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Original Article

Phase I Trial of Escalating-dose Cisplatin with 5-fluorouracil and Concurrent Radiotherapy in Chinese Patients with Esophageal Cancer

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We defined the maximum-tolerated dose (MTD) of chemoradiotherapy (cisplatin (CDDP) with 5-fluorouracil (5-FU) and concurrent chemoradiotherapy) for Chinese patients with esophageal cancer. Twenty-one previously untreated patients with primary esophageal cancer were entered into this study. Escalating doses of CDDP with 5-FU were administered in a modified Fibonacci sequence, with concurrent conventional fractionation radiotherapy (CFR) of 60 Gy or 50 Gy. The starting doses were CDDP 37.5 mg/m^2 on day 1, and 5-FU 500 mg/m^2 on days 1–5, respectively. The regimen was repeated 4 times every 28 days. If no dose-limiting toxicity (DLT) was observed, the next dose level was applied. The procedures were repeated until DLT appeared. The MTD was declared to be 1 dose level below the level at which DLT appeared. DLT was grade 3 radiation-induced esophagitis at a dose level of CDDP 60 mg/m^2 with 5-FU 700 mg/m^2 and concurrent 60 Gy CFR. MTD was defined as CDDP 52.5 mg/m^2 with 5-FU 700 mg/m^2 and concurrent 50 Gy CFR. The MTD of CDDP with 5-FU and in concurrent chemoradiotherapy for Chinese patients with esophageal cancer is CDDP 52.5 mg/m^2 on day 1 and 5FU 700 mg/m^2 on days 1–5, repeated 4 times every 28 days, and concurrent 50 Gy CFR. Further evaluation of this regimen in a prospective phase II trial is ongoing.

Key words: esophageal neoplasm, concurrent chemoradiotherapy, cisplatin, 5-fluorouracil, dose escalation

Esophageal cancer is the 8th most common cancer worldwide, with 462,000 new cases per year, and the 6th most common cause of death from cancer, with 386,000 deaths in 2002 [1]. The age-standardized incidence rate in China was the highest in the world [1] At present, esophageal cancer remains an aggressive, malignant neoplasm with dismal prognosis. Patients undergoing surgery alone had a median survival ranging from 13 to 19 months and a 5-year survival rate of 15% to 24% [2]. The 5-year survival rate with conventional doses of radiation alone is 0% to 10% [3].

Since the results of RTOG85–01 were reported, concurrent chemoradiotherapy was considered to be

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the standard therapy for local advanced esophageal cancer [4, 5]. However, different schemas have been adopted in different countries. The schema used in America is a protocol of 50 Gy/25 fractions, 2.0 Gy/fraction, CDDP 75 mg/m^2 d1, and 5-Fu 1,000 mg/m^2 d1-d4. A modified schema is used in Japan: 60 Gy/30 fractions, 2 Gy/fraction, with an interval of 7 days after 30 Gy, CDDP 70 mg/m^2 d1, and 5-Fu 700 mg/m^2 d1-d5. There are no standard schemas in China, and different schemas have led to different survival results [6–9]. The classical schema in RTOG is widely used because of its good survival results [4, 5]. However, therapy-induced side effects were severe at the same time. Herskovic *et al.* [4] reported that the rates of severe and life-threatening side effects were 44% and 20%, respectively, and 2% of deaths were observed to be iatrogenic. Supportive therapy in China is not comparable with that in America because of economic issues. This difference, together with racial differences, makes it unclear whether the schema used in RTOG is suitable for Chinese patients. The purpose of our escalation trial is to search for a suitable schema for Chinese patients with esophageal cancer. At present, the cost of concurrent chemoradiotherapy is less than that of surgery in China. Moreover, the quality of life of patients who received chemoradiotherapy is better than that of the patients who underwent an operation. If we can prove the efficiency of radiotherapy with concurrent cisplatin and 5-flurouracil chemotherapy, it would be clinically meaningful in China, where the incidence of esophageal cancer is the highest in the world. Now we are planning a phase II trial based on the results of this phase I trial. Thus, different strategies for treating esophageal cancer have been adopted in China than in Western countries due to their different cultures and economies [10].

In China, late-course accelerated fractionation radiotherapy (LAFR) alone is widely used [11, 12], and has results comparable to surgery. LAFR was performed as follows: Patients received conventional fractionation radiotherapy, at 2 Gy/fraction, to a dose of 30 Gy in 15 fractions over 3 weeks, followed by accelerated fractionation radiotherapy, twice a day, at 1.5 Gy/fraction, with a minimal interval of 6 h between fractions, and the overall treatment time was 5 weeks. The total dose was 60 Gy. Shi *et al.* [11] and Han *et al.* [12] have reported 33% and 32% 5-year survival rates with the use of LAFR, respectively. With controversial survival results [6–8, 13], the role of concurrent chemoradiotherapy in China has not been confirmed.

In this study, we conducted a Phase I clinical trial of chemoradiotherapy consisting of cisplatin (CDDP) with 5-fluorouracil (5-FU) and concurrent conventional fractionation radiotherapy (CFR) in advanced esophageal carcinomas.

Materials and Methods

Eligibility. The 5-year survival rate for concurrent chemoradiotherapy in RTOG85–01 was 26%, which was comparable with that of the surgery. The eligibility criteria in RTOG85–01 included clinical phase II patients. Moreover, the quality of life in patients who received chemoradiotherapy was better than that of the patients who underwent an operation. Upon notification of the above issues, patients themselves decided whether to receive chemoradiotherapy or surgery.

Patients (aged $\geqq$18 years and $\leqq$70 years) with primary esophageal squamous cell carcinoma proven by histology and staged by thoracoabdominal helical computed tomography (CT) (T2–4, N0–1, M0–1) were eligible for this study. Due to the fact that endoscopic ultrasound was not available in our center, we evaluated clinical staging based on CT scans [14]. The T stage was defined by the maximal transverse diameter of the esophageal tumor: T1 $\leqq$ 2 cm, T2 $>$ 2 cm and $\leqq$ 4 cm, T3 $>$ 4 cm. Tumors indicating an invasion of any adjacent structures were classified as T4. If the minimal transverse diameter of the lymph nodes, in mediastinal and celiac, was larger than 1 cm, the lymph nodes were classified as N1; otherwise, they were classified as N0. Patients should not have received any prior radiotherapy or chemotherapy. All patients were requested to have a Karnofsky performance status $\geqq$ 60. The required laboratory tests included a neutrophil count $\geqq 2.0 \times 10^9$/L, a platelet count $\geqq 100 \times 10^9$/L, a hemoglobin count $\geqq$ 100 g/L, and serum creatinine, aspartate aminotransferase, alanine aminotransferase, and a total serum bilirubin $\leqq$ the upper limits of normal. The exclusion criteria consisted of any of the following: pregnancy; lactation; tracheoesophageal fistula; a history of other malignancies, with the exception of carcinoma *in situ* of the cervix, nonmelanomatous skin

cancer, and cancer from which the patient had not been disease-free for 5 years; a general medical condition preventing combined modality therapy; and a known hypersensitivity to CDDP or 5-FU; as well as any use of a concurrent antineoplastic therapy. The procedures were approved by the Ethics Committee of Hebei Medical University and were performed in accordance with the ethical standards of human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. All patients provided written informed consent.

Pretreatment evaluation. Pretreatment evaluation included medical history, complete physical examination, barium esophagraphy, chest and abdominal helical CT scan, upper gastroesophageal endoscopy, electrocardiography, bronchoscopy and bone marrow scan (if clinically indicated), complete blood count, and biochemical profile. These pretreatment tests were performed during the 2 weeks before treatment initiation. Patients received physical examinations, and blood counts were taken once a week or more often if necessary. A biochemical profile was obtained and electrocardiography performed before every chemotherapy cycle.

Treatment plan. The trial was designed as an open-label, nonrandomized dose-escalation study. Groups of at least 3 patients received sequentially increasing doses of CDDP and 5-FU concurrently with radiotherapy according to Table 1.

Chemotherapy. We conducted 4 chemotherapy cycles beginning on the first days of weeks 1, 5, 9, and 13. The first and second cycles were concurrent with CFR. CDDP was administered at an infusion rate of 1 mg per min on day 1, followed by a continuous daily intravenous infusion of 5-FU (at least 8 h) from day 1 through day 5. The chemoradiotherapy schema is shown in Table 2.

Radiotherapy. Radiotherapy was performed with conventional fractionation on the first day of week 1. Multifield, external-beam megavoltage radiation was delivered using 6-MeV linear accelerators. Patients were treated with 5 daily fractions of 2.0 Gy per week over a 6-week period. The total radiation dose was 60 Gy. All fields were treated each day. Treatment was given with a combination of anterior-posterior, oblique, or lateral fields, such that the dose-to-target volume did not differ from the dose specified at the isocenter by more than 10%. The administered dose was prescribed to the isodose line covering the volume at risk. Port films were taken of 2 fields per week, or more often if clinically indicated. The superior and inferior borders of the radiation field were 4 cm beyond the tumor, and the anterior, posterior, and lateral borders were 2 cm beyond the tumor, as defined by barium esophagography and CT. Wan *et al.* [15] and Minsky *et al.* [16] have reported that higher radiation doses do not result in better survival. So after we reached more than two DLTs with radiotherapy of 60 Gy, we continued to treat 6 patients at a DLT dose level equivalent to the radiotherapy schema, except with a total dose of 50 Gy. The radiation dose was reduced to 50 Gy in the level 5 dose for the following reasons. 1) At present, concurrent chemoradiotherapy is regarded as the standard regimen in patients with local advanced esophageal cancer. RTOG85–01 adopted the radiation dose

Table 1 Dose escalation schema

Dose level	Radiotherapy 2 Gy/d	CDDP mg/m^2	5-FU mg/m^2	Patient number
1	60 Gy	37.5	500	3
2	60 Gy	45	600	3
3	60 Gy	52.5	700	3
4	60 Gy	60	700	6
5	50 Gy	60	700	6

Table 2 Chemoradiotherapy schema

week	1	2	3	4	5	6	9	13
radiotherapy *	||||| |||||	||||| |||||	||||| |||||	||||| |||||	||||| |||||	|||||		
chemotherapy	X				X		X	X

*The last 6 patients received radiation treatments of 50 Gy.

of 50 Gy [4, 5]. Moreover, the subsequent trial RTOG94-05 confirmed that increasing the radiation dose did not result in an improved survival rate [16]. Thus, 50 Gy was the final radiation dose we planned to adopt. 2) At the very beginning of our study, we adopted a relatively low chemotherapy dose — half the dose in RTOG85-01. However, the radiation dose of definitive radiotherapy alone in patients with esophageal cancer is 60 Gy-70 Gy. For this reason we could not guarantee that the effect of radiation at 50 Gy plus half of the chemotherapy dose in RTOG85-01 would be at least equal to the effect of definitive radiotherapy alone with a dose of 60 Gy-70 Gy. We adopted the radiation dose of 60 Gy at the beginning of our study for reasons of medical ethics. After we reached DLT at the 60 Gy level, we reduced the radiation dose to 50 Gy in order to reduce the toxicities of concurrent chemoradiotherapy. We finally concluded the maximum-tolerated dose (MTD) at the 50 Gy dose level. 3) In our subsequent phase II clinical trial of concurrent chemoradiotherapy in patients with esophageal cancer we adopted this MTD regimen. In that trial, late-course accelerated hyperfractionation radiation with a 5-year survival rate of 33% [11] was used in the control group. The preliminary results were as follows: The 1-year local control rate and the 1-year survival rate in the concurrent chemoradiotherapy group were 90.2% and 70.4%, respectively. The comparable survival results proved the effect of the MTD regimen.

Dose escalation and definition of DLT. Concurrent chemotherapy dose escalation was performed using a modified Fibonacci sequence. Based on the significant toxicities observed in RTOG85-01 [4], we chose relatively low doses as the initial dosage: CDDP 37.5 mg/m^2 on day 1 and 5-FU 500 mg/m^2 on days 1 to 5. The regimen was repeated 4 times every 28 days. The escalation doses were CDDP7.5 mg/m^2 and 5-FU 100 mg/m^2. Every cohort contained at least 3 patients. If no dose-limiting toxicity (DLT) was observed after the completion of full-dose radiotherapy and concurrent two-cycle chemotherapy, the next dose level was applied. However, repeated administration to the same patient was not allowed. If 1 of 3 patients treated within a dose level experienced a dose-limiting toxicity, 3 additional patients were treated at the same level. If a second patient experienced the same dose-limiting toxicity, escalation was stopped and the MTD was defined as the level below the dose. In the escalation trial of phase I, one dose level below DLT was found to be safe, and its toxicities were tolerable. This dose level was defined as MTD according to the international routine [20-22].

Chemotherapy-induced toxicities were graded according to the National Cancer Institute common toxicity criteria version 2 [17], and radiotherapy-induced toxicities were graded according to the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria [18]. Dose-limiting toxicity was defined as follows: Grade 3 febrile neutropenia or any Grade 4 neutropenia, Grade 3-4 thrombocytopenia, Grade 3-4 anemia, and Grade 3-4 nonhematologic toxicity except for Grade 3 nausea, vomiting, and anorexia.

Dose attenuation. All patients were required to finish the full-dose radiotherapy and at least 2 concurrent cycles of chemotherapy or be withdrawn from this study. If Grade 3-4 thrombocytopenia, Grade 3-4 anemia, Grade 4 neutropenia, or Grade 3-4 nonhematologic toxicity occurred (except for Grade 3 nausea, vomiting, and anorexia), both RT and CDDP with 5-FU were withheld until the Grade 3 or 4 toxicities were no longer present. If this did not occur within 2 weeks, the patient was withdrawn from the study. If Grade 3 neutropenia alone or Grade 2 thrombocytopenia occurred, chemotherapy was stopped and radiotherapy continued. Chemotherapy was resumed at the same dose level when the toxicity disappeared.

Response. Patients were re-evaluated within 4 weeks after the completion of radiotherapy with concurrent chemotherapy. Thoracoabdominal helical CT, barium esophagram, and upper gastroesophageal endoscopy with biopsy were performed. Clinical responses were classified using the World Health Organization definitions of tumor response as follows. Complete response (CR) is the disappearance of all clinical evidence of active tumor. Partial response (PR) is a 50% or greater decrease in the size of the primary lesion. Stable disease (SD) is a less than 50% decrease to a 25% increase in tumor mass, with no new lesions. Progressive disease (PD) is a more than 25% increase in tumor mass or an appearance of new lesions.

Results

Patient characteristics. Between February 2005 and May 2006, 22 patients with previously untreated, histologically proven primary esophageal squamous cell carcinoma were enrolled in this trial. The patients' characteristics are listed in Table 3. One patient who only completed one cycle of chemotherapy for personal reasons was withdrawn from the trial. The other 21 patients were assessable for toxicity. Twelve patients (57%) were men and 9 (43%) were women. The median age was 63 years (46–70), and the median Karnofsky performance status was 80. 5 patients had clinical Stage IIA of the disease, while 2 had Stage IIB, 6 had Stage III, 1 had Stage IVA, and 7 had Stage IVB (6 were located at the mid-thoracic esophagus with supraclavicular lympha nodes metastasis, and 1 with bone metastasis).

Hematologic toxicity. Table 4 describes the hematologic toxicities according to dose-level cohort. Although rhG-CSF was administered in 71.4% (15/21) of patients, when the white blood count was below 4.0×10^9 and/or the absolute neutrophil count was below 2.0×10^9, the white blood count was considered to be below the lower limit of normal, the rates of leucopenia and granulocytopenia were 71.4% and 66.7%, respectively. However, most hematologic toxicities were mild to moderate. Only 9.5% (2/21) of patients experienced Grade 3 toxicity. Three DLTs occurred in 1 patient at the dose level 5 of CDDP 60 mg/m^2 with 5-FU 700 mg/m^2 after 42 Gy radiotherapy had been delivered. The nadir of the Grade 4 leucopenia, granulocytopenia, and thrombocytopenia in that patient were 0.6×10^9/L, 0×10^9/L and 8×10^9/L, respectively. Before the blood counts were recovered 24 days later, thrombocyte infusion, antibiotics, rhG-CSF, and interferon-11 were administered. Anemia was not common, and was mild when it occurred. No other hematologic DLTs occurred during the course of the study. We therefore did not presume that hematologic toxicities can define DLT.

Nonhematologic toxicity. Nonhematologic toxicities of Grade 1–3 are listed in Table 5. In spite of the appearance of common toxicities, the therapy was well-tolerated. Most of the toxicities were mild and manageable. Superficial phlebitis occurred in all cases. Most of the phlebitis cases did not require

Table 3 Patient characteristics

Characteristic	No. of patients N = 21	Percentage of patients (%)
Gender		
Male	12	57
Female	9	43
Age		
Median	63	
Range	46–70	
Karnofsky performance status		
Median	80	
Range	70–90	
Histology		
Squamous cell carcinoma	21	100
Stage		
IIA	5	24
IIB	2	9
III	6	29
IVA	1	5
IVB	7	33
Tumor location		
Upper	7	33
Middle	14	67
Lower	0	0

Table 4 Hematologic toxicity

Toxicity grade	Dose level (number)					Percentage (%)
	1	2	3	4	5	
WBC						71.4
1	0	0	0	2	0	9.5
2	1	3	0	4	3	52.4
3	0	0	1	0	0	4.8
4	0	0	0	0	1	4.8
ANC						66.7
1	1	2	0	4	2	42.9
2	0	1	0	1	1	14.3
3	0	0	1	0	0	4.8
4	0	0	0	0	1	4.8
PLT						9.5
2	0	0	0	1	0	4.8
4	0	0	0	0	1	4.8
HGB						28.6
1	1	0	1	0	2	19.0
2	0	0	1	1	0	9.5

ANC, absolute neutroplil count; HGB, heamoglobin; WBC, white blood cell.

medical care other than a hydropathic compress of odynolydsis in several patients. All patients experienced fatigue and anorexia. Some of them were supported with temporal fluid replacement. Neither feeding tubes nor intravenous hyperalimentation were needed. None of our cases stopped or delayed planned therapy because of fatigue and/or anorexia.

At dose level 4, one of the initial 3 patients experienced Grade 3 esophagitis. At that point, 3 more patients were enrolled. Another case of Grade 3 esophagitis was observed in 1 patient. Similarly, 2 of 6 patients at dose level 5 experienced Grade 3 esophagitis. We defined Grade 3 esophagitis occurring in dose levels 4 and 5 as DLT. When the same four DLTs were observed in 4 patients, the doses at the completion of radiotherapy were 38 Gy, 36 Gy, 18 Gy, and 50 Gy, respectively. Dose levels 4 and 5 corresponded to the occurrence of 68.2% (15/22) of Grade 3 and 4 nonhematologic toxicities, as noted in Table 6, while only 18.2% (4/22) of such toxicities occurred at dose level 3. We defined CDDP 52.5 mg/m^2 with 5-FU 700 mg/m^2 and CFR 50 Gy as MTD for Chinese patients with esophageal cancer.

Response. All 21 patients were assessable for clinical response. It should be noted that 19% (4/21) of the patients achieved CR, 52% (11/21) achieved PR, and 29% (6/21) achieved SD. No PD was observed. The total response rate was 71% (15/21).

Table 5 Nonhematologic toxicity

Toxicity grade	Dose level (number)					Percentage (%)
	1	2	3	4	5	
Esophagitis						81.0
1	1	1	1	3	1	33.3
2	0	2	2	1	1	28.6
3	0	0	0	2	2	19.0
Trachitis/bronchitis*						
1	1	1	1	3	2	38.1
Nausea and vomiting						95.2
1	2	0	0	1	1	19.0
2	1	2	2	3	4	57.1
3	0	1	0	2	1	19.0
Anorexia						100.0
1	3	0	1	0	1	23.8
2	0	1	0	3	3	33.3
3	0	2	2	3	2	42.9
Fatigue						100.0
1	3	0	1	4	3	52.4
2	0	3	2	2	3	47.6
Superficial phlebitis						100.0
1	3	3	3	3	5	81.0
2	0	0	0	3	1	19.0
Gastritis 2	0	1	1	0	1	14.3
Dematitis**						100.0
1	2	3	3	6	5	90.5
2	1	0	0	0	1	9.6
Constipation 2	0	2	2	1	2	33.3
Diarrhea 2	0	0	0	1	0	4.8
Albumin						81.0
1	1	3	2	4	3	61.9
2	1	0	1	1	1	19.0
ALT						38.1
1	2	1	0	2	2	33.3
2					1	4.8
AST 1	1	0	0	1	3	23.8
GGT 2	0	0	0	0	1	4.8
Bilirubin 1	0	1	1	2	0	19.0

*: radiation-induced trachitis and/or bronchitis
**: radiation-induced dermatitis
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyltransferase.

Table 6 Grade 3/4 toxicity

Toxicity grade	Dose level (number)					Percentage (%)
	1	2	3	4	5	
Esophagitis						
3	0	0	0	2	2	19.0
Nausea and vomiting						
3	0	1	0	2	1	19.0
Anorexia						
3	0	2	2	3	2	42.9
WBC						
3	0	0	1	0	0	4.8
4	0	0	0	0	1	4.8
ANC						
3	0	0	1	0	0	4.8
4	0	0	0	0	1	4.8
PLT						
4	0	0	0	0	1	4.8
Total						
number	0	3	4	7	8	
percentage (%)	0	13.6	18.2	68.2%		
compare	< CDDP60 mg/m^2, 5-Fu 700 mg/m^2			> CDDP60 mg/m^2, 5-Fu 700 mg/m^2		
number	7			15		
percentage (%)	31.8%			68.2%		

Discussion

Esophageal cancer is a chemosensitive tumor. CDDP combined with 5-FU has been studied widely, and this regimen has been advocated as the standard treatment for squamous cell cancer [19]. Chemoradiotherapy can be delivered as a definitive local therapy without surgery in the treatment of esophageal cancer. In RTOG85-01, the survival rates for chemoradiation at 5 and 8 years were 32% and 22%, respectively [5]. Although a phase I study with a novel regimen including paclitaxel [20], oxaliplatin [21], and irinotican [22] has been performed with concurrent radiotherapy, the survival benefits remain unclear. What is more, because of financial problems, such novel drugs are not widely accepted by Chinese patients with esophageal cancer who are primarily from impoverished areas in China. We adopted CDDP with 5-FU combined with concurrent CFR for an escalating trial.

The results of this Phase I study have indicated that the combination of CDDP with 5-FU and concurrent CFR as a definitive therapy is easily tolerated and may have clinical benefits for Chinese patients with esophageal cancer. The toxicities below the DLT dose level were generally mild to moderate and could be managed with conventional strategies. The doses at the MTD level in our trial seem to be somewhat lower than those used in other studies from East Asia.

A phase II study from the Japan Clinical Oncology Group Trial (JCOG) [23] delivered CDDP 70 mg/m^2 on days 1 and 29, and 5-FU 700/m^2/day on days 1-4 and 29-32, with concurrent CFR (60 Gy in total, 5 daily fractions per week) to treat esophageal cancer. However, there was an interval of 7 days after 30 Gy, which might have lessened the treatment toxicities. Nevertheless, only 77% (46/60) of the patients completed the whole schema, and 3.3% (2/60) of toxicities were observed to be iatrogenic.

In another similar study from Japan [24], higher doses of CDDP 80 mg/m^2 on day 1 and continuous infusion of 5-FU 800 mg/m^2/day on days 2-6 were reportedly administered with radiotherapy (66.6 Gy in total, 1.8 Gy/day, 5 fractions per week), every 3 to 4 weeks, for 2 cycles. Only 70% (21/30) of the patients completed the planned treatment. Grade 3 and 4 toxicities were observed in 23 (77%) patients. We do not concur that the doses of these 2 chemotherapeutic regimens are suitable for Chinese people.

Lee has reported a prospective phase II neoadjuvant chemoradiotherapy study in Korea [25]. In this study, the treatment consisted of 2 cycles of CDDP 60 mg/m^2 on day 1 and 5-FU 1,000 mg/m^2 daily as a continuous intravenous infusion for 5 days from day 2 to day 6, with concurrent hyperfractionated radiotherapy for a total dose of 48 Gy in 40 fractions. Due to severe toxicities, including 1 death, the dose of 5-FU during the first cycle of chemotherapy was reduced, and it was omitted during the second cycle in the latter course of this study. These results indicated that the 5-FU dose of this regimen was too intensive.

Zhao *et al.* [8] have reported the results of a phase III randomized study from one of the largest cancer centers in China. The chemotherapeutic regimen consisted of CDDP 25 mg/m^2/day and 5-Fu 600 mg/m^2/day i.v. from days 1-3 every 4 weeks, with the first and second cycles given during concomitant radiation sessions. No survival benefits were achieved, partly because of severe acute therapy-induced toxicities, as follows. Grade 3 and 4 toxicities occurred in 46% of patients, and 6% of patients had Grade 5 acute toxicities. Obviously, toxicities also result in poor compliance: Only 43% of patients completed all 4 cycles of chemotherapy.

In summary, the concurrent chemoradiotherapy schema of MTD dose level is feasible and safe for Chinese people with esophageal cancer. We recommend the following dosage levels in this schema: CDDP 52.5 mg/m^2 on day 1 and 5-FU 700 mg/m^2 on days 1-5, repeated 4 times every 28 days, plus CFR of 50 Gy. The effectiveness of this schedule in esophageal cancer is currently being further evaluated in a prospective Phase II trial.

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