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EDITORIAL

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Back to the basics: How the preclinical rationale shapes the immunotherapy landscape for hepatocellular carcinoma

EDITORIAL

Few types of cancers have witnessed such a dramatic change of the treatment paradigm in the last year as hepatocellular carcinoma (HCC). 2020 has been a milestone year, establishing atezolizumab plus bevacizumab as the new standard of care for first-line treatment of unresectable HCC, based on the results of the phase III IMbrave150 trial.[1,2] The success of the combination of an anti-programmed death-ligand 1 (PD-L1) monoclonal antibody (mAb) and an antiangiogenic agent is the result of a strong preclinical rationale, which has been widely studied in HCC, paving the way for its widespread clinical application. The positive results of the IMbrave150 study are just the tip of the iceberg, with several immunotherapy combinations currently under investigation in phase I-III studies. Immune checkpoint inhibitors (ICIs) used as monotherapy have led to disappointing results in HCC, both in first line, with nivolumab failing to demonstrate any survival advantage over sorafenib in the CheckMate 459 trial,[3] and in second line, with pembrolizumab not confirming the promising results of the previous phase II trial in the KEYNOTE-240 trial.[4] For this reason, combining ICIs with other drug classes could overcome innate tumour resistance and eventually increase the number of patients benefitting from immunotherapy. The novel treatment strategies under the spotlight include PD-1/PD-L1 mAbs plus antivascular endothelial growth factor (VEGF) mAb, PD-1/PD-L1 mAbs plus multikinase inhibitors (MKIs) and ICI combinations (PD-1/PD-L1 mAbs plus cytotoxic T lymphocyte antigen [CTLA]-4 mAbs). In preclinical studies, these combinations have shown to enhance the efficacy of the single agents, thus suggesting a potential synergistic effect.

The use of anti-VEGF agents rests on the principle that HCC is a richly vascularized cancer, and several proangiogenic factors play a central role in tumour growth and distant spread. In addition, preclinical research unravelled a whole world of immunomodulatory effects of the VEGF pathway, thus suggesting the possible use of bevacizumab in combination with immunotherapy. Indeed, VEGF receptors and the downstream effectors induce an immunosuppressive microenvironment by acting on innate and adaptive immune response. VEGF pathway can enhance the action of immature dendritic cells, myeloid-derived suppressor cells (MDSCs) and tumour-associated macrophages, while at the same time increasing the percentage and the action of regulatory T cells (T-regs) in the tumour microenvironment.[5] In preclinical models, the use of bevacizumab has shown to revert these VEGF-induced immunosuppressive mechanisms, and, when bevacizumab is combined with an ICI, antitumor immune response induced by PD-1 blockade seems to be enhanced, even in ICI-resistant HCC models, thanks to an immunostimulatory T cell reprogramming.[6] Based on a similar rationale, the immunomodulatory properties of MKIs with a known antiangiogenic action were extensively studied. In particular, sorafenib, lenvatinib, regorafenib and cabozantinib can promote the immune-mediated antitumor response via a pleiotropic range of actions, from the enhancement of CD4+ and CD8+ T cell infiltration and function to the inhibition of T-regs and MDSCs in the tumour microenvironment.[7] When combined with an ICI, MKIs can exert a synergistic antitumor effect, mainly via an IFN-γ-mediated mechanism or via the induction of the expression of major histocompatibility complex class 1 antigens on tumour cells, which become more sensible to T cell-mediated killing.[7] Based on these promising preclinical results, phase I trials investigating MKI-ICI combinations have obtained remarkable results in terms of tumour response[8] and ongoing phase III trials are testing these novel treatment strategies in large populations (COSMIC-312: NCT03755791; LEAP-002: NCT03713593). Differently from bevacizumab, which is a pure antiangiogenic agent, MKIs have a wide spectrum of action, targeting multiple molecular pathways. Currently, we do not know if this can translate into a different clinical benefit for HCC subgroups, or if the broader spectrum of action of MKIs could be exploited in patients not benefitting from the combination of ICI and anti-VEGF.

Finally, a well-established combination strategy is the double immune checkpoint blockade that, targeting different proteins involved in the regulation of immune response, addresses the multiplicity of immune escape mechanisms. In particular, since CTLA-4 is expressed on intratumoural T-regs, the use of anti-CTLA-4 mAb, such as ipilimumab or tremelimumab, in combination with anti-PD-1/PD-L1 enhances CD8+ T cell immune activation by inhibiting the immunosuppressive activity of T-regs. This is of particular importance in liver cancer, since carcinogenesis is often associated to an immune-permissive microenvironment, characterized by an increased and sustained expression of inhibitory receptors and an increased number of FoxP3+ CD25+ T-regs, thus priming T cells to dysfunction and creating a cancer-permissive microenvironment.[9] After the

promising results obtained in pretreated HCC patients,[10] large phase III trials are investigating the role of these combinations in first line (CheckMate 9DW: NCT04039607; HIMALAYA: NCT03298451). Moreover, further clinical development could come from the identification and characterization of additional T cell checkpoints, such as lymphocyte activation gene-3 (LAG-3), and T cell immunoglobulin mucin-3 (TIM-3), among others, or the use of agonistic antibodies activating immune cells via immune-stimulating targets, such as the glucocorticoid-induced TNFR-related protein. Another promising strategy is targeting indoleamine 2,3-dioxygenase, a key enzyme of the innate immune response: its inhibition, combined with an anti-CTLA-4 mAb, showed interesting results in an HCC murine model.[11]

Future studies should investigate the variations induced by atezolizumab plus bevacizumab in tumour microenvironment, especially in patients not responding to or progressing on immunotherapy. Given the lack of clinical data guiding the choice for second-line treatment, a possible answer for treatment sequencing could come from preclinical studies. Newly arising evidence seems to correlate non-alcoholic steatohepatitis-related HCC to a worse response to immunotherapy, because of the accumulation of exhausted, unconventionally activated CD8+PD1+ T cells in the liver.[12] Should we adopt different treatment strategies for different etiologies? Can new immunotherapy combinations work also in ICI-refractory patients?

2020 is the year marking the start of immunotherapy era for HCC treatment: IMbrave150 was just the first of many steps, and to foresee the future developments of immunotherapy combinations, we need to look back at the basics of preclinical models.

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CONFLICT OF INTEREST

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