Editorial

Targeting Multiple Biological Pathways as a Strategy to Improve the Treatment of Cancer

Michael S. O'Reilly[1]

University of Texas M. D. Anderson Cancer Center, Departments of Radiation Oncology and Cancer Biology, Houston, Texas 77030

Introduction

Over the past several years, the concept of targeted biological therapy for the treatment of cancer and other disease has emerged. However, a better understanding of these targets and their interactions with tumor cells and the surrounding stromal cells is required before they can be effectively translated into clinical practice. Two very interesting biological targets are angiogenesis and the EGFR.[2] A number of agents that target angiogenesis (1) or EGFR (2) have now been described, and many of these are currently in clinical trials in cancer patients. However, no angiogenesis inhibitor or EGFR antagonist has been approved for widespread clinical use. Furthermore, clinical trials with these agents used as monotherapy have not yet demonstrated the same degree of antitumor efficacy as has been observed in preclinical studies. It had been hypothesized and hoped that a single target would be adequate to control advanced cancer. However, it is now clear that this is not realistic for most, if not all, malignant diseases, and therapies that target multiple steps that contribute to malignant progression will be needed.

Although antiangiogenic and anti-EGFR agents show great promise in preclinical cancer models, their use, particularly when administered as monotherapy, has been associated with a number of potential limitations and problems (3). In preclinical studies, angiogenesis inhibitors stabilize tumor growth and can induce tumor regression but are associated with a delayed onset of activity (4) and tumor progression before response to therapy (5). In clinical studies, antiangiogenic therapy with IFN-α required several months of continued therapy before a significant clinical response was observed (6). Perhaps the most significant limitation of antiangiogenic monotherapy is the inability of these agents to completely eradicate disease even after prolonged administration with the potential for tumor recurrence after cessation of therapy (5). Prolonged therapy with endostatin did induce a self-sustained dormancy for a wide variety of tumors that persisted off therapy yet residual microscopic disease was still present in all of the treated mice. Furthermore, recent work shows that endothelial cells in different organs express different surface receptors (7) and have different patterns of gene expression (8) suggesting that endothelial cells in different tissue beds may respond differentially to antiangiogenic therapy and that targeted therapy may have to be customized on an individual basis.

Many receptor tyrosine kinases are important for both tumor cells and endothelial cells (9). For example, blockade of EGFR directly targets both the tumor cell and tumor-associated endothelial cells (9), and also down-regulates the expression of proangiogenic factors by tumor cells (10). Thus, these agents offer the potential for both indirect and direct effects on both the tumor and endothelial cell compartments. However, although strategies to target receptor tyrosine kinases offer great promise, they are also associated with several potential limitations. The expression of receptor tyrosine kinases varies markedly between different tumor types, and not all of the tumor cells will express each receptor. Therefore, it will be critical to first screen tumor specimens for both the ligand and its receptor before initiating therapy with a specific protein tyrosine kinase inhibitor. In addition, most advanced malignant tumors produce multiple growth factors, and so targeting only one may not be adequate for complete tumor control (3). Although relatively little toxicity has been observed to date for antiangiogenic or anti-EGFR agents (11), their prolonged use could result in late effects. In clinical trials, vascular endothelial growth factor/vascular permeability factor inhibitors have been associated with thrombotic or hemorrhagic complications and hypertension (12). Furthermore, resistance to antivascular endothelial growth factor and anti-EGF strategies have been observed in preclinical models (13, 14), and even tumors that express the targeted growth factor receptor could eventually become resistant to the individual agents by expressing different growth factors and/or their receptors (15).

For patients with advanced metastatic and/or locally advanced disease, the limitations of biological monotherapy may make the use of these agents impractical. However, by combining biological agents with each other and conventional agents, it may be possible to reduce the dose required and frequency of administration, and make their use more practical (16). One strategy to overcome the limitations of targeting individual growth factors is to design small molecules that can target multiple factors. However, instead of developing drugs that have multiple targets, it may be prudent to combine individual drugs that target different growth factors so that therapy can be optimized on an individual basis and to allow for a dynamic target optimization. In this issue, Li *et al.* (17) demonstrate that combined therapy with endostatin and EGFR-antisense is superior to monotherapy with either agent in a series of well-designed and clinically relevant studies. In their studies of squamous cell carcinoma in mice, they demonstrate that the combination of endostatin with EGFR antisense induced a rapid, durable, and near complete inhibition of tumor growth, whereas monotherapy was associated with only modest inhibition of

Received 8/22/02; accepted 8/23/02.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] To whom requests for reprints should be addressed, at University of Texas M. D. Anderson Cancer Center, Departments of Radiation Oncology and Cancer Biology, 1515 Holcombe Boulevard, Houston, TX 77030. E-mail: moreilly@mdanderson.org.

[2] The abbreviations used are: EGFR, epidermal growth factor receptor.

tumor growth. The combination of anti-EGFR agents with antiangiogenic therapy is particularly attractive given that EGFR can have direct and indirect effects on angiogenesis and the tumor vasculature (9). By combining antagonists of EGFR with antiangiogenic agents, the limitations of either agent administered as monotherapy can be overcome as was observed by Li *et al.* (17). These studies provide a strong basis for therapeutic strategies against multiple biological targets. It may be especially beneficial to combine direct inhibitors of angiogenesis with agents that target proangiogenic molecules and tumor cells directly.

The translation of biological therapies into the clinic is now inevitable. However, it will only be by combining multiple biological agents with conventional strategies such as chemotherapy and radiation therapy that advanced cancer can be eradicated and/or controlled. Before biological agents can be successfully incorporated into clinical strategies to treat cancer and other diseases, a greater understanding of their activities and interactions with the tumor and its microenvironment is required. It will also be critical to closely monitor patients receiving biological therapies and to customize therapy on a patient-specific basis that may need to change based on the patterns of tumor growth over time.

References

1. Folkman, J. Clinical applications of angiogenesis research. N. Engl. J. Med., *333:* 1757–1763, 1995.

2. Mendelsohn, J., and Baselga, J. The EGF receptor family as targets for cancer therapy. Oncogene, *19:* 6550–6565, 2000.

3. O'Reilly, M. S., and Fidler, I. J. The development of antiangiogenic agents for the clinic. *In:* V. T. DeVita, S. Hellman, and S. A. Rosenberg (eds.), Progress in Oncology 2002, pp. 129–157. Sudbury: Jones and Bartlett Publishers, Inc., 2002.

4. O'Reilly, M. S., Holmgren, L., Chen, C., and Folkman, J. Angiostatin induces and sustains dormancy of human primary tumors in mice. Nat. Med., *2:* 689–692, 1996.

5. Boehm, T., Folkman, J., Browder, T., and O'Reilly, M. S. Antiangiogenic therapy of experimental cancer does not induce acquired drug resistance, Nature (Lond.), *390:* 404–407, 1997.

6. Kaban, L. B., Mulliken, J. B., Ezekowitz, R. A., Ebb, D., Smith, P. S., and Folkman, J. Antiangiogenic therapy of a recurrent giant cell tumor of the mandible with interferon α-2a. Pediatrics, *103:* 1145–1149, 1999.

7. Arap, W., Pasqualini, R., and Ruoslahti, E. Cancer treatment by targeted drug delivery to tumor vasculature in a mouse model. Science (Wash. DC), *279:* 377–380, 1998.

8. St. Croix, B., Rago, C., Velculescu, V., Traverso, G., Romans, K. E., Montgomery, E., Lal, A., Riggins, G. J., Lengauer, C., Vogelstein, B., and Kinzler, K. W. Genes expressed in human tumor endothelium. Science (Wash. DC), *289:* 1197–202, 2000.

9. Baker, C. H., Solorzano, C. C., and Fidler, I. J. Blockade of vascular endothelial growth factor receptor and epidermal growth factor receptor signaling for therapy of metastatic human pancreatic cancer. Cancer Res., *62:* 1996–2003, 2002.

10. Hirata, A., Ogawa, S-I., Kometani, T., Kuwano, T., Naito, S., Kuwano, M., and Ono, M. ZD1839 (Iressa) induces antiangiogenic effects through inhibition of epidermal growth factor receptor tyrosine kinase. Cancer Res., *62:* 2554–2560, 2002.

11. Ranson, M., Hammond, L. A., Ferry, D., Kris, M., Tullo, A., Murray, P. I., Miller, V., Averbuch, S., Ochs, J., Morris, C., Feyereislova, A., Swaisland, H., and Rowinsky, E. K. ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. J. Clin. Oncol., *20:* 2240–2250, 2002.

12. Kuenen, B. C., Rosen, L., Smit, E. F., Parson, M. R. N., Levi, M., Ruijter, R., Huisman, H., Kedde, M. A., Noordhuis, P., van der Vijgh, W. J. F., Peters, G. J., Cropp, G. F., Scigalla, P., Hoekman, K., Pinedo, H. M., and Giaccone, G. Dose-finding and pharmacokinetic study of cisplatin, gemcitabine, and SU5416 in patients with solid tumors. J. Clin. Oncol., *20:* 1657–1667, 2002.

13. Yu, J. L., Rak, J. W., Coomber, B. L., Hicklin, D. J., and Kerbel, R. S. Effect of p53 status on tumor response to antiangiogenic therapy. Science (Wash. DC), *295:* 1526–1528, 2002.

14. Viloria-Petit, A., Crombet, T., Jothy, S., Hicklin, D., Bohlen, P., Schlaeppi, J. M., Rak, J., and Kerbel, R. S. Acquired resistance to the antitumor effect of epidermal growth factor receptor-blocking antibodies *in vivo:* a role for altered tumor angiogenesis. Cancer Res., *61:* 5090–101, 2001.

15. Relf, M., LeJeune, S., Scott, P. A., Fox, S., Smith, K., Leek, R., Moghaddam, A., Whitehouse, R., Bicknell, R., and Harris, A. L. Expression of the angiogenic factors vascular endothelial cell growth factor, acidic and basic fibroblast growth factor, tumor growth factor β-1, platelet-derived endothelial cell growth factor, placenta growth factor, and pleiotrophin in human primary breast cancer and its relation to angiogenesis. Cancer Res., *57:* 963–969, 1997.

16. O'Reilly, M. S. The combination of antiangiogenic therapy with other modalities. Cancer J. *8*(Suppl. 1)*:* S89–S99, 2002.

17. Li, M., Ye, C., Feng, C., Riedel, F., Liu, X., Zeng, Q., and Grandis, J. R. Enhanced antiangiogenic therapy of squamous cell carcinoma by combined endostatin and epidermal growth factor receptor-antisense therapy. Clin. Cancer Res., *8:* 3570–3578, 2002.

Clinical Cancer Research

Targeting Multiple Biological Pathways as a Strategy to Improve the Treatment of Cancer

Michael S. O'Reilly

Clin Cancer Res 2002;8:3309-3310.