
Metronomic Chemotherapy

Guido Bocci • Giulio Francia
Editors

Metronomic Chemotherapy

Pharmacology and Clinical Applications

 Springer

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ISBN 978-3-662-43603-5 ISBN 978-3-662-43604-2 (eBook)
DOI 10.1007/978-3-662-43604-2
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014947232

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Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

Metronomic chemotherapy has arrived. In 2014 we are beginning to learn of phase III clinical trial results on this form of cancer treatment, defined by the continuous low-dose administration of conventional chemotherapy drugs. The emerging clinical data will be of paramount importance in allowing us to assess the impact of metronomic chemotherapy on different tumor types. Indeed, it is likely that the next decade will see a major reassessment of the possible applications of metronomic chemotherapy for the management of cancer. Furthermore, the clinical trial results will likely profoundly affect the direction of the preclinical laboratory efforts that are going on in parallel, aimed at improving this therapeutic strategy.

This book is our attempt to compile the history of metronomic chemotherapy that has brought us to this pivotal moment. In our view, it is important to learn from the successes, as detailed in the various chapters of this book, which allowed the transition of metronomic chemotherapy from the lab to the clinic in under two decades. It is also imperative that we catalog any errors and missteps that occurred along the way, so that their repeat may hopefully be avoided in the future, either by researchers studying metronomic chemotherapy or conceivably those developing entirely different therapeutic strategies. Insofar as this book is a catalog of what went right and what went wrong in developing a new therapeutic concept, we hope that it will be of interest to a general readership.

Scientists and clinicians caring for advanced cancer patients are well aware of the challenges in dealing with these diseases. Although metastatic cancers are responsive to a range of conventional cytotoxic agents, they generally recur and prove to be fatal. In facing the major obstacles to improvements in cures, the expectation today is that a different approach to preclinical and clinical research on chemotherapy will translate into genuine progress in routine therapy. While there is still much to be understood about the molecular mechanisms and pharmacology of metronomic chemotherapy, we are already seeing progress in the clinical use of this innovative therapy. Indeed, at the end of the 1990s, researchers such as Robert S. Kerbel and Judah Folkman began to investigate the antiangiogenic activity of frequent administration of low-doses of chemotherapeutic drugs, as a mechanism potentially contributing to their antineoplastic activity *in vivo*. During the past decade, a number of studies have shown that such metronomic chemotherapy has preclinical and clinical activity that may be ascribed to various mechanisms of action, including the inhibition of angiogenesis and the induction of an increase in

the immunological response. Oncologists, such as Marco Colleoni in Milan, have established numerous phase I and phase II clinical trials, investigating the use of metronomic chemotherapy in different tumors, and phase III clinical trials are currently ongoing. It is likely that the rapid acceptance of metronomic chemotherapy as a novel and interesting therapeutic strategy owes much to the almost parallel development of the concept in the lab and in the clinic.

The chapters of this book analyze all aspects of this new therapeutic approach and its possible future development. After an opening section on the pharmacodynamic bases of metronomic chemotherapy, including its antiangiogenic effects and impact on immunity, preclinical studies on some classes of drug are discussed. Clinical applications of metronomic chemotherapy in a wide variety of tumors are then addressed in detail, including description of the results of published studies. Where there are diverse views on what constitutes metronomic scheduling in the clinic, we tried to ensure that this book incorporates all points of view. The clinical pharmacology of metronomic chemotherapy is also considered in depth, encompassing pharmacokinetics, pharmacogenetics, and adverse drug reactions. Since cost of care is essential both in drug development and in the availability of treatment, there is also a chapter on pharmacoeconomics. The book ends with a description of the role of this therapy in the veterinary clinic, which we believe is an area of increasing importance in the development of most new therapies for cancer. The book's target audiences are oncologists, pharmacologists, veterinarians and translational researchers in the field of cancer.

This remains an incredibly exciting time for metronomic chemotherapy. The leaps in knowledge in the molecular and pharmacological aspects of this novel approach, and the clinical results, have been objectively remarkable. We hope you find the information contained in this book useful, guiding your translational research and everyday practice. Clearly new information continues to emerge on a monthly basis, and this of course is encouraging. And yet, we believe that there is a role for a book that provides a concise overall picture of metronomic chemotherapy, especially in 2014, which is a particularly eventful year for treatment developments that should result from the ongoing phase III clinical trials.

Metronomic chemotherapy was borne out of the ideas of Judah Folkman and Robert Kerbel, the pioneering laboratory work of Timothy Browder, and the early clinical studies by Marco Colleoni and colleagues. Two of those four pioneers have contributed to this book. Tragically, Dr. Folkman and Dr. Browder are no longer with us, and they missed out witnessing the results of the phenomenal translational work they initiated. This book is dedicated to their memory. Several chapters in the book are from researchers that were instrumental in the early years at the turn of this century in defining the concept of metronomic chemotherapy, and in highlighting its versatility as a treatment strategy. We apologize for any researchers that we may have omitted for reasons of time or space in the preparation of this book.

Finally, over the last year a team consisting of editors and authors have diligently worked to have this book published in its present form. We would like to use this

opportunity to thank each and every one of these contributors for the wonderful job you have done. Without their help and support we would have not been able to publish this book.

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