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ORIGINAL ARTICLE

Modified 3-week schedule of gemcitabine plus cisplatin for non-small cell lung cancer treatment

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Summary

Purpose: *Gemcitabine-cisplatin combination is one of the most used schedules for non small cell lung cancer (NSCLC). Aiming to enhance dose intensity and reduce toxicity, the original 4-week schedule was modified or transformed into a 3-week schedule. The purpose of this study was to report the efficacy and tolerability of a modified 3-week regimen of gemcitabine-cisplatin.*

Methods: *Our patients were treated with gemcitabine (1000 mg/m²) on days 1, 8 and cisplatin on day 8 (75-100 mg/m²). The toxicity was recorded according to the NCIC criteria.*

Results: *From October 2000 to December 2009 a consecutive series of 196 patients with a median age of 62 years and III-IV stage NSCLC received gemcitabine-cisplatin as induction therapy (76 patients) or palliative treatment (120 patients). The median dose intensity was 89%. In relation to day 8 of chemotherapy, 16.2% of the treatments were delayed due to hematologic toxicities. Grade 3-4 anaemia, neutropenia and thrombocytopenia was reported in 3.5, 43.8 and 4.6%, respectively. Response rate (RR) and median overall survival (OS) were 74% and 11 months in patients with locally advanced disease, and 46.7% and 9 months in metastatic patients, respectively.*

Conclusions: *In comparison with standard or modified schedules of literature, our modified 3-week regimen of gemcitabine-cisplatin demonstrated to be equally active, similar for dose intensity and well tolerated, with better hematologic toxicity profile in terms of anaemia and thrombocytopenia.*

Key words: *cisplatin, gemcitabine, modified schedule, non small cell lung cancer*

Introduction

Lung cancer is the most common cancer worldwide [1] and chemotherapy represents the milestone of treatment. In NSCLC, cisplatin is the most active drug, which is usually combined with gemcitabine, vinorelbine, pemetrexed or docetaxel, both in early stages, as neoadjuvant or adjuvant treatment, and in advanced stages, as palliative therapy [2]. In particular, the combination of cisplatin and gemcitabine is widely used for advanced disease, particularly for squamous subtype, showing advantages in terms of both activity [3] and economic burden [4]. However, since this doublet was firstly described in the literature [5], several changes have been proposed in terms of both drug doses and scheduled timing, in an attempt to reduce toxicity and, at the same time, maintain disease control. Over the time, cisplatin dose was reduced from 100 to 75-80 mg/m², while gemcitabine dose was increased from 1000 to 1250 mg/m². Furthermore, the 4-week schedule, which was adopted in the first studies [5,6], was replaced by a 3-week schedule, where cisplatin was usually administered on day 1 or 2 and gemcitabine on days 1 and 8. Several phase III studies compared this doublet to other combinations, confirming its manageable toxicity profile [7-10].

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However, the administration of both cisplatin and gemcitabine on day 1 may produce a cumulative hematologic toxicity reducing the ability to administer gemcitabine on day 8. In this view, a potential advantage in treatment delivery could derive from scheduling cisplatin administration on day 8, allowing a 2-week interval when patients may recover from any hematologic toxicity before the next cycle.

To the best of our knowledge, this modified schedule has been described only in one small study [11]; furthermore, other two studies described a limited series of patients treated with gemcitabine on days 1 and 8 and carboplatin on day 8 [12,13]. The present report describes our experience with a modified 3-week schedule of gemcitabine-cisplatin (GC), which provided cisplatin administration on day 8 of the cycle, for patients with locally advanced/advanced NSCLC.

Methods

Patient selection

We retrospectively reviewed the clinical records of all patients treated at the Medical Oncology Department of Trento from 2000 to 2009 for histologically or cytologically confirmed diagnosis of NSCLC and stage IIIB (pleural effusion or not amenable to radiation therapy) or stage IV disease according to the 6th Edition of International Staging System for Lung Cancer. Furthermore, we also reviewed the clinical records of patients who had received a platinum-based chemotherapy as induction treatment before surgery (for N2 IIIA stage or unresectable T4 IIIA stage) or radiotherapy (for N3 IIIB stage). We selected and registered all patients who had received the GC doublet. According to the common clinical practice, all patients were considered as eligible for this treatment if they had an Eastern Cooperative Oncology Group (ECOG) performance status (PS)≤1; adequate hematologic function (WBC>3,500/μL, platelet count>100,000/μL, and hemoglobin>10 g/L); adequate hepatic and renal function (bilirubin<1.5 mg/dL, AST and ALT<3x the upper limit of normal, and creatinine<1.5x the upper limit of normal). Patients aged above 70 years were considered eligible for the treatment only if they were fit and without relevant comorbidities. Patients were considered not eligible for GC treatment if they had other relevant pathologies (such as active infection, hypercalcemia, or uncontrolled systemic disease) that contraindicated the treatment at the discretion of the clinicians. According to the purposes of the present study, we excluded from the analysis patients showing one of the following conditions: absence of measurable disease, radiotherapy on target lesions (palliative radiotherapy on bone or brain was allowed unless it was completed less than two weeks before chemotherapy start), diagnosis of a second primary tumor (except for *in situ* carcinoma of the cervix or non melanoma skin cancers or other cancers diagnosed more than five years before NSCLC diagnosis in absence of relapse).

Treatment

All patients received a 21-day cycle with gemcitabine given intravenously on days 1 and 8 and cisplatin given intravenously on day 8 (with appropriate hydration and antiemetics). The doses of the drugs changed over the time according to the data provided by literature. Until 2003 cisplatin was administered at the dose of 100 mg/m^2, thereafter at 75 mg/m^2. Gemcitabine was administered at the dose of 1000 mg/m^2 until 2008, then at 1250 mg/m^2. Patients treated with induction chemotherapy received a maximum of three courses of chemotherapy. The others received the therapy for as long as they remained stable or responded to treatment, for a maximum of six cycles.

Supportive care included blood-product transfusions and administration of antiemetics, antibiotics, and analgesics, as appropriate, at the discretion of treating physicians.

Similarly, use of hematopoietic growth factors was allowed only to manage febrile neutropenia or prolonged neutropenia, and never as primary prophylaxis. During treatment, palliative radiotherapy was allowed in an attempt to control painful lesions.

Treatment was stopped in case of disease progression, unacceptable toxicity or patient's request.

Chemotherapy doses on days 1 and 8 were delayed if neutrophil count was ≤1,500/μL and platelet count ≤100,000/μL. Before each cycle, serum creatinine, creatinine clearance, and serum electrolytes, including magnesium, were analyzed. If the serum creatinine concentration was ≥1.4 mg/dL the treatment was delayed for one week with forced hydration; after one week, if serum creatinine concentration failed to decrease within normal range, cisplatin administration was suspended and the drug was replaced by carboplatin. In the case of grade 3-4 non-haematological toxicities the treatment was suspended.

Treatment evaluation

Baseline assessment included complete medical history and physical examination, Karnofsky performance status and full laboratory assessments. Disease assessment was performed with thoracic and abdominal computed tomographic scan. If brain metastases were suspected, a brain computed tomography scan or magnetic resonance imaging (or both) was performed. From 2009, a PET/CT scan was usually performed at baseline. In the case of induction, treatment response was evaluated at the end of therapy, otherwise disease reassessment was performed every three chemotherapy cycles by using the same exams performed at baseline. If a patient treated with palliative therapy suspended the treatment in absence of progression after he/she received the maximum number of six courses, the disease evaluation was performed every three months.

Complete blood counts, blood chemistry and physical examination were repeated at the beginning

of every new treatment cycle. Complete blood counts were repeated on day 8.

Statistics

Patient demographics, disease characteristics, treatments and outcomes were assessed using descriptive statistics.

According to the purposes of the present report, collected were data concerning the activity and toxicity profile of the modified GC combination.

For the activity we evaluated the RR, the progression free survival (PFS) and the OS. The RR was defined according to the RECIST criteria version 1.0 (Terrasse).

PFS was calculated from the date of starting chemotherapy to the date of the patient's disease progression or the date of the last follow-up examination.

OS was calculated from the date of starting chemotherapy to the date of the patient's death or the date of the last follow-up examination. Kaplan-Meier curves were used to display the survival data.

Toxicity profile was defined according to the common toxicity criteria version 3.0 [14].

The dose intensity was calculated by using the method described by Longo et al. [15].

Separate analyses were performed according to disease stage and treatment aims (induction vs palliative) and to different drug doses (G1000 + C100 vs G1000 + C75 vs G1250 + C75).

RR were compared using Fisher's exact test and the log-rank test was used to compare the survival curves. A p value <0.05 was considered as statistically significant.

Statistical analyses were performed using the Statistical Package for Social Sciences software, version 11.0 (SPSS Inc., Chicago, IL).

Results

Patients

A consecutive series of 196 patients were selected, who received GC doublet in the modified schedule. Seventy-six patients received the treatment as induction therapy for locally advanced disease and 120 as first line therapy for metastatic

Table 1. Baseline patient characteristics

Characteristics	*All cohort*		*Induction therapy*		*Palliative therapy*	
	n	%	*n*	%	*n*	%
No. of patients	196		76		120	
Age, years	196		76		120	
Median	62		64		61	
Range	31-77		39-77		31-76	
Sex						
Male	153	78.1	61	80.3	92	76.7
Female	43	21.9	15	19.7	28	23.3
Histology						
Squamous cell carcinoma	54	27.6	30	39.5	24	20.0
Adenocarcinoma	80	40.8	22	28.9	58	48.3
Large-cell carcinoma	8	4.1	3	3.9	5	4.2
Unspecified / Other	54	27.6	21	27.6	33	27.5
Stage						
T4 IIIA	21	10.7	21	27.6	NA	
N2 IIIA	40	20.4	40	52.6	NA	
N3 IIIB	15	7.7	15	19.7	NA	
IIIB (pleural – supraclavicular)	19	9.7	NA		19	15.8
IV	101	51.5	NA		101	84.2
Metastatic disease sites						
Brain	35	17.9	NA		35	29.2
Lung	40	20.4	NA		40	33.3
Liver	22	11.2	NA		22	18.3
Bone	37	18.9	NA		37	30.8
Lymph nodes	25	12.8	NA		25	20.8
Adrenal	24	12.2	NA		24	20.0
Drug doses						
C 100/ G 1000	78	39.8	33	43.4	45	37.5
C 75/ G 1000	92	46.9	29	38.2	63	52.5
C 75/ G 1250	26	13.3	14	18.4	12	10.0

C=cisplatin, G=gemcitabine

disease. Most of the patients were male, while adenocarcinoma and squamous histological types predominated in the palliative and induction groups, respectively. The patient median age was 62 years (range 31-77). A detailed description of patients characteristics is shown in Table 1.

Chemotherapy delivery

A total of 757 chemotherapy courses were assessed (259 and 498 in the induction and in the palliative groups, respectively), with each patient receiving a median number of 3 courses in the induction group and 4 courses in the palliative group. The administration of day 1 was on scheduled time in 87.2% of the cases, delayed in 12.6% of the cases (6.5, 0.8 and 5.3% of the cases due to hematologic toxicities, non-hematologic toxicities, and other causes, respectively), and cancelled in 0.2% of the cases. The administration of day 8 was on time in 75.6% of the courses, delayed in 20.3% of the courses (15.9, 0.7 and 3.7% of the cases due to hematologic toxicities, non-hematologic toxicities, and other causes, respectively), and cancelled in 4.2% of the courses. No differences were observed according to either treatment aim (induction vs palliative) or drug doses in administration time of both days 1 and 8.

The median dose intensity was 87% with 69.9% of the patients receiving at least the 80% of the planned dose. As expected, in the group of patients with more advanced stage disease (palliative group) the dose intensity was significant-

Table 2. Percent toxicities in all patients

Toxicities	*G1*	*G2*	*G3*	*G4*
Anemia	26.5	29.1	3.6	0
Leukocytes	10.7	13.8	6.1	0.5
Neutrophils	8.2	17.3	33.7	10.2
Platelets	19.4	5.6	4.1	0.5
Nausea / vomiting	13.8	20.4	7.7	0
Liver	19.9	10.2	0	0
Fever	14.3	1.0	0	0
Renal	4.6	1.0	0.5	0
Neurological	6.1	2.6	0.5	0
Fatigue	9.2	10.2	0	0
Constipation	4.6	1.5	0.5	0
Diarrhea	0	1.5	0.5	0
Stomatitis	3.6	3.1	0	0
Febrile neutropenia	0	0	0	0.5
Motor neuropathy	0.5	0	0	0
Ototoxicity	2.0	0.5	0.5	0

Table 3. Percent toxicities in all M1 patients

Toxicities	*G1*	*G2*	*G3*	*G4*
Anemia	25.8	37.5	5.0	0
Leukocytes	10.8	16.7	5.8	0
Neutrophils	9.2	19.2	30.0	9.2
Platelets	21.7	5.8	5.0	0.8
Nausea / vomiting	12.5	23.3	5.8	0
Liver	21.7	15.8	0	0
Fever	15.8	0.8	0	0
Renal	5.8	0.8	0.8	0
Neurological	7.5	4.2	0.8	0
Fatigue	10.8	8.3	0	0
Constipation	5.8	0.8	0.8	0
Diarrhea	0	1.7	0	0
Stomatitis	4.2	2.5	0	0
Febrile neutropenia	0	0	0	0
Motor neuropathy	0	0.8	0	0
Ototoxicity	3.3	0	0.8	0

ly lower than that observed in the other group (mean 83.2 vs 87.8; p=0.013). No differences were observed according to the different drug dose groups.

Toxicity and supportive care

The toxicity profile was mild and mainly related to hematologic toxicities (Table 2). The most frequent grade 3-4 toxicities were anaemia (3.6%), leukopenia (6.6%), neutropenia (43.9%), thrombocytopenia (4.6%), and nausea/vomiting (7.7%). Other toxicities were observed at the higher degrees in <1% of the cases. In particular, febrile neutropenia was observed in 0.5% of the patients. Granulocyte colony stimulating factor (G-CSF) was used in 15.4% of the patients, while 10.2% of the patients received red blood cell transfusions. Patients treated with palliative intent experienced a significant higher toxicity compared to others in terms of anaemia (p<0.0001), liver toxicity (p=0.001), and sensorial neurotoxicity (p=0.02); toxicities observed in this group of patients are shown in the Table 3. As expected, the use of cisplatin at 100 mg/m^2 was associated with higher hematologic and non-hematologic toxicities compared to the dose of 75 mg/m^2 (Table 4).

Clinical outcomes

a) Patients treated with induction therapy:

Among the 76 patients receiving chemotherapy as induction therapy we observed one complete response, 56 partial responses (for an overall re-

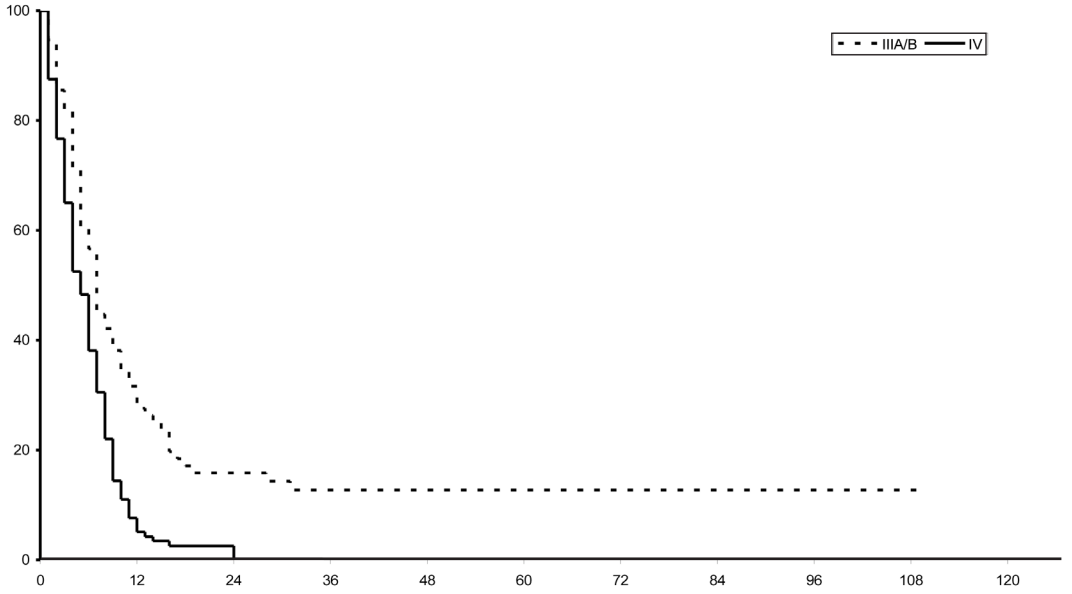

Figure 1. Kaplan-Meier progression free survival.

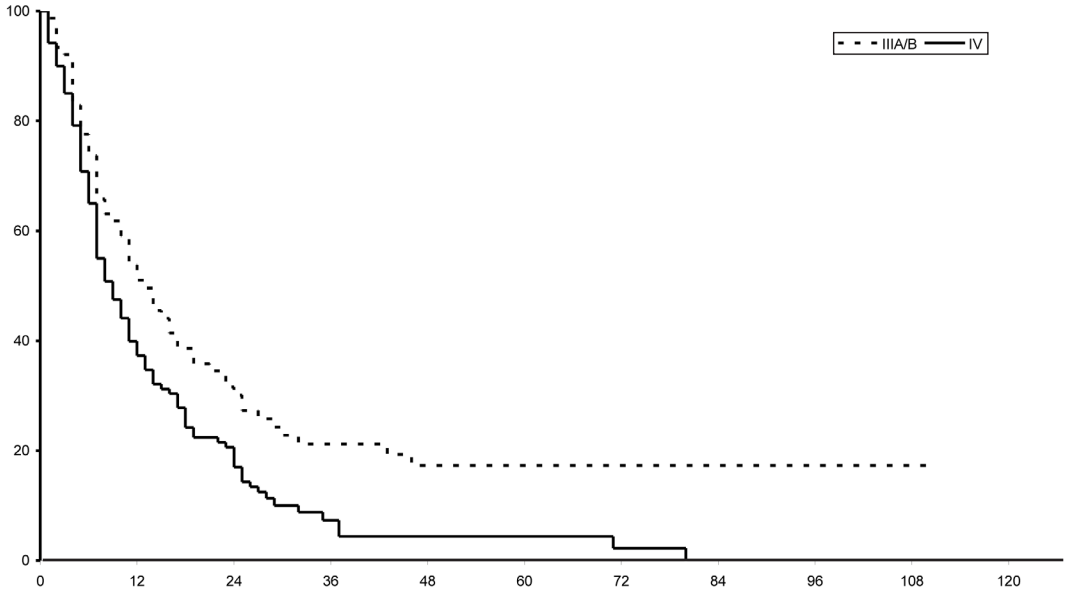

Figure 2. Kaplan-Meier overall survival.

Table 4. Hazard ratio (95% confidence interval) for main toxicities reported by the three different cisplatin/gemcitabine schedules

Toxicities	*C 100 / G 1000*	*C 75 / G 1000*	*C 75 / G 1250*	*p value*
Anaemia	1.14 (0.95-1.33)	0.95 (0.75-1.14)	0.42 (0.08-0.77)	0.002
Leukopenia	0.97 (0.73-1.22)	0.36 (0.19-0.53)	0.08 (-0.03-0.19)	0.0001
Nausea & vomiting	1.28 (1.04-1.52)	0.50 (0.31-0.69)	0.23 (-0.01-0.47)	0.0001
Liver	0.56 (0.40-0.73)	0.35 (0.22-0.48)	0.12 (-0.02-0.25)	0.006
Renal	0.18 (0.06-0.30)	0.01 (-0.01-0.03)	0.04 (-0.04 -0.12)	0.006
Sensorial neuropathy	0.24 (0.12-0.37)	0.07 (-0.01-0.14)	0	0.008
Constipation	0.19 (0.07-0.31)	0.03 (-0.02-0.08)	0	0.1

C=cisplatin, G=gemcitabine

sponse rate of 75%), 4 stable disease, and 4 progressive disease cases. Nine patients underwent radical surgery and five underwent radical radiotherapy after induction therapy.

After a median follow-up of 12.5 months, 16 patients were alive and 60 had died. The projected 1 and 2-year PFS rates were 27.6 and 15.8%, respectively; the median PFS was 7 months. The same figures for OS were 51.0 and 30.1%, with a median value of 13 months (Figures 1,2).

b) Patients treated with palliative therapy:

Among the 120 patients treated with palliative intent the RR was 46.7% (56 patients achieved partial response), while 7 patients (5.8%) were not evaluable for response; 19 (15.8%) and 38 (31.7%) showed a stable and progressive disease status, respectively. Sixty-nine (57.5%) patients received a second line systemic therapy, 31 (25.8%) a third line, and 8 (6.7%) a fourth line.

After a median follow-up of 9 months, 9 patients were alive and 111 had died. The projected 1-year PFS and OS rates were 5.1 and 37.3%, respectively; the median PFS and OS were 5 and 9 months, respectively (Figures 1,2).

Discussion

Despite the evolving role of targeted therapy and immunotherapy, platinum-based chemotherapy remains the milestone in the treatment of NSCLC. It is used both in early stages of disease, when an induction or adjuvant chemotherapy is indicated, and in advanced disease stages, with palliative purposes. In the latter case, except for tumors with druggable mutations (no more than 10-15%), most of fit patients receive a combination of platinum (cisplatin or carboplatin) plus a second generation agent (gemcitabine, vinorelbine, paclitaxel or pemetrexed), as first line treatment, according to the histological subtype. In particular, during the last decade, the gemcitabine-cisplatin doublet has become the treatment of choice in Europe for treating squamous NSCLC, while in non-squamous cancers it was replaced by the pemetrexed-based doublets [2].

The first phase II studies, that demonstrated the activity of this combination, adopted a 4-week schedule, where gemcitabine was administered weekly on days 1, 8 and 15, while the day of cisplatin administration varied [5,6]. The same 4-week schedule was adopted in phase III trials that confirmed the superiority of this combination in comparison with the reference treatments [8,9]. However, such studies found thrombocytopenia and neutropenia as the main dose-limiting toxicities of this doublet. The possibility of reducing hematologic toxicity by changing the day of cisplatin administration was suggested by studies where cisplatin was administered on day 15: these studies reported lower incidence of anaemia and thrombocytopenia in comparison with studies where cisplatin had been given on day 1 or 2, while the incidence of neutropenia was not modified [16-19]. The reduction of myelotoxicity also led a dose intensity improvement [20]. Furthermore, the best therapeutic index for 4-week GC combination was achieved by administering cisplatin on day 15 (as on day 2) [21].

Another strategy to reduce the hematologic toxicity rates avoided the day 15 gemcitabine administration, shortening the schedule from 4 to 3 weeks. Some phase II studies demonstrated that the 3-week schedule was active [22,23] and a phase III trial confirmed its superiority compared to previous adopted combinations [7]. Moreover, one randomized phase II trial confirmed that the 3-week schedule was equally active but less toxic compared to 4-week one [24].

Over the time, changes of the drugs dose have been proposed: for example, a GC combination at low doses (gemcitabine 1000 mg/m^2 on days 1, 8 plus low-dose fractionated cisplatin 20 mg/m^2 on days 1, 2, 3 of every 3 weeks) showed to be safe and active in older patients with advanced NSCLC [25]. Anyway, the reference schedule for GC combination may be considered gemcitabine 1250 mg/m^2 on days 1,8 and cisplatin 75 mg/m^2 on day 1 [10].

Considering that the optimal sequence provides a loading gemcitabine dose followed by cisplatin [26], it was supposed that in a 3-week schedule the administration of cisplatin on day 8 could both maintain the combination activity and reduce the toxicity.

Our retrospective study also confirmed that the modified 3-week schedule of GC is safe, feasible, and able to reproduce the clinical outcomes reported in the literature with the standard schedule (with cisplatin on day 1) of the same combination. Furthermore, the administration of cisplatin on day 8 may improve the hematologic compliance by reducing the grade of anaemia and thrombocytopenia.

In our experience the main grade 3-4 hematologic toxicity was neutropenia which occurred in about 40% of the patients while grade 3-4 anaemia or thrombocytopenia in only 5%. From these results it appears that by using the modified GC schedule the rates of grade 3-4 anaemia and thrombocytopenia are reduced compared to those observed with the standard schedule (Table 2). It is noteworthy that similarly to the drug administration delay on day 8 in our 3-week modified schedule, the delay of cisplatin on day 15 in the 4-week schedule was able to reduce the incidence of anaemia and thrombocytopenia, but not of neutropenia [16,19].

In terms of activity, patients with locally advanced disease showed a 75% RR and a 2-year OS

Table 5. Comparison between grade 3-4 toxicities of the current study and those of different schedules available in the literature

Study	*Phase*	*Schedule administration*		*Stage*	*No. of patients*	*Grade 3-4 toxicities (%)*			
		GEM	*CIS*			*Anaemia*	*Thrombocytopenia*	*Neutropenia*	*Febrile neutropenia*
Abratt 1997 [16]	II	1000 mg/m² d 1,8,15	100 mg/m² d 15	Adv	53	13.4	21	58	NR
Anton 1998 [17]	II	1200 mg/m² d 1,8,15	100 mg/m² d 15	IIIB-IV	40	12.5	15	56.4	2.5
Cardenal 1999 [7]	III	1250 mg/m² d 1,8	100 mg/m² d 1	IIIB-IV	69	22	55	64	7
Crinò 1999 [8]	III	1000 mg/m² d 1,8,15	100 mg/m² d 2	IIIB-IV	155	30.9	63.9	39.7	NR
Sandler 2000 [9]	III	1000 mg/m² d 1,8,15	100 mg/m² d 1	III-IV	260	25	50.4	57	4.6
Chen 2000 [18]	II	1000 mg/m² d 1,8,15	80 mg/m² d 15	IIIB-IV	32	3.1	3.1	21.9	0
Cortesi 2001 [19]	II	1000 mg/m² d 1,8,15	100 mg/m² d 15	III-IV	51	4	16	35	0
Scagliotti 2002 [27]	III	1250 mg/m² d 1,8	75 mg/m² d 2	IIIB-IV	197	17.7	36.6	38.1	0.4
Zatloukal 2003 [28]	III	1200 mg/m² d 1,8	80 mg/m² d 1	IIIB-IV	85	13.2	16.4	23.5	NR
Alberola 2003 [29]	III	1250 mg/m² d 1,8	100 mg/m² d 1	IIIB-IV	182	11	19	32	4
Mazzanti 2003 [30]	II	1200 mg/m² d 1,8	80 mg/m² d 2	IIIB-IV	62	3	17	53	NR
Smit 2003 [31]	III	1250 mg/m² d 1,8	80 mg/m² d 1	IIIB-IV	160	11.9	36.3	43.1	2.5
Wachters 2003 [32]	III	1125 mg/m² d 1,8	80 mg/m² d 2	III-IV	119	17	56	32	2
Martoni 2005 [33]	III	1200 mg/m² d 1,8	75 mg/m² d 1	IIIB-IV	135	3.9	9.3	17.7	NR
Kim 2006 [34]	II	1250 mg/m² d 1,8	75 mg/m² d 1	III-IV	40	12.9	18	48.7	2.5
Esteban 2007 [35]	III	1250 mg/m² d 1,8	50 mg/m² d 1,8	IIIA-B	78	7	5	32	0
Akcali Z 2008 [11]	II	1250 mg/m² d 1,8	75 mg/m² d 8	IIIB-IV	67	6	6	46	3
Present study		1000 mg/m² d 1,8	100 or 75 mg/m² d 8	III-IV	120	5	5.8	39.2	0

NR: not reported

of 15.8%. The median survival of patients with metastases was 9 months with a RR of 46.7%. These results are in line with those reported in the literature.

In comparison with similar studies, the present retrospective analysis included several limitations. First, we evaluated a heterogeneous population including both patients who received chemotherapy as induction treatment for locally advanced NSCLC and patients with metastatic disease. As expected the impact of the treatment in terms of toxicity was quite different between the two population groups, with metastatic patients having worse compliance. Therefore, we conducted a separate analysis for the two groups and considered only the homogeneous group of metastatic patients for the comparison with data from literature (Table 5).

Second, we used three different drug doses over the time. However, the majority of patients received G1000/C100 or G1000/C75 that, in our experience, showed a significant higher grade of anaemia while did not produce any statistically significant difference in terms of thrombocytopenia. This reinforces the idea that the administration of cisplatin on day 8 may reduce the incidence of anaemia and thrombocytopenia.

On the other hand, being observed in an unselected population from the daily clinical practice, our results suggest that the adopted modified schedule is safe and well-tolerated in a heterogeneous population of patients, regardless of the disease stage.

In conclusion, compared to the standard schedule, the modified 3-week gemcitabine-cisplatin doublet with cisplatin on day 8 proved to be equally active, similar for dose intensity and well-tolerated, with a better hematologic toxicity profile in terms of anaemia and thrombocytopenia. Therefore, it could represent a proposable therapeutic option in the daily clinical practice.

Conflict of interests

The authors declare no conflict of interests.

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