Thesis Abstract

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Title: Role of circulating endothelial progenitor cells and angiogenic regulators in patients with multiple myeloma

Objectives: The aim of this study was to 1) To enumerate and characterize the circulating endothelial progenitor cells (cEPC) in peripheral blood of patients with multiple myeloma (MM). 2) To evaluate the expression of angiogenic regulators in patients with MM. 3) To study the correlation of angiogenic regulators with circulating endothelial progenitor cells, response to treatment and treatment outcome in patients with MM.

Research Findings:

Objective 1: Stage dependent increase in the cEPC levels demonstrates that cEPC are extension of tumor microenvironment and may serve as non-invasive biomarker of disease activity. cEPC are reflective of tumor burden in MM as they correlate with markers of disease activity (serum β2-microglobulin levels) and thus serve as potential biomarker of disease severity.

Objective 2: Ang-2, bFGF, VEGF and HiF-1α were increased and Ang-1 and Ang-1/Ang-2 ratio were decreased as compared to healthy controls in MM patients. Levels of VEGF, Ang-2, bFGF , Ang-1, Hif-1α, Ang-1/Ang-2 ratio correlates with ISS stage of diseases and with well known marker of disease activity (serum β2-microglobulin levels). This suggests that these regulators may play an important role in degree of angiogenesis in MM patients.

Objective 3: cEPC significantly correlates with angiogenic regulators (Ang-1, Ang-2 and VEGF) which indicates that are involved in mobilization or regulation of cEPC, may lead

to a development of new therapeutic approaches to inhibit the release of these angiogenic regulators by combination treatment in MM patients. After anti-angiogenic based therapy in MM patients, the levels of cEPC and Ang-2 is decreased with an increase in Ang-1/Ang-2 ratio in responder suggesting that Ang-2 is one of the key regulator of cEPC in myeloma. The reduced baseline levels of serum level of Ang-1/Ang-2 ratio were the only statistically significant independent predictor for response to anti-angiogenic therapy in MM patients. The circulating levels of VEGF and Ang-2 act in synergy and their expression levels at presentation were independent predicators for poor prognosis and thus, simultaneous inhibition of both these cytokines may be more beneficial than targeting VEGF alone in MM.

Conclusion: The study suggest that the circulating levels of angiogenic regulators are an extension of the bone marrow microenvironment into the peripheral blood, and also provide evidence for the role of angiogenesis in disease load and progression in MM. This study would facilitate the use of combined anti-angiogenic (VEGF & Ang-2) drug therapies for treatment of MM in future prospective studies. This combined anti-angiogenic drug therapies will help to target not only the tumor cell but also the BM microenvironment that initiate the process of angiogenesis in MM which would represent a promising treatment paradigm not only for MM, but also for other malignancies.

Future prospects: Further research is required to confirm and expand on these findings, with a focus on the potential proteomics approach, and clinical trials based on anti-angiogenic regulators in patients with MM.

Publications:

1. **Bhaskar A**, Gupta R, Kumar L, Sharma A, Sharma MC, Kalaivani M, Thakur SC Circulating endothelial progenitor cells as potential prognostic biomarker in multiple myeloma. Leuk Lymphoma 2012; 53:635-640.
2. **Bhaskar A**, Gupta R, Sreenivas V, Kumar L, Sharma A, Sharma MC, Das P, Thakur SC. Angiopoietins as biomarker of disease activity and response to therapy in multiple myeloma. Leuk Lymphoma 2013; 54: 1473-1478.
3. **Bhaskar A**, Gupta R, Sreenivas V, Kumar L, Sharma A, Thakur SC. Synergistic effect of vascular endothelial growth factor and angiopoietin-2 on progression free survival in multiple myeloma Leuk Res 2013; 37: 410-415.