REVIEW

Propranolol for the treatment of vascular sarcomas

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Abstract: Vascular sarcomas are abnormal proliferations of endothelial cells. They range from benign hemangioma to aggressive angiosarcoma, and are characterized by dysregulated angiogenic signaling. Propranolol is a β-adrenergic receptor inhibitor that has demonstrated clinical efficacy in benign infantile hemangioma, and is now being used experimentally for more aggressive vascular sarcomas and other cancers. In this review, we discuss the use of propranolol in targeting these receptors in vascular tumors and other cancers.

Keywords: propranolol, vascular sarcoma, angiosarcoma, β-blocker, cancer

Introduction

Vascular sarcomas are abnormal proliferations of endothelial cells (ECs). They range from benign hemangioma to aggressive angiosarcoma, and are characterized by dysregulated angiogenic signaling.[1] Benign infantile hemangiomas (IHs) are among the most common vascular tumors, with an incidence of approximately 3%.[2] The natural history of IH is to first expand during a proliferative phase, and then regress during an involuting phase. Lesions that are symptomatic or otherwise problematic can be treated with topical or systemic agents, including corticosteroids or β-adrenergic receptor inhibitors.[3] Propranolol is a nonselective β-adrenergic receptor blocker that has been implicated in several cancers and has had success in treating IH.[4]

Angiosarcoma is an aggressive cancer of ECs. It can occur anywhere in the body, with the most common sites being cutaneous lesions in the head and neck, breast, and extremities. They can be further subclassified into primary and secondary angiosarcoma, with the latter as a result of chronic lymphedema or radiation exposure. Outcomes for patients with angiosarcoma, even those who present with localized disease, are poor. For patients who develop metastatic disease, median survival is about 1 year.[5–7] Primary treatment usually includes a combination of cytotoxic chemotherapy, surgery, and radiation. The advent of drugs targeting angiogenesis pathways were theoretically promising for treating tumors of ECs, but clinical results have been disappointing. Response rates to drugs targeting the VEGF/VEGFR axis range from 9%–20%.[1] Combining bevacizumab, an anti-VEGF antibody, with paclitaxel yielded no clinical benefit.[8] Drugs targeting other angiogenesis pathways such as the angiopoietin–TIE2 axis have also thus far been unsuccessful.[9] The PI3K/AKT/mTOR pathway has also been implicated in both benign and aggressive vascular tumors.[10,11]

Molecular and genomic characterization has yielded some insights into the drivers of angiosarcoma, but to date no targeted agents have demonstrated a clear benefit for

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most patients. Some angiosarcomas harbor activating mutations in KDR[12] or PLCG1,[13] and others have CIC mutations or rearrangements[14] which serve as potential driver events. Secondary angiosarcomas are characterized by MYC and FLT4 amplification.[15] Even with this improved understanding as a result of high-throughput sequencing of several cohorts of angiosarcomas, driver events for most cases remain unknown. Recently, focus has sharpened on the β-adrenergic receptors that play a key role in normal EC function and may play a role in supporting angiosarcoma growth. In this review, we will discuss the use of propranolol in targeting these receptors in angiosarcoma and other vascular tumors.

β-adrenergic signaling and cancer

Adrenergic receptors are 7-transmembrane G-protein coupled receptors that consist of α, β, and γ subunit subtypes.[16] β-adrenergic receptors play a vital role in several physiologic processes and are key mediators of the physiologic stress response. Drugs have been developed to inhibit the recep-

tors with varying levels of affinity. Modulators of adrenergic signaling are some of the oldest drugs in clinical use, with clinical benefit particularly for cardiovascular disease and prevention of esophageal varix bleeding in advanced hepatic cirrhosis.

Recently, β-adrenergic signaling is gaining attention as a potential therapeutic target in cancer.[17] Several mechanisms by which β-blockers improve outcomes in cancers have been proposed, including both direct anticancer effects and effects on multiple cell types in the cancer microenvironment (Figure 1).

β-adrenergic pathway modulators have direct effects on cancer cells of various subtypes in culture. Stimulation with β-agonists increases cell proliferation in a cAMP-dependent manner in lung adenocarcinoma cells.[18] Activation of the β2-adrenergic pathway increases IL-6 production and inactivates the tumor suppressor LKB1 in EGFR mutant lung adenocarcinoma cells, and is a proposed mechanism for resistance to EGFR inhibitors. Indeed β-blocker use was
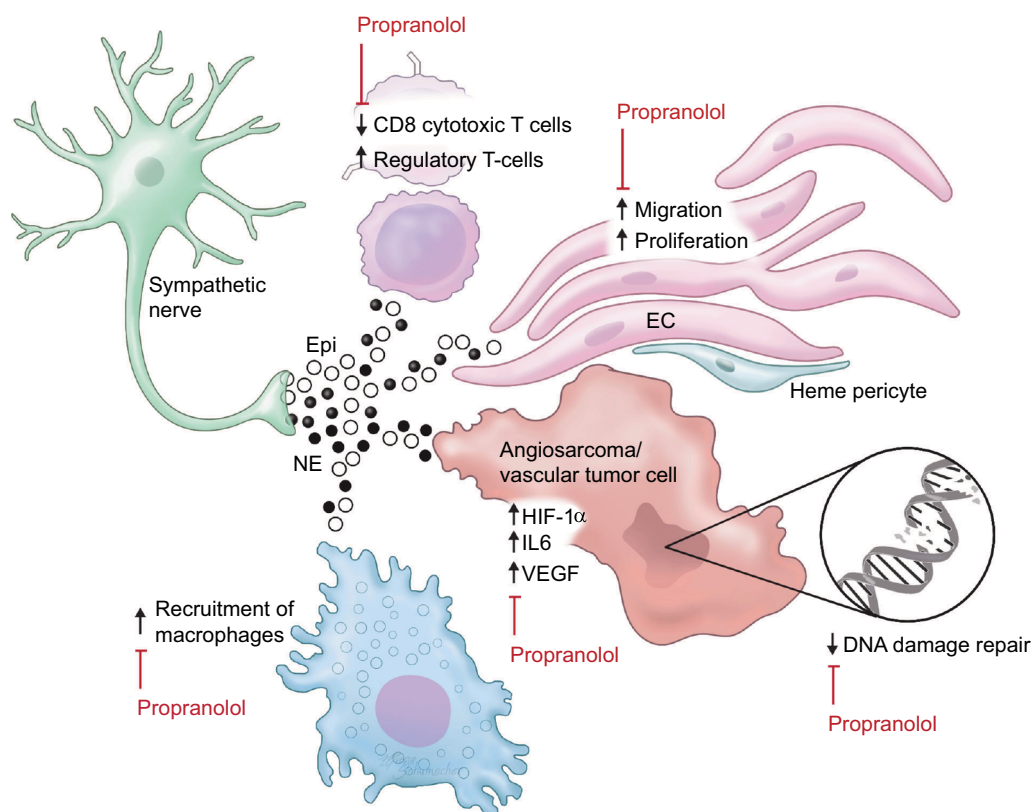

Figure 1 Adrenergic signaling in the vascular tumor microenvironment.
Notes: Epi and NE produced in sympathetic nerves act on β-adrenergic receptors present on T-cells, ECs, macrophages, and tumor cells. Activation of adrenergic receptors decreases infiltration by cytotoxic T-cells, increases the number of regulatory T-cells, and increases the recruitment and differentiation of tumor-associated macrophages. Sympathetic signaling also increases the migration and proliferation of normal ECs. In tumor cells, adrenergic signaling stimulates production of other proangiogenic and inflammatory mediators such as HIF-1α, VEGF, and IL-6 and suppresses the DNA damage response. Propranolol inhibits these oncogenic changes by blocking the β-receptors through which Epi and NE act.
Abbreviations: Epi, epinephrine; NE, norepinephrine; EC, endothelial cell.

associated with improved benefit from afatinib in the Phase III LUX-Lung3 study.[19,20] Similar increases in cancer cell-specific measurements such as proliferation and invasiveness were seen in pancreatic cancer cells[21] and ovarian cancer cells.[22] Adrenergic stimulation led to chemoresistance in colon cancer cells[23] and ovarian cancer,[24] the latter by stimulating DUSP1. β-blockers are synergistic with cytotoxic chemotherapy against breast cancer[25] and neuroblastoma[26] cells. Although some of the effect seen in lung cancer seems to be specific for EGFR mutant-containing cells, broader pathways such as DNA damage repair pathways are also regulated in part through β-2 receptors.[27]

Propranolol is a small molecule nonspecific inhibitor of β-1 and β-2 adrenergic receptors, and is the focus of this review. In addition to the effects on cancer cells themselves, β-receptor inhibition with propranolol decreases proliferation, migration, and differentiation of ECs.[28] Propranolol treatment inhibits angiogenesis in EC lines, but has little to no effect on vascular disruption.[25] Preclinical studies in cancer models have demonstrated that increased adrenergic signaling through the β-2 receptor results in increased VEGF production in cancer cells[29] and increased tumor vascularization.[30] Similarly, the β-agonist isoprenaline stimulates autocrine VEGF signaling in gastric cancer cells and associated ECs via β-2 receptor-mediated signaling.[31]

Clinical evidence for β-receptor inhibition in cancer

Some of the first retrospective clinical data in support of β-blockers in cancer were seen in breast cancer, where β-blocker use for hypertension is associated with improved cancer-specific survival compared with patients using other types of antihypertensive medications.[32] The specificity of β-receptor inhibition has an effect on survival, with a beneficial effect seen in breast cancer patients receiving the nonselective β blocker propranolol but not with the β-1 antagonist atenolol.[33] Carvedilol, another nonselective β-blocker, reduces the risk of multiple cancer types with the largest effect seen in upper gastrointestinal and lung cancers in a large study from Asia.[34] Additional studies show benefit of β-blocker use in patients with colorectal[35] and pancreatic[36] cancer. A prospective nonrandomized study of propranolol in the adjuvant setting for resected melanoma found an 80% reduction in melanoma recurrence.[37] Overall, prospective clinical evidence supporting a role for propranolol in cancer treatment or prevention is limited. A summary of the largest existing clinical studies describing

the impact of β-blockers on cancer incidence and outcomes is provided in Table 1.

Treatment of IH

The antiangiogenic properties of propranolol have led it to be used in vascular tumors. Indeed, propranolol has seen perhaps its greatest success in oncology in IH. There is significant controversy surrounding the cell of origin, with evidence that there is a hemangioma stem cell (HemSC) which induces proliferative changes in adjacent cells in the microenvironment.[38] Despite the tendency of these tumors to first proliferate and then regress in characteristic phases, some IHs are problematic and require treatment.[3] The proliferating phase of IH is characterized by VEGF-A production which stimulates hemangioma endothelial cell (HemEC) proliferation.[39] Indeed, patients with IH have high increased circulating levels of VEGF-A.[40,41] At the receptor level, VEGFR1 expression levels in hemangiomas are lower than those in normal ECs,[42–45] consistent with its accepted role as a VEGF-A trap counteracting the stimulatory effects of VEGF-A ligand binding to VEGFR2. Decreased VEGFR1 expression levels in HemECs results in increased VEGFR2 signaling,[43] and VEGFR2 knockdown in HemECs decreases cell viability and increased apoptosis, whereas VEGFR2 overexpression has the opposite effect.[46] Proliferating IH has a relatively high expression of Ang2 and low expression of Ang1,[47,48] as do hemangioma-derived pericytes;[49] however, hemangioma-derived cell lines demonstrate increased migration and survival in response to Ang1, but not Ang2, highlighting the complicated roles these 2 ligands play.[48]

The tumor microenvironment also plays a critical role in hemangioma formation. Jagged1 expression on ECs and cell–cell contact between HemECs and HemSCs is required for HemSC differentiation into pericyte.[44] Hemangioma-derived pericytes do not stabilize developing blood vessels as would be expected with physiologic pericytes.[49] Jagged1 and Notch4 expression levels in proliferating IH are 6.5-fold and 3.2-fold higher, respectively, than those in placenta vessel control.[47] Notch effector proteins HEY1, HEYL, and HES1 are highly expressed in HemSCs, whereas HEY2 is highly expressed in HemECs alone.[50] Interestingly Notch1, Notch4, and Jagged1 have increased expression in involuting hemangioma ECs, and it was concluded that the involution was at least partially caused by the cells' differentiation into a more determined EC phenotype as a result of increased Notch signaling.[51]

Table 1 Clinical evaluation of β-blockers in multiple cancer subtypes

Study	Year of publication	Tumor type	Total number of patients (# in BB group)	Finding
Powe et al[32]	2010	Breast	466 (43)	Risk of metastasis HR 0.430 (95% CI: 0.200–0.926) 10 year mortality HR 0.291 (95% CI: 0.119–0.715)
Barron et al[33]	2011	Breast	5,263 (525)	Breast cancer-specific mortality HR 0.19 (95% CI: 0.06–0.60)
Melhem-Bertrandt et al[82]	2011	Breast	1,413 (102)	RFS HR 0.30 (95% CI: 0.10–0.87)
Botteri et al[83]	2013	Breast	800 (74)	HR for metastasis 0.32 (95% CI: 0.12–0.90) and HR for breast cancer related mortality 0.42 (95% CI: 0.18–0.97)
Jansen et al[35]	2014	Colorectal	1,820 (509)	OS HR 0.50 (95% CI: 0.33–0.78)
Beg et al[36]	2017	Pancreas	13,702 (5209)	OS HR 0.90 (95% CI: 0.85–0.95)
De Giorgi et al[84]	2011	Melanoma	121 (30)	Recurrence HR 0.03 (95% CI: 0.01–0.28)
De Giorgi et al[85]	2013	Melanoma	741 (79)	DFS HR 0.03 (95% CI: 0.01–0.17) OS HR 0.62 (95% CI: 0.43–0.9)
Lemeshow et al[86]	2011	Melanoma	4,179 (372)	HR for melanoma death 0.87 (95% CI: 0.64–1.20) and for all-cause mortality was 0.81 (95% CI: 0.67–0.97)
De Giorgi et al[a,37]	2017	Melanoma	53 (19)	Recurrence HR 0.18 (95% CI: 0.04–0.89)
Nilsson et al[19]	2017	Lung		Improved benefit from afatinib in Phase 3 trial compared with benefit seen in patients not on BB
Johannesdottir et al[87]	2013	Ovarian	4,406 (300)	OS in current BB users HR 1.17 (95% CI: 1.02–1.34) Previous BB users HR 1.18 (95% CI: 0.90–1.55)
Watkins et al[88]	2015	Ovarian	1,425 (269)	Longer median OS was observed among users of a nonselective β-blocker compared with nonusers (38.2 vs 90 months; log rank $P<0.001$)
Huang et al[a,89]	2016	Ovarian	110 cases	No impact of β blockers on ovarian cancer risk HR of ovarian cancer risk in current users of BB =0.88 (95% CI: 0.47–1.64)
Grytli et al[90]	2013	Prostate	6,303 (776)	Prostate cancer-specific mortality HR 0.14 (95% CI: 0.02–0.85) No effect on overall mortality HR 0.88 (95% CI: 0.56–1.38)
Grytli et al[91]	2014	Prostate	3,561 (1115)	Prostate cancer-specific mortality HR 0.79 (95% CI: 0.68–0.91) No effect on all-cause mortality HR 0.92 (95% CI: 0.83–1.02)

Notes: [a]Prospective studies. All others are retrospective.
Abbreviations: HR, hazard ratio; RFS, relapse-free survival; DFS, disease-free survival; OS, overall survival; BB, β-blocker.

Treatment with the β-blocker propranolol at a dose of 2 mg per kg of body weight per day leads to regression of cutaneous IH lesions[4] as well as potentially more life-threatening infantile hepatic hemangiomas[52] and subglottic hemangiomas.[53] Conversely, the use of β-2 sympathomimetic tocolytics doubled the rate of IH in preterm infants from 11% to 22% in the group studied.[54] Although the mechanism remains unclear, 1 proposed mechanism by which propranolol may induce regression is by reducing the expression of HIF-1α, which in turn decreases HIF-1α-mediated signaling through the VEGF and STAT3 pathways.[55] Moreover, propranolol may be targeting Hempericytes.[49] Interestingly, GLUT1-positive cells derived from proliferating hemangiomas exhibit stem-like properties, and their growth is inhibited by mTOR inhibition but not by propranolol.[56] mTOR and HIF-1a contribute to hemangioma proliferation via an autocrine VEGF signaling loop.[57] Interestingly, treatment with propranolol leads to similar gene expression changes in IH and normal ECs, suggesting that the regression seen with propranolol is multifactorial, involving drug effect on multiple cell types in the microenvironment.[58]

Propranolol in intermediate-grade vascular sarcomas and angiosarcoma

Given their clinical success in IH, β-blockers have been studied in models of other vascular tumors. β-receptors 1, 2, and 3 are present on hemangioendothelioma and angiosarcoma by immunohistochemistry, and treatment with high doses of propranolol causes apoptosis and is synergistic with cytotoxic

chemotherapy in hemangioendothelioma and angiosarcoma cell lines.[59] Compared with hemangiomas, fewer of the aggressive tumors express β-2 and β-3 receptors, with about 40% of the 44 angiosarcomas in 1 series staining strongly for β-2 receptor and variable staining across the various types of hemangioendothelioma.[60] mRNA expression profiling of transformed mouse ECs that behave like angiosarcoma cells revealed a broad array of differentially expressed genes after treatment with propranolol.[61]

The role of β-2 receptor signaling in both adaptive and innate immunity[62] also makes propranolol appealing for treatment of angiosarcoma. B- and T-lymphocytes express the β-2 adrenergic receptor and are responsive to β-agonists.[63] Chronic β-adrenergic receptor signaling suppresses CD8+ cytotoxic T-cells, thus reducing T-cell responses to immune checkpoint inhibitors.[64] Lymphocyte egress from lymph nodes and interferon transcription is regulated by sympathetic innervation and norepinephrine.[65,66] The presence of infiltrating CD8+ T-cells correlates with survival in angiosarcoma patients.[67] Furthermore, β-adrenergic signaling affects myeloid cells in the microenvironment by regulating secretion of IL-6 and IL-8.[68,69] Macrophage recruitment to tumors may be increased by beta adrenergic mediated secretion of chemotactic molecules by tumor cells.[70] IL-6 production in angiosarcoma tumor cells increases the number of tumor promoting macrophages.[71] Small reports aimed at targeting tumor-associated macrophages in angiosarcoma were promising,[72,73] suggesting that the anti-inflammatory effect of propranolol will be beneficial in angiosarcoma.

Unfortunately much of what is known clinically about propranolol and its utility in treating angiosarcoma specifically are based on case reports. In 1 patient, serial biopsy before and 1 week after initiation of propranolol 40 mg twice a day resulted in a decrease in proliferative index of the tumor assessed by Ki67 staining from around 30% of positive cells to around 20%, causing a reduction in proliferation of 34%.[74] As this was a single case report, and so this difference may be accounted for by sampling variance, and any determination of clinical benefit is confounded by the addition of cytotoxic chemotherapy and radiation in this patient's treatment course.

Most reports combine propranolol with cytotoxic chemotherapy. In a preclinical model of transformed ECs, propranolol was synergistic with vinblastine, but not the chemotherapeutic agents more commonly used for angiosarcoma, such as doxorubicin or paclitaxel.[75] Several patients treated with propranolol combined with metronomic vinblastine and methotrexate derived clinical benefit from this combination, though distinguishing the potential contribution of propranolol in this combination is impossible based on the described studies.[75,76]

Metronomic chemotherapy has been shown to have anti-angiogenic effects and can improve the anticancer effects of cyclophosphamide in some settings.[77] Due to the anti-angiogenic effects of low-dose metronomic chemotherapy, this strategy presented a promising method for treating angiosarcoma. Treatment with metronomic trofosfamide, pioglitazone, and rofecoxib led to clinical responses in 3 of 5 angiosarcoma patients in 1 small series.[78] Due its better toxicity profile, metronomic chemotherapy with cyclophosphamide was used in elderly patients with angiosarcoma with evidence of efficacy.[79] Case reports combining propranolol combined with metronomic cyclophosphamide in angiosarcoma suggest promising results that warrant further investigation.[80,81] The optimal dose of propranolol for angiosarcoma is not currently known. A dose finding study is currently underway in France investigating increasing dosing of propranolol combined with a stable dose of cyclophosphamide (NCT02732678).

Conclusion and future directions

The prospect of utilizing propranolol in angiosarcoma is a promising one, with hints of benefit in preclinical work and small case series and reports. However, in spite of the excitement describing the revolutionary potential of propranolol in angiosarcoma, the current role for propranolol remains an open question. Confounding factors in all of the published reports, combined with the fact that all of these studies are small case series or reports, limit the ability to make conclusive recommendations. Prospective studies with larger numbers of patients are needed. One potential study design would incorporate propranolol in the adjuvant setting to investigate a specific benefit from β-2 inhibition without the confounding impact of coadministered chemotherapy. Alternatively, incorporating propranolol into currently used systemic regimens may be preferred, but with the rarity of angiosarcoma and lack of consensus on initial management particularly for localized disease this may be difficult. Thankfully, propranolol is a relatively cheap and well-studied drug for other indications. A prospective, multicenter randomized trial should be feasible and would be able to answer once and for all if we should be including propranolol in our angiosarcoma treatment schema.

Disclosure

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