Drug Dosage

The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

All rights reserved.

No part of this publication may be translated into other languages, reproduced or utilized in any form or by any means, electronic or mechanical, including photocopying, recording, microcopying, or by any information storage and retrieval system, without permission in writing from the publisher.

© Copyright 1984 by S. Karger AG, P.O. Box, CH-4009 Basel (Switzerland)
Printed in Switzerland by BDV Basler Druck- und Verlagsanstalt, Basel
ISBN 3-8055-3699-2

Contents

Brain Tumor Therapy

The papers with emphasis on 'Brain Tumor Therapy' are published in this volume. The papers with emphasis on 'Brain Tumor Biology' are published in vol. 27 of the series (see table of contents on p. VI).
Contributors List VIII
Preface XII
Acknowledgment XIV
Dedication XV

Specificity of Treatment
Rosenblum, M.L.; Gerosa, M. A. (San Francisco, Calif.): Stem Cell Sensitivity 1
Schold, S. C., Jr.; Friedman, H. S. (Durham, N. C): Human Brain Tumor Xenografts 18

Cytotoxic Therapy
Stewart, D. J. (Ottawa, Ont.): Novel Modes of Chemotherapy Administration 32
Neuwelt, E.A. (Portland, Oreg.): Therapeutic Potential for Blood-Brain Barrier Modification in Malignant Brain Tumor 51
Fingert, H. J.; Hochberg, F. H. (Boston, Mass.): Megadose Chemotherapy with Bone Marrow Rescue 67
Bourdon, M.A.; Coleman, R.E.; Bigner, D.D. (Durham, N.C.): The Potential of Monoclonal Antibodies as Carriers of Radiation and Drugs for Immunodetection and Therapy of Brain Tumors 79

Biologic Response Modifiers
Oredsson, S.M.; Marlon, L.J. (San Francisco, Calif.): Potential Uses of Polyamine Biosynthesis Inhibitors in Tumor Therapy 102

Contents VI


Local Therapy
A. Radiation Therapy
Fike, J. R.; Sheline, G. E.; Cann, C. E.; Davis, R. L. (San Francisco, Calif.): Radiation Necrosis 136
Douglas, B. G. (Vancouver, B.C.); Castro, J.R. (San Francisco, Calif.): Novel Fractionation Schemes and High Linear Energy Transfer 152
Gutin, P.H.; Bernstein, M. (San Francisco, Calif.): Stereotactic Interstitial Brachytherapy for Malignant Brain Tumors 166
Deen, D.F.; Tofilon, P.J. (San Francisco, Calif.): Combined Effects of Drugs and Radiation against Tumor Cells 183

B. Hyperthermia
Dewey, W. C; Holahan, E. V. (San Francisco, Calif./Bethesda, Md.): Hyperthermia – Basic Biology 198
Salcman, M. (Baltimore, Md.): Feasibility of Microwave Hyperthermia for Brain Tumor Therapy 220
Britt, R.H.; Pounds, D.W.; Lyons, B.E. (Stanford, Calif.): Feasibility of Treating Malignant Brain Tumors with Focused Ultrasound 232

Appendix: Supplementary Reference List 246

Subject Index 255

Brain Tumor Biology
Published as vol.27 in the series Progress in 'Experimental Tumor Research'.

Contents

Contributors List VIII
Preface XII
Acknowledgment XIV
Dedication XV

Carcinogenesis
Kleihues, P.; Rajewsky, M.F. (Freiburg/Essen): Chemical Neuro-Oncogenesis: Role of Structural DNA Modifications, DNA Repair and Neural Target Cell Population 1
Laerum, O.D.; Mørk, S.J. (Bergen); De Ridder, L. (Ghent): The Transformation Process 17

Contents VII

Tumor Pathology
Rubinstein, L.J.; Herman, M.M.; VandenBerg, S.R. (Charlottesville, Va.): Differentiation and Anaplasia in Central Neuroepithelial Tumors 32
Shapiro, J. R.; Shapiro, W. R. (New York, N.Y.): Clonal Tumor Cell Heterogeneity 49
Bigner, S. H.; Mark, J. (Durham, N.C./Skövde): Chromosomes and Chromosomal Progression of Human Gliomas in vivo, in vitro and in Athymic Nude Mice 67
Hoshino, T. (San Francisco, Calif.): Heterogeneity of Tumor Cell DNA Content 83
De Armond, S. J.; Eng, L. F. (Stanford, Calif./Palo Alto, Calif.): Immunohistochemistry: Techniques and Application to Neurooncology 92
Tribolet, N. de (Lausanne); Carrel, S.; Mach, J.-P. (Epalinges): Brain Tumor-Associated Antigens 118

Tumor Physiology
Groothuis, D.R. (Evanston, Ill.); Molnar, P.; Blasberg, R.G. (Bethesda, Md.): Regional Blood Flow and Blood-to-Tissue Transport in Five Brain Tumor Models. Implications for Chemotherapy 132
Wise, R.J.S.; Thomas, D.G. T.; Lammertsma, A.A.; Rhodes, CG. (London): PET Scanning of Human Brain Tumors 154
Kornblith, P.L.; Cummins, C.J.; Smith, B.H.; Brooks, R.A.; Patronas, N.J.; Di Chiro, G. (Bethesda, Md.): Correlation of Experimental and Clinical Studies of Metabolism by PET Scanning 170
Bartkowski, H.M. (San Francisco, Calif.): Peritumoral Edema 179

Tumor Cell Resistance
Rosenblum, M. L.; Gerosa, M. A.; Bodell, W. J.; Talcott, R. L. (San Francisco, Calif.): Tumor Cell Resistance 191

Appendix: Supplementary Reference List 215

Subject Index 225

Contributors List

Henry M. Bartkowski, MD, PhD, Assistant Professor of Neurological Surgery, School of Medicine, University of California, San Francisco, and Assistant Chief, Neurosurgery Service, San Francisco General Hospital Medical Center, San Francisco, Calif., USA
Mark Bernstein, MD, Research Fellow, Departments of Neurological Surgery and Radiation Oncology, Brain Tumor Research Center, School of Medicine, University of California, San Francisco, San Francisco, Calif., USA; currently Resident in Neurosurgery, University of Toronto, Toronto, Ont., Canada
Darelt D. Bigner, MD, PhD, Professor of Pathology, Division of Neuropathology, Duke University Medical Center, Durham, N.C., USA
Sandra H. Bigner, MD, Associate Professor of Pathology, and Director, Section on Cytogenetics, Division of Cytopathology and Cytogenetics, Duke University Medical Center, Durham, N.C., USA
Ronald G. Blasberg, MD, Senior Investigator, Laboratory of Chemical Pharmacology, Membrane Transport Section, National Cancer Institute, National Institutes of Health, Bethesda, Md., USA
William J. Bodell, PhD, Assistant Research Biochemist, Department of Neurological Surgery, Brain Tumor Research Center, School of Medicine, University of California, San Francisco, San Francisco, Calif., USA
Mario A. Bourdon, PhD, Predoctoral Fellow, Department of Pathology, Duke University Medical Center, Durham, N.C., USA
Richard H. Britt, MD, PhD, Assistant Professor of Neurosurgery, Stanford University School of Medicine, Stanford, Calif., USA
Rodney A. Brooks, PhD, Research Physicist, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Md., USA
Christopher E. Cann, PhD, Associate Professor of Radiology, School of Medicine,
University of California, San Francisco, San Francisco, Calif., USA
Stefan Carrel, PhD, Unit of Human Cancer Immunology, Lausanne Branch, Ludwig Institute for Cancer Research, Epalinges, Switzerland
Joseph R. Castro, MD, Professor of Radiation Oncology, and Vice Chairman, Department of Radiation Oncology, School of Medicine, University of California, San Francisco, and Director of Radiotherapy, Lawrence Berkeley Laboratory, Berkeley, Calif., USA

Contributors List IX

R. Edward Coleman, MD, Director of Nuclear Medicine, Department of Radiology, Duke University Medical Center, Durham, N.C., USA
Craig J. Cummins, PhD, Senior Staff Fellow, Surgical Neurology Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Md., USA
Richard L. Davis, MD, Professor of Pathology (Neuropathology), Neurological Surgery, and Neurology, School of Medicine, University of California, San Francisco, San Francisco, Calif., USA
Stephen J. DeArmond, MD, PhD, Assistant Professor of Pathology, School of Medicine, University of California, San Francisco, San Francisco, Calif., USA
Dennis F. Deen, PhD, Associate Professor of Neurological Surgery and Radiation Oncology, Brain Tumor Research Center, School of Medicine, University of California, San Francisco, San Francisco, Calif., USA
Leo de Ridder, SM, Senior Scientist, Department of Experimental Cancerology, Radiotherapy and Nuclear Medicine, Academic Hospital, DePintelaan, Ghent, Belgium
Nicolas de Tribolet, MD, Privat-Docent, Neurosurgical Service, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
William C. Dewey, PhD, Professor, Department of Radiation Oncology, School of Medicine, University of California, San Francisco, San Francisco, Calif., USA
Giovanni Di Chiro, MD, Chief, Neuroradiology and Computerized Tomography Section, Surgical Neurology Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Md., USA
Bruce G. Douglas, BASc, MD, FRCP (C), Radiation Oncology, Vancouver, B.C., Canada
Lawrence F. Eng, PhD, Professor of Pathology (Research), Stanford University School of Medicine, Stanford, Calif., and Chief, Chemistry Section Laboratory Service, Veterans Administration Medical Center, Palo Alto, Calif., USA
John R. Fike, PhD, Assistant Professor of Radiation Oncology, Radiology and Neurosurgery, School of Medicine, University of California, San Francisco, San Francisco, Calif., USA
Howard J. Fingert, MD, Research Fellow in Medicine, Division of Cell Growth and Regulation, Dana-Farber Cancer Institute and Hematology-Oncology Unit, Massachusetts General Hospital, Harvard Medical School, Boston, Mass., USA
Henry S. Friedman, MD, Assistant Professor, Division of Hematology-Oncology, Department of Pediatrics, Duke University Medical Center, Durham, N.C., USA
Massimo A. Gerosa, MD, Assistant Professor, Istituto di Neurochirurgia, Università di Verona, Italy
G. Yancey Gillespie, PhD, Research Associate Professor of Surgery and Pathology, Division of Neurological Surgery, and Member of the Cancer Research Center, University of North Carolina, Chapel Hill, N.C., USA
Dennis R. Groothuis, MD, Assistant Professor of Neurology, Northwestern University, Evanston Hospital, Evanston, Ill., USA
Philip H. Gutin, MD, Associate Professor of Neurological Surgery and Radiation Oncology, Brain Tumor Research Center, School of Medicine, University of California, San Francisco, San Francisco, Calif., USA
Mary M. Herman, MD, Professor of Pathology, Division of Neuropathology, University of Virginia School of Medicine, Charlottesville, Va., USA

Contributors List X

Fred H. Hochberg, MD, Department of Neurology, Harvard Medical School, and Neurology Service, Massachusetts General Hospital, Boston, Mass., USA
Eugene V. Holahan, Jr., PhD, Captain, United States Army, Research Biophysicist, Armed Forces Radiobiology Research Institute, Bethesda, Md., USA
Takao Hoshino, MD, DMSc, Professor of Neurological Surgery, Brain Tumor Research Center, School of Medicine, University of California, San Francisco, San Francisco, Calif., USA
Paul Kleihues, MD, Professor and Director, Division of Neuropathology, Institute of Pathology, University of Freiburg, Freiburg, FRG
Paul L. Kornblith, MD, Chief, Surgical Neurology Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Md., USA
Ole Didrik Laerum, MD, Professor of Experimental Pathology and Oncology, The Gade Institute, Department of Pathology, University of Bergen, Haukeland Hospital, Norway
A. A. Lammertsma, MRC Cyclotron Unit, Hammersmith Hospital, London, England
Bernard E. Lyons, BA, Research Associate, Division of Neurosurgery, Department of Surgery, Stanford University School of Medicine, Stanford, Calif., USA
Jean-Pierre Mach, Associate Professor, Unit of Human Cancer Immunology, Lausanne Branch, Ludwig Institute for Cancer Research, Epalinges, Switzerland
M. S. Mahaley, Jr., MD, PhD, Professor of Neurological Surgery and Neurobiology, University of North Carolina School of Medicine, Chapel Hill, N.C., USA
Joachim Mark, MD, Associate Professor of Pathology, and Head, Laboratory of Cytogenetics, Central Hospital, Skövde, Sweden
Laurence J. Marton, MD, Professor of Laboratory Medicine and Neurological Surgery,
Brain Tumor Research Center, and Chairman, Department of Laboratory Medicine, School of Medicine, University of California, San Francisco, San Francisco, Calif., USA
Peter Molnar, MD, Fogarty Research Fellow, Laboratory of Chemical Pharmacology, Membrane Transport Section, National Cancer Institute, National Institutes of Health, Bethesda, Md., USA; currently with the Department of Pathology, University Medical School of Debrecen, Debrecen, Hungary
Sverre J. Mørk, MD, Consultant in Neuropathology, The Gade Institute, Department of Pathology, University of Bergen, Haukeland Hospital, Norway
Edward A. Neuwelt, MD, Associate Professor of Neurosurgery, Assistant Professor of Biochemistry, School of Medicine, Oregon Health Sciences University, Portland, Oreg., USA
Stina M. Oredsson, MS, Visiting Predoctoral Fellow, Brain Tumor Research Center, Department of Neurological Surgery, School of Medicine, University of California, San Francisco, San Francisco, Calif., USA; currently Doctoral Candidate, Department of Zoophysiology, University of Lund, Sweden
Nicholas J. Patronas, MD, Staff Radiologist, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Md., USA
Douglas W. Pounds, BS, Research and Development Engineer/Physicist, Division of Neurosurgery, Department of Surgery, Stanford University School of Medicine, Stanford, Calif., USA
Manfred F. Rajewsky, MD, Professor and Director, Institute of Cell Biology (Cancer Research), University of Essen, Essen, FRG

Contributors List XI

C.G. Rhodes, MRC Cyclotron Unit, Hammersmith Hospital, London, England
Mark L. Rosenblum, MD, Associate Professor of Neurological Surgery, Brain Tumor Research Center, School of Medicine, University of California, San Francisco, San Francisco, Calif., USA
Lucien J. Rubinstein, MD, Professor of Pathology, and Director, Division of Neuropathology, University of Virginia School of Medicine, Charlottesville, Va., USA
Michael Salzman, MD, FACS, Associate Professor of Neurological Surgery, and Chief, Neuro-Oncology Service, University of Maryland School of Medicine and Hospital, Baltimore, Md., USA
S. Clifford Schold, Jr., MD, Associate Professor of Neurology, Department of Medicine, Duke University Medical Center, Durham, N.C., USA
Joan Rankin Shapiro, PhD, Research Associate, Department of Neurology and George C. Cotzias Laboratory of Neuro-Oncology, Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, N.Y., USA
William R. Shapiro, MD, Professor of Neurology, and Head, George C. Cotzias Laboratory of Neuro-Oncology, Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, N.Y., USA
When Dr. Thomas Karger suggested the need for a companion volume on brain tumor therapy to accompany the monograph on Brain Tumor Biology in this series on 'Progress in Experimental Tumor Research', we recognized the timeliness of his idea. We saw the value of gathering into a single reference source the experience of experts in the various areas of the field, many of which have never been combined in such a book.

This volume focuses on innovative therapies conceived and directed on the basis of the recent laboratory research findings. Its 15 chapters represent work that is being conducted in institutions actively engaged in brain tumor therapy. The authors review the areas of specificity of treatment, cytotoxic and noncytotoxic treatments, and local therapy. They describe new means of administering cytotoxic agents to improve the therapeutic index, discuss biological response modifiers, and review the status of local therapy with irradiation and hyperthermia. Rather than
merely summarizing work presented in previously published material, they include their speculations on the reasons for the success and failure of the individual therapeutic modality and its place among other methods. In compiling these chapters, we have asked the authors to review concisely the well-established data in their area and the completed results and published concepts underlying their own work. However, the primary emphasis in each chapter is the relevant preliminary findings in a particular area of interest that will serve as the basis for research over the next several years. We believe that this book and its companion volume will serve as a guide for future investigations and possibly new directions for brain tumor therapy.

Preface XIII

Our selection of the topics presented reflects personal bias, but selectivity was required because of necessary limitations on the volume's size. Several areas not represented here in which there recently has been significant progress are included in an appendix of selected readings, compiled with the aid of our authors to provide pertinent references that will supplement the work represented in the invited chapters. We hope that the reader interested in topics that are not covered will understand the restrictions of this or any other monograph concerned with evolving and rapidly changing clinical research.

M. L. Rosenblum and C. B. Wilson

Acknowledgment

The timely editing of this monograph could not have been accomplished without the superb collaboration of the editorial staff of our Department of Neurological Surgery at the University of California, San Francisco. For this, we are indebted to Susan Eastwood-Berry, and Beverly H. McGehee.

To our patients