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Mini Review

Immunotherapy in the Treatment of Hepatocellular Carcinoma: The Role of Atezolizumab

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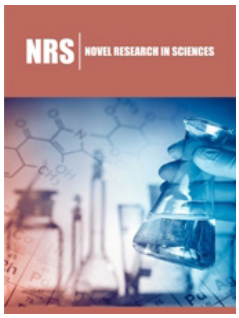

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Abstract

Hepatocellular carcinoma is responsible for great morbidity and mortality, being the fourth commonest cause of cancer-related deaths worldwide. While related to viral infections, alcohol abuse and metabolic syndrome, these tumours tend to affect patients with an already compromised liver and overall worse health status. Along with an advanced stage at diagnosis, curative treatment options are often not available, highlighting the need for systemic therapies. At the moment, immunotherapy has shown great results in the treatment of advanced stage HCC, with the combination of atezolizumab and bevacizumab showcasing improved overall survival and progression free survival, with manageable adverse events.

Keywords: Atezolizumab; Hepatocellular carcinoma; Immunotherapy; PD-L1

Abbreviations: CTLA-4: Cytotoxic T Lymphocyte-Associated Protein 4; FDA: Food and Drug Association; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; ICI: Immune Checkpoint Inhibitor; PD-1: Programmed Cell Death 1; PD-L1: Programmed Cell Death Ligand 1; PFS: Progression Free Survival; ORR: Overall Response Rate; OS: Overall Survival

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Introduction

Hepatic cancer has an important role regarding global health, being the fourth leading cause of cancer-related death in the world, with HCC being the most common type of liver cancer [1-3]. Common etiologic factors include viral infections such as Hepatitis B and C, alcohol abuse and non-alcoholic steatohepatitis, commonly found in patients with metabolic syndrome [1,2,4]. Although current therapies for HCV infection have reduced the incidence of HCC, this infection is still responsible for several cirrhosis cases, with this liver alteration being responsible for a very increased risk of developing HCC [1]. On the other hand, metabolic syndrome is a growing aetiology of HCC, especially in western countries [1]. However, around two-thirds of HCC diagnosis are not candidates for curative treatment options [3,5], showcasing the need for other therapeutic alternatives. Given the importance of HCC, besides prevention and early diagnosis, therapeutic options have a major role in the management of patients with HCC and with the emerging role of immunotherapy in different cancer scenarios ICIs have proven to play an important part in the treatment of patients with HCC, motivating this mini review. A PubMed database search was made in September 2021, using the query "(Atezolizumab) AND (Hepatocellular Carcinoma OR HCC OR Hepatic cancer)" and filtering the results for articles published in the last year, refining for English and Portuguese articles only. Using the referred query, the articles in this mini review were obtained and used.

Current Treatment Options for HCC

At the moment, the FDA approved therapies for HCC include surgery such as hepatic resection and liver transplantation, local ablation with radiofrequency as well as systemic

therapies with sorafenib, lenvatinib, regorafenib, cabozantinib, ramucirumab and the combination of atezolizumab with bevacizumab [1-3]. Surgical interventions remain the backbone of curative treatment of patients with HCC, with a 5-year survival around 70-80% [1,4]. In intermediate-stage HCC, Transarterial Chemoembolization (TACE) is also an available treatment widely used [1]. Given the advanced stage many HCC are diagnosed, the emergence of new therapeutic options such as immunotherapies with ICIs have a growing part [4,6].

Immunotherapy in the Treatment of HCC

T CD8+ cells have a very important role in anti-tumour immunity, mainly regarding the host's response to tumour cells [1,4]. However, analyses have shown non-functional CD8+ T cells, mainly due to Treg cells, enabling tumour cells to evade the immune system and, therefore, facilitate disease progression [1,4]. Besides, the overexpression of immune checkpoints such as CTLA-4 and PD-1 also plays a role in the development of HCC [1]. T-cell activation is inhibited due to the interaction of PD-1 and its ligands (one of them being PD-L1), facilitating tumour expansion [7]. In addition, tumour cells can also express PD-L1, binding to PD-1 and avoiding immune attack, justifying the use of PD-L1 blocking drugs such as atezolizumab [3]. Currently, the most effective single-drug treatments revolve around sorafenib and lenvatinib. However, studies show great clinical benefits with the use of immunotherapy in around 15-20% of patients with HCC [1]. In fact, the VEGF pathway results in a immunosuppressive environment, with the activation of Treg cells [5], making this the rationale behind the use of combination therapy atezolizumab+bevacizumab, since blocking PD-L1 enables the host's immune system to be active [1,7].

Atezolizumab and HCC

Atezolizumab is an anti-PD-L1 antibody, blocking the interaction between PD-L1 and the PD-1 and B7-1 receptors [5], currently approved in combination with bevacizumab (anti-VEGF antibody), in the treatment of advanced HCC [1,2]. The expected median survival of patients with advanced HCC is around 8 months without treatment, but studies have shown the benefit of atezolizumab+bevacizumab with almost twice this number [1]. The IMbrave150 trial compared sorafenib with atezolizumab+bevacizumab as first-line therapy for advanced HCC with a median survival of 19.2 months (vs 13.4 months with sorafenib). Besides, an improvement in PFS was also observed with 6.8 months vs 4.3 months using only sorafenib [1,2,5]. The objective response rates obtained were 27.3% in the atezolizumab+bevacizumab group, compared with the 11.9% in the sorafenib group [5], with an ORR of 36% in the combination group [7]. The disease control rate in the group using atezolizumab+bevacizumab was 73.8% compared to 55.3% in the sorafenib group [5]. Furthermore, 87.6% of the patients in the combination group had a response longer than 6 months when compared to 59.1% in the sorafenib group [5]. In addition, patients referred slower deterioration of life quality using atezolizumab+bevacizumab when compared to sorafenib (11.2 months vs. 3.6months). Candidates to this treatment should have oesophageal varices ruled out with a esophago gastroduodenoscopy due to the risk of bleeding [2]. On the other hand, the most common adverse events related to the use of immunotherapy with atezolizumab include autoimmune events, occurring in around 15% of patients [3], nonetheless more tolerable than the commonly found with other therapeutic agents, with only around 6% grade 3 or higher [1]. The commonest grade 3 or higher event with the treatment combination was hypertension in around 15% of patients [5]. Some of these adverse events include skin rash, diarrhoea, joint ache and organ immune-related toxicity such as myocarditis, pneumonitis and enterocolitis [1,4,7]. Several other studies regarding the use of atezolizumab in the treatment of patients with HCC are currently undergoing, namely ORIENT-32 with the aforementioned combination and COSMIC-312, assessing an association of atezolizumab+cabozantinib (a tyrosine kinase inhibitor) [7].

Conclusion

Hepatocellular carcinoma is responsible for a high rate of mortality and morbidity worldwide, responsible for a high number of cancer-related deaths. Furthermore, HCC tends to be diagnosed in an advanced stage and in patients with already compromised liver tissue and overall health status, making curative therapeutic interventions less likely to succeed. In fact, with this in mind, systemic therapies are often the offered treatment to patients with HCC. With the growing role of immune checkpoint inhibitors such as atezolizumab, patients with HCC may have greater life expectancy with an acceptable adverse-events rate. However, given that only a percentage of patients with HCC have shown good response to these therapies, this highlights the need for biomarkers of response to these drugs. Besides, the high costs associated with these drugs make them less appealing, and this should be a weighting factor in the future, hopefully lowering the costs and allowing for a broader use of ICIs. In short, immune checkpoint inhibition with drugs such as atezolizumab has shown great results in the treatment of patients with HCC, making immunotherapy an option in the management of these patients.

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