E19. Angiogenesis inhibitors in breast cancer

Harold J. Burstein*

Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

It is widely accepted that angiogenesis – the formation of new blood vessels – is an essential aspect of tumour growth and dissemination. Angiogenesis inhibitors, agents designed to target that process, are in development for many tumors, including breast cancer. To date, most clinical development has centred on agents that target the growth factor VEGF (vascular endothelial growth factor), known to be a potent mediator of angiogenesis, or its cognate receptors. However, many proteins are involved in the normal and pathological regulation of blood vessel formation, repair and growth, and are potential therapeutic targets in cancer.

Bevacizumab, the humanised monoclonal antibody that neutralises VEGF, has been the most widely studied of the anti-angiogenesis agents in breast cancer. Bevacizumab has limited activity as monotherapy in advanced breast cancer, yielding response rates on the order of 10% by itself. In the first-line treatment of metastatic breast cancer, the addition of bevacizumab to paclitaxel chemotherapy improved response rate and time to progression compared with chemotherapy alone, though there was no difference in overall survival. Smaller trials have examined the safety and efficacy of bevacizumab paired with vinorelbine, docetaxel, or low-dose 'metronomic' chemotherapy for advanced breast cancer. In a randomised trial conducted among patients previously treated with anthracycline- and taxane-based chemotherapy, the addition of bevacizumab to capecitabine led to no significant improvement in time to progression compared to capecitabine alone. It is unclear what accounts for the different efficacy results seen in these two trials. One explanation centres on the differences in the line of treatment, and the possibility that in more refractory cancers, tumour growth is no longer dependent on VEGF in a way that can be tacked clinically by neutralisation of VEGF. An alternative explanation is that the chemotherapy backbone affected the results, and in particular that weekly paclitaxel might be more efficacious with bevacizumab than capecitabine-based therapy.

Other anti-angiogenesis agents are also being studied in advanced breast cancer, including tyrosine kinase inhibitors. Sunitinib, which targets the VEGFR and PDGFR, has shown limited clinical activity, with response rates on the order of 10 to 15%, in chemotherapy-refractory breast cancer. Other kinase inhibitors such as sorafenib, AZD2171, and AZD6474 are under study.

The side effect profile of anti-angiogenesis inhibitors in breast cancer patients is consistent with findings in other cancer patients. Side effects frequently include hypertension, and less commonly, proteinuria. Bevacizumab can be associated with headache and sinus/nasal congestion, and there remain concerns about wound healing and predisposition to bowel perforation. Sunitinib and other TKIs can contribute to hypertension, fatigue, and thyroid dysfunction, as well as nausea and myelosuppression.

Fundamental questions about the optimal use of anti-angiogenic agents persist in breast cancer, as in all solid tumours. It is unclear if tyrosine kinase inhibitors (TKIs) achieve comparable clinical results as VEGF-neutralising agents, and whether broader spectrum TKIs that may inhibit the enzymatic activity of multiple growth factor receptors in the angiogenesis pathway may have clinical advantages over narrower spectrum agents. It is not clear whether pairing VEGF-neutralising therapies with VEGFR-inhibiting agents will be feasible, and if so, valuable, in breast cancer patients. The need for chemotherapy as an adjunct to success with anti-angiogenic agents is still being sorted out. Should combination treatment prove the mainstay of drug development, it is nonetheless unclear which chemotherapy agents would most lend themselves to use with angiogenesis inhibitors. Finally, there are to date no markers that predict adequately which patients or tumours are most likely to benefit from anti-angiogenic therapy. The search for such markers remains a high priority in this area of clinical investigation.

Clinical trials examining combinations of chemotherapy with anti-angiogenesis agents, novel pairs of anti-angiogenesis drugs and trials for early stage breast cancer are all underway around the world.

Conflict of interest statement

None declared.

1359-6349/$ – see front matter