Evaluating Antiangiogenesis Agents in the Clinic: The Eastern Cooperative Oncology Group Portfolio of Clinical Trials

Joseph A. Sparano, Robert Gray, Bruce Giantonio, Peter O’Dwyer, and Robert L. Comis
Eastern Cooperative Oncology Group, Philadelphia, Pennsylvania

Abstract
Recent evidence indicates that treatment with a humanized monoclonal antibody (bevacizumab) directed at vascular endothelial growth factor improves response and survival in metastatic colorectal cancer when added to standard chemotherapy, validating angiogenesis as a therapeutic target. Investigators from the Eastern Cooperative Oncology Group (ECOG) have initiated a number of Phase III studies that will help further define the role of antiangiogenic agents for the treatment of breast, colon, lung, renal, and head and neck cancer, as well as melanoma and myeloma. The agents being evaluated target various biological functions involved in angiogenesis, including vascular endothelial growth factor (bevacizumab), endothelial cell proliferation (thalidomide, IFN-α), and matrix metalloproteinases (marimastat). These clinical trials include correlative laboratory studies aimed at elucidating how these agents may exert their clinical effects. The portfolio of Eastern Cooperative Oncology Group studies will serve to further define the role of this therapeutic strategy for patients with advanced cancer.

Introduction
It has been 30 years since Folkman hypothesized that the tumor vasculature was a good target for developing therapeutic strategies to treat human cancer (1). Although this hypothesis initially was met with skepticism, greater interest slowly developed over the years in developing novel treatment approaches targeting tumor-associated angiogenesis by a variety of different approaches (2). A great deal of public interest developed in 1998 when a front page article in the Sunday edition of New York Times announced “Hope in the Lab: A Special Report—A Cautious Awe Greets Drugs that Eradicate Tumors in Mice” (3). This heightened interest came at a time when many new antiangiogenic agents first entered the clinic. Although the specific agents that led to great excitement (e.g., endostatin) have not realized their lofty expectations (4–6), many studies evaluating antiangiogenic agents are currently in progress. It has also been recognized that many commonly used antineoplastic agents have potent antiangiogenic properties (7), and, in some cases, the basis for these antiangiogenic effects have been elucidated (8). This has served to challenge our notion as to how best to administer these agents to exploit both their cytotoxic and antiangiogenic properties. The topic has been extensively reviewed in the basic science and clinical literature (9, 10).

Investigators from the Eastern Cooperative Oncology Group (ECOG) have initiated or completed a number of Phase III studies that will help define the role of antiangiogenic agents for the treatment of advanced breast, colon, lung, and renal cancer, and are planning studies for early-stage breast and colon cancer. For the most part, the studies in advanced disease used time to disease progression rather than objective response as the primary clinical end point, reflecting our expectation that these agents would not induce tumor regression but, rather, stabilize their growth. The agents being evaluated target various biological functions involved in angiogenesis, including vascular endothelial growth factor (bevacizumab), endothelial cell proliferation (thalidomide, IFN-α), and metalloproteinases (marimastat; Table 1). The purpose of this review is to provide a summary of these studies for clinicians engaged in clinical research, to review the premise that led to the study designs, and to review the correlative laboratory studies that may lead to an improved understanding of how these agents exert their effects.

Bevacizumab
Two Phase III studies that evaluated the role of bevacizumab, a humanized monoclonal antibody directed at vascular endothelial growth factor, have been reported. A trial presented at the 2003 American Society of Clinical Oncology meeting demonstrated a survival benefit when bevacizumab was combined with standard chemotherapy as a first-line treatment for metastatic colorectal cancer (11). The study included more than 900 patients who received irinotecan, 5-fluorouracil, and leucovorin (IFL) plus bevacizumab (n = 412), or IFL plus a placebo (n = 403); a third arm that included 5-fluorouracil/leucovorin plus bevacizumab was discontinued after accrual of 110 patients when the IFL regimen was proven to be superior to 5-fluorouracil/leucovorin (12). The IFL-bevacizumab arm was associated with improved response rate (45% versus 35%; P = 0.0029), median response duration (10.4 versus 7.1 months; P = 0.0014), median time to disease progression (10.6 versus 6.2 months; P < 0.00001), and median overall survival (20.3 versus 15.6 months; P = 0.00003). The addition of bevacizumab was associated with a significantly greater incidence of grade 3 hypertension (10.9% versus 2.3%), but there was no significant difference in the incidence of thrombosis (19.3% versus 16.1%), grade 3 bleeding (3.1% versus 2.5%), or proteinuria (0.8% in both arms). A second trial presented at the 2002 San Antonio Breast Cancer Symposium compared capecitabine alone versus capecitabine plus bevacizumab as in 462 patients with meta-

Received 9/16/03; revised 10/18/03; accepted 10/22/03.
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Requests for reprints: Joseph A. Sparano, Montefiore Medical Center-Weiler Division, Department of Oncology, 2 South, Room 47–48, 1825 Eastchester Road, Bronx, NY 10461. Phone: (718) 904-2555; Fax: (718) 904-2892; E-mail: sparano@jimmy.harvard.edu.
static breast cancer who had no more than two previous chemotherapy regimens for metastatic disease (13). Although the addition of bevacizumab resulted in a significant improvement in objective response rate (20% versus 10%), there was no significant difference in median time to disease progression (the primary end point) or overall survival.

Other trials have also suggested that bevacizumab may have activity in other diseases. A randomized Phase II trial that compared two doses of bevacizumab (3 or 10 mg/kg every 2 weeks) with a placebo infusion in 110 patients with metastatic renal cell cancer demonstrated a significant improvement in median time to disease progression for patients treated with the 10-mg/kg bevacizumab dose compared with placebo (median, 4.8 versus 2.5 months; \( P < 0.001 \); Ref. 14). A randomized Phase II trial in non-small cell lung cancer (NSCLC) that compared carboplatin/paclitaxel alone or in combination with bevacizumab suggested an improvement in median time to disease progression for patients in the bevacizumab arm (15).

The results of the colorectal trial and renal cell trial have clearly validated angiogenesis as a therapeutic target. The ECOG is currently performing several Phase III trials evaluating bevacizumab as a component of therapy for patients with advanced breast, colon, and NSCLC. Previous studies have demonstrated the safety of combining bevacizumab with IFL (16) and with oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX4; Ref. 17), as well as combining bevacizumab with carboplatin/paclitaxel in NSCLC of the non-squamous cell type (18). In the NSCLC trial, there was an excess risk of fatal pulmonary hemorrhage in patients with squamous cell histology. The trial included 99 patients with advanced NSCLC who were randomized to carboplatin/paclitaxel for six cycles alone or in combination with a low (7.5 mg/kg) or high (15 mg/kg) dose of bevacizumab given every 3 weeks. Twenty % of patients had squamous cell carcinoma. There were three cases of life-threatening hemorrhage in the two bevacizumab-containing arms, four of which proved fatal. Tumor-related bleeding originating from pulmonary tumors may have caused all six events. In a case–control analysis of the data, squamous cell carcinoma and bevacizumab therapy emerged as the most likely factors associated with this complication. For this reason, the current NSCLC study (E4599) includes only patients with non-squamous histology.

Because of concerns regarding disease-specific complications such as pulmonary hemorrhage, and because of other complications associated with bevacizumab such as thrombosis, hypertension, and proteinuria, a safety analysis of four ongoing or completed ECOG studies that included bevacizumab was recently reported (19). Bevacizumab was used either alone or in combination with standard chemotherapy in 519 patients with breast, colon, and NSCLC (of the non-squamous cell type); there was no significant increase in the risk of thrombosis or bleeding associated with bevacizumab (Table 2). There were three bleeding-related deaths in the bevacizumab-containing arms, including two deaths from pulmonary hemorrhage in the NSCLC study (E4599) and one death due to central nervous system hemorrhage in the colorectal study (E3200). There was no increased risk of thrombosis. Proteinuria was uncommon and never grade 3 or 4. There was an increased risk of grade 3–4 hypertension, but the incidence was low. The NSCLC study has been amended to exclude patients with a history of gross hemoptysis (defined as bright red blood of a 1/2 teaspoon or more). This analysis has confirmed other reports indicating the safety of using bevacizumab in combination with standard cytotoxic therapy for these disease types.

### Thalidomide

The antiangiogenic effects of thalidomide first became evident in the 1950s when pregnant women who took the drug for its approved indication as a sedative bore children who had phocomelia, or deformity of the limbs, because of the inhibition of blood vessel formation in developing limb buds (20). Subsequent studies have confirmed that the drug inhibits angiogenesis

<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Agent</th>
<th>Phase</th>
<th>Accrual</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>E4599</td>
<td>Stage IV non-squamous, non-small cell lung, first line therapy</td>
<td>Bevacizumab</td>
<td>II–III</td>
<td>640</td>
<td>Carboplatin/paclitaxel +/− bevacizumab 15 mg/kg every 3 weeks</td>
</tr>
<tr>
<td>E2100</td>
<td>Stage IV breast cancer, first line therapy</td>
<td>Bevacizumab</td>
<td>II–III</td>
<td>685</td>
<td>Weekly paclitaxel +/− bevacizumab 10 mg/kg every 2 weeks</td>
</tr>
<tr>
<td>E2200</td>
<td>Stage IV colorectal cancer, second line therapy</td>
<td>Bevacizumab</td>
<td>II–III</td>
<td>835</td>
<td>Oxaliplatin/5-FU/leucovorin vs. oxaliplatin/5-FU/leucovorin + bevacizumab 10 mg/kg every 2 weeks; bevacizumab 10 mg/kg every 2 weeks</td>
</tr>
<tr>
<td>E3598</td>
<td>Stage IIIA–B non-small cell lung cancer, first line therapy</td>
<td>Thalidomide</td>
<td>III</td>
<td>588</td>
<td>Sequential carboplatin/paclitaxel ⇒ irradiation +/− thalidomide ≥ 200 mg p.o. daily</td>
</tr>
<tr>
<td>E2898</td>
<td>Stage IV renal cell carcinoma</td>
<td>Thalidomide</td>
<td>III</td>
<td>353</td>
<td>IFN-α 1 μg, BID s.c. +/− thalidomide ≥ 200 mg daily</td>
</tr>
<tr>
<td>E1A00</td>
<td>Stage III myeloma</td>
<td>Thalidomide</td>
<td>III</td>
<td>207</td>
<td>Dexamethasone +/− thalidomide 200 mg daily</td>
</tr>
<tr>
<td>E1301</td>
<td>Stage III–IV head/neck squamous cell carcinoma</td>
<td>IFN-α</td>
<td>III</td>
<td>418</td>
<td>Surgery ⇒ IFN + 13-cis retinoic acid vs. no therapy</td>
</tr>
<tr>
<td>E1697</td>
<td>Stage T3–N1 or microscopic N1 melanoma</td>
<td>IFN-α</td>
<td>III</td>
<td>1420</td>
<td>IFN-α 20 μg/M2 daily 5/7 days × 4 weeks vs. no therapy</td>
</tr>
<tr>
<td>E2196</td>
<td>Stage IV breast cancer, after first line therapy</td>
<td>Marimastat</td>
<td>III</td>
<td>190</td>
<td>Marimastat 10 mg BID vs. placebo</td>
</tr>
</tbody>
</table>

\(a\) +/−, with and without; 5-FU, 5-fluouracil; BID, twice a day.

\(b\) Completed accrual goal, data maturing.

\(c\) Results reported.
Evaluating Antiangiogenesis Agents in the Clinic

A number of reports have indicated no benefit for MMP inhibitors (MMPIs) when used either in combination with chemotherapy or sequentially after first-line chemotherapy in a variety of disease types, including small cell lung (42), non-small cell lung (43), colorectal (38), renal cell carcinoma (32), and melanoma (31). In addition, several reports have indicated that the combination with other agents such as thalidomide (34) or cis-retinoic acid (35) is associated with enhanced antiangiogenic effect. These considerations have provided the basis for an ECOG study that have evaluated the role of α-IFN used in combination with cis-retinoic acid for head and neck carcinoma (E1301), or in combination with thalidomide for renal cell carcinoma (E2898). In addition, based on previous evidence demonstrating a beneficial effect for α-IFN in high-risk operable malignant melanoma (31), an ongoing ECOG study is evaluating the role α-IFN in patients with intermediate-risk disease (E1697).

MMP Inhibitors

The matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that are responsible for degradation and remodeling of the basement membrane and extracellular matrix (36). MMPs play a critical role in multiple steps in the metastatic cascade and also facilitate neoangiogenesis. Overexpression of MMPs by tumor or tumor-associated stroma has been associated with a worse prognosis in a variety of cancer types, including esophageal (37), colon (38), and pancreas (39). Numerous inhibitors of MMPs have been developed, including marimastat, that bind the zinc atom in the active catalytic domain of most MMPs (40). The ECOG performed a randomized Phase III trial comparing marimastat with placebo in patients with metastatic breast cancer who had responding or stable disease after first-line chemotherapy (E2196). Marimastat therapy was not associated with an improvement in progression-free survival or overall survival (41). Only about 20% of patients in the marimastat arm were documented to have a trough plasma marimastat level of at least 40 ng/ml, a level considered therapeutic because there is at least 90% enzyme inhibition for most MMPs above this threshold. Higher marimastat levels were surprisingly found to be associated with an increased risk of death but not progression; higher levels were also associated with an increase in plasma MMP-9, suggesting a compensatory increase in MMP production as a consequence of enzyme inhibition.

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cell lung (43, 44), gastric (45), and pancreatic cancers (46–48), as well as glioblastoma multiforme (49). In fact, two studies demonstrated diminished survival with one MMPI (BAY12-9566) evaluated in pancreatic cancer (when compared with gemcitabine) and small cell lung cancer (when compared with placebo after induction chemotherapy). The disappointing results observed for the MMPIs in clinical trials suggest that we have an incomplete understanding of this target and these agents. No additional trials evaluating MMPIs are currently planned by ECOG, and many pharmaceutical companies have suspended clinical development of these agents.

Correlative Studies in Antiangiogenesis Trials

The ECOG breast cancer study (E2196) illustrates the potential value that correlative studies may have, even when the parent study is negative. Although we might have concluded that an agent was not effective because of failure to achieve “therapeutic” levels, we paradoxically noted a worse survival for those that achieved “therapeutic” levels. In addition, the correlation between a higher marimastat concentration and elevated MMP-9 level provides a potential explanation for this finding. MMP-9 has been reported to function at an angiogenic level provides a potential explanation for this finding. MMP-9 has been reported to function at an angiogenic switch” (50). By up-regulating MMP-9 production, the MMPIs may paradoxically serve to enhance rather than inhibit tumor-angiogenesis. This may explain the worse survival noted for patients treated with MMPIs that are more specific for prognostic value or predictive of response to therapy

Another objective specific to the locally advanced non-small cell trial (E3598) will be to identify genes inactivated by aberrant CpG island methylation as prognostic and predictive markers, and as markers for detecting subclinical disease. For example, inactivation of the p16 tumor suppressor gene is a frequent and early event in the development of squamous cell carcinoma (52), and aberrant methylation of p16 has been detected in sputum and in DNA recovered from the serum of patients with NSCLC, as well as the sputum from some high-risk, cancer-free subjects (53). E3598 includes correlative studies that will evaluate aberrant methylation of genes [e.g., p16, O6-methylguanine-DNA methyltransferase (MGMT), DAP-kinase, and tissue inhibitor(s) of metalloproteinase-3] within

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*a VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; NSCLC, non-small cell lung cancer; TNF, tumor necrosis factor; MMP, matrix metalloproteinase.

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biological fluids and tumor that are designed to address the following questions: (a) will the detection of gene dysfunction in critical genes through analysis of sputum and/or serum be useful for screening?; (b) does inactivation of these critical genes affect response to standard treatment or survival? and (c) can serum methylation markers be useful in diagnosis or in predicting response to an antiangiogenic agent?

Although a more detailed description of the rationale for these correlative studies is beyond the scope of this review, our previous experience highlights the importance of performing such studies when evaluating new therapeutic agents.

Conclusion

The encouraging results observed with a bevacizumab in colorectal cancer and renal cell cancer has validated angiogen-

esis as a therapeutic target. The current portfolio of ECOG studies will serve to further define the role of this therapeutic strategy for patients with advanced cancer. All of the active studies are currently listed on the Cancer Trials Support Unit (CTSU) roster, offering the opportunity for any interested in-

vestigator to participate in trials evaluating antiangiogenic ther-

apy in advanced breast (E21000), lung (E4599, E3598), and head and neck cancer (E1301), as well as intermediate-risk operable malignant melanoma (E1697).

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