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Beta blockade as adjunctive breast cancer therapy: A review

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ABSTRACT

Pre-clinical data has shown that beta adrenergic stimulation can affect the development and progression of many types of cancer. The use of beta blockers as an anti-neoplastic therapy has been studied in retrospective trials and observational trials, but no definitive conclusions about efficacy have been made. Within the realm of breast cancer, significant advances in therapy have led to improved survival outcomes, yet there is room for improvement. Beta adrenergic blockade may prove an effective adjunct to standard breast cancer therapy, with little associated toxicity. This article provides a review of the published literature on beta blockade as an adjunctive cancer therapy, with a focus on breast cancer.

1. Introduction

Recently, there has been an explosion of new agents added to our anti-neoplastic arsenal. However, the repurposing of some agents, which has the advantage of a known safety profile, ready availability, and low cost, should continue to be explored. Results of observational studies have suggested that treatment with beta blockers (BBs) may improve relapse-free (RFS) and/or overall survival (OS) in patients with multiple types of cancer, including breast cancer. Pre-clinical data indicate that some cancer cells may utilize adrenergic stimulation as a mechanism for metastasis, thus becoming potentially susceptible to blockade of the adrenergic pathway. Other potential mechanisms of the anti-cancer effect include epigenetic manipulation, immune system alteration, and cell proliferation pathway inhibition (Lin et al., 2018; Zhou et al., 2016a). Beta-receptor blockade is inexpensive with typically only minor side effects and may prove an effective adjunctive anti-cancer therapy.

2. Methods

A literature search from 2010 to 2019 was performed for studies of BBs as an adjunct to anti-cancer therapy. The literature searches were performed on PubMed, Google Scholar, DynaMED Plus, and the Cochrane Database of Systematic Reviews. Search items included beta blockers and cancer, beta blockers and cancer treatment, propranolol and cancer treatment, propranolol and breast cancer, and beta blockers and breast cancer. Secondary searches were then carried out from the references in the studies identified by the search engines. Manuscripts focused on BBs or other anti-hypertensive agents and the risk of developing breast cancer were not included as they were not the focus of this review. No published randomized controlled trials of BBs given concurrently with chemotherapy or hormonal therapy were identified.

3. Review of pre-clinical data

There are extensive preclinical data exploring the mechanisms by which stress-induced endogenous beta agonists trigger tumorigenesis, angiogenesis, and tumor metastasis. Very likely, there are multiple mechanisms at play, including upregulation of the pro-angiogenic factor, vascular endothelial growth factor (VEGF), activation of genes associated with metastasis and inflammation, activation of cell proliferation pathways, and modulation of the immune system (Lin et al., 2018; Zhou et al., 2016a; Cole and Sood, 2012). These effects seem to be mediated primarily via the beta-2 receptor, suggesting that propranolol (a non-selective beta-1 and beta-2 receptor antagonist) might be more effective than a selective beta-1 receptor antagonist and may have the greatest potential as an anti-cancer agent (Cole and Sood, 2012).

3.1. Potential mechanisms

3.1.1. Epigenetic mechanisms

In a study using ovarian cancer cell lines, Kang and colleagues demonstrated that adrenergic stimulation by norepinephrine increased activity of the MAPK pathway via the overexpression of the MAPK phosphatase DUSP1. In this study, overexpression of DUSP1 was associated with resistance to paclitaxel while gene silencing of DUSP1

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increased the response to paclitaxel and increased apoptosis (Kang et al., 2016). This may be a mechanism by which catecholamines inhibit chemotherapy-induced apoptosis. Accordingly, combining BBs with chemotherapy may have a synergistic effect, as shown in a study using cancer cell lines treated with propranolol and cytotoxic chemotherapy. Low concentrations of propranolol potentiated the effects of chemotherapy and when used in an orthotopic mouse model of human triple negative breast cancer, the combination resulted in sustained anti-neoplastic effects and increased median OS (Pasquier et al., 2011).

3.1.2. Modulation of the immune system

A study examining the role of beta-adrenergic agonists and blockers on NK cell activity studied rats inoculated with an adenocarcinoma cell line known to metastasize to the lung. The rats were then exposed to metaproterenol (MP), a beta agonist. MP suppressed NK cell activity in the blood and led to an increase in the number of tumor cells retained in the lungs one day after inoculation. Both propranolol and nadolol blocked suppression of NK activity (Shakhar and Ben-Eliyahu, 1998). In another experimental rat model, activation by isoprenaline, a beta agonist, led to a decrease in Natural Killer (NK) cell activity and an increase in metastasis. The addition of non-selective BB nadolol reversed this effect (Chung et al., 2016). Exactly how beta agonists decrease NK cell activity and the immune response has not been elucidated, but NK cells are thought to play a role in resistance to cancer metastasis (Shakhar and Ben-Eliyahu, 1998). Furthermore, research on cell lines has demonstrated that catecholamines can inhibit cytotoxic T-cell function and increase regulatory T-cell activity, potentially diminishing innate anti-cancer immunity and suggesting that blockade of sympathetic nervous system signaling may be an effective approach in enhancing innate immunity and increasing the efficacy of chemotherapy (Cook-Mills et al., 1995; Kohm and Sanders, 2001).

3.1.3. Pathway inhibition

Another possible mechanism includes activation of the phosphatidylinositol 3-kinase (PI3K) pathway, protein kinase B (AKT) pathway and hypoxia-inducible factor-1α (HIF-1α) pathway. In a study by Lin and colleagues, the effect of propranolol was assessed in mice implanted with infantile hemangioma tissue. Results showed that propranolol decreased tumor size and was associated with decreased expression of PI3K, AKT, and HIF-1α, suggesting a possible link between activity of those pathways and beta blockade (Lin et al., 2018). Zhou and colleagues investigated pathway activation in a melanoma cell line and showed that propranolol inhibited phosphorylation of AKT, BRAF, MEK1/2 and ERK1/2 in mice, resulting in smaller tumors compared to mice that did not receive propranolol (Zhou et al., 2016b).

Metformin and propranolol may have synergistic effects, possibly regulated through the PI3K, HIF-1, and MAPK pathways or through insulin dependent cell growth pathways (Cufí et al., 2013; Wheaton et al., 2014; Rico et al., 2016). Rico and colleagues showed that the growth of triple negative breast cancer cells lines was decreased by propanolol and further decreased by the combination of propranolol and metformin. The investigators also injected M-406 breast cancer cells intravenously into mice and showed that both propranolol alone and propranolol with metformin resulted in slower tumor growth and decreased the number of metastatic tumors to the lung (Rico et al., 2016).

3.2. The role of adrenergic activation in cancer growth and metastasis

Using an orthotopic mouse model, a study by Sloan and colleagues found that the sympathetic nervous system may be involved as a regulator of breast cancer metastasis. With stress-induced neuroendocrine activation, there was a 30-fold increase in metastasis to distant organs, with the effect mediated by beta-adrenergic signaling. Accordingly, the authors speculate that therapies that target the beta-adrenergic pathway may mitigate the risk of breast cancer recurrence (Sloan et al., 2010). Another study using an orthotopic mouse model found that ovarian tumors in stressed animals had a significant increase in vascularization and found that beta-adrenergic activation was a major mechanism of stress-induced tumor angiogenesis (Thaker et al., 2006). Campbell and colleagues had similar findings in their work on breast cancer bone metastasis, which showed that sympathetic activation of breast cancer bone metastasis can be blocked with propranolol in a mouse model (Campbell et al., 2012).

Sood and colleagues demonstrated that norepinephrine increased the invasiveness of ovarian cancer cell lines in a membrane invasive culture system. Propranolol completely blocked this increase in invasiveness (Sood et al., 2006). A follow up study reported that in a mouse model of ovarian cancer, restraint stress increased norepinephrine and epinephrine, which protected the cancer cells from cell death and promoted growth by activating focal adhesion kinase (Sood et al., 2010).

Benish and colleagues examined the possible role of peri-operative use of BBs and COX inhibitors, to determine if these agents played a role in stress-induced immune suppression and tumor proliferation in the perioperative period. First, rats were inoculated with tumor cells and were assessed for lung tumor retention (LTR). The rats then underwent laparotomy after treatment with a COX-1 or -2 inhibitor, a BB, or a combination of COX-2 inhibitor and BB. Results showed that surgery increased LTR; treating with a combination of pre-operative etodolac (COX-2 inhibitor) and propranolol eliminated this negative impact (Benish et al., 2008).

Signaling in the adrenergic pathway is incompletely understood. In work done by Pinero and colleagues, the effects of beta-agonists, BBs, and alpha-2 blockers in 5 breast cancer cell lines were examined. While cell proliferation was increased by the natural agonist adrenaline, the synthetic agonists salbutamol and isoprenaline inhibited growth. BBs had a variable effect, depending on whether there was concomitant presence of a beta agonist, while the alpha-2 blocker rauwolscine consistently inhibited tumor growth (Perez Pinero et al., 2012). Slotkin and colleagues found that the beta agonists isoproterenol and 8-bromo-cAMP reduced DNA synthesis in vitro by about 25% but propranolol did not decrease DNA synthesis. When propranolol was given with the agonists, it blocked their effect on DNA synthesis (Slotkin et al., 2000). Maccari and colleagues looked at the efficacy of propranolol in mice bearing B16F10 melanoma, a cell line which expressed beta adrenergic receptors. They found that low doses of propranolol inhibited growth of the melanoma while higher doses stimulated growth (Maccari et al., 2017).

4. Review of breast cancer clinical studies

Clinical data on the use of BBs and their effect on breast cancer survival outcomes is limited to retrospective and observational data, which provide inconsistent results. As such, no definitive conclusions can be made about efficacy, however, results of the studies presented in this section may be hypothesis-generating for future research.

In a study assessing the Ki-67 proliferative index of 404 tumor specimens from patients with early breast cancer, investigators found that patients with Stage I breast cancer who took BBs had tumors with a significantly lower Ki67 than BB non-users. The investigators also performed a “window of opportunity” case study in which the Ki-67 was measured in a patient's breast tumor pre-propranolol treatment and again post-propranolol treatment. The Ki-67 was reduced by 23% (Montoya et al., 2017).

In a study evaluating 1,413 breast cancer patients who received neoadjuvant chemotherapy, survival outcomes were assessed for patients taking any BB at the start of neoadjuvant therapy and for those not taking a BB. While there were only 102 patients on BBs, RFS was significantly better in those on BBs (HR = 0.52, $p = 0.015$). The OS was not significantly improved. Similarly, in a subgroup analysis of women

Table 1
Breast cancer clinical studies showing statistically significant results.

Author	Type of beta blocker used	Selected results
Montoya et al. (2017)	Selective and non-selective	66% Ki-67 reduction ($p < 0.0001$) in non-selective BB users vs non-users
Melhem-Bertrandt et al. (2011)	Selective and non-selective	[a]RFS = 87% [b]BB group vs 77% non-BB group ($p = 0.008$)
Powe et al. (2010)	Selective and non-selective	Development of distant metastasis = 11.6% in BB group, 30.6% in non-BB group ($p = 0.028$)
Parada-Huerta et al. (2016)	Selective and non-selective	Non-selective BB associated with lower distant metastasis risk (0% vs 30% with selective BB, $p = 0.04$)
Barron et al. (2011)	Atenolol or Propranolol	Breast cancer-specific mortality lower for propanolol users ([c]HR 0.19, 95%CI 0.06–0.60)
Botteri et al. (2013)	Selective and non-selective	5-year cumulative incidence of breast cancer events = 13.6% BB group vs 27.9% non-BB group
Choy et al. (2016)	Selective and non-selective	Perioperative BB use decreased recurrence and metastasis (HR 0.51, $p = 0.041$)
Spera et al. (2017)	Selective and non-selective	Median [d]PFS in BB group = 10.3 months vs 8.3 in non-BB group ($p = 0.038$)

[a] RFS, relapse-free survival.
[b] BB, beta blocker.
[c] HR, hazard ratio.
[d] PFS, progression-free survival.

with triple negative breast cancer, RFS was significantly improved (HR = 0.30, $p = 0.027$) but OS was not (Melhem-Bertrandt et al., 2011). A retrospective trial of 466 breast cancer patients who took BBs prior to breast cancer diagnosis showed that patients who had taken BBs had a significant decrease in metastasis and cancer relapse, longer disease-free survival (DFS) and a 71% reduction in 10 year mortality (Powe et al., 2010). Similarly, in a study of 120 Mexican women with breast cancer, those with hypertension who were on a non-selective BB had significantly fewer metastatic recurrences than women with treated with a selective beta-1 blocker or other types of anti-hypertensive medications (Parada-Huerta et al., 2016).

Another study identified 70 women with a prescription for propranolol in the year prior to breast cancer diagnosis, 525 women with a prescription for atenolol in the year prior to breast cancer diagnosis and 4,738 women with no BB prescription in the year prior to diagnosis. Patients on propanolol were less likely to have a T4 tumor and less likely to have N2, N3, or M1 disease compared to matched non-users. However, women on atenolol had no difference in T4, N2, N3 or M1 disease than matched non-users. The hazard ratio for breast cancer specific mortality was 0.19 (95% CI 0.06–0.60) in propranolol users (Barron et al., 2011).

Botteri and colleagues evaluated the effect of BBs on relapse and survival post-surgery in women with triple negative breast cancer. They identified 800 women with post-menopausal triple negative breast cancer, of which 74 were on BBs at diagnosis. The risk of distant or local relapse was 13.6% in patients who were on BBs and 27.9% in those not on BBs ($p = 0.02$). After adjustment for age, tumor stage, treatment, peritumoral vascular invasion, use of other anti-hypertensive medications, antithrombotics or statins, the benefit of BBs remained statistically significant (HR = 0.52, 95% CI 0.28–0.97). With more than 5 years of follow up, 8.1% of women on BBs had a breast cancer-related death and 19.4% of non-users had a breast cancer-related death (Botteri et al., 2013).

Choy and colleagues also examined the risk of cancer recurrence in women with triple negative breast cancer. They found that in women with stage II disease (68% of their cohort), those who received perioperative beta blockade had a lower risk of metastasis (HR 0.51, 95% CI 0.23–0.97, $p = 0.041$). There was no difference in outcome for patients with Stage III disease and no OS difference in either group. Their in vitro studies on the breast cancer cells of women with triple negative breast cancer suggested propranolol could decrease the risk of brain metastasis (Choy et al., 2016).

Spera and colleagues examined the effect of BBs on patients who had been treated in a randomized clinical trial of docetaxel with or without ramucirumab. Previous research had showed a small improvement in OS for patients on this study who developed treatment emergent hypertension (TEH). The investigators hypothesized that this benefit may have been secondary to concomitant treatment with BBs and not to the development of TEH itself. Out of 1,144 women, 153 (13%) had been treated with BBs. The PFS was 10.3 months for those who had taken a BB and 8.3 months for those who had not ($p = 0.038$). Patients who started a BB only after enrollment on the trial had a PFS of 15.5 months. There was no difference in OS between the groups (Spera et al., 2017).

One meta-analysis evaluating BBs and breast cancer outcomes showed that there was a reduction in risk of breast cancer mortality (HR 0.50, 95% CI 0.32–0.80) (Childers et al., 2015). By contrast, there are other reports suggesting that BBs are not helpful in treating breast cancer. A meta-analysis of 6 retrospective studies examined whether BBs were helpful as an adjunct to breast cancer treatment (Kim et al., 2017). The authors found no difference in cancer specific death rate, overall death rate or disease relapse between patients taking BBs and those who did not. This included one study using a non-selective blocker (propranolol); the other 5 studies used primarily selective beta-1 blockers.

Cardwell and colleagues examined mortality in a retrospective study of propranolol users vs non-users (Cardwell et al., 2016). There were 4,746 breast cancer patients who used a non-selective BB after diagnosis. No association was found between propranolol use and breast cancer-specific or all-cause mortality. Shah and colleagues retrospectively examined cancer outcomes associated with BB usage in a cohort of patients in the United Kingdom. There was no survival benefit to BB therapy in any type of cancer, including breast cancer (Shah et al., 2011). In a cohort of Danish women with nonmetastatic breast cancer, no benefit was seen in risk of recurrence for patients using BBs (Sørensen et al., 2013). A study evaluating breast cancer patient outcomes by metoprolol use showed no difference in OS or DFS among metoprolol users versus non-users (Sendur et al., 2012). A retrospective study by Ganz and colleagues examined the influence of BBs and ACE inhibitors on the risk of breast cancer recurrence. No statistically significant improvements were observed for recurrence or cause-specific mortality (Ganz et al., 2011). Table 1 reviews the outcomes of studies showing benefit to beta blockade in breast cancer while Table 2 reviews studies that did not show benefit.

5. Prospective clinical trials

As of March 2019, there were 4 clinical trials registered on

Table 2
Breast cancer clinical studies showing no benefit in breast cancer outcomes.

Author	Type of beta blocker used
Cardwell et al. (2016)	Non-selective
Shah et al. (2011)	Selective and non-selective
Sørensen et al. (2013)	Selective and non-selective
Sendur et al. (2012)	Metoprolol
Ganz et al. (2011)	Selective and non-selective

Table 3
Prospective clinical trials studying BBs as breast cancer therapy.

Clinicatrials.gov ID	Description
NCT02596867	Single arm propranolol administration for 3 weeks prior to breast surgery
NCT00502684	Randomized perioperative administration of propranolol and etodolac vs placebo
NCT01847001	Single arm of Propranolol + neoadjuvant chemotherapy
NCT02013492	Single agent Propranolol for unresectable locally recurrent and metastatic solid tumors

Clinicaltrials.gov testing the effect of propranolol on breast cancer. One trial examined the effect of 3 weeks of neoadjuvant propranolol on the tumor proliferative index. It appears that recruitment to this trial was terminated due to poor accrual, however results available on Clinicaltrials.gov reveals that of the 2 analyzed patients, both had a decrease in Ki-67 after receiving propranolol (ClinicalTrials.gov ID: NCT02596867). A second trial is also studying the effect of propanolol in newly diagnosed breast cancer patients undergoing standard neoadjuvant therapies along with beta blockade (ClinicalTrials.gov ID: NCT01847001). A third trial examines the effect of pre-operative administration of a COX-2 inhibitor and a BB (ClinicalTrials.gov ID: NCT00502684). The recruitment status of this trial is unknown. Lastly, there is a trial evaluating propranolol in patients with unresectable locally recurrent or metastatic solid tumors, including breast cancer (ClinicalTrial.gov ID: NCT02013492). This trial is currently recruiting. Table 3 provides pertinent details of these clinical trials.

6. Angiosarcoma

While the clinical data presented up to this point centered on the effect of BBs on cancers of the breast epithelium, it also shows potential as an adjunctive therapy for breast angiosarcoma, a rare and typically aggressive malignancy (Kunkiel et al., 2018; Nascimento et al., 2008). Prior radiation to the breast is a risk factor for development (Buatti et al., 1994). Several studies have shown that beta blockade is an effective therapy for treating benign vascular tumors, such as infantile hemangioma, thus making it a promising investigational therapy for malignant vascular tumors, such as angiosarcoma (Nguyen et al., 2014). While the exact mechanism of action against vascular tumors is not clear, BBs are thought to impair angiogenesis and induce apoptosis (Chisholm et al., 2012). A study by Amaya and colleagues showed that BBs decreased viability of angiosarcoma tumor cell lines. Additionally, this study included a prospective clinical investigation of 9 patients with metastatic angiosarcoma, where each patient was treated with propranolol or carvedilol. Results of the study showed a median PFS of 9 months, compared to 3–6 months in historical controls (Amaya et al., 2018). A patient case study assessing propranolol effect in a patient with cutaneous angiosarcoma showed a 34% decrease in the tumor proliferative index after 1 week of propranolol therapy and over 8 months, resulted in tumor regression (Chow et al., 2015). Propranolol may also work synergistically with chemotherapy for angiosarcoma, as shown in work by Pasquier and colleagues (Pasquier et al., 2016).

7. Beta blockade as supportive care in breast cancer

BBs might also have benefits as a component of supportive care in breast cancer therapy. A trial which included 174 women with breast cancer examined the distress of a new cancer diagnosis and found that those patients on BBs had 32% fewer cancer-related intrusive thoughts than newly diagnosed breast cancer patients not using BBs (Lindgren et al., 2013). Additionally, BBs are cardioprotective and may be useful in patients receiving cardiotoxic systemic therapy. A recent review of 8 studies involving patients receiving an anthracycline with or without trastuzumab found that the use of BBs resulted in a significant reduction in heart failure incidence compared with patients who did not use BBs (Gujral et al., 2018). Two of the studies in this review, the PRADA trial and the MANTICORE trial, utilized different schedules of preventative therapy (Gulati et al., 2016; Pituskin et al., 2017). Therefore, optimal timing of starting a preventative BB is not clear, especially if the patient is only receiving anthracycline. There are several ongoing randomized clinical trials evaluating BBs as cardioprotective agents.

8. Future directions

In this era of precision medicine, new anti-cancer therapies are ideally linked to a predictive biomarker. At this time, we do not know if the beta-2 adrenergic receptor level in the tumor is a biomarker for predicting the efficacy of beta blockade. Moreover, we do not know the optimal type, dose and schedule to utilize. It is also not known how BB therapy efficacy may differ with regard to receptor status of the breast tumor. It is interesting to speculate on how BBs may interact with anti-estrogen therapy or anti-HER2 therapy, or if they could offer patients with triple negative cancer another treatment option. Small trials in each of these populations should be explored to direct a subsequent randomized trial in target populations which might benefit from such a therapy.

Conflicts of interest

Sneha Phadke has no conflicts of interest to declare. Gerry Clamon has no conflicts of interest to declare. No funding was provided for this project.

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