Published in final edited form as:

Leuk Lymphoma. 2009 May ; 50(5): 679. doi:10.1080/10428190902893835.

Targeting angiogenesis: A novel, rational therapeutic approach for Non-Hodgkin's Lymphoma

Jia Ruan and John P. Leonard

Center for Lymphoma and Myeloma, Division of Hematology/Oncology, Department of Medicine, Weill Cornell Medical College and New York-Presbyterian Hospital, New York, New York, USA

The importance of the tumor microenvironment in the initiation and progression of cancer was recognized over a century ago by Paget who coined the term of “seed and soil” to describe their symbiotic co-evolution [1]. A vital part of this interaction is dependent on the negotiation and establishment of a functional vascular network which supports neoplastic proliferation. Many aspects of tumor angiogenesis have been extensively studied in the context of nonhematopoietic neoplasms in the past three decades [2], and anti-angiogenic strategies have become an important therapeutic modality for solid tumors in various clinical settings including metastatic colorectal, lung, breast, renal and liver cancers.

While the precise role of tumor angiogenesis in lymphoma pathogenesis remains under active investigation, emerging data on the angiogenic properties of the neoplastic lymphoma cells and the tumor microenvironment suggest that angiogenesis is highly relevant in a number of lymphoma subtypes. Lymphoma growth and progression appears to be potentiated by at least two distinct angiogenic mechanisms: autocrine stimulation of tumor cells via expression of VEGF (Vascular Endothelial Growth Factor) and VEGF receptors by lymphoma cells, as well as paracrine influences of the proangiogenic tumor microenvironment on both local neovascular transformation and recruitment of circulating bone marrow-derived endothelial progenitors. VEGF expression has been demonstrated in aggressive subtypes of Non-Hodgkin's lymphoma (NHL) including peripheral T-cell lymphomas (PTCL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), primary effusion lymphoma, and indolent histologies such as chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL/SLL). The presence of both VEGF and VEGF receptors expression by tumor cells in CLL, MCL and DLBCL implicates both autocrine and paracrine survival mechanisms [reviewed in 3].

The lymphoma microenvironment has been increasingly recognized to influence neoplastic progression, in part by modulating angiogenic responses to distinct proangiogenic growth factors and cytokine milieu. In follicular lymphoma (FL) and DLBCL, large-scale gene expression profiling studies demonstrated that genetic signatures expressed by stromal and infiltrating immune cells define distinct prognostic groups [4,5]. Monocytic infiltration in FL predicted an inferior clinical outcome. Increased hematopoietic infiltration by myeloid progenitors and monocytes has been correlated with aggressiveness of lymphoma histology, suggesting that hemangiogenesis may reflect an angiogenic switch and the development of a pro-angiogenic phenotype, as myeloid cells have been shown to provide both perivascular structural and paracrine support to neovessels in aggressive NHL [6]. A multivariate survival-predictor model analyzing gene expression in 414 patients with newly diagnosed DLBCL

treated with either CHOP-like or R-CHOP regimens demonstrated that stromal gene-expression signatures alone predicted survival. Specifically, the prognostically favorable stromal-1 signature reflected extracellular-matrix deposition and histiocytic infiltration, while the stromal-2 signature encoded endothelial and other angiogenesis-specific markers, and was associated with increased tumor microvessel-density and inferior survival. These findings underscore the biological heterogeneity of DLBCL, and directly link angiogenesis and related aspects of the tumor stroma to clinical outcome in a distinct subgroup [5].

Greater understanding of the various stromal angiogenesis targets has led to the introduction of novel anti-angiogenic treatment strategies into the clinic. The prototypic anti-angiogenic agent, namely the humanized monoclonal antibody bevacizumab, targets the VEGF-A signaling axis, thereby disrupting autocrine and paracrine survival mechanisms mediated by VEGFR-1 and VEGFR-2 [7]. In this issue of *Leukemia and Lymphoma*, Stopeck et al reported the final analysis of the Southwest Oncology Group phase II trial S0108 of single agent bevacizumab in 52 patients with relapsed DLBCL and MCL [8]. Single agent bevacizumab was given at 10mg/kg every 2 weeks for a maximum of 48 doses, or until either disease progression or the development of unacceptable toxicity. Treatment was generally well tolerated with most significant toxicity of grade 3 hypertension reported in 2 patients. While the response rate was just 2% with one DLBCL patient achieving a partial response, stabilization of disease was observed in a significant subset (25%) with a median time to progression of 5.2 months. The authors also performed exploratory angiogenesis biomarker analysis on patient tissues, blood and urine samples. VEGFR-1 expression was found predominantly on lymphoma cells while VEGFR-2 was predominantly expressed in tumor endothelial cells. In subgroup analysis, baseline urine VEGF and plasma VCAM levels appeared to correlate with survival. One of the largest studies to date targeting angiogenesis in aggressive NHL, SWOG S0108 is an important proof-of-concept study.

The low objective response rate with single agent bevacizumab is not surprising in this study, given the relatively focused targets of anti-VEGF, the multitude of tumor angiogenesis pathways, and the complex interplay between tumor cells and their stromal microenvironment. In addition to the VEGF family, several other angiogenic pathways including the platelet-derived growth factor (PDGF) family, and the chemokine SDF-1 β / CXCR4⁺ axis are known to participate in the elaborate regulation of angiogenic switch and maintenance. For instance, PDGF-BB (a ligand of PDGFR- β) produced by endothelial cells recruits pericytes that are important for vascular maturation [9]. Chemokine SDF-1 α promotes recruitment of vasculogenic CXCR4⁺ endothelial progenitors (EPCs) from the bone marrow [10]. It is conceivable that compounds targeting multiple stromal angiogenesis pathways could have synergistic vascular inhibition as opposed to anti-VEGF alone, while treatment strategies combining anti-vascular agents with chemotherapy would be expected to synergistically target both tumor cells and the stroma. The combination of bevacizumab with standard R-CHOP was shown to be safe and well-tolerated in a pilot feasibility study in 13 patients with untreated DLBCL [11]. Currently, phase II trials of R-CHOP-Bevacizumab in previously untreated DLBCL and MCL patients are underway at multiple institutions in US, and phase III international trials of R-CHOP-Bevacizumab in *de novo* DLBCL are ongoing. Efficacy data from these bevacizumab studies are awaited.

In addition to anti-VEGF, a growing list of agents with anti-angiogenic effects has demonstrated evidence of activity in NHL. Immunomodulatory compounds (iMiDs) including thalidomide and lenalidomide, either as single agent or in combination with fludarabine or rituximab, have demonstrated clinical activity in NHL subtypes of DLBCL, CLL and MCL. Metronomic low dose chemotherapy appears to have broad clinical applicability in lymphoma, including relapsed and refractory settings. Novel biological agents, targeting receptor tyrosine kinases (RTK) including VEGF and PDGF receptors, and various downstream targets along

the angiogenic signaling pathways which regulate HIF-1 α and VEGF expression (including HDAC inhibitors, mTOR inhibitors, or proteasome inhibitors), are in various stages of clinical development and investigation in human lymphoma patients [reviewed in 3]. Successful implementation of future clinical trials assessing anti-angiogenic approaches is contingent upon a thoughtful understanding of the biology of lymphoma angiogenesis in NHL subtypes, and validation of clinically useful biomarkers that predict response. For instance, prospective clinical studies are needed to validate the prognostic utility of the stromal gene expression signature in DLBCL, and identify subtypes that would benefit the most from an anti-angiogenic approach. Correlative assays which reflect the dynamics of drug and target interaction are being developed in the context of clinical studies of specific anti-angiogenics. This information will provide much-needed insights for the rational design of more effective anti-angiogenic regimens that are optimized for specific clinical settings.

REFERENCES

1. Paget S. The distribution of secondary growths in cancer of the breast. *Lancet* 1889;1:571–573.
2. Folkman J. Tumor angiogenesis: therapeutic implications. *New England Journal of Medicine* 1971;285:1182–1186. [PubMed: 4938153]
3. Ruan J, Hajjar K, Rafii S, Leonard JP. Angiogenesis and antiangiogenic therapy in non-Hodgkin's lymphoma. *Annals of Oncology* 2009;20:413–424. [PubMed: 19088170]
4. Dave SS, Wright G, Tan B, et al. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *New England Journal of Medicine* 2004;351:2159–2169. [PubMed: 15548776]
5. Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large-B-cell lymphomas. *N Engl J Med* 2008;359:2313–2323. [PubMed: 19038878]
6. Ruan J, Hyjek E, Kermani P, et al. The magnitude of stromal hemangiogenesis correlates with histologic subtype of non-Hodgkin's lymphoma. *Clin Cancer Res* 2006;12:5622–5631. [PubMed: 17020964]
7. Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nature Reviews. Drug Discovery* 2004;3:391–400.
8. Stopeck AT, Unger J, Rimsza LM, et al. A phase II trial of single agent bevacizumab in patients with relapsed, aggressive non-Hodgkin lymphoma: Southwest Oncology Group study S0108. *Leuk Lymphoma*. 2009
9. Abramsson A, Lindblom P, Betsholtz C. Endothelial and nonendothelial sources of PDGF-B regulate pericyte recruitment and influence vascular pattern formation in tumors. *Journal of Clinical Investigation* 2003;112:1142–1151. [PubMed: 14561699]
10. Jin DK, Shido K, Kopp HG, et al. Cytokine-mediated deployment of SDF-1 induces revascularization through recruitment of CXCR4+ hemangiocytes.[erratum appears in *Nat Med*. 2006 Aug;12(8):978]. *Nature Medicine* 2006;12:557–567.
11. Ganjoo KN, An CS, Robertson MJ, et al. Rituximab, Bevacizumab and CHOP (RA-CHOP) in untreated diffuse large B-cell lymphoma: safety, biomarker and pharmacokinetic analysis. *Leuk Lymphoma* 2006;47:998–1005. [PubMed: 16840188]