first-line treatment) and 24 pts had sensitive disease. A total of 154 courses have been administered (median 4 per patient).

To date 41 pts were evaluable for toxicity and 35 for response. Response rate (RR) was 48.8%, no complete responses were observed. 20% of pts showed stable disease (SD) and 31.5% progression (PD). The RR in refractory disease was 43%, SD 14% and PD 43%. In sensitive disease RR was 52%, SD 24% and PD 24%. The median duration of response was 3.7 months (95% C.I: 2.2 ± 8.8 m) and median time to progression 4.9 months (95% C.I: 4.1 ± 10.1 m) and median survival 7.1 months (95% C.I: 2.3 ± 7.1m).

Grade 3/4 neutropenia, anemia and trombocytopenia were observed in 7.5%, 2.5% and 5% of the patients respectively. Non-hematological toxicity was very mild. Grade 3 alopecia was observed in 25% of pts, grade 3 nausea/vomiting in 2.5%, grade 2 peripheral neuropathy in 6% and grade 2/3 skin toxicity in 5%.

Conclusions: This combination shows an encouraging activity in sensitive and even in refractory patients Toxicity is moderate and manageable. Further development of this combination is warranted in both untreated and pretreated patients.

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The value of prognostic factors in small cell lung cancer: results from a randomised multicenter study with minimum 5-year follow-up

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Purpose: Demographic, clinical and laboratory parameters at the time of diagnosis have clinical significance. In a prospective study, we investigated the prognostic value of 22 pretreatment attributes in 436 small cell lung cancer (SCLC) patients.

Methods: Pretreatment clinical and laboratory parameters were registered at time of diagnosis [Age, gender, disease extent, ECOG performance status (PS), weight loss, erythrocyte sedimentation rate (ESR), haemoglobin level (Hgb), total WBC count, platelet count, serum g-glutamyl transferase (gGT), serum alkaline phosphatase (ALP), serum lactate dehydrogenase (LDH), neuron-specific enolase (NSE), serum sodium, number of metastases, and metastasis to seven different sites]. The minimum follow-up was 5 years. The prognostic value of the different variables was evaluated by univariate analysis (log rank test) and by the Cox multivariate regression model.

Results: Among all patients, the univariate analysis found gender, disease extent, PS, weight loss, ESR, Hgb, WBC count, platelet count, gGT, ALP, LDH, NSE, serum sodium, no. of metastases, adrenal metastasis, lung metastasis, bone metastasis, liver metastasis, and brain metastasis to be significantly associated with survival. The multivariate Cox model identified gender, disease extent, PS, weight loss, platelet count, LDH, and NSE as independent prognostic factors. In subset multivariate analyses performed according to extent of disease, PS, Hgb, WBC count, and NSE were identified as significant prognostic indicators for survival in limited-stage disease, while PS, weight loss, LDH, no. of metastases, liver metastases, and brain metastases were independent prognostic factors in extensive-stage disease. A significant correlation between serum LDH and NSE levels was observed.

Conclusion: Overall, gender, disease extent, PS, weight loss, Hgb, WBC count, platelet count, LDH, and NSE were found to be independent prognostic factors for SCLC survival. The prognostic value of these factors depends, however, highly on whether all SCLC patients or subsets of these are studied.

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Phase II study of sequential dose-dense paclitaxel followed by topotecan in extensive small-cell lung cancer (SCLC)

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Purpose: Patients (pts) with extensive SCLC have a poor pronostic. New therapeutic approaches are needed. In this phase II study paclitaxel and topotecan have been combined sequentially in a dose-dense schedule in chemonaive pts. These two drugs were chosen on the basis of their single-agent activity in previously untreated SCLC pts and because high doses of these agents could be administered in a dose-dense fashion.

Patients and Methods: Pts with untreated extensive SCLC received 3 cycles of paclitaxel 250 mg/m2 over 3 hours given at 14-day intervas folowed by 3 cycles of topotecan 2.5 mg/m2 x 5 days given every 21 days. Prophylactic filgastrim (G-CSF) was given. Pts progressing during the paclitaxel or topotecan and those not achieving complete response at completion of the full sequence subsequently received etoposide/cisplatin for 4 cycles. Between July 2000 and March 2001, 42 pts had been included (30 have completed chemotherapy tratment). Pts characteristics: median age 58 yr; 96% males; PS 0/1/2 in 9/27/5 pts.

Results: After paclitaxel, 53% (16/30 pts) had response; 26.6% (8/30 pts) stable disease (SD), and 20% (5/30) progressive disease. No pts were hospitalized due to febrite neutropenia during paclitaxel treatment and a 30% developed grade II peripheral neuropathy. Twenty-one pts that responded or had SD to paclitaxel received topotecan. Toxicites due to topotecan included febrile neutropenia in 5/30 pts (24%) with one toxic death and 5/21 (24%) needed blood product transfusion. Nonhematologic toxicities were frequent but mild. The median survival time was 10.5 months and the median progression free survival was 8 months.

Conclusion: Sequential dose-dense paclitaxel folowed by topotecan is well tolered and appears to be a higly active regimen in extensive SCLC.

Clinical pharmacology

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Renal safety of ibandronate 6 mg intravenously administered with shortened infusion times (15 and 30 minutes) in human volunteers: higher peak concentrations do not result in adverse renal effects

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Background: Intravenous bisphosphonate administration has been associated with renal toxicity, as seen with tubular damage in preclinical investigations, elevated serum creatinine (zoledronate), and rare events of acute renal failure in clinical trials. Toxicity may be associated with the total dose administered or also with the peak concentrations achieved. The current investigation was conducted to determine if shortening of infusion time and thus increasing peak concentrations of an established safe dose of ibandronate is accompanied by any signs of early renal toxicity. In addition, the pharmacokinetics of the different infusion regimens were investigated.

Patients and Methods: Single infusions of 6 mg ibandronate administered within 60 (reference with demonstrated safety in Phase III trial), 30 or 15 min were investigated in parallel groups of 20 volunteers. Renal safety was monitored prior to and up to 3 days after infusion by measuring creatinine clearance and markers of tubular or glomerular damage (urinary excretion of albumin, alpha1- and beta2-microglobulin, and N-acetyl-beta-D-glucosaminidase [NAG]). Plasma and urine concentrations were determined at selected time points up to 28 h.

Results: With shortening of the infusion time, peak ibandronate concentrations increased from 307.9 ± 44.8 ng/mL (60 min) to 383.9 ± 41.3 ng/mL (30 min) and 396.7 ± 94.5 ng/mL (15 min). Serum creatinine concentrations and creatinine clearance were not changed by ibandronate and were not different between the three groups. Albumin, alpha1- and beta2-microglobulin, and NAG were also similarly unaffected by ibandronate infusion with any infusion time.

Conclusion: The increase of mean peak concentrations of ibandronate from 300 ng/mL (range 237-417) to about 400 ng/mL (range 227-582) did not lead to any adverse acute renal effects. Ibandronate 6 mg may be safely administered by a 15-min infusion. Infusions every 3 to 4 weeks can be viewed as separate single administrations from a pharmacokinetic viewpoint and should therefore provide the same safety profile. This should be confirmed in clinical studies using multiple administrations.