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 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 antiangiogenesis 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.

Conflict of Interest: No conflicts declared.

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Geriatric assessments rather than clinical judgement should guide treatment in 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<sup>ink4a</sup>, 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<sup>ink4a</sup> 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.

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

Acknowledgements

NCl P30 CA054174


