STUDY SHOWS ANTIANGIOGENIC DRUG THERAPY FOR CANCER PRODUCES MIXED RESULTS IN PRECLINICAL MODELS: CLINICAL IMPLICATIONS AND FUTURE RESEARCH DIRECTIONS

Dr. Robert Kerbel and his lab at Sunnybrook Research Institute have found that antiangiogenic drugs, shown to slow tumour growth in some cancer patients, might also accelerate metastasis in certain preclinical circumstances. The journal *Cancer Cell* published the results on March 3; here, Dr. John Ebos, a postdoctoral fellow in the Kerbel lab and lead author of the study, discusses what the findings mean for patients and the field of antiangiogenesis research.

Dr. Robert Kerbel is a senior scientist at Sunnybrook Research Institute and a professor at the University of Toronto. He holds the Canada Research Chair in Tumour Biology, Angiogenesis and Antiangiogenic Therapy.

What are antiangiogenic drugs?

Perhaps one of the most significant advances in the development of new anticancer strategies in the past five years has been the clinical approval of drugs that aim to block new blood vessel development, a process termed “angiogenesis” that is critical for tumours to grow and survive. The list of these new “antiangiogenic” drugs now being given to patients with metastatic cancer of varying types is growing, and many more new drugs are being tested. In our studies we used two: sunitinib and sorafenib, which have been approved for use in metastatic kidney cancer, liver cancer (sorafenib only) and gastrointestinal stromal cancers (sunitinib only).

Why did you do this work?

Although these advances in antiangiogenic drug development have been considerable, an emerging question is why these drugs are not working better. Many patients show benefits and respond to drug treatments, but it is unknown why these effects have not translated into more stabilization of disease for longer periods, or even into a cure. So, we had two main questions when we started this study. We wanted to understand why, in some patients who receive these drugs, the disease sometimes grows faster and more aggressively when it does eventually return. And, we wondered if these drugs would be beneficial in earlier disease stages, such as when a drug is given “neoadjuvantly” (when treatment is used to shrink a tumour before it is surgically removed) or “adjuvantly” (when a primary tumour is surgically removed, and then treatment is given to increase the probability that all remaining cancer is eliminated and patients are cured).

What are the major findings in this study?

All of our studies were preclinical—that is, we used animals and varying tumour models to test antiangiogenic drugs in different cancer settings. These cancer models included

those with a more localized “primary” tumour as well as those with more advanced disease that has spread systemically, or “metastatically,” throughout the organism.

What we found was that treatment with sunitinib could potently limit the growth of a primary tumour, something that is consistent with the noted clinical efficacy of the drug. In contrast to this, however, we also found that the same drug had less effect on early metastatic disease, or could even speed its growth. This surprising result depended on various experimental conditions, such as how long the therapy was given and the stage of the disease when treatment was initiated. For example, we tested short-term and long-term treatment schedules and we compared instances where drug was given *before* the cancer was implanted or *after* it was removed. Importantly, we found that the short-term therapy in both instances could accelerate the disease. Again, this result contrasted with the potent anti-tumour effects we observed when the same animals with local primary tumours received identical treatments. Thus, we found the drug could have two effects on tumour growth, both inhibition and enhancement, depending on the circumstance.

What is the mechanism to explain these results?

Unfortunately, we don’t have an answer to this question yet. What is fascinating is that, due to how we did our experiments, we can speculate about some possibilities. For instance, because we treated the mice *before* they received the cancer cells, it suggests that antiangiogenic treatment may force a reaction by the body to the drug, which in turn may create conditions more favorable for tumour growth in some cases. Such an effect could be viewed as a “host” response to treatment and thus be an effect largely independent of how the tumour responds to drug. But it is likely that other mechanisms could be playing a role as well. For example, our study has been published in *Cancer Cell* with a companion paper by investigators at the University of California in San Francisco, Dr. Doug Hanahan and Dr. Gabrielle Bergers and colleagues, in collaboration with Dr. Oriol Casanovas, Catalan Institute of Oncology, Barcelona, Spain, who found results similar to ours, albeit with a different explanation. In their study, these researchers found that prolonged inhibition of angiogenesis in mice—while able to slow the cancer growth initially—eventually resulted in disease that was more invasive and capable of spreading to distant organs. Thus, both studies show the limitations of antiangiogenic drugs, which could result from how both the body and the disease are reacting to the treatment.

What are the implications of these findings for patients receiving these drugs?

It is important to keep in mind that these studies were conducted in mice and are meant to serve as an experimental setting for us to test hypotheses in “proof of principal” experiments. So what happens in mice may not always be true for what happens in humans. However, such studies allow us to raise questions that can be tested or observed clinically. As mentioned, our results and the results of the other group may provide some explanations for why the benefits of such antiangiogenic drugs (like many others) have been more modest for patients than anticipated. This could entail a shift in biology that could compromise some of the initial benefit gained. Again, it’s important to note that the overall effect of these drugs is still one of a net clinical benefit for certain cancer patients.

As well, our results indicate that use of such therapies in earlier stage disease, that is, in the neoadjuvant or adjuvant settings, should be closely monitored and evaluated. Findings such as ours reinforce the view that antiangiogenic drugs should not be used "off-label" in situations where they are not yet approved on the basis of results obtained in prospective, randomized clinical trials.

What is the next step for research in this area?

First, it will be important to monitor closely the clinical use of these drugs and observe whether our results are relevant to what happens in cancer patients. Second, it is possible that our findings may indicate why these drugs have not been working better for people overall. For this reason we are currently trying very hard to decipher the underlying mechanisms at work here, which, if found, might lead to antiangiogenic therapies being used in combination with other compounds which may limit these effects. It's possible that this approach could vastly improve results for patients.

Supporting this research are The Terry Fox Foundation through the National Cancer Institute of Canada, and the Ontario Institute for Cancer Research.