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 $\geq 60$ 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 $\geq 55$ 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 $\geq 60$ 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 $\geq 60$ 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 ($\geq 60$ 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.


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References


