Counterpoint: Chemosensitivity Assays for Recurrent Ovarian Cancer

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Abstract
Unfortunately, no reliable evidence-based data have shown any in vitro chemosensitivity assay strategy to be clinically useful in the management of recurrent ovarian cancer, despite frequent use. Several clinical trials have been proposed with the potential to support or refute the relevance of these approaches. (JNCCN 2011;9:121–124)

Prognostic Versus Predictive Testing in Oncology
After cancer has been diagnosed and pathologically confirmed on histologic or cytologic review, it has become routine practice to attempt to obtain additional clinical and laboratory-based data to help oncologists determine the statistically defined likelihood the patient will experience a more- or less-favorable outcome (prognostic testing). In ovarian cancer, validated and useful prognostic tests include tumor grade, surgical stage, volume of residual disease after primary surgical cytoreduction, and, in the case of advanced disease, morphologic subtype (e.g., mucinous vs. papillary serous).

Importantly, however, even if this prognostic information helps patients and physicians make the decision to manage the disease more or less aggressively based on a recognized good or poor prognosis, nothing inherent in these data recommends the use of a particular strategy to alter that outcome (predictive testing).

For example, while patients with high-grade stage I ovarian cancer may have a substantial risk for relapse and require adjuvant chemotherapy, the objective finding of a grade III tumor does not alone permit the selection of a specific therapeutic regimen that can favorably change that risk or improve survival. Furthermore, despite the increasing recognition that advanced mucinous ovarian cancers exhibit minimal (if any) response to platinum-based chemotherapy, and that these patients have inferior overall survival to what is anticipated in those with the more common papillary serous subtype, available data unfortunately do not realistically suggest a particular alternative management approach that can alter the outcome.

Given the staggering rise in the cost of cancer care, and the likely added cost of several proposed novel testing strategies (e.g., genetic/molecular tumor profiles), one must seriously question the legitimate value of additional information in the absence of objectively solid evidence that these data would favorably influence individual patient management.

However, a critical need remains, in ovarian cancer and other malignancies, for clinically useful predictive tests. The reported result of a validated predictive test will assist in the selection of antineoplastic therapy designed to optimize potential for a favorable clinical outcome or (conversely) avoid treatment involving an ineffective or excessively toxic strategy. In addition, through reducing the delivery of unnecessary treatments, beneficial predictive testing also should ultimately help control the costs associated with the management of malignant disease (e.g., KRAS testing in metastatic colon cancer).
Chemosensitivity Testing in Ovarian Cancer

With the demonstrated substantial success of laboratory-based tests to document both sensitivity and resistance to antimicrobial agents in the treatment of bacterial infections, it was natural that cancer researchers would attempt to develop similar strategies to define sensitivity and resistance of anticancer agents in the management of malignant disease.\textsuperscript{1–4} Ovarian cancer has been no exception, and considerable research has been reported in this area over the past several decades.\textsuperscript{5–12}

Unfortunately, for several well-documented, practical (e.g., time required, and inability to grow many cancer types in in vitro systems), and other more theoretical reasons (e.g., uncertainty of the actual relationship in the resistance/sensitivity patterns revealed in vitro with the viable malignant cell population within the patient), and despite major efforts of numerous research teams, the benefits of this testing in routine cancer management have been difficult to show.

An extensive review of this topic, conducted by an independent panel organized by ASCO in 2004, concluded that,

The use of chemotherapy sensitivity and resistance assays to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting. Oncologists should make chemotherapy treatment recommendations on the basis of published reports of clinical trials and a patient’s health status and treatment preferences.\textsuperscript{13,14}

Unfortunately, since the publication of this important report, no evidence-based data have become available to alter the fundamental conclusion of this expert panel.

Specifically, in the management of ovarian cancer (primary or recurrent disease), several retrospective evaluations of the relationship between laboratory-based chemoresistance or chemosensitivity testing have shown that patients with cancers determined to be resistant in vitro to one or more chemotherapeutic agents had a worse prognosis and were less likely to experience response to chemotherapy (individual drugs or overall) than those whose cancers were determined to be more sensitive. If correct, these results may have prognostic relevance. However, not all published reports in the peer-reviewed literature support even the potential prognostic usefulness of this testing, arguing that in the experience of these groups, in vitro evaluations did not reliably even correlate with clinical outcome.\textsuperscript{15–17}

However, the essential question remains whether, even assuming these chemosensitivity (or chemoresistance) test results provide some degree of objectively valid prognostic data, the information is of genuine relevance in individual clinical management? Is another test really needed to determine if a particular cancer is relatively chemotherapy-sensitive, when the results simply fail to inform whether the patient has a better opportunity to benefit from an agent/regimen that was specifically defined by the test (predictive test)?

Finally, considering the previously noted staggering rise in the cost of cancer care, is another expensive prognostic test in ovarian cancer necessary for which cost-effectiveness has never been documented?\textsuperscript{18,19}

Currently, no solid data support the conclusion that the use of any in vitro chemosensitivity (or chemoresistance) test improves outcome in recurrent (or previously untreated) ovarian cancer compared with the selection of therapy by an individual oncologist based on both existing evidence of the clinical efficacy of various strategies documented in phase III trials (e.g., platinum-based combination chemotherapy vs. single-agent platinum in recurrent ovarian cancer) and specific patient characteristics (e.g., preexisting neuropathy from, or excessive bone marrow suppression during, primary chemotherapy).

In fact, one can rationally argue that the use of in vitro chemosensitivity testing data may actually be harmful to a patient if the oncologist elected to blindly use this unvalidated information and ignored a relative or absolute contraindication based on available unique individual clinical data (e.g., a patient with recurrent ovarian cancer, with an 7-month platinum-free interval whose in vitro testing showed sensitivity to platinum, but who had experienced a serious/severe carboplatin-associated hypersensitivity reaction after the last cycle of primary chemotherapy).

Finally, the critical issue remains as to what is next. After all this time, discussion, and essentially completely unsubstantiated and unvalidated claims for the clinical efficacy of chemosensitivity or chemoresistance assays in ovarian cancer management, can a trial (or trials) be designed and conducted that actually answers the question? Table 1 outlines sev-
eral possible scenarios of clinical trial designs (listed in the opinion of this author in the order the results may provide reliable evidence for clinical efficacy) that investigative groups might consider to define the value of this testing.

The first concept represents the evidence-based gold standard (phase III randomized trial). Unfortunately, for several reasons, this option is the most difficult. First, the population will be heterogeneous (e.g., number of prior regimens, variable degree of chemoresistance, persistent toxic effects from previous treatment impacting choice of therapy), requiring large numbers of patients for a valid conclusion. Second, the time from initial diagnosis (and availability of tissue to test in vitro for chemosensitivity) and the intervening therapies will raise the legitimate question of the relevance of the in vitro data to the current tumor status. Finally, the results of this testing will need to be made available rapidly from the time of randomization, because delaying treatment to any extent in symptomatic individuals will be inappropriate.

The second concept suffers by not being a randomized trial, but all patients with advanced disease who agree to participate in this study will already have their previously obtained (but unreported) assay results available for the selection of second-line treatment if their cancers progress quickly, and if all other eligibility criteria are satisfied (including the presence of measurable disease).

The third concept is the most difficult to critically define, but the goal will be to prospectively and blindly (both the clinician to the test results, and testing laboratory to the clinical data) determine if a reasonable number of patients treated with a particular single cytotoxic agent can be found to satisfy one of the following two criteria: 1) experienced objective response to the drug (RECIST or CA-125 criteria) and the in vitro assay also predicted they would experience response; 2) they failed to experience a response and the in vitro assay predicted they would not experience response. Furthermore, it will be essential to also find very few or preferably no patients in whom the opposite pattern was observed (i.e., experienced a clinical response but the assay predicted resistance, or experienced no response and the assay predicted sensitivity).

Finally, in this trial design, the first two criteria must be individually satisfied in a reasonable number of patient samples for a single antineoplastic drug. If this does not occur, one could appropriately conclude that the assay may provide evidence of general chemotherapy sensitivity or resistance (prognostic test), but no evidence that the results represent a pattern specific for that individual agent (predictive test).

How many “correct” sets (patients fulfilling the first two criteria) will be required is difficult state precisely, in the absence of “incorrect” sets (patients ful-

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**Table 1 Potential Trial Concepts Designed to (Finally) Objectively Evaluate the Clinical Efficacy of In Vitro Chemosensitivity Testing in Recurrent Ovarian Cancer**

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>Proposed End Points</th>
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<tbody>
<tr>
<td><strong>Concept 1</strong></td>
<td>Primary: Progression-free survival</td>
</tr>
<tr>
<td><strong>Phase III trial comparing treatment based on the “best” regimen predicted</strong></td>
<td>Secondary: Overall survival; response rate; quality-of-life</td>
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<tr>
<td><strong>by in vitro results versus regimen selected by judgment of treating</strong></td>
<td><strong>Concept 2</strong></td>
</tr>
<tr>
<td><strong>physician</strong></td>
<td>The study will be prospectively stated to have</td>
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<tr>
<td><strong>Concept 2</strong></td>
<td>a positive outcome if the observed objective response rate is ≥ 40%. (Note: based on existing</td>
</tr>
<tr>
<td><strong>patients registered before undergoing primary chemotherapy</strong></td>
<td>data in this population, the anticipated response</td>
</tr>
<tr>
<td>**Chemosensitivity assay performed (results not provided to patient/</td>
<td><strong>Concept 3</strong></td>
</tr>
<tr>
<td><strong>treating physician)</strong></td>
<td><strong>Patients treated with single-agent therapy selected by their oncologist</strong></td>
</tr>
<tr>
<td><strong>If rapid progression (&lt; 3 mo after completion of primary therapy)</strong></td>
<td>**Chemosensitivity testing performed: 1) results not used to select treatment; 2)</td>
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<tr>
<td><strong>the next treatment regimen determined by most active drug in the</strong></td>
<td>physician not informed of in vitro results;</td>
</tr>
<tr>
<td><strong>previously obtained chemosensitivity assay</strong></td>
<td><strong>See text</strong></td>
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<tr>
<td><strong>Concept 3</strong></td>
<td><strong>See text</strong></td>
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filling the last 2 criteria), to conclude (even if only in retrospect) that chemosensitivity testing provided relevant predictive information. However, if 20 to 25 patients are found who fulfill the first criterion, and a similar number who fulfill the second criterion, without any patients fulfilling either of the last 2 criteria for a particular single agent routinely used in clinical practice in the second-line setting, this will be a most interesting result.

The conduct of each of these trials will require large numbers of patients and the critical support of one (or more) organization/company involved in the development of in vitro chemotherapy testing strategies. However, if the gynecologic cancer community and patients with ovarian cancer are ever to learn if in vitro chemosensitivity testing has any legitimate value, this effort must be initiated, completed, and reported in the peer-reviewed medical literature.

References