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# LHRH-agonist versus chemotherapy in premenopausal breast cancer?

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Endocrine and chemotherapy are the major standard treatment modalities in breast cancer. Endocrine therapy for breast cancer consists of a variety of medical and surgical ablative treatments. For premenopausal patients with metastatic breast cancer, the classic treatment is ovariectomy. After DeSombre and colleagues showed that a luteinising hormone-releasing hormone (LHRH) analogue could induce tumour regression in an experimental tumour model system (1976), the results of the first clinical study with a LHRH-analogue were reported by Klijn and de Jong in 1982 [1]. Since then, a series of more than 13 phase II studies with various LHRH-agonists (such as goserelin, buserelin and others) have shown an objective response in 161 (38%) of 419 patients [2]. Overall, the objective response rate in Oestrogen Receptor (ER) positive tumours was 50%.

Although direct antitumour effects of LHRH-analogues have been demonstrated *in vitro* and specific LHRH-binding sites have been found in 52–67% of primary human breast cancers, the main mechanism of action of LHRH-analogues is medical castration. The application of depot formulations (long-acting subcutaneous or intramuscular implants) of various LHRH-agonists caused long-term suppression of ovarian oestrogen secretion [2,3]. A relatively large randomised study of 138 premenopausal patients with oestrogen receptor-positive and progesterone receptor-positive metastatic breast cancer showed that treatment with the LHRH-agonist goserelin resulted in a failure-free survival and overall survival similar to those observed after ovariectomy [4]. In addition, other small studies showed no difference between ovariectomy and tamoxifen or a LHRH-analogue.

Recently, a meta-analysis [3] of four trials concerning 506 patients (Table 1) showed that combined LHRH-agonist + tamoxifen treatment was significantly superior to LHRH-agonist treatment alone with respect to response rate ($P = 0.03$), progression-free survival ($P = 0.0003$) and overall survival ($P = 0.02$). In the unique three-arm European Organization for Research and Treatment of Cancer (EORTC) trial (10881), tamoxifen appeared equipotent to LHRH-agonist treatment, but induced a 3–4-fold increase of plasma oestradiol levels [2]. Oestrogen suppression by adding an LHRH-agonist to tamoxifen treatment in the third arm (resulting in postmenopausal oestrogen levels) statistically significantly increased the antitumour efficacy of tamoxifen with respect to all three efficacy parameters with a doubling of the 5-year overall survival to 34% and a lengthening of the median overall survival by 1 year [2]. In addition, a high response rate in patients with (ER-positive) visceral disease was found (60% during combined treatment). On the other hand, the efficacy of standard combined chemotherapy can not be improved by high-dose chemotherapy.

15-year follow-ups from the EBCTCG overview analysis shows that ovarian ablation is as effective as standard adjuvant combined chemotherapy in patients with ER-positive primary breast cancer. Patients with a chemotherapy-induced amenorrhoea have a significant better prognosis than patients with a continuing ovarian function. Four randomised trials showed similar efficacy by surgical or medical castration in comparison with standard adjuvant chemotherapy. Five other randomised trials demonstrated that combined endocrine therapy by ovarian ablation plus tamoxifen showed a trend to or indeed a significantly better disease-free survival when compared with standard chemotherapy [5].

## 1. Conclusions

In ER-positive premenopausal breast cancer combined endocrine treatment with a LHRH-agonist + tamoxifen is presently the first choice of treatment,

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Table 1
Summary of results by treatment group (meta-analysis of four studies concerning 506 patients)

| Endpoint | LHRH-agonist alone ($n = 256$) | LHRH-agonist plus tamoxifen ($n = 250$) | Hazard Ratio/Odds Ratio (95% CI) |
|---|---|---|---|
| Objective response (%) | 29.7 | 38.8 | 0.67 (0.46–0.96) |
| Median progression free-survival (months) | 5.4 | 8.7 | 0.70 (0.58–0.85) |
| Median survival (years) | 2.5 | 2.9 | 0.78 (0.36–0.96) |

95% CI, 95% Confidence Interval. From Ref. [3].

while in ER-negative disease chemotherapy is preferred. For the near future, the application of aromatase inhibitors, pure anti-oestrogens, and molecular targeted treatment modalities within the treatment regimens has to be considered.

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