Analyses of clinical prognostic factors in the treatment of advanced non-small cell lung cancer (NSCLC): Cox regression analysis based on 789 patients from three consecutive randomized Phase II trials using gemcitabine and docetaxel

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Background: The results concerning treatment efficacy and toxicity of the three studies have been in part been presented in Clin Lung Cancer 2005, 7: 208-214 and 2007, 8: 245-251 and at WCLC (2005, Abstract # 1297). Gemcitabine or docetaxel was either applied in patients with advanced NSCLC as single agents in different schedules and doses or as a platinum free doublet. Aim of this retrospective analysis is the identification of clinical factors influencing the patient prognosis.

Methods: Commonly used patients eligibility criteria included histologically confirmed stage “wet IIIB” with malignant pleural effusion or stage IV; WHO performance status (PS) 0-2, and no previous chemotherapy. As a result, overall survival was similar in all three studies. Of the 819 patients enrolled in 1998-2004 in the three studies 798 were evaluable for this analysis: 85% of patients had stage IV disease and WHO performance status PS≤1. Univariate as well as stepwise multivariate Cox regression analyses were performed to evaluate the measure of impact for baseline characteristics and quality of life on overall survival.

Results: Four factors have shown a significant impact on overall survival: the laboratory parameters hemoglobin and LDH (p<0.0001), WHO performance status (PS) (p=0.001) and the quality of life measure for lung cancer of the EORTC, lung cancer questionnaire LC13, (p=0.0006), respectively (see table).

Multivariate Cox Regression Analysis

<table>
<thead>
<tr>
<th>Factors associated with prognostic power</th>
<th>Hazard-ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO PS02 (vs 0 or 1)</td>
<td>1.443</td>
<td>0.001</td>
</tr>
<tr>
<td>HGB &lt;11 g/dl (vs 11 g/DL or more)</td>
<td>1.905</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDH 200 or more (vs &lt; 200)</td>
<td>1.585</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EORTC-LC13-Score &gt; 1.5 (vs 1.5 or less)</td>
<td>1.365</td>
<td>0.0006</td>
</tr>
<tr>
<td>Male gender (vs female)*</td>
<td>1.201</td>
<td>0.0703</td>
</tr>
<tr>
<td>*Male gender (vs female) univariate</td>
<td>1.263</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

If the gender was measured univariately the influence was also significant on overall survival (p=0.0085) but this factor has less impact in the setting of the multivariate model (p=0.07). The factor age discriminated dichotomously at 65 (<65 vs 65 and older) is not of prognostic value with overall survival (HR=0.92, p=0.39), as well as threefold discriminated baseline histology (adeno/squamous/other) (HR=0.99, p=0.90). The examination of other factors as tumor stage (“wet IIIB” vs IV), the presence of extra-thoracic metastases, the number of co-morbidities, and surgical and radiological pretreatment also have shown no prognostic influence on overall survival. As a matter of fact, the analysis for the effect of smoking on overall survival could not be performed since only few patients never smoked status.

Conclusions: The retrospective analysis of our three consecutive studies in the treatment of NSCLC with gemcitabine or docetaxel confirms the prognostic value of serum hemoglobin, and LDH, the WHO-performance status, and the quality of life questionnaire LC13 measure as influential clinical determinants for overall survival.

Biweekly docetaxel and gemcitabine as first line chemotherapy in advanced non small cell lung cancer (NSCLC)

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Background: The activity and tolerability of third-generation agents led many investigators to evaluate doublet combinations in the hope that platinum analogues could be eliminated from the treatment of advanced NSCLC. To improve the therapeutic index of this combination, we performed a study with biweekly gemcitabine and docetaxel. Primary objective was determination of objective response rate (ORR). Secondary objectives were time to progression, tolerability and overall survival.

Methods: Patients histologically confirmed of non-small cell lung cancer, aged >18, ECOG PS 0-2, measurable lesion according RECIST criteria, adequate bone marrow, renal and hepatic function were included. Prior chemotherapy was not allowed. Patients received treatment with a combination of Docetaxel 50 mg/m2 and Gemcitabine 2000 mg/m2 each 15 days for a maximum of 8 cycles.

Results: Fifty patients were included between July 2005 and October 2006. Now we present the results of the first 45 patients: 88% were male, median age was 62.7 years old, 75% had ECOG 0-1 and 73% of patients had stage IV. Histology was squamous cell carcinoma (53%) adenocarcinoma (31%) and large cell carcinoma (16%). A total 300 cycles were administrated. Over 41 patients evaluable for response, none achieved CR, 16 PR (39%), 11 SD (27%) and 14 PD, with an overall response rate of 39%. Median follow up of patients is 19 months. Grade 3-4 toxicity per patient was: neutropenia (6%). Grade 1-2 toxicity per patient was: asthenia (75%), and nausea (30%).

Conclusions: These results suggest that biweekly schedule of gemcitabine / docetaxel is a safe and active regimen in first line advanced NSCLC patients. Updated results will be presented.

Pulmonary toxicity in patients treated with a combination of gemcitabine (G) associated to docetaxel (D) or vinorelbine (V) for advanced non-small cell lung cancer (NSCLC): outcome data on a randomized phase II study

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Background: Previous comparative studies have shown similar efficacy and less toxicity with either, the GV or GD combination respect to platinum-based chemotherapies in patients with advanced NSCLC. This trial was designed to test the efficacy and safety of both, GV and GD combination in non-selected patients with advanced NSCLC.

Methods: Patients (n=39) with ≤75 years old, KPS ≥60% and adenocarcinoma histology (55%). Treatment indicated objective response of 7 versus 3. Grade 2-4 haematological toxicities in 5 versus 2 patients.

Results: Baseline characteristics were comparable in GV (n=20) and GD arms: median age (67 years) and KPS (70%), most of patients were male (79%), had metastatic disease (85%) and adenocarcinoma histology (55%). Treatment indicated objective response of 7 (35%) versus 6 (31%) patients, median time-to-treatment failure of 120 versus 90 days, and overall survival of 209 versus 177 days in GV and GD arms respectively. The most common non-haematological toxicities were (GV versus GD; no. of patients): grade 2-4 pulmonary toxicity in 1 versus 7 (37%); grade 2-3 diarrhoea in 0 versus 4 (21%) and oedemas 1 versus 3. Grade 2-4 haematological toxicities in 5 versus 2 patients. All side effects were reversible phenomena since resolution was achieved by suspending the treatment and in the case of the pulmonary toxicity, by the prescription of additional corticoids.

Conclusion: The combination of Gemcitabine/Docetaxel does not have favourable safety profile with this schedule of administration, particularly in terms of pulmonary toxicity. Further patients’ accrual was stopped and the study has been terminated. This kind of toxicity and alternative schedules of GD combination warrants further investigation.

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Gemcitabine and oral vinorelbine in elderly patients with advanced non-small cell lung cancer (NSCLC). A phase II study conducted by the Galician Lung Cancer Group (GLCG)

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Background: The combination of gemcitabine (G) and vinorelbine (V) is one of the most effective non-cisplatin based treatment regimens for advanced NSCLC. Oral vinorelbine (Ov) has been employed in NSCLC treatment with similar bioavailability and response rates and a more favourable toxicity profile compared to i.v. form. The GLCG conducted a phase II study to determine the efficacy and safety of GOv combination in elderly patients with advanced NSCLC. The primary objective was response rate (RR) Secondary objectives included time to progression (TTP) overall survival (OS) and toxicity.

Methods: 32 chemo-naive pts histologically confirmed NSCLC, aged>70, stage IIIIB/IV, ECOG 0/1, measurable lesions according RECIST criteria and adequate bone marrow, renal and hepatic function were included. Pts received G 1000 mg/m²i.v. followed a Ov 60 mg/m² (days 1 and 8 every 3 weeks for a maximum of 6 cycles)

Results: Between July 2005 and January 2007, 32 pts were included and 130 cycles were administrated. Male / Female 29/3; median age 76.8 years (range 70-86), all ECOG 1, 21 squamous cell carcinoma, 9 adenocarcinoma and 2 large cell. Stage IIIIB/IV: 9/23. To date, 26 pts were evaluable for response and 30 for toxicity. The RR was 38% (95% CI: 20-56) PR:38%, SD:27% and PD 35%. The median TTP was 4.5 months and the median OS was 9 months. The main toxicities were anemia grade 3-4 in 4 pts, neutropenia grade 3-4 in 3 and plaquetopenia grade 3 in 2; non-haematological grade 3-4 toxicities included grade 3 asthenia in 3 pts and grade 3 emesis in one pt.

Conclusions: The GOv regimen is effective and well tolerated in elderly pts with advanced NSCLC.

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Nedaplatin and docetaxel combination therapy in patients with squamous cell lung cancer

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Background: Nedaplatin (CDGP) is a cisplatin derivative developed in Japan. Its response as monotherapy has been reported to be 20.5% in non-small cell lung cancer, while when used in combination with vindesine (VDS), its efficacy is similar to cisplatin (CDDP). Particularly in squamous cell carcinoma (SQCC), it is said to achieve response rates that are superior to CDDP+VDS. With respect to adverse effects, it causes less nausea/vomiting and nephrotoxicity compared to CDDP. Since we have used CDGP in combination with the new agent docetaxel (TXT) principally for SQCC of the lung, the retrospective data to evaluate the efficacy and the safety of this combination are reported here.

Methods: Forty patients (male/female 34/6; mean age 65.9 (42-89) years) with non-small cell carcinoma treated with chemotherapy. Thoracic radiation was used separately in 6 patients. Treatment consisted of 80-140mg/body CDGP and 80-140mg/body TXT on day one with about 1,000 ml of hydration every 3-4 weeks.

Results: Seventy five cycles were given to 40 pts (mean cycles 1.88) and the mean dosages actually administered were 66.7 mg/m² for CDGP and 65.4 mg/m² for TXT. An over all response rate was 55.0% (2 CR, 20 PR, 11 NC, 1 PD). The mean survival time was 17.2 months and the survival rate was 63.0% at 1 year, 37.8% at 2 years, and 33.1% at 3 years. Thirty patients without resection after treatment (24 advanced and 6 recurrent cases) had a mean survival time of 14.6 months and a survival rate of 53.7% at 1 year, 20.7% at 2 years, and 10.3% at 3 years. NCI-CTC grades 3-4 neutropenia, thrombocytopenia, nausea/vomiting occurred in 50 (66.7%), 2 (2.7%), 2 (2.7%) cycles, respectively. There was no grade 3-4 anemia and nephrotoxicity.

Conclusions: We conclude that a combination of CDGP and TXT has adequate tolerability, gives high response rates, and thus is a useful therapy for advanced or recurrent squamous cell carcinomas in lung.