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PREDICTIVE SCORE AS TREATMENT BASE FOR METASTATIC BREAST CARCINOMA

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The hormone dependence of breast carcinoma is difficult to assay, when the receptor status is unknown. At that moment the choice between a good tolerated hormonal treatment and a more agressive cytotoxic therapy is based on few arguments. To prevent such a dilemma, we developped a predictive score based on well known prognostic factors such as : age, metastatic free period, menopausal status, tissue receptor status, number and localisation of metastasis, response on previous hormonal therapy, previous adjuvant chemotherapy and performance status. This score(S) can theoretically vary between -50 and +60. In order to check this predictive score and to set the limit above which patients should be preferentially treated with hormonotherapy, we reviewed the case reports of 44 evaluable patients. The scores varied from -15 till 32.5(mean:9.3). We first evaluated the correlation between duration of response to a certain treatment and S. The mean duration of response of the whole group was 12.65 months. Patients with a high score(S>20) were treated with hormonotherapy, the low scores with a combined chemo-hormonotherapy. Patients with S>20 had a median response duration (MRD) of 35.5m. and those with S<0 a MRD of 4.64m.($p<0.01$). There was also a significant difference ($p<0.01$) between the group with S<0 and S 0-20 (MRD:4.64 vs 17.14m. respectively). When the limit was put at +10 the MRD was 21.4m. (S>10) and 13.02m.(S<10). ($p<0.05$). Based on this review we can conclude that this predictive score is valuable to classify patients into groups with long or short response duration and that those with a high predictive score should probably benefit from a hormonal treatment, a hypothesis that will be evaluated in a prospective study.

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QUANTITATIVE PROGESTERONE RECEPTOR ACTIVITY (PGR) AND RESPONSE TO FIRST ENDOCRINE THERAPY IN ADVANCED BREAST CANCER

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Data on the predictive value of quantitative PgR analyses with regard to the response to endocrine therapies,are scarce. We studied the clinical significance of quantitative PgR levels in 52 patients with ER+PgR+ breast cancer who received their first endocrine therapy (tamoxifen or ovariectomy). Twelve of these patients had received prior chemotherapy and the remaining 40 did not receive such therapy.Overall, 31 of the 52 (60%) patients responded.Patients with high PgR levels (>100 fmol/mg.protein) responded more often than those with low levels (<100 fmol/mg.protein):17 out of 22 (77%) vs 14 out of 30 (47%) resp.($0.05<p<0.1$)In the group of 25 patients with PgR analyses performed ≤6 months prior to the start of treatment,equal response rates were found for the high and low level groups:7 out of 10 vs 9 out of 15 resp. However,if PgR was analysed >6 months prior to the start of treatment,the quantitative PgR results had a high predictive value:at levels 50 fmol/mg.protein only 1 out of 6 (17%) patients responded;at levels between 50 and 100 fmol/mg. protein 4 out of 9 (44%) responded and at levels >100 fmol/mg.protein 10 out of 12 patients (83%) showed a remission. ($p<0.04$) No significant differences in the other prognostic variables were found between the different subgroups. These data show that high PgR levels as measured long before the start of the first endocrine therapy,have a high predictive value of subsequent response to such treatment.If PgR is analysed closely prior to the start of treatment,merely the presence of PgR is indicative of hormonal responsiveness.

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PROGESTERONE RECEPTOR ACTIVITY (PgR) AND RESPONSE TO FIRST ENDOCRINE THERAPY IN ADVANCED BREAST CANCER:SIGNIFICANCE OF TIMING OF RECEPTOR ANALYSIS.

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The presence of PgR in breast cancer tumor tissue is believed to be a better indicator of hormonal responsiveness than that of the estrogen receptor (ER).Since PgR is more liable to changes in the course of the disease than ER,we studied the predictive value of PgR with special emphasis on the timing of PgR analysis,in a group Of 63 patients with ER+ advanced breast cancer who received endocrine therapy (tamoxifen or ovariectomy) as their first systemic treatment.PgR levels>10 fmol/mg protein were considered positive.In the group of 18 patients with PgR analyses performed immediately prior to the start of treatment,91% of the PgR+ (10/11) and only 29% of the PgR- (2/7)patients responded.($p<0.04$)If the therapy was started ≤6 months after PgR analysis,still a significantly higher response rate was found for the PgR+ patients than for the PgR- ones:72% vs 27%.($p<0.05$) However,if the interval between PgR analysis and start of treatment exceeded 6 months the response rates for the PgR+ and PgR- patients were identical:59% (13/22) vs 50% (6/12) resp.There were no significant differences in any of the other prognostic variables between the PgR+ and PgR- patients.We conclude that the PgR status of breast cancer tissue is useful in predicting the response to the first endocrine therapy only if the PgR status is measured ≤6 months prior to the start of such therapy.

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TAMOXIFEN INHIBITION OF PROTEIN KINASE C.

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Tamoxifen has recently been demonstrated to inhibit rat brain protein kinase C (PKC) in vitro (O Brian et al; 1985, Cancer Research: 45;2462) PKC has an established role in tumour promotion, cell surface signal transduction and also activates the oxidase mechanism in neutrophils. We have utilised the neutrophil as an experimental model to assess the effect of tamoxifen on PKC activity in intact human cells.

Neutrophils from six healthy volunteers were separated through Ficoll-Hypaque centrifugation and stimulated by phorbol-12-myristate-13 acetate (PMA). Neutrophil oxidase activity was markedly stimulated as assessed by both oxygen consumption and oxygen radical production. These parameters were measured by a Clark electrode and luminol dependent chemiluminescence respectively. Tamoxifen inhibited the stimulation in all six examples, $IC50 = 6.1 \pm 1.6\mu M$ ($\bar{x} \pm SEM$). Measurement of intracellular ATP and application of the Trypan Blue Exclusion test showed no significant difference before and after tamoxifen. Other PKC stimulators, Mezerein and Oleoyl Acetyl Glycerol were also inhibited by tamoxifen.

These experiments suggest tamoxifen inhibits PKC in vivo. This inhibition may be central to its antitumour action.