CLINICAL CONSIDERATIONS ON THE METASTASES OF MAMMARIAN CANCER

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Summary: The Authors examine the prognostic value of metastatic breast cancer and the consequent possibility of therapy. They discuss the role of steroid receptor determination both in prognosis and in planning treatment. Their personal experience confirms the positivity of Progestinic receptors as a more specific index of hormono-sensitivity in regard to the positivity of the single estrogen receptors. Concerning therapy, in metastatic breast cancer the association between chemo- and hormono-therapy may offer better results, acting on different cell populations, though it probably does not improve the survival rate.

The important acquisitions obtained in recent years in treating breast cancer are related to a deepened understanding of the natural history of the neoplasia. In particular it is of fundamental importance to note the concept according to which mammarian cancer must be considered a systemic disease right from the moment of diagnosis ([1]). In fact it is known how often a mammarian carcinoma classifiable as early from a clinical instrumental point of view can demonstrate the biological behaviour of advanced stage neoplasia.

Such observation explains the high incidence of failure with traditional loco-regional therapies, even when they are carried to the extreme limits of radicality and of integration. In fact if we observe the localisation of relapses after treatment regarded as radical, we can see how the incidence of distant localisation (43% visceral, 28% osseous) is significantly greater than loco-regional ones (28%), indicating how it is not so much the local radicality that has failed, but rather the failure of recognition of the metastases already present at the time of diagnosis ([2]).

It is already well known how the presence of lymphnodal metastases indicate the probability that the mammarian neoplasia has passed the limits of loco-regional extent to become a systemic disease.

The presence of lymphatic diffusion is accompanied in a significantly statistical way by worsening prognosis, also dependent upon the number of the lymphnodes interested.

It is notable too how the increase in the volume of the neoplasia increases the risk of lymphnodal diffusion ([4]), while no relation between the receptorial state and the incidence of lymphnodal metastases seems to exist. This last revelation therefore supports the concept that the receptorial state is a prognostic indication independent of other biological and clinical characteristics of the neoplasia. If, however, we consider the relative risk of relapse, both in relation to the lymphnodal and the receptorial states a positivity of lymphnodal metastases may be asserted which is prognostically unfavourable to the receptorial state (tab. 1) ([16]).

Also in the range of patients with positive lymphnodes it is possible to recognise some sub-groups of patients with diversified prognoses on the basis of some histopathological characteristics of the neoplastic tissue (tab. 2).

Of these characteristics the one that seems most relevant is the presence or otherwise of metastatic cells on the inside of vessels attatched to the affected lymphnode. Such characteristics of the ag-

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Table 1. — *Relative risk of breast cancer recurrence associated with ER and lymph nodes metastases.*

		R.R.	P
LN−; ER−	VS LN−; ER+	1.26	0.62
LN+; ER+	VS LN−; ER+	2.65	0.002
LN+; ER−	VS LN−; ER+	4.64	0.0003

Date from F. F. Parl, 1984.

Table 2. — *Breast cancer with L.N. metastases significant variables in the proportional hazard method in descending order of magnitude.*

	p. value
Tumour cells in efferent nodal vessels	0.000
Mean nuclear area	0.001
No. positive nodes	0.002
Tumour diameter	0.015
Grading	0.017

Maehle B. O. (*Br. J. Surg.*, 1985, vol. 71), pp. 459.

gressivity of mammarian neoplasias with lymphatic metastases is also refelected in the therapeutic problems which the introduction of precautionary chemotherapeutic problems has raised.

In fact, from what has emerged from the clinical study controlled by the Tumour Institute of Milan ([7]), premenopause patients with lymphatic diffusion of up to a maximum of three lymphnodes affected seem to find benefit from auxiliary chemotherapy.

From this derives the fact that today, even with post-surgical treatment of the systemic type it is not possible to modify significantly the unfavourable prognosis of patients with gross lymphnodal disease. Besides the 20% of neoplasias judged clinically operable we may note the intensive preoperative staging of distant metastases, which prejudices the possibility of radical treatment ([8]).

The distribution of the metastatic localisations shows, as we know, a wide spectrum, and, what is most interesting, conditions the different clinical behaviour of the neoplasia. This indicates that there are extremely diversified biological aspects, varying from case to case in such a way as to even alter the sensitivity to various treatments.

It is in fact significant that the percentage of response to treatment differs in relation to the type of metastatic localisation (soft tissues. skeleton, visceral metastases) ([9, 10]). Furthermore, the response to treatment has proved different within each of these single categories of localisation. In particular the visceral metastases show different sensitivity to pharmacological treatment in relation to the parenchyma involved, and thus with the soft tissues; which therefore indicates further biological differences in the neoplasia ([11]).

With the aim of identifying such biological differences in the neoplasia the emerging datum of recent literature which has shown most significance in predictability of clinical responses to treatment is that related to the determination of the hormonal receptors.

In fact, in our experience and from the data in literature, it appears that the percentage of response to hormonal-therapy in function of the positivity of the estrogenic receptors is highly significant. With the only parameter ER it is possible to distinguish neoplasias at different degrees of hormone-sensitivity and with different probabilities of response to hormone therapy (tab. 3). When both the receptors for the estrogens and those for progesterone are present the prognosis of the therapy is more favourable, with percentages of positive response to hormonal therapy up to 76% compared with 9% observable when both the receptors are negative (ER–, PR–) (tab. 4). The contemporary study of the receptors to the estrogens and progesterone therefore allow us to establish a different gradient of hormone-sensitivity among the ER– neoplasias themselves, with the possibility of further

Table 3. — *Response rate to endocrine therapy according to ER status in advanced and metastatic breast cancer.*

	Cases	Response rate
ER−	8/72	11%
ER+/−	13/87	15%
ER+	29/58	50%
ER+++	34/46	74%

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Table 4. — *Response rate to endocrine therapy according to ER and PgR status in advanced and metastatic breast cancer.*

	Cases	Response rate
ER+/PgR+	62/81	76%
ER−/PgR+	11/39	28%
ER+/PgR−	7/26	27%
ER−/PgR−	7/78	9%

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recourse to hormone-therapy in those of PgR+ in relation to the PgR–.

Such recent acquisitions, as well as the different distribution of the hormonal receptors in relation to the metastatic site ([12]), justify, from the biological point of view, what has already been noted from the clinical point of view regarding the different hormonal-sensitivity of the metastatic localisation related to the different receptorial concentrations. The parenchimal metastases proved in fact less hormone-sensitive inasmuch as they are related to a neoplasia of lower receptorial tone and therefore to a more aggressive clinical approach.

From a therapeutic point of view however, such biological-clinical correlations may not always be respected. This is related to the fact that, inside the tumour itself exist heterogeneous populations of cells of varius receptorial concentrations. Such cellular heterogeneity may prove particularly important in metastatic neoplasias since:

— the original site of the neoplasia and its metastases can demonstrate the different levels of response to treatment, just like the different levels of hormonal receptors ([13]);

— treatment both with chemo-therapy and with hormone-therapy can modify the receptorial concentration, justifying the progress which may be observed after a transitory favourable response ([14]).

That, from a clinical point of view, has led to the recourse, in cases of metastatic disease, to combined chemo-hormonal treatments, with the aim af acting contemporaneously on hormono-sensitive cellular clones and on the hormono-insensitive ones, leaving out of the global consideration hormone sensitivity related to the determination of the receptors.

Even if controlled clinical studies on the subject are still limited, we may observe that:

1) the chemo-hormonal therapy association produces significantly better results in respect to chemo-therapy alone in terms of complete or partial reponse ([15, 16, 17]).

2) probably, however, it does not increase the index of survival in metastatic mammary carcinoma ([18]).

CONCLUSION

From what has been stated we may conclude that from a clinical point of view, the metastases reflect the different biological behaviour in mammary neoplasia sufficiently to be able to identify, even within the disease in its advanced stage, three different types of clinical behaviour:

1) Neoplasia with slight aggressiveness;

2) Neoplasia with moderate aggressiveness;

3) Highly aggressive neoplasia.

This on the basis of the site of the metastatic localisation, on the free interval after primary treatment, on the recep-

torial condition, and on the pre- or post-menopausal condition ([19]).

Our clinical experience and the data in literature indicate how, in the present state of our knowledge, chemo-hormonal-combined therapy is prevalently indicated when we are in the presence of highly aggressive disease, that is:

— patients with multi-metastatic localisations, including the visceral;

— the appearance in pre-menopausal age;

— with brief free interval;

— with neoplasia having slight hormone-receptor content.

Such integrated treatment in fact, acting on different cellular populations and with diverse mechanisms, modulated and in rapid sequence, seems to lead not so much to addictions as to synergism of action on a heterogenous and highly aggressive cell population.

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