Secondary Neoplasias following Chemotherapy, Radiotherapy, and Immunosuppression
Secondary Neoplasias following Chemotherapy, Radiotherapy, and Immunosuppression

Volume Editors
U. Rüther, Ludwigsburg
C. Nunnensiek, Reutlingen
H.-J. Schmoll, Halle/Saale

38 figures, 8 in color, 22 tables, 2000
Contributions to Oncology
Beiträge zur Onkologie

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 2000 by S. Karger GmbH, Postfach, D-79095 Freiburg, and S. Karger AG, P. O. Box, CH-1009 Basel
Printed in Germany on acid-free paper by Konkordia Druck GmbH, Bühl
ISBN 3-8055-7116-X
Contents

Preface .................................................................................................................. VII

**Basic Concepts and Pathogenesis**

Basic Concepts of Tumor Biology ................................................................. 1
  Nordheim, A. (Tübingen); Lüscher, B. (Hannover)

Herpesviruses in Secondary Tumorigenesis ............................................... 17
  Schwarzmann, F.; Wolf, H. (Regensburg)

Carcinogenicity of Cytostatic Agents – Secondary Malignancies after Chemotherapy ........ 36
  Haussmann, W. (Sigmaringen)

Mechanisms of Action of Immunosuppressants and Immunoinductors .............. 62
  Haussmann, W. (Sigmaringen)

Immune Surveillance and Tumor Recognition ................................................. 94
  Eichhorst, S.T.; Elser, B. (Heidelberg)

Malignant Lymphomas and Lymphoproliferative Disorders following Organ Transplantation and Immunomodulatory Therapy ......................................................... 117
  Müller-Hermelink, H.K.; Rüdiger, T. (Würzburg)

Chromosomal Aberrations and Molecular Changes in Therapy-Related Leukemias ........ 139
  Staratschek-Jox, A.; Bullerdiek, J. (Bremen)
Clinical Presentations

Secondary Tumorigenesis after Radiotherapy ........................................ 147
Ammon, J. (Aachen)

Secondary Primary Cancers after Cancer and Immunosuppressive Chemotherapy and
Radiotherapy .......................................................... 165
Roelianto Soedirman, J. (Utrecht/Amsterdam)

Secondary Malignancies after Allogeneic or Autologous Marrow Transplantation .... 203
Witherspoon, R.P.; Deeg, H.J.; Fischer, L.; Schoch, G.; Storb, R. (Seattle, WA)

Malignancy following Kidney Transplantation ...................................... 225
Olbricht, C.J. (Stuttgart)

Malignancy after Heart and Lung Transplantation ................................. 242
Wendler, O.; Schäfers, H.-J. (Homburg/Saar)

Secondary Neoplasms following Liver and Pancreas Transplantation .......... 256
Nashan, B. (Hannover)

Emerging Therapies and Preventive Measures

Therapy of Secondary Acute Myeloid Leukemia and Secondary
Myelodysplastic Syndrome .................................................. 264
Rüther, U.; Rothe, B. (Stuttgart); Nunnensiek, C. (Reutlingen)

Immunological Aspects of the Pathogenesis of Tumors Associated with Epstein-Barr Virus:
Vaccines for Prevention and Therapy .................................... 275
Benninger-Döring, G.; Wolf, H. (Regensburg)

Live Attenuated Varicella Vaccine ............................................ 286
Gershon, A.A. (New York, NY)

Posttransplant Lymphoproliferative Disorder – New Approaches to Monitoring and
Management ........................................................................ 305
Leitch, H.A.; Cantarovich, M.; Mangel, J.E.; Laneuville, P. (Montreal, Que.)

Cytoprotection as a New Supportive Strategy in the Treatment of Solid Tumors .... 347
Büntzel, J.; Glatzel, M.; Fröhlich, D.; Küttner, K. (Suhl)

Subject Index ........................................................................ 363
Reports of secondary neoplasia developing after successful curative chemotherapy and/or radiotherapy for malignancies are increasing. Also of growing concern is the diagnostic and therapeutic problem of tumorigenesis during posttransplantation immunosuppressive therapy. With chapters contributed by internationally renowned researchers, this book discusses several aspects of this issue.

The first part covers the various causes of primary and secondary tumorigenesis and of neoplasia occurring during posttransplantation immunosuppressive therapy. As survival times lengthen and overall remission rates increase for patients with Hodgkin’s disease, germ-cell tumors, non-Hodgkin’s lymphomas or leukemia, the potential risk of developing therapy-associated secondary malignancy is becoming a focus of attention. What makes this problem even more relevant are the many breast and colon carcinoma patients who receive adjuvant chemotherapy after complete resection of the primary tumor or even of metastases. In addition, an increasing number of patients with chemosensitive disease are receiving high-dose chemotherapy with autologous peripheral-blood stem-cell transplantation.

Post chemotherapy, the most common secondary neoplasm is secondary acute myeloid leukemia, which develops primarily after treatment with alkylating agents or topoisomerase inhibitors. While secondary leukemia after alkylating-agent therapy often commences with a preleukemic phase of myelodysplasia, secondary leukemia associated with epipodophyllotoxin is acute, and lacks this preceding myelodysplasia. The correlating chapters in this book discuss in depth the risk of the individual cytostatic agents for inducing secondary malignoma, and include the aspects of cumulative dose dependency and chronology of administration.

Other chapters discuss the role of immunosurveillance and the immune system’s recognition of tumors. In this area, our knowledge is constantly growing, in
particular with respect to the molecular processes responsible for the changes on tumor cells and immune cells, the structure and function of a wide variety of surface receptors and ligands on these cells, lymphocytic signal transduction pathways, the characterization of murine tumor-specific transplantation antigens, and human tumor-associated antigens. Although far from complete, our understanding of cellular immune response to tumors has improved considerably, as has our understanding of how tumor cells escape detection by the immune system.

As more and more tumors develop during posttransplantation immunosuppressive therapy, today’s findings on the underlying processes will lead to innovative changes in existing therapeutic concepts. Already, we must increasingly deal with aspects such as the antigenic characteristics of transformed cells, host-tumor interaction, molecular mechanisms of cell-dependent cytotoxicity, identification of components that generate and control effective immune response, induction of tolerance or of T-cell anergy, and immunologic effects of the host on the neoplastic growth of tumor cells. One therapeutic aspect is the modulation of the immune system or of tumor cells such that the latter can be more easily recognized and eliminated by immunoeffectors. In addition, this book covers the role and significance of herpesviruses in these areas.

The last part of this book discusses the prevention of secondary tumors and tumors occurring during immunosuppressive therapy. Here, the major substances for cytoprotection during chemo- and/or radiotherapy are presented. Also described are new vaccine strategies for treating varicella- and herpesvirus-associated tumors. These vaccines can be applied not only for treatment of infections, but are beginning to play an important role in tumor prevention as well. Of special interest is the chapter dealing with immunomodulatory therapy of posttransplantation lymphoproliferative disorders.

The authors repeatedly stress that early detection is a prerequisite for successful treatment of secondary neoplasms and neoplasms occurring during immunosuppression. Therefore, patients who are successfully treated for malignancy in particular require long-term follow-up including checks for therapy-associated late sequelae. However, this applies also to patients who, after organ transplantation, receive immunosuppressive therapy.

In closing, we can again only reiterate that our international group of authors underscores the importance of global collaboration if we are to find diagnostic and therapeutic solutions to these problems.

The editors wish to express their appreciation to Diane E. Crawford, who carefully and thoroughly translated and edited the manuscripts, and to Dr. Joachim Sick, Bene Meritus.

U. Rüther, Ludwigsburg
Ch. Nunnensiek, Reutlingen
H.-J. Schmoll, Halle/Saale