C225 and PDT Combination Therapy for Ovarian Cancer: The Play’s the Thing

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The prognosis for women diagnosed with advanced-stage epithelial ovarian cancer is poor, with fewer than one-third of patients surviving 5 years. Locally advanced pelvic tumors are often associated with diffuse peritoneal carcinomatosis and bulky tumor lesions involving the omentum, bowel, mesentery, and diaphragmatic surface. Even after aggressive cytoreductive surgery and platinum-based chemotherapy, most of these patients experience local progression or recurrence. The reasons for treatment failure probably relate to difficulties inherent to surgery within the peritoneal cavity, problems related to administering cytotoxic agents to the tumor cells in cytotoxic concentrations, and the ability of ovarian cancer cells to develop resistance to standard chemotherapies.

In this issue of the Journal, del Carmen and colleagues (1) present evidence that intraperitoneal administration of C225, a humanized murine monoclonal antibody directed against the epidermal growth factor (EGF) receptor (EGFR), and benzopheremin derivative monoaclid-A (BPD)–based photodynamic therapy (PDT) act synergistically to prevent or inhibit tumor cell growth and extend survival in a murine model of ovarian cancer peritoneal metastasis. In these studies (1), mice were injected intraperitoneally with human ovarian cancer-derived NIH:OVCAR-5 cells and subjected to PDT using BPD on days 10 and 20 after tumor cell inoculation. C225 was administered intraperitoneally on days 11, 14, 17, and 19 after tumor cell inoculation. As compared with mice treated with either C225 or PDT alone, mice treated with combined PDT + C225 showed a decrease in mean tumor burden as measured on day 21 after tumor cell inoculation and an increase in overall survival when mice were followed up to day 180, with three of nine C225 + PDT mice achieving cure of disease.

When used separately, both intraperitoneally administered C225 and PDT have theoretical advantages that exploit different aspects of ovarian carcinoma tumor biology and may help make up for some of the deficiencies in the current standard therapies. Through inhibition of EGFR signaling, C225 has the potential to inhibit both the survival and the spread of ovarian carcinoma cells, regardless of their resistance or sensitivity to chemotherapy. Autocrine growth factor signaling networks involving lysophosphatidic acid (LPA) and EGFR ligands such as heparin-binding epithelial-like growth factor (HB-EGF) have been implicated in the development of the malignant ovarian cancer phenotype, the intraperitoneal spread of ovarian tumors, the growth and survival of ovarian cancer cells, and the resistance of ovarian cancer cells to chemotherapy (2–4). Activation of LPA receptors can act directly to stimulate carcinoma cell survival, growth, migration, and invasiveness (2). Ovarian carcinoma cells have also been found to overexpress EGFRs, and EGFR overexpression has been associated with poor clinical outcome (5). Conversely, inhibition of EGFR signaling by both small-molecule and immunoglobulin-derived EGFR inhibitors leads to inhibition of ovarian carcinoma cell growth and survival (5). In addition, cross-talk between LPA and EGFRs may occur at multiple levels: LPA receptor activation can lead to tyrosine phosphorylation/activation of EGFRs either directly through proteolytic release of the EGFR-stimulating ligand, membrane-bound HB-EGF, or indirectly through activation of Src family kinases (2–4). These preclinical data provide a strong rationale for the use of inhibitors of EGFR signaling in ovarian carcinoma therapy, and there are multiple ongoing phase II and III trials of systemically administered EGFR inhibitors in patients with ovarian carcinoma. However, the potential advantages of intraperitoneal administration of these drugs are relatively undereexplored. In this context, it is interesting to note that in the study by del Carmen et al., intraperitoneal administration of C225 alone showed some efficacy against ovarian carcinoma.

PDT using Photofrin, a first-generation photosensitizer, has been used with some success as an adjuvant for surgical cytoreduction of thoracic and peritoneal malignancies (6–8). For example, among patients with peritoneal carcinomatosis treated with surgical cytoreduction followed by Photofrin PDT, the median survival had not yet been reached after 18.5 months median follow-up (7). However, only two of the 13 ovarian carcinoma patients treated in this trial did not have a recurrence, and 43 of the 49 patients with any type of intraperitoneal carcinomatosis treated in this trial experienced treatment failure within the peritoneal cavity (8). Thus, the finding by del Carmen et al. that C225 and PDT act synergistically in a murine model of peritoneally disseminated ovarian carcinoma is highly exciting and represents proof of principle that the combination of these two alternative modalities may be able to improve on the results obtained with Photofrin PDT for the treatment of ovarian carcinoma patients.

The interactions between EGFR signaling and PDT are complex and may to some extent be dependent on the cell line or the PDT method used. Some investigators (9,10) have suggested that EGFR activation is important for survival of carcinoma cells after PDT and that PDT increases EGFR signaling. Others (11,12) have found that PDT causes a temporary degradation or inactivation of cell surface receptors, including EGFRs. It is interesting that, in both of these cases, inhibition of EGFR signaling might be expected to augment PDT-mediated cancer cell killing. However, it is also possible that inhibition of EGFR activation is unrelated to the manifestation of the synergistic effects of the combination of C225 + PDT. In experiments with small-molecule tyrosine kinase inhibitors, direct inhibition of either target or nontarget receptor tyrosine kinases probably accounts for most cellular effects of tyrosine kinase inhibitors. In contrast, the mechanism of action for immunoglobulin-derived inhibitors

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of receptor tyrosine kinase signaling can also include alterations in receptor endocytosis, targeting of receptors to the proteosome, and antibody-directed cell-mediated cytotoxicity. In addition, immunoglobulin binding and oligomerization of receptor tyrosine kinases may alter the local organization of other plasma membrane microdomains or even result in subtle alterations in functionality within the receptor signaling complex. Thus, the mechanism for observed cellular effects of immunoglobulin-derived receptor tyrosine kinase inhibitors may not be readily apparent. The potential for complexity in the mechanism of action of immunoglobulin-derived receptor tyrosine kinase inhibitors is perhaps best illustrated by the recent finding that the binding of trastuzumab to ErbB2 causes release of Src kinase from the receptor complex, resulting in increased membrane localization of PTEN and a subsequent decrease in phosphatidylinositol 3'-kinase signaling (13). Thus, it remains unclear whether the synergy between C225 and PDT reported by del Carmen et al. stems from modulation of EGFR signaling or whether some other mechanism may account for this phenomenon, such as increased sensitivity to PDT due to membrane destabilization. In addition, further study will be required to determine the optimal dose and delivery schedule of PDT and C225.

Scientifically, questions of target and mechanism are critically important and may serve to help identify those populations of cancer patients who are most likely to respond to a particular therapy. Minimally toxic, individualized cancer therapy is and should remain the holy grail of the molecularly targeted therapy crusade. Both the mechanism by which C225 augments PDT-mediated killing of intraperitoneal ovarian cancer cells as well as the optimal dose and delivery schedule of these therapies urgently requires further preclinical study. However, it is important to keep in mind that translation can be a two-way street. Although much can be learned about potential mechanisms and targets of a new therapy from preclinical model systems, analyzing the efficacy and molecular profiles of responders and nonresponders in clinical trials can be equally valuable. In addition, the importance of testing the efficacy and toxicity of combination therapy with C225 + PDT in clinical trials should not be underestimated given the pressing need for better therapies in intraperitoneally disseminated ovarian cancer. From the perspective of the patient and the clinician, it is not nearly so important how a new treatment works as that it works where the standard treatments have failed.

REFERENCES