Duration of chemotherapy in non-small-cell lung cancer: multicenter, randomized, prospective clinical trial comparing 4 vs 6 cycles of carboplatin and gemcitabine. (Portuguese Lung Cancer Study Group 03/03)

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ABSTRACT

Background: So far there are few published data on optimal duration of chemotherapy in patients with stage IIIB (with pleural effusion) and IV non-small cell lung cancer (NSCLC). The goal of treatment is to prolong survival and palliate symptoms. Recent guidelines recommend that first-line chemotherapy should be stopped at four cycles in patients who are not responding to treatment and also recommend that it should be administered no more than six cycles. We designed a phase III trial to compare 4 cycles vs 6 cycles of chemotherapy using a standard combination. Primary endpoint is overall survival (OS). Secondary endpoints included time to progression (TPP), overall response rate (ORR), one-year survival (1y -S) and safety.

Patients and Methods: Randomization was stratified by stage (IV vs IIIB) and performance status (0/1 vs 2). Patients received gemcitabine 1250 mg/m^2, day 1 and 8 + Carboplatin, AUC 5, day 1, every 21 days. Eligibility criteria: age > 18 years, histologically proven NSCLC, weight loss < 10%, no brain metastasis, adequate renal, hematological, hepatic functions and informed consent. The efficacy analysis (OS, TTP, 1y-S) will be performed on intent to treat basis.

Results: Between October 2002 and December 2004, 220 pts were enrolled. Arm A - 4 cycles (n=110) and Arm B - 6 cycles (n= 110) were well-balanced for patient characteristics: median age (A/B): 64,7 vs 63,9 yrs; male/female (A/B) 86/24 vs 86/24; ex and smokers (A/B) 82 vs 83; IIIB/IV (A/B) 24/86 vs 29/81; PS 0,1 vs 2 (A/B) 90/20 vs 91/19; adenocarcinoma (A/B) 59 vs 57; squamous (A/B) 35 vs 37. ORR and toxicity was evaluated in 204 pts (7.2% pts were not evaluated). At Jan/2005, 193 pts completed chemotherapy as planned (A vs B); ORR% (43,8 vs 47,3); median number courses (3,5 vs 4,8). Disease progression was the main reason for stopping chemo % (A vs B) (20,4 vs 34,7). Grade 3/4 toxicities included neutropenia (10,2% vs 13,6%); thrombocytopenia (3.1% vs 5,2%); anemia (1,0% vs 2,1%). All grades of nausea/vomiting (14,2% vs 16,8%). At Jan/2005 151 pts (A vs B) have progressive disease (49% vs 51%) and 129 (50,4% vs 49,6%) died. Fifteen pts (Arm A) and sixteen pts (Arm B) have had a second line therapy (docetaxel) after disease progression.

Conclusions: Overall response rate is not statistically different between 4 vs 6 cycles. Major haematologic toxicitiy was neutropenia. Mature data of Overall Survival, One-Year Survival and Time to Progression will be available by the time of the meeting.

INTRODUCTION

Non-small-cell lung cancer (NSCLC) accounts for about 80% of all newly diagnosed lung carcinoma, with 1.2 million new cases worldwide each year [(1)]. In Portugal, we diagnosed more than 4.500 thousand new cases per year. Palliative chemotherapy is now widely used in the treatment of advanced NSCLC. Most trials have shown a survival advantage over best supportive care. This has been confirmed by a meta-analysis[(2)]. Platinum compounds were combined with newer third generation chemotherapy agents, such as gemcitabine, vinorelbine or taxanes (docetaxel and paclitaxel). The goal of treatment in stage IIIB (with metastatique pleural effusion) / IV NSCLC is to prolong survival and palliate symptoms[(3)]. Gemcitabine/platinum combinations appear to offer patients superior efficacy in terms of overall survival and progression-free survival. Gemcitabine / carboplatin therapy is validated as one of the standart of care in treatment of first line advanced NSCLC[(4)]. The optimal duration of treatment which maximizes the impact on survival and progression-free survival is not known[(3)]. Several datas of phase II trials indicate that more than 80% of patients had achieved response within 12 weeks and 98% within 24 weeks. The authors questioned the value of continuing chemotherapy treatment beyond 12 weeks in absence of objective response[(5) (6) (7)]. We designed a clinical trial to compare 4 cycles vs 6 cycles of chemotherapy using a standard combination (gemcitabine + carboplatin).

OBJECTIVES

- Primary endpoint: overall survival (OS).
- Secondary endpoints: time to progression (TPP), overall response rate (ORR), one-year survival (1y -S) and safety.

METHODS

Main eligibility criteria

- Histological confirmation of NSCLC
- Stage IIIB (with pleural effusion) or stage IV disease
- No prior chemotherapy
- Age > 18 years
- At least, one measurable site of disease
- ECOG performance status de 0, 1 and 2
- Weight loss < 10% (last 3 months)
- Estimated life expectancy > 12 weeks
- Adequate bone marrow, renal and liver function
- Without confirmed brain metastases
- Signed informed consent

Treatment plan

- Randomization was stratified by: stage (IIIB vs IV) and performance status (0/1 vs 2).
- Gemcitabine 1250 mg/m^2, on day 1 and 8 + Carboplatin AUC 5, on day1 (every 3 weeks)
- Carboplatin, AUC 5, on day 1 (every 3 weeks)
- Carboplatin dose was calculated using the Calvert's formula

Statistical methods

- Numerical variables were described by mean, standard deviation (SD), median and range. Categorical variables were summarized by means of counts (n) and percentages (%).
- Homogeneity between treatment arms was tested using the t-test and the chi-square test for numerical and categorical variables, respectively.
- Kaplan-Meier curves were computed for the analysis of time to event variables (survival and time to progression). Median and corresponding 95% confidence intervals (CI) were provided.
- Hazard ratios between treatment arms were calculated using the Cox proportional hazard regression.
- All statistical tests were two-sided and performed considering a significance level of 0.05.

RESULTS

Patient characteristics

- Between October 2002 and December 2004, 220 patients were enrolled from 10 centers. The baseline characteristics are summarised in table 1.

	4 cycles (n=110)	6 cycles (n=110)	Total (n=220)
Age, yrs			
Median	64.7	63.9	
N	110	110	220
mean (SD)	63.4 (8.6)	63.1 (9.3)	63.2 (8.9)
Median	64.5	64.0	64.0
Range	40.0-79.0	37.0-80.0	37.0-80.0
Gender, n(%)			
Male	86 (78.2)	86 (78.2)	172 (78.2)
Female	24 (21.8)	24 (21.8)	48 (21.8)
PS, n(%)			
0	0 (0.0)	1 (0.9)	1 (0.5)
1	90 (81.8)	90 (81.8)	180 (81.8)
2	20 (18.2)	19 (17.3)	39 (17.7)
Smoker, n(%)			
Yes	54 (49.0)	52 (47.7)	106 (48.4)
ex-smoker	28 (25.5)	31 (27.5)	58 (26.5)
No	28 (25.5)	27 (24.8)	55 (25.1)
Histology, n(%)			
Adenocarcinoma	59 (53.7)	57 (51.4)	116 (52.5)
CPNPC	13 (11.8)	16 (14.7)	29 (13.2)
Epidermoid	35 (31.8)	37 (33.9)	72 (32.9)

(cont.)	4 cycles (n=110)	6 cycles (n=110)	Total (n=220)
Stage, n(%)			
IIIB	24 (21.8)	29 (25.4)	53 (24.0)
IV	86 (78.2)	81 (74.6)	167 (76.0)
Cycles, no.			
N	110	110	220
mean (SD)	3.4 (1.0)	4.7 (1.8)	4.0 (1.6)
Range	1.0-4.0	1.0-6.0	1.0-6.0

Table 1 – Patients characteristics at baseline.

- The two treatment arms were homogeneous regarding demographics and clinical baseline variables. Overall age ranged from 37 to 80 years averaging 63 years. The majority of the patients were male (78.1%) and about one half were smokers (48.4%).
- The majority of the patients had a performance status (PS) 1 (81.8%).
- More than one half of the patients had adenocarcinoma (52.5%) and the majority had stage IV disease (76%).

Safety (grade 3&4)

Haematologic Toxicity	4 cycles (n= 110)		6 cycles (n= 110)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	1 (0.9%)	0	3 (2.7%)	1 (0.9%)
Leukopenia	12 (10.9%)	0	13 (11.8%)	0
Neutropenia	13 (11.8%)	0	14 (12.7%)	3 (2.7%)
Thrombocytopenia	2 (1.8%)	0	1 (0.9%)	0

Non Haemato-logic Toxicity	4 cycles (n= 110)		6 cycles (n= 110)	
	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	2 (1.8%)	0	9 (8.1%)	0
Vomiting	1 (0.9%)	0	1 (0.9%)	2 (1.8%)
Diarrhea	2 (1.8%)	0	2 (1.8%)	0
Infection	1 (0.9%)	0	1 (0.9%)	2 (1.8%)

All patients were evaluable for toxicity. No febril neutropenia occurred, neither septic death. Toxicity was well tolerated.

Reason for study discontinuation

	4 cycles (n= 110)	4 cycles (n= 110)	Total (n= 220)
Reason, n(%)			
Death	1(0.9)	0 (0.0)	1 (0.5)
Patient decision	1 (0.9)	1 (0.9)	2 (0.9)
Progression	25 (22.7)	39 (35.4)	64 (29.1)
Protocol	78 (70.9)	67 (61.0)	145 (65.9)
Toxicity	4 (3.6)	2 (1.8)	6 (2.7)
Other	1(0.9)	1 (0.9)	2 (0.9)

Efficacy

- Response to treatment

	4 cycles (n= 110)	6 cycles (n= 110)	
Response, n(%)			
Complete response	0 (0.0)	1 (0.9)	
Partial response	41 (37.3)	42 (38.2)	
Stable	38 (34.5)	41 (37.3)	
Progression	24 (21.8)	21 (19.1)	
Not evaluated	7 (6.4)	5 (4.5)	
			p. value
Overall response, n(%)	41 (37.3)	43 (39.0)	0.740
CI 95%	28.3-46.3	30.2-48.6	-

Time to progression

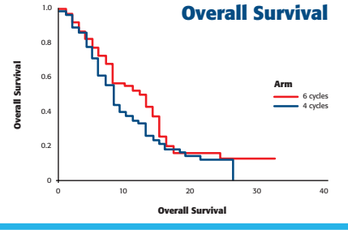
	4 cycles (n= 110)	6 cycles (n= 110)	p. value
Progressions, n(%)	102 (92.7)	96 (87.2)	-
Range, months	1.0-32.0	0.0-32.0	-
Mean, months	5.6	6.8	-
CI 95%	4.6-6.5	5.7-8.0	-
Median, months	4.0	5.0	0.078
CI 95%	3.1-4.9	3.9-6.1	-
Hazard ratio	1.25	-	0.118
CI 95%	1.0-1.7	-	-

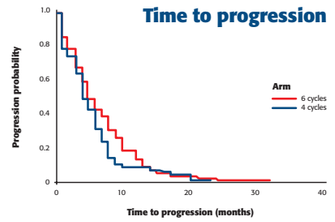
Overall survival

	4 cycles (n= 110)	6 cycles (n= 110)	p. value
Deaths, n(%)	86 (78.2)	81 (73.6)	
Range, months	0.0-26.0	1.0-32.0	
Mean, months	10.3	12.8	
CI 95%	8.8-11.8	10.9-14.6	
Median, months	8.0	12.0	0.070
CI 95%	6.9-9.1	9.7-14.3	

One-Year Survival

	4 cycles (n= 110)	6 cycles (n= 110)	p. value
1-year survival rate, %	33.0	49.4	-
CI 95%	23.8-42.2	39.6-59.2	-
2-year survival rate, %	11.9	12.7	-
CI 95%	4.3-19.5	4.7-20.7	-
Hazard ratio	1.29	-	0.097
CI 95%	1.0-1.8	-	-





SUMMARY OF RESULTS

- Overall survival was not statistically different between the two treatment arms (p=0.070). Median survival was 8 months (95% CI: 6.9-9.1 months) for 4-cycles regimen and 12 months (95% CI: 9.7-14.3 months) for 6-cycles regimen.
- Time to progression was statistically similar between the two treatment arms (p=0.078). Median time to progression was 4 months (95% CI: 3.1-4.9 months) for patients receiving 4 cycles and 5 months (95% CI: 3.9-6.1 months) for patients receiving 6 cycles.
- Overall response rate (CR+PR) was not statistically different between the two groups: 37.3% in 4-cycle arm (95% CI: 28.3-46.3%) and 39.4% in the 6-cycle arm (95% CI: 30.2-48.6%).
- One Year Survival rate was not statistically different between the two groups: 33.0% in 4-cycle arm (95% CI: 23.8-42.2%) and 49.4% in the 6-cycle arm (95% CI: 39.6-59.2%)
- Low incidence, without differences between two arms, in grade 3-4 toxicity haematologic and non-haematologic.
- Risk of progression was not statistically different between the two treatment arms (p=0.118). Patients receiving 4-cycles had a risk of progression 1.25 times higher than 6-cycles regimen (95% CI: 1.0-1.7).
- Risk of dying was not statistically different between the two treatment arms (p=0.097). Patients receiving 4-cycles had a risk 1.29 times higher than 6-cycles regimen (95% CI: 1.0-1.8).

CONCLUSIONS

- Globally we have better results in six-cycles arm, however overall survival, time to progression and one year survival was not statistically different between the two treatment arms. Risk of progression and dying are higher for patients receiving four cycles, but was not statistically different between the two treatment arms. We intend to continue clinical trial, with quality of life evaluation. At this moment we recommend that treatment has at least four cycles. If we get an objective response, we should extend the chemotherapy to six cycles.

References

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