Immune Checkpoint Inhibitors as a Treatment for Hepatocellular Carcinoma in the Early Stages Before Liver Transplantation

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Abstract

Hepatocellular Carcinoma (HCC) is one of the most frequent cancers in the world, and its frequency is on the rise. This review examines the present and expanding amount of evidence on the use of immune checkpoint inhibitors in patients with advanced HCC who are awaiting liver transplantation, as well as many of the unanswered concerns. Immunotherapy clearly has a function in HCC, and more clinical trials will assist to define the indications and criteria for its usage. Hepatocellular Carcinoma (HCC) is the most frequent kind of liver cancer and the third greatest cause of mortality from cancer in the world. Liver-directed medications for locoregional control or down-staging prior to final surgical therapy with hepatic resection or liver transplantation have been extensively explored and are the pillars of current treatment recommendations for early and intermediate-stage illness. Our existing treatment approaches are insufficient to enhance disease-specific and overall survival as the prevalence of HCC has continued to rise, and more patients are presenting with advanced illness. Until recently, sorafenib was the only systemic treatment available, and it had a poor track record. Immuno-arrival oncology's has piqued curiosity, and it has shifted the treatment paradigm for HCC. Combination regimens such as atezolizumab plus bevacizumab, durvalumab plus tremelimumab, and pembrolizumab with Lenvatinib have recently showed excellent responses of 25%-35%, which is much greater than single agent responses. In advanced-stage HCC patients, complete responses to checkpoint inhibitor treatment have been recorded.

Keywords: Hepatocellular Carcinoma (HCC) • Immune checkpoint inhibitors • Nivolumab neoadjuvant therapy • Barcelona Clinic Liver Classification (BCLC) • Liver transplant • Cirrhosis

Introduction

Despite the fact that Hepatocellular Carcinoma (HCC) is ubiquitous all throughout the world, there are regional differences in incidence and prevalence, as well as instigating reasons and treatment approaches. Among primary liver tumors, HCC is the most frequent malignancy (75% to 95%). Its prevalence in the United States is predicted to rise until 2030, with Hispanics, blacks, and whites being the most affected. The most significant risk factor for HCC is cirrhosis. In individuals with cirrhosis, current guidelines suggest screening for HCC every 6 months. Long-term hepatitis C infections, as well as obesity and diabetes, which result in Non-Alcoholic Steatohepatitis (NASH) and alcoholic liver disease, are the key causes of HCC development in North America and Europe. Hepatitis B is the most common cause of liver cancer in parts of Asia and Africa.

The BRIDGE (Bridge to Better Outcomes in HCC) research, which included data from 42 sites in 14 countries, looked at worldwide patterns and variance in HCC care. The committee noted the obvious need for greater monitoring to detect HCC sooner, as well as improved treatment of advanced illness. They found that up to 70% of HCC patients with advanced illness were only eligible for palliative care, with median overall survival of 15 months and 4 months for the Barcelona Clinic Liver Classification (BCLC) stages C and D, respectively. In reality, the most prevalent BCLC stage at diagnosis was C in North America, Europe, China, and South Korea, and A in Taiwan and Japan, according to the BRIDGE Study. Despite the wide range of treatments, loco regional therapy was the most common across all BCLC stages around the world (probably due to later presentation); the exceptions were Taiwan, where resection was the first treatment, and Japan, where percutaneous ethanol injection or radiofrequency ablation were the preferred first treatments. Trans Arterial Chemo Embolization (TACE) was determined to be the most prevalent method of loco regional treatment for BCLC stage C and palliation for stage D by the BRIDGE group. Sorafenib was the established systemic drug for palliation, with the added bonus of merely enhancing median overall survival by 2months to 3 months. Despite the fact that the American Association for the Study of Liver Disease (AASLD)/ European Association for the Study of Liver Disease (EASL) guidelines recommend sorafenib for BCLC Stage C disease, the BRIDGE study found low use in these patients worldwide, possibly due to a lack of resources and a high toxicity profile, as well as the lack of benefit. With the growing prevalence of HCC, advanced disease that is outside the standard treatment paradigm of liver resection or transplantation is increasingly common. Adjunct treatment with loco regional therapies has allowed tumor down-staging and future remnant growth, and has provided bridges to potential curative therapy in surgery. If fact, in some cases with less advanced disease, loco regional therapy can be curative. Because there is such a broad range of HCC clinical presentation within BCLC classes once granular clinical facts are established, HCC care must be tailored to each individual patient utilizing a multidisciplinary tumor board, as the BCLC 2022 update supports. The selection of BCLC Stage B and C patients with varying presentations of tumor burden, prior local-regional therapy, possible resection, and potential previous systemic therapy should be the focus for the development of novel treatment protocols when considering where upfront therapy for liver transplantation would be most beneficial. Alpha-Fetoprotein (AFP) is a useful biomarker for monitoring HCC development, recurrence, and response to therapy when expressed by HCC tumor cells, which occurs around 70% of the time. It is also an efficient prognosticator of HCC behavior. Its sensitivity and specificity in predicting disease progression have led to its use in US liver allocation policy and waitlist priority assignment. MELD exceptions are granted to HCC patients in the United States to reflect their mortality risk, which is connected to the AFP. With the introduction of Immuno-Oncology (IO), substantial anti-tumor effects have been documented in a variety of malignancies, including melanoma, non-small-cell lung cancer, and urothelial tumors, when these novel immunotherapeutic medicines were administered. Multiple medication classes that upregulate one's innate immune system to boost anti-tumor immunity and accelerate tumor cell death are referred to as immunotherapy. Sorafenib was the only proven systemic treatment for hepatocellular carcinoma until recently. Similar drugs, such as cabozantinib, lenvatinib, and regorafenib, all multi-targeted tyrosine kinase inhibitors, have showed survival advantages in recent years. Furthermore, ramucirumab, a vascular endothelial growth factor receptor-2 inhibitor, has been found to be effective and offers survival advantages. Immunotherapy agents fall into a variety of groups. Immunological modulation antibodies that disrupt immune regulatory checkpoints and CAR-modified T cells have been the subjects of the greatest research in advanced HCC. The Anti-Programmed Cell Death 1 (PD-1) and Anti-Programmed Cell Death Ligand 1 (PD-L1) drugs constitute the first category.

Nivolumab was one of the first to be researched and was initially given as an infusion to patients with advanced resistant malignancies such as melanoma, renal cell carcinoma, and non-small-cell carcinoma. Because of the low toxicity of these early experiences, pembrolizumab was eagerly studied and used for comparable disorders. Nivolumab received rapid FDA approval as a second-line therapy for HCC not long after. Pembrolizumab is now FDA-approved as a single treatment for previously treated advanced HCC. Finally, another FDA-approved therapy for previously treated HCC is the combination of nivolumab and ipilimumab. However, based on unfavourable findings, the FDA's Oncologic Drugs Advisory Committee decided to reject the fast approval of nivolumab monotherapy for patients with advanced hepatocellular carcinoma who had previously had sorafenib treatment. In the advanced HCC arena, there is clearly still a lot to learn about these drugs as single and combination therapies. Multiple investigations across many tumour types have led to some consensus guidelines in the management of these immune-related adverse events in terms of side-effect patterns and adverse occurrences. The most prevalent adverse effects are skin, gastrointestinal, endocrine, lung, and musculoskeletal, whereas cardiovascular, hematologic, renal, neurologic, and eye problems are far less common. Treatment-related mortality affects up to 2% of persons receiving treatment, with the percentage varied depending on the medicine. Even after medication discontinuation, most of these symptoms have a delayed onset and a lengthy duration, but they often occur within 3 months to 6 months after beginning. Immune-Related Adverse Events (irAEs) are common across many malignancies, with up to 70% of individuals receiving a PD-1/PD-L1 antibody and 90% of those getting an anti-CTLA4 antibody experiencing them. The Toxicity Management Working Group of the Society for Immunotherapy of Cancer has developed a consensus paper on how to present and treat immune-related side events when using this class of medications. They've listed some of the most common as well as some of the more unusual notable occurrences. These medicines are known to cause fatigue and infusion-related symptoms. Up to 40% of individuals develop a maculopapular rash and pruritus. Diarrhea is a common occurrence that must be separated from colitis. Colitis appears to be more common with combination treatment than with monotherapy. Hepatitis can occur in certain people, especially when nivolumab and ipilimumab are given together, and can occur up to 30% of the time.

Discussion

For HCC patients with impaired liver function, this must be carefully evaluated. The most prevalent endocrine side effects include thyroid dysfunction and hypopituitarism.

Pneumonitis is a rare ailment that affects fewer than 5% of people. Multiple adverse effects are prevalent in immunotherapy patients and should be constantly monitored. Care and experience are essential when using this class of medications, and because certain adverse outcomes can arise later, even after the drugs have been stopped, patients must be diligent in monitoring their health outside of their main diagnosis of HCC. More additions to the treatment paradigm are required as the prevalence of intermediate and advanced HCC rises. The arrival of the immunotherapy era holds a lot of promise for lowering the burden of HCC-related morbidity and death in patients with a lot of tumour.

Liver transplantation is a promising treatment option for selected patients with cirrhosis and early-stage HCC, with low recurrence rates and high survival. Because of the strong local control, the use of loco regional treatment for HCC prior to liver transplant has been linked to a decreased risk of waitlist dropout and has permitted the down-staging of patients with intermediate and advanced HCC within Milan criteria with outstanding results. The effectiveness of "down-staging" with loco regional treatment, as well as the promising findings of immunotherapy trials in advanced HCC, has prompted HCC doctors to consider if immunotherapy may be used as a down-staging therapy. Indeed, brave transplant and HCC tumour programmes have begun using immunotherapy off-label as "accidental neoadjuvant" therapy, in which the indication is advanced illness and immunotherapy is employed as the destination therapy. Only once remarkable clinical responses are observed is the move to the transplant pathway implemented. Based on these anecdotal experiences, it's unclear how immunotherapy will be employed as a neoadjuvant therapy prior to transplant, if it'll be combined with other treatment modalities, and what the most successful immunotherapeutic techniques for first-line and second line therapy will be.

Conclusion

We need to enhance intermediate and advanced HCC care in light of the rising global frequency of Hepatocellular Carcinoma and considerable cancer-specific mortality. Combining immunotherapy with bridge-to-transplant to extend survival is a promising treatment strategy, but it must be studied versus immunotherapy alone as well as transplant alone. Sorafenib has been the backbone of systemic treatment, although recent trials have focused toward immunotherapy for advanced illness. Immunotherapy may be used in the neoadjuvant and adjuvant stages after liver transplantation, as well as in the palliative stage, based on the significant responses seen.

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