AZD2171), selumetinib (AZD6244), orantinib (TSU-68), ramucirumab, vatalanib (PTK787/ZK 222584), tivantinib, and others.

In a randomized, placebo-controlled, double-blind, phase III trial (BRISK-PS study) by Llovet et al. [118], a total of 395 HCC patients—who failed sorafenib treatment (during or after therapy) or who were ineligible for sorafenib treatment in the first place—were enrolled in the study. Patients were randomized to receive brivanib (800 mg orally once per day) plus best supportive care (BSC) or placebo plus BSC. In brivanib versus placebo groups, the median OS was 9.4 months vs. 8.2 months ($P = 0.3307$), respectively, whereas TTP was 4.2 months vs. 2.7 months ($P < 0.001$), respectively. Treatment-related study termination occurred in 23% and 7% of brivanib and placebo groups, respectively. Grade 3/4 decreased appetite (10%), hyponatremia (11%), fatigue (13%), and hypertension (17%) were the most common drug-related harmful frequencies. The study concluded that patients who were previously managed with sorafenib, brivanib therapy did not substantially improve OS.

Tivantinib (ARQ 187) is a selective oral inhibitor of c-Met (tyrosine kinase receptor) with multiple roles in neoplastic cell proliferation, migration, invasion, and angiogenesis [33]. Santoro et al. [119] conducted a randomized placebo-controlled phase II trial and examined the role of tivantinib as a second-line novel molecularly targeted therapy in patients with advanced HCC. Major DCR, TTP and DFS advantages were attained in Met+ patients, with an initial OS inclination favoring tivantinib (HR = 0.47) and no negative effects in Met- patients.

For Met+ patients, tivantinib achieved higher DCR (50% vs. 20%) and OS (7.2 months vs. 3.8 weeks) than placebo-treated group [33, 119]. Four drug-related mortalities happened in tivantinib group. Grade 3/4 adverse events in tivantinib group included: neutropenia (14%) and anaemia (11%); none occurred in the placebo groups. The study concluded that tivantinib (compared to placebo) substantially benefited second-line HCC patients, particularly if Met+ patients with well-tolerated drug safety dosing at 240 mg twice daily. There is an ongoing prospective, randomized, double-blind, phase III study of tivantinib in Met-high advanced unresectable HCC patients with one previous administration of systemic therapy [33].

Table 3 exhibits a summary of major phase I and II studies on antiangiogenesis monotherapies in patients with advanced HCC. Among the antiangiogenic drugs, bevacizumab stands out as the most effective single-agent novel molecularly targeted therapy. Objective response and disease stabilization rates can be achieved in 7%-13% and 54%-57%, respectively, whereas PFS and OS durations can achieve durations of 3.5-6.9 months and 12.4 months, respectively. However, the drug-related toxicities of hypertension as well as major bleeding and thrombo-embolic events are major limiting factors [120-122].

	Reference	Authors	Year	Phase	Single-agent therapy	*n*	RR (%)	DS (%)	TTP (mon)	PFS (mon)	OS (mon)
Antiangiogenic agents	[122]	Schwartz et al.	2006	II	Bevacizumab	30	6.7	57	6.4	NR	NR
	[120]	Malka et al.	2007	II	Bevacizumab	30	12.5	54	NR	3.5	NR
	[121]	Siegel et al.	2008	II	Bevacizumab	46	13	NR	NR	6.9	12.4
	[151]	Hoda et al.	2008	II	Sunitinib	23	6	35	NR	NR	NR
	[152]	Zhu et al.	2009	II	Sunitinib	34	2.9	47	4.1	3.9	9.8
	[153]	Faivre et al.	2009	II	Sunitinib	37	2.7	35	5.3	3.7	8
	[154]	Koeberle et al.	2010	II	Sunitinib	45	2	40	2.8	2.8	9.3
	[155]	Finn et al.	2012	II	Brivanib	46	4.3	41.3	2.7	NR	9.79
	[156]	Yau et al.	2009	I	Pazopanib	27	7	41	4.6	NR	NR
	[157]	Toh et al.	2009	II	Inifanib (ABT-869)	44	8.7	NR	3.7	3.7	9.8
	[158]	Alberts et al.	2007	II	Cediranib (AZD2171)	28	0	NR	2.8	NR	5.8
	[159]	O'Neil et al.	2009	II	Selumetinib (AZD6244)	19	0	37.5	2	NR	NR
	[160]	Kanai et al.	2010	I/II	Orantinib (TSU-68)	35	8.6	42.8	2.1	NR	13.1
	[161]	Zhu et al.	2010	II	Ramucirumab	42	NR	50	NR	4.3	NR
	[162]	Koch et al.	2007	I	Vatalanib (PTK787)	18	0	50	NR	NR	7.3
Anti-EGFR agents	[128]	Philip et al.	2005	II	Erlotinib	38	7.9	59	NR	3.2	13
	[129]	Thomas et al.	2007	II	Erlotinib	40	0	43	NR	3.1	11
	[163]	O'Dwyer et al.	2006	II	Gefitinib	31	3	22.5	NR	2.8	6.5
	[164]	Ramanathan et al.	2009	II	Lapatinib	57	5	35	NR	2.3	6.2

	Reference	Authors	Year	Phase	Single-agent therapy	*n*	RR (%)	DS (%)	TTP (mon)	PFS (mon)	OS (mon)
	[165]	Lin et al.	2008	II	Imatinib	15	0	13.3	NR	NR	NR
	[166]	Zhu et al.	2007	II	Cetuximab	30	0	17	NR	1.4	9.6
	[167]	Gruenwald et al.	2007	II	Cetuximab	32	0	44	1.9	2	NR
Anti-mTOR agents	[168]	Blaszkowsky et al.	2011	I/II	Everolimus	28	4	44	NR	3.8	8.4
	[169]	Rizell et al.	2008	II	Sirolimus	21	4.8	23.8	NR	NR	6.5

n: sample size; RR: response rate; DS: disease stabilization; TTP: time to progression; PFS: progression-free survival; OS: overall survival; NR: not reported; mon: months

Table 3. Summary of major phases I and II studies on single-agent novel molecularly targeted therapy in advanced HCC patients

In summary, the inhibition of angiogenesis appears to be feasible and promising. The combination of antiangiogenic drugs (particularly bevacizumab) and other local/systemic therapies may further enhance survival outcomes in patients with advanced inoperable HCC. Additional research is needed and many randomized controlled trials are already in place.

4.3. Epidermal growth factor receptor (EGFR) inhibitors

The expression of numerous EGF family members (such as EGF, EGFR, transforming growth factor-alpha [TGF-α], heparin-binding epidermal growth factor, and others) has been confirmed in many HCC cell tissues [123-127]. Thus, disrupting the EGFR signaling pathway denotes a highly desired therapeutic target in patients with advanced inoperable HCC. Subsequently, two major categories of anti-EGFR have been created: EGFR tyrosine kinase inhibitors and monoclonal antibodies against EGFR. Numerous anti-EGFR drugs have already been introduced in clinical studies in monotherapies and combined therapies. Examples of EGFR tyrosine kinase inhibitors include erlotinib, gefitinib, lapatinib, and imatinib. The most commonly used monoclonal antibody against EGFR is cetuximab.

Among the anti-EGFR drugs, erlotinib stands out the most effective single-agent novel molecularly targeted therapy. In two randomized controlled trials [128, 129] examining the role of erlotinib in patients with advanced unresectable HCC, a total of 78 patients were enrolled. Although ORR ranged from 0% to 9%, the average disease stabilization rate reached 51%, whereas average PFR and OS achieved durations of 3 and 12 months, respectively. However, the most frequent drug-related toxicities were skin-related reactions and diarrhea. Apart from the fairly moderate antitumor effects associated with erlotinib, the remaining drugs belonging to EGFR inhibitors have failed to demonstrate any substantial antineoplastic effects as monotherapies in patients with advanced HCC [33].

Table 3 exhibits a summary of major phase I and II studies on single-agent EGFR inhibitors (novel molecularly targeted therapy) in patients with advanced HCC.

In summary, interfering with EGFR signaling pathway appears to be feasible, promising, and an exciting area for future research. The combination of anti-EGFR drugs (particularly

erlotinib) and other local/systemic therapies may further enhance survival outcomes in patients with advanced inoperable HCC. Additional research is needed and many randomized controlled trials are already in place.

4.4. Mammalian target of rapamycin (mTOR) inhibitors

The significance of the mTOR signaling pathway in HCC pathogenesis was explored in a large-sized research study involving 314 HCC and 37 noncancerous tissues that utilized a variety of molecular-based laboratory techniques [130]. The major study findings were abnormal mTOR signaling (p-RPS6) in 50% of patients, chromosomal gains in rapamycinin-sensitive companion of mTOR (RICTOR) in 25% of patients, and direct correlation between positive p-RPS6 immunohistochemical staining and HCC recurrence post surgical excision. Thus, disrupting the mTOR signaling pathway designates a highly potential therapeutic target in patients with advanced inoperable HCC. Numerous anti-mTOR drugs have already been introduced in clinical studies in monotherapies and combined therapies. Examples of mTOR inhibitors include everolimus, sirolimus, and temsirolimus.

Among the anti-mTOR drugs, everolimus stands out as the most effective single-agent novel molecularly targeted therapy despite the modest antitumor activities. Dose-limiting adverse events are common and include infection, diarrhea, elevated alanine aminotransferase, elevated total bilirubin, cardiac ischemia, and reactivation of HBV/HCV [131].

Table 3 exhibits a summary of major phase I and II studies on single-agent mTOR inhibitors (novel molecularly targeted therapy) in patients with advanced HCC.

In view of the modest antitumor activities of everolimus, Zhu et al. [132] conducted a multi-center, randomized, double-blind, phase III trial (EVOLVE-1) in 546 adult HCC patients who failed sorafenib treatment (during or after therapy) or who were ineligible for sorafenib treatment in the first place. Patients were randomized to everolimus plus best supportive care (BSC) (n = 362) and placebo plus BSC (n = 184) groups. No statistically significant differences in median TTP and OS were achieved among both treatment groups. However, a statistically significant DCR was achieved in everolimus versus placebo group (56.1% vs. 45.1%, respectively; P = 0.01), and mortality rate was comparable (83.7% vs. 82.1%, respectively). The most frequent grade 3/4 toxicities observed in everolimus versus placebo groups were generalized weakness (7.8% vs. 5.5%, respectively), diminished appetite (6.1% vs. 0.5%, respectively), and anemia (7.8% vs. 3.3%, respectively). No single patient encountered HCV flare-up, however, HBV reactivation was encountered by 29 everolimus and 10 placebo (n = 39 patients; overall 7%); all of which were symptom free. The study concluded that administration of everolimus did not improve OS in patients with advanced HCC whose cancer progressed during or after receiving sorafenib or who were intolerant of sorafenib.

4.5. Combination therapy with novel molecularly targeted therapy and systemic chemotherapy

Table 4 exhibits a summary of phases I and II on combined novel molecularly targeted therapy and systemic chemotherapy in patients with advanced HCC.

Reference	Authors	Year	Phase	Combined Therapy	*n*	RR (%)	DS (%)	TTP (mon)	PFS (mon)	OS (mon)
[144]	Louafi et al.[1]	2007	II	Cetuximab plus gemcitabine plus oxaliplatin	35	24	4.5	NR	NR	9.2
[170]	Asnacios et al.[1]	2008	II	Cetuximab plus gemcitabine plus oxaliplatin	45	20	40	NR	4.7	9.5
[171]	Sanoff et al.	2011	II	Cetuximab plus capecitabine plus oxaliplatin	24	12.5	71	4.5	NR	4.4
[172]	Zhu et al.	2006	II	Bevacizumab plus gemcitabine plus oxaliplatin	33	20	27	NR	5.3	9.6
[173]	Sun et al.	2007	II	Bevacizumab plus capecitabine plus oxaliplatin	29	11	78	NR	4.5	NR
[174]	Hsu et al.	2008	II	Bevacizumab plus capecitabine	45	9	41	NR	4.1	10.7
[175]	Thomas et al.	2009	II	Bevacizumab plus erlotinib	40	25	42.5	NR	9	15.7
[176]	Kaseb et al.	2012	II	Bevacizumab plus erlotinib	59	24	56	NR	7.2	13.7
[177]	Philip et al.	2012	II	Bevacizumab plus erlotinib	27	3.7	48	3	NR	9.5
[178]	Berlin et al.	2008	II	Bortezomib plus doxorubicin	39	2.3	25.6	NR	2.4	5.7
[179]	Knox et al.[2]	2008	II	Oblimersen (G3139) plus doxorubicin	17	0	35	1.8	NR	5.4

n: sample size; RR: response rate; DS: disease stabilization; TTP: time to progression; PFS: progression-free survival; OS: overall survival; NR: not reported; mon: months

[1] Overlap of patient cohorts cannot be excluded from abstracts.

[2] Terminated secondary to absence of efficacy.

Table 4. Summary of phase II studies on combined novel molecularly targeted therapy and systemic chemotherapy in advanced HCC

Several combination therapy regimens exist, such as bevacizumab based, cetuximab based, and others. Among all, bevacizumab-based regimens appear to have the most effective antitumor effects with ORR achieving 3.7%-25%, disease stabilization 27%-48%, PFS 4.1-7.2 months, and OS 9.5-15.7 months. Future studies comparing sorafenib-based versus bevacizumab-based combination therapies are needed.

4.6. Conclusion

Sorafenib remains the first-line standard of care management in patients with advanced unresectable HCC. Multimodal therapy with sorafenib and other local/systemic therapy is an exciting area for future exploration. Absolute advantages of combining novel molecularly targeted therapy (sorafenib or bevacizumab) and cytotoxic chemotherapy is not yet surely defined. Much more research is needed about efficacy of existing combination systemic

therapy (cytotoxic chemotherapy plus novel molecularly targeted therapy) versus sorafenib alone (the first-line therapy so far) for the management of patients with advanced unresectable HCC. Such studies should be addressed through large-sized randomized controlled phase II and III trials; some of which are already ongoing.

Several genetic and epigenetics take place during hepatocarcinogenesis. These signaling pathways include the Wnt-b-catenin pathway, the hepatocyte growth factor/c-Met pathway, IGF and IGF-R pathways, and PI3 K/Akt/mTOR pathway. Several drugs targeting these significant pathways are currently undergoing early-stage assessment in patients with HCC [33, 133].

5. Summary and final remarks

- Hepatocellular carcinoma (HCC) is a largely aggressive neoplasm that commonly takes place in the setting of chronic liver disease and cirrhosis.
- At the time of clinical diagnosis, roughly 60%-70% of HCC patients present with primary advanced inoperable, recurrent, or metastatic disease [7]. Moreover, tumor relapse (recurrence) following curative surgical management continues to be a substantial dilemma and is documented as high as approximately 70% at 5 years postoperatively [8].
- Systemic therapy is the most appropriate choice for patients with primary advanced, inoperable, recurrent, or metastatic disease who were inappropriate candidates for other local or loco-regional therapies.
- Systemic therapy is a rapidly developing area of research. Options of systemic therapy mainly include hormonal therapy, cytotoxic therapy, and novel molecularly targeted therapy.
- Single-agent tamoxifen or in combination with diverse chemotherapeutic drugs was unsatisfactory and failed to yield substantial worthy survival advantages. Similar discouraging results occurred with megestrol administration as well as somatostatin analogs (octreotide and lanreotide). It can be concluded that the use of hormonal therapy for the management of advanced inoperable HCC is not recommended. Its use may be only recommended in the context of clinical trials.
- HCC is largely a chemoresistant neoplasm [77]. The employment of systemic cytotoxic chemotherapy has been accompanied by low objective response rates, no survival advantages, and high frequencies of drug-related toxicities and adverse events. Moreover, there are no adequate data to endorse or approve any single-agent or combined chemotherapeutic cytotoxic regimens for the management of patients with advanced inoperable HCC [76].
- Systemic chemotherapy may still be regarded in patients whom their HCC get worse while on sorafenib and whom baseline liver function and performance status are adequate enough to endure it. The chemotherapy-related toxicities and adverse events should be carefully

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anticipated in such patients. This selection of cytotoxic chemotherapy should be guided by the available best evidence-based medicine.

- By far, sorafenib is the first-line standard of care therapy for patients with advanced unresectable HCC. Studies have shown feasibility and safety profiles in patients with hepatic dysfunction (CPS-A and CPS-B, but not CPS-C).
- The combination of sorafenib and anti-mTOR is feasible in recurrent HCC patients following orthotopic liver transplantation. However, therapy should be carefully checked due to the probability for severe adverse events. Dose modification may be needed.
- Studies of sorafenib-based combination therapy report better DCR, TTP, and OS benefits when compared to single-agent sorafenib therapy, without increased frequencies of excessive treatment-related toxicities and adverse events. However, such studies cannot be appropriately compared, and definitive conclusions are yet to be established.
- Multimodal therapy with sorafenib and other local/systemic therapy is an exciting area for future exploration.
- Absolute advantages of combining molecularly targeted therapy (sorafenib or bevacizumab) and cytotoxic chemotherapy are not yet surely defined.
- Further prospective research should continue to discover the mechanism of hepatocarcinogenesis and subsequently recognize significant molecular targets for therapeutic interventions.

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