Cooperative Group Bulletin Board

Cancer and Leukemia Group B 90206: A Randomized Phase III Trial of Interferon-α or Interferon-α Plus Anti-Vascular Endothelial Growth Factor Antibody (Bevacizumab) in Metastatic Renal Cell Carcinoma

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ABSTRACT

The majority of sporadic clear cell renal cell carcinoma (RCC) is characterized by loss of heterozygosity of the von Hippel-Lindau (VHL) tumor suppressor gene and somatic inactivation of the remaining VHL allele. The resulting VHL gene silencing leads to induction of hypoxia-regulated genes including vascular endothelial growth factor (VEGF). Thus, therapeutic inhibition of VEGF holds promise for treatment of this historically refractory malignancy. An antibody to VEGF (bevacizumab, Avastin) has demonstrated a significant prolongation of time to disease progression compared with placebo in patients with metastatic RCC. Interferon-α (IFN-α) is a standard initial cytokine therapy in RCC with a modest response rate and a survival advantage demonstrated in randomized trials. We hypothesized that the addition of anti-VEGF therapy to IFN-α would prolong survival in untreated metastatic RCC patients. A Phase III trial is now being conducted randomizing untreated, metastatic clear cell RCC patients to IFN-α alone or IFN-α plus Avastin.

INTRODUCTION

Von Hippel-Lindau (VHL) Gene Inactivation and Vascular Endothelial Growth Factor (VEGF) Overexpression in Renal Cell Carcinoma (RCC). VHL syndrome is an autosomal dominant disorder associated with increased susceptibility to vascular tumors including the prominent occurrence of clear cell RCC (1). The VHL gene has been mapped to chromosome 3p25–26 and functions as a tumor suppressor gene (2–4). Biallelic VHL gene inactivation is also seen in the majority of noninherited clear cell RCC via muta-tion and/or methylation (5–10). VHL gene inactivation leads to an altered VHL protein, which normally functions to degrade hypoxia-inducible factor α (HIFα). Lack of HIFα degradation in VHL-inactivated RCC results in constitutive HIFα expression. Stabilized HIFα translocates into the nucleus and associates with other HIF molecules, leading to induction of hypoxia-inducible genes, including VEGF. VEGF is the most poten proangiogenic protein yet discovered, leading to increased vascular permeability and endothelial cell proliferation/migration (11). VEGF mRNA transcript and/or protein expression has been demonstrated in the majority of RCC samples examined in several series and is markedly up-regulated compared with normal renal tissue from the same specimen (12, 13).

Taken together, these data provide compelling evidence for VHL inactivation in the majority of clear cell RCC leading to VEGF overexpression promoting angiogenesis. Inhibition of VEGF may, therefore, reduce tumor-associated angiogenesis in RCC and lead to tumor regression, delay in tumor progression, and, possibly, improved survival.

Antibody-Mediated Inhibition of VEGF. A humanized monoclonal antibody against VEGF (bevacizumab, Avastin) was created from the murine A.4.6.1 antibody using the IgG1 transcript and/or protein expression has been demonstrated in the majority of RCC samples examined in several series and is markedly up-regulated compared with normal renal tissue from the same specimen (12, 13).

The clinical utility of bevacizumab in RCC was investigated further in a randomized Phase II trial (17). One hundred sixteen patients with metastatic, refractory clear cell RCC were randomized to placebo, low-dose (3 mg/kg) bevacizumab, or high-dose (10 mg/kg) bevacizumab given i.v. every 2 weeks. Patients with disease progression on placebo crossed over to receive low-dose bevacizumab. The study was designed to detect a doubling of time to disease progression with either dose of bevacizumab compared with placebo. The study was closed after accrual of 116 of a planned 150 patients (as statistical efficacy end points had been met) with 108 patients demonstrating progressive disease at a median follow-up of 27 months. Treatment arms were well balanced with regard to established prognostic factors (18). There were 4 partial responses, all in the high-dose bevacizumab arm. Intent-to-treat analysis demonstrated a significant prolongation of time to progression in the high dose bevacizumab arm versus placebo (4.8 versus 2.5 months; P < 0.001 by log rank test).

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Interferon-α (IFN-α) in RCC. Several randomized trials have investigated the objective response rate and overall survival in metastatic RCC patients treated with IFN-α (Table 1;Refs. 19–21). Investigators have used "placebo-equivalent" control arms with agents such as medroxyprogesterone or vinblastine to address possible low compliance with placebo-controlled trials. Taken together, these studies support IFN-α as a standard of care for initial systemic treatment of patients with metastatic RCC with a 15% objective response rate and a modest overall survival benefit.

The antitumor activity of IFN-α is postulated to result from stimulation of the immune response, direct antiproliferative effects, and/or increased tumor antigen presentation. Investigators have thus attempted to augment the benefit of cytokine therapy in a myriad of ways, combination therapy (22, 23), dose modification, and administration of immunologically active cells such as lymphokine-activated killer cells (24, 25) or tumor-infiltrating lymphocytes (26). Each of these strategies sought to further the effect of cytokines, yet none resulted in significant clinical benefit. An additional mechanism of IFN-α in RCC may be antiangiogenesis, in part through down-regulation of basic fibroblast growth factor (27). The effectiveness of IFN-α in hemangioma and observed stromal effects of IFN-α in carcinoid patients support an angiogenic mechanism (28, 29). Given these facts, one strategy to augment the anti-RCC effect of IFN-α is combination with anti-VEGF therapy.

MATERIALS AND METHODS

On the basis of the considerations above, a randomized Phase III trial investigating the addition of bevacizumab to initial IFN-α therapy in RCC is ongoing through the Cancer and Leukemia Group B study demonstrated that baseline urine VEGF levels were independently prognostic for survival in hormone-refractory, metastatic prostate cancer (32). No adequately powered, prospective study on the predictive and/or prognostic value of angiokine proteins in metastatic RCC has been reported. Pretreatment plasma and/or urine angiokine levels and treatment-induced changes are hypothesized to correlate with clinical outcome. Collection of plasma and urine will be undertaken at baseline and during treatment (end of cycles 1, 2, and every other cycle until off study) to examine the prognostic and/or predictive impact of these markers. It is additionally hypothesized that expression of VEGF and related proteins (e.g., HIFα and basic fibroblast growth factor) in RCC tumor specimens will correlate with clinical outcome. Limited studies to date have not demonstrated independent significance of VEGF protein expression and clinical outcome (33, 34). Immunohistochemical staining of archived renal tumors will

![Fig. 1 Study Schema. Cycle length was 28 days. Patients will be evaluated by computed tomography/bone scan at baseline and every 12 weeks. Patients will be treated until unacceptable toxicity or progressive disease, defined as a ≥50% increase in the sum of the longest unidimensional measurements of target lesions or development of new lesions.](image)

### Table 1 Randomized trials of IFN-α in patients with metastatic RCC

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>Overall response rate (%)</th>
<th>Median survival (mos.)</th>
<th>Survival benefit (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steineck (19)</td>
<td>IFN-α2a vs. medroxyprogesterone</td>
<td>30</td>
<td>6</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>Ritchie (20)</td>
<td>IFN-α2b vs. medroxyprogesterone</td>
<td>167</td>
<td>14</td>
<td>8.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Pyrhonen (21)</td>
<td>IFN-α2a plus vinblastine vs. vinblastine</td>
<td>79</td>
<td>16.5</td>
<td>15.8</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Additional mechanisms of IFN-α in RCC include stimulation of the immune response, direct antiproliferative effects, and/or increased tumor antigen presentation. These strategies sought to further the effect of cytokines, yet none resulted in significant clinical benefit. Antiangiogenesis, in part through down-regulation of basic fibroblast growth factor, may be one additional mechanism of IFN-α in RCC.

The antitumor activity of IFN-α is postulated to result from stimulation of the immune response, direct antiproliferative effects, and/or increased tumor antigen presentation. Investigators have thus attempted to augment the benefit of cytokine therapy in a myriad of ways, combination therapy, dose modification, and administration of immunologically active cells such as lymphokine-activated killer cells or tumor-infiltrating lymphocytes. Each of these strategies sought to further the effect of cytokines, yet none resulted in significant clinical benefit. An additional mechanism of IFN-α in RCC may be antiangiogenesis, in part through down-regulation of basic fibroblast growth factor. The effectiveness of IFN-α in hemangioma and observed stromal effects of IFN-α in carcinoid patients support an angiogenic mechanism. Given these facts, one strategy to augment the anti-RCC effect of IFN-α is combination with anti-VEGF therapy.

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be performed for all of the patients and correlated with clinical outcome.

**DISCUSSION**

This is the first Phase III trial of VEGF-directed therapy in RCC. Demonstration of significantly prolonged survival in the combination therapy arm would alter a standard initial therapy for metastatic RCC patients. Furthermore, demonstration of a clinically relevant antitumor effect will validate VEGF as a crucial therapeutic target in RCC and support additional investigation into inhibition of this pathway.

**REFERENCES**

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