254 POSTER

Trastuzumab and Vinorelbine combination in the treatment of metastatic breast cancer

J.L. Bayo[1], J.I. Mayordomo[2], P. Sanchez Rovira[3], E. Gonzalez[4], J.M. Garcia Bueno[5], M. Ramos[6], C. Crespo[7], J. Illarramendi[8], J. Valerdi[8], A. Garcia Palomo[9]. [1]*Hospital Juan Ramón Jimenez, Oncology Dept, Huelva, Spain;* [2]*Hospital Clinico Lozano Blesa, Oncology Dept, Zaragoza, Spain;* [3]*Hospital Ciudad de Jaen, Oncology Dept, Jaen, Spain;* [4]*Hospital Virgen de las Nieves, Oncology Dept, Granada, Spain;* [5]*Policlinica Miramar, Oncology Dept, Palma de Mallorca, Spain;* [6]*Centro Oncológico, Oncology Dept, La Coruña, Spain;* [7]*Hospital Ramón y Cajal, Oncology Dept, Madrid, Spain;* [8]*Hospital de Navarra, Oncology Dept, Pamplona, Spain;* [9]*Hospital de León, Oncology Dept, León, Spain*

Trastuzumab and Vinorelbine combination has previously shown a very interesting activity and is a well tolerated regimen in metastatic breast cancer overexpressing Her2. From February 2001 to August 2003, 46 patients (pts) have been treated with this combination in 13 Spanish centers. The primary endpoint of the study was response rate and secondary objectives were TTP and to define the toxicity profile of the combination in this setting. Pts without previous treatment for metastatic disease or after first line therapy were included in this study. Only Her2 3+ or 2+ confirmed by FISH were eligible patients. Patients were treated with weekly Trastuzumab given at a dose of 2 mg/kg/d over 30′ (4 mg/kg/d over 90′ on the first infusion) followed by Vinorelbine at a dose of 25 mg/m2 over 6–10′.

Material and Methods: 46 female patients with measurable or assessable metastatic breast cancer were enroled. Patients remained in study up to six cycles consisting of 3 administrations of the combination and then up to the investigator some pts went on Herceptin alone or other CT regimen. All pts were followed until progression of the disease. Response assessments were scheduled after 2, 4 and 6th cycles.

Results: 29 pts had not received any treatment for metastatic disease and 17 had received one or more lines of treatment for metastatic disease. We have actually data from 41 pts evaluable for response. So far, the overall response rate is 66%. 7 pts have shown a CR (17%), 20 had a PR (49%), 7 had a EE (17%) and 7 had a PD (17%) as the best response to therapy. Toxicities led to study termination in only 1 pts, being G1–2 neurotoxicity and G3–4 neutropenia main toxicities. No cardiac events have been seen in this group of pts. No SAEs have been reported.

Conclusions: This regimen shows a remarkable activity with a good tolerance which should be taken under consideration while treating patients in this setting. Further data of the full cohort of patients will be presented at the meeting.

255 POSTER

Long-term (4-year) safety of intravenous ibandronate in metastatic breast cancer: an open-label study

M. Pecherstorfer[1], I.J. Diel[2], B. Bergstrom[3]. [1]*Wilhelminenspital, Vienna, Austria;* [2]*CGG-Klinik GmbH, Mannheim, Germany 3.Hoffmann-LaRoche Inc., Nutley, New Jersey, USA*

Background: Certain intravenous bisphosphonates for metastatic bone disease (zoledronic acid and pamidronate) have been linked to renal toxicity, with evidence to suggest that it may be caused by drug accumulation when receiving long-term therapy [1,2]. However, a 96-week, phase III clinical trial demonstrated that intravenous ibandronate 6 mg infused every 3–4 weeks has a renal safety profile that is similar to placebo in patients with bone metastases from breast cancer [3]. In order to better assess the renal adverse event (AE) profile and investigate the possibility of renal toxicity with drug accumulation, this abstract reports 4-year follow-up data from this trial.

Methods: Patients completing the placebo-controlled trial period were entered into a 2-year non-controlled study, in which intravenous ibandronate 6 mg was infused over 1–2 hours every 4 weeks (n=62). AEs and laboratory signs were recorded.

Results: As expected with advanced malignant disease, 10% of patients did not complete the 2-year follow-up period due to AEs, and the majority of patients (77%) experienced at least one AE. Disease progression accounted for 44% of all reported AEs. Serious AEs affected 26% of patients, but were not drug-related. The most common treatment-related AE was gastroenteritis, which affected just two patients. There were no clinically-relevant renal AEs or laboratory abnormalities.

Conclusions: Ibandronate has been shown to be effective and well-tolerated in 2-year placebo-controlled trials. This study demonstrates that intravenous ibandronate 6 mg has a favorable tolerability profile over 4 years of treatment, with no renal safety concerns. These results suggest that there is no renal toxicity accumulation issue with ibandronate. The long-term safety of intravenous ibandronate may reduce the time and cost burden associated with regular renal function monitoring (not required prior to each dose) and the management of drug-related AEs.

References

[1] Rosen LS, et al. Cancer J 2001;7:377–87.
[2] Johnson KB, et al. Proc ASCO 2003;22:738 (Abstract 2968).
[3] Diel I, et al. Support Care Cancer 2003;11:415 (Abstract A-106).

256 POSTER

Is the response duration to aromatase inhibitor anastrozole in metastatic breast cancer correlated with Her-2/neu status? Preliminary results of a prospective, non-randomized study

I. Glogowska[1], R. Sienkiewicz-Kozlowska[1], T. Pienkowski[1], S. Jaczewska[1], A. Jagiello-Gruszfeld[2]. [1]*The Maria Sklodowska-Curie Memorial Cancer Center, Breast Cancer & Reconstructive Surgery Department, Warsaw, Poland;* [2]*The Regional Cancer Center, Chemotherapy Department, Olsztyn, Poland*

Background: The aromatase inhibitor anastrozole is effective in metastatic breast cancer (mbc) in patients (pts) with ER/PgR positive tumors, both in first-line treatment and in pts pretreated with tamoxifen (Tam). Several data suggests the potential correlation beetwen Her-2 expression and benefit from hormonal treatment. Therefore, we performed a prospective, non-randomized trial of correlation with Her-2/neu status and the response duration (RD) to anastrozole in mbc.

Material and Methods: 35 postmenopausal, steroid receptors positive pts with metastatic disease were eligilible. 17 tumors were ER positive, 18 were both ER/PgR positive. 29 pts were pretreated with Tam as an adjuvant (14) or metastatic disease (15). 15 pts were previous treated with chemotherapy (chth) because of mbc. Median of number cycles chth was 1. In 8 pts anastrozole was the first-line therapy of mbc. Median of number metastatic sites was 2. Retrospectively Her-2/neu status was indicated (in 33 specimens by immunohistochemy DAKO test, in 2 specimens by FISH). In 19 tumors Her-2 were negative, in 10 Her-2 overexpression was confirmed, in 6 specimens Her-2 expression was evaluated on 2+ and in these cases FISH tests should be performed. The endpoint of this study is the duration response and time to progression (TTP) on anastrozole in Her-2 overexpressors to Her-2 nonoverexpressors.

Results: The median response duration (mRD) was 26 weeks in Her-2 positive and 30 weeks in Her-2 negative pts but without statistically significance. There were 7 cases (70%) of progression in Her-2 positive group with TTP 22 weeks and 7 (39%) cases of progression in Her-2 negative group with TTP 14 weeks. In the group with Her-2 status 2+ mRD was 20 weeks and in all cases progression was observed with mTTP 20 weeks. In this group FISH tests will be performed and results will be included to this analysis.

Conclusions: There is no significant differences in the response duration and time to progression in pts with mbc treated with anastrozole in dependence of Her-2 status in analysed group. Observations are not closed yet and new pts are included to the study. Final results will be presented in a few years time.

257 POSTER

Navelbine® (NVB) alternating oral and i.v. plus epirubicin (EPI) as first line chemotherapy of metastatic breast cancer (MBC): phase II study – final results

D. Serin[1], M. Verrill[2], A. Jones[3], T. Delozier[4], R. Coleman[5], B. Longerey[6], S. Lafaye de Micheaux[6]. [1]*Institut Sainte Catherine, Avignon, France;* [2]*Northern Centre For Cancer Treatment, Newcastle, UK;* [3]*Royal Free Hospital, London, UK;* [4]*Centre François Baclesse, Caen, France;* [5]*Cancer Research Centre, Sheffield, UK;* [6]*Institut de Recherche Pierre Fabre, Boulogne, France*

The combination of NVB IV 25 mg/m^2 on days 1 and 8 and EPI 90 mg/m^2 on day 1 every 3 weeks is an effective option for the first line treatment of MBC. In an effort to improve patient convenience, the day 8 administration of NVB was given orally at the dose of 60 mg/m^2 while NVB IV was used the day of EPI infusion. This study evaluated efficacy and tolerance of this new combination given for 6 cycles. Prior adjuvant chemotherapy completed at least 12 months before study entry was allowed with cumulative doses up to 180 mg/m^2 of doxorubicin, 360 mg/m^2 EPI and 72 mg/m^2 mitoxantrone. Patients had measurable disease (WHO criteria), normal LVEF and PS 0–1 at study entry. The characteristics of the 49 patients treated, were median age of 55 yrs, prior adjuvant chemotherapy in 51%, prior adjuvant hormonotherapy in 57.1%, disease free interval <2 years in 32.7%, visceral involvement in 81.6%

(liver 51%, lung 36.7%). Neutropenia was the main side effect: gr3/4 in 65.3% of pts and 29.1% of cycles, resulting in febrile neutropenia in 8.2% and neutropenic infection in 12.2% of pts. Stomatitis gr3/4 was seen in 10.2% of pts. The combination demonstrated to be effective with RR of 51% [95% CI = 36.3–65.6], and 54.5% [95% CI = 38.9–69.6] in ITT and evaluable population, respectively. Median PFS is 8.1 months [95% CI = 6.9–9.9] with 3 pts censored. The median overall survival is not reached with a median follow up of 23.7 months. The use of NVB oral for the day 8 administration of an NVB–EPI every 3-week cycle provides good results, improves patient convenience and allows better use of resources.

258 POSTER

Multicenter phase II trial of three-weekly docetaxel and weekly trastuzumab in HER-2-overexpressing metastatic breast cancer patients: Japan East Cancer Center Breast Cancer Consortium (JECBC 01 trial)

T. Tabei[1], M. Kimura[2], M. Sano[3], T. Asaga[4], J. Ando[5], H. Fujii[6], N. Yamamoto[7], M. Kurosumi[8], K. Inoue[9], N. Sato[10]. [1]*Saitama Cancer Center, Breast Oncology, Saitama, Japan;* [2]*Gunma Cancer Center, Surgery, Gunma, Japan;* [3]*Nligata Cancer Center, Surgery, Niigata, Japan;* [4]*Kanagawa Cancer Center, Surgery, Kanagawa, Japan;* [5]*Tochigi Cancer Center, Surgery, Tochigi, Japan;* [6]*Tochigi Cancer Center, Medical Oncology, Tochigi, Japan;* [7]*Chiba Cancer Center, Surgery, Chiba, Japan;* [8]*Saitama Cancer Center, Pathology, Saitama, Japan;* [9]*Saitama Cancer Center, Breast Oncology, Saitama, Japan;* [10]*Niigata Cancer Center, Surgery, Nligata, Japan*

Background: Docetaxel and trastuzumab can be considered to be active drugs for HER-2-overexpressing metastatic breast cancer (MBC). This study was conducted to determine the activity of combination therapy with docetaxel and trastuzumab in MBC patients (pts) by assessing the response rate (RR), time to progression (TTP) and safety.

Material and Methods: We administered the combination of docetaxel 70 mg/m^2 every 3 weeks and trastuzumab using a 4-mg/kg loading dose and thereafter 2 mg/kg weekly for HER-2-overexpressing MBC. One cycle was three weeks.

Results: Between March 2002 and May 2003, 40 pts with HER-2-positive (3+ by immunohistochemistry 39, FISH+ 1) MBC were enrolled in this study, and 39 pts were eligible. ITT analysis was performed for 40 pts. The median pt age was 57.5 years (range, 32–73). Prior chemotherapy was anthracycline-based in 16, non-anthracycline in 17, and radiotherapy in only 1. Only 6 pts were naive. Performance status ECOG: 0/1/2/unknown (23/11/4/2). Histology: invasive/other/unknown (38/1/1). Metastatic site: soft tissue 26 (primary: 5; lymph node: 15; skin: 6), visceral 32 (liver: 13; lung: 17; pleura: 2), bone 12, and other 1. Number of metastatic sites: 1/2/3/* 4 (20/12/5/ 3). Hormone receptor status: ER+/ER− (8/32), PgR+/PgR−/unknown (10/29/1). Menopausal status: postmenopausal/premenopausal/unknown (29/10/1). The median number of cycles administered was 6 (range, 1–13+). To date, 40 pts who received at least one cycle of this combination treatment have been assessable for efficacy. The overall RR was 70.0% (28/40) [95% CI 53.5%-83.4%], with 7 CR, 21 PR, 4 SD, 3 PD and 5 NE. The median follow-up time was 230 days, while the TTP was 135 days (range, 19–443). The number of pts assessable for safety was 40. NCI–CTC grade 3–4 toxicities were leukopenia 87.5% (35/40) and neutropenia 82.5% (33/40). The main non-hematological toxicities were anorexia 55%, diarrhea 55%, asthenia 72.5%, alopecia 90%, neuropathy 55%, rash 55%, edema 60% and nail changes 57.5%. All these toxicities were grade 1–2. NCI–CTC grade 3 toxicities were weight gain in 2 patients, and neuropathy, fever and rash in one pt each.

Conclusion: The combination of docetaxel and trastuzumab was a well-tolerated and very active regimen for the treatment of patients with HER-2-overexpressing MBC. We plan to investigate the predictive value of p-53, Ki-67, ER, PgR, etc.

259 POSTER

A clinical phase II study of cisplatin and vinorelbine followed by docetaxel as first line treatment in metastatic breast cancer

A. Shamseddine[1], N. Bitar[2], M. Dheiny[3], A. Chehal[1], Y. Abou Mourad[1], R. Jalloul[4], A. Dandashi[5], M. Wehbet[3], T. Abu Nasr[6], N.S. El Saghir[1]. [1]*American University of Beirut Medical Center, Internal medicine, Beirut, Lebanon;* [2]*Sahel General Hospital, Internal medicine, Beirut, Lebanon;* [3]*Hammoud Hospital, Internal medicine, Saida, Lebanon;* [4]*Makassed General Hospital, Internal medicine, Beirut, Lebanon;* [5]*Islamic Hospital, Internal medicine, Tripoli, Lebanon;* [6]*Arz Hospital, Internal medicine, Beirut, Lebanon*

Background: Based on our encouraging positive experience with Cisplatin and Vinorelbine combination (PVn) in first and second line treatment for advanced breast cancer (ABC) [Am J Clin Oncol 1999; 22(3): 298–302, Proc 12th ICACT Paris, February 2002; (abstract P 97)], and to explore additive effect of sequential docetaxel, we designed this phase II study to assess anti-tumor efficacy and safety of PVn followed by docetaxel in patients with metastatic breast cancer (MBC).

Material and Methods: From August 2002 to October 2003, 27 patients with MBC were recruited of whom 26 were evaluable for response. Median age was 49 years (range: 22–75). 13 (50%) patients were premenopausal. 80% of patients had 2 or more sites of metastasis. No previous therapy was allowed except as adjuvant. 10 (38%) patients were chemo naive and 16 (62%) patients underwent previous surgery for breast cancer and received adjuvant anthracycline chemotherapy regimen. 14 (54%) patients received locoregional radiotherapy, and 10 (38%) patients received hormonal therapy. Accrual of patients is still ongoing. Chemotherapy consisted of cisplatin 80 mg/m^2 given on day 1 of a three-week cycle and vinorelbine 30 mg/m^2 on days 1 and 8 for a total of 4 cycles with evaluation every 2 cycles. After the 4th cycle responding patients received docetaxel 75 mg/m^2 on day 1 every 21 days for a maximum of 4 cycles. Hormone receptor positive patients received hormonal therapy after the end of the study. Evaluation of measurable disease was done by physical examination and appropriate computerized tomography scans.

Results: After a median follow up of 9 months (range: 1–14), 22 (85%) patients completed the study with 4 (18%) patients showed CR, and 10 (45%) patients showed PR (ORR 63%). The median time to disease progression was 4 months (range: 2–9). 85% of patients survived for 1 year. The total number of cycles was 140. Dose reduction occurred in 32/140 (23%) cycles. Anemia Grade III observed in 8 (5%) cycles, and Grade IV in 13 (9%) cycles. Neutropenia Grade III in 8 (5%) cycles, and Grade IV in 11 (8%) cycles. Febrile neutropenia observed in 8 (5%) cycles. Thrombocytopenia Grade III in 4 (3%) cycles, and Grade IV in 10 (7%) cycles. Neurotoxicity Grade IV in 4 (3%) cycles. Nausea and vomiting Grade III in 30 (22%) cycles, and Grade IV in 14 (10%) cycles. Alopecia Grade I in 41 (29%) cycles and Grade II in 17 (12%) cycles.

Conclusions: PVn followed by docetaxel produces good results in MBC with acceptable toxicity. According to our previous experience with PVn as first line therapy in MBC (ORR 64%), it seems that sequential addition of docetaxel to PVn does not produce additional benefit.

260 POSTER

Efficacy and safety data of an outpatient regimen for pretreated metastatic or relapsed breast cancer (MBC): Vinorelbine, 5-Fluorouracil and Folinic Acid (FuFolNav) – a phase II study

A. Eniu[1], C. Vitoc[1], N. Todor[2], N. Ghilezan[2]. [1]*Cancer Institute Ion Chiricuta, Department of Breast Tumors, Cluj-Napoca, Romania;* [2]*Cancer Institute Ion Chiricuta, Department of Radiotherapy, Cluj-Napoca, Romania*

In incurable MBC patients (pts) with an indication for chemotherapy, low toxicity outpatient regimens that do not decrease the quality of life are a better alternative than more aggressive inpatient regimens, often without large difference in efficacy. For anthracycline (A) pretreated patients, the association Vinorelbine and 5-Fluorouracil + Folinic Acid (FuFolNav) represents a potentially non cross-resistant regimen. The purpose of this study was to evaluate the efficacy and tolerability of the combination administered as an outpatient regimen to patients with prior exposure to A.

Methods: 61 pts with MBC were treated with FuFolNav chemotherapy: 5-FU 600 mg/m^2, preceded by Folinic Acid 30 mg/m^2, and Vinorelbine 25 mg/m^2, day 1 and day 8, in an outpatient clinic, every three weeks.

Patients: A total of 61 pts were enrolled. Median age was 50 [33–67]. Metastatic sites: liver 19, lymph nodes 12, lung 11, multiple 9, skin 7, peritoneal 3. In our patient population, only two pts did not have prior exposure to A. Of the other 59, 31 pts received A as primary systemic therapy for locoregionally advanced disease, 19 pts received adjuvant A chemotherapy, and the remaining 9 pts received A as first line treatment for MBC. Out of the 31 pts treated with primary A therapy, 13 also received taxanes as sequential treatment after surgery. FuFolNav represented first line chemotherapy for MBC in the majority of pts (49). The other 13 pts received prior chemotherapy for metastatic disease, either with A or with T.

Results: We recorded 2 (3.3%) CRs (one in lung metastases, the other one in skin metastases), and 34 (55.7%) PRs, for an overall response rate of 59% (0.05 CI: 47–71%). In addition 15 (24.6%) pts had SD. Ten pts (16.4%) progressed under treatment. Overall, 51 patients (=83.6%, CI: 74.6–92.6%) had clinical benefit quantified as PR+SD and palliation of symptoms. A total of 268 cycles of FuFolNav were administered, with a median 4 cycles per pts (range 2–10). Toxicity was mild and there were no toxic deaths. Grade 3–4 toxicities included neutropenia (8%), ileus-like syndrome (6%), mucositis (5%) and peripheric neurologic toxicity (limbs) (4%) of cycles. No patient developed complete alopecia.

Conclusion: The combination of Vinorelbine, 5-Fluorouracil and Folinic Acid proved to be efficacious in the treatment of MBC pts previously