Wednesday, 17 March 2004 08:30–09:15

EUROPA DONNA TEACHING LECTURE

The rationale for primary medical treatment

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The rationale for primary medical treatment

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This lecture will concentrate on the rationale for primary chemotherapy and primary endocrine therapy.

Chemotherapy:

1. The first rationale of primary chemotherapy lies in its potential to perform more conservative treatments. This approach was first used in locally advanced breast cancer and has rendered operable many inoperable patients. More recently it has been used in large operable breast tumours and randomized trials demonstrated up to 50% reduction in the mastectomy rate.
2. The second rationale derived from preclinical models suggests that primary chemotherapy may have a larger impact on survival than adjuvant chemotherapy. Unfortunately these results have not been confirmed in clinical practice. We will summarize the data of randomized trials which compared adjuvant versus neoadjuvant treatment in more than 3000 patients.
3. Another clinical rationale is that primary chemotherapy should allow to tailor the treatment to clinical or pathological response. We will critically review this important, but still unanswered question.
4. Last but not the least, neoadjuvant chemotherapy allows to test in vivo the sensitivity of the primary tumour, instead of treating blindly as with the adjuvant approach. It gives the opportunity to develop new surrogate markers of response such as pathological complete response. If the increase in pathological response rate observed in recent trials transfers in a survival advantage, this may change the definition of endpoints in future clinical trials allowing to speed up the implementation of clinical trials results in practice.

Endocrine therapy:

1. As shown with chemotherapy, a preclinical study suggests that tamoxifen given prior to surgery improves survival of mice in this model. Unfortunately this rationale favouring primary endocrine therapy has not been tested in the clinical setting. There is no randomized trial comparing neoadjuvant endocrine therapy followed by surgery at an appropriate time versus surgery followed by endocrine therapy. It remains an underinvestigated area.
2. Data begin to emerge suggesting that primary endocrine therapy, more precisely antiaromatase treatment, should allow for more breast conservative surgery. We will review these trials.
3. As demonstrated in primary chemotherapy, an important rationale favouring primary endocrine therapy is that it allows to test the sensitivity of the tumour in vivo and to develop surrogate markers, of which we will present some examples.

Wednesday, 17 March 2004 10:30–12:30

KEYNOTE SYMPOSIUM

Primary medical treatment of breast cancer: from empirical to tailored medicine

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Selection factors: choice of treatment, choice of patients

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Although clinical trials evaluating the efficacy of primary medical therapy (PMT) started more than a decade ago, in current practice this treatment strategy can be offered as a consolidated option only to those patients presenting with large operable tumors, who are otherwise candidate to mastectomy. The lack of a targeted approach based on the tumor biological profile and on the type of response achieved after PMT has probably hampered a broader use of this treatment option.

Several data are now confirming that the efficacy of primary chemotherapy, evaluated in terms of response rates, is compromised in patients with endocrine-sensitive tumors. In this cohort of patients new clinical trials evaluating the activity of primary hormonotherapy combined with anti-HER receptors compounds are eagerly awaited in the attempt to increase/restore sensitivity to hormonal manipulations.

In endocrine-resistant tumors cytotoxic compounds are the only validated PMT. Preclinical and early clinical data suggest that tumors carrying p-53 gene mutations might be resistant to DNA-damaging agents such as anthracyclines and alkylating compounds but not to cytotoxics targeting the mitotic spindle like taxanes. In p-53 "wild type" tumors anthracyclines might be highly effective particularly in case of concomitant topoisomerase II alpha gene amplification and/or high proliferation rate. Prospective trials are ongoing in the attempt to validate these hypotheses currently based on early data.

Gene micro-array technology has given an early impulse to the identification of molecular profiles with a potential predictive value. Nevertheless, currently reported micro-array studies suffer of some methodology caveats such as the limited number of evaluated patients and the poor validation of the pilot study results. Moreover, quality control issues such as interlaboratory reproducibility assessments are still pending.

A new generation of trials testing new compounds and/or challenging the predictive value of some molecular profiles is currently ongoing and might lead to a broader use of PMT in the near future.

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Towards optimisation of endocrine treatment

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Neoadjuvant therapy given to patients with large operable or locally advanced breast cancers has the advantage that it can reduce tumour volume making inoperable tumours operable or patients who would have required a mastectomy, suitable for breast conserving surgery. Early studies with tamoxifen indicated that significant reductions in volume are achievable by giving primary hormonal therapy. In Edinburgh a series of postmenopausal patients with oestrogen receptor rich breast cancers were treated with three months of neoadjuvant aromatase inhibitors. Responses with letrozole, anastrozole and exemestane appeared greater than those with tamoxifen with higher rates of conversion from mastectomy to breast conserving surgery. Recurrence rates after breast conserving surgery following neoadjuvant endocrine therapy have also been acceptable with only one local recurrence in 79 patients who received post-operative radiotherapy at a median follow up of 4 years. A subsequent double dummy randomised multicentre trial performed in 337 postmenopausal patients with oestrogen receptor positive breast cancers which were locally advanced or required a mastectomy confirmed the superiority of the aromatase inhibitors. Letrozole 2.5 mg once a day was compared with tamoxifen 20 mg once a day for four months; there was a significantly greater response rate with letrozole clinically (55% v 36%, $p<0.001$), mammographically (35% v 25%, $p<0.001$) and on ultrasound (34% v 17%, $p<0.042$). Furthermore, greater numbers of patients in the letrozole group (45%) than in the tamoxifen group (35%) were suitable for breast conserving surgery at the end of the study, $p=0.022$. Letrozole was highly significantly superior to tamoxifen in the randomised study in patients whose tumours were ER and PgR positive and were erbB1 or erbB2 (HER2) positive. Recent data from Edinburgh indicate that anastrozole is also effective in the neoadjuvant setting in HER2 3+ over expressing cancers. Patients' own views on their experience of receiving neoadjuvant therapy with both letrozole and anastrozole will be included in this presentation. A recently completed study (IMPACT) has compared neoadjuvant anastrozole alone tamoxifen alone or the two combined in 330 postmenopausal women with ER positive disease and/or PR positive large operable or potentially operable breast cancers (130). Patients were randomised to receive anastrozole 1 mg a day, tamoxifen 20 mg a day or the two drugs combined for three months. Many of these patients had tumour biopsies at 14 days and these were assessed along with the excised tumour. This study demonstrated no differences in overall response rates – OR 37.2% for anastrozole, 36.1% for tamoxifen and 39.4% for combination – but did show a significantly improved rate of conversion to breast conserving surgery in patients who would have required a mastectomy, when treated by anastrozole alone compared to the other two groups. There were 124 patients requiring a mastectomy and the response rates in this group were 39% for anastrozole, 27.8% for tamoxifen and 35.7% for the combination. The rates of conversion from mastectomy to breast conservation were 45.7% for anastrozole, 22.2% for tamoxifen and 26.2% for the combination, anastrozole versus tamoxifen $p=0.03$, RR 2.05 (1.03–4.09). Pathological assessment of tumours demonstrated significantly greater reductions in