RESEARCH COMMUNICATION

Triplet Platinum-based Combination Sequential Chemotherapy Improves Survival Outcome and Quality of Life of Advanced Non-small Cell Lung Cancer Patients

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Abstract

Background: Maintenance chemotherapy is one strategy pursued in recent years with intent to break through the chemotherapy plateau for advanced non-small cell lung cancer (NSCLC). However, given the toxicity, platinum-based combinations are rarely given for this purpose. We carried out the present prospective study of triplet platinum-based combination sequential chemotherapy in advanced NSCLC to investigate if patients could tolerate and benefit from such intensive treatment. Methods: From Dec 2003 to Dec 2007, 190 stage IIIB and IV NSCLC patients in Sun yat-sen University sequentially received the 3 platinum-based combination (TP-NP-GP) treatment (T: paclitaxol175mg/m^2 d1; N: vinorelbine25mg/m^2 d1 and 8; G: gemcitabine1g/m^2 d1 and 8; P: cisplatin20mg/m^2 d1-5; repeated every 3 weeks). Patients were followed up to at least 3 years to obtain survival data. Treatment toxicities and the quality of life (QOL) were assessed during the whole treatment. Results: There were 187 patients evaluable. The TP, NP and GP response rates with sequential use were 42.8% (80/187), 41.1% (65/158) and 28.8% (21/73) respectively. Median survival time was 18.2 months and the 1, 2 and 3 year overall survival (OS) rates were 78.7%, 38.5% and 21.3%. Patients receiving > 6 cycles of chemotherapy had significantly longer OS and TTP (MST 25.3 vs. 14.5 months, TTP 15.1 vs. 9.1 months). The QOL on the whole for the patients was improved after chemotherapy. Conclusions: The sequential chemotherapy strategy with triplet platinum-based combination regimens can improve the survival outcome and the quality of life of advanced non-small cell lung cancer patients.

Keywords: Sequential chemotherapy - maintenance therapy - NSCLC - platinum-based combinations

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Introduction

Platinum-based combinations for no more than 6 cycles had been the current standard of 1st line care for advanced stage non-small cell lung cancer (NSCLC). However, the outcome of such treatment modality was under satisfactory with 1 and 2-year survival rates about 30-40% and 10-21% respectively (Fisher, 2000). In order to improve the treatment outcome and break through the so-called plateau of chemotherapy, novel treatment strategies had been taken to delay progression after first-line chemotherapy.

Efforts had been done in recent years with the concept sequential and maintenance chemotherapy which intent to prolong the treatment and tumor control. In fact, it is hard to differentiate the two modalities absolutely and we may generally consider another intensive regimen after the initial chemotherapy as sequential treatment (Grossi et al., 2007). Continuation of chemotherapy beyond four to six cycles in the 1st -line setting resulted in several past studies in added toxicity without a meaningful improvement in survival (Smith et al., 2001; Belani et al., 2003; Westeel et al., 2005; Brodowicz et al., 2006). However, most of these studies used the same prior regimen or one of the prior drugs in the prolongation stage and the negative results might partially due to drug resistance.

Recently, several randomized phase III studies have documented improvement in outcome with the use of maintenance therapy for patients with advanced stage NSCLC (Ciuleanu et al., 2007; Fidias et al., 2009; Cappuzzo et al., 2010). Despite the beneficial role reported recently for maintenance therapy, platinum-based combinations had been rarely used as the maintenance regimen given the cumulative toxicities. Since alternately using different platinum-based regimens may theoretically overcome the drug resistance, we carried out this prospective study of sequentially using 3 platinum-based combination regimens for advanced NSCLC to investigate if the patients could tolerate and benefit from such an intensive and prolonged treatment strategy.

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Materials and Methods

Eligibility

Eligibility included: histological or cytological diagnosis of treatment-naïve advanced NSCLC, stage IIIB or IV, age 18-70 years, ECOG 0-1, an estimated life expectancy of at least 12 weeks, adequate renal, hepatic and bone marrow function, measurable disease, and patients with brain metastases were not excluded. Patients with concurrent malignancy and life-threatening medical conditions were excluded. The study was approved by the ethics committee of Sun Yat-sen University and all enrolled patients were capable of understanding the diagnosis and the nature of the treatment, and signed the consent form.

Chemotherapy Plan

Patients sequentially received the following 3 chemotherapy regimens (TP-NP-GP). The TP regimen consisted of Paclitaxol 175 mg/m^2 on day 1, Cisplatin 20 mg/m^2 on days 1 to 5. The NP regimen consisted of Vinorelbine 25 mg/m^2 on days 1 and 8, Cisplatin 20 mg/m^2 on days 1to 5. The GP regimen consisted of Gemcitabine 1g/m^2 on day 1and 8, Cisplatin 20 mg/m^2 on days 1to 5. Treatment was administered every 3 weeks. Doses of all drugs in a regimen were reduced by 20% when hematological toxicity grade 4 and/or non-hematological toxicity grade 3-4 (excluding nausea/vomiting and alopecia). Subsequent cycles were delayed until recovery from hematologic toxicity and/or inadequate liver function, inadequate renal function.

Treatment Design and Assessment

At enrollment, all patients underwent complete medical history and physical examination, tumor assessment including chest X-ray and CT scan, bone scan and MRI scan of the brain. Each regimen was executed for at least 1 and no more than 4 cycles. CT scan was repeated every two cycles or at any time of disease progression. Whenever disease progression was confirmed, treatment went to the next sequential regimen. Hematologic toxicity and biochemistry test were monitored each cycle.

Thoracic radiation was offered to patients with stage IIIb 3 weeks following completion of TP regimen and before NP regimens. Concomitant whole brain radiotherapy (WBRT) was applied with TP regimen for patients with brain metastases. Palliative radiation was given in case of symptomatic bone metastases, backbone fracture or spinal cord compression. Total radiation dose were 60-68Gy for lung and mediastinal lesion, 40Gy for whole brain and 30Gy for bone lesions. Tumor response was defined by the Resist criteria (1999). Treatment toxicity was graded according to NCI CTC-V2.

Patients were followed up to at least 3 years to get the median survival time (MST), 1, 2 and 3 year overall survival (OS) rates.

QOL Assessment

Quality of Life (QOL) was measured by the validated Chinese translation of the Functional Assessment of Cancer Treatment-Lung (FACT-L) Questionnaire (Cella et al., 1993). Patients were asked to complete the self-administered questionnaire before treatment and after 3, 6, 9 and 12 cycle's chemotherapy.

Statistical Methods

Overall survival and TTP were estimated using the Kaplan-Meier method. The log-rank test was used for comparison of time-to-event endpoints, and the chi-square method was used for testing differences in toxicity and response rates. Changes in mean scores of QOL from baseline were compared using a paired t-test. TTP and OS were subjected to Cox's proportional hazards regression model. The influence of relevant prognostic factors on TTP and OS were investigated.

Results

Patient characteristics

From December 2003 to December 2007, a total of 190 NSCLC patients in medical department of Sun Yat-sen University entered the study. Three patients withdrew before treatment. Totally 187 patients were evaluable. Patient characteristics were shown on Table 1.

Treatment Delivery and Tumor Response

Since patients withdrew consecutively at different treatment stages for economic reason or unwilling to receive further chemotherapy, there were altogether 73 out of the 187 patients completed the whole TP-NP-GP sequential chemotherapy, whereas other 85 patients completed the TP-NP chemotherapy and the remaining 29 patients only received the TP regimen. A total number of 502, 405 and 180 cycles respectively for TP, NP and GP regimens were administered. Median cycle numbers for TP, NP and GP regimens were 2.7, 2.2 and 1.0 respectively.

Table 1. Characteristics of 187 Patients and MST in Subgroups

		No. of patients (%)	MST (month)	P value (Log-rank test)
Sex	Male	125 (66.8)		
	Female	62 (33.2)		
Median age (range)		53.0 (29.0-69.0)		
Performance Status	0	50 (26.7)	25.3	0.007
	1	137 (73.3)	16.1	
Histology	Adenocarcinoma	133 (71.1)	18.3	0.202
	Squamous	38 (20.3)	19	
	other	16 (8.6)	12.1	
Stage	IIIB	36 (19.3)	24.3	0.049*
	IV	151 (80.7)	16.1	
Organ metastasis	Lung			
	yes	67 (35.8)	19.7	0.894
	no	120 (64.2)	18.2	
Liver	yes	22 (11.8)	20.9	0.966
	no	165 (88.2)	18.2	
Bone	yes	64 (34.2)	17.9	0.148
	no	123 (65.8)	19	
Adrenal	yes	7 (3.7)	21.8	0.101
	no	180 (96.3)	17.7	
Distant lymph node	yes	12 (6.4)	8	0.024
	no	175 (93.6)	19	
Brain	yes	51 (27.3)	14.7	0.012
	no	136 (72.7)	20.9	

Table 2. Treatment Categorization of 187 NSCLC Patients and TTP, OS in Subgroups

	No. of patients (%)	TTP (month)	P value (Log-rank test)	1-year TTP (%)	2-year TTP (%)	3-year TTP (%)	MST (month)	P value (Log-rank test)	1-year OS (%)	2-year OS (%)	3-year OS (%)
No. of regimen											
1	39 (20.9)	7.6	0.006	25.3	13	0	14.2	0.001*	62.8	22.2	14.8
2	79 (42.2)	10.7		45.1	22	0	16.2		73.3	33.4	15.9
3	69 (36.9)	14.2		64.6	24.6	19.7	24.8		92.8	52.3	30.8
No. of cycle											
2-6	119 (63.6)	9.1	0	36.3	15.1	5.4	14.5	0	66.9	26.8	13.8
>6	68 (36.4)	15.1		67.6	19.5	11.7	25.3		98.5	57.9	33.8

Table 3. Treatment Toxicities of Sequential Chemotherapy (n=187)

	I-IV (%)			III-IV (%)			P
	TP	NP	GP	TP	NP	GP	
Neutropenia	78.8	90.3	67.8	6	24.4	7.8	0.000*
							0.000**
Anemia	33.1	42.7	48.3	0	0	2.8	0.003*
							0.207**
Thrombocytopenia	14	30.7	62.2	1	1.4	15	0.507*
							0.000**
Fever (neutropenia)	1.4	2	0	0	0	0	
Nausea/Vomitting	50	67.7	59.4	1	4.7	4.4	0.408*
							0.390**
Diarrhea	1.2	1.2	0	0	0	0	
Neurotoxicity	18.5	36.8	57.2	0	2.5	5	0.000*
							0.000**
Fatigue	15.7	35.5	45.6	0	0	0	0.000*
							0.019**
Alopecia	91.4	85.2	89.4	50.943		53.3	0.236*
							0.310**
Arthralgia	33.9	1.2	1.7	0	0	0	0.000*
Hepatic	3	1.2	2.8	0.2	0	0	
Hypersensitivity reactions	3.2	1	2.2	0.6	0	0	
Nephrotoxicity	1.2	2	2.2	0	0	0	
Ototoxicity	0.4	0.7	1.1	0	0	0	

*Grade 1-4 toxicity with NP compared to TP regimen; **Grade 1-4 toxicity with GP compared to NP regimen

When TP, NP and GP regimen sequentially used, the objective response rates were 42.8% (80/187), 41.1% (65/158) and 28.8% (21/73) and disease control rates 88.3% (165/187), 82.3% (130/158) and 76.7% (56/73) respectively.

Survival

Forty-one patients were followed up alive to present whereas 135 were followed-up to death and 11 patients lost. MST was 18.2 months and the 1, 2 and 3 year OS were 78.7%, 38.5% and 21.3% respectively. Median TTP was 11.7 months and the 1, 2 and 3 year TTP were 48.0%, 16.5% and 9.0% respectively (Figure 1).

The influences of patient characteristics on survival were investigated by log-rank test. There were no significant differences in survival with different sex and histology. Patients with baseline ECOG PS 0 and stage IIIB had longer OS than those with ECOG PS 1 and stage IV (Table 1). The influences of treatment strategies on TTP and OS were shown on Table 2. Patients were categorized by regimen number and cycle number of the sequential chemotherapy. Results showed significantly better prognosis on TTP and OS for patients received 3 chemotherapy regimens and more than 6 cycles chemotherapy (Figure 2).

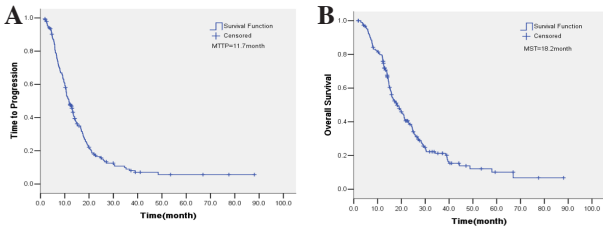

Figure 1. Time to Progression (TTP) (A) and Overall Survival (OS) (B) for 187 NSCLC Patients

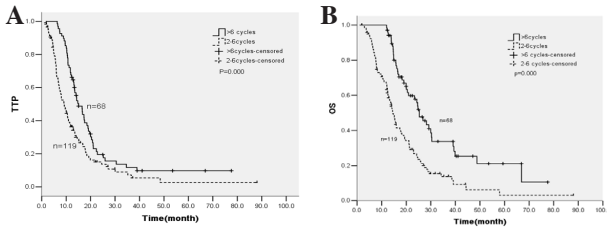

Figure 2. TTP (A) and OS (B) for Patients Receiving > 6 or 2-6 Cycles of Platinum-based Sequential Chemotherapy

Cox Regression Analysis

The influence of pre-defined treatment stratification factors (regimen number, cycle number) as well as other relevant prognostic factors (sex, baseline PS and disease stage, pathological subtypes, lung, liver, bone, adrenal gland , distant lymph node and brain metastasis or not) on OS and TTP were investigated using the Cox regression analysis. The multivariate analysis results confirmed the chemotherapy cycle number, disease stage and baseline PS as the independent OS prognosis factor. Patients received > 6 cycles of chemotherapy had the significantly longer OS (OR 0.409, P=0.000) and TTP (OR 0.528, P=0.000) (Figure 2).

Toxicity

Treatment toxicities were listed on Table 3. Neutropenia was most obvious in NP regimen whereas thrombocytopenia most occurred in GP regimen. More patients suffered from anemia, neurotoxicity and fatigue when received more cycles of chemotherapy.

QOL Assessment

The mean calculated values were listed on Table 4. When considering the relationship with doctor (RD), emotional well-being (EW) and additional evaluation (AE), the corresponding values after 3, 6 and 9 cycles of chemotherapy indicated the improvement of pretreatment QOL. However, physical well-being (PW) and functional well-being (FW) got worse after 3 cycle's chemotherapy and went back to the pretreatment levels after 6 cycles. The

Table 4. Mean Value of Functional Assessment of Cancer Treatment-Lung (FACT-L)

	before treatment	After 3 cycles	P	After 6 cycles	P	After 9 cycles	P
PW	16.4±2.7	20.7±3.2	0	16.2±2.2	0.877	18.0±2.1	0.27
SFW	22.1±3.6	21.7±3.4	0.51	20.9±3.0	0.074	20.5±2.6	0.12
RD	11.3±2.3	13.2±1.9	0.031	14.8±2.1	0.002	15.6±1.9	0
EW	16.4±2.6	18.5±2.2	0.001	19.5±2.5	0	19.6±2.6	0
FW	20.0±2.5	17.2±3.3	0	19.4±1.9	0.3	20.1±2.2	0.813
AE	25.0±3.8	19.3±3.3	0	17.1±3.0	0	15.1±2.4	0

PW, Physical Well-being; SFW, Social/Family Well-being; RD, Relationship with Doctor; EW, Emotional Well-being; FW, Functional Well-being; AE, Additional Evaluation

social/family well-being (SFW) remained stable during the whole treatment. Thus, the QOL on the whole for the patients were improved after chemotherapy.

Discussion

Platinum-based 3rd generation combinations have been the standard of care for advanced NSCLC with an overall median survival time of 8 to 12 months (Non-small Cell Lung Cancer Collaborative Group, 1995). Whatever platinum in combinations with paclitaxol, gemcitabine or vinorelbine, the outcomes of further survival prolongation have been limited (Schiller et al., 2002). Despite of the new targeted drugs which had brought the major treatment progress in NSCLC, is there anything we can do to forward a step of nowadays chemotherapy?

Maintenance therapy is one strategy that has been investigated extensively in recent years as a way of improving outcomes in patients with NSCLC. However, prior study in NSCLC comparing four or more courses of paclitaxol plus carboplatin have failed to show convincing clinical benefit as measured by overall survival advantage in patients treated with a prolonged course of chemotherapy (Socinski et al., 2002). Until now, it is intuitive that the duration of intensive chemotherapy should be short to minimize potential toxicity and the first line platinum-based combination chemotherapy was considered to be no more than 6 cycles.

Although treatment effect was not improved by adding chemotherapy cycles of the same regimen, the prolongation of chemotherapy by different regimens is worth investigation. When sequential chemotherapy offered, it is possible to overcome the drug resistance of single regimen used for a relatively longer period. Actually, the debate about maintenance therapy for advanced NSCLC had been re-ignited in recent years (Hosoe et al., 2003; Grossi et al., 2004; Chiappori et al., 2005; Pallis et al., 2006). The results of several randomized phase III studies reported showing a significant advantage of maintenance treatment in advanced NSCLC (Ciuleanu et al., 2007; Fidias et al., 2009; Cappuzzo et al., 2010). We noticed that all the trials with positive results had adopted different agents from the prior regimens as maintenance treatment. In our study, we sequentially use three different platinum-based regimens and got the very encouraging survival data, especially in those received relatively more chemotherapy cycles. Our study contributed to the nowadays evidences of maintenance chemotherapy in NSCLC. Although it was a single unit phase II study with potent bias, the encouraging survival data of our patients indicated the value of prolongation of intensive chemotherapy.

Effectiveness of a maintenance regimen may be essential for the final PFS and OS benefit. Theoretically, despite the tolerability, platinum-based combination regimens would be more effective than single agent. In our study, platinum combinations were sequentially used with the intent to control tumor by the greatest extent. Noticeably, NP regimen sequentially 2nd-line used achieved the similar response rate as that of 1st line chemotherapy and 20 non responders of initial TP regimen got further tumor remission. Although the efficacy of GP regimen was relatively lower when used as the sequential 3rd line chemotherapy, the disease control rate of 76.7% was as high as the previous two regimens.

Chemotherapy with platinum-based regimens for more than 6 cycles was usually considered unendurable (Edelman et al., 2004; Belani et al., 2006). However, in our study, we found that the myelosuppression toxicity remained generally tolerable during the whole treatment with G-CSF support. In our study, sequential platinum-based combination chemotherapy had brought more peripheral neurotoxicity, anemia and fatigue, but most manifested mildly or moderately.

Prolonged administration of platinum-based combinations had been considered theoretically with descending of QOL. Through the QOL investigation in our study, we found that PW and FW were temporarily decreased after 3 cycles due to the treatment toxicities whereas improved after 6 cycles due to recovery of the mental state and physical fitness following effective therapy. Moreover, the related lung cancer symptoms would be relieved through the tumor control and meanwhile improved the EW and RD. Thus, the whole QL for our patients was unexpectedly improved instead of descending. Despite the traditionally thought of worsen of QOL brought by intensive chemotherapy, it was shown from our study that treatment effectiveness might be the most important factor of QOL in NSCLC patients receiving chemotherapy.

Our study showed that the platinum-based combinations sequential chemotherapy may have certain prosperities with acceptable tolerance profile in advanced NSCLC. We consider it necessary to identify a subgroup of patients best suited for such intensive treatment and to those patients with good PS, strong willingness for treatment and responding to the 1st line chemotherapy, such active treatment may offer more chances for achieving long-term survivors.

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