Problems in Neoadjuvant Chemoradiotherapy Preceding Surgery for Advanced Squamous Cell Carcinoma of the Thoracic Esophagus

The adverse effect of neoadjuvant chemoradiotherapy on the postoperative course in esophageal cancer was studied in 9 patients undergoing neoadjuvant chemoradiotherapy preceding surgery for thoracic esophageal carcinoma possibly involving adjacent organs (neoadjuvant group), and 13 patients undergoing surgery without neoadjuvant therapy for same disease (control group). The two groups were compared for volume of intraoperative hemorrhage, surgical duration, frequency of postoperative morbidity, and for postoperative changes in blood platelet counts, and serum thrombopoietin and interleukin-6 levels. Mean intraoperative blood loss was 1121 g (580–1,662 g) in the neoadjuvant group and 546.5 g (274.7–778.3 g) in controls group (Student's T test: $p < 0.01$). No significant difference was seen found between the two groups in the degree of postoperative deterioration in cardiopulmonary function or in interleukin-6 levels. Blood platelet counts decreased in both groups until postoperative day 7, but recovery on postoperative day 14 was significantly depressed in the neoadjuvant group compared to controls. Serum thrombopoietin levels were higher in the neoadjuvant group than in controls (Mann-Whitney U-test: $p < 0.05$). We found that neoadjuvant chemoradiotherapy induces latent postoperative myelosuppression and may lead to intractable infection.
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Index words: esophageal cancer, chemoradiotherapy, neoadjuvant therapy

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The prognosis for patients with advanced esophageal carcinoma is dismal, even for those undergoing resection.[1] Recent success with neoadjuvant therapeutic modalities such as chemotherapy and chemoradiotherapy has been expected to lead to promising perspectives adding a new facet to the treatment of this disease.[2] Since 1992, we have used concurrent or sequential neoadjuvant chemotherapy combined with radiotherapy preceding surgery in patients with potential or actual T4 tumors. Problems remain, however, to be solved with these therapies. Our study was conducted to establish guidelines for the postoperative management of these patients.

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Subjects and Methods

From June 26, 1992, to April 1, 1998, 26 patients with advanced thoracic squamous cell carcinoma

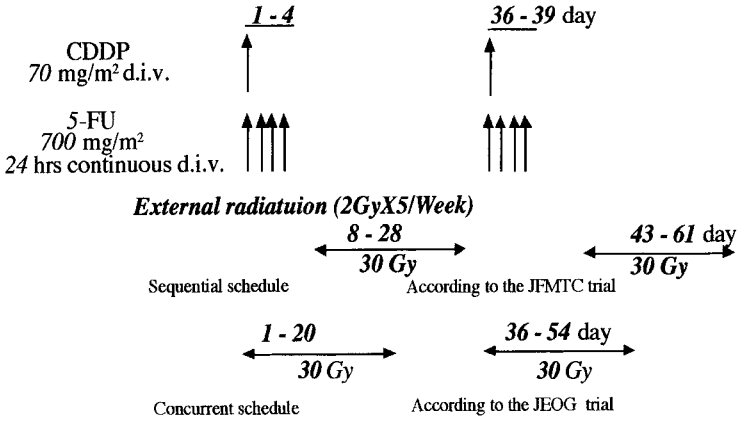

Fig. 1. Treatment schedule in the neoadjuvant group.

and potential or actual T4 tumors were studied. The diagnosis of T4 tumor was made through routine clinical procedures such as endoscopy, esophagography, computed tomography, bronchoscopy, and ultrasonography. Patients with solid organ metastasis were excluded. We then compared the postoperative course of patients receiving concurrent or sequential neoadjuvant chemotherapy combined with radiotherapy preceding radical surgery (Neoadjuvant group), and those undergoing surgery alone (controls). Informed consent was obtained from all patients studied.

The neoadjuvant treatment schedule (Fig. 1) generally involved giving cisplatin (CDDP) (70 mg/m^2 dissolved in 500 ml of saline) by slow drip infusion for 120 min on treatment days 1 and 36, and 700 mg/m^2 of 5-FU mixed in 2,000 ml of saline per day by continuous infusion for 24 hs on days 1–4 and 36–39. External radiotherapy (200 cGy/day, 5 times a week for 6 weeks for a total of 60 Gy) was conducted on days 8–28 and 43–61 (sequential schedule) or 1–20 and 36–54 (concurrent schedule). For tumors in the upper and middle third of the thoracic esophagus, the cervical region and mediastinum were irradiated in a T shape at a dose of 60 Gy. For tumors in the lower part of the thoracic esophagus, the celiac region and mediastinum were irradiated in a T shape with the celiac region dose reduced to 46 Gy to prevent the toxic effect on gastrointestinal function. We used response criteria given in "Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus" published by the Japanese Society of Esophageal Disease.[3]

Results

Clinicopathological features. The neoadjuvant group consisted of 26 patients (24 man and 2 woman) ranging from 48 to 74 years of age (mean: 59.7). Fourteen of the tumors found were in the upper third of the thoracic esophagus, 10 in the middle third, and 2 in the lower third. Clinical examinations showed that these T4 tumors infiltrated the aorta in 7 patients and, the trachea and or bronchus in 19.

The control group consisted of 13 patients (11 men and 2 women) ranging from 54 to 73 years of age (mean: 63.8). The TNM classification of the International Union Against Cancer (UICC) for the pathological stage showed 3 stage I, 3 in stage IIB, 5 in stage III, and 2 in stage IV. No statistically significant differences were seen between the groups in gender ratio or age distribution.

Routine preoperative tests such as a complete blood count and liver, renal, and cardiopulmonary function showed no significant differences between 2 groups. Patients in both groups underwent surgery (Table I).

Neoadjuvant treatment summary. All patients in undergoing chemoradiotherapy tolerated it well. r-G-CSF was given to 8 patients for leukopenia, however, and the CDDP dose was halved for < 40 ml creatinine clearance in 2 patients. The overall response rate in the 26 patients was 73.3%, involving

Table I. *Clinicopathological features of neoadjuvant and control groups*

		Control group	*Neoadjuvant group*
Age (years) Mean ± SD		63.8 ± 9.5	59.7 ± 7.1
Sex (male:female)		11:2	8:1
pTNMstage	I	3	1
	IIA	0	3
	IIB	3	0
	III	5	3
	IV	2	2
Location		Iu: 5, Im: 6, Ei: 2	Iu: 3, Im: 5. Ei: 1
Lymph node dissection		3 Field	3 Field
Surgical duration (min) Mean ± SD		325.4 ± 57.2	353.3 ± 48.4
Blood loss (g) Mean ± SD		546.5 ± 271.8	1121.0 ± 541.0*

*$p < 0.01$

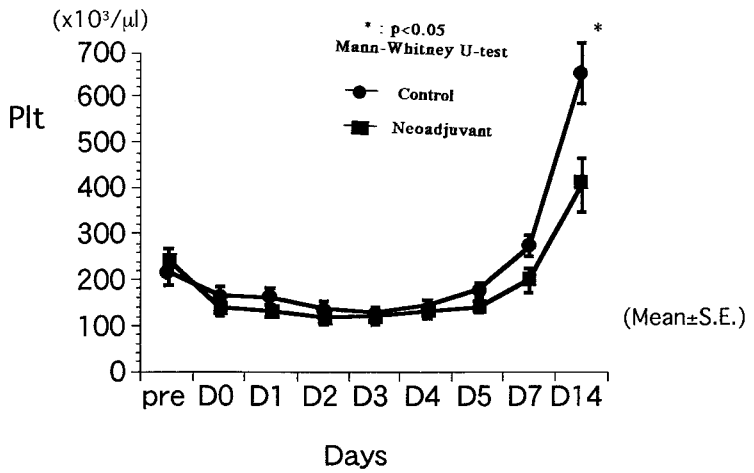

Fig. 2. Postoperative changes in mean blood platelet count. Blood platelet counts decreased in both groups until POD 7. Recovery on POD 14 was significantly depressed in the neoadjuvant group compared to controls.

4 complete responses (CR), 15 partial responses (PR), 1 minor response (MR), 1 no change (NC) and 5 progressive diseases (PD). Of these, 9 underwent transthoracic esophagectomy with lymphadenectomy, involving 8 of the PRs and the 1 NC.

Comparison of postoperative course. No significant difference in postoperative cardiopulmonary change or the frequency of severe complications was seen in the 2 groups.

The mean blood loss was 1,121 g (580.0–1662.0 g) in the neoadjuvant group and 546.5 g (274.7–778.3 g) in controls and thus statistically significantly higher (Student's T test: $p < 0.01$). Mean surgical duration was 353.3 min (304.6–401.7 min) in the neoadjuvant group and 325.4 min. (268.2–382.6 min) in controls.

In the neoadjuvant group, 3 mild air tract infections occurred, 2 caused by methycilline-resistant Staphylococcus aureus (MRSA) and 1 by Pseudomonas aeruginosa, along with 1 idiopathic retroperitoneal abscess.

No significant difference in the IL-6 levels was seen between the 2 groups.

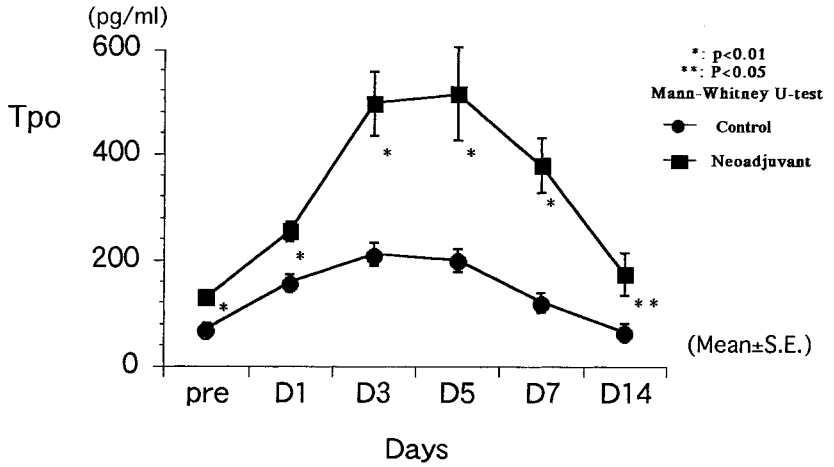

Fig. 3. Postoperative changes in Tpo levels. Tpo concentrations in the neoadjuvant group were statistically significantly higher than in controls.

Blood platelet counts decreased in both groups until 7 postoperative day (POD) but recovery on POD 14 in the neoadjuvant group was significantly depressed compared to controls. The mean platelet count was 360,000/μL on POD 14 in the neoadjuvant group, and 660,000/μL in controls (Fig. 2).

The mean thrombopoeietin level (Tpo) was 130.6 pg/ml on POD 1 and 253.1 pg/ml on POD 2, and 70.65 pg/ml on POD 1, 156.6 pg/ml on POD 2 in controls (Fig. 3) and thus statistically significant (Mann-Whitneys U-test: $p < 0.05$).

Statistical analysis was conducted using computer software Stat View-J 4.5 (Abacus Concepts, Berkeley, CA, USA) for Macintosh. Clinicopathologic parameters were based on the TNM classification of the International Union Against Cancer (UICC).[4]

Discussion

Despite considerable improvement in perioperative management and surgical techniques, the prognosis for patients with advanced esophageal carcinoma remains dismal, even for those undergoing combined resection of the mediastinal organs, e.g., trachea, main bronchus, and aorta, or extended lymph node dissection.[5]

Systemic phase II studies on chemoradiotherapy for treating advanced esophageal carcinoma were recently conducted in Japan.[6] Results suggest the possibility of treating potential or actual T4 tumors as resectable lesions and providing an R0 situation after surgery. Even if patients could tolerate such presurgical treatment, many problems after radical surgery remain unsolved and no predictive parameters have been reported that we could rely on to determine indications for treatment. Our purpose was to evaluate the postoperative course of patients receiving neoadjuvant therapy preceding surgery to those treated with surgery alone. No significant differences were seen between the 2 groups in postoperative cardiopulmonary change or the incidence of complications. The lymphocytes in neoadjuvant group appeared to have sufficient reaction to acute surgical stress, because no statistically significant differences was seen in postoperative IL-6 levels between the two groups. The frequency of postoperative infection was statistically significantly higher, however, in the neoadujvant group than in controls. We have a policy of strictly controlling the postoperative nutritional status of patients by providing calorie intake enterally or parenterally. Nutritional supplementation did not reducing infection, however, because neoadjuvant chemotherapy combined with radiotherapy, caused myelosuppression. Tpo levels in the neoadjuvant group were statistically significantly higher than in controls. Meng et al, reported that Tpo promotes the proliferation and maturation of megakaryocytes.[7] Measuring Tpo in patients with mild bone-marrow

hypoplasia would be useful for detecting whether thrombocytopenia is caused by decreased platelet production or peripheral destruction.

Our data suggests that preoperative chemoradiotherapy may cause prolonged myelosuppression not detected by routine laboratory examinations. The mean blood loss in the neoadujvant group was statistically significantly higher than those in controls. Thus, if the volume of blood loss and surgical stress during surgery is high in those receiving neoadjuvant therapy, such myelosuppression could induce that are potentially life-threatening problems.

Conclusion

Patients receiving neoadjuvant chemoradiotherapy preceding surgery had potential myelosuppression not detectable by routine laboratory examination. Surgeons must therefore decide strategic treatment carefully for these patients.

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