

Rationale for Combination Use of Targeted Agents in Ovarian Cancer

Do We Have One?

Robert L. Coleman, MD¹
Elise C. Kohn, MD²

¹ Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

² Molecular Signaling Section, Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland.

One of the most exciting (and harrowing) situations in solid tumor therapeutics has been the explosive development and availability of agents that provide specific or promiscuous targeting to biologic processes that mediate the survival of cells in the microenvironment. The successes of agents, such as trastuzumab in breast cancer¹; bevacizumab in colon, breast, and lung cancers²⁻⁴; sunitinib⁵ and sorafenib⁶ in renal cell cancer; and imatinib in gastrointestinal stromal tumors,⁷ are a few examples of the next iteration in evolutionary progress for targeted therapy. In some of these cases, patients were selected because their tumors expressed a targetable abnormality, which effectively was inhibited by the novel agent; and, in phase 3 investigation, the maneuver proved efficacious relative to those with a similar profile denied the drug. In others, unselected populations were administered the agent or agent combined with chemotherapy, and clinical investigation demonstrated a significant improvement in outcome relative to usual practice standards. But these advances stand on scores of negative clinical studies in tumor types with similar target expression, promising in vitro and in vivo preclinical data, and acceptable safety profiles in their early clinical development. This conundrum leaves us as investigators with the task of deciding whether the agent is truly 'inactive' or 'inappropriate for this tumor type' or was 'handicapped' by ... (*fill in the blank*: study design, statistical endpoints, patient selection, patient tumor burden, route of administration, schedule, dose, etc), all of which are problematic and leave a somewhat sophomore overview of the cancer treatment process. Furthermore, the clinical scenario under which some of the agents received their approvals complicates our inference of treatment effect. Imatinib, sunitinib, and sorafenib received their indications as single agents that demonstrated therapeutic benefit. Conversely, bevacizumab, perhaps the most broadly used agent other than the taxanes, had only

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Address for reprints: Robert L. Coleman, MD, Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center, 1155 Herman Pressler Drive, Houston, TX 77030; Fax: (713) 792-7586; E-mail: rcoleman@mdanderson.org

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a very modest effect as a single agent in the diseases for which it currently is approved. Did bevacizumab itself have an effect on the tumor in those patients, or did it somehow augment the efficacy of, or overcome resistance to, the chemotherapy? Thus, the key questions to advancing in this era of plenty become:

- Is the target necessary or sufficient for activity of the agent?
- Was the combination based on biochemical or molecular rationale?
- Must the targeted agent have activity of its own in the combination or must the combination 'work' in some fashion?
- If the target and rationale were present, then why was this combination and rationale preferred over other potential choices?
- Was the potential for interactive on- and off-target toxicities considered?

A good example of miscue in this regard is the story of gefitinib, a tyrosine kinase small-molecule inhibitor of the epidermal growth factor receptor (EGFR), in patients with nonsmall cell lung cancer (NSCLC). Early clinical investigation suggested that the activity of this agent was promising based on frequent target overexpression and single-arm, phase 2 studies demonstrating 'unexpected' clinical efficacy, particularly in patients with previously treated, refractory disease.⁸ On May 3, 2003, the United States Food and Drug Administration (FDA) granted accelerated approval to gefitinib requiring additional phase 3 studies to define and clarify its disease-specific role. At the time, 2 randomized, controlled clinical studies of gefitinib in combination with platinum-based regimens in patients with primary, advanced NSCLC proved *no* benefit and were available. On December 17, 2004, the FDA was informed that a placebo-controlled, phase 3 study of approximately 1700 patients demonstrated no improvement in overall survival. This prompted the FDA to amend its approval language on June 17, 2005, limiting drug use to only those patients for whom their treating physicians believed it would be beneficial.⁹ Fortunately, return to the laboratory demonstrated that patients who had activating mutations in the adenosine triphosphate-binding domain stood the most to gain with the agent.^{10,11} Subsequent analyses have teased out other clinicopathologic factors (never smoker, Asian heritage, *ras* mutation) that highlight the subpopulations of lung cancer patients most likely to benefit from agents in this class.^{12,13} A similar finding also was recognized in patients with ovarian cancer after reports of low response rates to erlotinib and gefitinib

(5.8% and 3%, respectively) in Gynecologic Oncology Group phase 2 studies.^{14,15} In the latter study, the lone responder was identified as the only patient who harbored an activating mutation in EGFR.¹⁵

In the current issue of *Cancer*, Matei et al from the Hoosier Oncology Group evaluate the combination imatinib mesylate and weekly docetaxel in women with recurrent and previously treated ovarian cancer.¹⁶ Their prospective, open-label, clinical study was designed based on the observations that c-kit, platelet-derived growth factor receptor (PDGFR), and c-abl (targets of imatinib) frequently are over expressed, either alone or in combination, on ovarian cancer cells and that the clinical activity of taxanes is well established in the disease. Efficacy rationale for that study also was 'supported' by preclinical observations that imatinib inhibited the proliferation of ovarian cancer cells *in vitro*; and rationale for dosing, schedule, and safety were derived from a modular phase 1 study in patients with prostate cancer who were treated with the combination. The investigation required expression of c-kit or PDGFR- β for patient eligibility and allowed any number of prior therapies. Although weekly administration of docetaxel is untested in ovarian cancer, conceptually, the schedule is desirable from a metronomic standpoint. Weekly paclitaxel has been evaluated in a randomized, phase 2 study of patients with recurrent ovarian cancer relative to every-3-week paclitaxel infusion and in 2 phase 2 studies of patients with paclitaxel-resistant, recurrent ovarian cancer demonstrating clinical efficacy. The novel combination regimen reported by Matei, et al, did produce responses, notably in a few complete responders; however, the authors conclude that the regimen has only modest activity.¹⁶

In fact, concern for toxicity of this combination may be warranted based on the frequent identification of edema for both agents individually and fluid accumulation (as ascites, effusions, etc) observed with imatinib as a single agent in patients with ovarian cancer.¹⁷ Further compounding the issue of observed treatment effect is the realization that these clinical features also may be part of the natural history of disease progression. A hypothesis for the imatinib effect lies in the indiscriminant PDGFR- β targeting of pericytes, which, under normal conditions, provide structural integrity to vessels in the microenvironment. Nevertheless, sequential and directed targeting to pericytes, tumor cells, and endothelial cells indeed may provide the most promising approach to therapy for this disease. In the current article, metronomic taxanes had demonstrated effects on tumor endothelial cells, and imatinib had demonstrated effects on pericytes and on some tumor cells; and, potentially, combined with an antivascular endothelial growth factor

molecule, as hypothesized by Pietras and Hanahan, may provide an optimal approach to microenvironment cytotoxicity.¹⁸ The rationale is generated mechanistically and is not reliant on potentially insignificant aspects, such as mere target over expression.

The real dangers in the interpretation of studies such as that by Matei et al¹⁶ are 1) discarding a relevant therapeutic agent that may be integral to a regimen rationally designed to the survival mechanisms of the microenvironment, 2) missing a potential therapeutic benefit of a targeted agent because of empiric combination rather than rational design, and 3) misleading patients with incomplete or incorrect interpretation of clinical trial rationale. Given the limited number of patient resources available, future investigations necessarily will need to be vetted in representative preclinical models, linked with relevant biomarkers, designed statistically to optimize patient resources, and prioritized by potential efficacy. The expanding menu of effective compounds vastly outpaces this process and further challenges us as investigators and treating physicians to develop an appropriate rationale for developing novel regimens.

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