endocrine therapy (tamoxifen). Prior palliative chemotherapy had been given to six patients (42.9%) and prior palliative endocrine therapy to 13 patients (92.9%) (goserelin+anastrozole and/or exemestane). Three patients (21.4%) had clinically apparent non-visceral metastases only, one patient (7.1%) had clinically apparent visceral metastases only and 10 patients (71.4%) had both. Eleven patients are currently evaluable for response: one patient had a partial response (PR) and four patients (36.4%) had stable disease (SD) $\geqslant$ 6 months, resulting in a clinical benefit rate of 45.5%. Also one patient had SD > 3 months but < 6 months. Both patients with HER2-positive disease experienced SD $\geqslant$ 6 months. Median time to progression was 5 months (range 2–12+ months). No local or systemic adverse events were reported.
Conclusions: Goserelin+fulvestrant appears to be an effective and well-tolerated treatment for premenopausal women with ABC including those with asymptomatic visceral metastases and HER2-positive disease. These data compare very favourably with similar data reported with fulvestrant treatment in naturally postmenopausal women with ABC. Further evaluation of fulvestrant in premenopausal women with iatrogenic menopause is supported in controlled clinical trials.

456 PUBLICATION

Phase II study of vinorelbine (VRL) alternating i.v. and oral in combination with docetaxel (DTX) as 1st line chemotherapy (CT) of metastatic breast cancer (MBC)

M. Blasinska-Morawiec[1], M. Campone[2], A. Tekiela[3], P. Koralewski[3], B. Longerey[4], I. Douville[4]. *[1]Wojewodzki Szpital Specjalistyczny im. M. Kopernika, Lodz, Poland; [2]Centre René Gauducheau, Nantes, France; [3]Wojewodzki Szpital Specjalistyczny im. L. Rydygiera, Krakow, Poland; [4]Institut de Recherche Pierre Fabre, Boulogne, France.*

Background: VRL and DTX are targeting tubulin-microtubule system, either inhibiting tubulin polymerisation (VRL) or microtubule depolymerisation (DTX). Both agents have proven activity in MBC.
Material and methods: This study was designed to evaluate the efficacy and the tolerance of the combination 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 no. 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 22 pts (44.9%) had *3 sites involved. A total of 261 cycles were given (median 6). Median relative dose intensities (RDI) of i.v. VRL and DTX were over 99% and median RDI of oral VRL was 76.4%. Neutropenia was the major side effect: 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 (all grades), 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). Only one patient experienced G4 dehydratation. G3 events were stomatitis, vomiting and amenorrhea (4.1% each) and fatigue, constipation, diarrhoea, nausea, infection, syncope and abdominal pain (2% each). The combination was highly effective with 24 responses documented and validated by an independent panel review, yielding a response rate of 49% [95%CI: 34–64] in the 49 enrolled pts. Median duration of progression-free survival was 5.5 months [95%CI: 4.2–7.2]. Median duration of overall survival has not 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 highly efficient and manageable in contrast with previous Phase II studies having used higher doses and different schedules. VRL i.v./oral D1/D15-DTX D1 every 3 weeks is an attractive option to combine DTX and VRL at doses which are convenient for every day practice in MBC.

457 PUBLICATION

Low value of serum Ca 15–3 and CEA in monitoring trastuzumab-based therapy of advanced breast cancer

R. Duchnowska, M. Miedzinska-Maciejewska, C. Szczylik, M. Konieczna, I. Pietrzak. *Military Institute Of Medicine, Oncology Clinic, Warsaw, Poland*

Background: Trastuzumab therapy has recently become standard management of HER-2 positive patients with advanced breast cancer. There are particularly few data on the usefulness of serum Ca 15–3 and CEA in monitoring of this management. We present here the relationship between serum levels of both markers and the outcomes of trastuzumab-based therapy assessed in a single-institutional retrospective study.
Material and methods: Study group included 43 patients (median age 50 years; range 31–71 years) with recurrent or advanced HER2/neu overexpressing breast cancer who were administered trastuzumab with or without additional systemic therapies. Serum levels of CEA and Ca 15–3 were measured prior to initiation of therapy and every 3 months during treatment. Samples were tested using ELISA assays. Ca 15–3 and CEA values below 30 U/ml and 5 ng/ml, respectively were considered normal. 36 patients were evaluable for this analysis, of whom 22 (61%) responded to treatment. The median follow-up in the entire group was 9 months (range 3 to 24 months). Correlation between serum levels of both markers and clinical outcomes was computed using linear regression analysis.
Results: Baseline Ca 15–3 and CEA levels were elevated in 62% and 48% patients, respectively. Changes in serum levels of both markers during therapy did not predict for relapse. Elevation of Ca 15–3 and CEA levels occurred in 7 (35%) and 6 (30%) of patients with progression, respectively, and the correlation factor for both markers was 0.34 and 0.30, respectively. Combined analysis of CEA and CA 15–3 did not increase their predictive value.
Conclusion: Monitoring trastuzumab therapy of advanced breast cancer patients with serum Ca 15–3 and CEA, considered as single tests or in combination is of limited clinical value.

458 PUBLICATION

Cellular immunotherapy with reactivated autologous Memory T-Cells from bone marrow in late stage breast cancer patients

F. Schuetz[1], K. Ehlert[2], I. Diel[1], V. Schirrmacher[2], A. Schneeweiss[1], G. Bastert[1], C. Sohn[1], P. Beckhove[2]. *[1]University Clinics Heidelberg, Dept. Obstetrics and Gynecology, Heidelberg, Germany; [2]German Cancer Research Center, Dept. Immunology, Heidelberg, Germany*

Tumorspecific Memory T-cells (MTC) can be found in the bone marrow (BM) in the majority of primary and metastatic breast cancer (BC) patients by using ELISpot-analysis. Upon specific restimulation with tumourantigen-pulsed dendritic cells (DC) those autologous T-cells exert specific effector functions like IFN-gamma or perforin production and specific cytotoxicity. Furthermore we have shown in NOD/Scid-mice that reactivated MTC are able to infiltrate autologous and heterologous tumor tissue, proliferate and kill tumor cells by induction of apoptosis, leading to a marked or complete tumor rejection within 21 days after transfer (Nature Med, 2001). Endocrine and cytostatic cancer therapies only have a limited influence on the frequency of tumorspecific MTC in BM of BC patients.
In a phase-I trial 11 patients with metastatic BC (inclusion criteria) were treated with autologous reactivated MTC of BM. Primary objective were feasbility, and toxicity, secondary were clinical response, and immunomonitoring. After testing patient's BM for presence of tumorspecific MTC those cells were reactivated by incubating them in vitro with autologous DC pulsed MCF-7 lysate for 12 days. Reactivated T-cells and pulsed DCs were injected once intravenously. Follow Ups were done after 7, 14, 21, 28, and 120 days. Study design was feasible in every way.
There were no side effects found during and after T-cell injection. There was a partial response in 3 of 5 measurable patients. In 5 Patients – who received a maximum of reactivated T-cells – we were still able to find these cells 7 days after vaccination.
We conclude that cellular immunotherapy with autologous reactivated MTC is an innovative way of BC treatment. We thus prepare a phase-II trial in metastatic and primary BC patients.

459 PUBLICATION

Risk factors for brain metastasis in patients with advanced breast cancer (abc)

G. Sanna, A. Rocca, L. Franceschelli, A. Balduzzi, C. Marenghi, L. Orlando, C. Catania, L. Adamoli, A. Goldhirsch, F. Nolè. *European Institute Of Oncology, Department of Medicine – Medical Care Unit, Milan, Italy*

Background: Incidence of brain metastasis is apparently rising in pts with ABC, possibly due to better therapeutic approach and longer survival. Occurrence of brain relapse severely affects quality of life and is associated with extremely poor prognosis.
Patients and Methods: A retrospective analysis of 84 consecutive pts with brain metastasis and ABC was performed (March 1999-December 2004). Evaluated variables were: age at diagnosis, staging and nodal status, oestrogen and progesterone receptor status, c-erbB2 over-espression, site of first relapse, previous chemotherapy.
Results: Thirty-three percent of pts aged less than 45 years (13% less than 35 years). Thirty-nine percent had T1 tumour, 28% T2 tumour, 41% had N0 disease and 46% N1 at diagnosis, therefore stage seems not a risk factor for developing subsequent cerebral metastases. Twenty-one percent of pts were metastatic at diagnosis. Brain metastases occurred more frequently in pts with lung (24%), bone (27%) and liver (20%) metastasis

as first site of recurrence. Thirty-seven percent of pts received taxol and 39% herceptin based regimens before cerebral relapse occurred. Among 81 pts with known hormone receptor status of their primary tumour, 42 (52%; 95%CI: 41–63%) had oestrogen and progesterone receptor negative tumours. C-erbB2 overexpression was identified in 38 of 78 assessed tumours (49%; 95%CI: 37–60%). These figures are significantly different from those expected in the general population of pts with breast cancer, where about 30% of cases are ER-/PgR-negative and roughly 25% show c-erbB2 overexpression ($p < 0.001$ for both comparisons, exact binomial test).
Conclusions: Pts with non endocrine responsive and Her-2/neu over-espressing disease may be considered at higher risk of brain relapse. In these subsets of pts screening and prophylactic measures should be investigated.

460 PUBLICATION

The significance of chemotherapy in the treatment of carcinomatous meningitis in breast cancer patients

H. Rudnicka, A. Niwinska, T. Pienkowski, J. Giermek, J. Surowinska, D. Larecka, J. Placzke. *Cancer Center, Breast Cancer Department, Warsaw, Poland*

Introduction: Carcinomatous meningitis is a severe and progressive cancer metastasis caused by infiltration of the leptomeninges and the cerebrospinal fluid by cancer cells.
Purpose: The aim of the study was to establish if systemic chemotherapy applied after intrathecal treatment and radiotherapy can influence on survival period in patients with breast cancer carcinomatous meningitis.
Materials and methods: 53 patients with breast cancer and carcinomatous meningitis were treated in Cancer Center, Warsaw, between 1999–2005. Three methods of treatment were applied: intrathecal treatment, intravenous systemic chemotherapy and radiotherapy. Intrathecal methotrexate, 10 mg per dose, was performed in 89% patients. 30% did not respond after 1–2 courses of treatment and in these cases palliative treatment was continued. The others continued treatment. An average of 6 cycles (1–15) was administered; initially metothrexate twice a week and after clinical improvement the treatment was continued once a week until the normalization of the cerebrospinal fluid, however not more than 15 intrathecal injections.67% women received systemic chemotherapy concurrently with intrathecal treatment. Individual schedules of systemic treatment were used, but the most common were vinorelbine with fluorouracil, antracyclines, cisplatin, taxanes, trastuzumab and capecitabine. 59% patients received radiotherapy to the brain or spinal cord.
Results: Clinical and laboratory response was achieved in 67% patients. The mean survival since diagnosis of carcinomatous meningitis was 18 weeks (1–80 weeks).
In severe condition patients (Karnofsky <60%) who were not treated the median survival period was 4 weeks and after chemotherapy treatment was prolonged to 18 weeks. In not treated patients with Karnofsky above 60% the median survival period was 12 weeks. After systemic chemotherapy it was prolonged to 20 weeks. Log rank test stratified for Karnofsky status was highly statistically significant ($p < 0.001$).
Conclusions: Our observations suggest, that systemic chemotherapy added to intrathecal treatment and radiotherapy is an important factor improving survival in breast cancer patients with carcinomatous meningitis.

461 PUBLICATION

Long-term safety of intravenous ibandronate throughout 4 years of treatment for metastatic breast cancer

M. Pecherstorfer[1], I. Diel[2], J.-J. Body[3], B. Bergström[4]. [1]*Wilhelminenspital, First Department of Medicine and Oncology, Vienna, Austria;* [2]*CGG-Klinik GmbH, Mannheim, Germany;* [3]*Université Libre de Bruxelles, Institut Jules Bordet, Brussels, Belgium;* [4]*Hoffman-La Roche Inc., Nutley, New Jersey, USA*

Background: Despite their widespread use in metastatic bone disease, some intravenous bisphosphonates are occasionally associated with renal toxicity, which may lead to discontinuation of supportive care as well as anticancer medications. Ibandronate is a non-cyclic, single-nitrogen bisphosphonate with a renal safety profile comparable with placebo that is highly effective against skeletal complications and metastatic bone pain. Here, we present safety data from a study of intravenous ibandronate over a 4-year period.
Materials and methods: During an initial 2-year study, breast cancer patients with bone metastases (n = 62) were treated with placebo (n = 16) or ibandronate 6 mg (n = 46) by intravenous infusion over 1–2 hours every 3–4 weeks. In a 2-year extension phase, all patients received active treatment but were classified according to their initial treatment (placebo/6 mg and 6 mg/6 mg groups). Safety was assessed by adverse event (AE) reports and clinical laboratory evaluations. Data from the initial (Years 1–2) and extension (Years 3–4) phases of the study were analyzed separately.
Results: During the initial study, 56.3% of placebo- and 67.4% of ibandronate-treated patients reported treatment-related AEs, compared to 6.3% of the placebo/6 mg group and 13.0% of the 6 mg/6 mg group during the extension phase. All treatment-related AEs were either mild or moderate. Thirty-three patients experienced serious AEs overall (initial phase: placebo 31.3%, 6 mg 26.1%; extension: placebo/6 mg 18.8%, 6 mg/6 mg 28.3%). Withdrawals occurred during the extension phase (placebo/6 mg 12.5%, 6 mg/6 mg 8.7%), but none were due to renal AEs. Laboratory parameters of renal functioning remained normal and there were no clinically-relevant renal AEs throughout the extension phase.
Conclusions: Ibandronate had a good safety and tolerability profile throughout the 4-year study, with no serious AEs caused by the treatment. The absence of treatment-related renal AEs and lack of laboratory abnormalities suggests that the renal safety profile of ibandronate is better than other intravenous bisphosphonates.

462 PUBLICATION

Phase II trial of weekly paclitaxel (wP)+UFT for the treatment of patients with advanced breast cancer(ABC)

H. Ogata, M. Tsuduki, K. Miyamoto, T. Nishikawa, H. Kawamoto, Y. Yabuki, T. Ohta, M. Fukuda. *St. Marianna University School of Medicine, Breast and Endocrine Surgery, Kawasaki-shi, Japan*

Purpose: Phase II trials of combined chemotherapy for ABC using paclitaxel and 5-fluorouracil (Fu) have resulted in high response rates (50 to 60%) inspite of using as second line therapy following doxorubicin. Whereas wP has been reported for its effectiveness and usefullness, continuous administration of 5-Fu to maintain its plasma concentration (pc) needs hospitalization. We have already reported the effectiveness of addition of 5-Fu to wP, Phase I trial for wP+UFT orally, where the pc of 5-Fu is maintained by metabolic inhibition by uracil(ASCO 2002 Abs #1983). The recommended combination of wP+UFT for the treatment of patients with ABC is UFT 400 mg/body/day orally for 6weeks and P 80 mg/m^2 i.v. weekly for 6weeks of an 8-week cycle. A Phase II trial of wP+UFT for the treatment of patients with ABC is designed. The preliminary data of Phase II trial will be presented.
Methods: Patients with HER-2 negative, ABC without prior taxane in any setting were eligible. Patients were treated with or without Ps administered weekly for 6 weeks of an 8-week cycle. While the daily oral dose of UFT was fixed at 400 mg/body for 6 weeks, the dose of P was 80 mg/m^2 weekly as an hour infusion.
Results: A total of 21 patients were registered and randomized between 05/01 and 11/04, with 20 eligible for analysis(12 in wP+UFT, 8 in wP). The over all response rate(RR) is 65%. RR of wP+UFT and wP is 84.6% and 57.1% respectively. Ten patients were anthracycline pre-treated ABC. The most common reasons for discontinuation being progression/relapse (5%) and adverse events (5%). Grade 3 adverse events were 25%.
Conclusions: The combination of wP plus UFT is feasible alternative for the weekly paclitaxel therapy for advanced breast cancer.

463 PUBLICATION

Gemcitabine (GEM) plus oxaliplatin (LOHP) as salvage treatment in anthracycline and taxane pretreated patients with advanced breast cancer (ABC)

A. Kalikaki, A. Potamianou, N. Malamos, K. Syrigos, K. Kalbakis, N. Androulakis, L. Vamvakas, V. Bozionelou, A. Kotsakis, D. Mavroudis. *Breast Cancer Group, Of the Hellenic Oncology Research Group (HORG) Heraklion, Greece*

Background: To evaluate the efficacy and toxicity profile of GEM and LOHP in women with ABC pretreated with anthracyclines and taxanes.
Methods: Patients with histologically confirmed and measurable breast cancer, pretreated with anthracycline- and taxane-based chemotherapy for advanced disease, ECOG PS $\leqslant 2$, and adequate bone marrow, renal and liver function, were eligible. Patients received GEM 1500 mg/m^2 on day 1 and 8 and LOHP 130 mg/m^2 on day 8 every 3 weeks until progression or unacceptable toxicity. Toxicity was evaluated in each cycle and response every 3 cycles.
Results: Between 3/2001 and 6/2004, 31 patients were enrolled and all were evaluable for toxicity and response. The median age was 63 (range 46–72) years. Eight (26%) patients had received 1 and 23 (74%) 2 prior chemotherapy regimens. Bone metastases were present in 11 patients, liver mets in 11 pts, lung mets in 17 pts and lymph node mets in 10pts; 17 (55%) pts had $\geqslant 2$ metastatic sites. A total of 127 cycles were administered (median 3 cycles; range, 1–9). Grade 3–4 neutropenia occurred in 14 (45%) pts, thrombocytopenia in 6 (19%) pts, and asthenia in 4 (13%) pts. CR was achieved in 1 (3%) and PR in 4 (13%) patients (ORR = 16%;