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Short Communication

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# Combining Immunotherapy with Anti-angiogenic Therapy: The New Standard of Care for Hepatocellular Cancer?

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## Abstract

Advanced hepatocellular cancer (HCC) is the fourth most common cause of cancer death. Two of the major HCC characteristics are neoangiogenesis and the immune suppression within its limits. Indeed, chronic inflammation promotes vascular alterations by producing several angiogenic factors. Cancer and stromal cells, together with the angiogenic factors, guide the development of a tumor immunosuppressive microenvironment by recruiting regulatory T cells, upregulating the expression of immune checkpoint molecules, and exhausting effector T cells. On this basis, anti-angiogenic therapy has taken on a predominant role in the treatment of HCC, however, it only had a limited impact on overall survival. In this scenario, the combination of immunotherapy and anti-angiogenic therapy could represent a promising novel therapeutic strategy. Recently, atezolizumab plus bevacizumab has been approved as the first-line standard of care thanks to the IMbrave 150 trial results. Data from other ongoing trials could drastically change the clinical approach to HCC treatment.

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## Short Communication

Hepatocellular cancer (HCC) represented the sixth most incident malignancy and the fourth most common cause of cancer death worldwide, in 2018 [1]. Although curative treatment such as hepatic resection (HR), liver transplantation, and locoregional therapies are considered the gold standard for early-stage HCC, recurrence after HR is up to 70% in 5 years [2]. Moreover, HCC is often diagnosed in the advanced unresectable stage and the prognosis remains poor, with a median overall survival (OS) of 2 years [3].

HCC tumorigenesis is linked to chronic inflammation (CI). CI promotes constant liver architecture remodeling, through functional alterations of hepatic stellate cells (HSCs) and hepatic microenvironment modifications toward a stromal one. This process favors not only hepatocyte transformation, tumor development, growth, and invasion, but also an immunosuppressive landscape and angiogenesis [4].

HSCs, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSC), endothelial cells (ECs), and dendritic cells (DCs) take part in the development of an immunosuppressive tumor microenvironment (TME) by recruiting regulatory T cells (T-reg), upregulating the expression of immune checkpoint molecules such as programmed death-ligand 1 (PD-L1), cytotoxic T- lymphocyte protein 4 (CTL4), lymphocyte activation gene 3 protein (LAG-3), B and T lymphocyte attenuator (BTLA) and T cell immunoglobulin-3 (Tim-3). These cells also release growth factors and cytokines like IL-10 and TGF-β which contribute to the suppression of T cell-mediated immune response by increasing the expression of programmed death 1 (PD-1) on natural killer cells, T and B lymphocyte surface [5-7].

HSCs, together with HCC cells, promote angiogenesis and vascular alterations by producing several angiogenic factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), angiopoietin (angpt) 1 or 2, placental growth factor, and transforming growth factor. However, the obtained new vessels are both structurally and functionally abnormal [4]. These alterations lead to the extravasation of proteins and fluid, peritumour edema, and interstitial hypertension, which are responsible at last for hypoxia and acidosis. Moreover, hypoxia increases the expression of hypoxia-inducible factor 1 (HIF-1), a strong angiogenic factor, which is upstream of multiple pro-angiogenic genes, in particular VEGF family members and PDGF [8,9].

VEGF family members also take part in the immune system suppression within the tumor in different ways. VEGF binding with VEGF receptor (VEGFR) 2 on DCs membrane can determine inhibition of nuclear factor-κB signaling, leading to a defect of DCs maturation and, consequentially, a reduced tumor-antigen presentation capacity of these cells. This binding can also upregulate DCs PD-L1 expression, which brings to the suppression of T cells function. When VEGFR2 is activated by VEGF on T cell surfaces, it directly suppresses their

proliferation and cytotoxic function. Moreover, VEGF can induce overexpression of PD-1, CTLA4, TIM3, and LAG3, thus contributing to CD8+ T cells exhaustion. In reverse, VEGF binding to VEGFR2 on T-reg cells increases the number of T-reg cells in peripheral blood, while VEGF linkage to the VEGF co-receptor neuropilin 1 facilitates T-reg tumor homing. VEGF can also increase the percentage of MDSCs and reduce the natural killer cells cytotoxicity, by activating VEGFR3. VEGF also modifies the clustering of intercellular adhesion molecules intracellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), on ECs, reducing the homing and tumor infiltration by the immune cells. Always on ECs, VEGF seems to induce expression of both FAS antigen ligand (FASL), causing the CD8+ T death, and PD-L1 and PD-L2. Other than that, angiogenic-induced hypoxia, and acidosis guide to preferential recruitment of pro-tumor immune cells such as Tregs, MDSCs, M2-phenotype TAMs. Another angiogenic factor, angpt 2, is involved in monocyte and neutrophil recruitment and stimulates monocyte to release interleukin 10, a cytokine responsible for inhibition of effector T cell and expansion of Treg cells. Further, angpt 2 upregulates PD-L1 expression on TAMs [10].

Considering the molecular background previously described, anti-angiogenic therapy has assumed a predominant role in the treatment of HCC. These agents, which target are represented by either VEGF or VEGFRs, can normalize the irregular tumor vascularization by making vessels less leaky, less dilated, and less tortuous, and by increasing the vessels pericyte coverage that improves their stabilization. In this way, they favorite the decrease of interstitial fluid pressure and the increase of tumor oxygenation, improving penetration of cytotoxic agents [11]. Moreover, anti-angiogenic TKIs seem to enhance the uptake of antigen presentation in DCs, the switch of immunosuppressive M2-phenotype TAMs to inflammatory M1-phenotype TAMs, and the activation of cytotoxic T-cells. Anti-angiogenic TKIs-induced normalization of the tumor vasculature can also reduce immunosuppression exerted by Tregs and regulatory B-cells [12,13].

This scenario suggests that a combination of immunotherapy and anti-angiogenic therapy might have a potent synergic anti-tumor effect and could represent a promising novel therapeutic strategy for inhibiting HCC progression, relapse, and metastasis.

Recently, the combination of atezolizumab, an anti-PD-L1 monoclonal antibody (mAb), and bevacizumab, an anti-VEGF mAb, has been approved by the US Food and Drug Administration (FDA) and European Medicine Agency (EMA) as the first-line standard of care in advanced HCC based on data of the phase Ib GO30140 Study and of the phase III IMbrave 150 Study. In the last one, advanced HCC patients were randomized 2:1 to receive atezolizumab + bevacizumab or sorafenib (a multi-target TKI, approved since 2007 for first-line treatment of HCC, which can block the RAS, VEGFR, PDGFR, FMS related tyrosine kinase 3, and KIT kinases) until loss of clinical benefit or unacceptable toxicity. Co-primary endpoints were OS and progression-free survival (PFS) by independent review facility (IRF)-assessed response evaluation criteria in solid tumors (RECIST) 1.1, whereas key secondary endpoints were IRF-overall response rate (ORR) per RECIST 1.1 and IRF-ORR per HCC modified RECIST (mRECIST). The primary data analysis showed that in the intent-to-treat (ITT) population, at a median follow-up of 8.6 months, ORR was 27% in patients receiving atezolizumab and bevacizumab vs 12% in patients receiving sorafenib ($P < 0.0001$) per IRF RECIST 1.1 and 33 vs 13% ($P < 0.0001$) per IRF HCC mRECIST for experimental arm vs control arm, respectively. The median treatment duration was of 7.4 months for atezolizumab, 6.9 for bevacizumab, and 2.8 for sorafenib. Moreover, the association of atezolizumab and bevacizumab was well tolerated and procrastinated the time to deterioration (TTD) of the quality of life of the patients [median TTD, 11.2 vs 3.6 months; hazard ratio (HR), 0.63 (95% CI: 0.46, 0.85)], physical functioning [median TTD, 13.1 vs 4.9 months; HR, 0.53 (95% CI: 0.39, 0.73)], and role functioning [median TTD, 9.1 vs 3.6 months; HR, 0.62 (95% CI: 0.46, 0.84)] compared with sorafenib. Furthermore, the combination therapy postponed TTD in patient-reported symptoms (loss of appetite, fatigue, pain, diarrhea) and led to meaningful clinical symptoms deterioration in a lower proportion of patients [14,15].

Further results are expected about the combination of durvalumab, a PD-L1 inhibitor, and ramucirumab, an anti-VEGFR mAb. The safety and effectiveness of this association were preliminarily tested in a phase Ib study composed of different cohorts of advanced pre-treated cancer patients, including one cohort of 28 HCC subjects (NCT02572687). In this last cohort, ORR was 11%, but in patients that had "high" PD-L1 expression (≥25% of tumor cells or immune cells) achieved 18%. No significant differences in median PFS were observed accordingly to PD-L1 expression (4.4 in overall patients and 5.6 months in patients with high PD-L1 expression) as well as in Mos (10.7 and 16.5 months, respectively). Hypertension, anemia, and fatigue were the most frequent treatment-related adverse events (TRAEs) reported [16].

The association of lenvatinib [a multi-TKI which works against VEGFR-1/2/3, fibroblast growth factor receptor (FGFR)-1/2/3/4, PDGFRa, KIT, and RET, approved by both FDA and EMA for first-line treatment of unresectable HCC], with the anti-PD-1 pembrolizumab, has been analyzed in the first line setting by the preliminary phase Ib study NCT03006926. Data reported an ORR of 42.3%, and a median PFS of 9.69 months (95% CI 5.55–not evaluable). The most frequent any-grade TRAEs were those described in the other trials [17].

VEGF Liver 100 Study is a Phase Ib study assessing the feasibility of the combination of the anti-PD-L1 mAb avelumab plus axitinib, a TKI selective for VEGFR-1/2/3, in treatment-naïve patients with HCC in terms of harmlessness and effectiveness. Provisory results showed an ORR of 13.6% based on RECIST 1.1 and 31.8% based on mRECIST criteria. MPFS was 5.5 and 3.8 months, according to RECIST and mRECIST, respectively. Tumor shrinkage was reported in 68.2% of patients by RECIST and 72.7% of patients by mRECIST. OS data were still immature. The study also showed a manageable safety profile, like the other trials [18].

An open-label, dose-escalation (phase Ia) and expansion study (phase Ib) evaluated the safety and efficacy of the camrelizumab, an anti-PD-1 mAb, and the VEGFR-2 inhibitor apatinib combination therapy in advanced HCC patients (NCT02942329). The main goals were harmlessness and tolerability. A grade 3 TRAE was reported in 60.6%. Hypertension and elevated AST were the most common. Results showed that camrelizumab and apatinib combination had a feasible safety profile and activity against cancer cells in HCC patients [19]. Several ongoing trials are testing the combination of immunotherapy with anti-angiogenic treatment in the first line setting of advanced HCC [20]. The combination of sorafenib and the anti-PD-1 nivolumab is being assessed in phase II, multicenter pilot trial (NCT03439891). Lenvatinib combined with nivolumab is under examination in the exploratory, open-label, single-arm, multicenter phase II IMMUNIB (NCT03841201).The association of lenvatinib plus pembrolizumab compared to lenvatinib in Child-Pugh class A patient is being studied in phase III multicenter, randomized, double-blinded, active-controlled, LEAP-002 trial (NCT03713593).

Efficacy and tolerability of regorafenib (a multi-target TKI that actively suppresses VEGFR-1/2/3, PDGFR, TIE-2, FGFR1, KIT, RET, and B-Raf) plus pembrolizumab combination therapy is being assessed in a multicenter, non-randomized, open-label, dose-escalation, phase Ib study (NCT03347292). Cabozantinib (a TKI targeting VEGFR-2, c-MET, AXL, RET and FLT-3) plus atezolizumab versus sorafenib are being evaluated in the phase III COSMIC-312 trial. Patients will be randomized in a 2:1:1 ratio to take cabozantinib plus atezolizumab, sorafenib, or single agent cabozantinib (NCT03755791). Finally, the combination of camrelizumab plus apatinib compared to sorafenib is currently under study in a randomized, open-label, international, multicenter, phase III trial (NCT03764293).

Soon, results of these trials could drastically change the clinical approach to HCC treatment, just as it has already been happening since the publication of the IMbrave 150 study.

## Competing Interest

The authors declare no competing interests.

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