Resistance to Targeted Anti-Cancer Therapeutics 8
Series Editor: Benjamin Bonavida

Alexey Larionov *Editor*

Resistance to Aromatase Inhibitors in Breast Cancer

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Resistance to Targeted Anti-Cancer Therapeutics

Volume 8

Series editor

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For several decades, treatment of cancer consisted of chemotherapeutic drugs, radiation, and hormonal therapies. Those were not tumor specific and exhibited severe toxicities in many cases. But during the last several years, targeted cancer therapies have been developed. Targeted cancer therapies—sometimes called "molecularly targeted drugs—are drugs or other agents (e.g., anti-bodies) that block the growth and spread of cancer by interfering with specific gene products that regulate tumor cell growth and progression".

We have witnessed in the last decade a significant explosion in the development of targeted cancer therapies developed against various specific cancers. These include drugs/antibodies that interfere with cell growth signaling or tumor blood vessel development, promote the cell death of cancer cells, stimulate the immune system to destroy specific cancer cells, and deliver toxic drugs to cancer cells. One of the major problems that arises following treatment with both conventional therapies and targeted cancer therapies is the development of resistance, preexisting in a subset of cancer cells or cancer stem cells and/or induced by the treatments. Tumor cell resistance to therapies remains a major problem and several strategies are being considered to reverse the resistance to various manipulations. *Resistance to Targeted Anti-Cancer Therapeutics* focuses on the basic and translational research behind the molecular mechanisms of resistance found in many kinds of anti-cancer therapeutics.

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Preface

Breast cancer is the most common female cancer, affecting up to 10 % of women in the developed world through their lifetime. Aromatase inhibitors (AIs) are indicated to treat postmenopausal estrogen receptor positive (ER+ve) tumors, which constitute the majority of breast cancer patients. AIs significantly improve treatment outcomes compared to previously used endocrine treatments. However, 10–15 % of patients relapse within 5 years of adjuvant treatment, about 25–50 % of the patients do not respond to AIs in a neo-adjuvant or metastatic setting, and the majority of metastatic patients who initially respond develop resistance within 3 years. Thus, there is a need to understand the mechanisms and to develop methods of preventing or overcoming the resistance to AIs.

While some of the mechanisms of AI resistance may be in common with other endocrine treatments, such as Tamoxifen, there is no absolute cross-resistance in different endocrine treatments. This book reviews current experimental and clinical data specifically focused on AIs, including (i) genetic regulation and protein structure of aromatase, (ii) molecular mechanisms and markers of AI resistance, and (iii) data from clinical trials combining AIs with novel-targeted treatments. The goal was to bring together the current knowledge from different areas, ultimately putting the biological and experimental facts into the clinical context.

While each chapter has its own focus, they have been written to talk about different aspects of the same story, rather than as a collection of isolated stories. The book starts and ends with clinical chapters, which frame the central core focused on the biology of aromatization and on different mechanisms of resistance. In Chap. 1, Prof. David Cameron provides a concise introduction to the history and current role of aromatase inhibitors in breast cancer clinics. Then, Prof. Nobuhiro Harada gives a comprehensive review of structure, regulation, and polymorphisms of the aromatase gene, with particular focus on the alternative tissue-specific promoters and genetic regulatory elements. In Chap. 3, Prof. Debashis Ghosh and coauthors describe structural studies of the aromatase protein. They review the overall crystal structure, positioning in the membrane, and the possibility of oligomerization, as well as motion and flexibility within the aromatase molecule. This chapter also illustrates how new knowledge about the enzyme's active site lays the foundation

for the development of new aromatase inhibitors. Further, the book advances to a chapter on experimental models which have been devised to study aromatase inhibition in breast cancer, comparing a variety of cell lines and xenografts resistant to aromatase inhibitors, as reviewed by Gauri Sabnis and Angela Brodie. Then, Prof. Per Lonning addresses an apparently simple question of how can we measure the efficiency of aromatase inhibition in clinic. Plasma estrogen levels are low in postmenopausal women, in particular when on aromatase inhibitor therapy. Professor Per Lonning reviews methodical challenges of applying radio-immunoassays to measure estrogen levels in blood and tissues of breast cancer patients. In fact, because of the expertise required for such measurements, until very recently, the data on estrogen levels in AI treatments were limited by a relatively small number of studies with small numbers of enrolled patients. These studies reviewed by Per Lonning indicated the exquisite potency of AIs, which led him to the conclusion that inefficiency of inhibition is an unlikely cause for resistance (at least in a carefully controlled research setting). However, in a dramatic turn, just after the completion of this chapter, a new study was published, which implements mass spectrometry for simultaneous measurements of estrogens, AIs, and their metabolites in a large multicenter study with several hundreds of patients [1]. This study suggests that in a real-life clinical environment, there is possibility of inefficient inhibition in 8 % of patients. In some isolated cases, no drug was detectable in blood and the estrogen concentration was increasing during treatment. This study is discussed in a later chapter by Alexey Larionov and William Miller, who speculate that such variation in efficiency of AIs may be linked to differences in drug metabolism as well as to issues with treatment adherence or patient selection.

To characterize mechanisms of AI resistance in one word, a suitable term would be “diversity.” This is fully reflected in the following four chapters that focus on the mechanisms of AI resistance in cases when the aromatase inhibition had been efficient. Elizabeth Sweeney with Craig Jordan highlighted that not only can estrogens stimulate growth, but they can also cause apoptosis of breast cancer cells. The balance between these apoptotic and growth-stimulating aspects of estrogens is changed during estrogen deprivation. The authors review the biology of estrogen-induced apoptosis and relate it to the new concept of using “breaks” in aromatase inhibitor therapy (as tested in the SOLE clinical trial). The role of ligand-independent ER signaling in AI resistance is reviewed by Jean McBryan and Leonie Young, who discuss various sites of ER phosphorylation, role of ER cofactors, and involvement of the cross talk between ER and growth factor pathways into hypersensitivity of ER to low concentrations of estrogens. Epigenetic determinants of resistance to aromatase inhibitors are reviewed by Raffaella Maria Gadaleta and Luca Magnani. Starting with the epigenetic regulation of the aromatase gene, they then discuss the role of histone modifications and pioneering factors in facilitating ER-mediated transcription, specifically focusing on the recent studies relating genome-wide ER-binding patterns to AI response. This chapter also discusses epigenetic regulation of ER itself, and describes the current state of epigenetic-based medicine in the context of endocrine therapies. The section on diversity of molecular mechanisms of AI resistance is concluded by Abdul Aziz Bin Aiderus and

Anita Dunbier, who describe experimental aspects of resistance via non-endocrine signaling pathways (including PI3K/mTOR, IGF, GDNF, and Myc pathways) as well as the role of tumor microenvironment (including inflammatory immune cells and adipocytes) in AI resistance. A series of recent studies highlighted role of activating mutations in ligand-binding domain of ER, which might be detected in 20–50 % of breast cancers, acquired endocrine resistance [2, 3]. Interestingly, these mutations are not present in primary breast cancers [4]. A chapter was commissioned about the role of ER mutations in AI resistance. However, circumstances prevented completion of this chapter. Readers interested in this mechanism of resistance are advised to read recent papers of Robinson et al. [2] and Toy et al. [3] as well as earlier studies and comprehensive reviews of Prof. Fuqua [4, 5].

The final section of this book brings the reader back into the clinical realm. It includes three chapters, which (i) discuss prediction of response to aromatase inhibitors, (ii) review clinical trials aimed to prevent or overcome AI resistance, and (iii) describe clinical use of aromatase inhibitors beyond breast cancer. Accurate prediction of response is needed to select an effective treatment and to avoid unnecessary side effects in patients who are unlikely to respond to AIs. Numerous studies have evaluated the utility of routine biomarkers (ER, PgR, HER2, and Ki67), multigene signatures (e.g. Intrinsic subtypes, Oncotype Dx, SET, Endopredict, and others), and multi-component clinical indices (e.g. PEPI and Adjuvant! online). These studies and markers are reviewed by Alexey Larionov with William Miller; they also discuss the technologies of biomarker development and some future markers, which could be used for the patients' selection and monitoring. Numerous clinical trials attempted combining AIs with novel-targeted agents (including HER2, EGFR, mTOR, PI3K, Akt, CDK4/6, FGFR, HDAC, IGF-1, Src, Proteosome-, and angiogenic-targeted agents). These trials are reviewed by Hazel Lote and Stephen Johnston. A number of the combinations have not yet fulfilled expectations (e.g. the combination with anti-angiogenic agents). On the other hand, the first examples of success are the combinations of AIs with mTOR and with CDK4/6 inhibitors. An important aspect of the combined treatments is that the new agents need companion biomarkers, to personalize the treatment selection (consistent with the experimental data about diversity of AI resistance mechanisms). Finally, in the last chapter of this book, Prof. Lev Berstein summarizes AIs use outside of the treatment of breast cancer, including other malignancies (e.g. endometrial cancer and endometrial uterine sarcoma) and some non-oncological indications (e.g. endometriosis, fertility treatment and abortion).

Many of the chapters provide extensive historical overviews that show the inner logic of the field and connect the historical studies to the present state of the art. Overall, the book brings together current knowledge from different relevant areas, including molecular and clinical aspects of AIs resistance, and is directed at scientists developing new treatments for ER+ve breast cancer and at medics treating breast cancer patients with aromatase inhibitors.

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