

Editorial

Should Therapy of Ovarian Cancer Patients Be Individualized Based on Underlying Genetic Defects?

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This year in the United States, ~26,800 women will be newly diagnosed with ovarian cancer, and 14,500 will die from the disease (1). The dismal prognosis for ovarian cancer patients results from an inability to detect the tumor at an early, treatable stage as well as from lack of effective therapies for advanced disease. Ovarian cancers show high response rates to chemotherapy, which, unfortunately, do not translate to high cure rates (2). Indeed, although chemotherapy has improved survival times, there has been no significant improvement in cure rates in the last 30 years, with only 20% of patients with stage III and IV ovarian cancers surviving 5 years (1, 2). The most likely way to develop new, effective therapies for advanced epithelial ovarian cancer patients is to improve our understanding of and ability to identify the genetic changes leading to the initiation and progression of ovarian cancer and to sensitivity and resistance to chemotherapy.

In the United States, the majority of ovarian cancer patients are treated with a platinum analogue combined with a taxane derivative. The best response rates to platinum-based combination chemotherapy are ~70% (3), indicating that at least 30% of ovarian cancer patients are exposed to the toxic effects of platinum-based chemotherapy without significant benefit. Similarly, the response to Taxol alone is ~50% (3), suggesting that half of patients may not benefit from the addition to Taxol to a platinum analogue. Furthermore, an initial round of platinum-based therapy may delay selection of an effective chemotherapy drug and may also decrease the patient's physiological reserve. In patients previously treated with a platinum-based regimen, new anthracyclines (doxorubicin and liposomal doxorubicin preparations), nucleoside analogues (gemcitabine), topoisomerase I and II inhibitors (oral etoposide, topotecan, and camptothecins), *Vinca* alkaloids (vinorelbine), and orally active prodrugs (hexamethylmelamine) as well as hormonal manipulation (tamoxifen and gonadotropin-releasing hormone analogues) have all demonstrated activity in clinical trials (2). A number of novel chemotherapy drugs aimed at specific molecular targets are being evaluated in ovarian and other cancers. It is not clear whether the same or different patients will respond to the new chemotherapeutic regimens. In the future, a method to select an appropriate chemotherapy regimen up front or for "salvage" patients who have failed conventional chemotherapy could con-

tribute to an improved outcome in ovarian cancer, both by increasing efficacy and decreasing toxicity.

It is not clear what degree of predictive value would be sufficient to justify individualization of patient therapy. As the response rate for salvage therapy is 15–20%, would a test indicating that 40% of patients will respond be useful? Conversely, is the use of a chemotherapy drug appropriate if the patient has a 10, 5, or a 1% chance of response? At what point does the decreased quality of life in the majority of patients receiving a therapeutic regimen overwhelm the potential benefit to a few? One potential indication is that breast cancer patients with <5% chance of responding to tamoxifen (estrogen receptor negative, premenopausal) do not usually receive tamoxifen either because of physician preference or patient choice.

A number of rapidly emerging technologies including CGH,² RNA expression array analysis, multiplexed loss of heterozygosity analysis, serial analysis of gene expression, differential display, suppressed subtractive hybridization, high-throughput expressed sequence tag sequencing, and proteomics are beginning to allow analysis of global genetic changes in an individual tumor and correlation of these changes with pathophysiology, response to therapy, and patient outcome. Indeed, the opportunity to link molecular diagnostics to patient management is the underlying tenet of the current National Cancer Institute Director's challenge. Of these approaches, CGH is particularly attractive because it is currently available and allows a genome-wide scan in a single step (4, 5). However, the sensitivity and resolution of conventional chromosome-based CGH is likely limited to changes that are 5–10 Mb (4, 5). As an example, an amplicon located at 19p, which contains *AKT2*, is frequently present in ovarian cancer cells but is too small to be detected by classical CGH (5–7). Similarly, the frequency of copy number abnormalities at 3q is greater when it is analyzed by fluorescent *in situ* hybridization with region-specific probes than when it is assessed by chromosome-based CGH (8). A new technology, designated array CGH (9), has greatly increased sensitivity, allowing detection of copy number abnormalities that affect smaller genomic regions. Importantly, copy number abnormalities detected by classical CGH may reflect a sum of multiple distinct small areas of copy number abnormality. Array CGH due to increased ability to resolve areas of copy number abnormalities (9) may exhibit improved predictive value and also facilitate the identification of the gene or genes driving specific genomic amplifications or deletions. Array CGH is also likely to be more robust and less tedious than classical chromosome-based CGH.

Development of an effective strategy for individualization of patient therapy will require not only application of the emerg-

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² The abbreviations used are: CGH, comparative genomic hybridization; PI3K, phosphatidylinositol 3-kinase.

ing genomic and proteomic technology but also high-quality clinical samples as well as innovative clinical trials. These trials may require the development of research protocols of sufficient power in which patients are randomized to single-agent therapy prior to receiving combination chemotherapy and where tissue samples are obtained before and after each regimen. As a first step, genomics- and proteomic-quality flash-frozen patient samples with minimal vascular compromise should be obtained from all patients undergoing Phase II clinical trials and, whenever possible, from patients receiving standard therapy. These samples must be linked to patient follow-up and outcome and be made available to the research community if we are to be able to develop and evaluate technologies to develop effective strategies to individualize patient therapy.

In this issue of *Clinical Cancer Research*, Kudoh *et al.* (10), evaluating a limited number of ovarian cancer samples demonstrate that the presence of increased copy number at 1q21 and 13q12 correlate with a lack of response to a chemotherapy regimen consisting of cisplatin (50 mg/m²), doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²). Of the 11 individuals with increased copy number at 1q21, 2 (18%) responded to this chemotherapeutic regimen, whereas the remainder did not. Strikingly, of the five patients with an abnormality at 13q12, none of the patients responded to therapy. Although it is not clear that the presence of an increased copy number at 1q21 has sufficient predictive value to alter patient management, the presence of an increased copy number at 13q12, if confirmed in larger studies, may identify a subgroup of patients who would not benefit from this platinum-based chemotherapy. Indeed, although the differences between responders and nonresponders were not statistically significant, none of the four patients with an increased copy number at 12p13 responded to chemotherapy. This suggests that a CGH-based analysis of alterations in gene copy number, particularly if multiple sites are assessed, could identify patients who are unlikely to respond to specific therapeutic regimens. These patients may benefit from any or several of the other chemotherapeutic drugs demonstrated to have activity in ovarian cancer or, alternatively, could at least be spared the toxicity of ineffectual therapeutic regimens.

Previous CGH studies have demonstrated that patient outcome correlates with the number of copy number abnormalities, particularly with increases in 1p22–31, 3q25, 8q24, and 11q14 and decreases in 16q and 17pter–q21, which are frequently observed in ovarian cancers (6). Patient outcome is most likely dependent, at least in part, on response to the platinum analogue used, suggesting that these changes may also relate to response to platinum-based therapeutic regimens. Alternatively, assessing the number of copy number abnormalities by CGH may identify tumors with underlying genetic instability, which could contribute to a worsened outcome.

Intriguingly, the pattern of genetic changes observed in the study by Kudoh *et al.* (10) were somewhat different from that described previously in studies of predominantly white patients with serous epithelial tumors (5, 6, 10). The discordance between these could reflect the relatively small number of patients analyzed, enrichment for nonresponders in the study by Kudoh *et al.* (10), differences in the underlying genetic changes in Asian ovarian cancer patients or alternatively, histotype-specific differences in genetic changes, as the study by Kudoh *et al.* (10)

had a high number of clear cell and endometrioid ovarian cancers. Indeed, CGH analysis has detected different patterns of CGH abnormalities in tumors of specific histological subtypes (11).

CGH may prove a useful approach to identify genomic regions that harbor oncogenes and tumor suppressor genes of particular importance in a specific tumor type. Indeed, identification of the genes driving the copy number abnormalities at 1q21 and 13q12 reported by Kudoh *et al.* (10) may allow higher resolution analysis of copy number abnormalities with greater concordance with outcome and also provide mechanistic information related to the processes causing chemosensitivity and chemoresistance. Several of the copy number changes in ovarian cancers may be explained by known abnormalities in genes involved in ovarian tumorigenesis (loss of 17pter–q21 and *p53*, gain on 17q and amplification of *HER2/Neu/erbB2*, amplification on 8q24 and *myc*, and gain at 3q26.3 and amplification of the p110 catalytic subunit of PI3K) providing unique targets. The *p53* tumor suppressor has been explored as a target for gene therapy in ovarian cancer. *HER2/Neu/erbB2* is being targeted by antibody-mediated therapy (herceptin) and E1A-mediated gene therapy. The PI3K signaling cascade provides multiple targets for molecular therapeutics. Indeed, we have demonstrated that molecular therapeutics targeting the PI3K pathway markedly decrease cell proliferation and lead to programmed cell death through apoptosis in ovarian cancer cells with increased PI3K copy number both *in vitro* and in a xenogeneic ovarian cancer model (8, 12).³ Identification and characterization of the genes driving the copy number abnormalities at 1q21 and 13q12 reported by Kudoh *et al.* (10) may provide new therapeutic targets in ovarian cancer, which may directly affect tumor cell growth or alter sensitivity to chemotherapy.

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