Circulating Tumor and Endothelial Cells as Pharmacodynamic Biomarkers in a Phase I Clinical Trial of Intravenous Bevacizumab in Combination with Escalating Doses of Oral Cediranib for Patients with Advanced Malignancies

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Objective

Rare circulating tumor cells (CTCs) and endothelial cells (CECs) offer a feasible approach for studying the pharmacodynamic effects of investigational agents. We investigated the effects of Bevacizumab (B) and Cediranib (C) on CECs and CTCs, inhibition of VEGFR and correlated these changes with dose and clinical response.

Background

• Bevacizumab and Cediranib are inhibitors of angiogenesis; B is a humanized monoclonal antibody that inhibits VEGF interaction with its receptors; C is an oral tyrosine kinase inhibitor of the three VEGF receptors.
• The angiogenic marker CD105 is upregulated in tumor-associated endothelial cells (CD31).
• The VEGFR family includes three receptors (VEGFR 1, 2 and 3). In cancerous cells, they can initiate a cellular response to VEGF that induces angiogenesis, tumor growth and metastasis.
• CTC enumeration at baseline can accurately predict progression-free survival (PFS) and overall survival OS in metastatic breast, colorectal, and prostate cancer.
• ERK is a MAP kinase that can modulate downstream cellular response to VEGF.

Hypothesis

• Treatment with B and C inhibits pVEGFR2 and induces apoptosis in CD105+ and CD31+ CECs.
• Treatment with B and C reduces CTCs and overall tumor burden.

Methods

Peripheral blood was obtained at baseline, 24 hours and at C2D26-30 post-treatment from patients (n=18) undergoing dose escalation of intravenous B and oral C. CTCs and CECs (CD31+ or CD105+) were isolated and immunofluorescently stained. We used laser scanning cytometry (LSC) to enumerate CTCs and quantify the expression levels of each biomarker.

Results

• B was administered at an initial dose of 3mg/kg and then escalated to 5mg/kg. C was initiated at a dose of 20mg/day and escalated to 30mg/day, then 45mg/day.
• RECIST was assessed on 16 patients (4 withdrew prior to restaging). Patients were categorized as PR (n=2), SD (n=10), and PD (n=4).
• Treatment with B and C reduces CTCs and CECs in the blood.
• pVEGFR-2 / VEGFR-2 (MFI) and pERK / ERK (MFI) were measured using LSC.

Effects on pVEGFR2

• Treatment with B significantly increased pVEGFR2 at lower doses (83%; 3mg/kg) compared to the higher doses (1.9%; 5mg/kg) in CD31+ CECs.

Effects on pERK/ERK

• A dose-dependent significant increase in pERK/ERK ratio was also observed at 24 hrs (avg. 34%; p=0.046) and at C2D26-30 (avg. 33%; p=0.043).

Conclusions

• Bevacizumab and Cediranib are feasible surrogates for monitoring the effects of anti-angiogenic therapies.
• The CellSearch™ profile kit with LSC analysis offers a more sensitive method for CTC recovery and downstream molecular characterization.
• CTCs may provide an early quantitative measure of metastatic tumor burden.

References


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