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**Adjuvant chemo-hormonal therapy with cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) with or without medroxyprogesterone acetate for node-positive cancer patients. Update at 7-year follow-up**

The Comprehensive Cancer Center Limburg trial 82-01 is a prospective randomized investigation of the value of the addition of high-dose medroxyprogesterone acetate (MPA) to CAF chemotherapy in patients with node-positive (N+) operable breast cancer (T1-3, N1). The results of 408 evaluable patients, after a median follow-up of 42 months, have been published in *Annals of Oncology* [1] and can be summarized as follows: high dose MPA ameliorates CAF side effects and reduces the risk of metastatic disease in elderly breast cancer patients. Patients >60 years benefitted most from MPA treatment, in particular if freedom from distant metastasis was taken as endpoint (p = 0.02). Overall survival (OS) showed a significant advantage in patients >55 years (p = 0.002). In this letter we report the updated results after a follow-up of 7 years.

After a median follow-up of 84 months the conclusions of the study remain unchanged. No differences in disease-free survival (DFS), distant-metastasis-free survival or OS were found for the patients as a whole (p-values were 0.12, 0.12 and 0.18, respectively). OS curves of all patients whether treated or not with MPA are shown in Fig. 1. Subset analysis revealed a significantly better DFS for the patient group aged between 40 and 60 years than for the group <40 or >60 years (p = 0.002). This difference is MPA treatment independent.

Patients >60 years showed a significantly longer DFS and OS when MPA was added to CAF chemotherapy (p-values 0.05 and 0.008, respectively) (Fig. 2).

By contrast, in the subgroup of patients <40 years, the addition of MPA to chemotherapy proved detrimental: the relative risk (RR) for relapse of breast cancer was 1.6 versus 1.1 for patients with and without MPA, respectively, while the RR in the group >60 years was lower (0.7 vs. 1.0), in favor of the MPA-treated group.

In conclusion, this trial suggests a beneficial effect of MPA in combination with chemotherapy in elderly patients (>60 years). The beneficial effect may in part be explained by higher estrogen receptor (ER) levels in elderly breast cancer patients. In young breast cancer patients (<40 years) MPA added to adjuvant chemotherapy has a detrimental effect, possibly caused by its protective effect on ovarian function during CAF chemotherapy [2], which prevents CAF chemotherapy-induced ovarian ablation. An alternative explanation may be that MPA reduces the cellular ER and PgR content in breast cancer cell lines [3]. This down-regulation of ER content in pre-menopausal breast cancer patients could have a negative influence of endogenous estrogen on the tumor-cell cycle (lower percentage of tumor cells in the proliferative phase) causing a reduced effect of adjuvant chemotherapy on tumor cells in premenopausal patients.

The previously described bone marrow protective effect of MPA [1] is supported by two recent studies demonstrating in vitro that MPA causes a cell-cycle arrest of hematopoietic precursors which protects them from the toxicity of chemotherapy [4], and in vivo that MPA induces a mitotic arrest in hematopoietic stem cells [5].

The combination of MPA and chemotherapy deserves further exploration in postmenopausal breast cancer patients.

P. Hupperets,1 J. Wils,1 L. Volovics,1 L. Schouten,1 M. Fickers,1 H. Bron,1 H. Schouten,1 J. Jager,1 J. de Jong,1 L. Beex,2 H. Hillen1 & G. Blijham3

1Breast Cancer Study Group of the Comprehensive Cancer Center Limburg, Academic Hospital Maastricht, 6202 AZ Maastricht; 2Department of Internal Medicine,
Section of Endocrinology, Academic Hospital Nijmegen; Department of Internal Medicine, Academic Hospital Utrecht, The Netherlands

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