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GEMCITABINE / PLATINUM VS. VINORELBINE-PLATINUM IN PATIENTS WITH ADVANCED NON-SMALL- CELL LUNG CANCER

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RESUME:

Background: A platinum- based doublets with a third-generation agents /Gemcitabine, Vinorelbine/ represent the standard first- line treatment for advanced patients with non-small- cell lung cancer /NSCLC/ and good performance status. Aim: The aim of this study was to evaluate the two commonly used newer platinum- based regimes in response rate and survival. Methods: In the period 2005- 2007 ninety-four inoperable patients with NSCLC entered the study. The treatment schedule consist of Gemcitabine 1250 mg/m2 day 1 and 8 and cis- Platinum 80 mg/m2 with hydratation day 1- 46 patients /arm GP/ and Vinorelbine 30 mg/m2 day 1 and 8 and cis- Platinum 80 mg/m2 with hydratation day 1- 48 patients /arm VP/, every 21 days. Results: Overall response rate was 39% for GP and 32% for VP. Median survival was 10,3 and 9,8 months respectively. Neutropenia was significantly higher in arm VP as was thrombocytopenia on the GP arm. Conclusions: That data suggest that both regimes remain reasonable choices for patients with advanced NSCLC with slight prevalence of GP.

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

INTRODUCTION

Non-small- cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases and is generally resistant to chemotherapy /1/. The treatment options for these patients are limited, but treatment with chemotherapy has been associated with a modest but significant survival advantage when compared with the best supportive care. A metaanalyses have verified a significant improvement in the survival of patients with advanced NSCLC treated with Platinum- based chemotherapy with 10% absolute improvement in the 1-year survival rate /2/. Recently, several new drugs as Gemcitabine and Vinorelbine with novel mechanisms of action have been developed and also have demonstrated a promising antitumour activity against NSCLC, with documented responses ranging from 14% to 38%. 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 Platinum plus one of these new agents have been shown to improve survival compared to Platinum plus existing agents such as Mitomycin C 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 Platinum 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.

Vinorelbine is the most active of the vinca alkaloids. It induces high objective response rates as a single agent. Phase III studies has confirmed Vinorelbine is active in the treatment of NSCLC when combined with Platinum producing response rate approximately 39 %

The aim of this study was to evaluate the response rate and survival of the two commonly used newer platinum-based regimes- Gemcitabine/ Platinum and Vinorelbine-Platinum in patients with advanced non- small- cell lung cancer.

PATIENTS AND METHODS

In the period 2005- 2007 ninety- four patients with inoperable, morphologically proven stage III/IV NSCLC, treated in Oncological center- Pleven, Department of chemotherapy, entered the study. Patients have not been received any chemotherapy before. Eligibility criteria included World Health Organisation /WHO/ performance status 0 to 2; 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 jmol/L/ and hepatic function /serum bilirubin level < 21 jmol/L/; absence of active infections; no overt cardiac disease; at least one measurable and/or assessable tumour lesion. Measurable disease was assessed either by palpation or radiological assessment (x-ray, abdominal ultrasound, or computed tomography scan). The treatment schedule

consist of: Gemcitabine 1250 mg/m2 by intravenous infusion day 1 and 8 and Platinum 80 mg/m2 with hydratation on day 1- 46 patients /arm GP/; and Vinorelbine 30 mg/m2 by intravenous infusion day 1 and 8 and Platinum 80 mg/m2 with hydratation day 1- 48 patients /arm VP/. Treatment was administered every 3 weeks until progression. Patients were evaluated for tumour response before treatment and after third and sixth course of chemotherapy. Tumour 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).

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 tumour 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 tumour 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 94 patients were entered in the study over a 24- months period- arm GP- 46 patients and arm VP- 48 patients. All patients, regardless of their length of treatment, were included in analysis. Antitumour effects were evaluated for all 94 cases. Some patient's characteristics are listed in Table 1. The safety was assessed in all 94 patients. Median treatment period was 6,5 months. The median follow-up period was 9,5 months.

Antitumour effects

The resulting antitumour effects are presented in Table 2. The overall response rate /ORR/ was 39 % /36 patients/, showing that chemotherapy had induced a significant efficacy. Three complete and 25 partial remissions were obtained. Median time to disease progression was 8,4 months. A one- year survival rate was 76.5%.

Safety

Table 3 presents the incidence of adverse drug reactions that occurred in entire group/grade III and IV only/. 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 haematology toxicity was observed in 29,7 % 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 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 Platinum. Platinum 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 and Vinorerbine have different mechanism of action. Gemcitabine appears to inhibit this repair process. Other mechanism of action of Gemcitabine is incorporation into replicating DNA and inhibition of DNA synthesis /14/. Vinorelbine is the most active of the vinca alkaloids. It binds to a specific site on tubulin and prevents the polymerization, and mitotic spindle formation.

In this study we wanted to compare efficacy and safety of treatment with Gemcitabine/ Platinum versus Vinorelbine/ Platinum in patients with advanced stage NSCLC cancer. Response rates- 39% in arms GP and 32% in arm VP are not significant. They are better that single agent chemotherapy response rate and are promising given the acceptable toxicity profile. The survival duration- 9,7 months for all group is encouraging. The reported survival times of sample Platinum- containing chemotherapy regimens include 9,2 months for Mitomycin- Platinum- Ifosfamide, 6,5 months for Platinum and Etoposide and 5,5 months for Mitomycin, Vinblastine and Platinum/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 haematological and nonhaematological toxicity was mild to moderate and chemotherapy was not stopped because of toxicity.

In conclusion, this trial in advanced NSCLC has shown some survival advantages for the combination of Gemcitabine / Platinum in comparison with Vinorelbine / Platinum with of survival rate of 9,7 months. Statistical significance has not been reached in the overall survival comparison. The results indicate that the both combinations- GP and VP appear promising, with low haematological toxicity and nonoverlapping toxicity of the two drugs combinations. This observation requires further confirmation by other randomized controlled trials.

Table 1. Patient characteristics

Patient characteristics	Number of patients- GP= 46	Number of patients- VP= 48
Age (years)	45 – 73	39- 72
Sex		
Males	37	43
Females	9	5
Dominant site of metastasis		
Pleura	18 (38,1%)	21 (41,8%)
Hepar	10 (21,7%)	11 (21,9%)
Lung	6 (12,4%)	5 (10,5%)
Soft tissue	6 (12,4%)	6 (12,6%)
Bone	5 (10,8%)	4 (8,4%)
Other	1 (4,6%)	1 (4,8%)
No. of evaluable lesions		
1	26 (54,1%)	29(60,4%)
2	16 (34,5%)	11(22,9%)
e”3	4 (9,4%)	8(16,7%)
Lost weight		
< 5%	24 (52,2%)	21 (41,8%)
5-10%	16 (35,7%)	17 (37,4%)
>10%	6 (13,1%)	10 (20,8%)
Performance status		
0	14 (30,4%)	16 (33,4%)
1	23 (50,0%)	24 (50,0%)
2	9 (19,6%)	8 (16,6%)
Stage		
III	19 (41,3%)	18 (37,5%)
IV	27 (58,7%)	28 (62,5%)
Histology		
Squamous	31 (66,7%)	35 (72,9%)
Adenocarcinoma	11 (23,9%)	9 (18,7%)
Large-cell	4 (9,4%)	4 (8, 4%)

Table 2. Objective responses

Patients/ Response	CR	PR	NC	PD	ORR%
GP=42	2	14	21	9	39%
VP=48	1	11	24	12	32%

ORR= CR + PR .

GP= Gemcitabine/Platinum

VP= Vinorelbine/Platinum

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 GP=42	Number of patients VP=48
Gastrointestinal	6 (13,0 %)	5 (10,4 %)
Grade 3	3 (6,5 %)	2 (4,1 %)
Grade 4	3 (6,5 %)	3 (6,2,%)
Haematological	5 (10,8 %)	5 (10,4%)
Grade 3	3 (6,5 %)	3 (6,2 %)
Grade 4	2 (4,5 %)	2 (4,1 %)
Neurological	4 (8,9 %)	3 (6,2%)
Grade 3	2 (4,5 %)	2 (4,1%)
Grade 4	2 (4,5 %)	1 (2,0%)

REFERENCES

1 Marino P, Pampallona S, Preatoni A, et all, Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. Chest 1994;106:861–5

2. Non-small cell lung cancer collaborative group. Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomized clinical trials. BMJ 1995; 311: 899–909.

3. Bunn PA. Chemotherapy for advanced non-small-cell lung cancer: who, what, when, why? J Clin Oncol 2002; 20: 23s–33s.

4. Ranson M, Davidson N, Nicolson M et al. Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 2000; 92: 1074–1080.

5. Baggstrom MQ, Socinski MA, Hensing TA, Poole C. Third generation chemotherapy regimens (3GR) improve survival over second generation regimens (2GR) in stage IIIB/IV non-small cell lung cancer (NSCLC): a meta-analysis of the published literature. Proc Am Soc Clin Oncol 2002; 21: 306a (Abstr 1222).

6. Yana T, Takada M, Origasa H et al. New chemotherapy agent plus platinum for advanced non-small cell lung cancer: a meta-analysis. Proc Am Soc Clin Oncol 2002; 21: 328a (Abstr 1309).

7. Kaye SB. Gemcitabine: Current status of phase I and II trials. J Clin Oncol 1994;12;1527-1531

8. Abratt RP, Bezwoda WR, Falcson G et al. Efficacy and safety profile of gemcitabine in non- small- cell lung cancer: A phase II study. J Clin Oncol 1994; 12; 1535- 1540

9. Crino L, Scagliotti G, Marangolo L et al. Cisplatin- gemcitabine combination inadvanced non- small- cell lung cancer: A phase II study. J Clin Oncol 1997; 15; 297-303

10. Miller AB, Hoogstraten B, Staquet M et al. Reporting results of cancer treatment. Cancer 1981; 47; 207-214

11. Brimdage MD, Pater JL, Zee B: Assessing the reliability of two toxicity scales: Implications for interpreting toxicity data. J Natl Cancer Inst 1993; 85; 38-48

12. Kaplan EL, Meyer P: Non-parametric estimation from incomplete observations. J Am Stat Assoc 1959; 53; 457- 481

13. Crino L, Tonato M, Darwis S et al. A randomised trial of 3 cisplatin containing regimens in NSCLC. A study of the Ummbrian Lung Cancer Group. Cancer Chemotherapy Pharmacol 1990; 26; 52-56

14. Zamble DM, Lippard SJ: Cisplatin and DNA repair in cancer chemotherapy. Trends Biochem Sci 1995; 20; 435-439

15. Weick JK, Crowley J, Natale RB et al. A randomized trial of five cisplatin-containing treatments in patients with metastatic non- small- cell lung cancer: A Southwest Oncology group study. J Clin Oncol 1991; 9; 1157- 1162

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