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Three-week versus four-week schedule of cisplatin and gemcitabine: results of a randomized phase II study

H. Soto Parra[1]*, R. Cavina[1], F. Latteri[1], A. Sala[1], M. Dambrosio[2], G. Antonelli[3], E. Morenghi[1], M. Alloisio[4], G. Ravasi[4] & A. Santoro[1]

[1]*Department of Medical Oncology and Hematology and* [4]*Division of Thoracic Surgery, Istituto Clinico Humanitas, Rozzano-Milan;* [2]*Division of Medical Oncology, Multimedica Hospital, Sesto San Giovanni;* [3]*Division of Medical Oncology, San Vincenzo Hospital, Taormina-Messina, Italy*

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Background: The cisplatin and gemcitabine (GC) regimen is usually administered as a 4- or 3-week schedule; however, the best schedule to use is still unclear. We therefore started a randomized phase II trial to compare toxicity and dose intensity (DI) between these two GC schedules.

Patients and methods: Ninety-six patients with non-small-cell lung cancer (NSCLC) and an additional 11 patients with an advanced epithelial neoplasm [bladder ($n = 5$), head and neck ($n = 3$), cervix ($n = 1$), esophageal ($n = 1$) or unknown primary carcinoma ($n = 1$)] were randomized to receive cisplatin 70 mg/m^2 intravenously on day 2 plus either gemcitabine 1000 mg/m^2 on days 1, 8 and 15 of a 28-day cycle or gemcitabine 1000 mg/m^2 on days 1 and 8 of a 21-day cycle. Planned DI (PDI) for the 4-week schedule was 750 mg/m^2/week for gemcitabine and 17.5 mg/m^2/week for cisplatin; for the 3-week regimen PDI was 666 mg/m^2/week and 23 mg/m^2/week for gemcitabine and cisplatin, respectively.

Results: From July 1998 to March 2000, 107 patients were randomized. Grade 3/4 neutropenia was observed in 27.8% of patients in the 3-week versus 22.5% in the 4-week arm ($P = 0.69$), while grade 3/4 thrombocytopenia was higher in the 4-week arm (29.5% versus 5.5% of patients; $P = 0.14$). A total of 398 cycles of therapy were delivered. Overall, 51% of cycles were modified in dose, timing or both in the 4-week arm, and 19% in the 3-week arm. The 21-day schedule of GC leads to a similar received DI of gemcitabine and higher cisplatin DI. Both regimens had activity in NSCLC, with a response rate of 39% (38% for the 4-week arm, and 42% for the 3-week arm).

Conclusions: The 3-week schedule has similar DI to the 4-week schedule. However the 3-week regimen has a better compliance profile and a comparable response rate in NSCLC, supporting the use of such a schedule.

Key words: chemotherapy, cisplatin, dose intensity, gemcitabine, NSCLC

Introduction

The combination of cisplatin and gemcitabine (GC) is one of the most active regimens currently available in the treatment of solid tumors. In advanced non-small-cell lung cancer (NSCLC), platinum-containing regimens, in particular GC, achieve response rates ranging from 28% to 54%, with significant survival benefit [1–5]. In bladder cancer, GC provides a similar survival advantage to MVAC (methotrexate, vinblastine, doxorubicin and cisplatin), with a better safety profile and tolerability [6], while for malignant pleural mesothelioma, this regimen has demonstrated a response rate of 40% in phase II trials [7]. One of the most commonly used schedules for this combination is to deliver cisplatin 100 mg/m^2 on day 1 or 2, and gemcitabine 1000 mg/m^2 on days 1, 8 and 15 of a 4-week cycle. However, the high incidence of severe thrombocytopenia and neutropenia compromises the gemcitabine dose intensity (DI), because at least 50% of patients require a reduction in or omission of the day 15 dose [3, 4].

In order to improve compliance while maintaining DI, particularly for gemcitabine, the 4-week schedule was modified in a randomized phase III trial by eliminating day-15 administration of gemcitabine, increasing the gemcitabine dose to 1250 mg/m^2 and shortening the cycle duration to 21 days [8]. In this study, the response rate for the 3-week schedule (40.6%) was similar to that achieved with the 4-week regimen. In addition, a randomized phase II study in advanced NSCLC compared two 3-week schedules with dosages of cisplatin (70 mg/m^2 versus 100 mg/m^2) combined with gemcitabine 1000 mg/m^2 weekly for two doses [9]. This study demon-

**Correspondence to:* Dr H. Soto Parra, Department of Medical Oncology and Hematology, Istituto Clinico Humanitas, Via Manzoni 56, Rozzano-Milan, 20089, Italy. Tel: +39-02-82244559; Fax: +39-02-82244591; E-mail: hector.sotoparra@humanitas.it

strated the superiority of the lower cisplatin dose schedule in terms of gemcitabine DI and toxicity with a similar therapeutic activity.

To assess further this drug combination we began the current randomized phase II trial, with the aim of comparing the toxicity profile and the actual DI of 3- and 4-week schedules of GC in NSCLC and other advanced epithelial carcinomas.

Materials and methods

Patient selection

Criteria for including patients in the study were: documented histological or cytological diagnosis of NSCLC at any stage or advanced epithelial neoplasm like bladder, cervix, head and neck or unknown primary carcinoma; no prior chemotherapy, immunotherapy or radiation therapy; age between 18 and 70 years; ECOG performance status <2; no active infection; adequate bone marrow reserve as indicated by a white blood cell (WBC) count $>3.5 \times 10^9$/l, platelet count $>100 \times 10^9$/l, hemoglobin level >10 g/dl; adequate renal and liver function, informed consent. Patients with brain metastases were excluded.

Pre-treatment evaluation included complete history and physical examination with determination of performance status, complete blood cell (CBC) count and serum chemistry analysis, and ECG.

Radiological evaluation, including chest X-ray, abdominal ultrasound or total body computed tomography scans, were performed for staging purposes and for tumor measurement.

Treatment schedules

Patients were randomized to receive a 3- or 4-week schedule of GC. In the 3-week treatment arm, gemcitabine was administered i.v. at 1000 mg/m^2 on days 1 and 8 of a 21-day cycle, whereas in the 4-week treatment arm, gemcitabine was administered at the same dose on days 1, 8 and 15 of a 28-day cycle. In both arms, cisplatin (70 mg/m^2 on day 2) was delivered over 30 to 60 min with at least 2 l of fluid and with appropriate antiemetic therapy. We reduced the cisplatin dosage from 100 to 70 mg/m^2 in an attempt to increase the received DI of gemcitabine above the 525 mg/m^2/week found in the Crinò study [4], which was lower than that reported (587.7 mg/m^2/week) during the 3-week regimen of the Rinaldi study [9]. Our results supported our decision, because the administration of cisplatin 70 mg/m^2 in a bladder cancer study yielded a DI of gemcitabine of 80%, equal to 600 mg/m^2/week [6].

Supportive therapy included blood-product transfusion and the administration of antibiotics, antiemetics and analgesics, as appropriate. Hematopoietic growth factors were permitted in presence of prolonged neutropenia. Radiotherapy was not allowed during chemotherapy. Treatment was discontinued if the patient requested it or if toxicity from the drug regimen was considered to be unacceptable.

Patients with stage IV NSCLC or with other solid tumors received a maximum of six cycles of chemotherapy. Patients with locally advanced NSCLC were treated with three or four cycles of chemotherapy followed by a local approach with radiotherapy or surgery, when feasible.

Dose adjustment and evaluations during treatment

Intra-cycle dose adjustments were made for gemcitabine according to the following guidelines:

- Seventy-five per cent of the dose was given when the platelet count was $50–75 \times 10^9$/l; the dose was omitted if the platelet count was $<50 \times 10^9$/l.
- The dose was omitted if the neutrophil count was $<0.99 \times 10^9$/l.
- Patients with grade 3/4 non-hematological toxicities, except alopecia, received 50% of the dose of gemcitabine or the dose was omitted at the discretion of the physician/investigator.

Further cycle dose adjustments for gemcitabine, and timing adjustments, were made as follows. Whenever febrile granulocytopenia requiring antibiotic therapy or grade 4 thrombocytopenia occurred, the gemcitabine dose was reduced to 75% for subsequent treatment cycles. The whole cycle was delayed by 1 week if the WBC count fell below 3.5×10^9/l and/or platelet count was $<100 \times 10^9$/l on day 1 of each new cycle. Serum creatinine was evaluated on the first treatment day of each cycle. The treatment was delayed by 1 week if the serum creatinine was >1.5 mg/dl; cisplatin was reduced by 25% or omitted for subsequent cycles if the serum creatinine level was 1.6–2 or >2 mg/dl, respectively. The dose of cisplatin was also modified in the event of severe neurotoxicity.

Response evaluation

Response was evaluated according to WHO criteria [10]. Complete response was defined as the complete disappearance of all clinically detectable malignant disease and the return of all abnormal tests to normal values for a period of at least 4 weeks. Partial response required a decrease of at least 50% of the sum of the cross-sectional areas of all measured lesions in the absence of progression of any existing lesion for at least 4 weeks or the appearance of any new lesions within that time. Stable disease was defined as an evaluation that failed to qualify for any of the responses noted. Progressive disease was defined as an increase of at least 25% in the size of one or more measurable lesions or the appearance of any new lesions. CBCs were repeated every week. Side effects were graded according to the Southwest Oncology Group toxicity criteria [11].

Evaluation of DI

Dose intensity was calculated with the method described by Hryniuk [12], this being the number of milligrams of drug delivered per square meter per week during the whole treatment from day 1 of the first cycle to the last cycle day (day 28 for the 4-week and day 21 for the 3-week schedule). Planned DI (PDI) for the 4-week schedule was 750 mg/m^2/week for gemcitabine and 17.5 mg/m^2/week for cisplatin; for the 3-week regimen PDI was 666 mg/m^2/week and 23.3 mg/m^2/week for gemcitabine and cisplatin, respectively. The mean dose received was calculated as the total dose the patient received divided by the total dose the patient should have received during their time on study.

Statistical analysis

Primary end points of the study were response rate in NSCLC, toxicity and feasibility. Feasibility was determined following consideration of the number of cycles requiring dose modification and the received DI. The secondary end point was survival.

With regard to response, this randomized phase II study was treated statistically as two simultaneous phase II studies, and the Simon two-stage design was applied separately for each arm [13]. For a total of 37 subjects with stage III and IV NSCLC, 17 had to be accrued during stage 1 and 20 during stage 2. The alpha level of the design was set equal to 0.10 and the power was 0.90.

If three or fewer responses were observed during the first stage then the trial would be stopped early. If 10 or fewer responses were observed by the end of the trial, no further investigation of the drug would be warranted. The response rate was estimated on all assessable patients in each of the two arms, and a corresponding 95% confidence interval (CI)

for the response rate was calculated. If both schedules were between the pre-established ranges of response rate, the less toxic regimen would be chosen. In case of similar toxicity, the criterion for the better schedule would be that of feasibility.

For assessment of the toxicity and feasibility data, the two groups were compared using Fisher's exact test. Continuous data (received DI) were compared using Student's *t*-test. Survival was estimated by the product limit method of Kaplan–Meier and the log-rank test was used for comparing mortality in the two groups.

Results

From July 1998 to March 2000, 107 patients were enrolled into the study; 86 males and 21 females; approximately half of the patients had ECOG performance status equal to 0. Fifty-four patients were enrolled in the 4-week arm and 53 in the 3-week arm. Patient characteristics were well balanced between the two arms, as summarized in Table 1 . Ninety-six patients (89.7%) had NSCLC: 18 received post-operative GC, 78 received up-front chemotherapy for locally advanced or metastatic disease (stage III–IV), and therefore were evaluated for response (42 in the 4-week arm and 36 in the 3-week arm).

Toxicity evaluation

Bone marrow suppression was the main toxicity in both arms. No significant differences were detected between treatment arms with regard to neutropenia, thrombocytopenia and anemia (Table 2). Severe neutropenia (grade 3/4) was more pronounced in the 3-week arm, occurring in 27.8% of patients, compared with 22.5% in the 4-week arm ($P = 0.69$), and grade 3/4 thrombocytopenia occurred more frequently in the 4-week arm (29.5% of patients), compared with 5.5% in the 3-week arm ($P = 0.14$). However, no bleeding events were observed and no platelet transfusion required.

Anemia occurred in 1.8% of those in the 4-week and 9.4% in the 3-week arm. One and four patients received packed red blood cells in the 4-week and the 3-week arms, respectively.

Non-hematological toxicity was mild, as listed in Table 2. Overall, three patients developed severe infections and one patient a grade 3 neuropathy. No toxic deaths were observed.

Treatment compliance and DI analysis

Overall, 398 cycles were delivered, 194 in the 4-week arm and 204 in the 3-week arm (Table 3). Dose modification of either

Table 1. Patient characteristics

Characteristics	4 week		3 week	
	No.	%	No.	%
Patients entered	54	100	53	100
Sex				
Male	40	74	46	87
Female	14	26	7	13
Age (years)				
Median	60		61	
Range	27–70		35–71	
Performance status (ECOG)				
0	25	46	23	43
1	28	52	28	53
2	1	2	2	4
Histological subtype				
NSCLC	48	89	48	90
Head and neck	1	2	2	4
Bladder cancer	4	7	1	2
Esophagus	–	–	1	2
Other	1	2	1	2
Chemotherapy for NSCLC				
Adjuvant	6	–	12	–
Neoadjuvant	16	–	16	–
Palliative[a]	26	–	20	–

[a]Treatment for any stage IV.

Table 2. Grade 3 and 4 toxicity per patient

Type of toxicity	4 week				3 week			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Hematological								
Neutropenia	15	27.8	–	–	9	16.9	3	5.6
Thrombocytopenia	11	20.3	5	9.2	2	3.7	1	1.8
Anemia	1	1.8	–	–	5	9.4	–	–
Non-hematological								
Nausea/vomiting	6	11.1	1	1.8	3	5.6	–	–
Mucositis	–	–	–	–	1	1.8	1	1.8
Hair loss	–	–	1	1.8	–	–	–	–
Fatigue	–	–	–	–	1	1.8	–	–
Allergic	1	1.8	–	–	–	–	–	–
Fever	–	–	–	–	–	–	–	–
Infection	2	3.7	–	–	1	1.8	–	–
Neurotoxicty	1	1.8	–	–	–	–		–
Cardiac	–	–	–	–	1	1.8	–	–

Table 3. Treatment compliance

	4 week		3 week	
	No.	%	No.	%
No. of cycles delivered	194	100	204	100
According to protocol	96	49	166	81
Modified in dose	75	39	18	9
Modified in timing	7	4	5	3
Modified in dose and timing	16	8	15	7
Causes of cycle modification				
Neutropenia	19	10	16	8
Thrombocytopenia	50	26	3	1.5
Non-hematological toxicity	12	6	8	4
Progressive disease	6	3	1	0.5
Patient related	4	2	4	2
Protocol violation	5	3	4	2
Other	2	1	2	1

cisplatin and/or gemcitabine or timing of chemotherapy delivery, or both, were necessary in 75 (39%), seven (4%) and 16 (8%) cycles in the 4-week arm and, 18 (9%), five (3%) and 15 (7%) cycles in the 3-week arm, respectively.

Hematotoxicity was the principal cause of treatment modification. Fifty (26%) and 19 cycles (10%) in the 4-week arm, and 16 (8%) and three cycles (1.5%) in the 3-week arm were modified due to thrombocytopenia and neutropenia, respectively. Other causes of treatment modification were not different between the two arms.

Overall, 42 patients in the 4-week and 39 patients in the 3-week arm completed the planned therapy. Therapy was discontinued in patients for the following reasons: toxicity in three and two, refusal in one and three and disease progression in eight and nine patients in the 4- and 3-week arms, respectively.

The received DI (RDI) of gemcitabine was similar in both arms of the trial: 592.82 mg/week in the 4-week arm and 589.7 mg/week in the 3-week arm ($P = 0.89$), while the RDI for cisplatin was significantly higher (21.48 mg/week versus 16.74 mg/week; $P = 0.0001$) in those in the 3-week arm (Table 4). The mean dose of gemcitabine was higher in the 3-week arm (817.4 mg/m^2 versus 936.4 mg/m^2), whereas the mean dose of cisplatin was comparable between the two groups (69.2–68.1 mg/m^2). The overall mean dose of gemcitabine was lower on day 15 and decreased progressively through subsequent courses of the 4-week schedule (Table 5).

Response and survival in NSCLC

Seventy-eight patients with stage III A/B (41 cases) and IV (37 cases) who received up-front chemotherapy were evaluated for response using an intention-to-treat analysis. The overall response rate was 39% (95% CI 28.1% to 49.8%) and duration of response was 141 days.

The 4-week regimen yielded 16 partial responses in 42 evaluable patients for an overall response rate of 38% (Table 6). The 3-week regimen yielded one complete remission and 14 partial response for an overall response rate of 42%. Median survival for these 78 patients was 371 days, and was similar in both treatment arms (279 days for the 4-week regimen, 367 days for the 3-week regimen; $P = 0.49$)

Table 4. Dose intensity analysis

DI (mg/m^2/week)	Gemcitabine		Cisplatin	
	3 week	4 week	3 week	4 week
Planned	666	750	23.3	17.5
Received	589.7*	592.82*	21.48**	16.74**
Relative DI (%)	88.5	79	91	95.4
Mean DI (mg/m^2)	936.4	817.4	68.1	69.2

*$P = 0.89$; **$P = 0.001$.

Table 5. Mean dose of gemcitabine (mg/m^2)

Cycle	4 week		3 week
	Day 8	Day 15	Day 8
1	944	610	961
2	917	618	923
3	975	628	781
4	884	612	952
5	943	416	779
6	752	333	841
Cumulative	928	586	887

Discussion

To our knowledge, this is the first randomized trial that compares a 3-week versus a 4-week schedule of GC. Our results demonstrate that despite the expected lower gemcitabine DI with the 21-day regimen, it leads to a similar received gemcitabine and higher cisplatin DI compared with that of the 28-day schedule. Toxicities of both treatment arms were quite similar, except for neutropenia and thrombocytopenia, and no unusual trend was noted. Severe neutropenia induced dose modification in 10% of cycles on the 28-day schedule and 8% on the 21-day schedule. In contrast, severe thrombocytopenia on the 28-day schedule caused a gemcitabine dose reduction and omission in 26% of cycles. Both toxicities induced dose modification on day 15 of the 28-day schedule, with a substantial decrease in the planned DI. In fact, the mean dose of gemcitabine was reduced from 92% on day 8 to 58% on day 15. Anemia was more pronounced in the 21-day schedule (9.4 versus 1.8%), and it could be reasonably attributed to the higher DI of cisplatin. However it was not a cause of dose modification in either regimen.

As previously reported, we delivered cisplatin at 70 mg/m^2 instead of 100 mg/m^2, and consequently this regimen had a lower PDI. Nevertheless, using this cisplatin dosage, the gemcitabine DI was not higher in the 28-day versus the 21-day regimen. Furthermore, no difference in response rates were observed in NSCLC, and objective responses were comparable to those reported in other studies.

Since GC combination could be evaluated with different schedules, DI is an important issue, because assuming that different schedules yield at least a similar DI, toxicity profile and feasibility become important aspects to improve compliance with the regimen.

In NSCLC, the most commonly used schedule is 4 weeks with cisplatin (100 mg/m^2) on day 1 or 2 and gemcitabine (1000–1250 mg/m^2) on days 1, 8 and 15. However, myelotoxicity, namely neutropenia and thrombocytopenia, has been observed in a large percentage of patients, and results in a reduction in DI of both drugs and a need for supportive therapy.

Two large randomized trials have confirmed these observations. The first, by Crinò et al. [3], compared cisplatin 100 mg/m^2 on day 2 and gemcitabine 1000 mg/m^2 on day 1, 8 and 15 in a 28-day schedule versus mitomycin, ifosfamide and cisplatin (MIC) in 307 patients with metastatic NSCLC.

Cisplatin was delivered at 21.8 mg/m^2/week, 87% of the PDI, whereas gemcitabine was considerably reduced to 525 mg/m^2/week, 70% of the PDI. Grade 3 and 4 WHO neutropenia, thrombocytopenia and anemia were documented in 40, 63.9 and 31% of cases, respectively. Twenty-three percent of patients received packed RBC transfusions and 15% required platelet transfusion in the GC arm, while febrile neutropenia and bleeding events were negligible.

In another large randomized study, Sandler et al. [5] treated advanced NSCLC with cisplatin 100 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on days 1, 8 and 15 every 28 days. Only 36% of patients received full doses, with thrombocytopenia and leukopenia being the main reasons for gemcitabine dose reduction and omission.

The Spanish group, led by Cardenal et al. [8], administered cisplatin 100 mg/m^2 on day 1 and gemcitabine 1250 mg/m^2 on days 1 and 8 of each 21-day cycle to 69 advanced NSCLC patients. The response rate was inside the range obtained for this combination (40.6%), and the toxicity level was acceptable. Severe grade 3 and 4 WHO neutropenia and thrombocytopenia were reported in 64% and 55% of patients and febrile neutropenia was observed in 7% of cases. Grade 3 anemia was recorded in 22% of patients and 29% required packed RBC. Gemcitabine was administered at a mean dose of 1117 mg/m^2. The mean dose for cisplatin was 91.6 mg/m^2.

Table 6. Response in 78 NSCLC patients (intention-to-treat analysis)

	4 week		3 week		Total	
	No.	%	No.	%	No.	%
Total	48	–	48	–	96	–
Not evaluable (adjuvant)	6	–	12	–	18	–
Evaluable patients	42	100	36	100	78	100
Stage III	22	52	19	52	41	53
Stage IV	20	48	17	48	37	47
Complete response	0	0	1	3	1	1
Partial response	16	38	14	39	30	38
Overall response	16	38	15	42	31	39
Stable disease	12	28	10	28	22	28
Disease progression	11	26	7	19	18	23
Not assessable	3	–	4	–	–	–

However, dose delays, received DI per week and therefore exposure for both drugs were not estimated. In addition, dose adjustment criteria were not specified in this paper.

Rinaldi et al. [9] compared two different 3-week schedules of GC in the treatment of 74 NSCLC patients, with two different cisplatin dose levels of 100 and 70 mg/m^2 administered on day 2, and gemcitabine 1000 mg/m^2 given on days 1 and 8. Gemcitabine was omitted when the leukocyte count was $<2 \times 10^9$/l and/or platelet count was $<50 \times 10^9$/l or reduced by 75% when the leukocyte count was $<2.9 \times 10^9$/l and/or platelet count $<99 \times 10^9$/l. Both regimens were feasible; however, a reduction of myelotoxicity was observed in patients treated with the lower cisplatin dose, as would be expected. Grade 3/4 WHO thrombocytopenia and neutropenia were observed in 35% and 11% of patients. RDI of gemcitabine was higher in the lower dose cisplatin arm (587.7 versus 529.4 mg/m^2/week) and the dose of cisplatin was 22.9 and 29.4 mg/m^2/week in the lower and higher dose arms, respectively. The two schedules were also shown to be similarly active, with a 42% (95% CI 27.8% to 56.7%) response rate for the lower dose and 47% (95% CI 31.6% to 61.5%) for the higher dose arm.

Other active schedules tested in NSCLC included the administration of cisplatin on day 15. Abratt et al. [14] delivered cisplatin 100 mg/m^2 on day 15 with gemcitabine 1000 mg/m^2 on days 1, 8 and 15 in a 28-day schedule with lower severe thrombocytopenia (21–25% of patients) but worse neutropenia (51–58%). However, no comparative studies are currently available.

Similar results have been also been reported in the treatment of bladder cancer with a 4-week schedule [6, 15].

It is quite consistent that the toxicity and DI of different scheludes reflect the influence of factors such as intra-cycle criteria of gemcitabine dose adjustment, and patient selection criteria like primary disease or performance status, and therefore, comparison of our results with other studies should take these limitations into account.

In summary, the choice of the best GC schedule remains an open question. This comparative phase II study demonstrates a better compliance profile, adequate DI and comparable activity, at least in NSCLC, of the 3-week compared with the 4-week GC schedule, and supports the use of such a schedule in clinical practice.

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