

2703-630 3

Synergism and Antagonism in Chemotherapy

Edited by

TING-CHAO CHOU

*Memorial Sloan-Kettering Cancer Center
New York, New York*

DARRYL C. RIDEOUT

*The Research Institute of Scripps Clinic
La Jolla, California*



ACADEMIC PRESS, INC.

Harcourt Brace Jovanovich, Publishers

San Diego New York Boston London

Sydney Tokyo Toronto

Contents

Contributors	xiii
Preface	xv

PART I

Reviews and Methods of Quantitation

CHAPTER 1

<i>Synergism, Antagonism, and Potentiation in Chemotherapy: An Overview</i>	3
DARRYL C. RIDEOUT AND TING-CHAO CHOU	
I. Drug Combinations in Chemotherapy	6
II. Mechanisms of Interaction	25
III. Condition-Related Aspects of Synergism, Antagonism, and Potentiation	51
References	53

CHAPTER 2

<i>The Median-Effect Principle and the Combination Index for Quantitation of Synergism and Antagonism</i>	61
TING-CHAO CHOU	
I. Introduction	62
II. Dose-Effect Analysis with Physicochemical Approach as Opposed to Empirical Approach	62
III. The Median-Effect Principle of the Mass-Action Law	65
IV. Dose-Effect Analysis of Combined Drug Effects	69

V. Summary	88
References	101
CHAPTER 3	
<i>Clinical Studies of Combination Chemotherapy for Cancer</i>	103
EMIL FREI III	
References	107
CHAPTER 4	
<i>Combined Chemotherapeutic Modalities for Viral Infections: Rationale and Clinical Potential</i>	109
RAYMOND F. SCHINAZI	
I. Introduction	110
II. Current Status of Research	111
III. Rationale for Combined Therapy with Antiviral Drugs	136
IV. Criteria for Usefulness of Combination Chemotherapy with Antiviral Agents	139
V. Methods of Analysis of Drug Interactions	139
VI. Mechanisms of Interaction	140
VII. Pharmacological Principles	143
VIII. Treatment of HIV, Opportunistic Infections, And Malignancies	146
IX. Drug Combinations as a Challenge for Drug-Resistant Viruses	148
X. Combination Chemotherapy and Combined Modalities for Viruses: Results and Proposed Mechanisms of Interaction	150
XI. Prospects	158
References	160
CHAPTER 5	
<i>Antimalarial Synergism and Antagonism</i>	183
J. L. VENNERSTROM, W. Y. ELLIS, W. K. MILHOUS, and J. W. EATON	
I. Introduction	183
II. Antifols	184
III. Combinations of Antifols with Other Antimalarial Drugs	190
IV. Quinolines	192
V. Quinoline/Antibiotic Combinations	195
VI. Artemisinin Combinations	196
VII. Oxidants/Oxidant Drugs and Other Factors in Combination	197
VIII. Nutritional Synergism and Antagonism	201
IX. Chelators as Potential Antimalarials	201

X. Miscellaneous Combinations	207
XI. Resistance Modulators as Adjunct Antimalarial Chemotherapy	209
References	211

CHAPTER 6

<i>Quantitation of Synergism and Antagonism of Two or More Drugs by Computerized Analysis</i>	223
---	-----

JOSEPH H. CHOU

I. Theory and Equations	224
II. Computerized Simulation and Automation	225
III. Illustration of Analysis with Examples	230
IV. Other Applications and Future Developments	237
References	241

PART II

Mechanisms of Interaction

CHAPTER 7

<i>Inhibition of Metabolic Drug Inactivation: Modulation of Drug Activity and Toxicity by Perturbation of Glutathione Metabolism</i>	245
--	-----

OWEN W. GRIFFITH and HENRY S. FRIEDMAN

I. Introduction	246
II. Glutathione Metabolism and Turnover	247
III. Glutathione as a Cellular Protectant	255
IV. Pharmacological Control of Glutathione Levels and Metabolism	259
V. Therapeutic Applications of Pharmacologic Manipulations of Glutathione Levels or Metabolism	271
VI. Glutathione Modulation: Perspective on Further Applications	277
References	279

CHAPTER 8

<i>Synergy and Antagonism in Polymerase-Targeted Antiviral Therapy: Effects of Deoxynucleoside Triphosphate Pool Modulation on Prodrug Activation</i>	285
---	-----

THOMAS SPECTOR and JAMES A. FYFE

I. Synergistic Antiherpetic Chemotherapy by Acyclovir (ACV) and an Inhibitor of Herpes Virus Ribonucleotide Reductase	286
II. Antagonism of 3'-Azido-3'-deoxythymidine (AZT) Antiviral Action by Ribavirin (RBV)	297

III. Summary	305
References	306
 CHAPTER 9	
<i>Reversal of Multidrug Resistance in Tumor Cells</i>	311
C.-P. HUANG YANG, L. M. GREENBERGER, and S. B. HORWITZ	
I. Introduction	311
II. Review of the Multidrug Resistance Phenotype	312
III. Reversal of Multidrug Resistance Phenotype	315
IV. Mechanisms Involved in Reversion of Multidrug Resistance	328
V. Clinical Implications	329
VI. Summary	331
References	332
 CHAPTER 10	
<i>Biochemical Mechanisms of the Synergistic Interaction of Antifolates</i> <i>Acting on Different Enzymes of Folate Metabolic Pathways</i>	339
JOHN GALIVAN	
I. Introduction	339
II. Rationale	343
III. The Effects of Combined Antifolates	348
IV. Discussion, Conclusions, and Prospects	355
References	357
 CHAPTER 11	
<i>Synergistic and Antagonistic Drug Interactions Resulting from</i> <i>Multiple Inhibition of Metabolic Pathways</i>	363
ROBERT C. JACKSON	
I. Introduction: Simultaneous Inhibition Effects as a Determinant of the Efficacy of Drug Combinations	364
II. Sequential Inhibition: A Historical Perspective	368
III. The Cell as an Open System in a Steady State	374
IV. The Main Patterns of Multiple Inhibitor Use	378
V. Multiple Inhibition in Highly Regulated Systems	388
VI. Approaches to a General Theory of Multiple Inhibition	394
VII. Conclusions: Combining Inhibitors to Optimize Selectivity	398
Appendix: A BASIC Program to Illustrate the Conclusions	403
References	407

CHAPTER 12

<i>Enhanced Effects of Drugs That Bind Simultaneously to the Same Macromolecular Target</i>	409
---	-----

LUCJAN STREKOWSKI and W. DAVID WILSON

I. Introduction	409
II. Interactions with Nucleic Acids	410
III. Interactions with Protein Targets	436
References	438

CHAPTER 13

<i>Biochemical Modulation of 5-Fluorouracil by Metabolites and Antimetabolites</i>	449
--	-----

ENRICO MINI and JOSEPH R. BERTINO

I. Introduction	449
II. Mechanism of Action of FUra	451
III. Sequential Methotrexate-FUra	452
IV. Leucovorin-FUra	464
V. Sequential MTX-LV-FUra	475
VI. 6-Methylmercaptapurine Ribonucleoside-FUra	477
VII. Phosphonacetyl-L-Aspartic Acid and/or Thymidine-FUra	477
VIII. Hydroxyurea-FUra	482
IX. Dipyridamol-FUra	482
X. Purines-FUra	483
XI. Allopurinol-FUra	484
XII. Uridine-FUra	485
XIII. Conclusions	487
References	488

CHAPTER 14

<i>Synergism and Antagonism through Direct Bond Formation between Two Agents in Situ</i>	507
--	-----

DARRYL C. RIDEOUT and THEODORA CALOGEROPOULOU

I. Introduction	508
II. Nonbiochemical Condensation Reactions Occuring <i>in Vivo</i> or Under Near-Physiological Conditions	508
III. Enhanced Cytotoxic and Antimicrobial Bioactivity of Polyfunctional versus Monofunctional Molecules	512

IV. Synergism Involving Covalent Self-Assembly of Cytotoxic and Antimicrobial Agents from Less Bioactive Precursors	520
V. Antagonism Involving Covalent Self-Assembly	528
References	534

CHAPTER 15

<i>Chemotherapeutic Potentiation through Interaction at the Level of DNA</i>	541
BEVERLY A. TEICHER, TERENCE S. HERMAN, and J. PAUL EDER	
I. Isobologram Methodology	542
II. Combinations of Alkylating Agents and Repair Inhibitors	545
III. Combined Alkylating Agent Studies	562
IV. Nitroimidazole and Perfluorochemical Emulsion/O ₂ Chemotherapy Combinations	570
References	576

CHAPTER 16

<i>Drug Synergism, Antagonism, and Collateral Sensitivity Involving Genetic Changes</i>	
VASSILIOS I. AVRAMIS, SHENG-HE HUANG, and JOHN S. HOLCENBERG	
I. Introduction	585
II. Over-Expression of Genes	586
III. Under-Expression of Genes	589
References	616

PART III

Condition-Selective Synergism and Antagonism

CHAPTER 17

<i>Schedule-Dependent Effects in Antineoplastic Synergism and Antagonism</i>	623
BARBARA K. CHANG	
I. Introduction	623
II. Schedule-Dependent Interactions Based upon Cell Cycle Considerations	626
III. Schedule-Dependent Interactions Based Primarily upon Biochemical Considerations: Combinations (Largely of Antimetabolites) Affecting the Enzymes Involved in DNA Synthesis	638
IV. Interactions Based upon Altered Drug Transport	643

V. Miscellaneous	646
VI. Summary	647
References	648

CHAPTER 18

<i>Effects of Drug Distribution and Cellular Microenvironment on the Interaction of Cancer Chemotherapeutic Agents</i>	659
--	-----

RALPH E. DURAND

I. Overview	659
II. Introduction	660
III. Quantitative Techniques for Heterogeneous Systems	664
IV. Interaction of Chemotherapeutic Agents	672
V. Additional Considerations	681
References	684

CHAPTER 19

<i>Synergistic Interactions at the Solid Tumor Level through Targeting of Therapies against Two or More Different Tumor Cell Subpopulations</i>	689
---	-----

DIETMAR W. SIEMANN and PETER C. KENG

I. Introduction	689
II. Background on Cell Subpopulations	690
III. Characterization of Tumor Cell Subpopulations	691
IV. Cell Subpopulations Influencing the Overall Tumor Response to Therapy	693
V. Improving the Therapeutic Interaction through Therapy Combinations Directed against Specific Tumor Cell Subpopulations	702
VI. Conclusions	709
References	710

CHAPTER 20

<i>Selective Synergism against the Target versus Host Bone Marrow Progenitor Cells</i>	715
--	-----

ELLIN BERMAN and TAI-TSUNG CHANG

I. Introduction	715
II. Azidothymidine and Recombinant Interferon Alpha: Synergistic Effects Against the Human Immunodeficiency Virus versus Normal Human Bone Marrow Progenitor Cells	716
III. Cancer Cell Purging in Autologous Bone Marrow Transplantation ...	726

IV. Selective Synergism: The Role for Data Analysis Using the Median-Effect Equation in the Design of Clinical Drug Trials	733
V. Conclusion	734
References	734
Index	739