Vascular Endothelial Growth Factor (VEGF-C) Signaling through FLT-4 (VEGFR-3) Mediates Leukemic Cell Proliferation and Survival

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Similar to solid tumors, growth of leukmia may also be angiogenesis dependent. Tyrosine kinase receptors specific to endothelial cells are expressed on certain subsets of leukemias.

In response to leukemia-derived pro-angiogenic cytokines, endothelial cells release increasing amounts of the vascular endothelial growth factor (VEGF) family member, VEGF-C. In turn, signalling of VEGF-C through the receptor tyrosine kinases VEGFR-3 (FLT-4) and VEGFR-2 (KDR) promotes leukemia survival and proliferation. VEGF-C induces receptor phosphorylation, leukemia proliferation and increased survival, as determined by increased Bcl-2/Bax ratios. This study included 30 newly diagnosed patients with leukemia: 20 ALL and 10 AML cases as well as 10 matched controls. Patients and control group were tested for the expression of VEGF-C, VEGFR-3 (FLT-4) and VEGFR-2 (KDR) gene using RT-PCR.

Among ALL patients (20 cases), VEGF-C, FLT-4 and KDR were expressed in 65%, 70% and 30% of cases respectively. Among AML patients (10 cases), VEGF-C, FLT-4 and KDR were expressed in 60%, 70% and 40% of cases respectively. Among ALL and AML cases (30 cases), 44.4% and 33.3% respectively showed associated expression of VEGF-C and FLT-4. While, 11.1% of ALL and none of AML cases showed associated expression of VEGF-C and KDR. Finally, 44.4% of ALL and 66.7% of AML cases showed associated expression of FLT-4 and KDR.

Ten patients were followed up, six ALL and four AML cases. Of the followed ALL cases (6 cases), 3/6 were in remission and were VEGF-C -ve (two were FLT-4 +ve and one was KDR +ve), 2/6 were resistant to treatment and were VEGF-C +ve and FLT-4 +ve (one was KDR+ve), while the remaining patient (1/6) died during induction and was VEGCF +ve, FLT-4-ve and KDR -ve. Of the followed AML cases (4 cases), 3/4 were in remission (one was VEGF +ve and 2 were FLT-4 +ve), while the remaining patient (1/4) was resistant to treatment and was VEGF-C, FLT-4 and KDR +ve. The number of either ALL and AML patients expressing both VEGF-C and FLT-4 was higher than those expressing both VEGF-C and KDR. This could lead to the assumption that VEGF-C acting through FLT-4 may play a more significant role than acting through KDR in the pathophysiology of acute leukemia.

These results may identify VEGF-C/FLT-4 pathway as novel therapeutic target for the treatment of leukemias.