THE RELATIONSHIP BETWEEN THE PATHOLOGICAL CHANGES AND RESPONSE RATE (RR) IN NON-SMALL CELL LUNG CANCER TREATED BY NEOADJUVANT CHEMOTHERAPY WITH MITOMYCIN (MMC), VINDESINE (VDS) AND CISPLATIN (DDP) COMBINATION

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ABSTRACT

Objective: To explore the change of pathology and the clinical response rate treated by neoadjuvant chemotherapy with MVP regimen for non-small cell lung cancer. Methods: This is a randomized study in patients with stage I-IIIa. Among them, 46 patients enrolled in neoadjuvant chemotherapy treated by 1–2 course MVP regimen. MMC was given 6 mg/M^2 by intravenous (I.V.) infusion on day$_1$, VDS 2.5–3 mg/M^2 I.V. on day$_{1,8}$ and/or day$_{15}$, DDP 90 mg/M^2 I.V. on day$_1$. The treatment was recycled every 28 days. The clinical RR evaluated with WHO criteria. All surgical samples were classified with pathology. Results: The overall response rate in 2 courses chemotherapy is better than that in 1 course (P<0.01). The number of patient with pathology grade I-II in 2 course chemotherapy is higher than that in 1 course (P<0.01). But the RR can not completely translated into pathology grade I-II. The pathology grade I-II is closely related with tumor involvement (T) (P<0.01) but not closely related with regional lymph node metastasis (N). It is reasonable to use RR together with PCR to judge the chemotherapy response. NR patients can not be regard as chemotherapy failure. No serve toxicities and surgical mortality were observed. Conclusion: MVP regimen is an effective neoadjuvant treatment regimen for I-IIIa NSCLC.

Key words: NSCLC, MVP regimen, Pathological grade

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Lung cancer is the leading cause of male cancer death in the big cities in China. The mortality is growing recent years. It has been confirmed that the best treatment for non-small cell lung cancer is the surgery-based multimodality therapy. But only 20% of NSCLC patients present with stage I and II disease and can be resected completely when the diagnosis is established. It is a trend for stage II and IIIa patients to use adjuvant chemotherapy in order to improve the 5-year survival rate and disease-free survival time. In patients with uncompletely resectable NSCLC, neoadjuvant chemotherapy based on cisplatin combined with a podophyllotoxin or a vinca, such as vindesine or vinblastine, etoposid, mitomycine and adriamycine may improve the completely resection rate and a few patients can get the pathology complete response rate (PCR) and prolong the survival time. We carried out a prospective and randomized study to investigate the effect of neoadjuvant chemotherapy on survival time. The aim of this article is to explore the change of the pathological and clinical response rate treated by neoadjuvant chemotherapy with MVP (MMC, VDS, DDP) regimen for non-small cell lung cancer in 46 patients who are confirmed by post-surgery pathological examination (including microscopy and electron microscopy examination).

MATERIALS AND METHODS

Patients

From February 1995 to February 1997, 90 patients with stage I–IIIa NSCLC entered into study. Among them 46 patients enrolled in neoadjuvant chemotherapy arm. All patients lived in Shanghai. The main characteristics of

eligible patients were male/female 31/15; median age 60 (39–75); Karnofsky PS≥80. All patients were staged according to standard protocol (X-rays and CT scan of the chest, CT scan of brain, CT scan of upper abdomen, bronchoscopy, bone scan). The stage system is TNM system of UICC in 1997.

Chemotherapy Regimen

MMC: 6 mg/m^2 iv d_1
VDS: 2.5–3 mg/m^2 iv $d_{1,8}$ and/or d_{15}
DDP: 90 mg/m^2 iv d_1

The regimen was recycled every 28 days. Standard antimeric treatment including 5-HT_3 receptor antagonists was administered before chemotherapy. The objective response was assessed after 21 days of chemotherapy. Among 46 cases, 11 cases accomplished 2 cycles of neoadjuvant chemotherapy (group A), others accomplished 1 cycles of neoadjuvant chemotherapy (group B).

The Criteria of Objective Response, Toxicity and Pathological Response

Objective response and toxicity were assessed in accordance with WHO criteria.[1] Pathological response was assessed in accordance with Lin's criteria[2] that is

I: The primary lesion disappeared and was replaced by fibrosis;

II: Scanty residual cancer tissues were seen by microscopy;

III: Degeneration and necrosis with fibrosis were present but active cancer tissue in small area were found;

IV: There was mild degeneration or no obvious changes. Pathological response is defined as I–II pathological staging.

RESULTS

The main pathological characteristics of 46 eligible NSCLC patients were: stage I 21 cases: histotype: epidermoid 10 cases, adenoca 8 cases, mixtype 1 case, others 2 cases; stage II 10 cases: histotype: epidermoid 5 cases, adenoca 3 cases, mixtype 2 cases; stage IIIa 15 cases: histotype: epidermoid 3 cases, adenoca 7 cases, mixtype 2 cases, others 3 cases.

The objective response were CR: 2 cases, PR: 13 cases (Table 1). The response rate 15/46 (32.6%). The following response observed in group A and B respectively: CR: 2 and 0 cases, PR: 6 and 7 cases, response rate: 73% and 20%.

Table 1. The relationship with the cycles of chemotherapy in clinical response rate and pathological response rate

Cycles	Clinical response rate			Pathological response rate (grade)		
	CR (%)	PR (%)	RR (%)	I (%)	II (%)	I–II (%)
One		7/35 (20)	7/35 (20)		1/35 (3)	1/35 (3)
Two	2/11 (18)	6/11 (55)	8/11 (73)	1/11 (9)	7/11 (64)	8/11 (73)
P value			<0.01			<0.01
Response rate		15/46 (32.6)			9/46 (19.6)	

Table 2. The relationship between response and stages

Stage	Cases	CR case (%)	PR case (%)	NR case (%)	PD case (%)	RR case (%)
I	21	1 (4.8)	7 (33.3)	13 (61.9)		8 (38.1)
II	10		3 (3)	6 (60)	1 (10)	3 (30)
III	15	1 (6.7	3 (20)	11 (73.3)		4 (26.7)
Total	46	2 (4.3)	13 (28.3)	30 (65.2)	1 (2.2)	15 (32.6)

The following pathological response were observed in group A and B respectively: I–II: 8 and 1, response rate: 73% and 3% (P<0.01) (Table 1). The clinical response rate were observed in stage I, II, III respectively: 38.1%, 30.0%, 26.7% (P>0.05, NS) (Table 2). In 15 clinical response patients, there were 5 cases got the pathological response (I–II: 33.3%) while in 31 no clinical response patients, there were 4 cases got the pathological response (II: 13%). In 2 CR cases, only one got the PCR result. This result suggested that the clinical response can not completely translate into pathological response.

The pathological response was closely related with

tumor involvement (T) (Table 3). The following pathological response were obvious in T_1, T_2, T_3 respectively: 71%, 12%, 0% (P<0.01). But it was not closely related with regional lymph node metastasis (N). The following pathological response were observed in N_0, N_1, N_2 respectively: 72%, 0%, 23% (P>0.05).

No Grade IV Leucopenia occurred. Grade I–II leucopenia occurred in 62.5%. In group A and B it occurred in 82% and 60% respectively. All patients recovered within 7 days. Non-hematological toxicity was moderate. Grade I–II nausea and vomiting occurred in 50%. Neurotoxicity occurred in 23.9% (Table 4).

No surgery related complications occurred. All patients are alive and were performed the adjuvant chemotherapy 5 weeks after surgery. All patients were followed up for survival time.

Table 3. The relationship between tumor involvement (T) and clinical response rate

	T_1	T_2	T_3	P
RR	3/7 (43%)	11/34 (32%)	1/5 (25%)	<0.01
CHR	5/7 (71%)	4/34 (12%)	0/5 (0%)	<0.01

Table 4. Toxicities

Toxicities	I case (%)	II case (%)	III case (%)	Total case (%)
Anemia	8 (17.4%)	5 (10.9%)	2 (4.3%)	15 (32.6%)
Leukopenia	12 (26.1%)	18 (39.1%)	0	30 (65.2%)
Thrombocytopenia	0	0	0	0
Nausea/Vomiting	17 (37.0%)	6 (13.0%)	2 (4.3%)	25 (54.3%)
Neurotoxicities	7 (15.2%)	4 (8.7%)	0	11 (23.9%)

Table 5. The relationship between clinical response and pathological

	Stage	Case	Clinical response			
			CR	PR	NR	PD
Pathological response	I	1	1			
	II	8	1	3	4	
	III	15		9	6	
	IV	22		1	20	1
Total		46	2	13	30	1

DISCUSSIONS

MVP regimen is one of the most common used regimen for NSCLC. The response rates ranged from 48% to 93%, while CR from 0%–5%.[3–8] But our result of response rate was 32.6%, while CR: 4.3%, PR: 28.3% and it was not related to the stages. The clinical response rate in 2 courses neoadjuvant chemotherapy group was significant higher than that in 1 course group, 73% and 20% respectively (P<0.01). The pathological response was also significant higher in 2 courses neoadjuvant chemotherapy group than that in 1 course one (P<0.01) (Table 5). Most patients in 1 course group have been observed with mild degeneration and necrosis in pathological examination but they didn't reach the clinical response criteria. It maybe results from dose insufficient. Thus 2 courses neoadjuvant chemotherapy are more recommended. In clinical NR patients, there were 13% patients with pathological response (grade I–II) while in clinical RR patients there were also 66.7% patients with no pathological response (grade I–II). So it inaccurately only use clinical response to judge the chemotherapy effect. As induction chemotherapy, we shouldn't give up the chance of surgery or radiotherapy if the chemotherapy

were NR. We should decide it in combination with other agents such as stage and involvement area of the tumor. This view is the same as other reporters.[8] The toxicities were moderate. Myelosuppression and nausea/vomiting were the most frequent side-effects but its intensity was mild. Grade I–II toxicities occurred 54.3% and 65.2% respectively. Only fewer cases were occurred grade III anemia. No side-effect of liver and renal toxicities were observed. No surgery related complications occurred and all patients recover from surgery quickly.

The results showed that the pathological response (grade I–II) is closely related with tumor involvement (T). The lower the T, the higher the pathological and clinical response rate, T_1, T_2, T_3: 71%, 12%, 0% and 43%, 32%, 25% respectively. But it is not closed related with regional lymph node metastasis (N). It is the same as others results. The results showed that MVP regimen has more effect on T_1 patients. So it is reasonable to use it as neoadjuvant chemotherapy regimen for stage I NSCLC. It needs to be confirmed by survival time. It is also necessary to carry out the large number of prospective and randomized studies. The results also showed that in clinical RR patients there were 33% (5/15) with pathological response while in clinical NR patients there were 13% (4/31) with pathological response. This difference showed the inaccuracy of traditional evaluated method.

In 2 CR patients, only one got the grade I pathological response (PCR). There were 8 patients got the grade II pathological response, that is scanty residual cancer tissues were seen by microscopy. It has been confirmed that PCR can prolong survival time. We can get the conclusion that MVP regimen is an effective neoadjuvant regimen for I–IIIa NSCLC and no server toxicities and surgical complications were observed.

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