"CANCER: Limitations of Therapies Exposed"

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STANDFIRST

Anti-angiogenic drugs, used for cancer treatment, target blood-vessel formation in tumours. Two studies show that such drugs can reduce the efficiency of other anticancer agents and increase the aggressiveness of tumours.

MAIN TEXT

Tumour growth depends on the concomitant outgrowth of an extended vascular network to ensure a continuous supply of oxygen and nutrients. Blocking the formation of new blood vessels with anti-angiogenic therapy is currently used to treat certain types of cancer. For its central role in promoting angiogenesis, vascular endothelial growth factor (VEGF) is the main target of the currently approved anti-angiogenic drugs. While several aspects of their mechanism of anti-tumour action are still unknown, evidence is slowly unravelling their concealed details and exposing their limitations. Recently, two decisive studies uncovered some of the limitations of anti-angiogenics to reveal that these therapies decrease chemotherapeutic drug delivery to tumours which could hinder their therapeutic benefits, and also describe tumour adaptation to therapy involving accumulation of more aggressive precursor tumour cells.

The mechanism how VEGF-blocking anti-angiogenic inhibitors provide additional anti-tumour effects when combined with cytotoxic drugs has been an unresolved mystery since the early positive results on combination trials[1]. The most widespread explanation, the "vascular normalization" theory was proposed by Rakesh K. Jain in 2001, where anti-angiogenic therapy induces a structural and functional change in the aberrant tumor vasculature to convert it to more normal characteristics, allowing for increased perfusion that consequently improves drug penetration and enhances efficacy of cytotoxic drugs[2,3]. Recently, Van der Veldt et al. performed a clinical study

on drug perfusion, uptake and retention in 10 advanced-stage non-small cell lung cancer (NSCLC) patients using radiolabeled drug tracing by PET imaging. Their specific and high sensitivity detection of [11C]Docetaxel chemotherapeutic drug clearly demonstrated that inhibition of VEGF with Bevacizumab induced a fast and sustained decrease not only in water perfusion but also in drug perfusion and uptake in tumors[4]. These results are in contraposition to previous clinical studies in rectal cancer and glioblastoma (GBM) patients where vascular normalization was documented and increased drug uptake (by glucose tracer) was suggested after Bevacizumab treatment[5,6]. Tumour type heterogeneity in vascularity and responses to anti-angiogenic therapies could underlie these discrepancies between GBM, rectal cancer and NSCLC, as anti-angiogenic therapies can differentially alter vascular functional characteristics such as fenestrations, permeation, edema or vasoconstriction in different tissues (i.e. tyroid[7], brain[6] ...). In any case, learning that at least in NSCLC patients anti-angiogenic drugs are not able to improve drug delivery to tumours but rather have the opposite effect, exposes a relevant limitation of combination treatments using anti-VEGF and chemotherapy or other blood-distributed anti-cancer drug. Indeed, this could be the cause of the modest benefits of these combination therapies in NSCLC but also in other tumour types[8]. Therefore, this potential drawback will have to be solved in the future by optimizing the scheduling of these therapeutic agents, for example, with sequential scheduling of chemotherapy or other targeted drugs followed by anti-angiogenics.

Another recent contribution on the limits of anti-angiogenic therapies has exposed the amplitude of tumour plasticity and high capacity of adaptation to these therapies. Tumours have long been shown to have remarkable plasticity and adaptability to chemotherapy and radiation, but it was initially postulated that anti-angiogenics would not induce the same adaptation and selection because they target endothelial cells rather than tumour cells[9]. Nevertheless, pre-clinical and clinical evidence has revealed that tumour adaptation and resistance to anti-angiogenic therapy does indeed occur, mostly due to tumour cell adaptation to therapy[10,11].

In this sense, Conley et al. have gone further to document that in animal models of Breast Cancer tumour adaptation to anti-angiogenics includes a hypoxia-driven accumulation of progenitor cells that confer these tumours with more aggressive characteristics[12]. As broadly reported, targeting VEGF ligand (Bevacizumab) or its main receptors (Sunitinib) were found to activate a hypoxia response programme, but they further reveal a subsequent induction of the Akt/β-catenin pathway which is implicated

in the regulation of progenitor cells in breast cancer. To identify this population, the authors use aldehyde dehydrogenase (ALDH), a metabolic enzyme that converts aldehydes from many different origins (carbohydrates, lipids and even alcohol) to carboxylic derivatives. While ALDH enzymatic activity was recently described as a precursor cell marker in tumours[13], it remains to be determined whether accumulation of cells with this enzymatic activity could be caused by atypical accumulation of metabolites driven by hypoxia.

In any case, while a selection for progenitor cells has been described in several tumour types treated with classical chemotherapy due to their higher resistance to these agents[14], similar effects with anti-angiogenic drugs had only been scarcely described in glioblastomas under combination therapies[15]. Thus, this study signifies a major advancement in understanding the benefits and limitations of anti-angiogenic therapies. Furthermore, it delineates a possible cellular and molecular mechanism for the previously reported tumour aggressiveness and metastatization effects of anti-angiogenic therapies in several animal models[16,17]. Indeed, the specific tumour cell populations that are selected or accumulated after anti-angiogenics in this study have been described to have enhanced tumour formation capabilities and a high metastatic potential[18]. Thus, the hypoxia-induced, Akt/β-Catenin mediated activation of these specific tumour cell populations could explain the enhanced tumour aggressiveness and metastatic potential observed after anti-angiogenic therapies in different tumour types. Therefore, the selection or accumulation of these more aggressive tumour populations is yet another limitation of anti-angiogenic therapies and will have to be addressed mechanistically and therapeutically in order to improve their effectiveness. One possibility would be the use of combinatorial treatments of anti-angiogenic therapies together with anti-hypoxia response agents or anti-Akt/β-catenin drugs; or the use pleiotropic recombinant molecules that can exert dual (or multiple) anti-cancer effects by targeting angiogenesis together with blocking invasion and impeding metastasis, such as the recently emerged Semaphorins family[19].

These two recent contributions on the limitations of anti-angiogenic therapies further emphasize the need of a carefully balanced evaluation of the benefits and limitations of anti-angiogenic therapies. But even more importantly, they warrant further studies on these pernicious aspects in order to improve effectiveness and extend the therapeutic benefits of anti-angiogenic agents. This could be achieved by sequential scheduling of

chemotherapy and anti-angiogenics, smarter combinations of anti-angiogenic drugs with others targeting progenitor cell pathways or new multi-targeting with pleiotropic molecules blocking angiogenesis and their limitations. Overall, despite many open questions, there is hope that an understanding of the limitations of anti-angiogenic therapies will translate into therapeutic benefits.

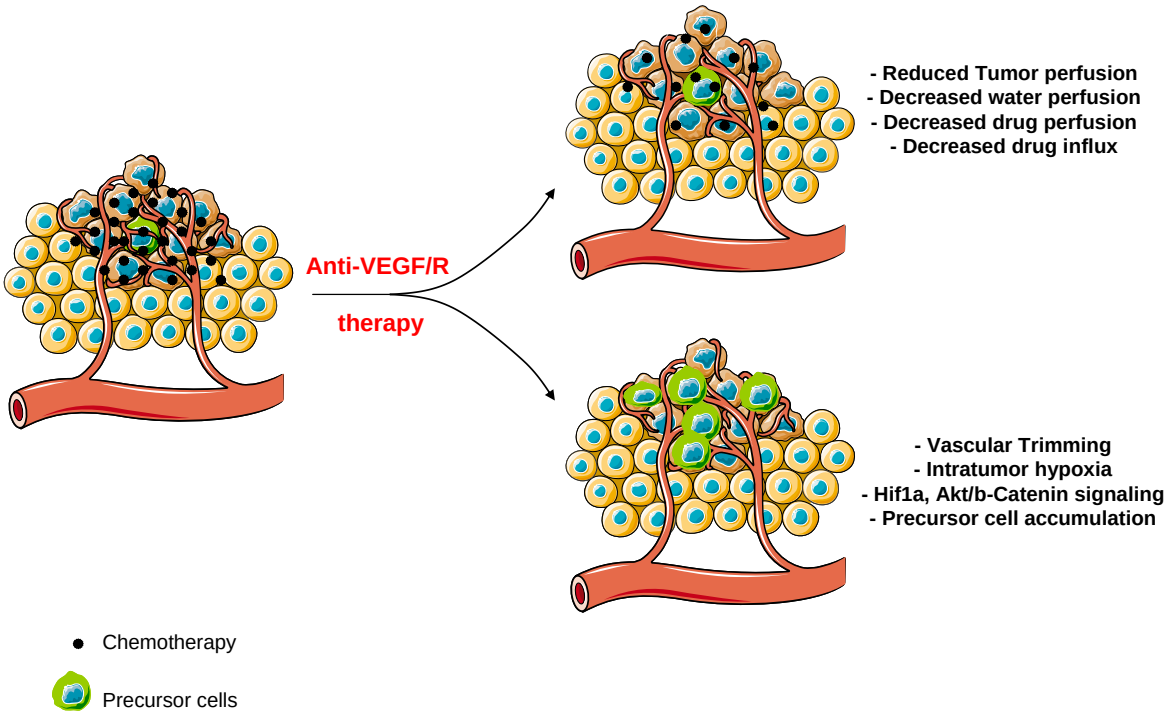

***FIGURE 1*: Some drawbacks of anticancer therapies.** a, By affecting blood vessel formation, anti-angiogenic drugs can enhance the efficacy of blood-distributed cytotoxic agents that inhibit the growth of cancer cells. However, some tumour cells known as cancer precursor cells are particularly dangerous because they can be more resistant to cytotoxic agents than the rest of the tumour cells, and they can spread to other organs and start new tumours. b,c, Anti-angiogenic therapy, however, can have negative effects too. b, It can reduce the distribution of cytotoxic agents in the tumour, and hence their efficacy. Van der Veldt et al.1 report an example of such undesirable effect in patients with non-small cell lung cancer. c, Moreover, anti-angiogenic drugs can, by reducing oxygen levels within the tumour, induce the accumulation of more aggressive cells that — like cancer precursor cells — have increased capacity to spread to other organs. Conley et al.2 document this phenomenon in mouse models of breast cancer.

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REFERENCES

1. Hurwitz, H. I. et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. J Clin Oncol 23, 3502-8 (2005).
2. Jain, R. K. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 7, 987-9 (2001).
3. Jain, R. K. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science 307, 58-62 (2005).
4. Van der Veldt, A. A. et al. Rapid Decrease in Delivery of Chemotherapy to Tumors after Anti-VEGF Therapy: Implications for Scheduling of Anti-Angiogenic Drugs. Cancer Cell 21, 82-91.
5. Willett, C. G. et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med 10, 145-7 (2004).
6. Batchelor, T. T. et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer Cell 11, 83-95 (2007).
7. Kamba, T. et al. VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature. Am J Physiol Heart Circ Physiol 290, H560-76 (2006).
8. Sandler, A. et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355, 2542-50 (2006).
9. Boehm, T., Folkman, J., Browder, T. & O'Reilly, M. S. Antiangiogenic therapy of experimental cancer does not induce acquired drug resistance. Nature 390, 404-7 (1997).
10. Bergers, G. & Hanahan, D. Modes of resistance to anti-angiogenic therapy. Nat Rev Cancer 8, 592-603 (2008).

11. Rini, B. I. & Atkins, M. B. Resistance to targeted therapy in renal-cell carcinoma. Lancet Oncol 10, 992-1000 (2009).
12. Conley, S. J. et al. Antiangiogenic agents increase breast cancer stem cells via the generation of tumor hypoxia. Proc Natl Acad Sci U S A.
13. Ginestier, C. et al. ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. Cell Stem Cell 1, 555-67 (2007).
14. Yu, F. et al. let-7 regulates self renewal and tumorigenicity of breast cancer cells. Cell 131, 1109-23 (2007).
15. Folkins, C. et al. Anticancer therapies combining antiangiogenic and tumor cell cytotoxic effects reduce the tumor stem-like cell fraction in glioma xenograft tumors. Cancer Res 67, 3560-4 (2007).
16. Paez-Ribes, M. et al. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Cancer Cell 15, 220-31 (2009).
17. Ebos, J. M. et al. Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. Cancer Cell 15, 232-9 (2009).
18. Charafe-Jauffret, E. et al. Aldehyde dehydrogenase 1-positive cancer stem cells mediate metastasis and poor clinical outcome in inflammatory breast cancer. Clin Cancer Res 16, 45-55.
19. Casazza, A. et al. Tumour growth inhibition and anti-metastatic activity of a mutated furin-resistant Semaphorin 3E isoform. EMBO Mol Med.