



Original Article

Response to anti-angiogenesis: An ever changing feature

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SUMMARY

Aims: Anti-angiogenic drugs have gained international approval for the therapy of advanced breast, lung, colo-rectal, kidney and central nervous system cancer. However, the clinical benefit associated with the use of these drugs has been so far limited.

Methods: This review discuss the possible rational developments of a new generation anti-angiogenic drugs.

Conclusion: Since most of the biological and clinical activity of the currently available generation of anti-angiogenic drugs targets VEGF and its related pathways, it seems relevant to (1) better understand mechanisms of resistance and/or escape from anti-VEGF and (2) identify and validate vascular targets complementary to anti-VEGF.

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Introduction

In the past 5 years, the anti-angiogenic drugs bevacizumab, sunitinib, sorafenib and pazopanib have been approved for the therapy of advanced breast, colo-rectal, lung, kidney and central nervous system cancer.¹ In randomized clinical trials, these drugs, alone or in combination with chemotherapy, have shown to be able to improve overall (OS) or progression-free survival (PFS) in cancer patients. However, the clinical benefit associated with these anti-angiogenic drugs has been so far limited to a few months, and the very large majority (if not all) of the treated patients has suffered clinical progression.

It is still unclear whether the limited impact on patients' OS and/or PFS is due to the presence of a small clinical benefit in every patient or to the presence of a larger benefit in a subpopulation of patients, an effect to be diluted in large clinical trials enrolling unselected patients. Also, the lack of validated biomarkers severely limits the ability to determine optimal biologic dose (OBD) and scheduling of these drugs.^{1–4}

Anti-VEGF: how does it work?

Anti-angiogenic drugs are currently thought to act against neoplasia by four major mechanisms: (1) neovessels' pruning; (2) vascular normalization resulting in improved delivery of chemotherapy drugs to tumor tissue and reduced tissue edema; (3) inhibition of the mobilization of pro-angiogenic cells towards the tumor; (4) inhibition of autocrine and paracrine growth factor cross talks between tumor, endothelium and stroma cells.^{1–4} As described by

Bergers and Hanahan,⁵ the adaptive mechanisms of resistance to the current generation of anti-angiogenic drugs targeting mostly VEGF, are likely to be (1) activation and/or upregulation of alternative pro-angiogenic signalling pathways within the tumor and/or recruitment of pro-angiogenic cells, both of which can obviate the necessity of VEGF signalling, thereby effecting reinitiation and continuance of tumor angiogenesis; (2) increased pericyte coverage of the tumor vasculature, in order to support its integrity and attenuate the necessity for VEGF-mediated survival signalling; and (3) activation and enhancement of invasion and metastasis to provide access to normal tissue vasculature without the need for neovascularization. There is also evidence that certain tumors may have a pre-existing tumor microenvironment supporting intrinsic resistance to anti-VEGF therapies.⁵

In advanced breast cancer patients treated with metronomic chemotherapy plus the anti-VEGF antibody bevacizumab,⁶ the risk of relapse was markedly increased in patients who – after two months of therapy – did not achieve a reduction of circulating VEGF levels below a given threshold.⁷ Thus, in patients with high VEGF levels in spite of bevacizumab treatment, a possible approach might be to increase to dosage of bevacizumab or to switch towards novel strategies of VEGF inhibition.

Along a similar line, a large clinical study enrolling about 2,000 patients with metastatic colorectal cancer whose first-line therapy consisted of bevacizumab plus chemotherapy has shown that the administration of bevacizumab beyond tumor progression was associated with an improved clinical outcome.⁸ These data deserves to be further investigated in a randomized confirmatory trial.

Innovative preclinical models should be generated to understand whether a benefit of prolonged anti-VEGF therapy in tumors escaping from therapy does exist and is due to vascular normalization (and better delivery of other anti-neoplastic drugs) or to an inhibition of other cellular and/or molecular pathways.

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Escape from anti-VEGF therapy: What's next?

As recently reviewed by Shaked and Voest,⁹ a large variety of circulating endothelial and hematopoietic cell populations are known to play a possible role in the generation and maintenance of cancer vessels. Myeloid cells may also play a crucial role in the escape from anti-VEGF therapies. CD11b⁺Gr1⁺ cells (also defined as myeloid-derived suppressor cells, MDSC) are frequently increased in the tumors and in the peripheral blood (PB) of tumor-bearing animals, and have been shown to promote tumor angiogenesis. MDSCs have a role in mediating refractoriness to anti-VEGF treatment by producing several angiogenic factors such as, among the others, G-CSF and Bv8.¹⁰ The mobilization of pro-angiogenic cells such as MDSCs involved in escape from anti-VEGF therapy might be targeted with appropriate drugs. This approach needs to be tested in clinical trials, and it remains to be elucidated by dedicated preclinical models what is the most appropriate timing (before or after the insurgenence of anti-VEGF refractoriness?) for such a therapeutic option.

Activin receptor-like kinase 1 (ALK1): a novel vascular target

In adults, the expression of the TGF-beta receptor ALK1 is virtually restricted to proliferating endothelial cells (ECs). Also, ALK1 plays a key role in vessel maturation, in recruitment and differentiation of perivascular cells (PCs), and in the organization and patency of neo-angiogenic vessels.^{11,12} A soluble ALK1/extracellular domain (ECD) Fc-fusion protein (RAP-041) reduced xenograft tumor burden in mice through anti-angiogenesis.¹³ The very recent study by Hu-Lowe et al.¹⁴ showed that VEGF and FGF stimulated ALK1-mediated signalling. In this same study, a fully human anti-ALK1 monoclonal antibody markedly inhibited these events, and a murine anti-ALK1 suppressed angiogenesis stimulated by VEGF and FGF in a matrigel-based model in mice, and inhibited xenograft tumor growth by attenuating both blood and lymphatic vessel angiogenesis. In a human melanoma model with acquired resistance to a VEGF inhibitor, the combination of anti-ALK1 with VEGF inhibitors delayed tumor growth and disturbed vascular normalization associated with VEGF receptor inhibition. Notably, anti-angiogenesis and antitumor efficacy of anti-ALK1 were associated with disrupted colocalization of ECs with desmin⁺ PCs, and reduction of blood flow primarily in large/mature vessels. These data imply that ALK1 may play a role in stabilizing angiogenic vessels and contribute to resistance to anti-VEGF therapies. A clinical phase I study of the fully-human anti-ALK1 antibody (PF-03446962) is currently ongoing and showing acceptable toxicity and early sign of clinical activity (C Gallo-Stampino, personal communication).

Thus, anti-ALK1 may represent an effective anti-angiogenesis therapy complementary to the currently available anti-VEGF drugs.

Conclusions

VEGF inhibition, alone or (more frequently) in combination with chemotherapy, has showed clinical activity in several types of cancer. However, the clinical benefit was transitory, and tumor growth was eventually observed. To overcome resistance and tumor escape, new strategies are urgently needed. Possible clinical

developments are in the inhibition of the VEGF pathway beyond clinical progression for patients who had a significant and persistent normalization of the tumor vasculature associated with an improved delivery of chemotherapy.^{1,2} For patients who did not achieve such a vessel normalization by VEGF inhibition, or in tumor types insensitive to chemotherapeutics associated to anti-VEGF, a switch towards drugs targeting different mechanisms of action might be considered, and we discussed the emerging new and EC-restricted target ALK1 as a paradigm.

In this context, there is also an urgent need for biomarkers able to select who, in a given patient population, is most likely to benefit from these new drugs and strategies and what will be the most appropriate therapy after escape.

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Conflict of interest statement

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