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Editorial

Cancer Chemotherapy as it Approaches Middle Age

Stephen K. Carter

Northern California Cancer Program,
1801 Page Mill Rd, Bldg. B, Suite 200, Palo Alto, California 94304, USA

Cancer chemotherapy is now an established methodology of cancer treatment. It was only a little more than a decade ago that many still questioned whether drug treatment would ever take an equal place with surgery and radiation as a weapon in the armamentarium of the clinical oncologist. For many years the cancer chemotherapist (soon to become, in many cases, the medical oncologist) would have to publicize his modality through emphasis on its oncologic accomplishments in tumors such as choriocarcinoma, Burkitt's tumor, childhood leukemia, malignant lymphomas, and childhood solid tumors. At the same time the chemotherapist would have to keep up his defences against attacks on the toxicities of his drugs, which would sometimes be derisively labeled 'poisons'.

It is now nearly thirty-five years since the discovery of nitrogen mustard and the list of established active anticancer drugs is impressive [1]. Drug development programs are increasing in number and scope. Combination chemotherapy is now utilized in a wide range of human malignancies. The concepts of combined modality treatment, although not new, are now being widely applied in investigational studies. Immunotherapy is now the newest modality being hailed as meaningfully active. While this new therapeutic approach attempts to validate and establish itself, cancer chemotherapy now settles back into the comfortable role of a full member of the club which now will carefully scrutinize the credentials of any new application for admittance.

As cancer chemotherapy leaves its youthful decades and enters into the maturity of early middle age, it is time to reflect on what has been accomplished and what the future directions need to be. Success brings with it new responsibilities and new problems which require a reevaluation of previously utilized concepts and techniques. For example drug development programs now have to establish a balance between searching for new structures and analogue development. Analogue searching requires different model sytems and different strategies of evaluation as compared to new drug screening. The toxicity aspect of the therapeutic ratio is now receiving increasing emphasis in analogue development as therapeutic success has brought to the fore chronic toxicity as a major factor.

The clinical evaluation of new drugs is now fraught with increasing difficulty, as there are established regimens for so many tumors which previously were virgin territory for the exploration of new drugs [2]. New drug testing must integrate itself into the disease-oriented strategies which now rightfully dominate as the multidisciplinary team approach is utilized in most cancer centers. The most responsive tumors to drugs are now closed to new drug evaluation until extensive prior combination chemotherapy has been shown to be of no further value to the patient. The expectations for activity in these tumors is also now considerably higher, thus requiring a new drug to show a high response rate in far advanced patients to be called 'active'. Drug development programs are switching their emphasis toward the more unresponsive solid tumors, recognizing the critical need for new drugs with activity in lung cancer, gastrointestinal cancer, genitourinary cancer, gynecologic cancer, head and neck cancer, melanomas, and sarcomas. These tumors require new experimental models and many candidates are now under active investigation. One of the difficulties is that drug development is not a rapid process, and, therefore, it will take many years before new experimental models can be clinically validated. Much work needs to be done in the development of strategies for validating new experimental models which needs to be a balance of retrospective analysis of data with known actives and inactives and prospective clinical study. Currently the heterotransplantation models are receiving increasing emphasis. These models are expensive and complex but offer the possibility of solid tumor prediction beyond that achieved with cur-

Reprint requests should be addressed to: S. K. Carter

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rent transplantation models. What is the strategy for validating the predictive ability of these models? While many meetings are held on the methodology of the models per se, few, if any, are held on the methodology of validation. This is one of many crucial areas where the experimentalist and the clinician have to develop a continuing dialogue and close interrelationship.

Combination chemotherapy has been the key to most of the major triumphs for drug treatment. It has been the combining of active single agents which has led to significant long term disease-free remission in childhood leukemia, Hodgkin's disease, diffuse histiocytic lymphoma, and testicular carcinoma. In addition a high percentage of remissions with resultant survival prolongation can now be achieved with combinations in diseases such as breast cancer, small cell anaplastic lung cancer, soft tissue and bone sarcomas, adult leukemia and multiple myeloma, with active investigation ongoing in many others. These combinations have been developed predominantly through the process of rational empiricism. While much work has been done testing drug combinations in transplantable rodent tumors, no system with established predictability has been illuminated. The MOPP combination, vincristine plus prednisone, the CVP combination, velban plus bleomycin, and most others were not tested because an experimental tumor predicted they would be synergistic. They were put together empirically since they were active as single agents, had apparent differing mechanisms of actions, and did not have totally overlapping toxicity patterns.

Not only has the choice of drugs for successful combination been mainly empirical but so has the critical variables of sequence, schedule, and ratio. When one contemplates how many ways there are to combine four drugs in regard to their ratios to each other and their own maximally tolerated dose levels, all integrated with their schedules and sequences, it becomes a sobering thought as to why one integration has been chosen and thousands of others excluded. When it is also remembered that the clinical pharmacology of most drug combinations has not been elucidated, then the empiricism becomes even more apparent. The rational empiricism of the experienced clinical investigator has achieved much and should not be denigrated. What are needed are better experimental models for predicting how to combine drugs more effectively and the development of comparative pharmacology approaches which will help us to put drugs together in such a way as to maximize the potential for synergistic effect and minimize the choice of a negative interaction. This is another area in which the experimentalist, pharmacologist, and clinician need to develop a continuing dialogue and interchange.

Combination chemotherapy has other impacts which relate again to drug development. New drugs need to be able to combine easily with other compounds if they are to be ultimately successful, barring of course the unlikely (in the short-term) development of a 'magic bullet' breakthrough. The acute toxicity patterns are of great import, and drugs which are not myelosuppressive are desired by all clinicians so as to be able to utilize them at full therapeutic dose levels in combination. Combination chemotherapy makes analogue clinical evaluation quite difficult. How is one to test a new vinca alkaloid in malignant lymphomas or childhood leukemia? How can one test a new thiopurine or antifole in childhood leukemia, or a new analogue of arabinosyl cytosine in adult leukemia. As a general rule the more successful the combination in a given tumor, the more difficult it will be to evaluate an analogue of one of the component drugs clinically in that same tumor.

The combined modality approach is now one of the major investigative approaches in clinical oncology. After initial successes in the pediatric solid tumors such as Wilms' tumor, Ewing's tumor, and embryonal rhabdomyosarcoma, the emphasis has now switched to the adult solid tumors. It is hoped that chemotherapy will be successful in eradicating the microscopic residual tumor cell burden after surgery and/or radiation therapy have ablated the primary tumor. The basic concepts of the cell kill hypothesis plus a wide range of experimental tumor studies lead investigators to hope that drugs which can give objective regression of metastatic disease will be able to give total cell kill of micro foci which should theoretically have more favorable kinetic patterns coinciding with their comparatively smaller cell numbers.

Preliminary results in breast cancer and osteogenic sarcoma have stimulated a great deal of enthusiasm that this approach would have a great impact on end-results in these tumors [3, 4]. As further analysis of these studies has taken place, the positivity has diminished and the cautions of the authors in their original papers as to the preliminary nature of their data have been shown to be valid [5, 6]. Unfortunately the cautions were not always heeded, and so there is a sense of disappointment in some quarters, although the studies still remain positive and clearly establish that we are on the right track. It is clear, however, that the immediate impact will not be as great as once had been hoped. It appears that we will need a greater degree of activity for our drugs in advanced disease than was previously thought, to achieve the desired cell kill in the adjuvant situation [7]. The possibility also exists that the exponentially growing rodent transplant models are not predicting accurately and that the kinetics of the residual tumor cell burden after surgery may not be as favorable as had been thought. The recent work of Norton and Simon at the NCI [8] indicates that a small tumor with a high growth fraction may not be as sensitive to a given cell kill dose

as an intermediate size tumor where the growth rate is maximal. The implications of this, if true, would be to increase the intensity of initial therapy after surgery and to utilize late intensification approaches after the induction of complete remission in advanced disease.

What has also been learned to date in adjuvant chemotherapy studies is that the analysis will have to be a long-term proposition. The initial phase of analysis will involve relapse rates and acute toxicity but the final story will be told by survival and chronic toxicity. Too great an emphasis on early relapse rate analysis can lead to a premature optimism. This problem is acutely enhanced if historical controls are used. We need further study of the use of actuarial techniques for relapse rate plotting so as to delineate when we can feel secure that the predictions will be validated by long-term follow-up. It is clear from the studies in breast cancer and osteosarcoma that as patients have been followed up for longer periods of time early curves which were highly positive have become less so.

Another aspect of adjuvant chemotherapy studies that requires emphasis is the point that some patients are being treated who have been cured by their surgery and/or radiation. We therefore have to become concerned about chronic organ site toxicity and carcinogenesis as points of analysis. There is new evidence that drugs such as adriamycin give subclinical cardiac damage in nearly all patients who receive moderate total doses in excess of 200 mg/m^2 [9]. In the adjuvant usage of the drug we have to develop techniques of analysis to search for diminishment of cardiac function five years later in the treated group as compared to the control groups. The same holds for the pulmonary toxicities of bleomycin, the renal toxicity of cis-platinum diammine dichloride, and the chronic toxicities of many other drugs. Carcinogenicity is a biological property of most of the active anticancer drugs [10]. As we analyze adjuvant studies we must develop techniques to analyze the occurrence of second tumors and to attempt to delineate those possibly due to adjuvant drug therapy as against those due to the increased propensity for individuals with cancer to develop a second malignancy. Until we have this information we will not be able to establish how active an adjuvant regimen is. It should not be forgotten, however, that concerns about chronic toxicity and carcinogenesis are manifestations of how successful chemotherapy has become. It is only because we expect patients to live so long after drug treatment that we need to raise these concerns. Chemotherapists should no longer cringe at the thought of discussing long-term complications. The radiation oncologist and surgical oncologist have been more comfortable in this area for years since they have confidence in the curative potential of their modality. It is time for medical oncology to do the same.

The combined modality approach is still another area where greater help is required from experimental studies. The questions which need answering are not only what drugs should be chosen for adjuvant study, but on what schedule, at what dose level, for what duration. When combination chemotherapy is used in the adjuvant situation the complexity goes up exponentially. To date all adjuvant regimens have been chosen empirically as to their components, their schedules, their durations, etc. When drugs and radiation are combined there is the question of potentiation as well as adjuvant cell kill which must be taken into consideration. Models need to be developed which can predict for how to use drugs and radiation, drugs and surgery, drugs and surgery plus radiation. How to validate their predictive ability is a thought for contemplation on long winter nights.

Cancer chemotherapy has made great strides. The vision of its pioneers has been proven correct. Those who developed the field in its initial years have much to be proud of. When a new area is explored everything is exciting. The risks are great, but the success may be dramatic. As an area is settled the work of consolidation begins. It is less exciting but nonetheless important. A balance begins to be established between new exploration and increased understanding. A country newly discovered has only explorers but few developers and no historians. With age the country continues to develop, but does so out of the perspective of its history and a deeper understanding of its origins and precepts. History and its perspectives do not foreclose the possibility of new breakthroughs and discoveries. Cancer chemotherapy will have many exciting new developments. Some will come out of refinements of existing knowledge. Others will come out of new conceptual breakthroughs which may make the old concepts obsolete. It is our hope that this new journal, Cancer Chemotherapy and Pharmacology, will be an important new tool of communication in this exciting area.

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