Management of Side Effects of Systemic Therapies for Hepatocellular Carcinoma

Guide for the Hepatologist

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KEYWORDS

• Hepatocellular carcinoma • Liver cancer • Liver cirrhosis • Chemotherapy
• Tyrosine kinase inhibitors • Checkpoint inhibitors • Immune-related adverse effects

KEY POINTS

- The number of agents approved in the United States for the treatment of advanced hepatocellular carcinoma has increased dramatically in the past few years.
- Although these discoveries provide patients additional opportunities for therapy, they also introduce adverse events that provide challenges for the treating physician.
- Common side effects of systemic therapies for HCC are predictable, manageable, and many improve with appropriate intervention.

INTRODUCTION

Liver cancer is the sixth most commonly diagnosed cancer and accounts for the fourth leading cause of cancer-related death worldwide.[1] Hepatocellular carcinoma (HCC) is by far the most common histologic cell type, accounting for 90% of all liver cancer in the United States.[2] The incidence of HCC in the United States has increased, with a 115% rise between the years 2000 and 2012, and is projected to continue to rise.[3] Because of its aggressive nature and that, typically, it is a sequela of advanced liver disease or cirrhosis, the mortality for patients with HCC is high: between 12% and 28% at 5 years.[4,5] Surgical therapy, either resection or orthotopic liver transplant, are options for patients diagnosed early in the disease course with small lesions. Unfortunately, most patients presenting with HCC are diagnosed with advanced disease that is not amenable to curative therapies.[6]

Until recently, sorafenib, a molecular targeting agent first introduced for HCC in 2007, was the only systemic therapy indicated for the treatment of unresectable

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HCC in patients. The landscape has changed drastically with the introduction of new molecular targeting agents and agents with additional mechanisms of action, such as immune checkpoint inhibitors (CIs) (Table 1). With the promise of new therapies for incurable HCC also comes the prospect of new and challenging side effects (Table 2). Thus, it is incumbent on the hepatologist to recognize these adverse effects and manage them effectively to reduce overall symptom burden and maximize the efficacy of these drugs. The treatment of liver cancer often involves managing two conditions: the malignancy itself and the underlying environment from which it developed, specifically cirrhosis and, often, decompensated cirrhosis. As such, the gastroenterologist and hepatologist will undoubtedly be intimately involved in the treatment of these patients. This review uses existing evidence to show that the common side effects of systemic therapies for HCC are predictable, manageable, and improve with appropriate intervention.

MOLECULAR TARGETING AGENTS

The molecular targeting agents are made up of medications that target specific molecules necessary for increases in tumor growth and further tumor progression. In HCC, this encompasses the two agents currently approved as first-line therapy by the Food and Drug Administration (FDA): sorafenib and lenvatinib. The other molecular targeting agents (regorafenib, cabozantinib, and ramucirumab) are approved as second-line therapy for those who did not respond or have stopped responding to sorafenib or lenvatinib. The side effect profile for these agents is similar but includes important differences that require attention from the hepatologist.

The First Line

Sorafenib and lenvatinib

Sorafenib is a multikinase inhibitor, acting through inhibition of the serine–threonine kinases Raf-1 and B-Raf, the activity of vascular endothelial growth factor (VEGF)

Table 1
Food and Drug Administration–approved systemic therapies for hepatocellular carcinoma

	Name of Agents	Mechanism of Action
First-line therapy	Sorafenib	Multikinase inhibitor acting through inhibition of the serine–threonine kinases Raf-1 and B-Raf, VEGF receptors 1–3, and PDGF receptor.[7,8]
	Lenvatinib	Multikinase inhibitor, targeting VEGF receptors 1–3, FGF receptors 1–4, PDGF receptor α, RET, and KIT.[11]
Second-line therapy	Regorafenib	Multikinase inhibitor, targeting VEGFR 1–3, KIT, RET, BRAF, and PDGFR.[30]
	Cabozantinib	Multikinase inhibitor, targeting VEGFR 1–3, MET, AXL, RET, KIT, and FLT3.[32,33]
	Ramucirumab	Recombinant human monoclonal antibody that binds to VEGFR-2, blocking endothelial proliferation.[40,42]
	Nivolumab Pembrolizumab	Inhibitor of PD-1, a receptor expressed on the surface of T cells allowing for increased immune response against tumor cells.[48]

Abbreviations: FGF, fibroblast growth factor; FLT, fms like tyrosine kinase; PDGF, platelet-derived growth factor; Raf, rapidly accelerating fibrosarcoma; RET, rearranged during transfection; VEGF, vascular endothelial growth factor.

Table 2
Common terminology criteria for adverse events for common events of systemic therapy for hepatocellular carcinoma

Side Effects	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
AST/ALT elevation	>ULN -3.0 x ULN if baseline was normal; 1.5–3.0 x baseline if baseline was abnormal	>3.0–5.0 x ULN if baseline was normal; >3.0–5.0 x baseline if baseline was abnormal	>5.0–20.0 x ULN if baseline was normal; >5.0–20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	—
Diarrhea	Having 4 more stools daily than patient's baseline	Having 4–6 more stools a day than a person's baseline	Having 7 or more stools a day than a person's baseline	10 or more than baseline, life-threatening condition	Death
Hand-foot skin reaction	Painless dermatitis, such as erythema and edema	Skin changes; painful blistering or peeling of the skin, which limits instrumental ADL	Skin changes, such as blisters, bleeding, peeling and edema; limits self-care ADLs	—	—
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL	—	—
Hyperbilirubinemia	>ULN -1.5 x ULN if baseline was normal; > 1.0–1.5 x baseline if baseline was abnormal	>1.5–3.0 x ULN if baseline was normal; >1.5–3.0 x baseline if baseline was abnormal	>3.0–10.0 x ULN if baseline was normal; >3.0–10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	—
Hypertension	Systolic BP of 120–139 mm Hg; diastolic BP of 80–89 mm Hg	Systolic BP of 140–159 mm Hg; diastolic BP of 80–89 mm Hg; recurrent or persistent for 24 h	Systolic BP of $\geq$160 mm Hg; diastolic BP of $\geq$100 mm Hg	Life-threatening condition; immediate intensive care	Death
Peripheral edema	5%–10% interlimb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10%–30% interlimb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	>30% interlimb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care ADL		

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Table 2
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Side Effects	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash	Papules and/or pustules covering <10% BSA	Papules and/or pustules covering 10%–30% BSA; limiting instrumental ADL	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL	—	—

Abbreviations: ADL, activity of daily living; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BSA, body surface area; ULN, upper limit of normal.

From Cancer.gov. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf Accessed 09/26, 2019.

receptors 1 to 3, and the platelet-derived growth factor (PDGF) receptor.[7,8] Sorafenib, 400 mg twice daily, was established as the standard of care for advanced HCC following the results of two large trials that demonstrated a survival benefit over placebo. The SHARP trial, a multinational phase 3, placebo-controlled trial encompassing nearly 600 patients, showed median survival and time to radiologic progression was nearly 3 months longer for the sorafenib group.[9] These results were corroborated shortly thereafter by the Asia-Pacific trial, another multinational placebo-controlled trial consisting of more than 200 patients, which similarly showed a significant yet modest survival benefit of 2.3 months.[10] Sorafenib was approved in 2007 as first-line therapy for unresectable HCC in the United States.

Unsurprisingly, both trials reported significantly higher adverse events for patients in the treatment group than those in the placebo group. In the SHARP trial, the incidence of treatment-related adverse events (TRAE) was 80% for the sorafenib group versus 52% for the placebo group. In the Asia-Pacific trial, nearly 82% of patients experienced TRAEs compared with about 39% for those receiving placebo. The incidence of TRAEs has important clinical ramifications, causing more than 50% of patients in both trials to either drop out or require dose reduction. The most common TRAEs identified in clinical trials include gastrointestinal symptoms, fatigue, hand-foot skin reaction (HFSR), rash, and hypertension (HTN).

Lenvatinib is a multikinase inhibitor that targets VEGF receptors 1 to 3, fibroblast growth factor receptors 1 to 4, PDGF receptor α, RET, and KIT.[11] Its noninferiority to sorafenib in patients with advanced HCC was demonstrated in a large randomized, phase 3, multicenter noninferiority trial. Median survival for lenvatinib dosed at 12 mg daily for patients greater than 60 kg and 8 mg daily for patients less than 60 kg was 13.6 months compared with 12.3 months for sorafenib (hazard ratio, 0.92; 95% confidence interval, 0.79–1.06), meeting criteria for noninferiority.[12] Lenvatinib also showed better progression-free survival and median time to progression than sorafenib. It was received approval by the FDA in August of 2018 for first-line therapy for advanced HCC in the United States.

Adverse events occurred in a similar proportion in the lenvatinib and sorafenib arms. Drug interruption in the lenvatinib arm occurred in 40% of patients, dose reduction in 37% of patients, and withdrawal in 9% of patients. Because of its similar mechanism of action, the adverse effects of lenvatinib and many of the other molecular targeting agents, specifically the second-line agents discussed separately later, are similar to those of sorafenib. For example, tyrosine kinase inhibitors as a class have been implicated in abnormal thyroid function tests and these levels should be monitored while on treatment.[13] Details regarding important adverse events that occur in more than 20% of patients treated with sorafenib and lenvatinib are outlined later.

Diarrhea Dose reduction caused by diarrhea occurs between 7.4% and 8% of patients receiving sorafenib for HCC, with an overall incidence of 38% to 39%. The incidence for patients receiving lenvatinib is similar. Most diarrhea symptoms are low-grade; however, grade 3 to 4 symptoms have occurred in up to 9% of HCC patients on sorafenib and 4% of patients on lenvatinib. Patients receiving sorafenib with sarcopenia may experience higher rates of dose-limiting diarrhea than those without.[14] Those patients who also suffer from hepatic encephalopathy should be counseled to adjust their lactulose doses if they experience diarrhea. In term of dietary modification, caffeine and dairy in particular can exacerbate diarrhea.[15] Patients should be encouraged to document and avoid other trigger foods. The mainstay of therapy refractory to supportive care is loperamide. Diphenoxylate/atropine may be

used if loperamide is ineffective. For grade 3 or 4 symptoms, dose interruption may be required until symptoms become low grade or return to baseline.[15,16]

Proteinuria The use of lenvatinib for HCC has been associated with development of proteinuria in up to 25% of treated patients.[12] For those with grade 1 proteinuria (1+ protein or 0.15–1.0 g/24 hours) treatment may be continued with close monitoring.[17] For grade 2 (2–3+ urine protein or >1–3.5 g/24 hours) lenvatinib should be held and urinalysis should be repeated until protein levels are less than 2 g/24 hours before restarting. For patients with grade 3 proteinuria (>4+ proteinuria or 3.5 g/24 hours) lenvatinib should be held and the patient should be evaluated by a nephrologist.

Hand-foot skin reaction Along with diarrhea, HFSR is one of the most common causes of dose reduction in sorafenib therapy for HCC. HFSR is a toxic dermatologic reaction causing a painful hyperkeratotic, erythematous rash of the hands and feet. It typically presents within the first 6 weeks of sorafenib therapy.[15,18] Among patients being treated with sorafenib regardless of cancer cause, the incidence of all-grade HFSR of is around 34%.[19] Most patients with HCC present with Common Terminology Criteria for Adverse Events grade 1 or 2 disease, which typically does not require dose reduction. Grade 3 disease is the most severe and often requires at least temporary discontinuation of the drug.

Patients receiving sorafenib or lenvatinib should have a full skin examination before starting therapy, be monitored closely for development of symptoms, and instructed to use emollients on pressure-receptive areas of the hands.[20] Urea-based creams have been shown in one randomized trial to have a prophylactic effect on the development of HFSR.[21] Common Terminology Criteria for Adverse Events grade 1 disease encompasses painless skin changes/erythema and is treated with keratolytic emollients with topical urea 10% three times daily. Grade 2 disease is characterized by painful blistering or peeling of the skin that limits instrumental activities of daily living. Treatment of grade 1 is continued and augmented with potent steroid ointments, such as clobetasol 0.05%, twice daily and topical analgesia (ie, lidocaine 4% creams or patches).[20] Dose reduction of lenvatinib is considered for grade 2 symptoms.[16] For grade 3 disease, or that which limits self-care activities of daily living, the medication is held for at least 7 days or until there is sign of disease resolution.[22] Treatment dose is typically reduced. If the patient does not develop recurrence, dose escalation to full treatment is considered.[16,20,22] The incidence of grade 3 disease for lenvatinib seems to be lower than that of sorafenib.[12,16]

Fatigue Reports of fatigue are common in treatment with molecular targeting agents. Fortunately, fatigue typically does not require dose reduction and usually subsides by Month 6 of treatment.[15] It is incumbent on the treating physician to exclude alternative causes of fatigue, including comorbid conditions, other medication effects, and psychosocial effects. Counseling patients about the possibility of fatigue and identifying and treating other etiologies is essential to managing the fatigued patient on molecular targeting agents.

Rash An often self-limiting macular papular skin rash is a common adverse effect of both medications, occurring between 16% and 30% of patients treated with sorafenib and about 10% of patients treated with lenvatinib in clinical trials.[9,10,12] Care is largely symptomatic and includes a change to milder, perfume-free soaps; encouraging loose fitting clothing; and avoidance of hot water.[15]

Hypertension Treatment induced HTN is a well-established adverse effect of sorafenib and lenvatinib. Three separate meta-analyses have shown that the incidence of

all-grade HTN in patients with any cancer treated with sorafenib is between 19.1% and 23.4%, with the incidence of high-grade HTN ranging between 4.3% and 5.7%.[23–25] The incidence seems to be higher in the treatment of renal cell carcinoma, because the incidence reported in the HCC trials are between 5% and 18.8%. Given sorafenib's inhibition of angiogenesis, an association has been found between the presence of HTN and favorable treatment effect.[26,27] The incidence of HTN and high-grade HTN seems to be higher with lenvatinib.[12,28] Patients with preexisting HTN should be identified and treated before starting therapy. Once therapy is initiated, all patients should have their blood pressure measured every 2 to 3 weeks to allow for prompt treatment.[29] Initiation of standard anti-HTN agents are recommended, including calcium channel blockers and angiotensin-converting enzyme inhibitors.

The Second Line

Regorafenib and cabozantinib

Regorafenib is an oral multikinase inhibitor affecting tumor angiogenesis (VEGFR 1–3), oncogenesis (KIT, RET, and BRAF), and metastasis (PDGFR).[30] Regorafenib, 160 mg daily, is currently FDA-approved as second-line therapy for patients with HCC previously treated with sorafenib. The efficacy of regorafenib as second-line therapy for HCC was suggested by a large double-blind, phase 3 multicenter trial of 567 patients with Child-Pugh A liver function and evidence of progression on sorafenib. Patients who received regorafenib had a median survival of 10.6 months versus 7.8 months for placebo.[31]

Similarly, cabozantinib is an inhibitor of multiple tyrosine kinases, including VEGF receptor 1, 2, and 3; the stem cell growth receptor KIT; MET; and AXL.[32,33] It is approved as second-line therapy at a dose of 60 mg daily for patients with HCC who have failed sorafenib, based on data published in 2018 from a phase 3 randomized, placebo-controlled trial. In a population of more than 700 patients who had previously progressed on sorafenib, those receiving cabozantinib displayed longer overall survival by more than 2 months.[34]

The incidence and nature of adverse effects for regorafenib and cabozantinib are similar to those seen in sorafenib and lenvatinib. For regorafenib, drug-related adverse events led to treatment interruption or dose reduction in 54% of patients and drug discontinuation in 10%. Adverse effects led to dose reduction in 62% of patients on cabozantinib and discontinuation in 16%. Similar to the previously mentioned first-line agents, the most common adverse effects seen with regorafenib/cabozantinib were HFSR (52%/46%; 13%/17% grade 3), diarrhea (33%/54%; 2%/10% grade 3), fatigue (29%/45%; 6%/10% grade 3), and HTN (23%/29%; 13%/16% grade 3 or 4). Because of their mechanistic similarity, the management of these conditions is similar to that described previously for sorafenib and lenvatinib. **Table 3** provides specifics regarding HFSR management. Liver dysfunction, described next, is an adverse effect commonly described with regorafenib.

Hepatic dysfunction Increased bilirubin and transaminase concentrations are a common adverse effect of regorafenib. The incidence of treatment-related hyperbilirubinemia in the treatment of HCC with regorafenib was found to be 19%, whereas an elevated aspartate aminotransferase (AST) was seen in 13% and increases in alanine aminotransferase (ALT) observed in 8%.[31] Severe (grade 3 or higher) events were rare. Although these abnormalities may be confounded by the presence of underlying advanced liver disease, increases in these markers were also seen in trials of patients with gastrointestinal stromal tumors and colon cancer.[35,36]

Grade 2 elevations are defined by 2.5 times the upper limit of normal (ULN) for AST and ALT, and 1.5 times ULN for bilirubin. These laboratory studies should be drawn

Table 3
Management of hand-foot skin reaction caused by molecular targeting agents

Before Initiation	Grade 1	Grade 2	Grade 3
Full skin examination Pedicure to address areas of hyperkeratosis Avoidance of hot water Avoidance of bare feet or tight shoes	Continue prophylactic measures from before initiation Encourage use of urea-based creams and topical moisturizers Maintain current dosing regimen	Continue prophylactic measures from before initiation and for grade 1 symptoms Clobetasol 0.05% ointment Analgesia using topical lidocaine, pregabalin, and opiates, as needed Consider 50% dose reduction for at least 7 d if symptoms do not improve to at least grade 1 If no improvement to reduced dose, discontinue therapy for 7 d until symptoms improve to at least grade 1; resume at half-normal dose	Continue measures from before initiation and grade 1–2 symptoms Stop agent for 7 d until symptoms improve to at least grade 1 If improved, restart at 50% full dose and re-escalate as tolerated If persistent recurrence with reintroduction, consider permanently discontinuing offending agent

Data from Refs.[20–22]

twice per week and then each week for a month to ensure stability and/or a return to baseline. If these laboratory studies continue to rise to grade 2 elevations (>2.5–5.0 x ULN for AST/ALT; 1.5–3.0 x ULN for bilirubin), the drug is delayed until laboratory studies return to grade 1 levels. The drug can then be restarted at a lower dose. If the patient experiences a grade 2 elevation from laboratory values that were previously normal, the drug is continued with laboratory monitoring twice weekly for 2 weeks and then weekly for 1 month. For Grade 3 elevations (5–20 x ULN for AST/ALT; 3–10 x ULN for bilirubin), the drug should be held until laboratory studies return to baseline. If the drug is restarted, it should be done so at a lower dose with frequent laboratory monitoring. For any grade 4 elevation (>20 x ULN for AST/ALT; >10 x ULN for bilirubin), the drug should be discontinued.[37,38]

Ramucirumab

Ramucirumab is a monoclonal antibody that binds with high specificity to the extracellular domain to VEGFR-2, blocking endothelial proliferation.[39,40] It was initially studied as a therapy for HCC in a phase 2 study of 42 patients who received no prior therapy and showed a median overall survival of 12 months.[39] A subsequent placebo-controlled trial in patients who had previously been treated with sorafenib did not demonstrate a survival benefit, except for a subset analysis that suggested patients with elevated α-fetoprotein (AFP) greater than 400 ng/mL (median survival of 7.8 months vs 4.2 months for placebo).[41] Ramucirumab was further evaluated in a phase 3 trial of patients who previously demonstrated disease progression on sorafenib, had no worse than Child-Turcotte-Pugh class A cirrhosis, and a serum AFP greater than 400 ng/mL.[42] Patients receiving ramucirumab had a 1.2-month increased overall survival (8.5 months vs 7.3 months). In light of these results, ramucirumab was

FDA-approved in 2019 at a dose of 8 mg/kg every 2 weeks as second-line therapy for patients with advanced HCC who have previously failed sorafenib and have an AFP level of greater than 400 ng/mL.

From an adverse event standpoint, one of the major advantages of ramucirumab is that it does not seem to cause HFSR. This makes it an ideal agent for patients who failed first-line therapy because of significant HFSR, have less advanced cirrhosis, and an elevated AFP. The most common side effects encountered by patients with HCC receiving ramucirumab in the phase 3 trial were fatigue (36%; 5% grade 3), peripheral edema (25%; 2% grade 3), HTN (25%; 13% ≥grade 3), abdominal pain (25%; 2% ≥grade 3) decreased appetite (23%; 2% >grade 3), and the onset of ascites (18%; 4% ≥grade 3).[42] The most common laboratory abnormality was thrombocytopenia (46%; 8% ≥grade 3).

Checkpoint inhibitors: nivolumab and pembrolizumab

Tumor cells are able to avoid immunosurveillance through several methods, including activation of immune checkpoint pathways that suppress immune responses against tumor cells. CIs act to interrupt these signaling pathways and revive antitumor immune surveillance.[43] CIs have been shown to be effective either in combination or as monotherapy for treatment in several advanced malignancies, including melanoma,[44] renal cell carcinoma,[45] non–small cell lung cancer,[46] and urothelial cell carcinoma.[47] There are two CIs approved by the FDA for second-line treatment of HCC: nivolumab and pembrolizumab. These agents are both inhibitors of programmed cell death protein 1 (PD-1), a receptor expressed on the surface of T cells that, when bound to the programmed cell death protein 1 (PDL-1) on the surface the tumor cell, act to dampen the immune system and prevent attack on the tumor cell.[48]

The efficacy for nivolumab is derived from a phase 1/2 dose escalation and expansion trial of adults with advanced HCC. Of the 255 patients who were studied for response, about 19% experienced an objective tumor response, including three complete responses.[49] An 83% of patients experienced at least one TRAE, but only one patient stopped treatment. Similarly, the initial benefit for pembrolizumab was demonstrated in a phase 2 trial of patients with HCC who had failed sorafenib, which showed objective response in 17% of those studied.[50] A 73% of patients experienced at least 1 TRAE, with 5% requiring discontinuation of therapy. In a subsequent placebo-controlled, phase 3 trial of pembrolizumab for patients previously treated with sorafenib, pembrolizumab showed a survival benefit over placebo in median overall survival (13.9 months vs 10.6 months) and progression-free survival (3 months vs 2.6 months), although these failed to meet statistical significance.[51]

Although the novel CI mechanism has been shown to be effective in the treatment of malignancy, it has been associated with a unique class of adverse events, termed immune-related adverse events (irAEs).[52] These events are thought to arise from the increased immune response created by checkpoint inhibition. Intuitively, the treatment of these conditions is administration of glucocorticoids or other immunosuppressive agents, which opens the risk of opportunistic infections in patients who require treatment of irAEs.

Broadly, in patients who experience moderate irAEs (grade 2), CI therapy is held and not restarted until symptoms become mild (grade 1) or better. If moderate symptoms persist for more than a week, initiate corticosteroids (ie, 0.5–1 mg/kg/d oral prednisone or equivalent doses of intravenous methylprednisolone if unable to tolerate by mouth). Patients experiencing more severe irAEs (grade 3 and 4) require indefinite withdrawal of CIs and higher doses of corticosteroids (ie, 1–2 mg/kg/d of prednisone

or methylprednisolone equivalent) until symptoms retreat to at least grade 1. At this point, steroids can begin to be tapered over at least a 4-week period.[53]

Specific irAEs often have nuanced management considerations, particularly in the setting of chronic liver disease. Immune related hepatitis (irH) is particularly common for patients receiving CIs for HCC and specifics related to this condition are outlined next. Notably, the reported mortality rates for pembrolizumab and nivolumab are 0.1% and 0.3%, respectively.[54]

Immune-related hepatitis The incidence of irH, mainly in the form of elevated transaminases, occurs in up to 21% of patients treated with nivolumab and 14% of those treated with pembrolizumab in data published from clinical trials.[49,50] The incidence has elsewhere been reported to be 30% and is the most common reason for CI treatment discontinuation in this patient population.[55] Notably, the reported incidence of irH in the treatment of melanoma with nivolumab and pembrolizumab is 1% to 3% because patients with HCC are likely more susceptible to irH.[56–58] Liver injury may occur at any time during treatment, but is typically seen between 6 and 14 weeks after initiation of therapy.[55,59] The differential diagnosis for patients on CIs with elevated liver tests is broad but requires careful consideration to ensure proper treatment and avoid unwarranted use of corticosteroids. Considerations include:

- Drug-related liver injury, particularly in patients who have recently started a new medication
- Herbal supplement use
- Alcohol use
- Opportunistic infection, such as Epstein-Barr virus or cytomegalovirus
- Thromboembolic disease, such as portal vein thrombosis or Budd-Chiari syndrome (hepatic vein thrombosis)
- Progression of underlying liver disease and/or cancer, particularly in the case of those with active hepatitis B or hepatitis C infection

Before initiation of CI therapy, viral hepatitis serologies should be sent and baseline liver tests should be established. Work-up for elevations in liver tests while on treatment should be targeted at ruling out the previously mentioned etiologies, including a careful history and physical examination, a thorough medication reconciliation, repeat viral hepatitis serologies, Epstein-Barr virus, and cytomegalovirus polymerase chain reaction. Autoantibodies may be positive in patients with irH, including anti–nuclear antibody, anti–smooth muscle antibody and anti–liver/kidney, although the impact of antibody positivity is unknown and therapy remains the same.[59] Imaging via ultrasonography or computerized tomography should be used to assess for disease progression, and to rule out the possibility of thromboembolic disease. Liver biopsy has been shown to accurately identify patients suffering from irH.[60] The pattern observed histologically with PD-1 irH is described as “heterogenous” but includes lesions of active hepatitis with areas of necrosis and mild to moderate periportal activity largely without granulomatous inflammation.[60] The lobular hepatitis seen on biopsy may be indistinguishable from autoimmune hepatitis.[61] There is no consensus about when to perform a liver biopsy in these patients; however, some advocate biopsy in patients with grade 3 and higher hepatoxicity (5–20 x ULN for AST/ALT; 3–10 x ULN for bilirubin).[59]

Treatment of CI-induced hepatitis is complex, although the mainstay of therapy is corticosteroids for grade 2 disease and higher.[61,62] There have been no clinical trials identifying the best agent or dosing regimen for irH. If there is no improvement in liver function tests after 1 week, addition mycophenolate mofetil is recommended.[63] **Fig. 1**

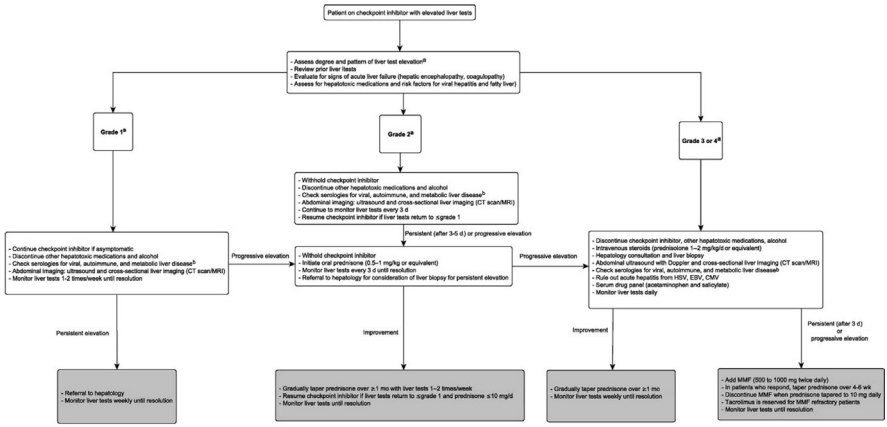

Fig. 1. Approach to the evaluation and management of checkpoint inhibitor hepatotoxicity. ANA, antinuclear antibody; ASMA, anti–smooth muscle antibody; CMV, cytomegalovirus; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; EBV, Epstein-Barr virus; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C; HCVAb, hepatitis C antibody; HSV, herpes simplex virus; LKM, liver kidney microsomal; MMF, mycophenolate mofetil. [a] Elevations in liver tests as per CTCAE version 5.0. Grade 1: AST or ALT >ULN - 3.0 x ULN if baseline was normal; 1.5 to 3.0 x baseline if baseline was abnormal and/or total bilirubin >ULN -15 x ULN if baseline was normal; >1.0 to 1.5 x baseline if baseline was abnormal. Grade 2: AST or ALT >3.0 to 5.0 x ULN and/or total bilirubin >1.5 to 3.0 x ULN. Grade 3: AST or ALT >5.0 to 20.0 x ULN if baseline was normal; >5.0 to 20.0 x baseline if baseline was abnormal and/or total bilirubin >3.0 to 10.0 x ULN if baseline was normal; >3.0 to 10.0 x baseline if baseline was abnormal. Grade 4: >20.0 x ULN if baseline was normal. >20.0 x baseline if baseline was abnormal and/or total bilirubin >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal. [b] Hepatitis serologies (HBsAg HBcAb, HBsAb, HCVAb, HCV RNA), iron panel, ANA, ASMA, anti-LKM, gamma globulin, ceruloplasmin, α-1 antitrypsin. (*From* Grover S et al., Gastrointestinal and Hepatic Toxicities of Checkpoint Inhibitors: Algorithms for Management, *American Society of Clinical Oncology Educational Book* 38 (May 23, 2018) 13-19. Reprinted with permission. © 2018 American Society of Clinical Oncology. All rights reserved.)

highlights the current expert consensus management guidelines from the American Society for Clinical Oncology. Resumption of CI is typically only considered for those who have suffered at most grade 2 hepatitis once liver tests have returned to the patient's baseline. Patients with more severe (grades 3 and 4) presentation should not be restarted on CIs.[62]

SUMMARY

The incidence of HCC in the United States is rising. For patients with advanced disease who are not candidates for curative therapies, treatment options have historically been limited. Recently, however, the approval of many new agents has increased the number of patients who can be treated for HCC. With the availability of new drugs, the hepatologist is faced with the specter of new and challenging adverse events that threaten to limit the ability to treat patients with advanced disease. Through prompt recognition and treatment, many of these adverse events can be managed, allowing patients to derive the maximum benefits of these therapies.

DISCLOSURE

The authors of this article have no conflicts of interest to disclose.

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