Clinical Study on HMVP, MVP and HVP Regimens in the Treatment of Patients with Advanced Non-Small Cell Lung Cancer

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Abstract **Objective** To evaluate the response, toxicity and survival time of HMVP, MVP and HVP regimens in the treatment of advanced Non-Small cell lung cancer (NSCLC). **Methods** A total of 134 cases with advanced NSCLC was randomized into 3 groups: HMVP group [46 patients, Hydroxycamptothecin (HCPT) 12 mg/m^2 from d 1 to d 5, Mitomycin C (MMC) 6 mg/m^2 d 1, Vindesine (VDS) 2.5~3 mg/m^{2}d 1 and d 8, Cisplatin (DDP) 50 mg/m^2 d 2 and d 3]; MVP group (44 patients, MMC, VDS and DDP were the same as HMVP group) and HVP group (44 patients, HCPT, VDS and DDP were the same as HMVP group). **Results** The response rates were 39.54% (17/43), 36.59% (15/41) and 26.19%(11/42) in the HMVP, MVP and HVP group respectively, but no significant difference was detected among the 3 groups (P>0.05). No significant difference was detected in the median time of remission, median survival time and 1-, 2-year survival rates among the 3 groups. Moreover, no significant difference was detected in the grade Ⅲ~Ⅳ leukopenia, grade Ⅲ~Ⅳ thrombocytopenia, grade Ⅲ~Ⅳ nausea/vomiting and grade Ⅲ~Ⅳ constipation among the 3 groups. **Conclusions** The response rate of MVP regimen is slightly lower than HMVP regimen, but HMVP regimen is not obvious superior, which may increase the expenses and the toxicity such as leukopenia, nausea/vomiting and constipation. The response rate of HVP regimen is lower than the other two regimens. In short, MVP regimen should be selected firstly among the 3 regimens in the chemotherapy of advanced NSCLC.

Key Words Non-Small Cell Lung Cancer (NSCLC); Chemotherapy; Mitomycin C(MMC); Hybroxycamptothecin(HCPT); Vindesine(VDS); Cisplatin(DDP)

Non-small cell lung cancer (NSCLC) is hyposensitive to chemotherapy. Camptothecin derivative is becoming one hot point in the treatment of advanced NSCLC. HCPT made in china, an inhibitor of topoisomerase I, has been applied in clinical treatment for over 20 years, but its effect in the treatment of NSCLC has not been investigated certainly yet till now. From June, 1998 to September, 2001, HCPT with MMC (mitomycin C), VDS(vindesine) and DDP (cisplatin) had been used to form HMVP, MVP and HVP regimens to treat 134 cases with advanced NSCLC in our haspital. And the short-term and long-term response and toxicity were had been evaluated. The objective of this article was to study the effect of HCPT in the chemotherapy of NSCLC.

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MATERIALS AND METHODS

Study object

Eligible patients: Karnofsky performance status score≥60; expected survival time>3 months; measurable clinical index; no other anticancer treatment; first-treated patients proved by histomorphology or cytogenetics. 134 cases were classified by WHO´s TNM standard in 1997. Complete blood counts and urine routine examination, hepatic or renal function test were required before treatment. After treatment, complete blood counts would be examined weekly, lasting 2 weeks. Within 2 weeks after treatment,

hepatic or renal function would be tested once. If the result was abnormal, the test would be continued once 2 weeks until it is normal. All the patients were randomized to HMVP, MVP and HVP groups (46, 44 and 44 cases respectively). Clinical characteristics of three groups were shown in table 1. All patients had fulfilled the treatment as planned except that 3 patients of HMVP, 3 patients of MVP and 2 patients of HVP group were rejected.

Methods

HMVP regimen HCPT 12mg/m^2, intravenously (i.v.) from Day 1 to Day 5; MMC 6mg/m^2, i.v. on Day 1; VDS 2.5~3.0 mg/m^2, i.v. on Day 1 and Day 8; DDP 50mg/m^2, i.v. over 2 hours on Day 2, 3 with adequate hydration.

HVP regimen HCPT 12mg/m^2, i.v. from Day 1 to Day 5; VDS 2.5~3.0 mg/m^2, i.v. on Day 1 and 8; DDP 50mg/m^2, i.v. over 2 hours on Day 2, 3 with adequate hydration.

HVP regimen HCPT 12mg/m^2, i.v. from Day 1 to Day 5; VDS 2.5~3.0 mg/m^2, i.v. on Day 1 and 8; DDP 50mg/m^2, i.v. over 2 hours on Day 2, 3 with adequate hydration.

Each reginem was repeated every 3~4 weeks. The response was evaluated after 3 cycles. Every case was treated by 3~5 cycles. 450 cycles were treated totally. Andansetron was used in three groups to prevent nausea/vomiting.

Criteria of response and toxicity evaluation

Tumor responses were evaluated by WHO criteria and classified into CR, PR, NC and PD. CR and PR were regarded effective. Toxicities (0~Ⅳ grade) were evaluated by National Cancer Institute (NCI) common toxicity criteria (version 2). The toxicity could be evaluated among all the patients. Except 8 cases who didn´t finish the treatment as planned, the responses and toxicities of other cases were evaluated.

Statistical analysis

The relationship among 3 groups and clinical parameters were analyzed by t test, χ^2 test and log-rank test. The overall survival analysis was undertaken by the Kaplan-Meier method, and the difference was compared by log-rank analysis. All the statistical analysis were performed by SPSS 10.0 statistical software.

RESULT

Short-term response

All groups had no CR case except one of HMVP group. The response rates were 39.53% (17/43), 36.59% (15/41) and 26.19% (11/42) in HMVP, MVP and HVP groups respectively. No significant difference was detected among the 3 groups (p>0.05) (see table 2).

Table 1 Clinical Characteristics of 134 NSCLC Patients

Clinical Characteristics	HMVP group	MVP group	HVP group	Total
Age (median)	64.0 (38~73)	63.5 (40~70)	65.0 (35~74)	64.0 (35~74)
Male	31	29	31	91
Female	15	15	13	43
Histologic grade				
Adenocarcinoma	23	24	22	69
Squamous cell cancer	18	17	20	55
Adeno−squamous cancer	3	1	1	5
Undifferentiated	2	2	1	5
Clinical stage				
Ⅲa	3	3	4	10
Ⅲb	19	20	18	57
Ⅳ	24	21	22	67

HMVP: HCPT+MMC+VDS+DDP; MVP: MMC+VDS+DDP; HVP: HCPT+VDS+DDP

HCPT: hybroxycamptothecin; MMC: mitomycin C; VDS: vindesine; DDP: cisplatin

Table 2 Comparison of Near-Term Response of Advance NSCLC with Treatment of HMVP, MVP and HVP Regimen

Group	Cases	CR(%)	PR(%)	NC(%)	PD(%)	OR(%)	P
HMVP	43	1(2.33)	16(37.21)	16(37.21)	10(23.26)	17(39.54)	>0.05
MVP	41	0	15(36.59)	16(39.02)	10(24.39)	15(36.59)	>0.05
HVP	42	0	11(26.19)	17(40.48)	14(33.33)	11(26.19)	>0.05
Total	126	1(0.79)	42(33.33)	49(38.89)	34(26.98)	43(34.13)	

CR: complete response; PR: partial response; NC: no change; PD: progression disease; OR: overall response;

Table 3 Comparision of Grade Ⅲ~Ⅳ Toxicity of Advance NSCLC with Treatment of HMVP, MVP and HVP Regimen

Toxicity	HMVP group		HMVP group		HMVP group		*P*
	Ⅲ	Ⅳ	Ⅲ	Ⅳ	Ⅲ	Ⅳ	
Leukopenia	16(34.78)	5(10.87)	14(31.82)	4(9.09)	15(34.09)	1(2.27)	>0.05
Thrombocytopenia	5(10.87)	1(2.17)	6(13.64)	0	5(11.36)	0	>0.05
Nausea/vomitig	13(28.26)	3(6.52)	13(29.55)	2(4.55)	12(27.27)	1(2.27)	>0.05
constipation	16(34.78)	0	14(31.82)	0	12(27.27)	0	>0.05

Toxicity

The main toxicities of the 134 cases were myelosuppression and digestive reaction. The incidences of grade Ⅲ ~ Ⅳ leukopenia were 45.65% (21/46), 40.91% (18/44) and 36.36%(16/44) in HMVP, MVP and HVP groups respectively. The incidences of grade Ⅲ ~ Ⅳ thrombocytopenia were 13.04%(6/46), 13.64% (6/44) and 11.36% (5/44) in the 3 groups respectively. The degree of inhibting the leukocytes and thrombocytes in the three groups were HMVP, MVP and HVP in turn, but no significant difference was detected among the three groups (P>0.05). The incidences of grade Ⅲ ~ Ⅳ nausea/vomiting were 34.78% (16/46), 34.09% (15/44) and 29.54% (13/44) in HMVP, MVP, and HVP groups respectively (see table 3). The incidences of grade Ⅲ ~ Ⅳ constipation were 34.78% (16/46), 31.82% (14/44) and 27.27% (12/44) in the three groups respectively. No significant difference was detected (P>0.05). Neither was significant difference detected in other toxicities. There was no grade Ⅲ ~ Ⅳ toxicities to neuritis, hepatic or renal function.

Follow-up study

Till June, 2003, there were 110 cases dead, 8 cases missed and 16 cases alive. After treatment, the median time of remission were 19 weeks, 20 weeks and 19 weeks in HMVP, MVP, and HVP groups respectively. The median survival time was 37 weeks, 38 weeks and 36 weeks in the 3 groups respectively. 1-year survival rates were 26.09% (12/46), 29.54% (13/44) and 27.27% (12/44), and 2-year survival rates were 8.70% (4/46), 9.09% (4/44) and 11.36% (5/44) respectively. No significant difference was detected in the median time of remission, median survival time and 1-, 2- year survival rates among the 3 groups (P>0.05).

DISCUSSION

Topoisomerase-I is indispensable to DNA duplication and usually activated in tumor cells. Ternary compound made by camptothecin and topoisomerase-I/DNA can counteract DNA duplication and result in the death of tumor cells. Besides, topoisomerase-I can exert anticancer effect by preventing the formation of endotheliocytes of tumor capillary vessel[1,2]. The response rates of topotecan, irinotecan-II and 10-hydroxycamptothecin in the treatment of NSCLC were 15%, 35% and 13.7% respectively, and that of topotecan or irinotecan combined with other anticancer drugs were 42% and 51.85% respectively[3-5]. HCPT had anticancer activity in colon cancer and hepatic carcinoma in vitro[6,7]. Drug hypersensitivity test of HCPT on fresh operational

samples from 34 cases of NSCLC proved that the tumor-inhibition rate was 72.35%[8]. It is a project concerned by chemotherapy field in china whether HCPT combined with kind of platinum or other anticancer agents in the treatment of NSCLC could cooperate well. For the moment, the response rates of HCPT combined with other chemotherapy drugs in the treatment of NSCLC were 42.90%~51.85% in some non-random comparative study[9,10].

MVP regimen is worldwide accepted as the first-line regimen whose response rate is 34.30% ~53.0%. This study showed that the response rate of HMVP regimen was a little higher than that of MVP (35.57%), while the response rate of MVP was a little higher than that of HVP (26.19%), but all the figures had no significant difference. The result hints that on the basis of MVP, the response is not visible that HMVP regimen with adding HCPT to treat advanced NSCLC, and the short-term response of MVP regimen is more obvious than that of HVP. The long-term response to advanced NSCLC has no significant difference among the 3 groups, since their median time of remission, median survival time and 1-2 year survival rates were similar. The main toxicities were myelosuppression, nausea/vomiting and constipation. The incidence of grade Ⅲ~Ⅳ leukopenia, nausea/vomiting and constipation in HVP regimen was slightly higher than that in the other two groups.

In short, compared with the classic MVP regimen in the treatment of NSCLC, HMVP regimen shows no significant superiority, and it is of great possibility that HMVP regimen increases toxicities such as leukopenia, nausea/vomiting and increases the patients´ financial burdens as well. The response of MVP regimen was slightly better than that of HVP regimen which took the place of MMC by HCPT.

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