Angiogenesis inhibition:
do tumours have a plan B?

Carmen Phillips

Hopes that angiogenesis inhibition could improve outcomes when used adjuvantly in colorectal cancer received a setback at the end of April, with the announcement that the NSABP C-08 trial had failed to meet its primary endpoint. Recent research into how tumours respond to these drugs may help explain the disappointing results.

This article was first published in the NCI bulletin shortly before the NSABP C-08 trial results were reported.

During tumour angiogenesis, cancerous tumour cells release molecules that send signals to surrounding normal host tissue. This signalling activates certain genes in the host tissue that, in turn, make proteins to encourage the growth of new blood vessels.

Angiogenesis inhibitors, drugs thought to work by attacking a tumour's vasculature, are following a familiar pattern. Having proven that, alone or in combination with chemotherapy, they can modestly improve progression-free and/or overall survival in patients with several forms of advanced cancer, their investigational use is expanding. Several are now being tested as adjuvant (after surgery) and neoadjuvant (before surgery) therapy in clinical trials involving patients with earlier stage disease.

The first efficacy results from a phase III trial using adjuvant bevacizumab (Avastin), an angiogenesis inhibitor that targets the growth factor VEGF, are expected some time this year. The trial, the National Surgical Adjuvant Breast and Bowel Project's C-08 trial, enrolled patients with stage II and III colorectal cancer.

While the oncology community anxiously awaits the results, animal model studies published last month have further intensified interest in the trial. Angiogenesis inhibition did indeed shrink tumours in the animal models. But after the initial response, the tumours often returned with increased aggression, were far more likely to metastasise, and in some cases decreased survival.

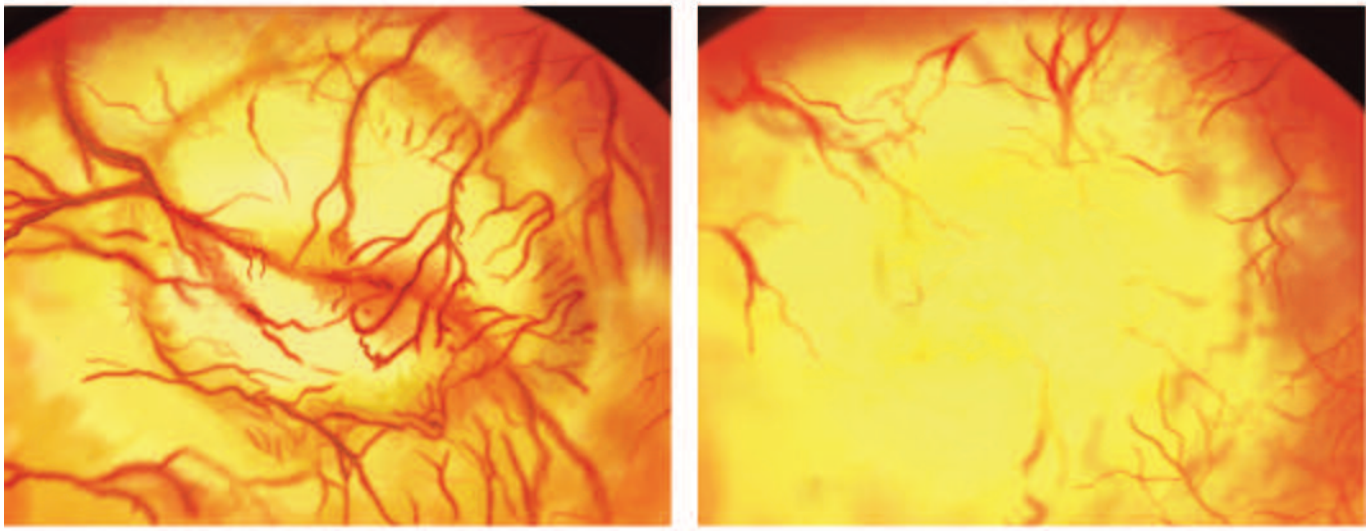
The fact that tumours are developing resistance to treatment isn't unexpected, researchers agree. But the findings may require closer scrutiny of how anti-angiogenic agents are tested in patients, argued Robert Kerbel, a leading angiogenesis researcher at the University of Toronto, whose lab conducted one of the animal model studies, because they suggest that rather than eliciting garden-variety resistance to treatment, these agents are radically altering the tumour's biology.

"If our mouse findings are relevant," he said, "you can see where one might predict that the outcome of [these] trials might not turn out as well as originally hoped or expected."

Like water on an oil fire

Other lab and animal model studies have hinted that angiogenesis inhibition could have such untoward effects. But these recent studies appear to provide the most direct evidence.

In the study from Kerbel's group, led by John Ebos and published in the



Angiogenesis inhibitors are designed to block the signals from tumour cells that stimulate the growth of new blood vessels

March issue of *Cancer Cell*, several of the experiments were "crude representations" of neoadjuvant or adjuvant therapy, Kerbel explained. For example, when sunitinib (Sutent), which inhibits several proteins essential to angiogenesis, was given for a short time before or after the intravenous injection of metastatic breast cancer cells, it accelerated metastasis compared with untreated mice and decreased overall survival.

A second study published in the same issue of *Cancer Cell* tested several anti-angiogenic approaches in mouse models of glioblastoma and pancreatic cancer. In the pancreatic cancer model, treatment for one week with an investigational angiogenesis inhibitor initially shrank tumours. But as treatment continued, the tumours grew, developing "wide fronts of invasion", stretching out into the surrounding tissue, wrote Marta Pàez-Ribes of the Catalan Institute of Oncology in Spain, and her colleagues. The untreated tumours, on the other hand, remained localised and were less invasive.

One intriguing aspect of these studies, explained Gabriele Bergers of the University of California, San Francisco, and a co-author on the Pàez-Ribes paper, is that the tumours are adapting even as the endothelial cells on the vasculature that feeds the tumours are still sensitive to the agents being used to target them.

"The tumours find other ways to reinitiate neovascularisation or to grow by becoming more invasive," she said. "This mechanism is very different and distinct from classical tumour cell resistance, in which tumour cells, for example, do not take up drugs anymore, or else expel them. The evasive adaptation allows the addition of other inhibitors that potentially block these evasive pathways. That is encouraging."

It's clear that angiogenesis inhibition elicits a strong response from the tumour and its microenvironment, Kerbel stressed. It actually increases, for example, levels of VEGF and PIGF-1, another growth factor important to angiogenesis.

"We've looked at G-CSF, SDF-1, SCF and osteopontin, among others," Kerbel said. "We looked across the board and saw a lot of these other growth factors and cytokines and chemokines all increasing. But we don't know why it's happening." All of these factors are known, he added, to promote tumour growth.

Although he warns that it's difficult to extrapolate findings from animal models to humans, Axel Grothey of the Mayo Clinic, who specialises in gastrointestinal cancers, said these data offer some important lessons.

"It makes us realise how much we still don't know about tumour biology," he said.

They suggest that... these agents are radically altering the tumour's biology

"The studies have no immediate clinical relevance, but give reason to rethink how we apply these agents"

Implications for practice?

The ongoing clinical trials of adjuvant and neoadjuvant therapy using anti-angiogenic agents will hopefully shed some light on the issues raised by the animal model work, said Helen Chen of the American NCI's Cancer Therapy Evaluation Program. However, she stressed, it's important not to have tunnel vision with regard to this subject, noting that some preclinical studies of radiation therapy have showed similar effects on cytokine release and tumour cell behaviour.

"This is a phenomenon of the body or the tumour responding to any stress," she explained. "The nature and magnitude of response as well as the net outcome, however, may vary depending on the specific agents and tumours under study."

Based on the body of data on anti-angiogenic agents, said NSABP C-08's lead investigator, Carmen Allegra, of the University of Florida Shands Cancer Center, the new studies don't have immediate clinical relevance. But, he continued, "they certainly give me reason to rethink how we apply these agents," particularly "in a potentially curative setting, where it's possible that the only disease [patients] have is what we see."

While differences in how the drugs were used complicates the comparison, evidence that the animal model results may not have clinical relevance, at least in the advanced-disease setting, come from the BRiTE study, led by Grothey (*JCO* 26:5326–5334). This observational, nonrandomised study of 1,900 patients demonstrated a more than two-year overall survival associated with the use of bevacizumab. However, in the more than 1,400 patients whose disease progressed while taking bevacizumab as part of first-line therapy, those who remained on bevacizumab even after disease progression had a 52% improvement in overall survival compared with patients taken off bevacizumab after their disease progressed. The median survival difference between the groups was nearly one year.

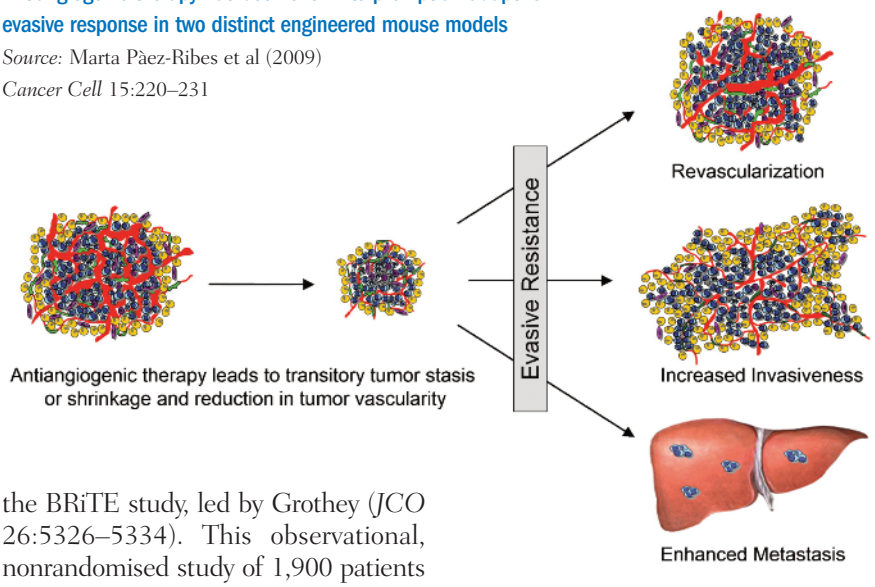
Although patients develop resistance to angiogenesis inhibitors, Grothey said, in patients he has treated he has not seen the type of hyper 'adaptive response' reported in the *Cancer Cell* papers. Even so, he stressed, those studies highlight the importance of not using these drugs off-label outside the confines of a clinical trial.

In the meantime, Chen added, lab and animal model studies can help investigators choose and prioritise the most potentially efficacious – and safe – therapies to test in combination with anti-angiogenic agents.

"The real challenge," she said, "is to understand what additional, compensatory pathways are involved and how to hit them in a rational way."

Antiangiogenic therapy has been shown to prompt an adaptive-evasive response in two distinct engineered mouse models

Source: Marta Pàez-Ribes et al (2009) *Cancer Cell* 15:220–231



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