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Editorial Comment

Tissue inhibitor metalloproteinase type-1 (TIMP-1), a novel cancer biomarker predicting response of adjuvant anthracycline-based chemotherapy in patients afflicted with primary breast cancer

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A central question relating to adjuvant systemic treatment of early breast cancer patients has been whether anthracyclines should be part of chemotherapy or whether it is appropriate to recommend the cyclophosphamide, methotrexate and 5-fluorouracil (CMF) regimen instead.[1] CMF chemotherapy was considered the standard adjuvant therapy for a long time but in a series of meta-analyses the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has established the importance of anthracyclines in the adjuvant setting.[2] Consequently, in the year 2000 the National Institutes of Health (NIH) consensus concluded that 'the inclusion of anthracyclines in adjuvant chemotherapy regimens produces a small but statistically significant improvement in survival over non-anthracycline-containing regimens'[3] even though treatment-related long-term toxicities such as cardiomyopathy and leukaemia were reported.[1] In line with this, several randomised trials conducted in Europe and Canada have examined the efficacy of anthracyclines in the adjuvant treatment of early breast cancer and have also demonstrated a benefit of anthracycline-based chemotherapy over CMF treatment alone.[4]

Epirubicine is an anthracycline drug used in combination chemotherapy for adjuvant breast cancer treatment and acts by intercalating DNA strands which leads to inhibition of DNA and RNA synthesis. Besides breast cancer, epirubicine is used to treat solid malignant tumours of the ovary, stomach and lung, and is also used to treat lymphomas. Epirubicine inhibits DNA cleavage by topoisomerase II-alpha and generates free radicals that may cause cell damage. Accordingly, topoisomerase II-alpha, in conjunction with HER2, has been suggested as a predictor for clinical benefit from adjuvant anthracyclines,[5] although this combination of cancer biomarkers has not yet been recommended for routine clinical decision making.[6]

The article published by Willemoe et al. (Lack of TIMP-1 tumour cell immunoreactivity predicts effect of adjuvant anthracycline-based chemotherapy in patients ($n = 647$) with primary breast cancer. A Danish Breast Cancer Cooperative Group Study) in this issue of the *European Journal of Cancer*[7] is yet another example of the necessity to personalise breast cancer care by considering cancer biomarkers as markers of risk assessment and therapy response prediction

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The authors correctly raise the hypothesis that breast cancer patients whose tumours contain the novel cancer biomarker tissue inhibitor metalloproteinase type-1 (TIMP-1) protein might be less sensitive to adjuvant epirubicine-containing chemotherapy than patients in whom the breast cancer cells were lacking the TIMP-1 protein. The hypothesis is based on the fact that TIMP-1 inhibits apoptosis, including chemotherapy-induced apoptosis.

To understand this hypothesis, one has to know that certain proteolytic enzymes such as the cathepsins, kallikrein-related peptidases, the urokinase-type plasminogen activator uPA and the matrix metalloproteases (MMP) are known to be conductive in promoting cancer cell invasion and cancer progression. Proteolytic action of these proteases is counter-balanced and controlled by endogenous inhibitors. From that, one might expect that endogenous inhibitors, eventually interacting with these proteases, would hinder the cancer process and that cancer patients with increased levels of such inhibitors in their tumour tissue would have a better prognosis than those with low levels of the inhibitors.

However, findings from human tumours have implied that the function of endogenous protease inhibitors such as PAI-1, targeting uPA, and TIMP-1, targeting MMPs, is to promote rather than prevent tumour progression.[8] For instance, high levels of PAI-1 or TIMP-1 correlate with poor prognosis in cancer of the breast, colorectum, stomach, or prostate.[9–11]

TIMP-1 belongs to the mammalian family of tissue inhibitors of metalloproteinases (TIMP) which encompasses three more members, TIMP-2, -3 and -4, all equipped with wide-ranging sequence homology and structural identity. TIMPs modulate extracellular matrix turnover by inhibition of the enzymatic activities of MMPs whereby TIMP-1 is the prototype inhibitor for most MMP family members.[10] Besides its antiproteolytic function, TIMP-1 binds to a cell surface protein complex consisting of CD63 (a member of the tetraspanin family mediating signal transduction events) and ß-1 integrin, causing cell proliferation and inhibition of apoptosis.[10]

In the study by Willemoe et al., a set of 647 tumour tissue specimens obtained from patients randomly assigned to CMF or cyclophosphamide, epirubicine and 5-fluorouracil (CEF) treatment in the Danish DBCG 89D breast cancer trial were immunostained for TIMP-1 protein in order to find out whether the benefit from different adjuvant chemotherapy regimens is related to tumour tissue TIMP-1 protein expression. Clearly, by the use of a simple immunohistochemical test, quantitative assessment of TIMP-1 immunostaining in tissue microarrays prepared from fixed, paraffin-embedded primary breast cancer tissue blocks, it was demonstrated that in the group of primary breast cancer patients subjected to epirubicin-containing adjuvant chemotherapy, absence of TIMP-1 tumour cell immunoreactivity is related to a favourable outcome for patients (Fig. 1). Another important take-home message of this article is that primary breast cancer patients with TIMP-1 protein expressed in their cancer cells would do equally well by receiving the far less toxic CMF instead of receiving anthracycline-containing chemotherapy.

The group of Nils Brünner, the senior author on the article being discussed, was also the first to show a statistically significant association between TIMP-1 and response to chemotherapy in breast cancer[12]; he and his colleagues also showed that cancer cell lines derived from wild-type and TIMP-1 gene-deficient mice displayed significant differences in sensitivity towards chemotherapeutics[13] based on differences in the induction of apoptosis in these TIMP-1 positive or TIMP-1 deficient cancer cell lines.

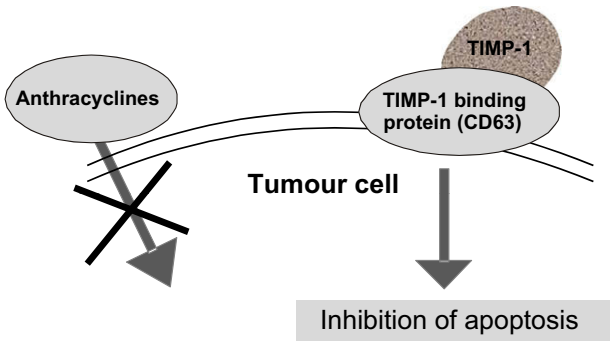

Fig. 1 – Schematic drawing of the antiapoptotic effect of TIMP-1 which in turn abolishes the cytotoxic effect of anthracyclines.

Since claims had been made that the single marker HER2 could identify breast cancer patients who would benefit from addition of anthracyclines in the adjuvant setting,[1,6] a study using the tumour tissue specimens collected within the DBCG 89D trial was conducted, independent from the data presented in the article now published in the *European Journal of Cancer*, comparing HER2, topoisomerase II-alpha, and TIMP-1 expression as single cancer biomarkers against the combinations of HER2 and TIMP-1 and topoisomerase II-alpha and TIMP-1, respectively. The results were presented by Nils Brünner et al. at the recent 2008 31st San Antonio Breast Cancer Symposium, demonstrating that topoisomerase-II-alpha, HER2, and TIMP-1 identify statistically independent subgroups of patients sensitive to anthracyclines.[14]

Furthermore, since anthracyclines are now considered standard chemotherapy agents in the adjuvant treatment of early breast cancer, and since a number of recent breast cancer trials demonstrated a survival advantage when taxanes were added to anthracycline regimens,[15] it is of utmost importance to perform clinical studies to reveal whether TIMP-1 expression in tumour tissue of primary breast cancer patients is of benefit for the patients when taxane-based chemotherapy is administered, in case they are not sufficiently responsive to anthracycline-based chemotherapy. Brünner et al. have already conducted pre-clinical tests showing that TIMP-1 transfected MCF-7 breast cancer cells become resistant to anthracyclines but not to taxanes.[16] From this, we can conclude that, for future trials, the choice of specific anthracycline/taxane regimens should be based on evidence from tumour tissue-associated cancer biomarker expression, such as TIMP-1, to tailor to the particular needs of the individual cancer patient.

Conflict of interest statement

None declared.

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