in one case and from 2+ to 0 in two cases. Nevertheless, the Her2 status of the metastatic tumors, as defined by FISH, did not change.

Conclusion: Our results suggest that Her2 status does not change in metastatic breast carcinoma. However, at present it is necessary to investigate the Her2 status of late metastases of breast carcinomas, because in many cases the Her2 status of the primary tumor is unknown.

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Correlation between hormonal receptor levels and efficacy of hormonal therapy and chemotherapy in metastatic breast cancer

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Endocrine responsiveness defined by HR predicts the response to HT. It seems that the level of expression of HR correlates with the response to HT or even ChT. The aim of our analysis was to evaluate the response to first line HT and/or ChT for metastatic disease according to the HR levels in primary tumour.

Data of 260 patients (pts) treated for early breast cancer (BC) at Institute of Oncology Ljubljana from 1994 to 2001, that developed distant metastases in the median follow up time of 8.23 (4–11) years were reviewed. Response to HT was revived in 201 pts (aromatase inhibitors: 62%), and response to ChT in 187 postmenopausal pts (antracycline or taxane based: 57%). Response to HT was defined as clinical benefit (CB), including CR, PR and S for at least 3 months, response to ChT was defined as response rate (RR), including CR and PR. Progression free survival (PFS) was defined as time interval from the beginning of treatment till the date of confirmed disease progression or death due to BC. Response and PFS were analysed in subgroups of pts according to the imunohistochemical expression of ER, PR or both (rich ⩾90%, intermediate 10–90%, poor <10%). Kaplan Meier curves, log rank tests and STEPP curves were used for statistical analyses.

Response to HT was significantly different in subgroups of ER rich, ER intermediate and ER poor pts (65%, 57% and 27%, respectively; $p = 0.001$), however no difference between ER rich and ER intermediate groups was found ($p = 0.355$). Even higher differences in response were seen in subgroups of PR rich, PR intermediate and PR poor (75%, 59% and 40%, respectively; $p < 0.001$), with a trend for significant difference also between PR rich and PR intermediate groups ($p = 0.063$). When both receptors were taken into account, response in HT was higher in ER rich/PR rich compared to ER rich/PR poor subgroup of pts (81% vs. 54%; $p = 0.065$). In STEPP analysis all ER positive (⩾10%) pts responded equally well to HT, while the response continuously rose from PR 0% to PR 100%. Similar results for PFS were obtained in all subgroups. In our set of pts no significant differences in efficacy of ChT according to HR levels were confirmed.

We confirmed that the level of ER and PR predict the response to HT. In addition, we assume that ER positivity as such predicts a good response to HT, while in PR the level of receptor expression matters.

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Exemestane after non-steroidal aromatase inhibitors for post-menopausal women with advanced breast cancer

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Aims: To assess the efficacy of the type 1, steroidal aromatase inactivator, Exemestane in post-menopausal women with locally advanced and/or metastatic breast cancer, who have previously received Tamoxifen and a non-steroidal third generation aromatase inhibitor (AI).

Methods and Materials: A retrospective analysis was performed on thirty one consecutive patients who commenced Exemestane 25 mg/day orally, from January 2000 to June 2005. Patients were required to have positive oestrogen receptor (ER) and/or progesterone receptor (PR) status or if unknown, had to have a clear response to previous hormonal treatment (n = 2). Previous hormonal treatment included Tamoxifen and a non-steroidal third generation AI (Anastrozole or Letrozole). Patients were followed up every 3 months until they developed clinical or radiological disease progression.

Results: Median patient age was 64 years (range 34–90 years). 12 patients had locally advanced disease alone, 19 had metastatic disease and 8 had both locally advanced and metastatic disease. Sites of metastatic disease include soft tissue (n = 4), lung (n = 4), liver (n = 8) and bone (n = 13). The average number of recurrences prior to starting Exemestane was three (range 1–6). 15 patients (48.4%) also had previous chemotherapy. There were 2 complete responses (CR), 4 partial responses (PR), 12 with stable disease (SD) and 12 with progressive disease (PD). The objective response rate (CR + PR) was 19.4% and the overall clinical benefit (CR + PR + SD ⩾24 weeks) was 41.9%. The median durations of objective response and overall clinical benefit were 18.3 months and 16.2 months respectively. One patient required discontinuation of Exemestane due to vertigo.

Conclusions: This data supports the anti-tumour activity of Exemestane 25 mg daily in patients with locally advanced and/or metastatic breast cancer who have been previously exposed to non-steroidal third generation AIs and Tamoxifen.

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Phase II study with dose finding of Oral Vinorelbine in combination with Capecitabine as first-line chemotherapy of Metastatic Breast Cancer (MBC): Preliminary results of the phase II part of the study

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Several drugs are active in MBC. However, only few are available orally. The combination of Oral vinorelbine (VRL) and Capecitabine (Cape) has the advantage of its ease of use with no overlapping toxicity. Results of the phase I part of the study showed no interaction when both drugs are given concomitantly and established the following regimen: Oral VRL 60 mg/m^2 weekly with Cape 2000 mg/m^2/d from D1 to D14 every 3 weeks as one of the recommended dose for the phase II (F. Nolè; ASCO 2005, abstr 666). The present study investigated this weekly schedule to evaluate efficacy and tolerance of this combination in patients (pts) who had received no prior line of chemotherapy (CT) for MBC disease. Prior adjuvant chemotherapy with anthracycline and/or taxanes was allowed. Patients had at least one measurable lesion (WHO criteria) and KPS ⩾ 70%. The characteristics of the first 23 patients treated, were median age of 59 years, prior adjuvant chemotherapy in 78.3%, prior adjuvant hormonotherapy in 69.6%, disease free interval <2 years in 21.7%, visceral involvement in 82.6% (liver 60.9%, lung 47.8%). A total of 169 cycles were given with a median of 7 cycles. Median relative dose intensity (RDI) for Oral VRL and Cape were 72.6% and 85.3%, respectively. Neutropenia was the main side effects with grade 3–4 in 52.2% of pts and 12.5% of cycles, without any episode of complicated neutropenia. Grade 1 stomatitis were reported in 26.2% of pts and 10.7% of cycles, hand foot syndrome was observed in 39.1% of pts and 26.1% of cycles, with no grade 3. This combination demonstrated to be effective with RR of 47.8% [95% CI: 26.8–69.4] in the ITT population of 23 pts and 55% [95% CI: 31.5–76.9] in the 20 evaluable patients.

Conclusion: the combination of oral VRL 60 mg/m^2 weekly with Cape 2000 mg/m^2/d D1-D14 every 3 weeks demonstrated to be effective and safe in patients with MBC as first line chemotherapy. A total of 45 evaluable patients is planned in the study.

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Continued use of goserelin to achieve ovarian function suppression in combination with a further aromatase inhibitor (exemestane) following prior treatment with anastrozole and/or tamoxifen in premenopausal women with oestrogen receptor positive advanced breast cancer

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Introduction: The use of goserelin to achieve ovarian function suppression is a well-established therapeutic strategy in premenopausal women with oestrogen receptor positive (ER+) breast cancer. We have previously reported clinical/endocrine data of combined use of goserelin plus tamoxifen or anastrozole (a non-steroidal aromatase inhibitor) in premenopausal women with ER+ advanced breast cancer. We now report the clinical experience of continued use of goserelin given alongside exemestane (a steroidal aromatase inhibitor) in the same setting following prior treatment with anastrozole and/or tamoxifen.

Methods: Thirteen patients [median age: 45 (33–54) years] (advanced primary = 1, bone only = 6, bone + pleura = 4, bone + liver = 2) seen over a 32-month period were treated with goserelin 3.6 mg 4-weekly plus exemestane 25 mg daily as second to fourth line endocrine therapy. All patients had disease assessable by UICC criteria and received therapy for ⩾6 months (except for those who progressed prior).

Results: All patients have progressed at the time of analysis. Five patients (38%) derived clinical benefit (CB) (compete response/partial response/stable disease for ⩾ 6 months) with a median duration of 9 (7–32) months. Details for the different subgroups are shown in the table.

Agents prior to G+E	N	CB(%)	Median duration of response (mo)
G+A	3	0	N/A
G+T, G+A	6	50	9 (9–32)
G+T, G+A, M	4	50	8 (7–9)

G = Goserelin; T = Tamoxifen; A = Anastrozole; E = Exemestane; M = Megestrol acetate.

Therapy was well tolerated and no patients withdrew due to side effects.

Conclusion: A combined use of goserelin and exemestane produces CB with long duration of response in significant proportion of premenopausal women with ER+ advanced breast cancer following prior use of other endocrine agents. The continued use of ovarian function suppression with goserelin alongside available endocrine agents allows further therapeutic opportunities (with much better side-effect profile than chemotherapy) in this setting. Further studies are warranted.

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Safety and efficacy of first-line docetaxel–gemcitabine in metastatic breast cancer

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Purpose: New combinations and strategies have been developed over the past 10 years including new drugs such as taxanes and Gemcitabine and this design demonstrates the feasibility of the most effective drugs, while minimizing toxicity.

Docetaxel (DXL) – Gemcitabine (GMZ) has shown significant activity against metastatic breast cancer (MBC) in a lot of studies.

Methods: From November 1998 to January 2000, 42 patients have been enrolled in the study and all patients had previously received adjuvant therapy.

Treatment: Patients received DXL: 75 mg/m^2 Day1 + GMZ: 1250 mg/m^2 Day 1 and Day 8, every 3 weeks without growth factor support. Median age was 57.5 years (range 27–74).

Results: Complete response was observed in 22.5% (9 patients) and partial response in 57.5% (24 patients) with an overall response rate of 80%. The probability of one-year survival was 83.5%. Main grade * toxicities were Neutropenia in 12.5% (5 patients) and Anaemia in 7.5% (3 patients). Nausea and vomiting grade 2–3 were in 19.2%.

Conclusion: DXL + GMZ is an active regimen in MBC. This scheme is of an easy administration, very well tolerated and effective in patients with MBC relapsing after an anthracycline based adjuvant treatment.

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Combination of vinorelbine alternating i.v. and oral in combination with docetaxel as 1st line chemotherapy of metastatic breast cancer

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Background: The combination of IV VRL and DTX was shown to be feasible and effective in MBC. In an effort to improve patient convenience a regimen alternating i.v. and oral VRL was investigated.

Methods: A phase II study was designed to evaluate the efficacy and the tolerance of i.v. VRL 20 mg/m^2 with DTX 60 mg/m^2 on day 1 and oral VRL 60 mg/m^2 on day 15 of a three-week cycle in first line treatment MBC for a maximum of 6 cycles (recommended dose established in phase I study, abstract n° 684, ASCO 2004).

Prior adjuvant CT was allowed if completed at least 12 months before study entry. At least one bidimensionnally measurable lesion (WHO criteria) was required.

Results: 49 patients (pts) were treated: with a median age of 53 years; 31 pts (63.3%) had received prior adjuvant chemotherapy; 44 pts (89.9%) had a KPS ⩾80%; and 38 pts (77.6%) had visceral involvement. A total of 261 cycles were given (median 6). Median relative dose intensities (RDI) of i.v. VRL and DTX were ⩾ 99% and median RDI of oral VRL was 76.4%. Neutropenia was the major dose-limiting event (grade (G) 4 in 51% of pts and 22.1% of cycles) but only complicated in 5 pts: 4 febrile neutropenia (8.2%) and one neutropenic infection (2%). In terms of non-haematological related toxicity, the most frequent events reported were alopecia (61.2%), fatigue (22.4%), weight loss (18.4%), stomatitis (16.3%) and constipation, diarrhoea and nausea (14.3% each). G3 events were stomatitis, vomiting and amenorrhea (4.1% each) and fatigue, constipation, diarrhoea, nausea, infection, syncope and abdominal pain (2% each). The single grade 4 event was dehydration. The combination was effective with 24 responses documented and validated by an independent panel review, yielding a response rate of 55.8% [95% CI: 40–71] in the 43 evaluable pts. Median progression-free survival was 5.5 months [95% CI: 4.2–7.2]. Median overall survival has not yet been reached with a median duration of follow-up of 9.7 months.

Conclusions: This combination with oral VRL on day 15 avoiding hospitalisation is effective and manageable. VRL i.v./oral D1/D15-DTX D1 every 3 weeks represents a convenient option to combine DTX and VRL for the palliative treatment of MBC.

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Trastuzumab (T) plus oral vinorelbine (OV) in patients with advanced breast cancer (ABC) overexpressing Her2/neu

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Background: Trastuzumab combined with i.v. Vinorelbine (ivV) is an active regimen for pts with ABC. We previously developed two effective chemotherapy (CT) regimens which included day 1 and 3 ivV (FLN, ViFUP). In order to further improve Quality of Life (QoL) of pts undergoing treatment for ABC, a new regimen using oV, day 1 and 3, plus q3wks T was tested (ToV).

Methods: Forty-one pts with ABC, HER2/neu 3+ or FISH positive, were enrolled to receive three different dose level of oV. Thirty-four pts (median age 48 yrs; 28–71) received 271 courses of T, 6 mg/kg (loading dose, 8 mg/kg) on d1, and oV 55 mg/m^2 on day 1 and 3, q3wks. Eight pts received previous CT for ABC. Three pts received 23 courses of oV at a dose of 75 mg/m^2 and 4 pts received 19 courses of oV 60 mg/m^2; for this dose level accrual is ongoing. Pts were treated until disease progression or unacceptable toxicity or treatment refusal.

Results: Thirty-four pts treated with oV 55 mg/m^2 were evaluable for response and toxicity and received a median of 8 courses (range,1–16). Treatment was well tolerated with no G3–4 NCI-CTC non-haematological toxicity but only G3 elevation of SGOT in 1 pt; G2 observed toxicity consisted of nausea (4 pts), diarrhoea (4 pts), mucositis (1 pt) and constipation (3 pts). Five pts had G3–4 neutropenia. Six pts required a ⩾25% oV dose reduction. Two pts had CR, 11 PR, 17 NC and 3 PD. Median TTP was 8.7 mos (1.6–21.4+) and median duration of response was 13 mos (2.4–20+). The combination with oV 75 mg/m^2 appeared unfeasible for G4 neutropenia in 2/3 pts, while the intermediate dose of oV 60 mg/m^2 was then selected to be evaluated and the first 4 treated pts do not show any relevant side effects.

Conclusions: The ToV combination is active and well tolerated. It allows once-every three weeks hospital admission and frees pts and care providers from the unpleasant effect of ivV. ToV 60 mg/m^2 is currently under evaluation with particular attention to QoL parameters and acceptance.

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Vinorelbine (V) plus docetaxel (D) followed by Capecitabine (C) as first-line treatment of metastatic breast cancer (MBC)

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Background: Vinorelbine (V), Docetaxel (D) and Capecitabine (C) were found to be active as single agent in metastatic breast cancer. In this trial, we evaluated the efficacy and tolerability of V and D combination followed by C in first line treatment of MBC.

Patients and Methods: Pts were eligible if they had recurrent or metastatic breast cancer, measurable disease, ECOG PS ⩽2, adequate organ function, ability to give informed consent and had received no chemotherapy for metastatic disease. All patients had received anthracycline-based chemotherapy in the adjuvant setting. Patients were treated with 6 cycles of V (25 mg/m^2) on days 1 and 8 and D (75 mg/m^2) on day 1 every 3 weeks. Patients who responded or had stable disease at the end of ND treatment, received 6 cycles of C (1250 mg/m^2 twice daily).

Results: From Feb 2001 to Dec 2002, 25 patients were enrolled. The median age was 41 years (range 34–61). The sites of metastasis were liver in 17 (27%), skin in 15 (24%), lymph nodes in 12 (19%), lung in 10 (16%) and soft tissue in 2 (3%) pts. Number of metastatic sites were: 3 in 13 pts, 2