EDITORIAL

Chemosensitivity Testing: Another Chapter

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In vitro chemosensitivity testing of anticancer agents for patient treatment has evolved gradually since the time of our report in 1978 (1) on the use of a human tumor cloning or tumor cell assay for this purpose. Although some technical problems remain, definite improvement has been seen in the frequency of in vitro sensitivity results with several assay systems (2-4). One important question that has not been tested directly is whether in vitro drug selection can result in better cancer treatment than that attained by clinicians selecting drugs empirically. Gazdar et al. (5) and Von Hoff and co-workers (6) address the question of "assay versus clinician" by using different in vitro assays and study designs.

In the study conducted by Gazdar et al. (5) of patients with extensive small cell lung cancer (SCLC), etoposide plus cisplatin was used for initial therapy in all patients. A three-drug regimen for second-line therapy for refractory patients was chosen on the basis of assay results (obtained only on derived cell lines). This approach was used partly because the size of the tumor sample investigators had was inadequate to test the patient's cells directly in the vital dye assay (6), or because their first priority was to derive tumor cell lines from the biopsy specimens. Because many suspected sites of tumor involvement were actually uninvolved, only 55% of the 141 specimens were histologically positive for SCLC. Of these, only 36% of the positive specimens gave rise to tumor cell lines, and among these, assay results were available on the cells of 26 patients.

Of prognostic interest, patients whose cells showed sensitivity in vitro to primary therapy (etoposide, cisplatin) had a higher response rate and a suggestion of better survival. Although drug assays were feasible with the lines, clinical limitations (including patient's death prior to the time of initiation of second-line therapy based on sensitivity information) resulted in only 16 patients being tested and entered prospectively in a "decision-aiding" mode (7) for selection of treatment for refractory SCLC. This subset of 16 patients included two technically ineligible patients, from whom tumor specimens were not obtained prior to initial treatment, but who were included because their cell lines were available from subsequent biopsies.

The first conclusion one can reach is that this strategy of tumor collection and cultivation before sensitivity testing is very inefficient. Data for selection of assay-directed drug treatment was useful for drug selection in only 14 of 141 (10%) patients whose tumor specimens were obtained for this specific trial. As a concomitant control for assay-selected treatments, 43 patients, who were biopsied but whose assay-results were unavailable, received vincristine, doxorubicin, and cyclophosphamide as a standard second-line regimen. In the prospective decision-aiding trial with the 16 patients for whom secondary combinations were selected on the basis of in vitro test findings, the results showed a trend toward better outcome than was seen in the 43 patients who received empirical secondary therapy. Given the limited number of patients for whom in vitro results could be used, it is not surprising that this result was not statistically significant. In the future, if the authors assay fresh biopsy samples rather than cell lines, perhaps the number of patients with extensive SCLC, who could have the "in vitro best regimen" substituted for empirical primary therapy within a few weeks, could be increased significantly. This approach is justified by the overall poor survival outcome of most patients with extensive SCLC, a disease with known intrinsic chemosensitivity.

The study conducted by Von Hoff and his colleagues (6) has several important features. First, they used a modified cloning assay methodology (in capillary tubes) that provided sensitivity results for 71% of the patients biopsied. Second, they used a randomized clinical trial design, wherein patients were to be treated either with the clinician's empirical choice of a drug or with the best single drug selected based on in vitro sensitivity results. Finally, 133 patients were randomly assigned into this two-armed study.

Despite these positive design features, some problems remain. Von Hoff and associates (6) included patients with a heterogeneous variety of solid tumor types, with most having received prior chemotherapy. Although the randomized patient groups were reasonably well balanced for various factors, the mix of tumor types included many that are far less sensitive to anticancer drugs currently available than is SCLC. Additionally, whereas most of the patients who were randomly assigned to in vitro selected therapy had results available for potential use, various problems limited the actual number of patients who could be evaluated for treatment outcome. Only 55% of the 65 patients randomized to the clinician's choice could be evaluated for response. The rate was even poorer in the in vitro selection arm; only 28% of the 68 patients who were randomly assigned to drug selection by capillary cloning were suitable for evaluation.

Nonetheless, the results in those patients evaluated are interesting. The partial response rate of 21% was significantly higher in the patients who had their treatment selected based on in vitro assay than the abysmal 3% response rate for patients with empirically selected therapy. Von Hoff et al. (6) concluded that in vitro drug testing improved the response rate, but not the survival of advanced cancer patients. The lack of improvement in survival is not surprising, given the resistant and previously treated tumor types tested, the use of single-agent therapy, the occurrence of only partial responses in the responders, and the limited number

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of beneficial drugs available for many solid tumor types. In fact, although most of the patients had received prior therapy, two of the four responders to assay-selected therapy had not previously received chemotherapy.

What conclusions can be reached at this point? I can suggest a few. First, continued development of new anticancer drugs and use of in vitro testing methods are important scientifically. The difficulties in new drug development have long been obvious, and the difficulties in prospective in vitro testing are made clearer by these two papers. Second, in lieu of availability of novel drugs with differing mechanisms of action, in vitro testing (outside of the research sphere) currently has, at best, limited clinical value.

It is now well recognized that there are common mechanisms of drug resistance for many of the standard anticancer drugs (e.g., P-glycoprotein-mediated resistance to plant alkaloids and anti-tumor antibiotics). Tumor cells expressing the P-glycoprotein characteristically show in vitro drug resistance (8) and presumably clinical resistance as well. In the future, greater emphasis can be placed on the evaluation of new drugs in vitro on biopsy specimens from previously untreated patients, and in selected circumstances, research on the significance of such findings prospectively in the clinical sphere.

Both the experimental designs and the results of the studies by Gazdar’s and Von Hoff’s groups help place the field of in vitro sensitivity testing into sharper perspective and encourage further research, because both studies indicate that in vitro drug testing does offer promise for the future. However, as can be appreciated from the logistic difficulties practicing oncologists encounter in trying to apply drug assay results for patients with advanced cancer in these studies, we have a long way to go before we can consider that predictive drug testing will make a difference for many patients. On the other hand, it is also clear from these studies that use of empirical regimens for second-line therapy has very limited value for many forms of cancer. This finding provides strong support for oncologists entering their patients in clinical trials of new agents (including those selected by in vitro assay), rather than using cookbook second-line empirical drug regimens for patients with drug-resistant solid tumors.

References

(2) VON HOFF DD: Plating efficiencies of human tumors in capillaries versus petri dishes. In Human Tumor Cloning (Salmon SE, Trent JM, eds). Orlando, FL: Grune & Stratton, 1984, pp 153-161

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