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Palliative care and hepatobiliary malignancies: say no to late referral

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Abstract: Hepatobiliary malignancies (HBMs), primarily hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), share the common traits of having a generally poor prognosis, late presentation, and high symptom burden related to both the disease process itself and underlying poor liver function. The incidences of both malignancies have been rising in recent decades for unclear reasons. Curative options remain limited given the general aggressive disease course despite advances in diagnosis, therapies, and surgery. Early integration of palliative care into the routine care of patients with HBMs is an essential, but underutilized, component of care to improve the functional and symptomatic quality of the lives of patients and their families. While formal guidelines for its integration are currently lacking, palliative care can and should be provided in parallel to disease specific care at any stage to address the physical, emotional, and spiritual needs of patients with HBMs. In this review, the special needs of this patient population are examined ranging from early symptom management at the time of diagnosis all the way through to end-of-life care. Key barriers that prevent the early provision of palliative care for patients with HBMs are identified and discussed and recommendations provided on how to improve early integration.

Keywords: Hepatocellular carcinoma (HCC); cholangiocarcinoma (CCA); hepatobiliary malignancies (HBMs); palliative care

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Introduction

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (CCA) are the most common types of primary hepatobiliary malignancies (HBMs) accounting for 73% and 18% of all primary liver cancers, respectively. HCC is the second most common cause of cancer-related mortality worldwide with approximately 700,000 deaths annually (1-3). On average, 41,260 adults in the United States are diagnosed annually with a primary HBM and 30,520 will die from it (3). The incidence of HCC in the United States more than tripled from 1980 to 2015 and continues to rise (3). Incidence and mortality follow an approximately 3:1 ratio in men to women, respectively, and increase with age in all populations (2,3). Roughly half of all patients diagnosed with HCC do not receive any disease specific treatment due to late presentation and medical comorbidities, including cirrhosis and end-stage

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liver disease (ESLD) (4). Overall 5-year survival in the United States is less than 20% which is up from 3% four decades ago, but remains highly dependent on the disease stage at the time of diagnosis (3). It drops to less than 10% in Asia, where the disease is most common related to the geographical prevalence of hepatitis B and C (2,5). The most commonly used staging system is the Barcelona Clinic Liver Cancer (BCLC) system which ranges from stage 0 (very early), through A, B, C, and D (terminal). At stage 0, median survival is 38 months, whereas at the most advanced stage D, median survival declines to 6 months (6). Localized disease has a 5-year survival rate of only 35% and drops to 2.4% for metastatic disease (5-7). Curative therapies such as transplantation, ablation, and surgical resection can increase 5-year survival to >70%, but unfortunately <30% of patients are candidates for these therapies (8,9).

On the other hand, CCA is a cancer of the epithelial cells of the intrahepatic and extrahepatic bile ducts. The disease is uncommon in the United States, but highly lethal with primary sclerosing cholangitis (PSC) its most common risk factor. The incidence of CCA increases 100-fold in Southeast Asia where the most common risk factor is endemic liver flukes (10). Treatment for early-stage disease is surgical resection, but, unfortunately, the majority of patients are not surgical candidates at the time of presentation or will eventually recur despite surgery and adjuvant therapy. Although treatment of advanced CCA has improved in the recent years with the introduction of check point inhibitors and targeted therapy, the overall prognosis remains poor with overall 5-year survival for intra and extrahepatic CCA of 5% and 17%, respectively (11).

Patients with HCC and CCA are at especially high risk for significant symptom burden and poor quality of life (QOL). HCC occurs almost universally in the setting of underlying liver disease and liver function abnormalities are commonly seen in CCA secondary to tumor burden and or biliary obstruction (12). These patients face the complexity of navigating both cancer and liver disease. Notably, one study concluded that 43% of patients with unresectable HCC died from complications of their underlying liver disease rather than from their cancer, and liver disease frequently prevents patients from being able to receive cancer treatment (13). Patients living with HBMs face a multitude of symptoms from both their cancer and liver disease including pain, fatigue, insomnia, ascites, nausea, vomiting, anorexia, weight loss, jaundice, pruritis, depression, dyspnea, gastrointestinal bleeding, and encephalopathy. Optimal management of these symptoms requires a high-level understanding of both pharmacology and its interaction with the pathophysiology of liver disease, as well as familiarity with providing emotional, spiritual, and psychological support, which are within the purview of palliative care teams.

Case

Mr. B is a 62-year-old man with a history of hypertension, alcohol use disorder, untreated hepatitis C, and cirrhosis who initially presented to the emergency department with progressive fatigue, subjective weight loss, and generalized weakness. He was admitted to the hospital and found to have elevated liver enzymes, which prompted abdominal imaging. A computed tomography (CT) scan revealed a 1.1 cm hyperechoic mass within the right lobe of his liver and cirrhotic changes. His functional status improved with hydration and he was discharged home with a plan to follow up with his primary care physician. He underwent biopsy one month later which was consistent with HCC. After an initial visit with gastroenterology, he was lost to follow up. Twenty months after his initial hospitalization, he presented again to the emergency department with abdominal pain, distention, and generalized weakness. Labs revealed an alpha-fetoprotein level of 177,000 along with elevated liver enzymes and bilirubin. Repeat imaging revealed multiple liver masses with the largest in his right liver lobe at 3.6 cm along with diffuse pulmonary nodules and severe ascites. He was admitted to the hospital and underwent diagnostic and therapeutic paracentesis with improvement in his abdominal pain and dyspnea. His oncologist recommended against systemic therapy based on his poor functional status, untreated viral hepatitis, and advanced cirrhosis (Child-Pugh Score C). The palliative medicine team was consulted for further support; discussion with the patient and his family helped him process the diagnosis and understand his limited prognosis. He ultimately opted to shift to comfort-focused care and returned home with hospice.

Role of palliative care

Palliative care is a type of care that focuses on supporting patients with serious illness without regard to curative intent. It can be provided at any stage of a patient's illness, making it distinct from hospice care. It is inherently interdisciplinary and involves physicians, nurses, chaplains, social workers, and others in order to care for the physical, emotional, spiritual, and psychological needs of patients.

Palliative care physicians aim to understand what values are important to a patient in order to help discuss goals in the context of advance care planning and medical decision making. It also has a focus on aggressive symptom management with the overall aim to maximize QOL throughout the course of serious illness.

Early palliative care for patients with cancer provided in parallel to disease directed therapy has been shown to result in improved symptom control, higher patient satisfaction, care better aligned with patient values, and improved QOL—all without affecting mortality. In a landmark study involving non-small cell lung cancer, early palliative care was associated with an extended lifespan and improved QOL with less aggressive treatment (14).

Barriers to early palliative care

Despite the poor prognosis and heavy symptom burden of primary HBMs, early palliative care remains underutilized. In one study of patients with ESLD who were delisted or declined for liver transplant, only 11% were ultimately referred to palliative care. This cohort of patients had a median survival time of 52 days after transplant denial and spent a median of 14 of those days hospitalized with 48% admitted to the intensive care unit. There was widespread documentation of pain (65%), ascites (61%), hepatic encephalopathy (HE) (59%), nausea (58%), variceal bleeding (52%), anorexia (49%), dyspnea (48%), anxiety (36%), and depression (10%). An additional 30% of patients went on to develop hepatorenal syndrome and 17% underwent renal replacement therapy along with other interventions not targeted toward improving QOL. Only 28% had documentation of a do not resuscitate order (DNR) and over half died in the hospital setting. Only 3.9% received hospice care at the end-of-life (15). These data points represent missed opportunities for palliative care interventions to improve symptom management, have earlier and increased hospice referrals, and limit aggressive end-of-life interventions.

Despite the demonstrated benefits of early palliative care, it remains underutilized in HBMs with significant barriers at all levels, including disease-specific, patient, physician, and institutional barriers. The characteristic late presentation of primary HBMs and the variable course of ESLD make early palliative care referral challenging. Stigmatization around HBMs and their risk factors can compound this and create further delay in accessing the support afforded to patients and families by palliative care teams. In one qualitative study assessing patient narratives, breast cancer was described as a "badge of honor… not hidden… free hats and a big basket and coffee pot and cookies." HCC, however, was described as "there is no camaraderie... liver cancer is cold. You're all by yourself" and "when you say where you got cancer… their attitude is like 'you're a drunk' or 'you're a druggy'… I don't have the high tech, the good cancer…" (16). The most cited barriers to palliative care referral noted by hepatologists and gastrointestinal oncologists include the cultural perception of palliative care (95%), unrealistic patient expectation of prognosis (93%), and competing demands for physician time (91%) (17).

The reasons for the underutilization of palliative care are multifactorial. One common reason is the stigma associated with the risk factors of HCC. The underlying liver disease in HCC can most commonly be traced to behaviors related to excess alcohol use, viral hepatitis B and C, obesity, intravenous drug use, and sexual intercourse. Notably, an estimated 70% of cases of HCC could be prevented by elimination of these risk factors (3). Societal disapproval of these behaviors can make it difficult for patients with HCC to find support and may delay presentation to the health care system. Although this stigma is less commonly seen with CCA, referral to palliative care remains uncommon related to the rarity and the complex nature of the disease in which multidisciplinary management of the disease overshadows treatment of the patient.

The medical community's misunderstanding of palliative care may also drive delayed referral, especially for patients awaiting liver transplantation. Only 10% of patients removed from the liver transplant wait list in one study eventually received palliative care. That number was even smaller for those still on the transplant wait list, despite significant symptom burden impacting their QOL (14). Palliative care is often mistakenly confused with end-of-life care which can limit its utilization by transplant services. A model in which palliative care is routinely integrated into pre- and post-transplant care may facilitate earlier palliative care through development of close and trusting relationships (18,19). Given the large number of patients eventually delisted from the transplant waiting list, including approximately 20% due to disease progression, transplant consideration could be a natural point to trigger an early palliative care consultation (20,21).

Another reason that palliative care involvement is often late is difficulty with prognostication of the ESLD that underlies HCC and develops in the later stage of CCA. The unpredictable disease course with periods of symptomatic

and functional decompensation followed by periods of relative improvement leaves patients confused regarding the trajectory of their illnesses. Not surprisingly, 90% of surveyed hepatologists believe that patients and caregivers have unrealistic expectations about prognosis (17). This discrepancy between physician and patient prognostic understanding creates further barriers to early palliative care referral. Patients with other disease processes that are defined by unpredictable disease courses, such as heart failure, have benefitted from regular follow up and integrative models with early upstream palliative care focused on supporting patients with symptom management and avoiding hospitalization (22).

Perhaps most importantly, formal guidelines defining patient needs and on how best to provide hepatobiliary specific palliative care do not exist. While the American Society of Clinical Oncology (ASCO) recommends routine palliative involvement for all malignancies, this is not mirrored by hepatology societies whose members provide the bulk of care for patients with ESLD, HCC, and CCA (23). Instead, best supportive care is recommended for patients with BCLC stage D without specific criteria or evidence on how to provide such care (24). Treatments for patients with BCLC stage B and C are palliative, yet there are no formal guidelines on integration of specialty palliative care teams or how to manage symptoms from the cancer or its treatments. Advocacy and high-quality research exploring patient needs and how best to deliver palliative care early in HBMs is needed to shift the current paradigm of limited and late referrals.

Palliative needs in hepatobiliary cancer

Symptoms

Patients with HBMs and ESLD often have high symptom burden and poor QOL, comparable to that associated with other advanced serious illnesses such as chronic obstructive pulmonary disease (COPD) or heart failure (25). Underlying altered hepatic physiology can preclude effective symptom management and place patients at high-risk for medication related complications. Decreased hepatic blood flow, porto-systemic shunting, both endogenous and iatrogenic, a reduction in functional hepatocytes, and low circulating albumin can all contribute to supratherapeutic levels of medications and their metabolites and precipitate adverse medication-related events. Cytochrome P450 (CYP450) isoenzymes additionally have varying levels of sensitivity to hepatic dysfunction, further complicating medication choice and dosing. Impaired biliary excretion must also be considered when selecting and dosing medications in the context of biliary obstruction or cholestatic liver disease from underlying HBMs (26).

Estimates of renal elimination in patients with cirrhosis can be deceiving as many patients have impaired renal clearance despite normal creatinine levels as a result of poor nutrition and muscle wasting (27). In more advanced disease, hepatorenal syndrome may result in even further renal insufficiency and further complicate estimation of the renal elimination of medications and their metabolites. The Cockcroft and Gault equation may be a better option to estimate creatinine clearance and medication dosing in these situations (27). Beyond the liver and kidneys, increased central nervous system effects may be seen with opioids, sedatives, and anxiolytics related to poorly understood alterations in the blood brain barrier, enhanced gamma-aminobutyric acid-mediated neurotransmission, and increased sensitivity, density, and affinity of drug receptors (26).

Unfortunately, guidance on prevention and management of adverse medication effects in this population is limited because patients with ESLD are rarely included in clinical trials. One review of Food and Drug Administration (FDA) approved medications found only 23 medications with recommended dose adjustments for levels of hepatic impairment (28,29). Furthermore, there is no measure of liver disease analogous to creatine clearance or glomerular filtration rate as in renal disease that can guide medication dose adjustment. Child-Pugh classification and the Model for End-Stage Liver Disease (MELD) are helpful prognostication tools, but have no utility in medication dose adjustment. This complexity in pharmacologic pain and non-pain symptom management in patients with HBMs necessitates an expert symptom management team to ensure an optimal focus on maximizing QOL. Side effects of chemotherapy and/or targeted therapy will not be discussed as they are beyond the scope of this review.

Pain

HBMs are usually asymptomatic in early stages, but can lead to back, flank and abdominal pain as tumors grow. Notably, patients with ESLD and HBMs report similar pain levels as do patients with lung and colon cancers (30). In one study, pain was the most common symptom in 75% of patients. The initial pain in hepatobiliary cancers stems from direct tumor-related mass effect, liver capsular irritation and distension, gastric compression, ascites, visceral organ

involvement, and neuropathy. As the disease progresses, metastases to bones and other organs can lead to more widespread pain.

Acetaminophen can be safely used at reduced doses in ESLD and HBMs. It is metabolized by the liver via glucuronidation and sulfation to non-toxic metabolites, a process which is well preserved in cirrhosis. Half-life may be prolonged in cirrhosis, but glutathione stores are generally adequate to avoid hepatotoxicity. The current recommendation is a maximum of 2–3 g/day of acetaminophen in patients with cirrhosis, but there is evidence that up to 4 g/day had no adverse effects when used for fewer than 2 weeks, even in patients who consume regular alcohol (27,31,32). Due to lack of sedation and nephrotoxicity, acetaminophen is the analgesic of choice in patients with liver disease (26).

Management of pain and use of opioids, which are the mainstay of cancer-pain management, can be challenging in patients with HBMs for multiple reasons. Clinicians may be hesitant to prescribe opioid medications to patients with histories of substance or alcohol use disorders. Opioids can exacerbate HE or contribute to constipation making treatments for it less effective. Many medications require the liver and biliary tract for metabolism and clearance. Morphine is extensively metabolized by the liver and decreased first-pass metabolism in patients with cirrhosis results in higher plasma levels and decreased clearance when taken orally. Morphine clearance is estimated to be decreased by 35–60% in patients with cirrhosis, leading to a near doubling of its half-life, necessitating decreased and less frequent doses to avoid supratherapeutic levels and overdose (33,34). In co-existing renal impairment, morphine plasma levels can be even further elevated, leading to neurotoxic signs of delirium, somnolence, myoclonus, or seizures. Codeine, hydrocodone, and oxycodone all require metabolism via the hepatic CYP450 system to be converted to morphine, hydromorphone, and oxymorphone, respectively, leading to variable serum levels and possible inadequate analgesia given ineffective metabolism (27). Fentanyl and methadone elimination do not seem to be affected by hepatic impairment, but present practical challenges with administration that make expert guidance essential. Reduced dose hydromorphone or fentanyl are generally the preferred agents if an opioid is required in order to minimize the serious risks of opioid toxicity including respiratory depression and neurotoxicity (27). Reduced dose oxycodone may be a reasonable alternative (26). Buprenorphine is also an increasingly utilized agent for cancer related pain given its favorable safety profile due to a ceiling effect on respiratory depression resulting from its partial agonist pharmacology without a corresponding analgesic ceiling effect. It is cleared by glucuronidation rather than the P450 system and is not affected by renal impairment leading to more stable serum concentration levels (35). Regardless or opioid choice, the general principle of lower doses and slower titration should be followed to minimize risks of adverse events.

Methadone is worth further noting as it is an effective and valuable medication for the treatment of cancer-related pain and has several properties that make it a good choice for patients with underlying substance use disorder. Along with fentanyl and hydromorphone, methadone metabolism does not result in toxic metabolites, potentially leading to better tolerance at reduced doses then are other opioids (36,37). However, given its variable half-life and known medication interactions, methadone should only be used with expert assistance. While no prospective studies exist that demonstrate the safety of methadone in patients with stable liver disease, there is evidence to suggest that continuing a patient's usual methadone maintenance dose for treatment of opioid use disorder is likely safe (27). In general, long-acting formulations of all opioids should be used with caution in patients with ESLD due to prolonged half-lives in the setting of impaired metabolism and clearance. Aggressive laxative use should be considered with opioids to avoid exacerbating HE.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated in patients with HBMs and cirrhosis. Due to their inhibition of prostaglandins and subsequent decrease in renal perfusion via constriction of the afferent glomerular arterioles, they pose a significant potential for precipitating hepatorenal syndrome in this high-risk population (27). NSAIDs are also highly protein bound, leading to elevated plasma levels in patients with cirrhosis. Their effects on platelets further elevates the risk of gastrointestinal and variceal bleeding and HCC rupture (27).

Adjuvant analgesics are an important component of multi-modal analgesia in HBMs. Neither gabapentin nor pregabalin undergo extensive hepatic metabolism nor protein binding and are generally considered safe to use in HCC and cirrhosis (27). Desvenlafaxine is the preferred serotonin-norepinephrine reuptake inhibitor (SNRI) because it is not metabolized by the CYP450 system (26). Tramadol and tapentadol should be avoided in patients with cirrhosis, especially, who are receiving serotonergic antidepressants, due to an elevated risk of serotonin

syndrome. Corticosteroids are effective for liver capsular pain or pain related to bony metastases. Dexamethasone is the preferred steroid given low mineralocorticoid effect leading to less fluid retention. Prednisone should be avoided given it requires the liver to be converted to the active agent, prednisolone (38-40).

Pain is a devastating symptom for patients that has a negative impact on QOL in many ways. Medications should be used with caution for patients with HBMs because of the altered pharmacokinetics, yet harms and benefits should be thoroughly considered and treatments aligned with the values and goals of each individual patient. Managing the complex symptoms encountered with HBMs is an area well suited for expert palliative care input. We need to create a similar table with some changes.

Ascites

Ascites is the most common reason for hospitalization in ESLD and a major contributor to symptom burden and poor QOL in HBMs. The ascites is most commonly transudate and related to the underlying liver disease. Sodium restriction <2 g/day and use of the diuretics furosemide and spironolactone are the mainstay of treatment and have been shown to be effective for >90% of patients (15,41-43). Some patients with CCA can present with exudative ascites and diuretics are not recommended in that setting. Paracenteses can be effective for symptomatic relief of refractory ascites, but may need to be performed regularly. Some palliative care teams are equipped to perform paracentesis in alternate healthcare locations without requiring hospitalization, further highlighting the benefit of early referral. Transjugular intrahepatic portosystemic shunting (TIPS) is another option that can reduce the need for recurrent large volume paracentesis and has shown a trend toward improved survival in patients with cirrhosis, but carries an increased risk of encephalopathy. TIPS is generally not recommended for patients with end-stage malignancies (43,44).

There is currently no standardized approach to the management of refractory malignant ascites. It can contribute to a heavy symptom burden including orthopnea, dyspnea, abdominal discomfort, nausea, vomiting, difficulty ambulating, and poor body image (44). Repeat paracenteses is the most common palliative approach, but the drawbacks include frequent hospital or clinic visits and the physical discomfort of the procedure. When patients require paracentesis weekly or even more frequently, an indwelling catheter can be a beneficial alternative. Indwelling catheters may not be as widely utilized as they could be given the tendency to avoid procedures near the end-of-life, concern for infection, cost, and concerns regarding the ability of the patient and/or caregiver to manage the device. Despite the theoretical infection risk, one systematic review found the median rate of peritonitis to be 5.9% with catheters overall providing successful symptomatic control with an acceptable adverse event profile. The median time to death from placement was 36 days with a range of 4–660 days (44). Early goal-directed discussions with a palliative care team can help determine when an indwelling catheter makes sense and when paracenteses are no longer beneficial for the patient (45-47). A skilled palliative team can also help to arrange timing of catheter placement so as to not delay eventual enrollment in hospice or when the patient is close to the end-of-life and no longer a candidate for intervention.

HE

HE is a chronic, burdensome ailment associated with HBMs and underlying ESLD. Its mechanism is not well understood, but results in neuropsychiatric symptoms including chronic mild cognitive dysfunction, personality changes, abnormal sleep, acute confusion, and coma. Lactulose has been the mainstay of treatment since the 1960s (48). While effective, lactulose is widely disliked by patients because of its sweet taste, associated bloating, and chronic loose stools. Non-absorbable antibiotics such as rifaximin are also options and have shown to be at least as effective as lactulose and have similar outcomes in regards to improvement in mental status and safety. At approximately $4/pill, however, rifaximin can be cost-prohibitive, making it a second-line treatment after lactulose (47,49,50).

Recent studies have introduced polyethylene glycol 3,350-electrolyte solution (PEG) as a safe and effective alternative to lactulose (51). The HELP trial demonstrated that PEG offered rapid resolution of HE with a median time of 1 day, representing a 50% decrease in time when compared to that required with lactulose. It had few adverse events and was generally well tolerated across patient populations with less severe electrolyte disturbances (52). Given the more rapid resolution of HE with PEG, it is likely that significant cost savings are associated with its use. Interestingly, >50% of patients desired to continue PEG at discharge as opposed to lactulose (51).

Psychological symptoms

Depressive symptoms contribute to the poor QOL

experienced by patients with HBMs and have a prevalence rate of 30–40% (53). Patients with high physical symptom burden have been shown to have more severe depressive symptoms. Importantly, these same patients show significant improvement in depressive symptoms after early palliative care intervention and improvement in symptom burden. Interestingly, only 23% of patients were on pharmacologic treatment for mood at the beginning of an early palliative care intervention and standardized assessments of mood significantly improved despite no increase in antidepressant use. While depression is typically managed with antidepressant medications, it appears that in patients with ESLD and HBMs, first-line management of depression should be aggressive physical symptom control and early supportive care (54). This is consistent with findings in a landmark study that demonstrated improved QOL and fewer depressive symptoms in patients with other types of cancers who received early palliative care without respect to antidepressant use (14).

Pruritis

Pruritis can develop in patients with HBMs and contributes to poor QOL. Its pathogenesis is not well understood, but it is thought to result from accumulation of a pruritogenic substance most commonly related to cholestasis. If pruritis is related to extrahepatic biliary obstruction, management typically focuses on the underlying disease via surgical intervention, stenting, or percutaneous drainage (49,50).

Pruritis related to intrahepatic cholestasis has a number of management options. Cholestyramine is a nonabsorbable resin that binds bile salts and pruritogenic substances and facilitates excretion in the stool. Roughly 80% of patients will respond to this agent with good effect. It is generally taken early in the morning and before breakfast after pruritogens have accumulated in the gallbladder overnight. Patients should be warned it will impair the absorption of fat-soluble vitamins and medications and thus needs to be timed accordingly (49,50,55,56).

Rifampicin is a semisynthetic antibiotic that has good efficacy in the short-term, but is limited in long-term use due to hepatotoxicity, renal injury, and hemolytic anemia. Notably, it is an enzyme inducer which may impact the clearance of co-administered medications. Patients should be warned that it will cause an orange-red discoloration of urine and tears (49,50,57).

Opioid antagonists such naloxone and naltrexone have shown efficacy in the treatment of pruritis in HBMs and underlying liver disease. This was first reported in 1979 and dramatically changed management of intractable pruritis (58). In the course of cholestasis, biliary cells synthesize opioid peptides which mediate pruritis through central receptors and peripheral nerve endings. Opioid receptors down regulate in the central nervous system in response to increased endogenous opioid circulation. In the initial time period, this can induce a temporary withdrawlike syndrome as opioid-antagonists are introduced for pruritis. This can be managed via co-administration of adjuvant medications such as clonidine in addition to starting with subtherapeutic doses of naloxone or naltrexone. Alternatively, when opioid-antagonists are used long-term for pruritis, the central opioid receptors will upregulate in response to chronic blockade, leading to increased endogenous sensitivity and the perception of worsening pruritis. This can be managed by uptitration of the opioid antagonist or weekly brief drug holidays (49,50,59).

Advance care planning

Advance care planning is among the most important and yet most challenging aspects of early palliative care for patients with HBMs and underlying liver disease. The highly variable clinical course alone creates a great deal of prognostic uncertainty and planning difficulties are further compounded by the uncertainty brought on by potential transplantation. Not all patients are candidates for transplantation and for those who are, such candidacy may change over time as their disease progresses. This has been referred to as the "death/life paradox" for patients on the transplant list as they must simultaneously plan for death without transplantation or a new life following transplantation (60). Between these extremes lie the possibilities of listing, delisting, lack of organ availability, catastrophic decline, and complications from transplant itself. Lastly, these discussions are time sensitive and should occur early in the disease course given that HE can impact decision-making capacity. They should be revisited with every change in functional status, disease status, or treatment. Identifying surrogate decision makers at an early timepoint should be made a priority (49,50,60).

Conclusions

Patients with HBMs experience a plethora of symptoms related to both their disease and underlying abnormal liver function. Early referral to palliative care should be considered even in the setting of curative care for the

numerous reasons discussed above. Palliative care addresses the patient, not the disease, and can be provided in parallel to disease specific care. It will help to treat the symptoms of the disease as well as those associated with its treatments. Palliative care addresses the physical, emotional, and spiritual needs of both patients and their caregivers. Formal guidelines for provision of palliative care for patients with HBMs are lacking at this time, but their absence should not be a barrier to offering such care as early as possible to all patients with HBMs.

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