acid exhibited a 50% inhibitor concentration (IC_{50}) of 15 μM, which was approximately 50-fold lower than the IC_{50} of clodronate, and demonstrated synergistic antitumor effects with paclitaxel and doxorubicin. Moreover, in animal models of breast cancer metastasizing to bone, zoledronic acid was shown to significantly reduce skeletal tumor burden and to prevent the formation of new bone metastases at lower concentrations than any other bisphosphonate tested. These studies suggest that concentrations of zoledronic acid achievable in bone tissue are capable of inhibiting tumor growth. Therefore, studies are planned or ongoing to investigate the clinical benefit of zoledronic acid and other bisphosphonates in the adjuvant setting. The AZURE study is now recruiting patients and is evaluating the effect of zoledronic acid on disease-free survival in 3400 patients with stage II/III breast cancer receiving standard adjuvant chemotherapy and/or hormonal therapy. Patients will be randomized to placebo versus zoledronic acid (monthly × 6, every 3 months × 8 doses, then every 6 months × 5 doses). In addition, the Southwest Oncology Group will soon commence a large randomized trial to compare the benefits of oral clodronate (1600 mg/day), oral risedronate (30 mg/day), and IV zoledronic acid (4 mg every 3 wks for 6 months, and every 3 months thereafter) for 3 yrs as an adjunct to standard adjuvant therapy in women with stage I, II, or IIIA breast cancer.

Conclusions: Preclinical data and data from the metastatic setting support the investigation of zoledronic acid as an adjunct to standard adjuvant therapy to prevent bone metastasis in patients with early-stage breast cancer.

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Gemcitabine/epirubicin/paclitaxel as primary chemotherapy in stage II–IIIA operable breast cancer: Final results of a multicenter Italian study

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The purpose of this study was to evaluate pathologic complete response rate (pCR) and toxicity of preoperative chemotherapy (CT) with Gemcitabine, Paclitaxel and Epirubicin (GET) in patients with stage II/IIIA operable breast cancer. An additional endpoint was to evaluate the expression and modulation of some biological markers with prognostic and/or predictive potential. pCR was defined as the absence of invasive tumor cells in the breast. From October 2000, 44 patients have been enrolled: all patients received Gemcitabine 1000 mg/sqm days 1 and 8 plus Epirubicin 90 mg/sqm day 1 and Paclitaxel 175 mg/sqm day 1, every 21 days for 4 courses, followed by surgery. Median age was 49 years (27–67); clinical staging was IIA, 11 pts; IIB, 18 and IIIA, 15. Hormonal status was positive in 33 patients, negative in 10 and unknown in 1. Grade III/IV neutropenia occurred in 63.9% of cycles and febrile neutropenia in 1.9% of the cycles; G-CSF was administered in 3.2% of the cycles to shorten the duration of G4 neutropenia. Non hematological toxicity included G3 NV in 4.5% of patients, G3 mucositis in 6.8%, G3 diarrhoea in 2.3% and G3 alopecia in 100%. 41 patients completed the chemotherapy programme and received surgery: overall clinical RR was 90.2% (29.3% CR; 61% PR). Absence of invasive breast cancer (pCR) was documented in 6 pts (14.6%) and was associated with negative axillary nodes in 3 of them. pCR raised up to 40% and 22.2% in T < 3 cm and in node negative patients, respectively. The following biological markers were assayed at baseline and on the surgical specimens: HS, Mib1, SBR grade and Her 2-neu expression. Mib 1 > 20% was present in 83% of the patients at baseline and in 17% at surgery; Her2 neu was positive in 27% of the pts at baseline and in 9% at surgery. Final results from this study will be presented at the meeting.

65 POSTER

Pharmacoeconomic aspects of adjuvant early breast cancer treatment in postmenopausal women with anastrozole or tamoxifen: a Slovenian perspective

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Background: A cost-of-care analysis was performed to compare the costs associated with adjuvant treatment in postmenopausal early breast cancer (EBC) patients using either anastrozole (AN) or tamoxifen (TAM). Our intention was to establish which of the two approaches imposes less on society.

Methods: Cost-of-care analysis was used in this assessment. The efficacy of both drugs was obtained from an ATAC trial after the median observational time of 33.3 months. All health care costs were acquired mainly from the Institute of Oncology, Ljubljana and Institute of Health Insurance of Slovenia. In order to calculate the overall costs we had to evaluate the costs of treatment of a primary EBC, new primary EBC, and the costs of disease progression. In order to estimate the costs related to disease progression a group of 20 randomly assigned metastatic breast cancer patients was chosen. The patients' medical charts were examined and costs of treatment for a period of 3 years were calculated. Since no economic evaluation of human life exists in the Slovenian health care system, these costs could not have been included in the analysis. Additionally, the analysis that we made did not take into account the costs related to adverse effects of both treatment arms.

Results: The hypothetical cost calculation based on the treatment of 450 postmenopausal women with EBC, which is also the approximate number of new cases per year in Slovenia, showed that AN results in higher overall treatment costs than TAM. The total sum of all direct healthcare costs over 33.3 months was 4.665 million EUR (10,367 € per person) in the AN arm, and 3.081 million EUR (6847 € per person) in the TAM arm. Despite the higher overall treatment costs associated with AN we succeeded to show a conversion of drug cost ratio of AN/TAM = 7.3/1 to a ratio of only 1.5/1 in favour of TAM, considering overall treatment costs.

Conclusions: The overall treatment cost ratio of 1.5/1 in favour of TAM shows that despite its higher initial costs AN could be an acceptable choice of treatment even in countries with smaller health care budgets.

66 POSTER

The benefits of adjuvant hormonal therapy in patients with early breast cancer 35 years old or younger

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Purpose: The purpose of our study was to determinate the benefits of adjuvant hormonal therapy (HT) in patients (pts) with hormone receptor (HR) positive breast cancer ⩽35 years (y).

Patients and methods: The data from 51 breast cancer pts ⩽35 y treated at the Institute of Oncology Ljubljana from September 1993 to October 2002 were analysed. All pts received radical local treatment and adjuvant systemic therapy was preformed according to the institutional guidelines.

$\chi 2$ test was used to calculate the differences in tumour characteristics; Kaplan Maier curve and log-rank test were applied to present the differences in survival between the subgroups.

Results: HR positive (+) tumours were found in 28 pts (56%) out of 51 pts; in one patient HR status was unknown. HT was preformed in only 12/28 (42%) pts with HR+ tumours (tamoxifen in 10 pts and tamoxifen and LHRH agonist in 2 pts). Sixteen HR+ pts did not receive HT, which was according to the institutional guidelines valid until 1998 (8pts), for 8 pts the reason is not known. In the majority of pts (84%) adjuvant chemotherapy was preformed.

Between the subgroups of HR+ pts, treated or not by HT, no significant differences in terms of percentage of pts treated by adjuvant chemotherapy and in terms of tumour characteristics (size, grade, number of lymph nodes involved) were found.

After the median follow up of 3.3 years the 3-y disease free survival (DFS) for the whole group of pts was 70%; for HR+ pts 72% and for HR− pts 66% (p=NS), respectively. 3-y DFS for HR+ pts treated by HT was as high as 100% and it was only 53% for HR+ pts not treated by HT (p=0.0063).

Conclusion: Our results clearly showed the benefit of HT in the HR+ early breast cancer pts ⩽35 y.

67 POSTER

Cost-effectiveness of various guidelines for adjuvant systemic therapy in primary breast cancer

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Background: During the previous decade guidelines for adjuvant systemic therapy for primary breast cancer repeatedly changed. The impact of the implementation of new guidelines on the workload of medical specialists and outpatient nurses and on the hospital-budget is rarely taken into account. In this study the change in the total number of eligible patients

for adjuvant therapy was estimated as well as the cost-effectiveness of treatment according to the 1998 guidelines compared to the conventional policy (year 1994) and of treatment according to the 2001 guidelines compared to the 1998 guidelines.

Methods: Estimated percentages of patients eligible for adjuvant therapy in 1994, 1998 and 2001 were based on clinical data from 128 patients who were operated in 1994. 10-Years overall survival rates were used as a measure of effectiveness, based on two EBCTCG meta-analyses [Lancet, 1998]. For the costs of the treatment options, actual resource costs were calculated. With a decision analytic model, the incremental cost-effectiveness ratios (conventional (year 1994) *versus* 1998 and 1998 *versus* 2001) were calculated to estimate the incremental costs per life years gained resulting from implementing the novel guidelines.

Results: The introduction of the 1998 guidelines resulted in a relative increase of 96% in the total number of eligible patients compared to 1994 (from 36% to 70%), with minimal differences for the 2001 guidelines. With an estimated absolute increase of 2% 10-years overall survival the 1998 guidelines were found to have an expected incremental cost-effectiveness ratio of approximately 3400 euro per life-year gained compared to the conventional policy.

Conclusion: The implementation of these new guidelines considerably affected the workload of medical specialists, as a result from a substantial increase of the number of patients eligible for adjuvant systemic therapy. However, the incremental cost-effectiveness ratio is well within the range of values that are generally considered acceptable.

68 POSTER

Darbepoetin alfa given once every 3 weeks (Q3W) either synchronously or asynchronously with Q3W chemotherapy (ctx) improves anaemia in patients with breast cancer: results of a randomised, open-label study

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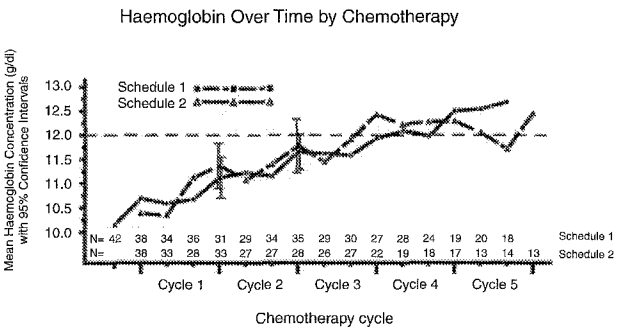
Background: The timing of administration of erythropoietic therapy relative to multicyclic ctx in anaemic patients (pts) with cancer may affect the response of the pt (Hartley et al., 2003; Glaspy, 2002). To evaluate the effect of timing and efficacy of Q3W administration, darbepoetin alfa (DA; Aranesp®) was given Q3W either synchronously or asynchronously with Q3W ctx treatment in pts with non-myeloid malignancies.

Materials and Methods: This was a randomised, multicentre, open-label study. Eligible pts were ⁎18 years old, diagnosed with a non-myeloid malignancy, anaemic (haemoglobin [Hb] ⁎9 and ⩽11 g/dL), and were receiving ctx on a Q3W schedule. Pts were randomised 1:1 to receive DA at 6.75 mcg/kg Q3W on schedule 1, asynchronous (day 15; ie, 7 days prior to the next ctx cycle) or schedule 2, synchronous (day 1 of ctx cycle) for up to 16 weeks. The primary endpoint was Hb assessment after 6 weeks to prevent confounding effects of delays to ctx, pt attrition, and differential dose escalation in the 2 treatment groups. An optional pharmacokinetic study was available to pts to assess concentrations of endogenous erythropoietin and of DA at prespecified time points within the first 3 weeks of the first administration of study drug. Pts were allowed to continue DA treatment if receiving Q3W ctx treatment.



Note: Available Data analysis: Error bars represent 95% Confidence intervals at end of chemotherapy cycle 1 and 2

Results: A total of 81 pts were randomised (43 to schedule 1; 38 to schedule 2). The breast cancer pts comprised 40% of the study population (20 on schedule 1; 12 on schedule 2) and represented the most common tumor type in the study. Of all pts, most were women (74%). For all pts, the mean (95% CL) change in Hb from baseline at week 7 (ie, primary endpoint) was 0.95 (0.56, 1.33) g/dL for schedule 1 and 1.03 (0.58, 1.47) g/dL for schedule 2. Hematopoietic response (Hb ⁎ 12 g/dL or Hb rise from baseline ⁎ 2 g/dL; Kaplan-Meier proportion) was similar between the schedules, at 74% (95% CL: 61, 87) for both groups combined. For all pts, the median (95% CL) time to a hematopoietic response was 49 (36, 5) days. Safety data will also be presented.

Conclusion: DA Q3W for the treatment of chemotherapy-induced anemia is effective regardless of the timing of administration relative to ctx. Less frequent administration of DA is possible due to the approximate 3-fold longer half-life compared with epoetin alfa. In pts with breast cancer, Q3W administration of DA allows for once-per-cycle dosing, as many breast cancer ctx regimens are given Q3W.

69 POSTER

NNBC-3 Europe Study: A trial to improve risk estimation and risk adapted adjuvant chemotherapy in node negative breast cancer patients by using new uPA and PAI-1 and to analise the efficacy of a sequential FEC–taxane chemotherapy versus a standard FEC–chemotherapy regimen

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Introduction: Recent results demonstrated strong evidence for the routine use of the invasion markers uPA and PAI-1 as prognostic factors in node-negative breast cancer patients. In contrast to risk estimation by St Gallen criteria, the use of these tumour-biological factors can spare approximately 50% of all node-negative breast cancer patients from adjuvant chemotherapy. Node-negative patients with elevated tumour tissue levels of uPA and PAI-1 had a similar risk recurrence as node-positive patients. Using adjuvant CMF therapy, a remarkable reduction of recurrences in high risk patients has been achieved. However, in these patients anthracycline and taxane combinations might be even more efficient.

Study Design: In order to evaluate these questions, we initiated a trial with the following design: Centres who participate have to decide whether they would perform risk estimation by traditional clinico-pathological factors or by tumour-biological factors uPA and PAI-1. After risk estimation by one of these methods low risk patients will be observed without adjuvant chemotherapy. High risk patients will be randomised to adjuvant chemotherapy using six courses FEC-100 versus three courses FEC-100 followed by three courses Docetaxel. All patients who had steroid receptor positive tumours will receive adequate endocrine therapy. Patients with HER-2/neu overexpressing tumours can be included into the adjuvant Herceptin® trial "HERA".

The study is planned to recruit 2392 patients in the high risk group. The study is performed in association with the EORTC Receptor and Biomarker Group and the German AGO Breast Group.

Questions: Two questions have to be answered:

- Does tumour biological risk estimation provide a more precise identification of patients who will benefit from adjuvant chemotherapy than traditional clinicopathological selection?
- Is an anthracycline and taxane containing sequence (FEC-Docetaxel) more efficient?

70 POSTER

The influence of classical prognostic factors and adjuvant chemotherapy on disease outcome in early grade 3 node-negative, and 1–3 node-positive breast cancer patients treated with adjuvant cyclophosphamide, methotrexate and fluorouracil (CMF), or untreated patients

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We evaluated a group of early breast cancer patients, diagnosed from 1986 to 1994, who were treated either with adjuvant CMF chemotherapy, or received no further therapy.

Sixty-six women with node-negative disease and grade 3 invasive breast carcinomas, and 95 women with 1–3 involved lymph nodes regardless of tumor grade received cyclophosphamide 500 mg i.v. D1–D4, methotrexate 35 mg i.v. D1 and D4, and fluorouracil 500 mg i.v. D1–D4 every 4 weeks. Untreated group consists of 25 node-negative women with grade 3 breast cancers and 49 patients with 1–3 involved nodes not treated with adjuvant systemic therapy, which were diagnosed and operated at the same time as were the women in CMF group. Log rank test was used to assess