RECENT ADVANCES IN

CLINICAL ONCOLOGY

Edited by C.J. Williams and J.M.A. Whitehouse

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C. J. WILLIAMS
J. M. A. WHITEHOUSE

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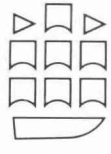

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Preface

Few advances in medicine arrive in a spectacular fashion. Where real progress can be identified it is often after many years gestation and the result of combining different resources and different skills.

Those remote from specialist cancer practice tend to assess the therapy of cancer rather loosely by the 'cure rate'. This is an unsatisfactory assessment when applied to medicine as a whole but even more so when applied to cancer. However, when one reflects on the number of drugs screened for anticancer activity since the 1940s and the small number in clinical practice today it is not entirely surprising that using such crude criteria some feel the impact of chemotherapy to have been rather limited. In fact the opposite is true. The limitations of local therapy — either surgery or radiotherapy — when applied with curative intent are readily apparent against the background of cancer as a whole. Indeed, prior to the development of anticancer drugs those patients who either failed local therapy or presented with disease too advanced for local treatment to be relevant were largely abandoned. It is the distorted historical perspective of those times which still influences the thinking of the lay public where cancer is concerned. Chemotherapy, without necessarily guaranteeing cure has radically and to an immense degree altered the approach to managing those patients who previously might have been abandoned because their disease was no longer amenable to local treatment. Furthermore, since many patients have failed local therapy despite apparently localised disease the whole approach to these patients has come under careful scrutiny. Early clinical trials have been replaced by sophisticated studies which monitor the change in natural history of a particular neoplasm induced by a specific therapy. Improvements in histopathological methods in immunological techniques and electronmicroscopy have led to the identification of subtypes of cancers which were previously regarded as a single entity. The cell and molecular biologists are using sophisticated technology to examine the mechanism of neoplastic change. The pharmacology and metabolism of each drug, previously ignored, have now been largely documented. Developments are not solely confined to basic sciences. The realisation that a significant impact can now be made on many varieties of cancer resulting in improved survival and an improvement in quality of life has stimulated integration of different disciplines. The surgeon's expertise — no longer confined to simple tumour excision but an essential for definitive tumour staging — has combined with that of modern radiotherapists and now with the specialist cancer physician to ensure optimum therapy while maintaining a critical attitude to the consequences of their decisions. Included too in this clinical evolution has been the specialisation of nursing care thus ensuring comprehensive support for the patient, both within the hospital complex, and within his home environment.

The purpose of this book is not only to examine the 'state of the art' but also for

those with particular clinical or basic research interests in promising fields to present their work within the context of the whole. It is far beyond the scope of this exercise to cover the field in breadth and depth; we have therefore sought to identify areas of particular interest to stimulate and inform the practising clinician and also to give some insight into potential future developments.

Southampton, 1982

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SECTION 1

New approaches and drugs in the management of cancer

1. In vitro evaluation of anticancer drugs with the human tumour stem cell assay

S. E. Salmon D. D. Von Hoff C. J. Williams

Development of new and effective anticancer drugs has been a very difficult and time-consuming procedure. The process, which initiates from rational design, serendipitous discovery or random screening using a few signal mouse tumours, has probably missed a number of compounds which were inactive in L1210 or P388 leukaemia, but would have had activity against other tumour types. Even a broadened panel of 5–6 transplantable mouse tumours of different histopathologies would be the conceptual equivalent of testing a new drug on 5–6 patients, each with a different type of cancer. Viewed from this perspective, it is perhaps surprising that useful drugs have been identified! In fact, many drugs have been identified through other mechanisms in various countries. After a new drug is found to be active in screening, it must pass preclinical and clinical toxicology studies before it can be brought into large scale clinical Phase II and Phase III studies in various tumour types. The recent development of *in vitro* soft agar colony assays for putative human tumour stem cells now shows significant promise of shortening and simplifying new drug development including preclinical drug screening for active compounds, clinical trials of new agents, and the final selection of treatment for individual patients. In this paper we have provided an updated evaluation (as of May 1980) of studies by various investigators using the in vitro clonogenic assay for human tumour cells. A more detailed description of clonogenic assay methods for human tumours has recently been published in book form (Salmon, 1980).

METHODS

Detailed descriptions of the methods of cell culture and measurement of drug sensitivity have been reported previously (Hamburger et al, 1978; Salmon et al, 1978; Salmon et al, 1980). In brief, a single cell suspension is prepared from the fresh tumour biopsy using mechanical dissociation techniques or from malignant effusions or bone marrow containing tumour cells. Several groups (Pavelic et al, 1980; Rosenblum et al, 1980; Pavelic et al, 1980) have recently reported on the use of enzymes together with mechanical dissociation in an attempt to increase the yield of viable cells per unit weight of tumour. Further comparative studies comparing techniques are required to define the best method of obtaining the maximum number of viable cells in single cell suspension. Specific methods may be required for individual tumour types and Pavelic et al (1980) have shown that an enzymatic method worked well in melanoma and sarcoma but produced lower viability in pulmonary carcinoma when compared to mechanical dissociation. Cells are viable and have been shown to form colonies after preservation in liquid nitrogen for up to one and a half years.

Aliquots of cells are exposed for 1 hour at 37°C to at least 2 concentrations of each of a series of 6–10 anticancer drugs. Drugs are studied in vitro only at low concentrations generally ranging up to 1.0 ug/ml, with emphasis on concentration-time exposures (CxT) which are in a range which would be pharmacologically achievable in vitro. Dose-finding studies for new agents on which pharmacokinetic data are not available are carried out over a 3 log concentration range from 0.1 to 10 ug/ml. Subsequently, the cells are washed twice by centrifugation, and suspended at a concentration of 500 000 cells per ml in an enriched tissue culture medium containing 0.3 per cent molten agar. One ml of this mixture is plated in one 35 mm plastic Petri dish on top of a 0.5 per cent agar feeder layer containing various nutrients and growth stimulants. All drug assay points are plated in triplicate, incubated at 37°C in a humidified CO_2 incubator for 1–3 weeks, evaluated serially by inverted phase microscopy and counted when a sufficient number of colonies (consisting of $>$ 30 cells) develop to permit measurement of a 1–2 log reduction in survival of colony-forming units.

Elson et al (1980) have recently reported on a method using autoradiography of colonies plucked from the agar to measure depression of the labelling index. Untreated control colonies had a labelling index of 70 per cent on days 4 through to 6. Following exposure to drugs the labelling index depression seemed to correlate well with colony growth inhibition (colony count at 10–14 days).

Labelling methods may have the advantage of requiring fewer cells and do not require many colonies to produce a result. However, the technique is cumbersome and further correlation with results obtained by colony growth inhibition in human tumours are needed. Alternatively, sophisticated automated colony counters have been devised which may also be able to identify colonies in standard plates much earlier than at present (Kressner et al, 1980), and have the advantage of providing a type of serial non-destructive testing of the cultures.

Representative plates, after colony counting, are prepared for morphologic analysis using the recently described slide technique with Papanicolaou staining (Salmon & Buick, 1979). Criteria for in vitro sensitivity for the individual standard drugs are based on calculation of the area under linear survival-concentration curves and ranking relative areas based on an initial training set of patients who were studied in vitro and with in vivo clinical trials (Salmon et al, 1978). For new drugs wherein pharmacologic parameters are less certain, we use an operational definition of sensitivity of at least 70 per cent reduction in survival of ovarian tumour colony-forming cells at a relatively low dose of the drug. This is based on our overall experience to date, and is analogous to the types of curves seen with standard drugs that meet our quantitative sensitivity index criteria using an 'area under the curve' technique (Salmon et al, 1978). In all instances, wherein pharmacokinetic data were available, the doses to achieve at least 70 per cent reduction in survival of tumour colony forming units (T-CFU's) had to be less than the maximally achievable concentration-time product in vivo. Patients for whom clinical correlations were made in relation to in vitro sensitivity had to achieve at least 50 per cent tumour regression (a partial remission) to be considered clinically sensitive to the agent tested in vitro. Drugs requiring metabolic activation in vivo were not studied. Melphalan served as the standard in vitro index alkylating agent for clinical trials (Salmon et al, 1980). Clinical trials for correlation were carried out with single agents or simple two-drug combinations of the index agents studied in vitro (Salmon et al, 1980). Techniques