Medical Sciences

Systemic Treatment of Advanced Hepatocellular Carcinoma in Older Adults

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Over the past 30 years, the incidence in of hepatocellular carcinoma (HCC) in the United States has tripled, largely due to untreated chronic Hepatitis C virus, alcoholic hepatitis, and non-alcoholic steatohepatitis (NASH). Additionally, the incidence of HCC among South Texas Hispanics is higher than elsewhere in the United States. The median age of HCC is 62 years in United States and 67 years in South Texas, with over 30% being 70 years of age or older. However, there is limited data on how to treat older adults with advanced HCC. In this review, we will discuss treatment options for older adults with advanced HCC, further emphasizing the need for prospective studies in this population.

hepatocellular carcinoma | older adult | treatment options | targeted therapy | sorafenib

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer globally and is the third leading cause of cancer deaths. Over 700,000 new cases of HCC are diagnosed each year worldwide with large geographic variation in both risk factors and incidence (1, 2). With an overall 5-year survival of <12%, HCC has become the fastest rising cause of cancer related death in the U.S. (2). Despite the decrease of incidence in the East, the incidence of HCC in the U.S. has tripled in the last 30 years. The incidence rates of HCC in Texas has increased 69% in the last decade and are 2.6 times higher in Hispanics compared with non-Hispanic whites (2-4). This is largely because of chronic Hepatitis C Virus (HCV), alcoholic liver disease, and non-alcoholic steatohepatitis (NASH) (2-4). Additionally, the incidence of HCC among South Texas Hispanics is higher than elsewhere in the U.S., which may be associated with greater prevalence of obesity and diabetes (4). The median age of HCC is 62 years in U.S. and 67 years in South Texas, with over 30% in patients 70+ years of age (4). With an increased longevity of the population, the number of older patients with HCC is expected to increase. HCC in the U.S. is a unique disease from the East, but most studies are based on non-U.S. patients. Therefore, more studies are needed to evaluate the biology of HCC in the U.S. population.

Characteristics of HCC in older adults

Retrospective analyses from international studies show mixed data on clinical and disease characteristics of HCC in older patients. Retrospective data, predominantly from non-U.S. patients show that older patients have similar stages, survival and toxicity (5-7). However, they have less liver fibrosis, receive less curative treatment, and have more HCV, NASH, and comorbidities as compared to younger patients (5-7). Therefore, prospective characterization of the unique biology of HCC in older U.S. adults would allow us to treat these patients with a personalized approach.

Treatment of HCC in older adults

Treatment patterns in older HCC patients would allow us to identify barriers to treatment and risk factors for increased morbidity in older patients. Due to the lack of assessments utilized to identify patients at higher risk of toxicity, treatment patterns vary among providers, with some older patients overtreated and others undertreated. Although fit older adults were represented in these global studies, patients who have vulnerability or frailty, organ dysfunction and comorbidities were excluded due to strict inclusion criteria. Therefore, applying results of large phase III clinical trials to older patients who are vulnerable or frail can result in increased morbidity and mortality.

Treatment of HCC in all older patients based on clinical trials of young patients and fit older adults without comorbidities may be inappropriate. For HCC confined to the liver, available treatment options include surgery, ablative therapies, such as radiofrequency ablation (RFA), or transarterial chemoembolization (TACE), all of which achieve modest response (2). Up to 80% of patients initially presenting with HCC have advanced unresectable or metastatic disease. Systemic therapy is the only option for patients with advanced metastatic disease. Currently, there are several treatment options for HCC, including multi-kinase inhibitors such as first-line agent sorafenib, second-line agent regorafenib, and immunotherapy agent nivolumab.

Sorafenib, a multi-kinase inhibitor of Raf/MEK/ERK signaling and the receptor tyrosine kinase, was shown to induce apoptosis and inhibit tumor proliferation as well as angiogenesis in a variety of tumors (8). The molecular involvement of the Raf-1 and tyrosine kinase signaling pathways has been well established in the pathogenesis of HCC and provides a rationale for the investigation of sorafenib in HCC treatment (9). Sorafenib is the first drug to demonstrate efficacy in HCC in a recent randomized, placebo-controlled study (SHARP), with mTTP improved from 2.8 months with placebo to 5.5 months with sorafenib, and median overall survival (mOS) improved from 7.9 months with placebo to 10.7 months with sorafenib (10).

In the SHARP trial, the mean age was 64.9 ± 11.2 years, whereas the Asia-Pacific trial mean was 51 years (range 23-86) (10). The eligibility criteria also included an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less, Child-Pugh liver function class A, and adequate bone marrow, liver and renal function. Therefore, this study included fit older patients, yet in clinical practice, sorafenib treatment is given to vulnerable or frail patients, without knowing the true impact on treatment morbidity and mortality.

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Table 1. CGA measures to consider in older adults with HCC.

Geriatric Syndrome	Geriatric Assessment Tools	Encouraged action for a positive finding
Medications	Prescribed, over-the-counter, herbal supplements	Decrease duplicated medications or medications not used. Consider Home Health for medication management.
Comorbidities	Charlson Comorbidity Index, prior hospitalizations	Referral to Geriatrician to assist with comorbidity management and review goals of care.
Cognition	MOCA	Referral to Geriatrician for possible cognitive impairment.
Functional assessments	Karnofsky performance scale index, timed up and go, Short Physical Performance Battery (SPPB), ADLs, IADLs, number falls in last 6 months	Referral to PT/OT, order mobility aides, home safety evaluation, provider services.
Nutrition	BMI, weight loss, Mini nutritional assessment (MNA) (27)	Referral to nutritionist.
Supportive care	MOS Social Support Scale	Referral to social work.
Depression Screen	Geriatric depression scale	Referral to Geriatrician and consider starting anti-depressant.

Retrospective analysis of advanced HCC patients receiving sorafenib from 2008-2013 at our institution showed mOS for <65 was 10.2 months vs 13.5 months for 65+, but not statistically significant, with no differences in mOS with dose reductions. In this cohort, 40% of patients <65 have Child-Pugh A cirrhosis versus 70% of patients 65+ have Child-Pugh A cirrhosis. Among 109 patients dose reductions in <65 vs 65+ were 64.6 vs 70% (P=0.66); survival difference were not statistically significant. We noted a trend to improved survival in 65+ patients with AST/Platelet Ratio (APRI) </=1.68, but not statistically significant. Sorafenib was tolerated in the older. Our analysis of older patients with advanced HCC showed similar mortality and toxicity to sorafenib (7, 11); but, this study was limited by its retrospective nature and lack of comprehensive geriatric assessment (CGA). The ideal candidate for sorafenib is the older adult with optimum liver function, good performance status and no co-morbidities; however, close monitoring should always be maintained (12).

In the last year, four new systemic therapies have been approved for HCC. Newer treatments, such as tyrosine kinase inhibitors, regorafenib and cabozantinib, have been approved for second-line treatment (13, 14). Most recently, lenvatinib has been approved for first-line based on a non-inferiority study in comparison to sorafenib (15). In the subgroup analysis, these studies showed that patients 65 or older received survival benefit of the new agent; however, toxicity data specific to older adults in this study have not yet been reported (13-15). Also, immunotherapy has shown to be efficacious in HCC as well. Nivolumab has been approved in HCC as a second-line treatment (16). In the CheckMate 040 study, 42% of patients were 65 or older in the escalation phase, and 47% of patients were 65 or older in the expansion phase, but the effect on toxicity and functional status is unknown in these fit older HCC patients (16). Future studies are needed to prospectively characterize the distinct disease and treatment patterns of older HCC patients as compared to younger patients.

Geriatric assessments in older adults with HCC

Geriatric assessments rather than clinical judgement should guide treatment in older patients with HCC. In addition to severity of cirrhosis, stage of HCC, and performance status (i.e., ECOG), clinical judgement has a predominant impact on the decision to treat and the type of treatments to give to older patients with HCC. Geriatric assessments have not been incorporated into the treatment algorithm for older HCC patients. As a result, the morbidity and mortality of HCC treatments is unknown in vulnerable and frail older adults. However, studies show that geriatric assessments do have significant impact on treatment decisions in older cancer patients and should be included in initial assessments (17).

CGA predicts survival and toxicity in older patients and would identify patients at-risk for increased toxicity from HCC treatments. Studies have shown that CGA is an effective method to identify older patients who benefit from treatment (18). Tools such as CARG chemotherapy tool (19) and CRASH score (20), have been validated in multiple studies to predict chemotherapy toxicity, Patients with HCC have not been studied with these tools, so it is unclear how to apply them to this particular population. Therefore, CGA should be evaluated prospectively in older HCC patients so we can identify patients who benefit from HCC treatments. We need to expand our baseline assessments to incorporate CGA to proactively address geriatric syndromes early in our treatment algorithm (Table 1).

Molecular aging in HCC

The impact of systemic treatments on molecular aging in HCC patients has not been defined. Chronologic aging has been associated with an increase in senescent cell populations throughout the body (21). Most senescent cells appear to express $p16^{Ink4a}$, a cyclin-dependent kinase inhibitor and tumor suppressor, and is known to increase with aging in pre-clinical and clinical models, including cancer patients (22-24). The causal relationship between cellular senescence and aging is not completely understood. It is thought that pro-inflammatory factor produced by senescent cells (IL-1, IL-6, IL-8, TNF-alpha, MCP1, MMP3), known as the SASP, mediate the aging phenotype (25). Chemotherapy is known to induce cellular senescence (24). Senescent cells, expressing $p16^{Ink4a}$ and senescence-associated secretory phenotype (SASP), also contribute to chemo-resistance (26). To date, these biomarkers have not been evaluated in HCC patients receiving sorafenib or other systemic treatments. Therefore, biomarkers of aging should be explored prospectively to determine if cellular senescence is associated with treatment outcomes. Further studies should explore the association of biomarkers of aging to treatment outcomes in HCC patients.

Conclusion

Although there is limited research indicating effective and safe treatment with tyrosine-kinase inhibitors and immunotherapy in older adults with HCC, there needs to be further research within the United States as this is a unique HCC population. Prospectively studying treatments in older adults with the incorporation of CGA are necessary so we can further individualize treatment in older adults with advanced HCC.

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