Edited by
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Chemotherapy I

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Preface

The International Society of Chemotherapy meets every two years to review progress in chemotherapy of infections and of malignant disease. Each meeting gets larger to encompass the extension of chemotherapy into new areas. In some instances, expansion has been rapid, for example in cephalosporins, penicillins and combination chemotherapy of cancer - in others slow, as in the field of parasitology. New problems of resistance and untoward effects arise; reduction of host toxicity without loss of antitumour activity by new substances occupies wide attention. The improved results with cancer chemotherapy, especially in leukaemias, are leading to a greater prevalence of severe infection in patients so treated, pharmacokinetics of drugs in normal and diseased subjects is receiving increasing attention along with related problems of bioavailability and interactions between drugs. Meanwhile the attack on some of the major bacterial infections, such as gonorrhoea and tuberculosis, which were among the first infections to feel the impact of chemotherapy, still continue to be major world problems and are now under attack with new agents and new methods.

From this wide field and the 1,000 papers read at the Congress we have produced Proceedings which reflect the variety and vigour of research in this important field of medicine. It was not possible to include all of the papers presented at the Congress but we have attempted to include most aspects of current progress in chemotherapy.

We thank the authors of these communications for their cooperation in enabling the Proceedings to be available at the earliest possible date. The method of preparation does not allow for uniformity of typefaces and presentation of the material and we hope that the blemishes of language and typographical errors do not detract from the understanding of the reader and the importance of the Proceedings.

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ADVANCES IN CANCER CHEMOTHERAPY

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INTRODUCTION

Like all therapeutics, cancer chemotherapy began as a largely emperical effort with a major emphasis on the interplay between serendipity and screening. The first major point I would like to make in this presentation is that a scientific base for cancer chemotherapy and for the construction of clinical trials has developed rapidly in the past five to 15 years. Basic research on the nature of the neoplastic cell has provided an increasing number of leads with respect to therapeutic targets exploitable by chemotherapy and immunotherapy (Fig. 1). The sciences of pharmacology and its subsets and of cytokinetics and biostatistics, which some refer to as "bridging sciences", now impinge daily and importantly on the development and application of chemotherapeutic programs to man (Fig. 1). I would like to cite one important recent example that relates to structure activity studies.

Drug Development. One of the most important classes of antitumor agents are the anthracyclines (Fig. 2)(1). Adriamycin was introduced into the clinic four years ago and has substantial antitumor activity, not only in the hematologic neoplasms, but also in carcinomas and sarcomas (2). Adriamycin has a substantially superior therapeutic index in experimental systems and in man as compared to daunorubicin. Since the difference between these two compounds relates only to substitution on the 14 carbon further manipulation of this position seemed rational. The amino group of the aminosugar (Fig. 2) has been proposed, on the

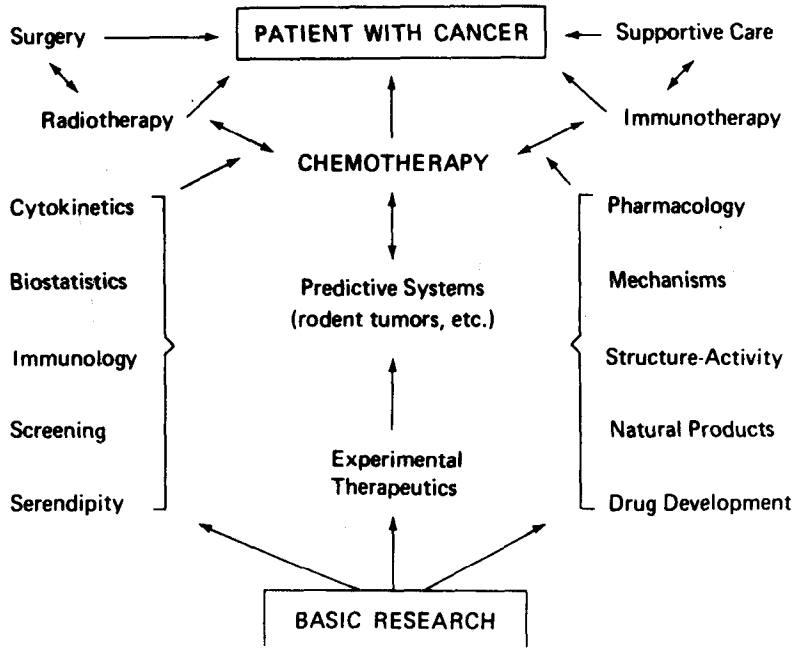

FIGURE 1
Chemotherapy: Relation to Clinical and basic disiplines.

basis of biochemical and by x-ray diffraction studies, to anchor the tetracycline portion of the molecule which intercalates between nucleotide base pairs in DNA to the phosphodiester exoskeleton of the DNA molecule (3). Hence manipulation of the amino group was also studied. Systematic substitutions in both of these positions led to the development of a compound known as AD 32, which has a 5 carbon ester substituted in the 14 position and in which the positive charge of the amino group in the amino sugar is reduced by a trifluoroacetyl substitution. At optimal that is, at equitoxic doses, AD 32 is superior to adriamycin with respect to both increasing the life span and curing the tumor bearing animals (Fig. 3). While these results remain to be confirmed, they provide an example of a rational, semiempirical approach to the development of a new compound.

Multimodality Therapy (Adjuvant Chemotherapy). The second major point I would like to make relates to multimodality treatment of cancer with particular emphasis on

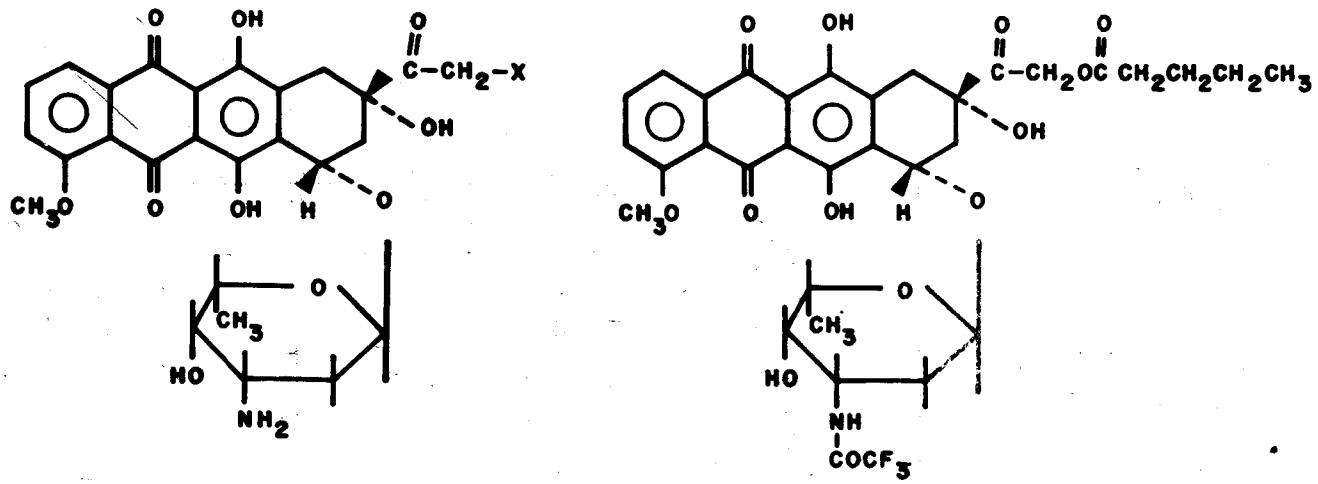

FIGURE 2

Structural relationship between daunorubicin, adriamycin and AD 32

Mouse Leukemia	Drug	Optimal Dose mg/kg/day, ip days 1-4	Increase in Median Life Span (%)	"Cure"*
L1210	Adriamycin	4	45	0/5
	AD 32	60	445+	4/5
P388	Adriamycin	4	132	0/6
	AD 32	40	429	4/5

*"Cure" = 30 day tumor-free survivors, expressed as a fraction of surviving/treated leukemic mice

FIGURE 3
Effect of Adriamycin Analog N-Trifluoroacetyl-l4-Valerate (SFCC AD 32) on Experimental Leukemias.

DISEASE	SCHEMA PRIMARY	CONTROL OF PRIMARY ACHIEVED WITH	SYSTEMIC METASTASES (MICROSCOPIC)		SYSTEMIC (ADJUVANT) CHEMOTHERAPY
			%	LOCATION	
Breast Cancer Stage II		Surg. + XRT	70	Liver, Lung, Bones	Designed to eradicate microscopic disease
Osteosarcoma		Amputation	90	Lungs	

FIGURE 4
Adjuvant Chemotherapy

the concept of adjuvant chemotherapy, that is, chemotherapy employed immediately following primary treatment with surgery and/or radiotherapy (Fig. 4). For examples of adjuvant chemotherapy I will employ osteogenic sarcoma and Stage II breast cancer. In both of these diseases the primary can usually be totally eradicated by surgery and/or radiotherapy. Unfortunately, at the time that such treatment is applied approximately 70% of patients with Stage II breast cancer have blood borne microscopic metastases usually in the lungs, liver and/or bones. For patients with osteogenic sarcoma, the respective figure is 90%, and such microscopic metastases are present almost exclusively in the lungs. The classical approach has been to hope that a given patient was in the 10 or 30% of patients who did not have blood borne metastases and, therefore, to wait. The approach that I am about to present involves the use of systemic treatment or adjuvant treatment with chemotherapy, immunotherapy or both in an effort to eradicate microscopic metastases.

There is strong experimental basis for such studies. These are presented in abbreviated form in Fig. 5. First, it has been known since the studies of Goldin and thoroughly quantified in recent years by Schabel that, for any given effective treatment, microscopic tumor in rodents can frequently be cured whereas the same tumor allowed to advance until it is grossly evident, may undergo transient regression only (4). The number of tumor cells in a patient with microscopic disease, is estimated to be less than 10^9 whereas for overt metastases greater than $5x10^9$ cells must be present (5). In homogeneous in vivo experimental systems it has been demonstrated that destruction of tumor cells by chemotherapy follows first order kinetics (4). Thus, it is the fractional reduction of tumor cells by a given treatment rather than the absolute reduction that tends to be constant. Because of this, exponential considerations become paramount, and it is evident that a given treatment has a far greater likelihood of destroying, for example, 10^5 as compared to 10^{10} neoplastic cells. Employing sophisticated cytokinetic studies, it has been demonstrated that as tumors increase in size, the growth fraction, that is the proportion of cells in mitotic cycle decreases (4). It has been demonstrated that cells not in cycle are not necessarily end stage cells and may re-enter cycle when transplanted into syngeneic rodent systems. Since almost all of our drugs have varingly greater potency against cycling as compared to noncycling cells, the high growth fraction for microscopic tumor makes such tumor much more vulnerable to chemotherapeutic attack. Recent in vivo studies indicate

	Disseminated Metastases	
	Microscopic	Overt (bulk)
Transplanted tumor response to chemo.	Frequency cured	Rarely cured
No. of tumor cells First order Kinetics	$<10^9$ (ca I Gm)	$>5 \times 10^9$
Growth Fraction	>90%	<10%
Drug membrane active transport	3-4+	0-1+
pO_2	Normal	↓
Vascular supply	Adequate	Compromised
Competing metabolites	0	?+

FIGURE 5 : Experimental Data Supporting Adjuvant Chemotherapy.

that as a generality, cycling cells have a substantially greater capacity for drug transport than noncycling cells though this may relate simply to the fact that cycling cells are larger and therefore have a larger surface area (5). While the blood supply of microscopic metastases is presumably normal it is frequently comromised in patients with overt metastases and many of the above factors may relate to this compromised blood supply (6). Finally, competing metabolites derived from marginally viable tumor in the center of bulk metastases may prevent antimetabolite effect. In short, experimental models and experimental studies derived from basic and bridging sciences along with well conceived and designed clinical experiments provide a sound basis for the adjuvant approach.

Within the past three years two treatment programs, one involving high dose methotrexate followed by citrovorum rescue and the other, adriamycin, have been shown to be capable of producing tumor regression in 30-50% of patients with advanced metastatic osteosarcoma (7-9). Because of this, starting two to four years ago such treatment was applied in the adjuvant situation, that is immediately following amputation which is usually used to control the primary lesion (10, see references). In the historical control group at the Farber Center and in other

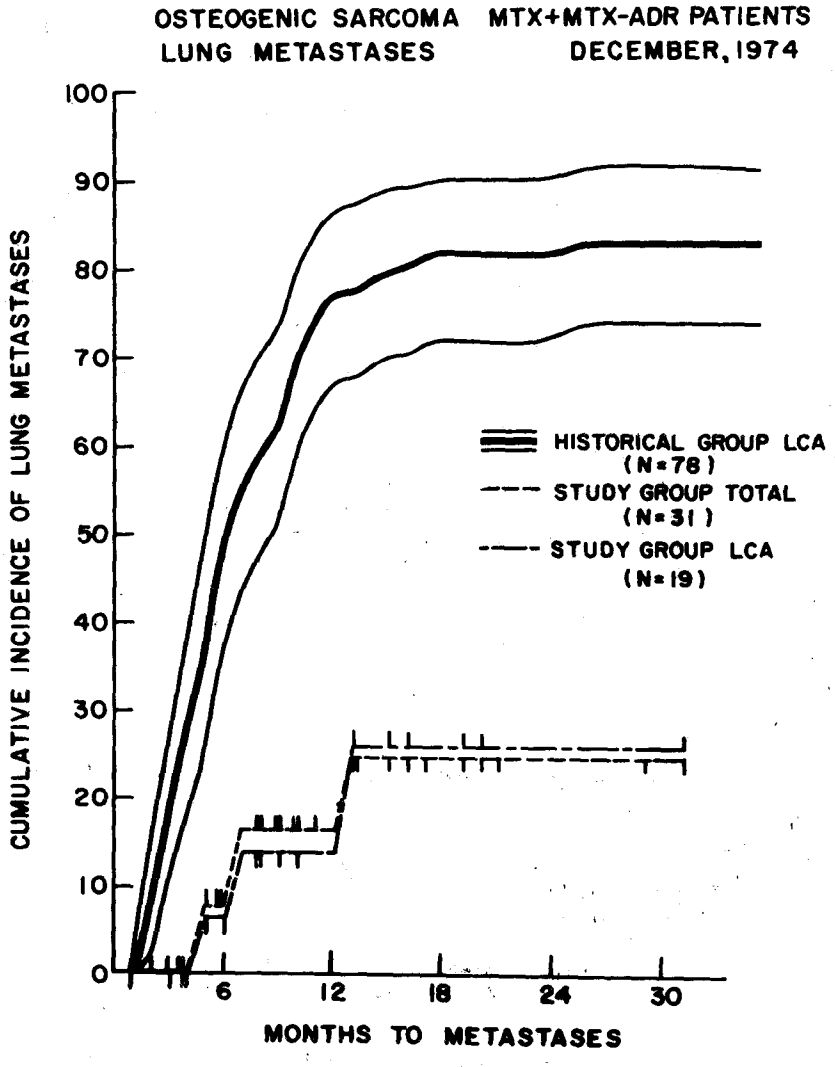

FIGURE 6 : Pulmonary Metastases in Historical and Study Groups (Adapted from Jaffe, et al)

centers such as Memorial-SKI, tumors appear in the lungs after local control has been achieved (Fig. 6). Thus, by six months over 50% have pulmonary metastases and by 12 months 80% of patients have developed pulmonary metastases.

Thus 80 to 90% of patients eventually die of pulmonary metastases. Most of the 10-20% of patients who remain free of metastases at 12 months remain so thereafter and are cured. Our adjuvant treatment program started three years ago. The rate of relapse during the first year was significantly reduced and, as with the controls, relapses did not occur after 12 months though the number of patients was small (Fig 6). In more recent studies employing more advanced principles of combination chemotherapy it has been observed that Mtx-CF rescue combined with adriamycin has reduced the proportion of patients relapsing during the first year in two series to less than 10%. The crucial question in any such study is whether such treatment has simply delayed the development of relapse by suppressing but not eradicating metastases. If such were the case, overt metastases would continue to appear particularly after cessation of adjuvant treatment. There was evidence from other Centers as well that metastases, if they occurred, tended to occur early and not after 12 months. Patient data from the major Centers employing adjuvant chemotherapy for osteogenic sarcoma was collected and pooled and the relapse after 12 months for those patients who were relapse free 12 months after the initiation of adjuvant treatment was plotted (Fig 7).

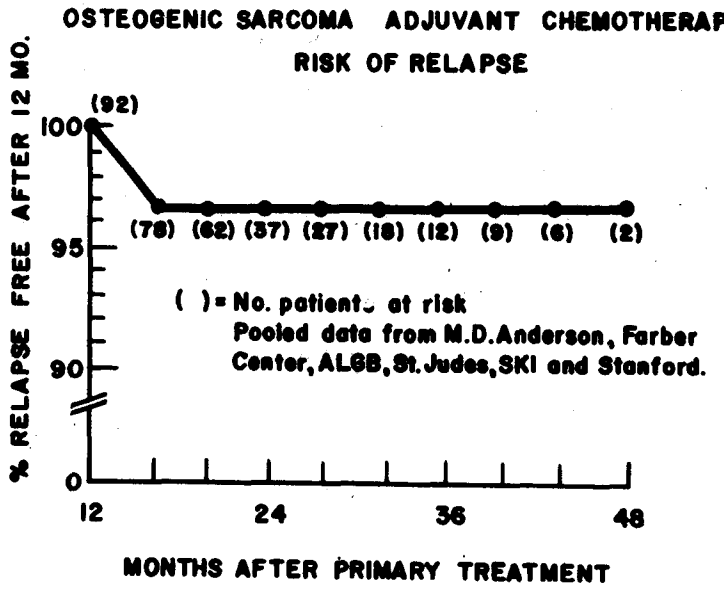

FIGURE 7

From studies at these institutes, 55-95% of patients by life table plot were free of metastases at 12 months and the number at risk falls off progressively up to a total of four years. Two patients relapsed in the 13th month after which there were no further relapse. This curve after 12 months was the same whether the adjuvant treatment was given for a total of only six months following amputation or for as long as 24 months. It thus seems increasingly probable that microscopic metastases in these patients are indeed eradicated and that a substantial increase in cure rate has probably been achieved.

These chemotherapeutic advances in osteogenic sarcoma have lead to preliminary studies involving treatment of the primary. Thus, in selected patients, chemotherapy is initiated prior to operation and depending upon the site of the primary and the degree of reduction in size as the result of chemotherapy, a segment of bone sometimes including a joint is removed and replaced by a titanium prosthesis. The effectiveness of such an approach to controlling the primary and the function of the preserved extremity will require more extended follow-up.

These observations in osteosarcoma have also been demonstrated for Wilm's tumor, Ewing's sarcoma, embryonal rhabdomyosarcoma and Stage IIIB Hodgkin's disease (10, see references). However, these are relatively rare diseases.

Breast cancer is the most common tumor in women and as already indicated (Fig. 4) patients with Stage II breast cancer have a 70% chance of having blood borne metastases as evidenced by recurrent overt metastatic disease. In contrast to osteogenic sarcoma breast cancer is kinetically less active. Thus, some 30-40% of patients will demonstrate metastases by two years, a total of 60% by 5 years and the risk of metastases after 5 years continue so that by 10 years as many at 70% of patients may manifest metastases. There are a number of agents, particularly combinations of chemotherapeutic agents which are capable of producing tumor regression in patients with established overt metastatic disease. Accordingly, adjuvant chemotherapy studies have been undertaken.

A number of institutes collaborated in the comparative study schematically presented in Fig. 8 (11). Following primary treatment with surgery all patients with Stage II disease were randomly allocated to the drug or to placebo. The alkylating agent, L-phenylalanine mustard, or L-PAM was chosen for the initial adjuvant study because it has significant activity against advanced disease and because