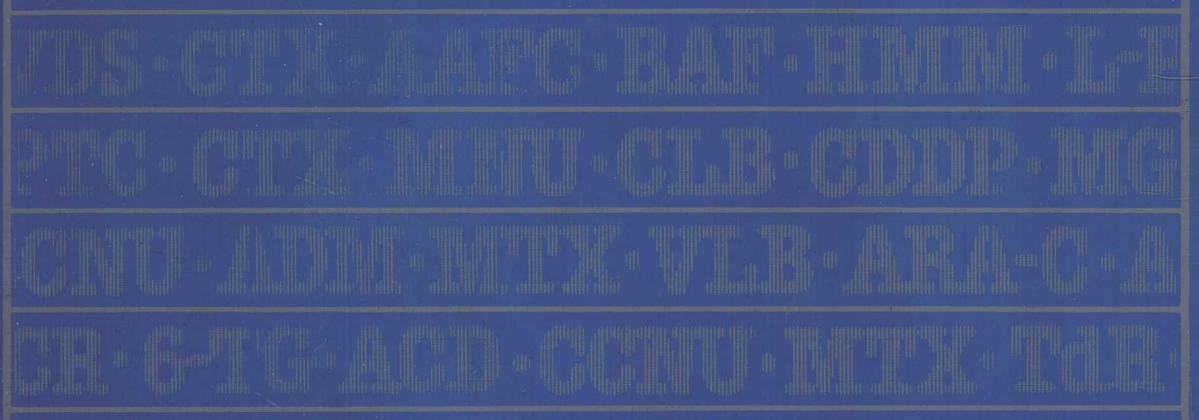
CANCER CHEMOTHERAPY/8

The EORTC Cancer Chemotherapy Annual



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The EORTC Cancer Chemotherapy Annual

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Introduction

H.M. Pinedo and B.A. Chabner

During the past year further progress has been made in the treatment of cancer with chemotherapy. In this introduction we will focus on a few of these important advances, some of them discussed in the first part of the book, which is dedicated to the various drugs, and some of them in the second, tumor-orientated part.

Biochemical modulation has been an important topic in cancer research for a considerable time. For years attempts have been made to translate preclinical examples of biochemical modulation into the clinic, and some encouraging results have been achieved. Leucovorin has been shown to increase the binding of 5-fluorouracil to thymidilate synthase resulting in an enhancement of the antitumor effect in murine tumors. Recent data indicate that leucovorin also enhances the antitumor effects of 5-fluorouracil in patients with increased response rates.

The growing knowledge on drug resistance, in particular resistance to doxorubicin, is reflected in the incorporation of a chapter by Fine on 'Multidrug resistance', a very valuable addition to the Annual. The author gives an excellent update of the knowledge on this most relevant topic and reviews key papers on multidrug resistance (MDR) published in 1985. Aspects covered are: (a) cell biology of MDR, including studies on drug accumulation, reversal of MDR, and the role of calcium and calmodulin, (b) markers found in the MDR cell, and (c) the genetics and molecular biology of MDR. Research is now also ongoing on resistance to other drugs, such as cisplatin.

Perhaps at the moment the clinically most relevant data in the fi eld of analog development are those on carboplatin, the most promising analog of cisplatin. This derivative is showing good antitumor activity and has been proven most useful in ovarian cancer, while small cell lung cancer also appears to be very sensitive to this drug. New structures with preclinical antitumor activity now in Phase I study include BWA770U mesylate, a propanediol compound; carbetimer, a polymeric compound; didemnin, a potent depsipeptide; and nafi dimide; next year we hope to report on the early clinical results.

Clinical research with biological response modifiers is acquiring a central role in cancer treatment. Promising results have been observed with interleukin in renal cell

cancer, melanomas, and colorectal cancer. Several studies are being initiated and important questions are to be answered, including (a) whether high-dose interleukin can exert antitumor activity on its own, (b) whether a further increase in the activity of LAK cells is feasible, (c) how to reduce toxicity to treatment with interleukin, (d) whether this biological is effective in patients with high as well as low tumor burdens, and finally (e) whether there is synergism with other biologicals. Other biologicals include growth factors and hormones, agents which are now entering clinical research and opening a whole new area of clinical investigation requiring adaption of the modes of research.

Monoclonal antibodies are acquiring an important place in cancer treatment research. They are proving of value for tumor labeling, while radioactive-labeled monoclonals are now also entering clinical trials for treatment purposes. Trials with immunotoxins have also been started.

From the second part of the volume it appears that steady progress is being made in the treatment of the hematological malignancies. In particular we are witnessing further developments of the techniques of molecular biology which are applied to these malignancies. For the malignant lymphomas it is anticipated that the systematic evaluation of biological products which is now taking place will lead to a further increase in the fraction of patients cured of this disease.

For breast cancer the recent Consensus Meeting on adjuvant chemotherapy suggested the administration of tamoxifen as standard treatment in postmenopausal ER-positive women. This is a very important decision, which should have a main overall impact on long-term treatment results in patients with breast cancer.

In ovarian cancer clinical research is focusing on the use of intraperitoneal chemotherapy for minimal residual disease, both after surgery for early stages and after chemotherapy resulting in remaining microscopal disease.

The search for less toxic regimens for good-prognosis testicular cancer continues and has led to positive results for nonseminomas as well as seminomas. The question of how to further improve treatment results in poor-prognosis patients, however, is yet awaiting an answer. The results with the 4-drug M-VAC regimen (methotrexate, vinblastine, doxorubicin, cisplatin) in advanced bladder cancer appear to be better than those with the combination of methotrexate and cisplatin.

In osteosarcomas the role of adjuvant chemotherapy has been shown more convincingly than before. While in soft tissue sarcomas the participants of the Consensus Meeting agreed not to advise routine treatment with adjuvant postsurgical chemotherapy unless this was performed in a clinical trial setting, preoperative chemotherapy in soft tissue sarcomas is now being studied and preliminary data are interesting. However, again these need to be evaluated in a randomized trial.

Research in AIDS has continued with the development of antibody assays and culture techniques which allow mass screening for viral exposure and further defining of risk groups. The emphasis in current research has moved towards the development of effective antiviral agents and immune modifying strategies as well as HTLV-III vaccins.

It is quite obvious that the advances being made in cancer chemotherapy justify the yearly appearance of this Annual. It is impossible to summarize all the important events of the past year, but we are sure that the reader will agree that besides its established role for advanced disease, cancer chemotherapy is acquiring an increasingly important place in presurgical treatment and pre-radiation therapy. Furthermore, the combined approach with radiotherapy as postsurgical adjuvant treatment is again comprehensively reviewed by many contributors. We sincerely hope that this volume will offer our fellow clinicians all the answers in this field. The book has proven most useful for teachers in medical oncology, and it appears that surgeons and radiotherapists are also finding their way to the Annual.

We wish to thank our collaborators for the timely submitting of their manuscripts and correcting of the proofs, which has again made it possible to have the book ready in time.

Contents

1 Antimetabolites

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During the past year much attention has been devoted to enhancing our understanding of the mechanism of action of the antimetabolite agents and the pathways by which neoplastic cells become resistant to these drugs. A more complete understanding of these mechanisms has led to new approaches aimed at increasing the therapeutic effectiveness of antimetabolites such as cytosine arabinoside (ara-C) by biochemical modulation and altered scheduling. Methotrexate polyglutamates are now recognized as a major determinant of tumor cell resistance. Investigations of the intracellular activation pathway of 5-fluorouracil and the transport of ara-C have led to important conclusions about mechanisms of resistance to these agents. Finally, several studies have demonstrated the importance of pharmacologic and pharmacokinetic determinants of clinical response to methotrexate and ara-C.

METHOTREXATE

Mechanism of action

Methotrexate (MTX) is felt to produce inhibition of cellular metabolic pathways through direct inhibition of dihydrofolate reductase (DHFR). It has been hypothesized that inhibition of DHFR results in an accumulation of dihydrofolate proximal to the inhibited reductase with subsequent depletion of the reduced folate cofactors. Lack of these cofactors would result in the cessation of the de novo purine/pyrimidine pathways and the synthesis of certain amino acids. While MTX itself has been reported to be a weak direct inhibitor of the folate-requiring enzymes in de novo purine synthesis (glycinamide ribonucleotide (GAR) and aminoimidazole carboxamide ribonucleotide (AICAR) transformylase) and de novo thymidylate synthesis (thymidylate synthase), new evidence reveals that the polyglutamates of MTX (MTXPGs) are potent direct inhibitors of these enzymes [1,2]. MTX pentaglutamate was found to have an inhibition constant (K_i) of 50 nM with respect to either the mono- or pentaglutamated 5,10-methylene tetrahydrofolate cosubstrate required for the enzyme

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