distant organs or vice versa: hence, the imperfect connection between axillary involvement and the involvement of distant organs. Furthermore, a large primary cancer could be large because of its pronounced mitotic activity or because it is an excellent self-seeder: hence, the imperfect connection between tumor size and metastatic behavior. Because of the site-specific nature of metastases, the abilities to self-seed or to seed distant sites should be imperfectly correlated as well. Therefore, we could envision a case in which a primary cancer is excellent at seeding axillary lymph nodes (via the sentinel node route) and/or distant organs, but not itself. Moreover, a small cancer that has demonstrated the capacity to seed a given number of lymph nodes may express node-specific and distant-organ metastatic genes but not self-specific ones. Therefore, it might be more aggressive, in terms of ultimate outcomes, than a larger cancer that involves the same number of axillary nodes. The larger cancer, in this instance, is better at seeding itself but less proficient at seeding regional lymph nodes or distant sites, so it needed more cells in the primary mass to accomplish the comparable degree of nodal involvement.

The important aspect of this discussion, then, is that simple anatomic reasoning—which has led to many advances in clinical oncology but also the clinical enigmas described above—may not be the most productive way forward in understanding the clinical behavior of cancers and hence prognostication. Elucidating the molecular mechanisms that underlie the biology of individual cancers would seem to be a more useful focus of our attention. Fortunately for us and for our patients, both technical and conceptual improvements are now available and are resulting in headway. These, coupled with insightful clinical observations as illustrated by the two articles in this issue,[1,2] herald a future of greater understanding and resulting clinical progress.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Expanding Our Therapeutic Options: Beta Blockers for Breast Cancer?

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See accompanying articles on pages 2635 and 2645

Despite the many advances in cancer therapy during the past 50 years, standard adjuvant chemotherapy for breast cancer has provided only modest benefit in terms of improvements in disease-free and overall survival, with many patients relapsing despite therapy and others likely not needing chemotherapy.[1,2] The survival benefit from adjuvant chemotherapy in younger women with breast cancer is likely derived in part from the secondary effects of treatment-induced amenorrhea, especially in hormone receptor–positive tumors, which affects the tumor microenvironment.[3,4] In contrast, targeted therapies, such as trastuzumab and tamoxifen, have had major impacts on mortality by their selective effects on tumor cells that overexpress specific characteristics within a particular breast cancer tumor. Historically, most drug development strategies have targeted metabolic and signaling pathways within the malignant epithelial cell,[5] with limited

consideration of the tumor microenvironment as a critical partner in the process of invasion and metastasis. The long latency period for recurrence, especially in hormone receptor–positive breast cancer, makes it even more important to understand the host microenvironment in which the dormant metastases reside and reactivate,[6,7] in that the stromal microenvironment may be an enriched source of estrogen production.[8-11] Observational epidemiologic studies have suggested a range of host factors that may influence survival and recurrence after breast cancer including adiposity and weight gain, physical activity, alcohol and tobacco use, and comorbid medical conditions.[12] Many of these factors are thought to influence the growth and metastases of breast cancer through their effects on hormonal and inflammatory pathways.[13] An emerging body of basic research has begun to suggest that neuroendocrine signaling pathways may also play a role in mediating effects of lifestyle factors on the metastatic microenvironment. These observations raise the intriguing possibility that medications originally targeted toward other diseases might also impact the tumor microenvironment, and thereby provide previously unappreciated opportunities for therapeutic control of disease progression, metastasis, and disease recurrence.

In the articles that accompany this editorial, two retrospective studies examine the association between the breast cancer patient's exposure to beta adrenergic antagonist medications and breast cancer recurrence and survival.[14,15] Beta adrenergic blockade has been a highly successful therapeutic approach in the context of cardiovascular disease for more than four decades. The current *Journal of Clinical Oncology* articles suggest that these generally safe, inexpensive, and well-understood agents may provide therapeutic leverage in the context of breast cancer as well. These studies arise in the context of recent animal model work in ovarian cancer and breast cancer indicating that activation of beta adrenergic receptors on primary tumor cells and stromal cells in the tumor microenvironment can influence the growth and metastatic dissemination of orthotopically implanted tumors.[16,17] A recent study from Powe et al[18] reported on a case series of women with breast cancer treated for hypertension, with or without β-blocker (BB) medication, demonstrating a remarkable reduction in risk of recurrence and improved survival in women receiving BB therapy. Results suggested benefit from both β_1 selective and nonselective beta (β_1/β_2) antagonist medications. This report was the first in humans to suggest a protective effect of targeting adrenergic receptors in the treatment of breast cancer. Previous epidemiologic studies had also indicated potential protective activity in prostate cancer progression,[19,20] and in vitro studies have suggested a biologic rationale for this approach in a diverse array of tumor types.[21]

The study by Barron et al[14] used a national tumor registry in Ireland and a publicly available pharmacy database for women receiving subsidized medication support. In combining data from these two sources, Barron et al set up a classical case-control comparison of women with breast cancer who were receiving either propanolol (β_1/β_2 antagonist, n = 70) or atenolol (β_1 antagonist, n = 525) in the year before and after diagnosis, and were matched 1:2 with women not taking a BB (n = 4,738). They asked whether or not the exposure to BB medication influenced the size of the primary tumor (T status); nodal or metastatic involvement at diagnosis; and time to breast cancer–specific mortality outcomes. Patients were generally well-matched for relevant cancer variables, and were matched for comorbid conditions by propensity score. Median follow-up time for the propanolol sample and controls was 3.5 years and for the atenolol sample and controls was 2.7 to 3.0 years. Resulting analysis found significant reductions in tumor size and nodal/metastatic distribution for propanolol users, but not for those exposed to atenolol. The cumulative probability of breast cancer–specific mortality was significantly lower among propanolol users (hazard ratio [HR], 0.19; 95% CI, 0.06 to 0.60), with no significant reduction in mortality for atenolol users compared to matched nonusers. These provocative findings suggest that the benefits of BB therapy accrued only in the nonselective formulation, implicating the β_2 adrenergic pathway as the likely mediator of the therapeutic benefit observed.[14] Limitations of this study include its retrospective design, the exclusion of more than 6,000 women in the tumor registry from analysis due to the fact that they were not in the pharmacy database which served primarily older and low-income individuals, and the confounding by indication for the BB medications.

The second article that accompanies this editorial by Melhern-Bertrandt et al[15] utilized a clinical database maintained at MD Anderson Cancer Center (Houston, TX) that focuses on outcomes in patients with breast cancer treated with neoadjuvant therapy. This database has previously been examined to probe the potential cancer therapeutic effects of noncancer-targeted agents such as antidiabetic therapy with metformin.[22] In the current study,[15] patients treated with neoadjuvant therapy between 1995 and 2007 were examined for concurrent use of BB medication during neoadjuvant therapy, with the authors comparing those with and without BB exposure for pathologic complete response, relapse-free survival, and overall survival. Only 102 of the 1,413 patients in the database were using BB therapy, and in comparison with the remainder of the sample, BB users were significantly older, had significantly higher body mass index, were more likely to have a diagnosis of hypertension, and more likely be on drugs targeting the angiotensin receptor pathway (all P values were $< .001$). There was no significant difference in the diagnosis of diabetes or use of metformin between the two groups. In the analysis examining pathologic complete response for the total sample, there was no difference in outcome for those taking BB or not. However, those on BB showed significantly greater relapse-free survival (HR, 0.52; CI, 0.31 to 0.88; $P = .015$) and a trend toward greater overall survival that did not reach statistical significance (HR, 0.64; CI, 0.38 to 1.07; $P = .09$). A secondary objective of this article was to examine the potential benefit of the BB therapy in the estrogen receptor–negative/progesterone receptor–negative/human epidermal growth factor receptor 2 (HER-2) –negative (triple-negative breast cancer; TNBC) subgroup, who represented 377 of the 1,413 women in the study. In analyses of TNBCs alone, there were significant effects for BB use on both relapse-free ($P = .03$) and overall survival ($P = .05$). In contrast, for the 908 patients with estrogen receptor–positive breast cancer, BB exposure was not associated with significant differences in survival outcomes.[15]

One issue that requires clarification in future studies is the relative effect of β_1-selective versus nonselective β_1/β_2 antagonists in breast cancer. This is particularly true because β_1-selective agents have largely replaced the shorter-acting and nonselective generic propanolol, as current therapy for common cardiovascular conditions and hypertension. In the Melhem-Bertrandt et al article,[15] medication usage was obtained through patient self-report as recorded in the medical record and then abstracted into the clinical research database, in contrast to the pharmacy record database used in the Barron et al study.[14] In the Melhem-Bertrandt et al study the most commonly reported BB medications used were β_1 selective agents (89% of total),

mainly metoprolol (42% of patients) followed by atenolol (37% of patients). Thus, the favorable relapse-free and overall findings from this study,[15] particularly in the TNBC group, would seem to contradict the negative findings regarding atenolol in the Barron et al study. However, neither metoprolol or atenolol is totally β_1 specific; both partially inhibit β_2 adrenergic receptors as well.[23] In fact, among β_1 selective antagonists, those two agents show relatively large off-target β_2 affinity (approximately six-fold selectivity, as opposed to an average 13-fold for other agents).[23] It is possible that even limited β_2 adrenergic inhibition by metoprolol or atenolol might be sufficient to improve breast cancer survival outcomes in the Melhem-Bertrandt et al study. Alternatively, both β_1 and β_2 adrenergic inhibition may contribute to protection, with the β_2 contribution failing to reach significance in the Melhem-Bertrandt et al article due to limited statistical power resulting from the small number of patients in that sample who were receiving nonselective beta antagonists. Some preclinical studies also suggest that nonselective BBs exert greater effects in breast and ovarian carcinoma model systems than do β_1 selective agents.[16,24,25] Thus, future clinical studies are needed to more accurately quantify survival effects for large samples of patients taking agents that effectively antagonize β_2 adrenergic receptors.

Another important topic that remains to be resolved regards possible variations in the effects of beta adrenergic inhibition across different subtypes of breast cancer, particularly as a function of estrogen receptor status, progesterone receptor status, HER-2 status, and TNBC. Laboratory studies have found considerable variation in beta adrenergic receptor expression levels and signaling activity across breast cancer cell types that differ in hormone and growth factor receptor status.[26-28] Because the Barron et al[14]study did not break down the patient population by receptor status, it is not possible to determine whether BB effects vary as a function of tumor receptor expression or whether the TNBC subgroup benefited more from BB therapy than did other tumor types. A large number of patients in the Barron et al study had unknown estrogen receptor, progesterone receptor, and HER-2 status (eg, 46% unknown HER-2 status), and tissue blocks are unlikely to be available for future analysis of that cohort. The Melhern-Bertrandt et al study[15] had more complete data on receptor expression, but the smaller overall sample size limits statistical power to determine whether BB effects truly differ as a function of estrogen receptor, progesterone receptor, or HER-2 status. Given that no existing study has formally tested for statistically significant differences in the magnitude of BB-related survival differences (ie, a TNBC $\times$ BB interaction term), and that routine typing of breast cancers for estrogen receptor, progesterone receptor, and HER-2 expression largely postdates the widespread use of nonselective BBs, it appears that new prospective studies will likely be required to clarify whether β_2-mediated protective effects vary as a function of hormone or growth factor receptor status. However, the stronger point estimate for BB protection among TNBCs in the study of Melhern-Bertrandt et al suggests that such studies need to be done to define the optimal contexts for possible assessment of BB protective effects. As Melhern-Bertrandt et al note, new therapeutic strategies are needed for TNBC, and the potential protective effects of BBs would thus represent a significant advance.

What might be the mechanism underlying a beneficial response to BB therapy preceding and during breast cancer therapy? Preclinical studies have shown that beta adrenergic signaling can influence several fundamental biologic processes underlying the progression and metastasis of carcinomas,[29] including the promotion of inflammation,[17] angiogenesis,[16] growth factor signaling,[30] resistance to programmed cell death,[31,32] and resistance to growth factor receptor–targeted therapy[33](see Fig 1). Sloan et al[17] recently used an imaging-based read-out of breast cancer metastasis in an syngeneic orthotopic mouse model, and found that beta adrenoreceptor activation by isoproterenol could increase the number and mass of distant metastasis by more than 10-fold without substantially impacting growth of the primary tumor. That effect was mimicked by experimental imposition of repeated stress, and those stress effects on metastasis were completely abrogated by the nonselective BB propanolol.[17] Adrenergic promotion of metastasis was mediated by increased macrophage recruitment into the primary tumor, resulting in increased expression of prometastatic genes such as *Ptgs2*/COX2, *Tgfb*, *Mmp9*, *Vegf*, *Vcam1* and *Csf1*/M-CSF, as well as reduced expression of progression-inhibitory genes such as *Ifnb*. Interestingly, the Sloan et al study found no effect of beta adrenergic signaling on growth of the primary breast tumor—only on the rate and magnitude of distant metastasis. Those results are consistent with previous observational studies that found no relationship between BB use and the incidence of new breast cancers. Beta adrenergic signaling appears to have little effect on the biologic processes involved in breast cancer initiation, but more strongly affects the biologic processes involved in the subsequent progression and metastasis of incipient tumors. Given these results from the laboratory, and the clinical results from three recent retrospective reports suggesting the potential to limit recurrence of incident tumors,[14,15,18] perhaps it is time to consider proof-of-concept trials testing the value of BB medication in the setting of breast cancer.

Several other host factors implicated in breast cancer progression and recurrence are also associated with increased beta adrenergic signaling and/or receptor expression, including adiposity, aging, metabolic dysregulation, reproductive hormone synthesis, and tobacco and alcohol consumption. Those associations raise the possibility that many general patient-level physiologic or behavioral risk factors may exert their biologic effects on breast cancer pathophysiology at least in part via beta adrenergic signaling. One example involves chronic inflammation linked to the pro-inflammatory cytokine interleukin 6 (IL-6), which has been identified as a driver of breast cancer progression in both observational studies of circulating biomarkers[28,34-41] and genetic analyses of *IL6* gene polymorphism.[42-44] *IL6* gene expression is also known to be upregulated by beta-adrenergic signaling, and a breast cancer–associated single-nucleotide polymorphism in the *IL6* promoter acts to enhance its transcriptional responsiveness to beta adrenergic signaling.[28,41] Thus, the genetic penetrance of *IL6* polymorphism on breast cancer outcomes appears to require beta adrenergic signaling for realization. Given the central role of adrenergic signaling in fight-or-flight stress responses, beta adrenergic regulation of carcinoma-related genes such as *IL6* might also underlie the long-conjectured but still controversial relationship between chronic stress and cancer progression.[13]

As the articles that accompany this editorial suggest, the microenvironment may be a critical target for future cancer treatment and prevention of recurrence. Future phase III breast cancer treatment trials should endeavor to collect prospective data on relevant medication exposures, weight and weight gain, comorbid conditions, and behaviors that have the potential to influence the microenvironment of the tumor, as these may be potent mediators of prognosis and survival, and may or may not be effectively accounted for in randomization. The recently launched National Surgical Adjuvant Breast and Bowel Project (NSABP) B-47 trial is an example of such a study that will capture prospective information on a

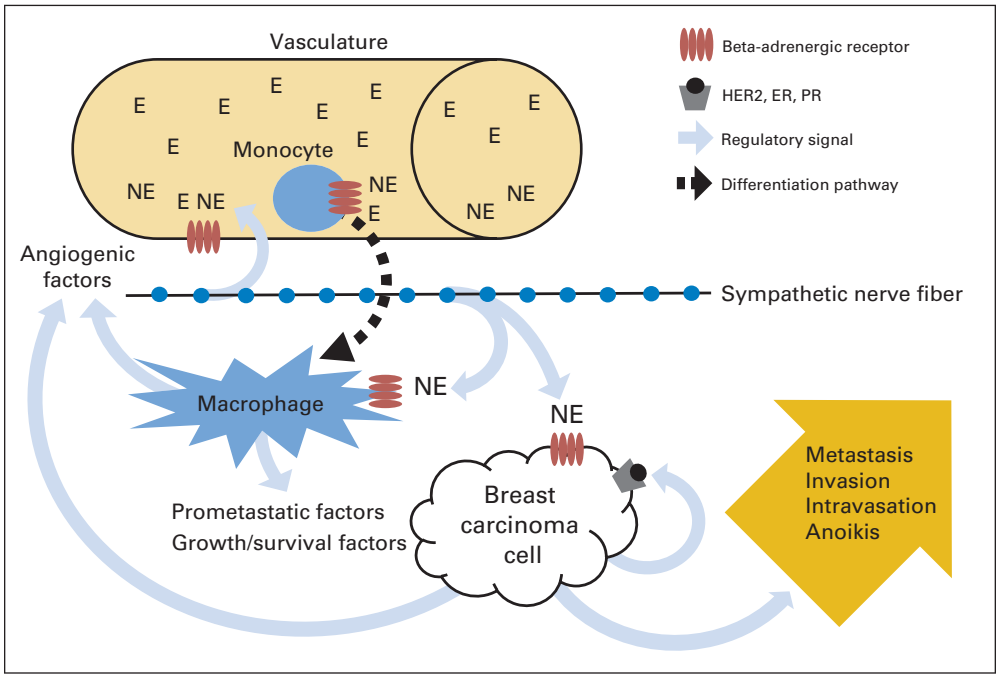

Fig 1. Pathways by which beta blockers might influence breast cancer progression. Beta adrenergic receptors are activated by epinephrine (E) released into the systemic vasculature by the adrenal gland and norepinephrine (NE) from local sympathetic nerve fibers (typically vasculature-associated fibers in breast cancer microenvironments). Resulting activation of beta adrenergic receptors can enhance myelopoiesis and differentiation of proinflammatory monocytes, upregulate angiogenesis, enhance recruitment of macrophages into the tumor parenchyma and surrounding microenvironment, upregulate macrophage and carcinoma cell expression of prometastatic gene products, growth and survival factors, and angiogenic factors, and enhance growth factor receptor-mediated signaling pathways including estrogen receptors (ERs)/progesterone receptors (PRs), and signaling through the epidermal growth factor/human epidermal growth factor receptor 2 (HER-2) axis. Beta adrenergic blockade has the potential to impact all of those regulatory relationships in parallel, providing pleiotropic biologic impact from a single therapeutic agent that is already known to be safe, well-tolerated, inexpensive, and easily managed.

variety of host lifestyle factors, medications, comorbid conditions, and treatment–induced amenorrhea, along with collection of pre- and post-treatment blood samples to track changes in inflammation over time, as well as to serve as a biorepository for future research related to the microenvironment and treatment effects. Only within the setting of randomized treatment assignment that targets the tumor will it be possible to examine the additional influence of host factors that may influence the microenvironment.

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Cabozantinib in Medullary Thyroid Carcinoma: Time to Focus the Spotlight on This Rare Disease

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See accompanying article on page 2660

In the article that accompanies this editorial, Kurzrock et al[1] report on findings from a phase I study of cabozantinib (XL184; Exelixis, South San Francisco, CA), a small molecule multikinase inhibitor with activity against rearranged during transfection (RET), vascular endothelial growth factor receptor 2 (VEGFR2), and MET. In this multi-institution study, 85 patients were enrolled onto a standard 3 + 3 dose-escalation design. Of these, 37 patients with advanced medullary thyroid cancer (MTC) were enrolled onto an expansion cohort limited to this one tumor. Beyond the attention given to the safety profile and optimal dosing strategy typical of a phase I study, this report highlights the efficacy data in patients with MTC treated with cabozantinib.

MTC is a rare tumor that arises from the thyroid gland's parafollicular C-cells, a tissue derived from the neural crest that secretes calcitonin. MTC accounts for 4% of all thyroid cancers, and thus fewer than 2,000 new cases of MTC would have been diagnosed in 2010 in the United States.[2,3] MTC can be either sporadic or hereditary in association with multiple endocrine neoplasia type 2 (MEN2), and sporadic MTCs account for 65% to 75% of all cases. Hereditary MTCs arise as a result of activating mutations in the receptor tyrosine kinase, RET, whereas many sporadic MTCs harbor somatically acquired RET mutations (most commonly M918T).[4] There is a strong correlation between particular RET mutations and the phenotype of MTC, and treatment guidelines for MEN2 have been formulated on the basis of the specific RET mutation.[5] For patients with sporadic MTC, there is a spectrum of disease severity that correlates with RET mutation status.[6] Even after complete RET gene sequencing, mutations are not found in all MTCs, which suggests that either regulatory mutations in RET or other genetic abnormalities can also drive the phenotype of MTC.

MTC may be surgically curable if detected at an early stage or by prophylactic thyroidectomy in patients with MEN2 who carry a germline RET mutation.[7-10] Patients with MTC may develop locally recurrent or distant metastatic disease. For patients with unresectable or metastatic MTC, the disease course is highly heterogeneous. Some patients have progressive disease during a period of months, whereas

