The Influence of Neoadjuvant Chemotherapy with Docetaxel, Nedaplatin and 5-Fluorouracil After Esophagectomy

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Abstract. *Background:* Neoadjuvant chemotherapy (NAC) with docetaxel, nedaplatin and 5-fluorouracil (5-FU) in esophageal cancer may adversely affect the postoperative clinical course following esophagectomy. *Patients and Methods:* We investigated the perioperative white blood cell count (WBC), C-reactive protein (CRP), serum albumin, body temperature (BT), heart rate (HR), respiratory rate (RR), water balance, partial pressure of oxygen in arterial blood (PaO_2)/fraction of inspired oxygen (FiO_2) ratio, postoperative complications and systemic inflammatory response syndrome (SIRS) in patients who underwent NAC or surgery alone (SA group). *Results:* In the NAC group, the preoperative WBC ($p=0.015$) and postoperative day (POD) 3 BT ($p=0.049$), as well as RR ($p=0.037$) were lower, whereas the POD 2 $\text{PaO}_2/\text{FiO}_2$ ratio was higher ($p=0.047$), compared to the SA group. No differences in the incidence of postoperative complications and SIRS were observed between the groups. *Conclusion:* NAC using docetaxel, nedaplatin and 5-fluorouracil was tolerated and feasible in esophageal cancer.

Recent advances in surgical techniques, postoperative care and treatment strategies have improved the surgical outcome of esophageal cancer. Recently, the utility of neoadjuvant chemotherapy (1-3) and chemoradiotherapy (4-7) for esophageal cancer was reported. In Japan, the usefulness of preoperative chemotherapy with cisplatin and 5-fluorouracil (5-FU) (CF) in cStage II/III esophageal cancer was shown in the JCOG9907 (8). However, it was also reported that preoperative treatment, particularly chemoradiotherapy, may

have adverse perioperative effects, such as increased postoperative complications (9-12). A recent study reported that preoperative chemotherapy with docetaxel, cisplatin and 5-FU (DCF) showed a survival benefit for esophageal cancer compared to CF (13, 14). However, DCF may adversely affect the perioperative condition of esophageal cancer patients because of adverse events, such as hematological toxicity. Therefore, there is a concern that preoperative chemotherapy using DCF may influence the postoperative course after esophagectomy.

Esophagectomy is one of the most invasive surgical procedures in gastrointestinal surgery. It is known that surgical stress induces various biological reactions, such as neuroendocrine response, which is regulated by adrenocortical and adrenomedullary hormones, and cytokine responses involving inflammatory mediators (such as tumor necrosis factor (TNF) α , interleukin (IL)-1 β , IL-6, IL-12 and IL-18) (15) and anti-inflammatory mediators (16), which are activated to maintain physiological homeostasis (17, 18). Increased heart rate (HR), body temperature (BT), respiratory rate (RR), white blood cell (WBC) and C-reactive protein (CRP) levels result from these various responses in the neuroendocrine, cardiovascular, metabolic and immunological systems. In addition, hypercytokinemia may subsequently lead to development of systemic inflammatory syndrome (SIRS), followed by the compensatory anti-inflammatory response syndrome (CARS) (19). SIRS often leads to organ dysfunction, such as acute lung injury (ALI) (20) and increases postoperative complications (21). Furthermore, multiple organ failure (MOF) may occur after a longer duration of SIRS (21). Therefore, it is important to control the inflammatory response to perform perioperative care safely. In particular, preventing ALI is important because it decreases the partial pressure of oxygen in arterial blood (PaO_2)/fraction of inspired oxygen (FiO_2) ratio and may cause severe complications in patients.

Although preoperative chemotherapy with DCF may influence these biological reactions and the postoperative clinical course because of adverse events, such as

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hematological toxicity, no previous study has assessed this in detail. The aim of this study was to clarify whether NAC increases the risk of pulmonary dysfunction, the incidence of SIRS and complications after surgery. We investigated the postoperative course based on biological parameters (HR, BT, RR, WBC and CRP), $\text{PaO}_2/\text{FiO}_2$ ratio and the incidence and duration of SIRS, as well as postoperative complications between patients who underwent NAC following surgery or surgery alone.

Patients and Methods

Patients. A retrospective study was performed in 50 consecutive patients who underwent transthoracic esophagectomy for cT3, cN0-1 or cM0 thoracic esophageal cancer at the Tokyo Women's Medical University Medical Center East between 2008 and 2013. Eighteen patients received NAC followed by surgery (NAC group) and 32 underwent surgery alone (SA group). The surgical procedures included transthoracic esophagectomy *via* a right fifth or sixth thoracotomy, left sixth thoracotomy, cervical esophagogastrotomy *via* the antethoracic, retrosternal or posterior mediastinal route with a two- or three-fold lymphadenectomy. Patients' data were retrospectively evaluated using all medical and nursing charts, including preoperative status, surgical procedures and the perioperative systemic response, including BT, RR, HR, water balance, WBC, serum CRP level, serum albumin level, $\text{FiO}_2/\text{PaO}_2$ ratio, the incidence and duration of SIRS by postoperative day (POD) 4 and the incidence of postoperative complications. Moreover, we calculated the surgical stress score (SSS), as previously described (22), to compare the surgical stress between the two groups.

At the end of the operation, all patients were admitted to the intensive care unit (ICU) and ventilated using Evita XL respirators (Dräger Medical, Lübeck, Germany) equipped with an automated weaning system SmartCare/PS version 1.1; they were extubated on POD 2. Methylprednisolone sodium succinate (5 mg/kg) was used at the start of surgery. A continuous intravenous (*i.v.*) infusion of 4.8 mg/kg/day sivelestat sodium hydrate was used from the end of surgery until POD 2.

SIRS was diagnosed according to the criteria proposed by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (23). SIRS was defined as two or more of the following: i) $\text{BT}>38^\circ\text{C}$ or $<36^\circ\text{C}$, ii) $\text{HR}>90$ beats/min, iii) $\text{RR}>20$ beats/min or $\text{PaCO}_2<32$ torr and iv) WBC count $>12,000$ or $<4,000$ cells/ mm^3 or $>10\%$ immature band forms.

Postoperative complications included non-infectious complications, such as recurrent nerve paralysis, atrial fibrillation, delirium and hepatic dysfunction (glutamic oxaloacetic transaminase (GOT) or glutamate pyruvate transaminase (GPT) ≤ 200 or hyperbilirubinemia (total bilirubin ≤ 3.0)), infectious complications, such as pneumonia, anastomosis leakage, surgical site infection (SSI), sepsis, central vein catheter infection and enteritis. Pneumonia was defined as respiratory symptoms, opacity in a plain chest X-ray and detection of pathogenic bacteria in sputum cultures. Postoperative complications were only included in the study when patients had a Clavien-Dindo classification $> \text{I}$ (24).

NAC. NAC consisted of a 1-h *i.v.* infusion of 50 mg/ m^2 docetaxel on day 1, a 2-h infusion of 12 mg/ m^2 /day nedaplatin on days 1-5 and continuous *i.v.* infusion of 500 mg/ m^2 /day 5-FU on

days 1-5. A second cycle of NAC was administered 3-4 weeks after the first cycle. Computed tomography (CT), upper gastrointestinal endoscopy and esophagography were performed approximately 2 weeks after each treatment cycle to assess efficacy, according to RECIST version 1.1 (25).

Statistical analysis. The data are expressed as means $\pm$ SEM. Statistical analyses were performed using Student's *t*-tests, Chi-squared tests and Fisher's exact tests. *p*-Values <0.05 were considered to be statistically significant. All analyses were performed using the JMP version 11 (SAS Institute, Inc., Cary, NC, USA).

Results

Patients. No differences were observed in age, gender or bodyweight between the two groups. Tumor diameter was significantly larger in the NAC group (81 ± 35.2 mm) compared to the SA group (55.2 ± 17.1 mm) ($p=0.0013$). Esophagogastrectomy *via* the posterior mediastinal route and three-region lymph node dissection were performed more frequently in the NAC group than in the SA group. The pathological assessment of tumor samples revealed no significant difference in tumor depth, lymph node metastasis, TNM classification or residual tumor volume between the treatment groups. There was no significant difference in surgical time; however, blood loss was significantly greater in the NAC group (927.5 ± 591.5 ml) compared to that in the SA group (460.8 ± 198.7 ml) ($p=0.00027$). Therefore, SSS was significantly higher in the NAC group compared with the SA group (0.879 ± 0.126 vs. 0.752 ± 0.069 ; $p=0.00005$). There was no significant difference in preoperative pulmonary function and/or ventilation time (Table I).

Laboratory data. The preoperative WBC count was significantly lower in the NAC group than in the SA group ($5,911\pm 1,308$ vs. $7,275\pm 2,027$; $p=0.015$). The postoperative WBC count in the NAC group was also less than in the SA group until POD 3, although not significantly. The serum CRP and albumin levels were lower in the NAC group compared with the SA group, although not significantly (Figure 1). BT in the NAC group was lower until POD 4, which was significant on POD 3 (37.1 ± 0.3 vs. 37.4 ± 0.5 ; $p=0.049$) compared with that in the SA group. RR was also lower in the NAC group, which was again significant on POD 3 (23.2 ± 2.3 vs. 25.2 ± 2.3 ; $p=0.037$). There was no difference in HR between the groups until POD 3; it was, however, increased in the NAC group after POD 4. In both groups, the water balance was negative on POD 2 but returned to positive on POD 4; no significant differences were observed during the postoperative course (Figure 2).

There were no differences in the preoperative $\text{PaO}_2/\text{FiO}_2$ ratio between the two groups. The $\text{PaO}_2/\text{FiO}_2$ ratio decreased after surgery in both groups; however, the decrease was smaller in the NAC group compared with that in the SA

Table I. Patients' and tumors' characteristics.

	NAC (n=18)	Surgery alone (n=32)	p-Value
Age	69.2±6.4	68.8±9.2	0.898 [‡]
Male/female	15/3	30/2	
Body Weight (kg)	54.7±10.1	56.5±10.7	0.574*
%VC	105.1±20.2	104.2±16.2	0.878 [‡]
FEV1.0	74.6±11.5	76.4±10.8	0.603 [‡]
Tumor location			0.165*
Upper	1	2	
Middle	12	13	
Lower	5	17	
Tumor size (mm)	81.0±35.2	55.2±17.1	0.001*
20-39	1	4	
40-59	4	14	
60-79	2	12	
80-	11	2	
pT			0.095*
1b	2	0	
2	2	2	
3	9	27	
4	3	3	
pN			0.304*
0	7	8	
1	11	24	
pM			0.239 [†]
0	15	30	
1b	3	2	
Pathological stage			0.622*
I	1	0	
IIA	3	9	
IIB	1	1	
III	10	20	
IVB	1	2	
Reconstruction route			0.011*
Antethoracic	1	1	
Retrosternal	16	16	
Posterior mediastinal	1	15	
Trans thoracic esophagectomy			1.000 [†]
R	17	31	
L	1	1	
Fields of lymphadenectomy			0.064 [†]
2	3	15	
3	15	17	
Residual tumor (%)	83.3%	81.3%	1.000 [†]
R0	15	26	
R1/R2	3	6	
Operation time (min)	443.0±62.8	426.1±73.2	0.423 [‡]
Bleeding (ml)	927.5±591.5	460.8±198.7	<.001 [‡]
Duration of ventilator dependence (min)	2992.8±39.4	2994.8±69.2	0.913 [‡]

*Chi-square test. [†]Fisher's exact test. [‡]Student's *t*-test. NAC: neoadjuvant chemotherapy; FEV: forced expiratory volume. Data are given as mean±SD.

group. In particular, the PaO₂/FiO₂ ratio was significantly higher in the NAC group on POD 2 (369.2±55.9 vs. 325.5±78.5; *p*=0.047) (Figure 2).

Postoperative complications. The postoperative complications are summarized in Table II. There were no differences in the frequency of infectious or non-infectious complications between the two groups. Although 12 patients had pneumonia, no cases required re-intubation or tracheotomy. Two patients in SA group had an astomotic leakage, which did not require re-operation. Apart from one patient in the NAC group who had Grade 3 recurrent laryngeal nerve palsy, all the reported cases of recurrent nerve paralysis were Grade 2.

SIRS. No difference was observed in the postoperative frequency of SIRS between the two groups (44.4% in the NAC group vs. 46.9% in the SA group) (Table IIIA). The incidence of SIRS in the NAC group was 50% (3/6) in patients with infectious complications and 41.7% (5/12) in those with non-infectious complications. In the SA group, the incidence of SIRS was 63.6% (7/11) in patients with infectious complications, compared with 38.1% (8/21) in those with non-infectious complications. However, the duration of SIRS was significantly longer in NAC patients with infectious complications compared with SA patients with infectious complications (98.7±30.2 h vs. 48.1±21.2 h; *p*=0.027) (Table IIIB). In contrast, the duration of SIRS tended to be shorter in patients in the NAC group with non-infectious complications compared to those in the SA group (11.0±7.0 h vs. 38.9±28.2 h; *p*=0.07) (Table IIIB). In the NAC group, the duration of SIRS was significantly longer in patients with infectious complications compared with those with non-infectious complications (98.7±30.2 h vs. 11.0±7.0 h; *p*=0.002). However, there was no difference in the duration of SIRS between patients with infectious and non-infectious complications in the SA group (48.1 h±21.2 h vs. 38.9±28.2 h; *p*=0.52).

Discussion

In the present study, we made two important clinical observations. First, the decrease in the PaO₂/FiO₂ ratio after surgery was suppressed in the NAC group and, significantly, on POD 2, despite of no difference in preoperative pulmonary dysfunction, PaO₂/FiO₂ ratio and the frequency of postoperative pneumonia between the groups. These findings suggest that excessive inflammatory response-induced ALI was suppressed in the NAC group. It is known that monocytes and macrophages in the surgical site are activated to produce inflammatory cytokines, mainly IL-1, TNFα and IL-6, after a highly invasive surgery. The inflammatory cytokines then activate monocytes, neutrophils and vascular endothelial cells, which produce inflammatory mediators, such as chemokines, platelet activating factor (PAF), neutrophil elastase and free radicals. Tissue damage, damage to the vascular endothelium (26, 27) and microcirculatory disorders due to microthrombus formation

Figure 1. Postoperative changes in the WBC, CRP, Alb and PaO₂/FiO₂ ratio balance in the NAC group (○), as well as surgery alone (SA) group (■). WBC, white blood cell count; CRP, C-reactive protein; Alb, serum albumin; POD, postoperative day; PaO₂/FiO₂, partial pressure of oxygen in arterial blood/fraction of inspired oxygen. * $p=0.015$, ** $p=0.047$.

Table II. Postoperative complications.

	NAC (n=18)	Surgery alone (n=32)	p-Value
Infectious complication (%)	6 (33.3)	11 (34.4)	0.950 [†]
Pneumonia	4 (22.2)	8 (25.0)	1.000 [†]
Anastomotic leakage	0	2 (6.3)	0.039 [†]
SSI	3 (16.7)	3 (9.4)	0.654 [†]
Sepsis	1 (5.6)	0	0.360 [†]
CV catheter infection	1 (5.6)	0	0.360 [†]
Infectious enteritis	0	1 (3.1)	1.000 [†]
Non-infectious complication (%)	13 (72.2)	21 (65.6)	0.631*
Hepatic failure*	3 (16.7)	12 (37.5)	0.199 [†]
Recurrent laryngeal nerve palsy	7 (38.9)	6 (18.8)	0.180*
Arrythmia	5 (27.8)	5 (15.6)	0.463*
Delirium	3 (16.7)	3 (9.4)	0.654 [†]

[†]Fisher's exact test. *Chi-square test. *Hepatic failure: presence of one or more of the following: 1) serum AST or ALT > 200 IU, 2) serum total bilirubin (mg/dl) >3.0. NAC: neoadjuvant chemotherapy; SSI: surgical site infection; CV: central venous.

(28), which was caused by activated neutrophils, all lead to organ dysfunction. In the lungs, accumulation of activated neutrophils and neutrophil elastase damages lung capillary

Table III. Postoperative frequency and duration of SIRS.

A All patients	NAC (n=18)	Surgery alone (n=32)	p-Value
SIRS (%)	8 (44.4)	15 (46.9)	0.869*
Duration of SIRS (h)	43.875	43.2	0.966 [‡]
Range (h)	4-120	8-88	
B Duration of SIRS (h)	NAC (n=8)	Surgery alone (n=15)	p-Value
Infectious complication	98.7±30.2	48.1±21.2	0.027 [‡]
Non-infectious complication	11.0±7.0	38.9±28.2	0.072 [‡]

*Chi-square test. [‡]Student's *t*-test. SIRS: systemic inflammatory response syndrome; NAC: neoadjuvant chemotherapy.

endothelial cells; this increases capillary permeability and, eventually, leads to pulmonary edema, resulting in ALI (29). Therefore, the production of cytokines may have been suppressed in the NAC group, preventing the progression of ALI. Consistent with this, BT and RR, which are affected by cytokines, such as IL-1, IL-6 and TNF- α , were lower in the

Figure 2. Postoperative changes in the BT, HR, RR and water balance in the NAC group (○), as well as surgery alone (SA) group (■). BT, body temperature; HR, heart rate; RR, respiratory rate; POD, postoperative day. * $p=0.049$, ** $p=0.037$.

NAC group until POD 4 compared with that in the SA group, which was significant on POD 3.

The factors that could induce cytokine production after surgery are as follows: i) the number of cytokine-producing cells, ii) surgical stress and iii) anticytokine therapy. Regarding the number of cytokine-producing cells, the preoperative WBC in the NAC group was significantly less than that in the SA group. In addition, the postoperative WBC was lower in the NAC until POD 3, although not significantly. Therefore, it is possible that the number of inflammatory cells, such as neutrophils, monocytes and macrophages, was decreased in the NAC group because of insufficient recovery from hematological toxicity with chemotherapy.

During surgical stress, the cytokine concentration increases in proportion to the level of stress. Sakamoto *et al.* reported that blood IL-6 levels increased with the amount of blood loss and surgery time (30). In addition, Haga *et al.* demonstrated that the maximum postoperative CRP and duration of SIRS were significantly correlated with patients' original SSS, which is determined by the amount of blood loss, surgical time and extent of surgery (22). A higher SSS indicates increased inflammatory cytokine secretion. Since the amount of blood loss was significantly larger in the NAC

group, despite a comparable surgical time, SSS was also significantly higher in the NAC group. This may have been caused by the larger tumor size and high frequency of three-region lymph node dissection in NAC patients, which exposed them to increased stress. Based on surgical stress, acute lung injury could be expected to increase in NAC patients in general. However, our results suggest that cytokine production may have been suppressed in the NAC group, which may be due to a suppression of the cytokine-producing cells during NAC.

Although the efficacy of anticytokine therapy for ALI, such as the inhibition of inflammatory cytokines using steroids (31) and the inhibition of neutrophil elastase using protease inhibitors, has been reported in a number of studies (32-34), inflammatory cytokines are not completely inhibited by treatment alone. Since patients in both the NAC and SA groups, in the current study, underwent the same anticytokine therapy, this is unlikely to have affected the results.

Increased microvascular permeability is a common feature of ALI; therefore, serum albumin levels, which affect water balance and colloid osmotic pressure, may play a role in pulmonary vascular permeability during ALI. Therefore, we investigated serum albumin levels and the water balance after esophagectomy. However, there were no statistically

significant differences in serum albumin levels or water balance between the two groups.

The second important clinical observation in the current study is that there was no difference in the frequency of SIRS or complications after surgery between the two groups. However, the duration of SIRS was significantly longer in NAC patients with infectious complications compared with SA patients with infectious complications, whereas the duration of SIRS in patients with non-infectious complications tended to be shorter in the NAC group compared with the SA group. Many previous studies reported no difference in the risk of preoperative chemotherapy-associated postoperative complications (35-38). In contrast, Schlag *et al.* (12) reported a considerable increase in the incidence of postoperative complications, such as infections and acute respiratory distress syndrome (ARDS) in patients who underwent preoperative chemotherapy for squamous cell cancer of the esophagus. Furthermore, Tujimoto *et al.* (10) reported that NAC resulted in a longer duration and higher incidence of SIRS, although no differences were observed in the frequency of postoperative complications between the preoperative chemoradiotherapy (CRT) and SA groups. In addition, Haga *et al.* (21) reported that a longer duration of SIRS was associated with an increased number of complications. Because of these conflicting reports, the influence of NAC on the postoperative clinical course, including the incidence of complications and SIRS, remains controversial. In the current study, the longer duration of SIRS in NAC patients with infectious complications suggests that NAC may have negatively affected SIRS. Further investigation of this issue will be needed.

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