Introduction to the Conference, Aromatase: New Perspectives for Breast Cancer

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Basic and clinical data suggest that human breast cancers can be divided into hormone-dependent and hormone-independent subtypes. The biological behavior and responsiveness to treatment of these two subgroups are different. Measurement of estrogen and progesterone receptors serves to characterize mammary tumors as hormone dependent or hormone independent with an overall accuracy of approximately 80%. Clinical and biochemical data suggest that one-third of human tumors fall into the hormone-dependent category and two-thirds are the independent subtype. Thus, of the 110,000 new cases of breast carcinoma diagnosed in the United States yearly, approximately 35,000 will be hormone dependent. A variety of data suggest that estrogen is the major hormonal stimulus for growth of the hormone-dependent type of breast carcinoma. The enzyme aromatase is the rate-limiting step in estrogen production. Consequently, it is logical to consider that this enzyme could play a key role both in the pathogenesis of hormone-dependent breast cancer and in its treatment.

The conference, Aromatase: New Perspectives for Breast Cancer, was organized to bring together a group of investigators with breadth and depth of expertise regarding aromatase. The speakers represented the disciplines of anatomy, biochemistry, physiology, endocrinology, obstetrics-gynecology, oncology, pharmacology, medicinal chemistry, and surgery. The multidisciplinary interchange which ensued stimulated new insights into the significance of aromatase and the potential of reversible and irreversible inhibitors of this enzyme.

During the conference, development of pharmacological methods to block estrogen synthesis as potential treatment of breast cancer was discussed. For the design of any new anticancer agent, two alternative investigative strategies, the inductive and deductive approaches, can be used. The first, or inductive, approach has been most commonly used in the last 15 years to develop new anticancer drugs. With this method, the need to develop cytotoxic antitumor drugs was first identified as a targeted goal. Multiple compounds were then screened in animals using the destruction of experimental tumors as the end point of therapeutic efficacy. Promising agents were then introduced into Phase I clinical trials in patients. After the antitumor activity of certain compounds was established, hypotheses were then developed to explain the exact mechanism of action of these agents. This strategy has led to the development of a wide variety of useful therapeutic agents.

The second strategy, the deductive approach, best describes the history of development of aromatase inhibitors. This strategy requires as the first step the development of a hypothesis. Experimental data are then collected to substantiate the hypothesis and to develop a broad understanding of the biological and biochemical mechanisms involved. Specific inhibitors or drugs with desired mechanistic effects can then be rationally developed. These must be tested in biological systems and compared with alternative therapy approaches.

The development of aromatase inhibitors for treatment of hormone-dependent breast cancer has generally followed the deductive approach. Because of this, the conference on aromatase was structured upon an outline of the deductive strategy. Several years ago, Dr. Peniti Siiteri first raised the hypothesis that aromatase, the rate-limiting step for estrogen biosynthesis, is important for the growth of breast and endometrial cancers (1). The speakers in the first two sessions, entitled "Physiology, Biochemistry and Biological Significance" and "Epidemiological Considerations: Aromatase, Obesity, and Breast Carcinoma," discussed the concepts related to this unifying hypothesis. The next several sessions covered experimental data regarding biochemical, biological, and structure-function studies of aromatase. The design of a number of competitive and suicide aromatase inhibitors was then reviewed in the sessions entitled "Pharmacological Inhibitors of Aromatase: Biochemical Studies," and "Pharmacological Inhibitors of Aromatase: In Vivo Studies."


The data presented at this workshop conference provided a framework for further study of the significance of aromatase and the importance of developing ideal inhibitors. Important target areas for further studies were identified. These included establishment of the significance of estrogen production directly in breast cancer tissue, further epidemiological studies of aromatase and its relevance for development of breast cancer, and the development of better treatment regimens with available aromatase inhibitors to reduce side effects and toxicity, and the development of more potent or selective aromatase inhibitors to allow inhibition of ovarian as well as extraglandular estrogen production.

References

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*Cancer Res* 1982;42:3268s.

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