Chemosensitivity Testing in Gynecologic Malignancies and Breast Cancer

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Chemosensitivity Testing in Gynecologic Malignancies and Breast Cancer

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Over the past four decades one or two new antineoplastic agents have become available to the clinician every other year. In tumors which are generally drug sensitive (lymphoma, leukemia, breast cancer, ovarian cancer), the number of potentially active agents often numbers more than a dozen. Potential 2-, 3- and 4-drug combinations usually exceed the number of active single agents severalfold. The choice of therapy outside a clinical trial is frequently semi-empiric and may be based on the clinician’s prior anecdotal experience or single clinical trials in small patient populations. As new compounds are developed, it becomes particularly difficult to evaluate these agents in drug-sensitive tumors since there is often a well-defined primary therapy as well as one or two active salvage regimens available. Thus, for many years the oncologist has wished for some in vitro assay with both a high positive and negative predictive value. Approximately 15 years ago Salmon and his group popularized the human tumor clonogenic assay (HTCA) as a method to more logically select cytotoxic drugs for individual patients. The problems with this approach are well known and have been reviewed extensively. In summary, the assay is rather labor intensive, it is technically feasible in only 20-50% of selected tumors, and is more efficient in terms of demonstrating drug resistance than drug sensitivity. Several clinical trials in which antineoplastic therapy was selected by HTCA or clinician choice have reached somewhat divergent conclusions. Nevertheless, there is overwhelming data that drugs with extreme resistance in vitro can be appropriately eliminated from the treatment regimen in a given patient. More recently, several assays evaluating total cell kill (HTCA evaluates cell
kill only in the clonogenic or proliferating faction) have been developed. These assays evaluate such parameters as exclusion of supravital dye, glucose utilization and cellular ATP concentration. Most of these more contemporary assays are reviewed in this text. In summary, these assays appear to have some significant advantages over the HTCA with regard to reproducibility, cost, evaluability rate, and sensitivity. To date, however, none of these assays have undergone prospective testing against clinician choice of drug therapy. Clearly, such prospective testing is necessary before there is any wider acceptance of such procedures in the guidance of chemotherapy selection. It is also important for us all to remember that drug-sensitive cells rarely kill the patient. Thus, the initial tumor response may not be a surrogate for cure. Efficient, cost-effective, and reliable assays may be just as important in selecting salvage therapy as in the selection of primary therapy. Perhaps the most valid test of in vitro analysis of drug sensitivity would be to select both primary and all salvage therapies either by clinician choice or by in vitro assay. Only such an approach will address the often-asked question as to whether or not such assays improve the most important patient outcome, survival. A study soon to be initiated by the Swiss Cancer Research Group will utilize the ATP-cell viability assay to select therapy for patients with ovarian cancer. Patients will randomize between clinician choice or one of six regimens chosen by in vitro assay. Since several drugs have activity in recurrent and refractory ovarian cancer, however, salvage therapy may also exert an impact on survival. Although one can never assume that tumor tissue will be available in the recurrent disease setting, it would seem appropriate that patients randomized to in vitro drug selection have that method utilized throughout the course of their illness, when possible. This textbook offers the clinical oncologist a broad overview of the topic of in vitro drug sensitivity testing. Whatever the bias of the clinician, it is recommended reading. As the array of drug and drug combinations increases and as patients and health-care providers alike demand a more efficient and cost-effective health-care system, it is likely that in vitro testing will play a larger role in cancer therapy as it has for years in the therapy of infectious disease.

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Introduction

The gynecologic oncologist is a specialist who provides comprehensive
treatment of patients with gynecologic cancer. In Europe, breast cancer is often
treated by the gynecologic oncologist, and therefore the management of breast
cancer is also reviewed in the first section of this book which gives an overview
of multimodality therapy in gynecologic oncology. Furthermore, overviews of
the currently used chemosensitivity test systems for gynecologic malignancies
and breast cancer, especially the very important in vitro and in vivo assays,
have been included.

Section two discusses each assay in detail: the clonogenic assay, short-term
assay, extreme drug resistance assay (taxol resistance and MDR-1 expression),
fluorescent cytoprint assay, MTT assay, DiSC assay, and in vivo test models;
the ATP-cell viability assay (ATP-CVA) is discussed in the third section. Also
included in the second section are a summary of the assessment of the
synergistic and antagonistic effects of chemotherapeutic agents in vitro, and the
clinical correlations for cell culture assays based on the concept of total tumor
cell kill.

In the last 5 years interest in the ATP-CVA has been growing both in the
USA and in Europe, and section three is devoted to discussing this technique.
The ATP-CVA has been used to study the in vitro response of cell lines and
fresh gynecologic human tumors, including breast carcinoma, to a variety of
antineoplastic compounds such as chemotherapeutic agents, hormones and
biological response modifiers. The assay has been further adapted to test the
effects of radiation therapy on cell lines in vitro. The methodology of the ATPCVA
is illustrated in detail, including use of the assay for the in vitro/in vivo
correlation of xenografts in nude mice. The chapters that follow summarize

the ATP-CVA and its different applications: review of cell line data of
gynecologic malignancies and breast cancer, evaluation of new drugs in gynecologic
oncology, assessment of the response of in vitro radiation therapy in
gynecologic cancer cell lines, and assessment of biologic response modifiers in
gynecologic cancer cells.

The book ends with a summary of the results of chemosensitivity testing of
fresh specimens from gynecologic malignancies and breast carcinomas, and
discusses the future directions of chemosensitivity testing.

The editors have tried to ensure that the contents of this book are correct;
however, the final responsibility lies with the authors. We would also like to
thank each of them for making possible this 19th Volume of 'Contributions to
Gynecology and Obstetrics', and for their valuable research in the field of
oncology. It is our hope that this work will provide constructive insights and
guidelines for basic researchers and physicians dealing with cancer patients.

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