Mini-Review

Resistance to anti-angiogenic agents: a brief review of mechanisms and consequences

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Introduction

A capacity for neoangiogenesis is a fundamental property of cancer (1,2). With the clinical application of multiple inhibitors of vascular endothelial growth factor (VEGF) signaling, angiogenesis is a validated therapeutic target in several malignancies including renal cell, colon and lung cancer. However, the overall clinical benefit of agents targeting VEGF has been less than what was hoped. This lack of benefit appears to be substantially due to primary or acquired resistance to these drugs (3).

The basic premise of antiangiogenic therapy is that tumors cannot grow beyond a very small volume without developing a new blood supply. Smaller tumors can obtain adequate oxygen and nutrients by diffusion. Therefore, if one can intervene to prevent development of the neovasculature the tumor is essentially starved and unable to grow. This basic premise is fundamentally different from other "targeted" approaches in that the target is not a pathway responsible for growth or proliferation of the cancer cell, but rather for the non-neoplastic endothelial cells. In effect, the drugs will work by altering the tumor environment, making it inhospitable to tumor growth and development. Therefore, it is appropriate to approach the issues of resistance to antiangiogenic agents through the prism of evolutionary biology (4-6). As with evolution of a species, the survival of the cancer cell is through adaptation to a hostile environment. The mechanisms of resistance to antiangiogenic agents have been extensively reviewed recently (7). This paper will briefly review the mechanisms of resistance to antiangiogenic agents in the context of evolutionary biology and discuss how this should impact the specific endpoints for clinical trials of antiangiogenic agents.

Alternative "food sources"

As an organism can adapt to a hostile environment by developing alternative food sources, a cell can adapt by developing alternative signaling pathways. Angiogenic signaling has numerous redundant pathways that can be upregulated to allow for this adaptation. It is clear that the complexity of angiogenic signaling was not initially appreciated. The development of a specific neutralizing antibody to VEGF such as bevacizumab, the decoy receptor aflibercept as well as the numerous inhibitors to tyrosine kinases with specificity for one or more of the VEGF receptors (e.g., sunitinib, sorafenib) was predicated on the hypothesis that the vascular endothelial growth factor (VEGF) was the angiogenic driver and that the inhibition would be beneficial. Unquestionably, there is some merit to this hypothesis as the agents have the ability to potentiate the activity of chemotherapy regimens, most notably in renal carcinoma, a malignancy that in many cases is at least initially driven by VEGF through disruption of the Von Hippel Lindau gene and consequent increase in hypoxia inducible factor (HIF) and downstream induction of VEGF (8). Other diseases, including non-small cell lung cancer (NSCLC), breast and colorectal cancer, have demonstrated at least some susceptibility to this strategy. However, in virtually all cases, there is relatively rapid escape from these agents. At least part of this can be attributed to upregulation of other angiogenic factors with overlapping activities, including fibroblast growth factor (FGF), angiopoetin and osteopontin (9). A related mechanism is the upregulation of other isoforms of VEGFR or alternative receptors for fibroblast growth factors 1 and 2, ephrin A1 and 2 and angiopoetin (10).

Evasive adaptation

Pericytes are vascular smooth muscle cells that envelop and support the vasculature. They are also constituents of the neovasculature. Increased pericyte coverage can enhance the viability of residual endothelial cells after anti-angiogenic therapies. Recent evidence has elucidated several pathways by which pericytes promote endothelial cell survival after exposure to antiangiogenic therapy (11). Dual targeting of pericytes and endothelial cells may be a viable approach to enhancing efficacy of antiangiogenic therapies. However, at least one experimental model has failed to validate this approach (12). Furthermore, there is evidence that pericyte depletion may actually result in enhanced dissemination of tumor cells (13).

Alternative ecological niche

Another unanticipated result of antiangiogenic therapy is that malignant cells can adapt by adopting a different ecological niche. A greater degree of invasiveness, particularly by spreading along existing vasculature or increased recruitment of existing vessels allows cancers to continue to develop in a hostile environment (14,15). Such diseases may be primarily refractory to antiangiogenic agents as they have evolved without the requirement for neoangiogensis. This seems to be at least part of the mechanism for intrinsic and acquired resistance to these agents in glioblastoma and pancreatic cancer (3).

Survival of the fittest

This is the most basic of evolutionary concepts and seems to be at work in angiogenesis resistance, in particular, as regards cancer stem cells (CSC). The CSC hypothesis has gained great currency in the past few years, though conclusive demonstration of its utility has been lacking (16). Interestingly, experimental models indicate that CSCs are increased in hypoxic environments (17). Hence, antinagiogenic agents, by causing such environments, may result in selection for greater numbers of CSCs which tend to be more resistant to eradication.

Convergent evolution

Perhaps the most interesting and remarkable adaptation by cancer cells is the ability of cancer cells to form vasculature in the absence of endothelial cells (18). This pseudovasculature ultimately anastamoses with existing vasculature to assure blood supply to the tumor (19). This process, originally demonstrated in melanoma, has also been demonstrated in other malignancies including lung cancer. The malignant cells forming these channels have an extremely aggressive and plastic phenotype. Therefore, this represents yet another resistant mechanism that results in not only disease that will not respond to a specific therapy against endothelial cells, but actually more malignant than prior to treatment.

Other issues

A common approach in the evaluation of new agents and particularly the "targeted agents" has been to combine them with chemotherapeutic agents or regimens with demonstrated activity in a particular setting. While there is some logic to this approach, it ignores the fact that different agents have different mechanisms of action as well as different consequences for the tumor environment. Of particular note, is that there is at least preclinical evidence that taxanes (paclitaxel, docetaxel) may result in an increase in circulating endothelial cells (CECs) which are vulnerable to the antiVEGF agents (20). There is some evidence that this may be clinically relevant. The only positive trial for overall survival with bevacizumab in NSCLC is in combination with paclitaxel/carboplatin (21). A virtually identical study with the non-taxane regimen of cisplatin/gemcitabine was negative (22). Therefore, mechanistic-based approaches should be emphasized in deciding combinations in future clinical testing of antiangiogenic agents.

Consequences of antiangiogenic resistance

Many of the laboratory models of antiangiogenic resistance demonstrate an initial slowing of tumor growth or even regression as there is enhanced efficacy of chemotherapy (either through improved drug delivery, a true antiangiogenic effect or inhibition of an off target pathway relevant for tumor survival) followed by an accelerated growth of malignancy as alternative pathways or ecological niches develop. This appears to reflect the clinical experience of a prolongation of progression free survival (PFS) without a change in overall survival (OS). It is quite remarkable that this has been observed in NSCLC trials with almost every one of the antiangiogenic agents, including bevacizumab, aflibercept, sunitinib, soraftenib etc (23). Only a single Phase III trial, ECOG 4599, has not demonstrated this outcome.

When studies of bevacizumab alone are considered, a recent metanalysis has indicated a modest degree of benefit at the expense of increased toxicity (24). As noted above, it is possible that this relates to the specific chemotherapeutic regimen employed (25). Given the above results, it is clear that PFS cannot be considered a valid intermediate/screening endpoint for these agents.

Even more importantly, is the related concept of disease free survival (DFS) in the adjuvant therapy context. In this setting the goal is cure, i.e., the permanent eradication of disease. Therapy is administered in a setting in which the patient has been surgically rendered "free of disease" and relapse occurs after growth of microscopic residual cancer. This may occur years later, even in aggressive diseases such as NSCLC. Given this initial delay, followed by rapid acceleration of tumor growth, it is quite possible that in the setting of adjuvant chemotherapy, early analysis (in the form of DFS) may demonstrate a beneficial effect. Additional follow-up might very well demonstrate that this DFS advantage diminishes or disappears. In colorectal cancer, an effect of this type was seen in which there was a transient DFS advantage followed by a loss of benefit over time (26). Furthermore, it is quite possible that this may come at the expense of cure as the antiangiogenic drug conceivably could facilitate the survival of CSCs and other more aggressive phenotypes which might otherwise have been eradicated by standard chemotherapy or even host immunity. The answer to this question in lung cancer will come with the completion of the current randomized study, ECOG 1505.

Conclusions

There is little question that the angiogenesis concept advanced by Folkman 40 years ago has resulted in significant progress in both the understanding and treatment of cancer. However, the early promise of this approach has not been fulfilled as the mechanisms of tumor neovascularization and the potential of tumors to evade therapy was not appreciated. An interesting and unique aspect of this approach to treatment in lung cancer and other diseases is evidence of early benefit followed by more aggressive disease. Further progress with these agents will likely require targeting multiple aspects of this aspect of tumor biology simultaneously.

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