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A CLINICAL REPORT OF REFRACTOTY CARCINOMA OF OVARY AND FALLOPIAN TUBE TREATED WITH TAXOL

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From September 1993 through March 1994, 30 cases of refractory carcinoma of the ovary and Fallopian tube were treated with Taxol. Complete response was seen in 4 and partial response in 8 cases with a response rate of 40%. The average length of remission was 5 months in CR and 3.9 months in PR. The major toxic side effect was decrease in total white cell count and in neutrophil count. Apart from flushing of face during Taxol infusion in 6 patients, no other allergic reaction was observed. Gastrointestinal, neurologic, liver and renal toxicities were mild. Taxol is a drug of choice in the treatment of patients with cancer of the ovary and Fallopian tube who are resistant to conventional chemotherapy.

Key word: Ovarian cancer, Fallopian tube carcinoma, Taxol.

Based on the phase I and II studies of Taxol, it is demonstrated that Taxol inhibit mitosis during cell proliferation with its unique anticancer mechanism, and it is surely effective to refractory cancer of ovary, breast, and lung, etc. From Sep. 1993 to Mar. 1994, 30 cases of refractory carcinoma of ovary and fallopian tube were treated with Taxol (provided by the Bristol-Myers Squibb Company). The method and results were summarized as follows:

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CLINICAL MATERIALS

Inclusion Criteria

Histologically proven epithelial carcinoma of the ovary or fallopian tube;

The patient has previously received chemotherapy regimen containing cisplatin or carboplatin with no effect;

The measurable and/or evaluable tumor clinically and/or radiologically documented;

The patients have not received chemotherapy, radiation, hormonal therapy for at least 6 weeks;

The patient has an ECOG performance status of 0, 1 or 2 or Karnofsky performance status > 60% and a life expectancy > 12 weeks;

Normal haematological tests (except haemoglobin), ECG, tests of liver and kidney functions.

In this group, 27 cases treated in Cancer Hospital, Shanghai Medical University; 3 cases in International Peace Children Health and Maternity Hospital. The average age was 51.6 yr. (23–73 yr.).

Pathological Diagnosis

All the 30 cases were pathologically diagnosed as epithelial carcinoma of the ovary or fallopian tube including 15 ovarian adenocarcinomas, 7 serous cystadenocarcinomas, 1 mucinous cystadenocarcinoma, 2 endometroid adenocarcinomas, 1 clear cell carcinoma and 4 carcinomas of fallopian tube.

Clinical Manifestation

Tumor Site

All cases in this trial were relapsed after prior chemotherapy or multi-drug resistant. Most of the tumors, totally 25 cases, were confined to pelvis. In addition, 3 cases metastases to abdominal cavity, liver and groin, respectively. 2 cases extended to abdominal para-aorta, 1 case has metastasis to lung, thoracic vertebrae, abdominal wall and left supraclavicular lymph nodes respectively.

Tumor Size

Cases with multi-tumor were measured by the maximum diameter of the biggest tumor. Maximum diameter of tumor less than 5 cm, 7 cases; 5–10 cm, 18 cases; more than 10 cm, 5 cases.

Previous Chemotherapy

Number of Prior Chemotherapy Regimens

8 cases (26.7%) were treated by one chemotherapy regimen, 12 cases (40.0%) by two regimens, and 10 cases by three or more regimens.

Number of Resistant Drugs

Less then 3, 2 cases; 3–4, 13 cases; more than 5, 15 cases. Half of the patients resisted to 5 or more anti-cancer drugs.

Treatment Schedule with Taxol

Pre-medication

All patients were premedicated with Dexamethasone 20 mg, PO, at 12 and 6 hour prior to administration Taxol, Diphenhydramine 50 mg, PO, and Cimetidine 300 mg, IV, respectively, 30 minutes prior to Taxol.

Taxol Dosage and Administration

The dose of Taxol was determined by the number of previous regimens of chemotherapy: 175 mg/m^2 for the patients treated by 1 or 2 previous regimens; 135 mg/m^2 for the patients treated with 3 or more previous regimens. Taxol should be administered by 3 hours, IV, continuous infusion every 3 weeks in dextrose or normal saline (NS). A concentration of 1.2 mg/ml should not be exceeded.

RESULTS

Criteria for Evaluation

Response Evaluation

Complete response (CR): Disappearance of all clinical evidence of tumor, determined by two observa-tions not less than four weeks apart.

Partial response (PR): Estimated decrease in tumor size of 50% or greater, determined by two observations not less than 4 weeks apart. There may be no appearance of new lesions for this category. Stable disease (SD): No significant change for at least four weeks. This includes stable disease, estimated decrease of less than 50%, and lesions with estimated increase of less than 25%.

Progressive disease (PD): Appearance of any new lesions not previously identified or estimated increase of 25% or more in existing lesions.

Toxicity Evaluation

Based on the WHO standard to evaluate toxicities.

Response Rate

Based on the Taxol protoxol, 30 cases with advanced and platinum resistant cancer of ovary and fallopian tube were enrolled into the Taxol trial. Totally 119 courses of treatment were conducted. In average, 3.9 courses (1–8 courses) were given to each case including 4 cases less than 3 courses, 20 cases between 3 to 6 courses and 6 cases more than 6 courses. Followed up by the end of Jun. 1994, CR 4 cases, the mean duration of remission was 5 months; PR 8 cases, the mean duration of remission was 3.9 months.

From Table 1, CR+PR is 40% (12/30) in which cases with fallopian adenocarcinoma and serous cystadenocarcinoma showed the best response, then the patients with ovarian adenocarcinoma, but worse response were found in those patients with mucinous

cystadenocarcinoma, endometroid adenocarcinoma and clear cell carcinoma.

The serum CA125 decreased paralleling with disease remission after Taxol therapy. The values declined to the normal range in 9 of 12 cases that reached their CR or PR.

Toxicity

Heamatologic Toxicity

As shown in Table 2, WBC, ANC, haemoglobin and platelet were examined, when reaching their nadir in each cycle of Taxol treatment. Taxol affects WBC count, which decreased to Grade I in 8 cases, Grade II in 11 cases, Grade III in 9 cases. For ANC, it was declined to Grade III in 4 cases and Grade IV in 5 cases. Generally, the WBC and ANC reached nadir in the 9th day after the Taxol infusion and recovered in two to three days. Referring to 119 total treatment cycles, the Grade III toxicity to WBC was 7.5% (9/119). As for ANC, the Grade III and IV toxicities were 4.2% (4/119). In the terms of toxicity to haemoglobin, 3 cases (10%) in Grade III and 2 cases

Table 1. Response rate in patients with ovarian and fallopian tube carcinoma

Pathological classification	Cases	Response rate				CR+PR cases (%)
		CR	PR	SD	PD	
Carcinoma of fallopian	4	2	1		1	3 (75)
Carcinoma of ovary serous cyst-adenocarcinoma	7	1	4	1	1	5 (71.4)
Ovarian adenocarcinoma	15	1	3	6	5	4 (26.6)
Mucinous cyst-adenocarcinoma	1				1	0 (0)
Endometroid adenocarcinoma	2			1	1	0 (0)
Clear cell carcinoma	1				1	0 (0)
Total	30	4	8	8	10	12 (40)

Table 2. Toxicities of Taxol (I)

Grade	0 cases (%)	I cases (%)	II cases (%)	III cases (%)	IV cases (%)	III+IV cases (%)
Haematology						
HB	8 (26.7)	2 (6.7)	15 (50)	3 (10)	2 (6)	5 (16.6)
WBC	2 (6.6)	8 (26.7)	11 (36.7)	9 (30)	0 (0)	9 (30)
ANC	8 (26.7)	6 (20)	7 (23.3)	4 (13.3)	5 (16.7)	9 (30)
PI	28 (93.4)	1 (3.3)	1 (3.3)	0 (0)	0 (0)	0 (0)
Liver and renal						
Creatinine	27 (90)	3 (10)	0 (0)	0 (0)	0 (0)	0 (0)
Bilirubin	29 (96.7)	1 (3.3)	0 (0)	0 (0)	0 (0)	0 (0)
AKP	30 (100)	1 (3.3)	0 (0)	0 (0)	0 (0)	0 (0)
ALT	28 (93.4)	1 (3.3)	1 (3.3)	0 (0)	0 (0)	0 (0)
EKG	30 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

(6.7%) in Grade IV. The average heamoglobin nadir was occurred in the 12th day after Taxol infusion. If it was calculated by the total 119 treatment cycles, Grade III and IV toxicity was 4.2% (5/119) and 1.6 (2/119) respectively. In this series, no patient was delayed for the Taxol trial because of the decreasing of WBC or PT.

Hypersensitivity

6 patients (20%) encounted mild flushing during the Taxol infusion (Table 3) and the symptom lasted for one to two days without any treatment. No other hypersensitive reaction occurred in this trial.

Gastrointestinal Toxicity

The toxicity was represented as anorexia, nausea and vomiting, abdominal distension, abdominal pain which were mostly Grade I and some Grade II (Table 3). The symptoms lasted for about 1 to 2 days and wee relieved by expectant treatment.

Table 3. Toxicities of Taxol (II)

Grade	0 cases (%)	I cases (%)	II cases (%)	III cases (%)	IV cases (%)	III+IV cases (%)
Anorexia	17 (56.7)	12 (40)	1 (3.3)	0 (0)	0 (0)	0 (0)
Nausea & vomiting	24 (80)	6 (20)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhoea	24 (80)	4 (13.4)	1 (3.3)	1 (3.3)	0 (0)	1 (3.3)
Alopecia	0 (0)	4 (13.4)	1 (3.3)	25 (83.3)	0 (0)	25 (83.3)
Numbness	8 (26.7)	18 (60)	4 (13.3)	0 (0)	0 (0)	0 (0)
Fever	18 (60)	6 (20)	6 (20)	0 (0)	0 (0)	0 (0)
Fatigue	17 (56.7)	4 (13.4)	4 (13.4)	1 (3.3)	0 (0)	1 (3.3)
Edema	27 (90)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal pain	13 (43.3)	12 (40)	5 (16.7)	0 (0)	0 (0)	0 (0)
Arthralgia	3 (10)	23 (76.7)	4 (13.4)	0 (0)	0 (0)	0 (0)
Myalgia	25 (83.4)	3 (10)	1 (3.3)	1 (3.3)	0 (0)	1 (3.3)
Abdominal distension	24 (80)	3 (10)	3 (10)	0 (0)	0 (0)	0 (0)
Flushing	24 (80)	6 (20)	0 (0)	0 (0)	0 (0)	0 (0)

Neurological Toxicity

The occurrence of this toxicity is very high, representing as slight numbness of fingers and feet in 22 cases, fatigue in 13 cases, arthralgia in 27 cases and myalgia in 5 cases. All these symptoms except numbness disappeared in 4 to 5 days.

Liver, Renal and Cardiac Toxicity

ALT increased in 2 cases including accompanied total bilirubin increasing in 1 case. Additionally, increased creatinine was observed in 3 cases. No cardiotoxicity was found in this series.

Others

Alopecia has been observed in all the patients, mostly Grade III (Table 3). Fever without infection was occurred in 12 cases. Edema was found in 3 cases.

DISCUSSION

Several authors[1-6] have demonstrated that Taxol was effective to the refractory ovarian cancer including those resistant to cisplatin or carboplatin. In this series, all the 30 cases were carcinoma of the ovary or fallopian tube that were reluctant to several drugs including cisplatin or carboplatin. The results showed a good response rate that were CR 13.3% (4/30), PR 26.7% (8/30) and thus CR+PR 40%. The results is similar to Mcguire, Thigpen's report (30–40%).[3,4] In addition, the patients could tolerate well with toxicities caused by Taxol after pre-medicated

with Dexamethasone, Diphendramine and Cimetidine.

Apart from flushing of face during Taxol infusion in 6 patients, no other allergic reaction was observed. Gastrointestinal, neurologic, liver and renal toxicities were mild. The old and advanced cases could tolerate as well.

From above, Taxol with its higher overall response rate and low toxicity is a good drug for the treatment of refractory ovarian cancer.

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