A Comparison Study on High Dose Impulsion Chemotherapy and Low Dose Density Chemotherapy of Taxotere Cisplatin Regimen in the Treatment of Advanced NSCLC

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Abstract **Objective** To evaluate and compare the efficacy, side effect and toxicity of high dose impulsion chemotherapy and low dose density chemotherapy of Taxotere Cisplatin regimen in advanced NSCLC. **Methods** A total of 71 advanced NSCLC patients(TNM, stage Ⅲ-Ⅳ) were enrolled in this study. 34 cases received high dose impulsion chemotherapy (HDIC group) and 37 cases received low dose density chemotherapy (LDDC group). HDIC group was administered taxotere 75-80mg/m^2, DDP 80-100mg/m^2 in day 1, BCNU 125mg was added for brain metastasized cases in days 1 to 3. After 4-6 weeks, they received the next course of therapy. LDDC group was administered taxotere 25mg/m^2 and DDP 40-60mg/m^2 on day 1, BCUN 125mg was added for brain metastasized cases in day 1. The chemotherapy was carried on once a week and one course of therapy consist of 4-6 consecutive weeks followed by 2-week's interval. HDIC group received antiemetic agent and hydration routinely whereas LDDC group only received antiemetic agent when necessary. **Results** In HDIC group, 96 courses of chemotherapy were administered totally, and 4 cases achieved complete response(CR), 12 cases had partial response(PR), the response rate was 47.1%, the median duration of response was 4 months. The 1-year survival rate was 44.1%(15/34). In the LDDC group, 112 courses of chemotherapy were administered totally, 4 cases achieved complete response, 15 cases had partial response, 12 cases had stable disease and 6 cases had progressive disease. The response rate was 51.4%. and the median duration of response was 5.5 months. The 1-year survival rate was 54.1%(20/37). The response rate and 1-year survival rate in LDDC group were both higher than that in HDIC group but there was no statistical difference(p>0.05) between them. The incidence of severe toxicity in LDDC group was lower than that in HDIC group. There was significant statistical difference (p< 0.005). There were 2 cases of chemotherapy related death in HDIC group (5.9%). The quality of life (Karnofsky score) was improved 1.5 points in HDIC group and 9.7 points in LDDC group averagely. **Conclusion** LDDC had better efficacy, slighter toxicity and could improve the quality of life better than HDIC.

Key Words non-small cell lung cancer; drug chemotherapy; taxotere; cisplatin; high dose impulsion chemotherapy (HDIC), low dose density chemotherapy (LDDC).

Recent years, with the changes of medical science model, the new psychosocial oncology model was formed. In the treatment of malignant tumors, in addition to the valuation of high remission rate and survival rate, people began to emphasize the function preservation and the good quality of life (QOL). High dose impulsion chemotherapy (HDIC) regimen, was accepted extensively in clinic and efficacy evaluation criterion have been doubted, in which the reduction of the tumor volume was only used. People began to emphasize a new kind of chemotherapeutic method, low dose density chemotherapy (LDDC).

From January 1999 to January 2003, we used HDIC and LDDC of taxotere cisplatin regimen to treat advanced NSCLC patients respectively, and compared the two kinds of chemotherapy methods, we found that the LDDC had higher efficacy, slighter toxicity and could improve the quality of life better.

PATIENTS AND METHODS

Patients 71 NSCLC patients who were diag-

nosed by pathologic and (or) cytologic examinations were enrolled in this study. They were divided into 2 groups randomly, and accepted the high dose impulsion chemotherapy and low dose density chemotherapy of taxotere cisplatin regimen respectively. Among the 34 cases in HDIC group, there were 21 males, 13 female. Their ages were from 34 to 78 (average 53) years old. The pathological types of these cases included 19 cases of squamous cell carcinoma and 15 cases of adenocarcinoma. The TNM stage included 9 cases of stage ⅢA, 17 cases of stage ⅢB and 8 cases of stage Ⅳ. 12 cases were treated for the first time, and 22 cases were not. Among the 37 cases in LDDC group, there were 24 males, 13 females. Their ages were from 28 to 84 (average 56) years old. Their pathological type included 21 cases of squamous cell carcinoma and 16 cases of adenocarcinoma. The TNM stage included 6 cases of stage ⅢA, 21 cases of stage ⅢB, 10 cases of stage Ⅳ. 11 cases were treated for the first time, and 26 cases were not. The karnofsky score of these 71 cases were all over than 60 points, and the estimated survival periods were all over 3 months.

Methods High dose impulsion chemotherapy group: taxotere 75-80mg/m^2 dissolved in 250ml of 0.9% saline was transfused intravenously within 1 hour and cisplatin 80-100mg/m^2 in 250ml of 0.9% saline was transfused intravenously on the day 1. BCUN 125mg dissolved in 250ml of 0.9% saline was added to transfuse intravenously within 1 hour on day 1 to day 3 in the brain metastasized cases. Next therapy course was carried on after 4-6 weeks. Low dose density chemotherapy group: taxotere 25mg/m^2 dissolved in 250ml of 0.9% saline transfused intravenously within 1 hour and cisplatin 40-60mg/m^2 in 250ml of 0.9% saline transfused intravenously on the day 1. BCUN 125mg dissolved in 250ml of 0.9% saline were added to transfuse intravenously within 1 hour on day 1 in the brain metastasized cases. The chemotherapy was carried on once a week and one therapy course consist of 4-6 consecutive weeks followed by 2-week interval. The hormone preconditioning was used the reformed and simplified method: 1 hour before the taxotere transfusion, dexone (dexamethasone) 10mg dissolved in 500ml of 10% glucose began to transfuse. After 30 minutes, dexone (dexamethasone) 10mg、benadryl (diphenhydramine) 20mg and cimitidine 300mg were added into the glucose successively. During the taxotere transfusion course, especially the beginning, the patients´ life signs, the face and skin reaction must be inspected closely. In the high dose impulsion chemotherapy group, the antagonist of 5-HT3 receptor was used routinely to prevent the nausea and vomitting, and hydration was routinely done for 3 to 5 days. In the low dose density chemotherapy group, only some cases needed antiemetic drugs and the hydration was not needed.

Evaluation criterion WHO antineoplastic efficacy evaluation criterion was used. Response rate was used CP+PR to calculate. Side effect and toxicity were assessed by the WHO criterions. The quality of life evaluation used Karnofsky performance status.

Statistics disposal The X^2 test (chi-square test) was used.

RESULTS

Eficacy In high dose impulsion chemotherapy group, 96 courses of chemotherapy were carried on in all 34 cases, average 2.8 courses every case. The response rate was 47.1%, the efficacy and the affect factors were shown in table 1. The duration of response was 1.5-8 months and the median duration of response was 4 months. The 1-year survival rate was 44.1% (15/34). In the low dose density chemotherapy group, 112 courses of chemotherapy were carried on in all 37 cases, average 3.0 courses every case. The response rate was 51.4%, the efficacy and the affect factors were shown in table 2. The duration of response was 2.5 –10 months and the median duration of response was 5.5 months. The 1-year survival rate was 54.1% (20/37). The response rate and the 1-year survival rate of LDDC group were both higher than HDIC group, but there were no statistic differences (P> 0.05).

Toxicity and side effect The incidences of serious toxicity and side effects (Ⅲ – Ⅳ grade, by WHO criterion) were seen in table 3. The incidences of the neotropenia, the thrombocytopenia, the anemia, nausea, vomiting, and diarrhea were higher in HDIC group than that in LDDC group. There was significant statistic difference (P<0.005). There were 2 cases of chemotherapy-related death in HDIC group, the chemotherapy-related death rate

was 5.9%. Both the 2 cases died from the myelosuppression, especially the neotropenia and the thrombocytopenia, which caused acute hematemesis, hematochezia, mucocutaneous hemorrhage, liver and renal function failure. There was no chemotherapy-related death in LDDC group.

The quality of life According to the Karnofsky performance status(KPS), the life quality improved . 5 points averagely in HDIC group and 9.7 points in LDDC group, which was shown in table 4.

Table 1 the efficacy and its affect factors in high dose impulsion chemotherapy

the affect factors	case number	CR number(%)	PR number(%)	SD number(%)	PD number(%)	RR number(%)	*P*
Therapy condition							
Untreated	12	2(16.7)	5(41.7)	3(25.0)	2(16.7)	7(58.3)	$p>0.05$
pretreated	22	2(9.1)	7(31.8)	8(36.4)	5(22.7)	9(40.9)	
Clinical stage							
Ⅲa	9	2(22.2)	4(44.4)	2(22.2)	1(11.1)	6(66.7)	$p>0.05$
Ⅲb	17	1(5.9)	6(35.3)	6(35.3)	4(23.5)	7(41.2)	
Ⅳ	8	1(12.5)	2(25.0)	3(37.5)	2(25.0)	3(37.5)	
Histology							
Squamous cell carcinoma	19	3(15.8)	7(36.8)	7(36.8)	2(10.5)	10(52.6)	$p>0.05$
adenocarcinoma	15	1(6.7)	5(33.3)	4(26.7)	5(33.3)	6(40.0)	
In summary	34	4(11.8)	12(35.3)	11(32.4)	7(20.6)	16(47.1)	

Table 2 The efficacy and its affect factors in low dose density chemotherapy

the affect factors	case number	CR number(%)	PR number(%)	SD number(%)	PD number(%)	RR number(%)	*P*
Therapy condition							
Untreated	11	2(18.2)	4(36.4)	3(27.3)	4(18.2)	6(54.5)	$p>0.05$
pretreated	26	2(7.7)	11(42.3)	9(34.6)	2(15.4)	13(50.0)	
Clinical stage							
Ⅲa	6	1(16.7)	3(50.0)	1(16.7)	1(16.7)	4(66.7)	$p>0.05$
Ⅲb	21	2(9.5)	9(42.9)	7(33.3)	3(14.3)	11(52.4)	
Ⅳ	10	1(10.0)	3(30.0)	4(40.0)	2(20.0)	4(40.0)	
Histology							
Squamous cell carcinoma	21	3(14.3)	9(42.9)	7(33.3)	2(9.5)	12(57.1)	$p>0.05$
adenocarcinoma	16	1(6.3)	6(37.5)	5(31.3)	4(25.0)	7(43.8)	
In summary	37	4(10.8)	15(40.5)	12(32.4)	6(16.2)	19(51.4)	

Table 3 The serious toxicity and side effect in HDIC and LDDC group

Serious toxicity and side effect	Ⅲ		Ⅳ		Ⅲ+Ⅳ		*P*
	HDIC	LDDC	HDIC	LDDC	HDIC	LDDC	
	Num(%)	Num(%)	Num(%)	Num(%)	Num(%)	Num(%)	
neutropenia	12(13.5)	5(13.5)	9(26.5)	2(5.4)	21(61.8)	7(18.9)	$P<0.005$
Thrombocytopenia	11(32.4)	4(10.8)	5(14.7)	1(2.7)	16(47.1)	5(13.5)	$P<0.005$
Anemia	7(20.6)	3(8.1)	6(17.6)	0(0.0)	13(38.2)	3(8.1)	$P<0.005$
Nausea and vomitting	12(35.3)	2(5.4)	6(17.6)	0(0.0)	18(52.9)	2(5.4)	$P<0.005$
diarrhea	10(29.4)	2(5.4)	7(20.6)	0(0.0)	17(50.0)	2(5.4)	$P<0.005$
alopecia	28(82.4)	26(70.2)	6(17.6)	5(13.5)	34(100.0)	31(83.8)	$P>0.5$
hypersensitiviy	2(5.9)	4(10.8)	1(2.9)	0(0.0)	3(8.8)	4(10.8)	$P>0.9$

Table 4 The changes of life quality in HDIC group and LDDC group (KPS score)

score	HDIC group (34 cases)		LDDC group (37 cases)	
	Before treatment	After treatment	Before treatment	After treatment
100 points	1	3	1	5
90	2	5	3	8
80	1	4	2	5
70	4	6	3	7
60	26	9	28	8
50		2		3
40		3		1
30				
20				
10				
0		2		
Average point/case	64.7	66.2	65.4	75.1

DISCUSSION

Aout the antineoplastic therapy model and the criterion of efficacy evaluation.

In the past long time, the reduction of tumor volume was taken as the single criterion to evaluate the antineoplastic therapy. So the radical en-blos operation, the high dose impulsion chemotherapy and the high dose large field radiation were prevailing in the clinical work. These therapies usually got good effects according to the old criterion, for they really reduced the tumors volume acutely. But these therapies usually brought several acute complications and sequelas, the patients´ life qualities were very bad. The mortality rate of these therapies was 2-8% [1,2].

With the change of medical science model, people began to value the function preservation and the improvement of life quality. The efficacy evaluation criterion were devised and complemented, the most important was that the quality of life had been added in[3,4]. One single life includes life span and life quality. The life span can calculate, but the life quality is difficult to quantitate. Several life quality evaluation systems had been used in the clinic, like the Karnofsky performance status (KPS 1948)[5], the functional living index-carcen (FLIC, Schipper, 1984)[6], the cancer rehabilitation evaluation system (CARES, Schag, 1990)[7].

In this study, we used the KPS to evaluate the changes of patients´ life quality in the two groups after the chemotherapy, which was shown in table 4. The life indexes of the two groups were increased, 1.5 points in HDIC group and 9.7 points in LDDC group averagely, in addition, there were 2 cases of chemotherapy-related death in HDIC group, we think that the LDDC not only have better therapy efficacy but also can improve the quality of life better.

Basic research of low dose density chemotherapy Pharmacodynamic research

The therapeutic effects of chemotherapy drugs are positively related to the dose and the therapy time in certain extent [8]. We usually use the DI (dose intensity)[9] to evaluate the therapeutic effect of certain kind of drugs. We use the dose of chemotherapy drug divided the use-span to calculate. The unit is mg/m^2*w, that is the dose the patient accepted every week every body surface. The DI takes both the dose and the use span into account. So it is objective to use DI to evaluate the drug effect. The method to calculate the DI: the whole dose used in one course divided the during week numbers in one course. The week numbers should include both the treating course and the intervals. There are 3 kinds of methods to increase the DI: ① increase the drug dose level. ② decrease the duration of one course. ③ both of the above. Accordingly, there are 2 kinds of chemotherapy methods in clinic: high dose impulsion chemotherapy and low dose density chemotherapy [10]. The HDIC can get high peak plasma con-

centration and have strong tumor cell cytotoxic effect. But it also has acute toxicity and side effect, especially the marrow suppression. It often needs strong support therapies. The LDDC is to use fixed effective low dose in short period. That is the model of low dose, high frequency and short interval. The basis of this kind of chemotherapy method is that the tumor cell cytotoxic effects of chemotherapy drugs obey the first-order kinetic process. Simply increase the drug dose can only increase the cytotoxic ratio of the tumor cells. There will be a number of tumor cells remained. The remained tumor cells will propagate in the chemotherapeutic interval. The propagate of solid tumors obey the Gomppertzian model [11]. That is the doubling time will become shorter and shorter with the decrease of the tumor volume. The LDDC shorten the chemotherapeutic interval, that is to say, decrease the propagate time of the remained tumor cells. Although low dose only get low cytotoxic effect every time, high frequency and short interval will increase the whole cytotoxic ratio[12].

Although the dose we use in LDDC is small, we can increase the drug use frequency to increase the actual DI[13]. In our study, the DI in the HDIC group were 25-26.7 mg/m^2*w for taxotere and 26.7-33.3 mg/m^2*w for cisplatin; the DI in the LDDC group was 25 mg/m^2*w for taxotere and 40-60 mg/m^2*w for cisplatin. This is the theoretic comparison. In fact in clinic, because of the serious toxicity and side effect, the HDIC group was difficult to accept the next chemotherapy course after designed interval. In our study, the chemotherapy intervals of the HDIC group were 4-6 weeks and 6 weeks were dominant. So the real DI of the HDIC group decreased one half than that of the theoretic. That is the pharmacologic basis of our study. Abu-rustum had reported that the effective remission rate of weekly chemotherapy regimen was still about 28.9% after the failure of monthly chemotherapy regimen [14].

Cell and molecular biology research of taxotere

The taxotere is the commodity name of doxatel. It is the second kind of semi-synthetic docetaxel derivant used in clinic. On one hand, it can prompt the polymerization of the microtubule and suppress the depolymerization by the adhesion of the β-tubulin. So the splitting of the spindle will be stopped. The mitosis will be stopped in the M stage, which will lead to the death of the cell. The test in vitro has show that this activity of the taxotere is 1.3-12 folds as that of the docetaxel, and the IC50 of taxotere is 9 folds lower than the docetaxel[15,16]. On the other hand, taxotere can activate the phorylation of the apoptosis–suppressing gene Bcl-2, which will lead to the dysfunction of this gene[17]. Studies have shown that the pharmacologic effects of toxatere were different in different concentration. In high concentration it dominantly shows cytotoxic effect but in low concentration it dominantly induce the tumor cell apoptosis. So we can find the appropriate concentration that it can induce the tumor cell apoptosis but have no cytotoxic effect to the normal cells.

The dose and the duration of low dose density chemotherapy of taxotere cisplatin regimen

In the LDDC group, although the dose is low, the drug concentration must be above the minimum effective concentration. Although the toxicity and side effect are very little, the patient can´t be treated with the LDDC without interval. To get the best regimen, the dose and the duration must be studied very clearly. In the weekly toxatere cisplatin treatment tests [18–22], the dose of toxatere is 20–25mg/m^2 every week and the dose of cisplatin is 20-40mg/m^2 every week. There had no serious hematology toxicity after 6-8 weeks treatment consecutively. If increase the dose to 30mg/m^2 every week, the serious toxicity will show out, and the maximum tolerant dose (MTD) is 40-45mg/m^2, the recommend dose is 25-40mg/m^2 every week, recommend duration is 6 weeks consecutively. Use this regimen to treat advanced NSCLC (Ⅲ + Ⅳ stage), the response rate is 31.8-52.6%, median response duration is 4-7 months, 1-year survival rate is 35-58%, the serious hematology toxic side-effect rate is 17.4-52.6%, and have no chemotherapy–related death. In the high dose chemotherapy test[23–29], the MTD is 80-115mg/m^2 every 3 weeks. Use the dose 71-94mg/m^2, 52% patients will have Ⅳ stage hematology toxic side-effect, use the dose 95-105mg/m^2, the incidence will increase to 80%. The chemotherapy-related death rate is 2-4.3%, the effective remission rate is 31.9-58.7%, median remission period is 7.9 months (1.9-15.9), 1-year survival rate is 35-48%, and the recommend dose is 75-100mg/m^2 every 3 weeks.

To improve the methods of hormone preconditioning

The most serious problem of using taxotere is the hypersensitivity reaction. The incidence of hypersensitivity reaction was 18.9%-22.6%. The incidence of Ⅲ-Ⅳ grade acute hypersensitivity reaction was 6.6%[30–32]. The symptoms of hypersensitivity reaction include the dropping of blood pressure, bronchosapsm and the urticaria. To prevent the hypersensitivity reaction, the hormone preconditioning was routinely done before the transfusion of taxotere. There were two kinds of routine method. One was taking dexone (dexamethasone) 20mg orally 12 hours and 6 hours before taxotere transfusion; The other was taking dexone (dexamethasone) 16mg orally 3-5 days before taxotere transfusion and benadryl (diphenhydramine) 40mg intramuscularly injection, cimitidine 300mg intravenous injection 30 minutes before taxotere transfusion. According to the routine methods, the patient must take large amount of dexone (dexamethasone) orally and the duration is too long. It is not very convenient to patients, especially to the LDDC group patients. In this study, the hormone preconditioning was used by the reformed and simplified method: 1 hour before the taxotere transfusion, dexone (dexamethasone) 10mg added in 500ml of 10% glucose began to transfuse. So the patients will go into the immunosuppression stage in advance. And 30 minutes after, dexone (dexamethasone) 10mg, were added into the injection. This will add the immunosuppression effect. This method is very convenient. In this study after using this method, the incidence of hypersensitivity reaction is 8.8% in HDIC group and 10.8% in LDDC group. The incidence of hypersensitivity have no change, but the serious(Ⅲ-Ⅳ grade) hypersensitivity reaction have dropped evidently. According to the studies before[33–35], when the hypersensitivity reaction happens, the transfusion of taxotere must be stopped immediately and the patients must get oxygen inspiration and antispastic diaposal. After the hypersensitivity reaction of the patients ameliorate, the three kinds of agents as mentioned above is given and go on transfusing taxotere slowly with serious inspection. In this study, all the patients with the hypersensitivity reaction are disposed according the method above and get taxotere transfused successfully.

In this study, there are many cases survived more than 1 year, and even several cases more than 2-3 years. We didn´t analysize the 2-year survival rate and the 3-year survival rate. The reason was that most of these cases had other treatments 1 year after the chemotherapy. And some studies had found that the effects of chemotherapy to the survival period were evident in the first 6 months (23, 36). One research of the US Department of Health Services (37) had shown that the 5-year survival rate was not dependable in the evaluation of antineoplastic effects.

In the summary, we found that the LDDC had better efficacy, slighter toxicity and could improve the quality of life better in the treatment of advanced NSCLC.

REFERENCE

1. Xu Guangwei. The retrospect and prospect of tumor prevention and therapy in our country. Chinese Journal of Clinical Oncology. 2001, 28(3): 165–168.
2. Guan Zhongzhen. The chemotherapy of neoplasm. In: Zhang Tianze, Xu Guangwei, editors. Oncology. fist edit. TianJin: TianJin science and technology publishing house, 1996, 712–759.
3. Wang Chonghua, Zhang Canzhen, Song Yuanlong. The research on measurement for quality of life in patients with lung cancer. Bulletin of Chinese Cancer, 2001, 10 (2): 83–85.
4. Shi Chunlei, Liao Meilin. To emphasize the life quality of lung cancer patients. Chinese Journal of Oncology, 2002, 24(5): 519–520.
5. Ganz PA, Haskell CM, Figlin RA, et al. Estimating the quality of life in a clinical trial of patients with metastatic lung cancer using the Karnofsky perfarmance status and the Functional living Index–Cancer. Cancer, 1988, 61(4): 844–856.
6. Schipper H, Clinch J, McMurray A, et al. Measuring the quality of life of cancer patients: the functional living index-carcen: development and Valiation. Journal of Clinical Oncology,1984, 2(5): 472–483.
7. Schag CAC, Heinrich RL. Development of a comprehensive quality of life measurement tool:CARES. Oncology, 1990, 4: 135–138.
8. Feng Fengyi, Zhou Aiping. Dose intensity and high dose chemotherapy in the treatment of breast cancer. Chinese Journal of Oncology, 2002, 24(2): 200–202.
9. Hryniuk WM. The importance of dose intensity in the outcome of chemotherapy. J B Lipincott, 1988:121–142.
10. Fountzilas G, Papadimitriou C, Aravantinos G, et al. Dose–dense sequential adjuvant chemotherapy with e quirubicin, peclitaxel and CMF in high-risk breast cancer. Oncology, 2001, 60: 214–222.
11. Norton L. Evolving concept in the systemic drug therapy of breast cancer. Semin Oncol, 1997, 24 (10): S10–3.
12. Seidman AD, Hudis CA, Albanel J, et al. Dose–dense therapy with weekly 1-hour paclitaxel infusion in the treatment of metastatic breast cancer. J Clin Oncol, 1998: 3353–3361.

13. Finneelly D, Aghajanian C, Shapiro F, et al. Phase I and pharmacologic study of paclitaxel administered week ly in patients with relapsed ovarian cancer. J Clin Oncol, 1997, 15:187–192.
14. Abu–Rustum NR, Aghajanian C, Barakat RR, et al. Salavage weekly paclitaxel in recurrent ovarian cancer. Semin Oncol. 1997, 24(S15): 62–27.
15. Huang Zhaoming. Clinical advance of docetaxel in treat–ment of non–small cell lung cancer. Foreign medical sciences, cancer section. 2002, 29(1): 47–49.
16. Adjei AA, Argiris A, Murren JR. Docetaxel and irinote–can, alone and in combination, in the treatment of non–small cell lung cancer. Semin Oncol, 1999, 26(S16): 32–40.
17. Haldar S, Basu A, Croce CM. Bcl–2 is the guardian of microtubule integrity. Cancer Res, 1997, 57: 229–233.
18. Hainsworth JD, Burris HA, Litchy S, et al. Weekly docetaxel in treatment of elderly patients with advancer non–small cell lung carcinoma. Cancer, 2000, 89(2): 328–333.
19. Zhang Yu, Yu Lizhi, Chen Wenping. Combination chemotherapy with docetaxel and cisplatin in weekly schedule in the treatment of 30 cases of advanced non-small cell lung cancer, Chinese Journal of Lung Cancer. 2001, 4(3): 197–199.
20. Hainsworth JD, Barris HA, Erland JB, et al. Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. J Clin Oncol, 1998, 16(7): 2164–2168.
21. Burris H. Weekly schedules of docetaxel. Semin Oncol, 1998, 25(2S13): 21–23.
22. He Yong, Feng Fengyi. Current status of chemotherapy for advanced non–small cell lung cancer. Chinese Journal of Lung Cancer. 2001, 4(3): 207–210.
23. Liu Hao, Hou Mei, Zhu Jiang, et al. Combination chemotherapy of docetaxel and cisplatin totreat non-small cell lung cancer. Chinese Journal of Lung Cancer, 2002, 5(5): 352–353.
24. Lechaevalier T, Berille J, Zalcberg JR, et al. Overview of docetaxel cisplatin combination in non-small lung cancer. Semin Oncol, 1999, 2693S11): 13–18.
25. Zhang Li, Wu Haiying, Guan Zhongzhen. A phase II study of docetaxel for advanced non-small lung cancer. The practical journal of cancer. 2000, 1594): 420–423.
26. Jiang Liyan, Liao Meilin. The chemotherapy progress of non-small lung cancer. Journal of Practical Oncology. 2001, 16(4): 225–227.
27. Liao Meilin, Zhao Yizhuo. The status and progress of the non-small cell lung cancer therapy. Chinese Journal of Lung Cancer, 2001, 4(3): 161–164.
28. Zalcberg J, Millward M, Bishop J, et al. Phase II study of docetaxel and cisplatin in advanced no9n-small cell lung cancer. J Clin Oncol, 1998, 16(5): 1948–1953.
29. Georgoulias V, Androualakis N, Dimopoulos AM, et al. First–line treatment of advanced non-small cell lung cancer with dacetaxel and cisplatin: a multicenter phase II study. Ann Oncol, 1998, 9: 331–334.
30. Chen Yumin, Liu Jiwei, Zhang Jie, et al. Clinical observation of taxotere plus TPH-adri-amycin in treatment of advanced breast cancer. Chinese Journal of Clinical Oncology. 2002, 29(1): 40–41.
31. Li Yusheng, Zhang Xiaodong, Cui Chengxu, et al. A case report of serious hypersensitivity of taxotere. Journal of Practical Oncology. 2000, 15(6): 424–425.
32. Wu Shikai, Song Santai, Liu Xiaoqing, et al. A case report of serious hypersensitivity of taxotere. Chinese journal of oncology. 2001, 23 (4): 329.
33. Weiss RB, Donchower RC, Wiernik PH, et al. Hypersensitivity reaction for docetaxel. J Clin Oncol, 1990, 8(7): 1263–1268.
34. Olson JK, Sood AK, Sorosky JI, et al. Taxol hypersensi-tivity: rapid retreatment is safe and cost effective. J Gynecol Oncol, 1998, 68(1): 25–28.
35. Tang Shuiqin. A case report of docetaxel reperfusion after hypersensitivity. China Oncology, 2001, 11(6): 576.
36. Soquet PJ Chauvin F, Boissel JP, et al. Poly chemotherapy in advanced non–small cell lung cancer: a meta analysis. Lancet. 1993, 342(1): 19–21.
37. Fan Zhen. Translate. Is the 5–year survival rate useful to evaluate the antineoplastic efficacy? JAMA, 2001, 20(3): 115–118.