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EDITORIAL

Immunological and pleiotropic effects of individual β-blockers and their relevance in cancer therapies

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1. Introduction

Ubiquitously expressed β-adrenergic receptors including ADRB1, ADRB2, and ADRB3 constitute a part of sympathetic nervous system, which is triggered by catecholamines in eliciting response to stress. Chronic activation of the sympathetic nervous system leads to immune suppression, cardiovascular dysfunction, hypertension, and poorer prognosis among cancer patients via increased rate of metastasis and tumor recurrence. Although the investigation is still at its infancy, several retrospective studies have shown that patients on certain inhibitors of β-adrenergic receptors (β-blockers) survive longer due to reduced metastasis and tumor recurrence rates, and hence adjuvant use of β-blockers in cancer chemotherapy has been actively investigated. However, preclinical evidence accumulated so far suggests substance-specific anticancer benefits that are insufficiently explained by the intrinsic β-adrenoreceptor inhibition activity alone as widely contrasting *in vitro* antitumor effects were reported between α1, β1, β2-blockers carvedilol and labetalol, and between selective β1-blockers nebivolol and atenolol.[1] As each individual β-blocker is characterized with a different set of pleiotropic effects, consideration of each agent's unique pharmacological properties and their biological effects in the investigations may help establish valuable knowledge in identifying the optimal candidate β-blocker for adjuvant therapeutic use in cancer treatment.

The main function of β-blockers is to inhibit the activation of β-adrenergic receptors by catecholamines (adrenaline and noradrenaline), but each β-blocking agent is characterized with unique pharmacological properties due to variations in its adrenoreceptor specificities and pleiotropic effects, which include α-adrenoreceptor antagonism for vasodilation effect, intrinsic sympathomimetic activity, endothelial nitric oxide (NO) release stimulation effect, membrane-stabilizing effect, and the ability to cross blood–brain barrier among others. β-Blockers are conventionally classified into three subclasses: first-, second-, and third-generation β-blockers (Table 1). First-generation β-blockers (propranolol and nadolol) are non-specific inhibitors that equally inhibit ADRB1 and ADRB2 receptors, while second-generation β-blockers (atenolol and metoprolol) are specific inhibitors that only work against ADRB1 receptor. Third-generation β-blockers are different from the others in that they have vasodilating effects via α-adrenoreceptor antagonism (carvedilol and labetalol) or from stimulation of NO release from vascular endothelial cells via β3-agonism (nebivolol).[2] Additionally, studies have shown that some of these β-blockers are characterized with less-known pleiotropic effects. Carvedilol [3] and celiprolol have been characterized with nebivolol-like ability to stimulate endothelial NO release, while propranolol has been also reported with nominal ability to induce endothelial NO and vasodilation.[4] Another interesting property reported among few β-blockers is their normalizing effects in peripheral distribution and activity of natural killer (NK) cells against the effects of stress or β-adrenoreceptor stimulation.[5,6] Table 1 summarizes the reported accounts of these pleiotropic activities across 12 clinically utilized β-blockers, in addition to their reported clinical and preclinical anticancer benefits. Butoxamine, an experimental ADRB2-selective inhibitor, is also mentioned in the table for comparison.

2. β-Blockers normalize the stress-altered NK cell activities and peripheral distribution

NK cells play main roles in innate immunity and cancer immune surveillance by preferentially killing the cells with low major histocompatibility complex class 1 expression, such as virally infected cells and tumors. Also, increasing number of studies suggest their critical antimetastatic effects [7] and therapeutic effects as a part of adaptive immunity in cancer immunotherapies. Suppression of NK cell activities is, therefore, detrimental, particularly in cancer patients undergoing treatments.

In a rat model study of lung metastasis by MADB106 mammary adenocarcinoma cells, stress or nonspecific activation of β-adrenergic receptors by isoprenaline has been shown to reduce NK cell activities at both cellular and systemic levels with resulting increase in metastatic

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Table 1. Pleiotropic effects of widely used β-blockers.

Drug name	Subclass	Receptor antagonism selectivity	Clinical benefit	Preclinical benefit§	Endothelial NO release stimulation	NK cell normalizing effect	ISA	Vasodilating function
Propranolol	1st-gen	β1, β2	+	+	+** [4]	+ [5]	–	+ [4]
Carvedilol	3rd-gen	α1, β1, β2	+	+	++* [3]	NA	–	+
Nebivolol	3rd-gen	β1	NA	+	++* [3]	NA	–	+
Nadolol	1st-gen	β1, β2	NA	+	–	+ [6]	–	–
Labetalol	3rd-gen	α1, β1, β2	NA	–	–	NA	–	+
Pindolol	1st-gen	β1, β2	NA	NA	–	NA	+	–
Acebutolol	2nd-gen	β1	NA	NA	–	NA	+	–
Timolol	1st-gen	β1, β2	–	NA	–	NA	–	–
Atenolol	2nd-gen	β1	–	–	–	NA	–	–
Metoprolol	2nd-gen	β1	–	–	–	NA	–	–
Bisoprolol	2nd-gen	β1	–	NA	–	NA	–	–
Butoxamine		β2	NA	–	–	NA	–	–

ISA: intrinsic sympathomimetic activity; NA: not individually assessed by published studies.
§Details of the clinical and preclinical anticancer benefits are summarized in Table 2.
*Marked endothelial nitric oxide (NO) release stimulation effect.
**The extent of endothelial NO release stimulation by propranolol is, although significant,[4] only nominal compared to carvedilol and nebivolol. [3]
'+': Minimum one account of published confirmation of the activity.
'–': Confirmed lack of the activity.

burden, while addition of a nonselective β-blocker nadolol reversed these effects.[6] Specifically at cellular level, β-adrenoreceptor activation reduced the isolated NK cell cytotoxicity against MADB106 cells *in vitro*. At the systemic level, β-adrenoreceptor activation locally reduced the number of available NK cells in the lungs, with resultant compromise in the total pulmonary NK cell activity and increased pulmonary metastatic burden. In support of these findings, similar effects have been also reported with another nonselective β-blocker propranolol in a mouse stress model.[5] While the mechanism underlying the reduction in the peripheral NK cell availability upon β-adrenergic activation is unknown, suppression of NK cells leading to reduced organ-homing or alterations in microvascular hemodynamics due to volume-exclusion effects from increased leukocyte adherence [8] may be involved in the process.

3. Potential therapeutic benefits of endothelial NO release stimulation by certain β-blockers

Stimulation of endothelial NO release is a hallmark pleiotropic effect that is shared among some third-generation β-blockers such as nebivolol, carvedilol,[3] and to a lesser degree, propranolol.[4] Incidentally, carvedilol, nebivolol, and propranolol are among the few β-blockers that are characterized with preclinical chemo-potentiating effects.[1] Although these findings may be a coincidence, potential benefits of endothelial NO-release stimulation in cancer patients deserve mentioning.

An important clinical benefit of using third-generation β-blockers in cancer patients is their protective effects against the cardiotoxicity of cancer therapies. Specifically, carvedilol and nebivolol are among the widely investigated β-blockers for cardioprotective effects via preservation of β-adrenergic recruitment of β-arrestin and transactivation of epidermal growth factor 1. Furthermore, stimulation of endothelial NO release by nebivolol was also suggested to confer cardioprotective benefits against anthracycline.[9] A few clinical trials are underway for validation of their clinical protective effects against the cardiotoxic effects of cancer therapies. As cardiovascular complications are among the leading cause of the treatment-related mortality, cardioprotective benefits of carvedilol and nebivolol may deserve considerations in choosing the β-blocker during cancer treatment.

Another potential benefit of using endothelial NO-inducing β-blockers in cancer patients maybe indirectly deduced from the model cancer vaccine studies using NO-donating aspirin, NCX-4016 (NO-aspirin), which is under clinical investigation for its therapeutic use in cancer treatments.[10] Myeloid-driven cells (MSC) from primary tumor hypoxia play main roles in establishing premetastatic niche [7] and evasion from immunity by suppressing the activation and accumulation of tumor-infiltrating lymphocytes such as CD8 + T cells.[10] More specifically, using multiple cancer cell lines transplanted to BALB/c and C57BL/6 mice, De Santa et al. demonstrated that the NO donated by oral NO-aspirin corrected the T-lymphocyte dysfunction caused by MSC *in vitro* and *in vivo* by inhibiting the MSC's ARG1 and iNOS activities, while also reducing the intratumoral recruitment of MSC ($p < 0.01$). Furthermore, they demonstrated the NO-specific potentiation of cancer-vaccine efficacy by the NO-aspirin against the immunosuppressive CT26 and N2C tumors, which led to 20% and 56% cure rate at the end of 120 days study with tumor-specific memory responses that rejected the secondary tumor injection. In comparison, the same tumors were completely resistant to the vaccination effects without the oral NO-aspirin. As these effects are NO-specific, similar potentiation of immunotherapeutic effects against cancer by the endothelial NO-inducing β-blockers such as carvedilol, nebivolol, celiprolol, or to a lesser degree, propranolol (Table 1) may be expected, and hence warrants future investigation.

4. Anticancer effects of individual β-blockers: clinical and nonclinical evidence

Since the groundbreaking retrospective study by Powe et al. that reported significantly reduced metastasis (HR 0.430: 95% CI = 0.200–0.926) and 10-year survival (HR 0.291: 95%

Table 2. Selected clinical and preclinical studies on the effects of individual β-blockers.

Clinical			
Tumor type	Study name	Total patients (patients on β-blockers)	Study outcome
All sites: retrospective	Lin et al. (2015) [14]	13,542 (carvedilol: 6,771, nonuse: 6,771)	Long-term use of carvedilol with mean follow-up of 5.17 years led to reduced risk of cancer at all sites versus non-users (HR 0.74, 95%CI: 0.63–0.87, $p < 0.001$). Maximum risk reduction observed with stomach (HR 0.30: 0.14–0.63) and lung (HR 0.59: 0.37–0.94) cancers
Breast: retrospective	Barron et al. (2011) [12]	5801 (propranolol: 70, atenolol: 525)	Only propranolol use, not atenolol, showed reduced cancer-specific mortality risk (HR 0.19: 0.06–0.60), local invasiveness (OR 0.24: 0.07–0.85), and metastasis risk (OR 0.20: 0.04–0.88)
Breast: retrospective	Childers et al. (2015) [15]	291 (not distinguished)	Random effects meta-analysis across 4 clinical studies revealed significant reduction of cancer death (HR 0.50: 0.32–0.80), and nonsignificant reduction of recurrence risk (HR 0.67: 0.39–1.13) across 5 clinical study reports
Pancreatic: randomized, prospective	Battacharrya et al. (2015) [13]	23 (GemNab vs. PEGemNab): PE = propranolol + etodolac	Combined use of propranolol/etodolac with gemcitabine/paclitaxel (GemNab) led to increased progression-free survival (7.2 vs. 11.8 months) and overall survival (10.5 vs. 15.9 months) compared to GemNab treatment alone
Preclinical			
Tumor type	Study name & cytotoxin investigated	β-Blockers tested	Study outcome
Neuroblastoma: *in vitro* & human neuroblastoma MYC oncogene (MYCN) transgenic mouse model with competent immunity	Pasquier et al. (2013) [1]: Vincristine	Propranolol, atenolol, metoprolol, nebivolol, carvedilol, labetalol, butoxamine	Only carvedilol, nebivolol, and propranolol showed *in vitro* chemopotentiating effects with vincristine. *In vivo*, four-fold increase in median survival was observed with carvedilol cotreatment compared to vincristine treatment alone, which was accompanied by enhanced angiogenesis inhibition ($p < 0.001$) and tumor regression
Post-surgery metastatic effects. Breast: MADB106 in F344 rats	Avraham et al. (2010) [6]: Immunostimulation by IL-12	Nadolol (4.5 mg/kg) with indomethacin (4 mg/kg)	Surgery stress increased lung tumor retention (LTR) by seven-fold compared to no-surgery control. Nadolol/indomethacin (NI) treatment reduced the effect to three-fold ($p < 0.0003$). Combining NI with IL-12 treatment eliminated the surgery effect. Normalization of the number of pulmonary NK cells and individual NK cytotoxicity was responsible for the CP effect
Doxorubicin-resistant breast: Hs578T-Dox *in vitro*	Jonsson et al. (1999) [16]: Doxorubicin	Carvedilol	Multidrug resistance by P-glycoprotein is inhibited by carvedilol. Carvedilol, similar to verapamil, reduced the doxorubicin LD50 of Hs578T-Dox from 200 mg/L to 10 mg/L. by inhibiting P-glycoprotein
Breast: orthotopic MDA-MB-231 in NMRI-Foxn1nu (NMRI) immune-deficient nude mice	Pasquier et al. (2011) [17]: 5-flourouracil (5-FU) and paclitaxel	Propranolol	Combining propranolol use with 5-FU or paclitaxel improved the median survival by 19% and +79%, respectively, compared to the cytotoxin use only

CI = 0.119–0.75) among the breast cancer patients using non-distinguished β-blockers,[11] only one study so far has assessed the benefits upon long-term use of individual agents with sufficiently large patient pool. Briefly, Barron et al. reported a retrospective observational study that compared the effects of propranolol (n = 70) or atenolol use (n = 525) against those of nonuse (n = 4738) on the tumor stage at diagnosis and patient outcome.[12] Specifically, atenolol use within 1 year of diagnosis showed no effect on the tumor stage at diagnosis or patient outcome when compared to the nonusers. Propranolol use within 1 year of diagnosis, on the other hand, was characterized with significantly lesser local tumor infiltration (OR 0.24: 95% CI = 0.07–0.85) and nodal involvement/metastasis at diagnosis (OR 0.20: 95% CI = 0.04–0.88) when compared to nonusers. Furthermore, the patients on propranolol were also characterized with significantly lower cancer-specific mortality (HR 0.19: 95%CI = 0.06–0.60) (Table 2). Most importantly, a randomized investigator-initiated and prospective study on metastatic adenocarcinoma of pancreas reported that administration of propranolol and COX-2 inhibitor etodolac (PE) 1 week prior to the start of chemotherapy with nab-paclitaxel and gemcitabine (GemNab) improved progression-free survival (7.2 vs. 11.8) and overall survival (10.5 vs. 15.9 months) in comparison to GemNab treatment alone.[13]

Of an interesting note, the largest retrospective cohort study on a single β-blocker that compared the effects of long-term carvedilol use (n = 6771) against nonuse (n = 6771) was recently published with median follow-up of 5.17 years, which reported significant reduction of cancer risk across all cancer sites (HR 0.74: 95% CI = 0.63–0.87, $p < 0.001$), with maximum risk reduction in stomach (HR 0.30: 0.14–0.63, $p < 0.05$) and lung (HR 0.59: 95%CI = 0.37–0.94, $p < 0.05$) cancers [14] (Table 2). Interestingly, it also reported insignificantly reduced risk of hematological malignancy (HR 0.67: 95%CI = 0.27–1.63), head and neck (HR 0.68: 95%CI = 0.38–

1.22), colon (HR 0.96: 95%CI = 0.66–1.41), hepatoma (HR 0.74: 95%CI = 0.48–1.13), female breast (HR 0.95: 95%CI = 0.53–1.74), uterus (HR 0.67: 95%CI = 0.30–1.48), prostate (HR 0.74: 95%CI = 0.42–1.32), and other cancers (HR 0.74: 95%CI = 0.43–1.27). While therapeutic benefits of carvedilol in cancer treatment cannot be deduced from the study findings, antagonistic effects of carvedilol against general cancer biology at clinical level maybe suspected.

Chemopotentiating effects of the β-blockers aforementioned have been also reported in numerous preclinical studies concerning conventional cytotoxins and cancer immunotherapeutics. In a 2011 study, Pasquier et al. demonstrated chemopotentiating effects of propranolol when used with 5-flourouracil (5-FU) or paclitaxel in an orthotopic breast cancer model of NMRI-Foxn1nu (NMRI) immune-deficient nude mice with triple-negative MDA-MB-231 cancer.[17] In a follow-up study, the same group also reported potent chemopotentiating and direct antiangiogenic effects of propranolol, carvedilol, and nebivolol with vincristine against immune-competent human MYCN transgenic mouse model of neuroblastoma, which were attributed to their direct antiangiogenic and tumor-regressive properties.[1] Lastly, combinational use of nadolol with indomethacin and IL-12 immunostimulation was reported with additive benefits against the lung metastasis model of MADB106 breast cancer in immune-competent F344 rats via enhancement of pulmonary NK cell numbers and individual NK cell cytotoxicity.[6]

5. Expert opinion

Clinical benefits of β-blocker use as a class in cancer therapies have long been suspected from several retrospective clinical studies, but neither identification of the optimal β-blocker for adjuvant therapeutic use nor its clinical justification could be sufficiently argued from the study designs. These studies rarely assessed the effects of individual β-blockers, and the number of patients on each agent was often too small for a reliable analysis. Thus far, propranolol is the only β-blocker with individually reported clinical therapeutic utility in cancer treatment through both retrospective and randomized-prospective investigations,[12,13] although replicating studies have not been reported yet. Meanwhile, preclinical study findings thus far suggest carvedilol, nebivolol, and propranolol as promising candidate β-blockers with therapeutic effects as adjuvants to cytotoxins or immunotherapeutic treatments.[1,17]

Despite the reported role of ADRB1 and ADRB2 in cancer progression and drug resistance development,[6,18] intrinsic β-adrenoreceptor inhibition activity alone fails to explain the stronger chemopotentiating effects of ADRB1-selective nebivolol versus that of nonselective propranolol.[1] In contrast, several model studies have demonstrated significant antimetastatic and antitumor effects of β-blockers via normalization of NK cell distribution and cytotoxicity,[6] which can be also potentiated by drug-induced endothelial NO.[10] In this sense, once again, carvedilol, nebivolol, and propranolol maybe good therapeutic candidates as endothelial NO plays critical roles in sensitizing tumors to the cytotoxic effects by immune cells.[10] In further advantages, the same three agents were also characterized with direct antiangiogenic and antitumor properties.[1] Lastly, carvedilol has been also characterized with benefits relating to general cancer risk reduction,[14] attenuation of cancer drug resistance by inhibition of P-glycoprotein,[16] and cardioprotective effects against the cardiotoxicity by chemotherapeutic agents.

Additional prospective clinical studies on individual β-blockers are ultimately needed in identifying the best agents for cancer therapies, and those focusing on carvedilol, nebivolol, and propranolol may be a good start. And in doing so, incorporation of appropriate markers for NK cell and CD8+ T cell activities is additionally advised as several preclinical studies suggest the immune cells as integral parts of β-blocker's anticancer activity. Also, given the recent emergence of cancer immunotherapeutics into mainstream clinical investigations, a patient's individual β-blocker use maybe advised for their respective subgroup analysis.

Declaration of interest

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