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Letters

Cisplatin and Continuous Infusion Vindesine and 5-Fluorouracil in Non-small Cell Lung Cancer (NSCLC) (ATTIT 002)

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SO-CALLED "STATE-OF-ART chemotherapy" in advanced non-small cell lung cancer (NSCLC) is based on cisplatin (CDDP) and vinca alkakoids, such as vindesine (VDS) or vinblastine (VLB), or more recently, vinorelbine (VRL) [1, 2]. On the basis of our recent experience with VDS continuous infusion (CI) and CDDP in metastatic small cell carcinoma of the head and neck [3, 4], we decided to explore the feasibility, tolerability and activity of CDDP plus CI VDS and 5-fluorouracil (5-FU) (FVP regimen) in NSCLC. A retrospective (historical) comparison has been done with the results obtained by our own group in a previous trial with the reference MVP (mitomycin C, VLB and CDDP) regimen [5–8].

From February 1989 to November 1989, 53 consecutive previously untreated patients bearing measurable or evaluable NSCLC were entered into the trial. Patients' characteristics, stage and sites of metastasis are listed in Table 1.

FVP regimen: 5-FU 800 mg/m^2 by 24-h CI, on days 1 to 4; VDS 0.8 mg/m^2 by 24-h CI on days 1 to 4; CDDP 100 mg/m^2 on day 1 with hydration and mannitol-induced diuresis. Both 5-FU and VDS were diluted in 1000 ml of isotonic solution and administered by a catheter placed in the subclavian vein. Cycles were repeated every 3 weeks. VDS and 5-FU doses were adjusted according to white blood cell (WBC) counts on days 10, 14 and 20 after the previous cycle, with 20% reduction for grade IV myelotoxicity on days 10 and 14, and 50% reduction in cases of neutropenic fever.

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Table 1. Characteristics of 53 patients

Characteristics	Patients	%
Median age (years)	58	
Males	49	92
Karnofsky performance status		
80–100%	52	98
Histological subtype		
Adenocarcinoma	11	21
Epidermoid carcinoma	28	53
Large cell carcinoma	8	15
Not specified	6	11
Stage		
II	4	8
IIIa	13	25
IIIb	12	22
IV	24	45
No. of metastatic sites		
1	21	88
>1	3	13

VDS was discontinued in case of grade III or more severe neurotoxicity, or of serum bilirubin exceeding 2.5 mg/dl. Treatment was postponed for 1 week if, on day 20, WBC were <4000 or platelets <100 000/mm^3. Dose adjustment for CDDP was as described in our previous report [8].

Patients were evaluated after the third course of chemotherapy, using Eagan's response criteria [9]. After evaluating response, stage III responders underwent full-dose radiation, or exploratory surgery with radical curative intent. Administration of chemotherapy was continued for up to six courses in stage IV responders, and discontinued in non-responders. Response duration and overall survival, together with type of response, were used to construct Kaplan–Meier-type plots.

52 patients were evaluable for toxicity, and 53 for response. 1 patient progressed after the first course (objective toxicity not assessed). Toxicities (WHO grades) are reported in Table 2. Complications related to the venous central access were defined as early (arterial punction 1%, pneumothorax 1%) and delayed (thrombosis 3%, thrombophlebitis 3%, local or systemic infection 8 and 6%, respectively). All such local and systemic complications proved manageable, only 2 patients needing catheter removal because of cutaneous infection at the injection site after two and three courses, respectively.

Two complete responses (CR) (4%) and 13 partial responses (PR) (25%) (95% confidence interval 16–40%) were achieved out of 53 evaluable patients. By disease stage, 2 PR (50%) were obtained in 4 stage II patients, 1 CR (8%) and 5 PR (38%) in 13 stage IIIa, 1 CR (9%) and 4 PR (36%) in 12 stage IIIb, and 2 PR (8%) in 24 stage IV patients. By histological subgroups, there were 10 objective responses out of 28 patients with epidermoid carcinoma (36%), 1/11 with adenocarcinoma (9%), and 4/8 with large cell carcinoma (50%). Median duration of response was 5.5 months. In May 1991, with a median follow-up of 24 months (range 11–27), the overall median survival time (MST) was 8 months. MST by stage was 19.5 months for stage II–IIIa, 11.5 for stage IIIb, and 4.5 for stage IV. MST for responders has not yet been reached, with 8 patients still alive (15+, 17+, 17+, 17+, 18+, 20+, 21+, and 25+ months, respectively).

Table 2. Observed toxic effects in 154 cycles for 52 patients

	WHO grade				
	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
Leucocytes*	67 (44)	28 (18)	29 (19)	24 (16)	6 (4)
Neutrophils*	55 (36)	14 (9)	23 (15)	22 (14)	40 (26)
Platelets*	151 (98)	1 (1)	1 (1)	—	1 (1)
Haemoglobin*	117 (76)	25 (16)	10 (6)	1 (1)	1 (1)
Constipation†	86 (56)	32 (21)	35 (23)	1 (1)	—
Peripheral neuropathy†	134 (87)	11 (7)	7 (5)	1 (1)	1 (1)

*Lower nadir checked between two WBC per cycle made on days 10 and 14; 31 and 35; 52 and 56.
†Evaluated at days 21, 42 and 63.

We have previously reported comparable results with the MVP regimen (introduced by the Memorial Sloan Kettering Cancer Center), in term of both response rate (29 vs. 28%) and MST (9 vs. 8 months). Toxicities, either haematological or other, were also comparable, despite different drugs (5-FU by CI instead of mitomycin C) and different schedules of VDS (weekly bolus vs. three weekly CI). The present VDS schedule allowed us to optimise drug administration on a three weekly basis, and to avoid dose delay or reduction, that are often required with weekly VDS. Actually, in spite of the different VDS doses in the two regimens (3 mg/m^2 weekly in MVP vs. 0.8 mg/m^2 daily for 4 days every 3 weeks in FVP), weekly dose intensity was 1.8 mg/m^2 for MVP vs. 1.1 mg/m^2 for FVP (a 0.6 ratio). With respect to 5-FU by CI, dose intensity was clearly suboptimal, since the drug was administered at a lower dose compared to conventional schedules, namely 800 mg/m^2 daily for 4 days vs. 1000 mg/m^2 daily for 5 days. Accordingly, we started a new trial of the same FVP combination in NSCLC patients, adding folinic acid (leucovorin) with the aim to potentiate 5-FU activity.

In conclusion, the FVP could represent an alternative to MVP in NSCLC, in order to obviate the major risk associated with weekly VDS, namely delayed courses and reduced dose intensity.

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Ineffectiveness of Relaxation on Vomiting Induced by Cancer Chemotherapy

Kaija Holli

EMESIS IS a complex physiological and psychological process with multifactorial aetiology. The aim of the randomised study reported here was to evaluate the effect of a non-pharmacological method (relaxation) on vomiting induced by cancer chemotherapy.

67 adult inpatients (aged 19–84) from Tampere University Hospital area with different forms of cancer, whose performance status was good (Zubrod 0–1) and who were receiving chemotherapy participated.

Patients were randomised into controls (24) and cases (43) aiming at a case–control ratio of two to one. The controls received no active study intervention beyond completion of evaluation required of all participants. The cases were relaxed by a physiotherapist 1 h before chemotherapy infusion and they continued self relaxation during the infusion. Standard progressive deep-muscle relaxation was used [1]. Both groups were given the normal pharmacological antiemetics (mainly lorazepam, methylprednisolone and metoclopramide dihydrocloride) before chemotherapy infusion. 5-HT$_3$ receptor antagonists were not used routinely at the time.

Both self-reported (subjective) and observer-rated (objective) methods were used to report the time of onset, quantity and

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