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GEMCITABINE/CISPLATIN CONTAINING CHEMOTHERAPY IN PATIENTS WITH STAGE III-IV NON SMALL CELL LUNG CANCER

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SUMMARY:

Backgraund: A two- drug platinum- based regimens is the standard first- line treatment for inoperable non- small cell lung cancer /NSCLC/ patients with perfomance status /PS/ 0-2. The aim of this study was to evaluate the efficacy and safety of chemotherapy combination Gemcitabine- cis-Platinum in patients with advanced NSCLC. **Methods:** Thirty-four patients with unresectable, histologically proven stage III/IV NSCLC entered the study. Chemotherapy consist of Gemcitabine 1250 mg/m^2 on day 1 and 8 and CDDP 80 mg/m^2 with hyperhydration on day 1 with repetition after 21 days until progression. **Results:** One complete response and eleven partial response was obtained. The main grade toxicity included neutropenia, thrombocytopenia, nausea/vomiting, neuropathy. **Conclusions:** Gemcitabine/CDDP were feasible and effective in stage III/IV NSCLC patients with 35.5% response rate and mild to moderate toxicity.

Key words: Gemcitabine, Non small cell lung cancer, Response rate

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases and is generally resistant to chemotherapy /1/. A metaanalyses have verified a small, but significant improvement in the survival of patients with advanced NSCLC treated with Cisplatin- based chemotherapy with 10% absolute improvement in the 1-year survival rate over best supportive care alone /2/. Recently, new agents with novel mechanisms of action have been developed and some of them have already been reported to produce a significant survival advantage as a single-agent over the best supportive care alone in patients with advanced NSCLC /3,4/. Furthermore, doublets consisting of Cisplatin plus one of these new agents have been shown to improve survival compared to Cisplatin plus existing agents such as Vinorelbine or Etoposide in patients with advanced NSCLC /5,6/. Gemcitabine is a new nucleoside analogue with major antitumour efficacy in NSCLC /7/. Number of phase II and III have been reported with Gemcitabine as a single agent and in combination with Cisplatin in patients with NSCLC /8,9/. Gemcitabine in the first line chemotherapy have produced consistent response rates of 20% with a median survival of 9,5 months in stage III- IV NSCLC /8/. Gemcitabine is well tolerated and easy to administer on an outpatient's basis.

The aim of this study is to evaluate the efficacy and safety of treatment with Gemcitabine/Cisplatin in patients with stage III/IV NSCLC.

PATIENTS AND METHODS

Thirty-four patients with unresectable, histologically proven stage III/IV NSCLC entered the study. Patients have not been received any chemotherapy before. Eligibility criteria included World Health Organization /WHO/ performance status 0 to 2, no prior chemotherapy, adequate bone marrow function /absolute granulocyte count > 1,5x10^9/L, platelet count > 140x10^9/L/ as well as normal renal /serum creatinine level < 1,5 мmol/L/ and hepatic function/ /serum bilirubin level < 21 мmol/L/, absence of active infections, no overt cardiac disease and at least one measurable and/or assessable tumor lesion. Measurable disease was assessed either by palpation or radiological assessment (x-ray, abdominal ultrasound, or computed tomography scan). Chemotherapy consists of Gemcitabine 1250 mg/m^2 on day 1 and 8 by intravenous infusion and Cisplatin 80 mg/m^2 with hydration on day I by infusion. Treatment was administered every 3 weeks until progression. Patients were evaluated for tumor response before treatment and after third and sixth course of chemotherapy. Tumor response was evaluated according to WHO response criteria /10/. Response was defined as complete response (CR), partial response (PR), no change (NC), or progressive disease (PD). Duration of response was determined from the first infusion.

A CR was defined by the disappearance of all known disease, confirmed by two observations not less than 4 weeks apart. PR was defined as a decrease in tumor size of 50% or more (either measured or estimated in the case of measurable or assessable disease). In addition, there could be no appearance of any new lesions or progression of any known lesion(s). Objective tumor response included both confirmed CR and PR.

Safety was assessed using the WHO toxicity criteria /11/.

The duration of response was calculated from the day of the start of treatment to disease progression; overall survival was measured from study entry to death. The time to disease progression was calculated from study entry until the day of the first evidence of disease progression. The actuarial survival was estimated by the method of Kaplan and Meyer /12/.

RESULTS

A total of 34 patients were entered in the study over a 36- months period. All patients, regardless of their length of treatment, were included in analysis. Antitumour effects were evaluated for all 34 cases. Some patient's characteristics are listed in Table 1. The safety was assessed in all 34 patients. Median treatment period was 6,5 months. The median follow-up period was 10,5 months.

Antitumour effects

The resulting antitumour effects are presented in Table 2. One complete and eleven partial remissions were obtained. The overall response rate /ORR/ was 35,5 % (12 of 34), showing that chemotherapy had induced a significant efficacy. Median time to disease progression was 7,5 months. A one- year survival rate was 87.5%.

Safety

Table 3 presents the incidence of adverse drug reactions that occurred in entire group. The highest incidence was gastrointestinal, haematology and neurological toxicity. Most of these symptoms were rated as grade 1 or 2 and chemotherapy was not stopped or delays. Grade III- IV gastrointestinal and hematology toxicity was observed in 26,4 % of the patients. Abnormal values for laboratory tests related to hepatic function were observed such as elevation of, ASAT and AP.

DISCUSSION

The results, achieved by chemotherapy in advanced NSCLC continue to be unsatisfactory and are largely palliative in nature. Platinum- based combination therapy is currently the standard recommended treatment. This recommendation is based upon the higher response rate and the slightly improved survival benefit, small in extend but statistically significant, which can be attributed to this combination therapy when compared with single- agent chemotherapy /13/. The inclusion of platinum agents in combination chemotherapy produces better results than early combinations without Cisplatin. The two drugs have different mechanism of action. Cisplatin exerts its cytotoxic action by binding to DNA and producing DNA- DNA crosslinks. Resistance to Cisplatin occurs when the damaged DNA undergoes excision repair. Gemcitabine appears to inhibit this repair process. Other mechanism of action of Gemcitabine is incorporation into replicating DNA and inhibition of DNA synthesis /14/.

We initiated this study to evaluate efficacy and safety of treatment with Gemcitabine/Cisplatin in patients with advanced stage NSCLC cancer. Response rate- 35,7% is better that single agent chemotherapy response rate and is promising given the acceptable toxicity profile. The survival duration- 10,5 months is encouraging. The reported survival times of sample Cisplatin- containing chemotherapy regimens include 9,2 months for Mitomycin- Cisplatin- Ifosfamide, 26 weeks for Cisplatin and Etoposide and 22 weeks for Mitomycin, Vinblastine and Cisplatin /15/. Different studies can not be compared directly because of factors such as patients selection. However, they can be useful as indicators to access the promise of new regimes.

Both hematological and nonhematological toxicity was mild to moderate and chemotherapy was not stopped because of toxicity.

In conclusion, the results of the present study indicate that the Gemcitabine- Cisplatin combinations appears promising with of survival rate of 10,5 months, the low hematological toxicity and nonoverlapping toxicity of the two agents. The combination merits further evaluation in prospective trials with other Cisplatin regimes.

Table 1. Patient characteristics [means ± standard deviation (SD)] or number of patients

Patient characteristics	Number of patients
Age (years)	45 - 73
Sex	
Males	28
Females	6
Dominant site of metastasis	
Bone	14 (41,1%)
Pleura	10 (34,0%)
Soft tissue	9 (26,4%)
Hepar	6(17,6%)
Lung	1(3,4%)
Other	1(3,4%)
No. of evaluable lesions	
1	24 (70,7%)
2	9 (25,9%)
≥3	1 (3,4%)
Lost weight	
< 5%	5 (14,7%)
5-10%	19 (54,2%)
>10%	10 (31,1%)

Performance status	
0	13 (39,2%)
1	18 (52,8%)
2	3 (8.0%)
Stage	
III	12 (71.8%)
IV	22 (28.2%)
Histology	
Squamous	26 (55.5%)
Adenocarcinoma	6 (41,1%)
Large-cell	2 (3,4 %)

Table 2. Objective responses

Patients/ Response	CR	PR	NC	PD	ORR%
34	1	11	17	5	35,2%

ORR= CR + PR .

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; ORR, overall objective response rates;

Table 3. Adverse drug reactions by symptoms: grade 3 and 4

Adverse drug reactions	Number of patients
Gastrointestinal	5 (13,2 %)
Grade 3	2 (5,1 %)
Grade 4	3 (8,1,%)
Haematological	5 (13,2%)
Grade 3	3 (8, 1 %)
Grade 4	2 (5, 1 %)
Neurological	2 (5,1%)
Grade 3	1 (3,4 %)
Grade 4	1 (3,4 %)

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