

OPENING REMARKS

According to the WHO "estimate", about 100,000 women all over the world are going to develop breast cancer each year and half of them are still condemned to die of their disease, in spite of adequate treatment of primary tumor. There is now evidence that adjuvant therapy may provide a slight but significant improvement in survival following mastectomy.

However, the fate of patients following relapse, has not been improved by chemotherapy and hormonal manoeuvres and palliation still represents the main achievement for these patients. Indeed both chemotherapy and hormone therapy have reached a plateau in their capability to control the outcome of disseminated breast carcinoma, the only major advancement in this area being provided by the possibility of improving the selection of patients as far as hormonal treatment is concerned, on the basis of the availability of hormone-dependency indicators, such as specific receptors for estradiol and progesterone. Among the possibilities presently under investigation to improve results either in the adjuvant setting or those of disseminated disease, it is the concurrent administration of cytotoxic drugs with hormones which deserves particular attention on the basis of the following considerations:

(1) there is ample experimental and clinical evidence that human breast cancer results from different cell clones, which may have or acquire a different sensitivity to cytotoxic drugs and hormones;

(2) chemotherapy and hormone therapy have different mechanisms of action and their toxicities are usually not overlapping.

From a strategical point of view a combination of these modalities in breast cancer may be attempted to achieve different goals:

(1) hormones may be used to perturb tumor kinetics and in particular to increase the sensitivity of tumor cells to chemotherapy;

(2) the concurrent use of chemotherapy and hormone therapy may result in an additive, or better sub-additive, effect by killing simultaneously as many cell clones as possible.

Both strategies seem appealing, even if from the theoretical point of view they are not lacking in negative implications, whose significance in the clinical setting should be further defined.

In fact the former strategy may prevent the development of cytokinetic resistance to drugs, which certainly may play a role in explaining the relapse of patients during adjuvant chemotherapy or short-lived responses in patients with advanced disease, but it cannot overcome primary or acquired genetic re-

sistance to drugs, which has been shown to occur spontaneously in tumor cells. Indeed, repeated exposure of hormone-sensitive clones to cyclic pulses of hormones might produce an otherwise uncontrollable stimulation of tumor growth, which could be detrimental, especially in patients with early breast cancer. While the preliminary results of clinical trials adopting this strategy in advanced breast cancer do not appear to be superior to those achieved by chemotherapy alone, data in locally advanced breast cancer or in the adjuvant setting are still limited or missing. The second strategy may imply the risk of interfering with chemotherapy activity, as hormones, and in particular antiestrogens, *in vitro* have been shown to rest tumor cells in the G₀ phase of cell cycle. The results of trials employing chemotherapy and hormone therapy concurrently, whilst still contradictory, seem to confirm the existence of an additive effect on response rate and duration of response, which is however greater and also advantageous with respect to survival, only in some subsets of patients—the sequential use of these modalities still being preferable as a standard approach to patients with disseminated disease.

The symposium held in Lerici has been specifically asked to focus on these strategies in view of the data already available, with the hope of contributing to the stimulation of further fundamental and clinical research in order to answer a number of as yet unsolved questions and possibly open new therapeutic possibilities.

The organizers (Drs L. Santi, F. Boccardo, J. C. Heuson, I. Nenci and S. Toma) would like to convey their gratitude to the speakers as well as to all those who took part to the meeting, contributing to its success and would like to thank the town of La Spezia for its warm hospitality and the local authorities for their logistic and financial aid.

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They are also grateful to Dr S. Jacobelli and Dr M. Namer who determined that such symposium would take place as a satellite meeting of the 2nd International Congress of Hormones and Cancer, which was held in Monte Carlo previously.

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Editors