Pergamon

European Journal of Cancer Vol. 32A, No. 1, pp. 7–8, 1996

Printed in Great Britain
0959-8049/96 $15.00+0.00

0959-8049(95)00637-0

Editorial

The Prognostic Value of Cathepsin D in Breast Cancer. A Long Road to the Clinic

H. Rochefort

Institut National de la Santé et de la recherche Médicale, Unité 148-Hormones et Cancer, Université de Montpellier 1, 60 rue de Navacelles, 34090 Montpellier, France

THIS ISSUE of the *European Journal of Cancer* contains a review on cathepsin D in breast cancer [1] by two basic scientists (pp. 15–24)and an original paper written by physicians and asking a practical question: "What to add to the number of metastatic nodes to select high risk early breast cancer patients?" [2] (pp. 41–46). These two papers clearly illustrate the huge distance between an unchanged clinical practice and the explosion of new information provided by basic research. The issue of prognostic biological parameters is exemplary in this respect.

The review by Westley and May on the biology of cathepsin D in cancer [1] is well documented and objective and there is little to add except two recent findings. We have recently proposed that cathepsin D overexpression might stimulate cell proliferation of micrometastasis in nude mice by inactivating a secreted growth inhibitor [3] rather than by facilitating evasion through basement membrane. Moreover, the double knock out of the cathepsin D gene in mice [4] has recently indicated that, contrary to other proteases, which are often redundant in their function, cathepsin D is unique at weaning in preventing apoptosis in thymus and epithelial cell renewal in the small intestine. The homozygous new born mice, which develop normally *in utero*, die at day 25 with small intestine necrosis and thymocyte apoptosis. By contrast, the half-life of bulk proteins was unaltered. One major function of cathepsin D may therefore be to provide essential growth factors for renewal of certain epithelial tissues and to facilitate interactions between epithelial cells and components of extracellular matrix [5] rather than to degrade proteins in lysosomes where other cathepsins can replace cathepsin D.

Concerning the clinical significance of cathepsin D, the merit of the review by Westley and May is to integrate the different clinical studies performed independently from 1989 to date and to draw tentative conclusions on the prognostic value of cathepsin D. The overall bad prognostic significance of high cathepsin D levels, mostly in node positive patients, suggested in a 1992 review [6], now appears to be confirmed. Obviously, more prospective studies on a larger number of patients are required, mainly to define which markers are the best in a multiparametric study.

I fully agree with the authors, as we pointed out previously [7], that one should not mix data obtained by well standardised and controlled cytosolic assays, which consistently indicate worse prognostic value for high cathepsin D tumour, with those obtained by immunohistochemistry using different antibodies without standardised quantification, which are totally confusing. The discrepancy and confusion arise when these two methods of quantification are mixed.

To return to the practical question of the physicians "What to add to the metastatic nodes . . ." [2]. Perrone and associates suggest in this issue (pp. 41–46), adding only clinical and pathological parameters. Everyone would agree that node invasion and tumour size are two major prognostic indicators. The authors, however, seem to ignore all biochemical markers, understating that we do not need them at all. Oestrogen and progesterone receptor (ER and PR) assays, after at least one decade of debate and controversy [8,9], have nevertheless finally entered the clinical practice, mostly as first predictive markers of anti-oestrogen responsiveness. At this point, most physicians are confused by the increasing number of molecular parameters which are proposed and by conflicting results for the same marker. One reason for this confusion originates from mixing results obtained from reliable and non-reliable techniques (see above). Another reason originates from mixing the markers which have been only proposed as a hypothesis or on the basis of a small number of clinical studies dealing with a small number of patients, with the markers for which there has been a sufficient number of independent clinical studies. To reply to the practical question "What to add to the classical clinicopathological grading of the tumour" [2], I would propose that in 1996, rather than ignoring all new biological markers, we should really begin to perform at least

Received and accepted 16 Nov. 1995.

a partial molecular grading of the primary breast tumour at time of surgery. This staging can only be done once (contrary to circulating markers) and the information obtained will be useful to define a systemic treatment, either adjuvant or after relapse. Since not too many markers can be performed (lack of tissue and money), we should only select the more reliable markers that give biochemical, quantitative and objective information on three independent characteristics of the tumour: (1) its hormone responsiveness (ER, PR or PS_2, 2); its degree of proliferation (S-phase, or thymidine kinase, labelling index, K 67, etc.); and (3) its invasive capacity by assaying at least one protease (cathepsin D or urokinase) or one of its inhibitors (PAI-1) [10]. Cathepsin D and PAI-1 are particularly convenient since they can be assayed in the same cytosolic extract as ER and PR which have entered clinical practice.

This is not to propose that, in the future, other markers will not be shown to be as or more useful. For instance, the immunohistochemical assays of p53, particularly in node negative patients, and of Neu-$ErbB_2$, in predicting resistance to chemotherapy, appear to be most promising. In fact, clinical oncologists not only need reliable prognostic markers, generally useful in node negative tumours, but also need predictive markers to determine which adjuvant treatment will be useful and efficient in both node negative and positive tumours. In this respect, cathepsin D may be a marker of responsiveness to anti-oestrogen therapy [11], even though not correlated to the ER. More prospective studies on a greater number of patients, taking into account the type of adjuvant therapy, are needed to specify whether or not high cathepsin D is associated with resistance to the classical chemotherapy, which may explain its higher prognostic value in node positive patients in some of the studies. In the meantime, in order to stage the prognosis of breast cancer, it seems timely to begin using a few reliable and independent molecular markers which are available rather than no marker at all.

1. Westley BR, May FEB. Cathepsin D and breast cancer. *Eur J Cancer* 1996, **32A**, 15–24.
2. Perrone F, Carlomagno C, Lauria R, *et al.* Selecting high-risk early breast cancer patients: what to add to the number of metastatic nodes? *Eur J Cancer* 1996, **32A**, 41–46.
3. Liaudet E, Derocq D, Rochefort H, Garcia M. Transfected cathepsin D stimulates high density cancer cell growth by inactivating secreted growth inhibitors. *Cell Growth Differ* 1995, **6**, 1045–1052.
4. Saftig P, Hetman M, Schmahi, *et al.* Mice deficient for the lysosomal proteinase cathepsin D exhibit progressive atrophy of the intestinal mucosa and profound destruction of lymphoid cells. *EMBO J* 1995, **14**, 3599–3608.
5. Briozzo P, Badet J, Capony F, *et al.* MCF7 mammary cancer cells respond to bFGF and internalise it following its release from extracellular matrix: a permissive role of cathepsin D. *Exp Cell Res* 1991, **194**, 252–259.
6. Rochefort H. Cathepsin D in breast cancer: a tissue marker associated with metastasis. *Eur J Cancer* 1992, **28A**, 1780–1783.
7. Roger P, Montcourrier P, Maudelonde T, *et al.* Cathepsin D immunostaining in paraffin-embedded breast cancer cells and macrophages: correlation with cytosolic assay. *Hum Pathol* 1994, **25**, 863–871.
8. Jensen EV, Block GE, Smith S, *et al.* Estrogen receptors and breast cancer response to adrenalectomy. *Natl Cancer Inst Monogr* 1971, **34**, 55–70.
9. Osborne DK, Yochmowitz MG, Knight WA III, McGuire WL. The value of estrogen and progesterone receptors in the treatment of breast cancer. *Cancer* 1980, **12**, 2884–2888.
10. Foekens JA, Schmitt M, van Putten WLJ, *et al.* Plasminogen activator inhibitor-1 and prognosis in primary breast cancer. *J Clin Oncol* 1994, **12**, 1648–1658.
11. Ferno M, Baldetorp B, Borg A, *et al.* Cathepsin D, both a prognostic factor and a predictive factor for the effect of adjuvant tamoxifen in breast cancer. *Eur J Cancer* 1994, **30A**, 2042–2048.

Acknowledgements—This work was supported by the Institut National de la Santé et de la Recherche Médicale, the Université de Montpellier and the Région Languedoc Roussillon. I thank my colleagues Marcel Garcia and Thierry Maudelonde for their advice on this manuscript.