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REVIEW ARTICLE

Checkpoint inhibitors and anti-angiogenic agents: a winning combination

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The combination of immune checkpoint inhibitors and anti-angiogenic agents is a promising new approach in cancer treatment. Immune checkpoint inhibitors block the signals that help cancer cells evade the immune system, while anti-angiogenic agents target the blood vessels that supply the tumour with nutrients and oxygen, limiting its growth. Importantly, this combination triggers synergistic effects based on molecular and cellular mechanisms, leading to better response rates and longer progression-free survival than treatment alone. However, these combinations can also lead to increased side effects and require close monitoring.

INTRODUCTION

There is a sustained interest in the development of therapeutic combinations with immune checkpoint inhibitors (ICIs) [1]. A main reason for this undeniable interest lies in the efficacy of ICIs in cancer treatment, which, however, remains limited in terms of the number of patients who benefit from this category of drugs in the long term. This phenomenon is mainly due to intrinsic and induced resistance mechanisms pointing to the necessity to combine ICIs with other treatments [2]. An emerging strategy for combinations with ICIs is the association with anti-angiogenic agents [3] based on a strong rationale [4]. This rationale lies in mechanistic interactions in which vascular endothelial growth factor (VEGF) occupies the central place with the subsequent VEGF receptor (VEGFR) downstream cellular signalling and pathophysiological consequences. Preclinical knowledge underlines the role of VEGF in the development of an abnormal vascular network that can disrupt both immune effectors trafficking and delivery of ICIs to the tumour [5]. VEGF can also directly affect immune cell function and impair optimal anti-tumour immunity [6]. Therefore, there are both cellular and molecular signalling pathways that can be restored by anti-angiogenic agents in favour of improved efficacy of ICIs. Successful therapeutic strategies in renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC) have echoed this view clinically [7].

The aim of this review is to highlight the rationale for combining of ICIs with anti-angiogenic agent, to describe their clinical success, and to point out the limitations of this association in terms of induced toxicity, lack of knowledge of predictive markers, and the need to identify resistance mechanisms and corrective strategies.

IMPACT OF THE COMBINATION ON VESSEL STRUCTURATION

Long before the concrete clinical application of mechanistic and molecular considerations of ICIs and their combination with anti-angiogenic agents, Motz and Coukos [8] disclosed key molecular players on endothelial cells that later emerged as the cornerstones of this drug association. The authors emphasised the role of the endothelium in acting as a physical barrier to the passage of lymphocytes to sites of inflammation or tumour growth. Indeed, during the first physiological step of inflammation, there are molecular interactions such as tumour necrosis factor (TNF), which upregulates the expression of chemotactic proteins and adhesion molecules in endothelial cells including intercellular adhesion molecule 1 (ICAM1), and vascular adhesion molecule 1 (VCAM1). These molecules, by direct interaction with circulating T lymphocytes, promote their migration (diapedesis) to the inflamed tissues. The presence of tumour cells is responsible for the local diffusion of several growth factors, including VEGFA which downregulates the expression of ICAM1 and VCAM1 through its specific endothelial cell membrane receptor signalling. This phenomenon reduces T lymphocyte diapedesis. Moreover, this VEGFA-receptor interaction upregulates the expression of VEGFR1, which favours the diapedesis of T Reg cells, thereby down-regulating the potential anti-tumour immune response of T lymphocytes.

This visionary conception of the role that endothelial cells may play in cellular modulation of the anti-tumour immune response is echoed by recent arguments suggesting that tumour neo-angiogenesis favours immunosuppression [9]. Converging experimental data focused on a beneficial modification of the immune cellular trafficking by anti-angiogenic agents. For instance, Hodi and co-workers reported on the combination of CTLA4 blockade with ipilimumab and VEGF inhibition by bevacizumab in cancer patients [10]. The presence of bevacizumab significantly affected the changes in tumour vasculature and immune response.

Tumours exhibit abnormal vasculature, not only in terms of the molecular properties of the constitutive endothelial cells but also

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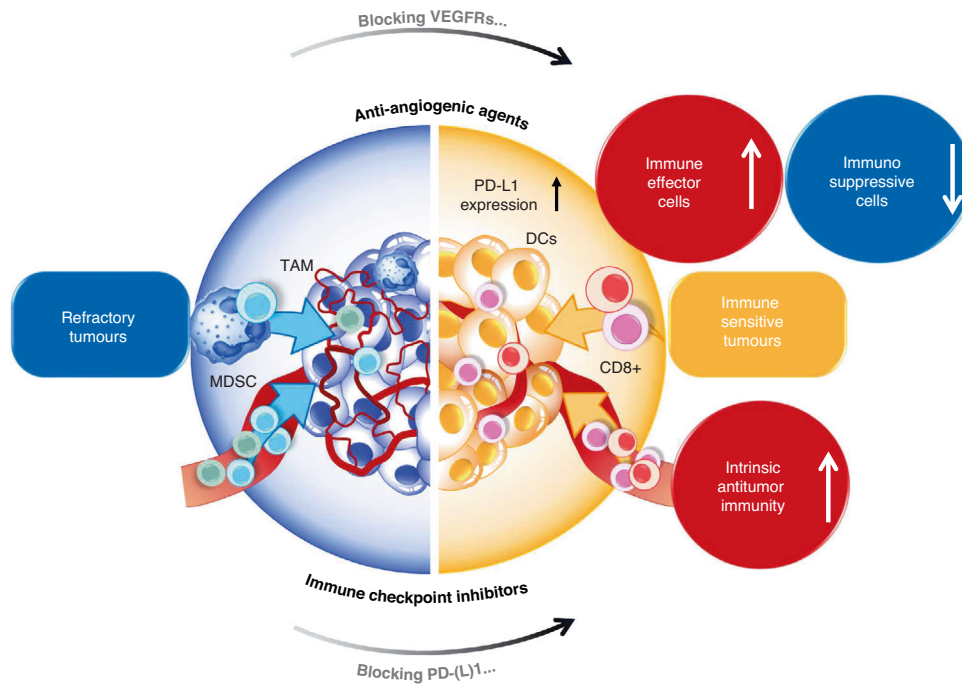
Fig. 1 The combination of anti-angiogenic therapy and ICIs is a winning approach to treating cancer. Anti-angiogenic therapy targets the formation of new blood vessels needed for the tumours to grow and spread, while ICIs reinvigorate the immune system's ability to attack cancer cells. This combination may win by improving the infiltration of immune cells and the delivery of ICIs to the tumour bed, potentially improving their effectiveness. Several clinical trials are underway to evaluate which patients will benefit most from this approach and how to optimise the promise of this combination. DCs Dendritic cells, TAM tumour-associated macrophages, MDSC myeloid-derived suppressor cells.

in terms of the global architectural loss of organisation of tumour vessels [4]. Globally, this abnormal tumour vasculature leads to hypoxia, acidosis and ultimately immune dysfunction. A more pronounced impact of anti-angiogenic treatment on vascular normalisation rather than vessel pruning has been reported [4]. This status of normalised tumour vasculature by anti-angiogenic agents is temporary and results in the intra-tumoral diffusion of immunological cells especially T lymphocytes and macrophages [11]. This so-called phenomenon of tumour vasculature normalisation is complemented by a change in the endothelial cell membrane composition resulting from the direct impact on VEGFR and its intracellular signalling. This relationship introduces some complexity as excessive dosage and duration of anti-VEGFR therapy could exacerbate tumour immunosuppression by reducing perfusion rate due to direct alteration of intratumor vessels [4]. So, it is clear that more experimental basis is needed in order to improve clinically translatable combinations of anti-angiogenic agents and ICIs. In particular, more preclinical data are expected regarding the applied doses of the combination partners as well as the effect of exposure time on final effects of the drug combination compared to the drugs alone.

IMPACT OF THE COMBINATION ON TUMOUR MICROENVIRONMENT

The tumour microenvironment (TME) refers to the cellular and molecular components that surround and interact with cancer cells in a tumour. TME includes various cell types such as cancer-associated fibroblasts, immune cells, and endothelial cells [12, 13]. An important aspect of the TME is the tumour immune microenvironment (TIME), which refers to the immune cells and molecules present in the tumour. TIME includes tumour-infiltrating immune cells, such as T cells and macrophages, as well as immune cells in the surrounding stroma. The presence of these immune cells in the TME can have critical effects on cancer progression

[14]. For instance, tumour-infiltrating T cells can help limit the growth and spread of cancer by recognising and attacking cancer cells (Fig. 1).

However, the TIME is a complex and dynamic system that is composed of various cells and molecules that modulate the immune response to cancer. This microenvironment can be influenced by several factors, including the genetic status of the cancer cells, the presence of other cells and molecules in the microenvironment, and the host immune response to the cancer [12]. The TIME may also be influenced by the stage of the cancer and the patient's overall health and immune status. For example, in early-stage cancer, the immune system may be able to effectively fight and eliminate cancer cells, whereas in advanced-stage cancer, it may be less effective at recognising and fighting cancer cells. In addition, since the efficacy of anti-PD-1 therapy in cancer patients depends in a great part on PD-1+CD8+T-cell proliferation and the activation and expression of CD28 in PD-1+CD8+T cells, the accumulation of senescent T cells with downregulation or loss of CD28 may compromise the response to immunotherapy [15–18].

Apart from immune cells itself, the TME can also promote the development of an immunosuppressive microenvironment that can inhibit the immune system's ability to effectively fight cancer cells. Since VEGFR signalling in immune cells is also associated with pro-tumoral TIME development, VEGF/VEGFR inhibitors also appear to act as factors to restore immune cell differentiation and function. However, previous experiments have shown that anti-angiogenic therapy upregulates PD-L1 in tumour tissues and RCC cell lines [19]. These results suggest that anti-angiogenic agents contribute to the restoration of anti-tumour TIME development, but this positive response may be suppressed by immune checkpoint expression, which is more likely to lead to tumour progression. In this context, then, ICIs should help to release extensive immune activity.

Dendritic cells are a type of immune cell that plays a critical role in the immune response by recognising and presenting foreign antigens to other immune cells [20]. They act as sentinels of the immune system, constantly surveying the body for signs of infection or abnormal cells. When dendritic cells encounter antigens, they engulf them and present them on their surface along with molecules of the major histocompatibility complex (MHC) [21]. This allows other immune cells, such as T cells, to recognise and respond to the antigens. VEGF, through the inhibition of NF-κB; decreases the production of certain inflammatory cytokines that play critical roles in both activation/maturation and migration and numbers of dendritic cells [22, 23]. Specifically, VEGF suppresses the migration of dendritic cells to lymph nodes, through the RhoA-cofilin1 pathway mediated by the VEGFR2, and to decrease the expression of MHC class II molecules on their surface [24]. Decreased expression of MHC class II molecules may also hinder the activation of T cells, which is essential for the destruction of cancer cells. In addition, VEGF decreases the number of dendritic cells in tumours, turning them in a pro-inflammatory immature population. This may be a double-edged sword, as reducing the number of dendritic cells may limit the immune system's ability to fight cancer, but it may also reduce the risk of immunologic side effects [20, 21]. In summary, VEGF has a significant impact on dendritic cells, affecting their activation, maturation, migration, and number. Therefore, VEGF inhibitors, by releasing the NFκB axis, may contribute to the recruitment and the maturation of DCs and their anti-tumour effects [22, 25].

The relationship between VEGF and T cells depends on the lymphocyte subpopulation. Treg cells can promote the development and progression of cancer by suppressing the immune response against cancer cells by favouring overexpression of checkpoints on T cells including PD-1, CTLA4, TIM3 and LAG3 [26]. Under hypoxia, Tregs can increase the expression of VEGF in tumours, which can promote the formation of new blood vessels and support the growth of cancer cells [27]. The use of anti-angiogenic agents (anti-VEGF and anti-ANG2) reduces Tregs influence and activates both CD4 and CD8 T cells and increases IFN-γ [28]. While cancer cells can use the loss of MHC-I expression to avoid CD8 recognition, the combination of anti-angiogenic and ICIs promotes antigen-specific T-cell migration and elevated MHC-I, Th1 and T effector cell markers and soluble biomarkers. In the clinic, bevacizumab administration in patients resulted in massive tumour infiltration by CD3+CD8+T cells [29, 30].

MDSCs (myeloid-derived suppressor cells) are a type of immune cell that can suppress the immune response against tumours. They accumulate in the tumour microenvironment and contribute to the growth and progression of tumours [12]. MDSCs promote the formation of new blood vessels in tumours through the production of VEGF and directly repress DC, NK cells, and T cells promoting immune tolerance. Hypoxic conditions fine tunes suppressive M2 tumour-associated macrophages (TAMs) [31]. Vessel normalisation will help to reverse the TAMs differentiation to M1 (anti-tumoral) phenotype promoting immune cell recruitment through soluble factors secretion [32].

Altogether, the combination of anti-VEGF therapy with other immunotherapies may be more effective at treating cancer than anti-VEGF therapy or ICIs alone, as it may target both the tumour's blood supply and the suppressive immune cells that promote its growth. In this context, studies on tumour-bearing mouse models have demonstrated that multi-targeted anti-angiogenic tyrosine kinase inhibitors (TKIs) increased tumour infiltration of CD8+ and CD4+ T cells by downregulating PD-1 expression, and decreased the number and activity of Tregs and MDSCs [26, 33, 34]. Similarly, sunitinib, a multi-tyrosine kinase receptor inhibitor (TKI), inhibited the expansion of Tregs and MDSCs in patients with RCC [35]. The VEGFR2-targeting TKI cabozantinib was also associated with a reduction in the number of Tregs and MDSCs, and simultaneously promoted tumour infiltration of CD4+ and CD8 + T lymphocytes, both alone and in combination with the anti-cancer vaccine MVA/rF-CEA/TRICOM [35].

CLINICAL APPLICATIONS AND THEIR LIMITS
More than 100 clinical trials are currently investigating the associations between immunotherapy and anti-angiogenic agents. The synergistic efficacy of combining immune checkpoint inhibitors (ICIs) with anti-angiogenic drugs, which results in considerable therapeutic advantages in a variety of solid tumours, is highly supported by the preclinical and experimental evidence now available. Notably, controlled studies show outstanding success in treating RCC [36–42] and HCC [43] (as highlighted in Table 1).

There is also rising interest in this combination used in other tumour types such as endometrial carcinoma. Extended efficacy and tolerability of the combination of lenvatinib plus pembrolizumab were demonstrated in patients with previously treated advanced endometrial carcinoma (EC) who were neither MSI-high or dMMr and who experienced progression on initial drug treatment [44, 45]. Advanced ovarian cancer represents an urgent medical need. In this latter tumour site, promising response rates have been recorded following treatment with a combination of bevacizumab and nivolumab [46]. More generally there are several indications of positive preliminary results that strengthen the notion of therapeutic benefit from the association of anti-angiogenic agents and ICIs across a broader spectrum of tumour sites [47]. Promising clinical data are also emerging from lung cancers [48]. For this latter localisation, a sustained interest in the combination is undeniable as stressed by real-world studies recently reported [49–51].

It is worth noting that the expression of vascular endothelial growth factor (VEGF) and programmed death-ligand 1 (PD-L1) is mainly regulated by hypoxia-inducible factor 2 alpha (HIF2A), which makes it a critical player at the intersection of anti-angiogenic and anti-immune checkpoint therapies. Promisingly, belzutifan, a HIF2A inhibitor, has demonstrated great potential alone or in combination with cabozantinib in treating von Hippel-Lindau disease and RCC [52, 53].

It is important to keep in mind the mechanism underlying the potential beneficial effect of the association between anti-angiogenic agents and ICIs. More specifically, when considering bevacizumab, the depletion of VEGF is related to the quenching of VEGFR2 signalling. In contrast, such a pure effect against VEGFR2 signalling does not occur with multi-target TKIs that have a more or less extensive effect on other membrane receptors with their own signalling [47]. This situation may complicate the final interpretation of the pharmacodynamic effects that follow the application of the combination especially regarding the potential supplement of toxicity introduced by multiple cellular pathways affected by TKIs. Other important aspects to consider as potentially influencing the final pharmacodynamic effects of the combination are the sequence order of drugs, their dosages and timing [4, 11]. For example, a study by Hamuro and co-workers showed a comparable benefit-risk ratio in patients with RCC treated with a less frequent schedule of nivolumab 480 mg every 4 weeks plus cabozantinib 40 mg daily compared with to nivolumab 240 mg every 2 weeks plus cabozantinib 40 mg daily [54]. The lessons from the use of ultra-low dose of immunotherapy are of value in the present context. This relates to a recent article by Patil et al. Patil et al., ($year$) [55], which showed that in the treatment of advanced head and neck cancer, a flat dose of nivolumab at 20 mg once every 3 weeks provided a significant overall survival benefit over treatment with methotrexate and erlotinib.

Cardiovascular toxicity is reported to occur more frequently during and after treatments with ICIs than previously thought [56].

Table 1. Approved combination in the clinic

Cancer	Immune checkpoint inhibitor	Anti-angiogenic agents	Study name	Clinical trial number	Reference
RCC	Atezolizumab	Bevacizumab	IMmotion151	NCT02420821	Rini, B et al. Lancet 2019 [40, 41]
RCC	Avelumab	Axitinib	JAVELIN Renal 101	NCT02684006	Motzer, RJ et al. NEJM 2019 [38]
RCC	Pembrolizumab	Axitinib	KEYNOTE-426	NCT02853331	Rini, B et al. NEJM 2019 [40, 41]
RCC	Nivolumab	Cabozantinib	CheckMate 9ER	NCT03141177	Choueri, TK et al. NEJM 2021 [42]
RCC	Pembrolizumab	Lenvatinib	CLEAR	NCT02811861	Motzer, RJ et al. NEJM 2021 [37]
HCC	Atezolizumab	Bevacizumab	IMbrave150	NCT03634540	Makker V et al. NEJM 2022 [45]
EC	Pembrolizumab	Lenvatinib	Study 309–KEYNOTE-775	NCT03517449	Finn RS et al. NEJM 2020 [43]

Since cardiac function is affected not only by the use of anti-angiogenic agents but also by ICIs, it is obvious that their combination schedule should be particularly well-weighted with respect to cardiovascular risk. It must be considered as central in the context of the drug combination. Therefore, the use of indicators of toxicity risk as well as predictive markers of treatment efficacy should be particularly welcome in the context of combination usage [57].

In this context of efficacy vs. toxicity risk ratio, there is a critical need to develop prognostic and predictive biomarkers of response to VEGFR-TKIs and ICIs., Measurement of plasma interleukin 8 (IL-8) is emerging as a potential candidate in this respect since elevated levels have been associated with enhanced intra-tumour neutrophils and reduced clinical benefit of ICIs [58, 59]. Other biomarkers such as ctDNA concentration or MIKI67 mutations have also been recently proposed to analyse the benefit of the combination [60]. Taken together, well-designed clinical trials in which the selection of optimal combination regimens and the setting of appropriate doses and sequences should be conducted in order to improve the therapeutic index of immunotherapy.

PERSPECTIVES

There is compelling preclinical and experimental data to support the clinical evidence for a beneficial combination of anti-angiogenic agents and ICIs. The evidence is particularly strong in patients with kidney, lung and liver cancers.

However, in the context of association, more data would be desirable. On one hand, one of the most neglected issues for combination with ICIs is a well-defined sequencing that could be explored on an experimental basis with relevant models like optimised tumour organoids [61, 62] or using implantable microdevices [63].

On the other hand, the preclinical setting has put the focus mainly on the effect of anti-angiogenic agents on the activity CPI, the reverse sequence (effects of CPIs on anti-angiogenic agents) could reveal complementary aspects and should not be neglected. For example, tumour-associated B lymphocytes could accelerate tumour progression by enhancing tumour angiogenesis by promoting the secretion of proangiogenic factors such as VEGF, FGF-2 and MMP-9 [64]. This implies that a larger understanding of the interaction between anti-angiogenic agents and ICIs could lead to optimal use of these agents in the clinical setting.

Better clinical use of the combination would also result from the identification of predictive clinical biomarkers. They would allow optimal application of this treatment option in potentially responsive patients as well as for potentially toxic effects. In addition, almost nothing is known about the mechanisms of acquired resistance resulting from the use of the combination. One possibility is that the drugs destroying blood vessels stimulate the development of tumour lymphatic vessels contributing to treatment failure [65]. Tumours from sunitinib-treated RCC patients in a neoadjuvant setting exhibit increased lymphatic vessels and increased lymph node invasion. This detrimental effect is explained at least by the stimulation of VEGFC expression following sunitinib administration [66]. This kind of information should pave the way for complementary treatments following clinical use of the combination. In final, peculiar attention could also be paid to the possibility that normalisation of tumour vasculature under the effect of anti-angiogenic agents could favour a better diffusion of therapeutic monoclonal antibodies.

So, while it is very satisfying to have a strong rationale for the use of the combination, more remains to be done to optimise this promising therapeutic option at the interface between immunotherapy and targeted therapy.

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COMPETING INTERESTS
The authors declare no competing interests.

ADDITIONAL INFORMATION

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