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.

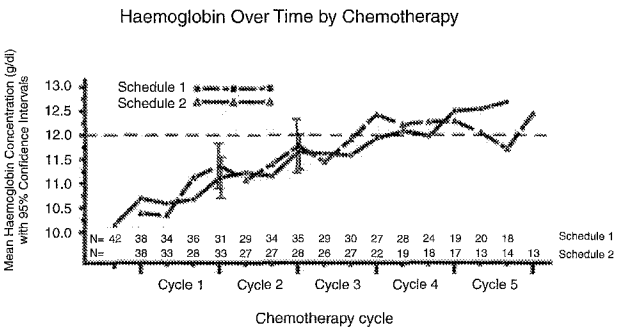
68 POSTER

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

M. Rahn Kim[5], J. Glaspy[1], D. Henry[2], R. Patel[3], N.S. Tchekmedyian[4], R. Berg[5]. [1]*UCLA School of Medicine, Los Angeles, USA;* [2]*Joan Karnell Cancer Center, Philadelphia, USA;* [3]*Comprehensive Blood and Cancer, Bakersfield, USA;* [4]*Pacific Shores Medical Group, Long Beach, USA;* [5]*Amgen Inc., Thousand Oaks, USA*

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

F. Herbst, N. Harbeck, V.P.R. Mueller, A. Oben, C. Meisner, F. Sweep, M. Schmitt, F. Jaenicke, C. Thomssen. *University Hospital Hamburg-Eppendorf, Clinc of Gynecology and Obstetrics, Hamburg, Germany*

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

S. Susnjar[1], I. Kezic[2], Z. Neskovic-Konstantinovic[1], D. Gavrilovic[2], D. Nikolic-Vukosavljevic[3]. [1]*Institute for Oncology and Radiology of Serbia, Medical Oncology, Belgrade, Serbia;* [2]*Institute for Oncology and Radiology of Serbia, Data Center, Belgrade, Serbia;* [3]*Institute for Oncology and Radiology of Serbia, Laboratory for Receptors and Biology of Malignant Cells, Belgrade, Serbia*

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

the importance of classical prognostic factors in early breast cancer: node status, cancer histology, tumor size, tumor grade, menopausal status, age, ER and PR content. Cox regression models were used to identify variables associated with progression and death and estimate hazard ratios.

The median follow–up period for the CMF group was 81 months, and 61.5 months for untreated group. Five-year disease-free survival (DFS) and overall survival (OS) for the CMF group were 64.9% (95% CI [57.5%–73.1%]), and 79.4% (95% CI [73.1%–86.3%]), respectively, and for the untreated group: 61.9% (95% CI [50.9%–75.4%]) and 70.7% (95% CI [59.7%–83.6%]). Node-positive patients in CMF group had significantly worse DFS than node-negative (Log rank test, p=0.003). Treated patients with PR-negative tumors had better DFS compared to women with PR-positive tumors (Log rank test, p=0.033). It appeared that steroid receptor status is quite important in node-negative group of patients: ER and PR negative patients had better DFS then ER and PR positive patients (for ER: Log rank test, p=0.009, and for PR: p=0.004). Overall survival remained unaffected by SR status in both, node-negative and node-positive patients who had received adjuvant CMF. Adjuvant chemotherapy significantly influenced OS (Log rank test, p=0.015), but not DFS. Furthermore, node-negative patients who took chemotherapy had better DFS and OS then those without adjuvant therapy (Log rank test, p=0.026 and p=0.022, respectively).

Our results showed that positive node status is the only significant predictor of disease progression (Likelihood Ratio test, p=0.007) in CMF and untreated group of patients. Furthermore, adjuvant CMF chemotherapy seems to decrease hazard of death more in a group of patients with negative lymph nodes (by 67%) then in a group of patients with positive nodal status (by 21%).

71 POSTER

The evolving role of bisphosphonates for the prevention of cancer treatment-induced bone loss in patients with breast cancer

R. Therialt[1], M. Gnant[2], J. Gralow[3]. [1]*The University of Texas MD Anderson Cancer Center, Department of Breast Medical Oncology, Houston, USA;* [2]*Vienna University, Vienna, Austria;* [3]*University of Washington Shool of Medicine Seattle Cancer Care Alliance, Seattle, USA*

Background: Cancer treatment-induced bone loss (CTIBL) is a common problem in patients with breast cancer receiving long-term adjuvant therapy with antiestrogens, aromatase inhibitors, or ovarian-ablative chemotherapy. As a result of CTIBL, patients are at increased risk of skeletal complications that may substantially increase skeletal morbidity and reduce quality of life. Studies have shown that bisphosphonates can preserve bone mineral density (BMD) in these patients, indicating a role for bisphosphonates in maintaining bone health when used during therapy for breast cancer. Oral bisphosphonates have been shown to prevent bone loss associated with chemotherapy-induced ovarian failure. Zoledronic acid, which is the most potent bisphosphonate available, has also been shown to preserve BMD in the adjuvant treatment setting with a convenient treatment schedule.

Materials and methods: Evidence supporting a role for zoledronic acid in the prevention of CTIBL in patients with primary breast cancer was reviewed and ongoing/planned trials are described.

Results: Recently Gnant et al. reported the results of ABCSG-012 trial (San Antonio Breast Cancer Symposium, 2002) demonstrating that 4 mg intravenous (IV) zoledronic acid every 6 months maintained BMD in premenopausal women receiving standard hormonal therapy with either tamoxifen or anastrozole (both in combination with goserelin). In patients treated with anastrozole + placebo, BMD in the lumbar spine and hip declined significantly within 12 months compared with zoledronic acid-treated patients. Zoledronic acid (4 mg every 3 months for 1 year) has also been shown to significantly increase BMD compared with placebo in patients with prostate cancer receiving long-term androgen-deprivation therapy (Smith et al., *J Urol*, 2003). Based on these promising results, we have initiated the Z-FAST and ZO-FAST trials. Postmenopausal women with hormone receptor-positive breast cancer receiving initial adjuvant therapy with the aromatase inhibitor, letrozole (2.5 mg/day) for 5 years are being randomized to receive 4 mg zoledronic acid every 6 months, either starting with the initiation of letrozole or at the time a patient exhibits a decline in BMD. Accrual to the Z-FAST trial in the United States is complete.

Conclusions: These studies will confirm the benefit of IV zoledronic acid for the prevention of CTIBL and a clinical strategy for maintaining bone health in patients receiving hormonal therapy for breast cancer.

72 POSTER

A computer programme to calculate for the individual the expected improvement in survival chance from adjuvant therapies

R. Blamey, D. Macmillan, G. Wishart, D. Morgan, M. Mitchell. *Nottingham City Hospital, Breast Institute, UK*

The EBCTCG overviews of adjuvant therapies provide figures of relative risk reduction (RRR). Applied to the survival chance of the individual, shown by the Nottingham Prognostic Index (NPI) the absolute improvement expected from therapies for that individual, may be calculated. The baseline figure ('observed 1980–86') is the survival in NPI groups before the introduction of adjuvant systemic therapies. The 'Expected' figures are the effects on these from the relative risk reductions (RRR) demonstrated in the EBCTCG overviews for each therapy.

Example: Women 50+, % 10 year survival

NPI Group	Observed 1980–86 No adjuvant	Expected Tam 5yr (ER+) RRR 27%	CMF RRR 11%
EPG	84	89	86
GPG	63	73	67
MPGI	59	70	64
MPGII	43	59	49
PPG	15	39	24

Patient age and pathological tumour characteristic (grade, LN stage, size, ER, VLI, herceptin) must be entered. The expected improvements will be given for individual NPI values rather than for groups. The computer programme will be demonstrated and will eventually be accessible on the EUSOMA website.

73 POSTER

Sequential dose dense usage of adriamycin, taxol, high dose cyclophosphamide with G-CSF support improved the survival of breast cancer with ten or more positive lymphnodes than A-CMF regimen

M.C. Liu[1], C.M. Chen[2], P.H. Yang[2], B.L. Yu[2], S.H. Cheng[3], M.H. Tsou[4]. [1]*Sun Yat-Sen Cancer Center, Hematology and Medical Oncology, Taipei, Taiwan;* [2]*Sun Yat-Sen Cancer Center, Surgery, Taipei, Taiwan;* [3]*Sun Yat-Sen Cancer Center, Radiation Oncology, Taipei, Taiwan;* [4]*Sun Yat-Sen Cancer Center, Pathology, Taipei, Taiwan*

Purpose: To evaluate the toxicity and efficacy of the dose dense sequential adjuvant usage of adriamycin followed by Taxol followed by cyclophosphomide for breast cancer with ten or more positive lymphnodes.

Materials and Methods: In the study performed by SYSCC, the patients with more than 3 positive lymph nodes were treated with sequential dose dense Doxorubicin followed by CMF, the overall survival for patients with more than 10 lymph nodes were 50.7% the disease free survival was 36.5% only. It is necessary to improve the adjuvant treatment of breast cancer. We therefore conducted a study of treating the patients of breast cancer with more than 10 positive nodes with dose dense taxol containing regimen.

Results: Totally 60 patient with 10 or more positive lymphnodes have been enrolled for this regimen. Twenty eight patients has completed the treatment for more than 2 years with a median follow up of 46 months. The general constitutional symptoms were tolerable. Although neutropenia and granulocytopenia occurred, only 7 cycles among 270 cycles developed fever, the infection rats were 2.6% (7/270). The disease free survival and overall survival as compared with previous patients treated with will A-CMF showed significantly improved.

Conclusion: Dose dense regimen of adriamycin followed by Taxol followed by cyclophosphamide is feasible. It showed improved DFS and OS as compared the A → CMF regimen.