study of intermittent pamidronate 120 mg infusions in 30 patients with bone metastases from breast cancer, we measured a variety of resorption markers including the peptide-bound N-telopeptide (Ntx) and C-telopeptide (Crosslaps) fragments of type 1 collagen, free deoxy-pyridinoline (Fdpd), and urinary calcium excretion (uCa). Response, measured by a pain score assessing the intensity of pain, analgesic consumption and performance status, was related to both the initial rate of bone resorption and the ability of pamidronate to normalise the rate of resorption. 14/20 (70%) of patients with Ntx levels $\leq$ 2x upper limit of normal achieved a subjective response compared with only 1/9 (11%) with Ntx > 2x normal ($p = < 0.01$). In those patients in whom the rate of bone resorption, as measured by Ntx, returned to normal, the subjective response rate was 66% but response was not seen in patients with persistently raised Ntx ($p = < 0.01$). Similar findings were found for Crosslaps and Fdpd but not with uCa.

PP-8-18 Long-Term Palliation of Metastatic Bone Pain with Intermittent Pamidronate

I. Zekri*, J. Vinholes, O. Purohit, R. Coleman. *YCRC Dept. of Clinical Oncology, Weston Park Hospital, Sheffield, England*

Pamidronate provides useful palliation in around one half of patients. Within this group of responders some patients experience repeated responses to treatment with control of their disease for many months. 52 women with painful, progressing, heavily pretreated bone metastases received pamidronate 120 mg as a 2 hour infusion. No new systemic treatments were allowed but endocrine therapy was continued to avoid a withdrawal response. Patients reporting clinical benefit were retreated on demand for worsening symptoms. The characteristics of the 14 patients (27%) who received $\geq$ 3 treatments have been assessed. They had a median age of 52 (range 36–75) years, median DFI of 32 (range 2–168) months, median time from 1st bone metastasis of 21 (range 2–96) months and 11 had disease confined to the skeleton. Bone resorption as measured by Ntx was > 2x normal in only 2 (14%) of these long term responders and normalised in 13 (93%) patients. Between 3 and 7 treatments (median 3) were received every 2–27 (median 11) weeks. Pamidronate was subsequently discontinued for clinically important skeletal (n = 8) or extraskeletal (n = 2) progression after a median of 47 (range 16–82+) weeks. 4 patients remain on treatment. Single infusions of pamidronate are of clinical value in patients with slowly progressive disease with only modest increases in the rate of bone resorption. For patients with more aggressive disease, more potent bisphosphonates or combined anticancer and bisphosphonate treatment may be required.

PP-8-19 Combination of Intraarterial Chemotherapy with Endocrine Therapy in the Treatment of Liver Metastases of Breast Cancer

E. Yayoi*, S. Maruhashi, M. Tokunaga, N. Masuda, S. Takiguchi, S. Matsui, H. Yano, H. Tateishi, M. Kinuta, H. Maruyama, J. Okamura. *Department of Surgery, Osaka Teishin Hospital 543 Osaka, Japan*

Between 1986 and 1995, we had treated 17 patients with liver metastases of breast cancer with a combination of intraarterial chemotherapy followed by endocrine therapy. Of 17 patients, 9 were treated with one shot intraarterial chemoembolization through hepatic artery using 40–50 mg/body of Farmorubicin and Lipiodol and the other 8 were treated with hepatic infusion chemotherapy using 20–30 mg/body of Farmorubicin every two weeks. All patients were followed by oral administration of 800–1200 mg/day of medroxy-progesterone acetate. The results were as follows: 1. The response rate between two groups was not substantially changed (44.4% in the former group versus 50.6% in the latter group). 2. A median duration of response was 25 months (range 4–45) and 8.7+ months (range 3–25+) 3. At two years, the survival rates were 44.4% and 25.0%. In former group, 5-year survival rate was 22.2%. These date suggest that this combination therapy is effective against liver metastases of breast cancer. Further studies are now in progress.

PP-8-20 Epirubicin (E) + Navelbine (NVB) as First Line Chemotherapy in Advanced Breast Cancer (ABC) Patients (PTS): A Multicentric Phase II Study

E. Baldini[1], C. Tibaldi[1], M. Da Prato[1], A. Chiavacci, M. Di Lieto[2], R. Taviani[3], P. Ghezzi[4], G. Francini[5], L. Fioretto[6], A. Michelotti[1], P.F. Conte[1]. [1] *Oncology Dept. of Radiotherapy and General Hospital of Pisa;* [2] *Oncology Dept. of Radiotherapy and General Hospital of Pistoia;* [3] *Oncology Dept. of Radiotherapy and General Hospital of Empoli;* [4] *Oncology Dept. of Radiotherapy and General Hospital of Arezzo;* [5] *Oncology Dept. of Radiotherapy and General Hospital of Siena;* [6] *Oncology Dept. of Radiotherapy and General Hospital of Firenze S.M. Annunziata*

We are performing a multicenter phase II study in ABC patients to evaluate the activity and the toxicity of the combination regimen EPI + NVB as first line chemotherapy. *Treatment:* EPI 90 mg/sqm i.v. bolus day 1, NVB 25 mg/sqm i.v. day 1 and 8 every 21 days. The treatment is administered on day 1 if WBC $\geq$ 3,500 and/or ANC $\geq$ 500 u/L and PLT $\geq$ 100,000 u/L. The dose of NVB on day 8 is as follows: G2 neutropenia: 25% dose reduction, G3 neutropenia: 50%, G4 neutropenia: NVB omitted. In case of: G4 neutropenia lasting more than 72 hours or febrile neutropenia G-CSF is administered until recovery and a 25% dose reduction is applied in the subsequent courses. *Patient characteristics:* so far 31 pts have been enrolled: median age 64 years (range 39–72), PS0 = 15, PS1 = 6, PS2 = 9. A total of 121 courses have been administered, with a median of 5 courses (range 1–7) for each patient. *Toxicities:* Neutropenia G3 21.1%, G4 70.4%; Thrombocytopenia G3 1.6%; Anemia G4 0.8%; Emesis G3 2.4%; Mucositis G3 4.9%; Diarrhoea G3 1.6%. The median duration of G4 neutropenia is 5 days (range 2–7). The doses on day 1 were reduced at 75% in 30.5% of the courses while the treatment was delayed in 14.8%. On day 8 NVB was omitted in 14.8% of the courses and reduced at 75% or 50% in 23.1% and 8% respectively; G-CSF was administered in 15.7% of the courses. Seven episodes of febrile neutropenia occurred. *Results:* 25 pts are evaluable for response: the overall response rate is 68% (95% C.I. 46.5%–85%) with 3 CR, 14 PR, 6 SD and 2 PD. 5 pts are not evaluable: 4 pts too early, 1 pt worsening PS. *Conclusions:* EPI + NVB is a very active combination regimen in ABC; however, considering the high percentage of neutropenia on day 8 requiring NVB dose reduction, we have modified the original schedule and NVB is now aministered on day 1 and 5. The study is ongoing.

PP-8-21 Response to Neoadjuvant Chemotheraphy in Locally Advanced Breast Cancer

G. Purkalne*, I. Kudaba. *Oncology Center of Latvia, Riga, Latvia LV-1079*

During 1993–1995 22 patients with locally advanced breast cancer (T2–4, N0–2, M0) were treated by the following regimen: two to three cycles of chemotheraphy with FAC schedule + mastectomy. Then almost all patients underwennt postoperative radiotheraphy to regional lymph nodes. Preoperative radiotheraphy was performed in four patients. Nine patients (40.9%) underwent ovariectomy. Adjuvant chemotherapy was continued in all cases for total 6 cycles. Patients with ER positive or unknown tumors then continued hormonetheraphy with Tamoxifen.

The median age of patients was 51 year (33–66). Cytology was diagnostic in 86% and information was as following: 5 patients (23%) had pourly differentiated tumours (G3) and 17 patients (77%) – moderately differentiated tumours (G2).

During the follow-up two patients (9%) died from metastatic dissemination, 14 patients (63%) were alive and free from any mts, 8 patients (36.4%) had further progression of disease. The median disease free survival was twenty one month.

Our experience suggest that neoadjuvant chemotheraphy combined with other treatment modalities is rather effective and possible to prolong disease free survival in locally advanced breast cancer patient group.

PP-8-22 Metastatic Dissemination in the Inflammatory Breast Cancer (IBC)

M. Burić*, S. Filipović, M. Projević, S. Veselinović.

The occurrence of inflammatory breast cancer is of 1 to 4% among all breast cancer. Most patients experience metastatic dissemination within first two years after diagnosis is made. At ou Institute 30 IBC patients were treated with chemotherapy III cycle (CAF regimen: ADR 50 mg/sqm day 1, iv, 5-FU 500 mg/sqm iv., day 1, and Cyclophosphamide 500 mg/sqm iv del, every 4 weeks), then all received radiotherapy, and after another III chemotherapy cycles.

Disease progression/dissemination was registered within mean 8 months (range 1 to 32 months). Local progression was noted in 22 patients, visceral metastases were seen first in 6 patients and bone metastases in one patient.

PP-8-23 Oral Clodronate for Bone Metastases in Breast Cancer

M. Projević*, S. Filipović, S. Veselinović, M. Burić. *Clinic of oncology-University Clinical center-Niš*

Pains due to osteolytic bone lesions may cause severe morbidity in breast cancer patients. Biphosphonates as supportive therapy were used in a group of 20 breast cancer patients with bone involvement. All patients were normocalcemic and were treated on outpatient basis. Clodronate was administered orally in a dose of 1600 mg/day for three months. All patients received Concommitant chemotherapy and/or hormonotherapy due to advanced/disseminated breast cancer. 15 of them received additional local radiotherapy.

Analgesio requirements, standard symptom scores and laboratory test were performed initially, monthly throughout and after treatment completion. X-ray were done initially and after treatment completion. Decrease in bone pain was noted in 12/20 patients with no change in disease status; in 6/8 patients without pain decrease progression of bone involvement was registered after treatment completion.

PP-8-24 The Effect of Vorozole on Tissue Aromatase Activity in Advanced Breast Cancer

P.Chr. de Jong*, J. vd Ven, J.W.R. Nortier, J.H.H. Thijssen, P.H.Th.J. Slee, M.A. Blankenstein. *Department of Endocrinology, University Hospital Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands*

In about 60% of breast cancers estrogens have a growth stimulating effect. Intratumoral estrogen levels depend largely on local production. The enzyme aromatase is considered to be the key enzyme in this respect. We have previously shown that Vorozole is an extremely potent inhibitor of peripheral aromatase activity (Cancer Research 53, 4563–4566, 1993). In the present study its effect on local, in situ, aromatase activity was evaluated. Ten breast cancer patients were treated with Vorozole, 2.5 mg daily, during the week preceding mastectomy. Intratumoral aromatase activity was measured and compared to the values of nine untreated patients. Median aromatase activity was eightfold lower in the treated patients compared to non-treated patients (0.85 vs 7.19 fmol/mg protein/2 h; $p = 0.0002$). These results suggest that Vorozole exerts its antitumoral effect largely through in situ aromatase inhibition in tumor tissue.

PP-8-25 The Clinical Relevance of Static Disease for 6 Months on Endocrine Therapy in Patients with Breast Cancer

J.F.R. Robertson*, P. Willsher, K.L. Cheung, R.W. Blamey. *City Hospital, Nottingham, UK*

This study assessed the value of static diseases (SD) in 255 breast cancer patients who received both first and second-line endocrine therapy.

Patients were categorised for therapeutic remission, complete or partial remission (CR or PR) or SD after 6 months (UICC 6/12). Patients who showed disease progression $\leq$ 6 months were categorised as PD.

UICC 6/12	1st Line therapy		2nd Line therapy	
	n	Md surv (wks)	n	Md surv (wks)
CR	23	140	7	140
PR	48	115	20	180+
SD	88	88	105	106
PD	63	38	118	43

There was no significant difference in survival between patients with SD and either PR or CR for first or second line treatments. All 3 categories survived significantly longer than patients with PD (between $p = 0.005$ and $p < 0.0001$). SD for 6 months appears a clinically useful criterion of therapeutic remission. It emphasises that the clinically important distinction should be made between non-progression (OR + SD) and progression (PD) — the latter being the clinically relevant indication to institute a change of therapy.

PP-8-26 Breast Cancer Bone Metastases Specifically Express Parathyroid Hormone Related Protein (PTHrP) and its Receptor

S.E. Downey*, J.A. Hoyland [1], A.J. Freemont [1], N.J. Bundred. *Dept. of Surgery, University Hospital of South Manchester;* [1] *Dept. of Osteoarticular Pathology, University of Manchester*

PTHrP, an osteolytic factor secreted by osteoblasts and tumour cells, is reported to predispose to bone metastasis. To determine whether expression of PTHrP or its receptor specifically enhance tumour cell survival in bone, we studied their expression in primary breast cancers (n = 107) and breast cancer metastases in bone (n = 33) and lung (n = 15). In situ hybridisation was used to identify the mRNA for both PTHrP and its receptor. Tumours were scored by 2 independent observers using the product of intensity of signal (1–3) and number of positive tumour cells ($1 < 20\%$, $20\% < 2 < 80\%$, $3 > 80\%$). Levels of PTHrP and its receptor mRNA were significantly higher in bone metastases than in primary breast carcinomas (protein: $p = 0.0379$; receptor: $p = 0.0008$) but significantly lower in lung metastases (protein: $p = 0.0027$; receptor: $p = 0.0003$). Osteoblasts in bone metastases over-expressed PTHrP mRNA compared to normal bone.

Overexpression of both PTHrP and its receptor in breast cancer cells produces site specific metastases in bone due to autocrine/paracrine growth stimulation by PTHrP.

PP-8-27 Analysis of Factors that Improve Quality-of-Life of Patients with Advanced or Recurrent Breast Cancer

K. Shimozuma*, H. Sonoo, K. Ichihara [1]. *Division of Breast and Thyroid Surgery, Kurashiki, Japan;* [1] *Dept. of Clinical Pathology, Kawasaki Medical School, Kurashiki, Japan*

Objective: The objectives of this study were (1) to examine the relationship between therapeutic efficacy and improvement of quality-of-life (QOL) of patients with advanced or recurrent breast cancer, (2) to reveal pre-treatment factors that improve their QOL by multiple regression analysis, and (3) to examine relationship between kinetic patterns of QOL scores over time and types of therapy. *Methods:* Monthly during the treatments, the QOL scores of 26 patients were assessed by the QOL questionnaire developed by the Ministry of Welfare in Japan (QOL-ACD). *Results:* (1) Therapeutic efficacy correlated well with the improvement of QOL (especially in activity, psychological and physical aspects). (2) Pre-treatment factors that improve their QOL were smaller numbers of previous therapies, shorter disease-free interval, lack of cutaneous or pleural metastases, and hospitalization. More precise analyses revealed that chemoendocrine or endocrine therapy incorporating medroxyprogesterone acetate (MPA) significantly improved psychological aspect of QOL. (3) The analysis of kinetic patterns revealed that chemoendocrine therapy tended to improve QOL quickly after initiation of the treatment although chemotherapy alone tended to deteriorate it quickly. *Conclusions:* To improve QOL of patients with advanced or recurrent breast cancer, we should attempt to obtain higher efficacy of treatments in the earlier period of their clinical course. Endocrine therapy incorporating MPA can improve psychological aspect of QOL.

PP-8-28 Usefulness of a Combination Chemoendocrine Therapy of Mitoxantrone, Doxifluridine and Medroxyprogesterone Acetate for Anthracycline-Resistant Advanced or Metastatic Breast Cancer

Y. Iino* [1], T. Yokoe [2], H. Takei [1], J. Horiguchi [1], M. Maemura [1], S. Ohwada [1], Y. Morishita [1]. [1] *2nd Dept. of Surgery, Gunma University School of Medicine, Maebashi, Gunma, Japan;* [2] *Emergency and Critical Care Medicine, Gunma University School of Medicine, Maebashi, Gunma, Japan*

Thirty-four patients with anthracycline-resistant advanced or recurrent breast cancer were treated with a combination chemoendocrine therapy of mitoxantrone (MIT), doxifluridine (5′-DFUR) and medroxyprogesterone acetate (MPA). Out of 34 patients, 28 were evaluable for efficacy of this combination therapy, and 30 including 2 incomplete cases were assessed for toxicity. Adriamycin (ADM) was pretreated in 12 patients, 4′-epi-ADM in 6, and THP-ADM in 12. In the eligible patients, 7.0 mg/m^2 of MIT were administered intravenously every 4-week, and 600 mg of MPA and 600 mg of 5′-DFUR were given orally every day. The median follow-up period was 31.5 weeks (range 2–90). Eleven (39.3%) out of 28 patients showed partial response. One (7.7%) out of 13 soft tissues, 8 (36.4%) out of 22 bone metastase and 3 (15.8%) out of 19 viscera responded to this treatment. The median duration of response was 31 + weeks (range 12–82). Hematological and