

EDITORIAL

Long-term Adjuvant Tamoxifen Therapy and Decreases in Contralateral Breast Cancer

Balkees Abdemahmoud, MD, Y. Craig Jordan, OBE, PhD, DSc, FMedSci

Tamoxifen revolutionized personalized medicine as the first targeted therapy proven to save lives in cancer.¹ The paradigm change proposed to block the breast tumor estrogen receptor (ER), apply long-term adjuvant therapy to block estrogen-stimulated recurrences,^{1,2} and apply the potential of

tamoxifen to prevent breast cancer.³ These strategic recommendations were translated, during the past 3 decades, to clinical care.⁴ A meta-analysis⁵ of randomized clinical trials revealed that the strategic use of long-term adjuvant tamoxifen therapy is the key to therapeutic success. In addition, we now know that treating metastatic breast cancer (MBC) is only palliative at the end of life, but the same medicine saves lives if applied as long-term adjuvant therapy. Nevertheless, the question has to be asked whether the results would be the same outside the clinical trials process.

The report in this issue of *JAMA Oncology* by Gierach and coworkers⁶ is reassuring because all the rules derived, until now, from randomized clinical trial overview analyses hold true.⁶ The authors⁶ performed a retrospective cohort study of contralateral breast cancer (CBC) in a population of 7541 patients from the records at Kaiser Permanente Northwest and Colorado from 1990 to 2008 and followed up through 2011. The median range of observation was 6.3 years, and 248 patients were identified to have developed CBC. Both tamoxifen and aromatase inhibitors reduced CBC, and longer adjuvant therapy proved to be more beneficial than shorter therapy. The authors⁶ estimate that 4 or more years of adjuvant tamoxifen therapy will prevent 3 CBCs per 100 women by 10 years after first diagnosis of ER-positive breast cancer. The authors⁶ stress that patients with breast cancer who are undergoing long-term adjuvant endocrine therapy should be encouraged to complete the full course. Indeed, this conclusion is even more important because in the future adjuvant endocrine therapy will last for 10 years.^{7,8} However, the challenge is adherence. Simply stated, no medicine, no benefit. A previous report⁹ calculates the number of deaths caused by nonadherence with adjuvant tamoxifen therapy. Low adherence results in early recurrence, increased medical costs, and a much worse quality of life.⁹

Gierach and coworkers⁶ report the persistence of the protective effects of adjuvant tamoxifen after treatment stops on CBC risk and that this effect is dependent on the duration of tamoxifen therapy. The authors⁶ cite a Danish study¹⁰ that found that current users of tamoxifen had a reduced risk of CBC,¹⁰ but former use of tamoxifen had no effect on CBC. Importantly,

the adjuvant therapy used was only for a short period (median, 1-2.5 years).¹⁰ Persistence of the protective effects of tamoxifen using 5 years of treatment in high-risk populations is noted in the National Surgical Adjuvant Breast and Bowel Project trial¹¹ to reduce the risk of primary breast cancer in high-risk women. These data¹¹ are supported by the 96-month follow-up of the International Breast Cancer Intervention Study trial and the 20-year follow-up of the Royal Marsden Breast Cancer Prevention trial.¹² The rule is clear: long-term treatment with tamoxifen (5 years) produces a sustained beneficial effect in preventing breast cancer, whereas short-term therapy does not.

This clinical reality now presents the medical community with a paradox. Tamoxifen is a competitive inhibitor of estrogen action at the tumor ER. However, long-term adjuvant tamoxifen therapy^{1,2} must be continuous because failure of tamoxifen to block the tumor ER will result in recurrence. However, this laboratory strategy³ was not predictive for 5 years of adjuvant therapy. Patients survive without the benefit of tamoxifen blocking the ER to prevent recurrence. Herein lies the paradox. Tamoxifen is not cytotoxic, so where does the cytotoxicity of long-term tamoxifen therapy come from to protect patients after 5 years of adjuvant tamoxifen therapy?

The answer comes from laboratory research on the evolution of acquired resistance to tamoxifen.^{13,14} Investigation of ER-positive breast tumors transplanted into tamoxifen-treated ovariectomized athymic mice results in the development of acquired resistance to tamoxifen within 1 to 2 years.¹² Uniquely, breast tumors develop because of tamoxifen treatment not despite tamoxifen treatment, and tumors use tamoxifen or estrogen to maintain tumor growth.^{15,17} This biological knowledge is the scientific foundation for using an aromatase inhibitor (to prevent the postmenopausal patient from synthesizing estrogen) or fulvestrant (which destroys the tumor ER as a pure antiestrogen) as second-line therapies for MBC in which tamoxifen treatment has not worked. Antiestrogenic therapy is the strategy of choice because estrogen stimulates tamoxifen-resistant tumor growth.

Additional transplantation of ER-positive breast tumors with early acquired resistance to tamoxifen into tamoxifen-treated athymic mice for up to 5 years replicates the clinical strategy of 5 years of adjuvant therapy.¹¹ Tamoxifen-stimulated growth continues, but paradoxically physiologic estrogen has a significant antitumor effect.¹¹ Estrogen is cytotoxic, and tumors disappear completely. Yao and coworkers¹⁶ proposed 2 clinical applications: (i) physiologic estrogen to treat MBC af-

Long Term Tamoxifen Treatment For Breast Cancer

Daniela Niemeyer



Long Term Tamoxifen Treatment For Breast Cancer:

Long-term Tamoxifen Treatment for Breast Cancer Virgil Craig Jordan, 1994 During the past twenty years tamoxifen has become the most widely prescribed and most successful drug used in the treatment of breast cancer In this volume editor V Craig Jordan provides articles that trace the development pharmacology and clinical research surrounding this drug which by the year 2000 could be used to treat as many as one million women annually Drawing from research conducted by specialists in the United States the United Kingdom and Italy the series of articles describes the clinical testing of tamoxifen highlighting the benefits Studies show that tamoxifen lowers cholesterol and can potentially protect women against osteoporosis and fatal coronary heart disease Equally important is a discussion of side effects and possible drug interactions and how these issues relate to patient concerns An investigation of the development of a new class of drugs for use after tamoxifen fails provides valuable insight into future treatments as the contributors consider possible resistance to tamoxifen This volume provides invaluable information for physicians and surgeons who care for patients with breast cancer and for women interested in exploring this therapeutic dimension **Tamoxifen and Breast Cancer** Michael W. DeGregorio, Valerie J. Wiebe, 1999-01-01 A discussion of the diagnosis of breast cancer and the risks benefits and limitations of treatment alternatives particularly tamoxifen This edition contains information on developments in the use of tamoxifen especially in the results of the Breast Cancer Prevention Trial

Treatment of the Postmenopausal Woman Rogerio A. Lobo, 2007-06-05 For anyone who treats postmenopausal women this latest edition of Rogerio Lobo s classic work combines the best from two well known references Menopause and the second edition of Treatment of the Postmenopausal Woman By adding significant discussions of the basic science behind menopause it is possible to objectively assess the clinical value and limitations of current approaches to treatment and provide a basis and rationale for strategies that will result in better individualized and specialized care Not only does the third edition discuss diagnosis and treatment of menopause but it covers biological anatomical physiological pathobiological and pharmacological aspects as well bringing together in one source all of the information needed to understand and treat postmenopausal conditions Over 50% new material representing the vast amount of information available since the Women s Health Initiative WHI clinical trials were completed making this the most up to date reference on postmenopausal women Includes several new sections on comparisons between clinical trials and observational data urology and pelvic support Each section is preceded by a preface to put the area into context with many chapters having suggested treatment regimens Biological and Hormonal Therapies of Cancer Kenneth A. Foon, Hyman B. Muss, 1998-01-31 This volume Biological and Hormonal Therapies of Cancer which is part of the series Cancer Treatment and Research presents selected new information concerning biologic and hormonal therapy of cancer We have attempted to provide the reader with topics of major interest in a timely fashion There is renewed interest in biologic therapy of cancer Two chapters review the role of interferon in the hematologic malignancies and in solid tumors Vaccine

therapies have come to the forefront of cancer therapy recently and two chapters approach different strategies of vaccine therapies one reviews the cellular vaccine therapies and another the anti idotype approach The hormonal therapy chapters focus on current uses of endocrine therapy in endometrial breast and prostate cancer In addition hormonal strategies for the prevention of breast cancer and endometrial cancer including exciting information relating to phytochemicals are presented The effects of tamoxifen on endometrium is a topic of major interest and is discussed in detail Finally there is a chapter on estrogen receptor expression and regulation in human breast cancer These chapters are all written by experts in the field and contain timely and relevant information of interest to laboratory and clinical scientists and practitioners alike Biologic and endocrine therapies represent major areas of cancer research interest The advent of newer biologic therapies including new antibody targeted treatments and the use of biologics as tumor modulators to enhance the effects of other treatment regimens is an exploding avenue of research

Tamoxifen Tales V. Craig Jordan, 2022-01-12 *Tamoxifen Tales* Suggestions for Scientific Survival presents a case study describing the academic journey of teams behind major advances in medical sciences highlighting lessons learned that are applicable to the next generation of scientists This book provides a manual on the successful mentoring of young scientists including stories describing how training experience shaped careers to become leaders in academia and the pharmaceutical industry The book documents Professor V Craig Jordan's 50 year career in medical sciences that led to the discovery and development of Selective Estrogen Receptor Modulators SERMs which became the standard of women's healthcare around the world Additionally it illustrates the versatility of a scientist with a commitment to serving societies This important resource will be a useful and interesting book for established medical scientists research mentors and advanced students wanting to chart a successful and impactful research career Highlights lessons learned from the journey behind discovery science that are applicable to the scientific journey of the next generation of scientists Provides a manual on the successful mentoring of young scientists to become leaders in academia and the pharmaceutical industry Examines cancer treatment based on a personal determination to challenge at the frontiers of the science and to relate to personal life experience Includes references for further research reading

Journal of the National Cancer Institute, 1990

Drug Therapy in Nursing Diane S. Aschenbrenner, Samantha J. Venable, 2009 This text presents a totally nursing focused framework for teaching and learning nursing pharmacology and places the patient at the center of all drug administration decisions and considerations The book presents core drug knowledge using prototypes of different drug classes and emphasizes core patient variables that influence the patient's response to therapy This thoroughly updated Third Edition covers newly approved drugs has separate chapters on drugs affecting fungal and viral infections and includes more pathophysiology information FDA Black Box warnings have been added to the discussion of each prototype when applicable and safety alerts have been added to emphasize prevention of common medication errors A companion Website offers student and instructor ancillaries including NCLEX style questions pathophysiology animations medication

administration videos and dosage calculation quizzes Cumulated Index Medicus ,1999 Holland-Frei Cancer Medicine
8 James F. Holland,2010 Holland Frei Cancer Medicine serves as a quick reference to current information on an extensive list of cancers including breast lung thyroid colorectal ovarian prostate and gastric cancer to name but a few Presented as an accessible pocket sized handbook the chapters are organized in an outline format offering only the most essential information on the etiology staging including TNM staging and treatment for each cancer type Individual chapters are devoted to the molecular biology of cancer cancer prevention cancer screening the mechanisms of chemotherapy and diagnostic imaging in cancer Additionally each chapter lists all the major phase III clinical trials and therefore serves as an excellent reference of the major randomized controlled trials for each cancer reported to date Specific chapters are also dedicated to the discussion of oncologic emergencies pain and palliation and prescription complications At the conclusion of the book a glossary of oncologic terms and chemotherapeutic drug programs a table of common cancer incidences and an overview of the mechanisms common uses and related toxicities of various anti cancer agents are featured In addition performance status tables mathematical formulas and a listing of common biomedical cancer web sites are highlighted Clinical Ocular Toxicology E-Book Frederick T. Fraunfelder,Frederick W. Fraunfelder,Wiley A. Chambers,2008-06-12 Written by international authorities in ocular toxicology including the Founder of The National Registry of Drug Induced Side Effects and its current Director this essential resource provides the clinically relevant information you need to effectively diagnose and manage herbal chemical and drug related ocular problems Comprehensive coverage of all drugs generic and trade drug names primary uses ocular and systemic side effects and clinical significance make this book like its best selling predecessor Drug Induced Ocular Side Effects the ideal reference for quick on the spot consultation Leaders in the field provide need to know information on all aspects of ocular toxicology all in one concise reference Data from the National Registry of Drug Induced Ocular Side Effects Casey Eye Institute Portland OR and the World Health Organization Uppsala Sweden help you recognize and avoid drug induced ocular side effects A highly templated format makes retrieval of essential knowledge quick and easy A wealth of full color photographs provide vivid visual diagnostic guidance The latest information on approved medications helps you stay up to date and provide state of the art care Extensive coverage of principles of therapy ocular drug delivery methods to evaluate drug induced visual side effects and the role of electrophysiology and psychophysics gives you the knowledge you need to manage any challenge in ocular toxicology Authoritative guidance on ocular drugs and their use in pregnancy helps you safely manage the unique needs of these patients The inclusion of the WHO classification system helps you determine whether a particular side effect is certain probable or likely to occur

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Table of Contents Long Term Tamoxifen Treatment For Breast Cancer

1. Understanding the eBook Long Term Tamoxifen Treatment For Breast Cancer
 - The Rise of Digital Reading Long Term Tamoxifen Treatment For Breast Cancer
 - Advantages of eBooks Over Traditional Books
2. Identifying Long Term Tamoxifen Treatment For Breast Cancer
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an Long Term Tamoxifen Treatment For Breast Cancer
 - User-Friendly Interface
4. Exploring eBook Recommendations from Long Term Tamoxifen Treatment For Breast Cancer
 - Personalized Recommendations
 - Long Term Tamoxifen Treatment For Breast Cancer User Reviews and Ratings
 - Long Term Tamoxifen Treatment For Breast Cancer and Bestseller Lists
5. Accessing Long Term Tamoxifen Treatment For Breast Cancer Free and Paid eBooks

- Long Term Tamoxifen Treatment For Breast Cancer Public Domain eBooks
 - Long Term Tamoxifen Treatment For Breast Cancer eBook Subscription Services
 - Long Term Tamoxifen Treatment For Breast Cancer Budget-Friendly Options
6. Navigating Long Term Tamoxifen Treatment For Breast Cancer eBook Formats
 - ePub, PDF, MOBI, and More
 - Long Term Tamoxifen Treatment For Breast Cancer Compatibility with Devices
 - Long Term Tamoxifen Treatment For Breast Cancer Enhanced eBook Features
 7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes of Long Term Tamoxifen Treatment For Breast Cancer
 - Highlighting and Note-Taking Long Term Tamoxifen Treatment For Breast Cancer
 - Interactive Elements Long Term Tamoxifen Treatment For Breast Cancer
 8. Staying Engaged with Long Term Tamoxifen Treatment For Breast Cancer
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers Long Term Tamoxifen Treatment For Breast Cancer
 9. Balancing eBooks and Physical Books Long Term Tamoxifen Treatment For Breast Cancer
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Long Term Tamoxifen Treatment For Breast Cancer
 10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
 11. Cultivating a Reading Routine Long Term Tamoxifen Treatment For Breast Cancer
 - Setting Reading Goals Long Term Tamoxifen Treatment For Breast Cancer
 - Carving Out Dedicated Reading Time
 12. Sourcing Reliable Information of Long Term Tamoxifen Treatment For Breast Cancer
 - Fact-Checking eBook Content of Long Term Tamoxifen Treatment For Breast Cancer
 - Distinguishing Credible Sources
 13. Promoting Lifelong Learning
 - Utilizing eBooks for Skill Development

- Exploring Educational eBooks

14. Embracing eBook Trends

- Integration of Multimedia Elements
- Interactive and Gamified eBooks

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