Published in final edited form as:

Nat Rev Endocrinol. 2018 June ; 14(6): 329–330. doi:10.1038/s41574-018-0021-5.

Anti-VEGF therapy — a role in obesity-related breast cancer

Coral Omene¹ and Elisa V. Bandera²

¹Division of Medical Oncology, Rutgers Cancer Institute of New Jersey, Rutgers University, Robert Wood Johnson Medical School, New Brunswick, NJ, USA

²Division of Population Science, Rutgers Cancer Institute of New Jersey, Rutgers University, Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Abstract

Obesity increases the risk of breast cancer and decreases the survival of patients with breast cancer, particularly for postmenopausal, oestrogen receptor-positive breast cancer. New findings now add to the evidence for the detrimental effects of obesity in patients with breast cancer by showing that obesity can cause resistance to therapy.

A recent article by Joao Incio and colleagues¹ helps shed some light on possible mechanisms of resistance to anti-vascular endothelial growth factor (VEGF) therapy in breast cancer, specifically in the setting of obesity. Using mouse models, they show that obesity hampers the effects of anti-VEGF therapy on angiogenesis, tumour growth and metastasis. To date, multiple clinical trials have failed to definitively support the use of anti-VEGF therapy as a proven option for the treatment of breast cancer either in the neoadjuvant (before surgery), adjuvant (after surgery) or metastatic settings². In the metastatic setting, in which the anti-VEGF therapy bevacizumab first gained accelerated approval in 2008, overall response rates were positive, but conflicting reports on progression-free survival and overall survival benefit led to the reversal of this approval in 2010. The reasons for the discrepancies in patient outcomes and lack of overall benefit are multifactorial and include what some researchers speculate are differences in study populations and angiogenesis resistance mechanisms.

One such mechanism has been investigated in detail. Incio et al.¹ hypothesized that obesity promotes resistance to anti-VEGF therapy in breast cancer via the overproduction of alternative angiogenic factors. To test this notion, the authors performed a subanalysis of a phase II clinical trial evaluating bevacizumab in the neoadjuvant setting. Results showed that patients with excess weight (BMI >25 kg/m²) present with larger and more hypoxic tumours than patients with BMI <25 kg/m². Patients who were overweight also had increased circulating concentrations of IL-6 and fibroblast growth factor 2 (FGF2) and expression of these factors in tumours was localized in close juxtaposition to adipocyte-rich areas¹.

Correspondence to: Coral Omene.

Competing interests

The authors declare no competing interests.

In order to evaluate whether obesity can alter the response to anti-VEGF therapy in breast cancer, the authors fed two syngeneic murine orthotopic models — reflecting either oestrogen receptor-positive breast cancer (E0771) or triple-negative breast cancer (MCAIV) — high-fat and low-fat diets to generate obese and lean mice. In the oestrogen receptor-positive breast cancer setting, treatment with B20, an anti-VEGF antibody, was more effective at inhibiting tumour growth in lean E0771 mice than in obese E0771 mice. Tumours have their own blood supply for nutrition and oxygenation and typically induce these blood vessels by secretion of angiogenic factors including VEGF. Tumours from obese E0771 mice had decreased blood vessel density and, similarly to what was observed in humans, higher levels of IL-6 than lean mice. Of note, the authors identified the source of IL-6 as adipocytes and infiltrating immune cells. In addition to increased IL-6, tumours from obese E0771 mice had increased expression of carbonic anhydrase 9 (CAIX) and glucose transporter 1 (two markers for hypoxia) compared with tumours from lean mice. This increase in hypoxia markers, which identify the oxygen-deprived state of the tumour, was associated with an increase in the number of cancer-associated adipocytes, which are fat cells that associate with or surround the tumour. Interestingly, Incio and colleagues found that IL-6 expression was localized in adipocyte-rich regions of E0771 tumours and colocalized with the expression of hypoxia markers¹.

The authors then performed IL-6 inhibition using an anti-IL-6 antibody in combination with B20, which reduced tumour growth and metastasis in obese mice to rates similar to those observed for lean mice receiving just B20. Importantly, IL-6 blockade did not improve the response to B20 in the lean setting, suggesting that IL-6 has an important role in tumour progression, but only in the context of obesity and anti-VEGF therapy¹. In obese, but not lean, mice, the combination therapy also increased tumour blood vessel density, decreased the expression of CAIX by ~60% and diminished the infiltration of immune cells¹.

The evidence for an association of obesity with triple-negative breast cancer is not consistent. While most studies have reported that obesity increases the risk of premenopausal triple-negative breast cancer, results for postmenopausal triple-negative breast cancer are inconclusive³. It is therefore interesting that in MCAIV mice the authors discovered that FGF2, but not IL-6, was strongly associated with obesity¹. As was the case with IL-6 in the oestrogen receptor-positive breast cancer setting, the authors found FGF2 to be highly expressed in adipocyte-rich areas, but they also observed FGF2 in activated cancer-associated fibroblasts, which are cells that surround the tumour and promote tumour growth by secreting angiogenic factors including VEGF. Tumours from obese MCAIV mice were less vascularized, more hypoxic and had increased resistance to B20 than tumours from lean mice. Of note, FGF receptor blockade improved tumour responsiveness to anti-VEGF therapy in obese mice¹.

The authors then treated MCAIV mice with B20 in combination with metformin, which reduces expression of FGF2. The results showed that metformin reduced expression of FGF2 in tumours from B20-treated obese MCAIV mice, inhibited FGF2 downstream signalling pathways (AKT, S6, ERK and signal transducer and activator of transcription 3 (STAT3)), reduced vessel density and resensitized tumours to anti-VEGF treatment¹.

“the findings by Incio and colleagues point the way for a comeback for anti-VEGF therapy”

One limiting factor in the generalizability of their findings is that Incio and colleagues did not investigate obesity-related human epidermal growth factor receptor 2 (HER2)-positive breast cancer. In HER2-positive breast cancer, activation of the IL-6 feedback loop expands the cancer stem cell population resulting in resistance to trastuzumab⁴. A phase III trial of docetaxel and trastuzumab did not show any significant differences in survival with the addition of bevacizumab⁵. It would have been interesting to evaluate whether IL-6 or FGF2 has a role in HER2-positive breast cancer or if another mechanism entirely was pertinent. It is conceivable that similar blockade of IL-6 in combination with anti-VEGF therapy would restore tumour sensitivity in HER2-positive breast cancer.

Overall, the findings by Incio and colleagues¹ point the way for a comeback for anti-VEGF therapy in breast cancer, specifically as it pertains to obesity-related breast cancer. The results provide valuable steps towards using a precision medicine approach in future clinical trial design. They also provide additional reasons for maintaining a healthy weight not only for breast cancer prevention, but also for better cancer management and survival.

Acknowledgments

C.O. is supported by NIH/National Cancer Institute grant K08CA172722.

References

1. Incio J, et al. Obesity promotes resistance to anti-VEGF therapy in breast cancer by up-regulating IL-6 and potentially FGF-2. *Sci. Transl Med.* 10:eaag0945.2018; [PubMed: 29540614]
2. Varella L, Abraham J, Kruse M. Revisiting the role of bevacizumab in the treatment of breast cancer. *Semin. Oncol.* 44:273–285.2017; [PubMed: 29526256]
3. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: mechanistic insights and strategies for intervention. *CA Cancer J. Clin.* 67:378–397.2017; [PubMed: 28763097]
4. Korkaya H, et al. Activation of an IL6 inflammatory loop mediates trastuzumab resistance in HER2+ breast cancer by expanding the cancer stem cell population. *Mol. Cell.* 47:570–584.2012; [PubMed: 22819326]
5. Gianni L, et al. AVEREL: a randomized phase III trial evaluating bevacizumab in combination with docetaxel and trastuzumab as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer. *J. Clin. Oncol.* 31:1719–1725.2013; [PubMed: 23569311]