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A randomised trial of buserelin and tamoxifen in metastatic breast cancer

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Keywords

Breast cancer, buserelin, endocrine therapy, tamoxifen

Introduction

Oestradiol deprivation and/or antagonism has for many years been the mainstay of the endocrine therapy approach to breast cancer treatment. The classical treatment approach is medical castration, which is possible with the use of the luteinising hormone-releasing hormone (LHRH) agonists such as goserelin and buserelin. An alternative to castration is the use of tamoxifen (Tam), a nonsteroidal anti-oestrogen, which, as one of its modes of action, blocks the oestrogen receptor on breast cancer cells. Tam therapy has been shown to induce high levels of plasma oestradiol, which may compete with tamoxifen for binding to the oestrogen receptor, thus leading to a decrease in antitumour effect. By combining Tam with an LHRH agonist, a complete oestrogen blockade could be achieved. This may in turn improve disease control in oestrogen-sensitive breast cancers.

Aims

To investigate the effect of combining oestrogen suppression with the LHRH agonist buserelin and oestradiol receptor blockade using Tam in patients with advanced breast cancer.

Comments

This interesting study asked whether combined endocrine blockade is superior to single agent endocrine therapy in premenopausal patients with advanced breast cancer. This is similar to prostate cancer management where combined androgen blockade versus single agent blockade has been highly controversial, and keenly studied. Unfortunately, this trial was slow to accrue and the numbers were small, falling far short of the original target of 348 patients. This markedly diminishes the power and impact of the study and really leaves the question unanswered. Another weakness in the study was the inclusion of patients with unknown receptor status. Obviously the inclusion of receptor-negative patients

will affecrt responses and outcomes. Hopefully, endocrine studies initiated in the mid to late 1990's will limit recruitment to proven receptor-positive patients, enabling a clearer picture of the true impact of endocrine strategies to emerge, and to help us to finally answer the question of what is the most appropriate approach to endocrine therapy in all stages of breast cancer.

Methods

Eligible patients were premenopausal with locally advanced/metastatic breast cancer and no previous treatment for advanced disease. Patients with receptor-negative tumours or with tumours of unknown receptor status who had a disease-free interval of less than two years were excluded. Adjuvant therapy with Tam (interval >12 months) and/or chemotherapy (interval >6 months) was allowed. Patients were randomised into one of three groups: (i) buserelin implants (6.6 mg subcutaneously every 8 weeks) alone; (ii) Tam (40 mg orally daily) alone; or (iii) a combination of the two drugs at the same doses. Upon progression, those patients on a single treatment were encouraged to cross over to the other single treatment. Plasma oestradiol levels were measured every 6-8 weeks during the first 12 months and thereafter every 16 weeks.

Results

Between 1988 and 1995, 161 patients were randomised (9 were ineligible and 7 not evaluable). Patient and tumour characteristics were well balanced among treatment groups. Median follow-up on all patients was 7.3 years, during which 76% of patients died, all of breast cancer. Combined treatment with buserelin and Tam appeared superior to either treatment alone. This was reflected in the objective response rates (combined 48%, buserelin 34%, and Tam 28% of evaluable patients; P=0.031); median progression-free survival (9.7 months, 6.3 months, and 5.6 months respectively; P=0.03); and median overall survival (3.7 years, 2.5 years, and 2.9 years respectively; P=0.01). The death hazard ratios for patients treated with buserelin or Tam alone were 1.95 (65% CI=1.23-3.10) and 1.63 (95% confidence interval (CI)=1.03-2.59), respectively, when compared to patients receiving the combined therapy. Actuarial 5-year survivals were 34.2% (95% CI=20.4%?48.0%), 14.9% (95% CI=3.9%?25.9%), and 18.4% (95% CI=7.0%?29.8%) respectively. Combined treatment or treatment with buserelin alone suppressed plasma oestradiol levels to normal postmenopausal values within 6 weeks of starting treatment. Patients treated with Tam alone had increased plasma oestradiol levels threefold to fourfold higher than pretreatment levels. Hot flushes were more common in patients treated with buserelin; nausea was more common in patients treated with Tam. Two of 161 patients (both on Tam alone) stopped treatment due to side effects (severe hot flushes).

Discussion

The administration of buserelin, either alone or in combination, resulted in prolonged suppression of plasma oestradiol levels. Tam use alone markedly elevated levels of oestradiol. Whether plasma oestradiol levels themselves impacted upon clinical outcome is unclear, as there was no difference in outcome when Tam-alone patients were compared with buserelin-alone patients. Patients receiving combined endocrine blockade had higher response rates, prolonged disease-free intervals and improved overall survival. This result is in concordance with those from two other studies comparing a single endocrine agent with combined blockade. There is increasing evidence to suggest that combined endocrine blockade is as effective as, and possibly superior to, treatment with standard dose chemotherapy in receptor-positive premenopausal women with early stage breast cancer.

References

1. Klijn JG, Beex LV, Mauriac L, van Zijl JA, Veyret C, Wildiers J, Jassem J, Piccart M, Burghouts J, Becquart D, Seynaeve C, Mignolet F, Duchateau L: Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: a randomised study. J Natl Cancer Inst. 2000, 92: 903-911.