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ORIGINAL ARTICLE

Multimodality treatment for advanced thymic carcinoma: outcomes of induction therapy followed by surgical resection in 16 cases at a single institution

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Abstract
Objective We reviewed our institutional experience with cases of multimodality treatment for advanced thymic carcinoma to determine patient outcomes and prognostic indicators.
Methods Between 1998 and 2014, 16 patients with a Masaoka stage III or IV thymic carcinoma underwent surgical resection after induction therapy at Osaka University Hospital. These were considered to have great vessel invasion or metastasis to the mediastinal or intrathoracic lymph nodes based on the preoperative workup findings, and received induction therapy.
Results Complete tumor resection was achieved in 11 (69 %) after the induction therapy. Pathological findings revealed that 10 patients had Masaoka stage III disease, 1 had IVa, and 5 had IVb. The histological diagnosis was squamous cell carcinoma in 13, neuroendocrine carcinoma in 2, and undifferentiated carcinoma in 1. The 5-year survival rate for all patients was 71 %. Survival was significantly better in patients who underwent a complete resection (R0 disease) as compared to those with incompletely resected tumors (R1 or R2 disease).
Conclusions Multimodality treatment offers encouraging results and complete resection provides high survival rate for patients with advanced thymic carcinoma.

Keywords Thymic cancer · Prognosis · Induction therapy · Complete resection · Great vessel invasion

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Introduction

Complete surgical resection is not always possible in cases of advanced stage thymic carcinoma because of local regional invasion [1]. It is considered that a multimodality treatment strategy may increase resectability, and reduce the incidence of local and systemic relapse for patients with advanced thymic tumors considered to be initially inoperable in preoperative workup findings [2]. We reviewed our institutional experience with cases of surgical resection after induction therapy for thymic carcinoma to determine patient outcomes and prognostic indicators.

Patients and methods

Between 1998 and 2014, 24 patients with a Masaoka stage III or IV thymic carcinoma underwent surgical resection at Osaka University Hospital. Sixteen were considered to have great vessel invasion or metastasis to the mediastinal or intrathoracic lymph nodes based on the preoperative workup findings, and received induction therapy. Their clinical and pathological data were retrospectively reviewed after obtaining approval from our Investigational Review Board.

Cases with World Healthy Organization (WHO) classification type B3 thymoma (well-differentiated thymic carcinoma) and carcinoid tumors were excluded from the study. Apparent pleural or pericardial dissemination, extrathoracic lymphogenous metastasis, or distant metastasis were not surgical indications, and thus such patients were also excluded from the study. Patients with a tumor involving the great vessels or metastasis to the anterior mediastinal or intrathoracic lymph nodes, as judged by joint consensus of a multimodal thoracic oncology team

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(thoracic surgery, medical oncology, radiation oncology), underwent induction therapy. Surgical resection after induction therapy was performed for patients with partial remission or stable disease, based on the computed tomography (CT) scan, magnetic resonance imaging (MRI), and ^{18}F-fluorodeoxy glucose-positron emission tomography (FDG-PET) scan findings, with a goal of complete resection to include the tumor and all attached structures, thymus, and involved lymph nodes. Complete surgical resection was defined as a macroscopically radical resection and disease-free resection margins shown in a histological evaluation. Postoperative chemotherapy or radiation was planned for cases with incomplete resection, as well as those judged to be at high risk for recurrence, such as patients with a close margin.

Overall survival (OS) rates were compared using a log-rank test. All statistical analyses were performed using JMP10 for Windows (SAS institute, Cary, NC, USA). A p value of <0.05 was considered to be statistically significant.

Results

Patient characteristics are presented in Table 1. Eleven were diagnosed preoperatively with Masaoka stage III disease, while 5 had IVb due to metastasis to the anterior mediastinal or intrathoracic lymph nodes. Of those, all patients were diagnosed with a thymic carcinoma based on the preoperative biopsy findings, of whom 13 showed invasion to the great vessels, such as the superior vena cava (SVC), ascending aorta, and main pulmonary artery, 3 had metastasis to the anterior mediastinal lymph nodes, and 2 had metastasis to the intrathoracic mediastinal lymph nodes, based on the findings of a preoperative workup performed by our oncology group. Two patients had both invasion to the great vessels and metastasis to the lymph nodes, thus a total of 16 received induction therapy. The sites of infiltration of the surrounding structures were evaluated preoperatively using CT or MRI, with those results shown in Table 1. The patients received cisplatin- or carboplatin-based chemotherapy, and the regimens are shown in Table 2. Twelve patients received concurrent radiation therapy at an irradiation volume of 40–60 Gy (mean 43 Gy). Induction therapy was well tolerated in all, with no episodes of major toxicity noted. When a partial remission (PR) was defined as a more than 50 % decrease in the size of any lesion and stable disease (SD) was defined as a less than 50 % regression of measurable lesions without new lesions, 7 patients had stable disease and 9, a partial response, while none showed progression during induction treatment.

Table 1 Patient characteristics

Sex (M/F)	11/5
Age (median)	52 ± 12
Clinical Masaoka stage	
III	11
IVa	0
IVb	5
Involved structures at POW	
Ao	9
SVC	6
Main PA	2
Lymph nodes	5
Resection	
Complete	11
Incomplete	5
Resected organs	
SVC replacement	6
BA replacement	2
Lobectomy	2
Aorta replacement	1
Phrenic nerve	10
Pathological Masaoka stage	
III	10
IVa	1
IVb	5
Histology	
Squamous cell carcinoma	13
Neuroendocrine carcinoma	2
Undifferentiated carcinoma	1

POW preoperative workup, *Ao* aorta, *SVC* superior vena cava, *PA* pulmonary artery, *BA* brachiocephalic artery, *N/A* not applicable

Table 2 Chemotherapy regimen for patients with thymic cancer

Modality	
CDDP + TXT	9
CBDCA + PTX	4
CODE	1
CDDP + VP-16	1
ADOC	1

CDDP cisplatin, *TXT* docetaxel, *PTX* paclitaxel, *VP-16* Etoposide, *CODE* cisplatin + vincristine + doxorubicin + etoposide, *ADOC* cisplatin + doxorubicin + vincristine + cyclophosphamide

Complete tumor resection was achieved in 11 patients (69 %). The reason for incomplete resection was a positive resected margin in 2, dissemination in 2, and impossible replacement of the aorta due to physical condition in 1. Two had a minimal residual tumor (R1 disease) and 3 had a grossly debulked tumor (R2 disease). The resection was

Table 3 Clinicopathological factorsand prognosis

Variables	Number of cases	5-year survival rate (%)	Significance (log-rank test)
Gender			
Male	11	72.4	0.08
Female	5	66.0	
Clinical Masaoka stage			
III	10	100	0.33
IV	6	50.0	
Effect of ITx			
PR	9	71.4	0.47
SD	7	75.0	
Resectability			
Complete	11	100	0.007
Incomplete	5	40.0	
Pathological Masaoka stage			
III	9	100	0.40
IV	7	53.6	
SVC replacement			
Yes	6	53.3	0.26
No	10	74.3	
Pathological vessel invasion			
Yes	6	60.0	0.04
No	10	75.0	

ITx induction therapy, *PR* partial response, *SD* stable disease, *SVC* superior vena cava

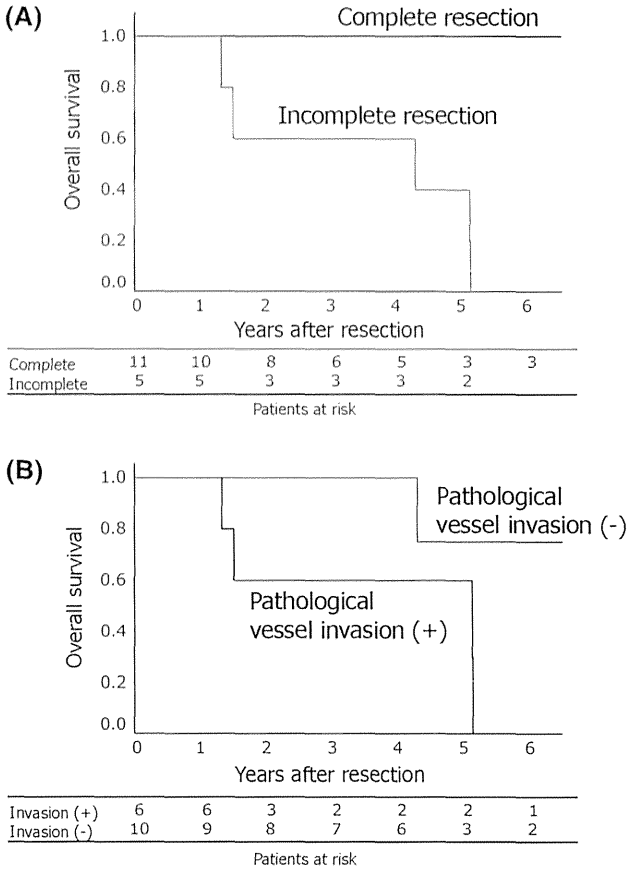

Fig. 1 **a** Overall survival according to resectability. **b** Overall survival according to pathological great vessel invasion

extended to the surrounding organs, with the details shown in Table 1. Pathological findings revealed that 10 patients had Masaoka stage III disease due to vessel invasion in 6, pericardium in 2, invasion to other organs in 2, 1 had IVa due to pleural or pericardial dissemination, and 5 had IVb due to metastasis to the anterior mediastinal lymph nodes in 2, cervical lymph nodes in 2, or the lung in 1. The histological diagnosis was squamous cell carcinoma in 13, neuroendocrine carcinoma in 2, and undifferentiated carcinoma in 1. Pathological down-staging (clinical Masaoka stage IVb to pathological Masaoka stage III) was found in 2 in whom preoperatively histologically examined lymph node metastasis was disappeared after induction therapy. However, upstaging was found in 3 because of dissemination or lymph node metastasis was found after operation.

No postoperative mortalities occurred in either group. Six patients had complications, such as bleeding, cardiac depolarization, cardiac tamponade, chylothorax, and bilateral recurrent nerve palsy, after surgery. The median follow-up period was 72 months and the 5-year survival rate for all patients was 71 %. Postoperative adjuvant therapy was performed in 6 (46 %) patients. Univariate analysis using gender, Masaoka staging, the effect of induction therapy, and replacement of superior vena cava (SVC) revealed no significant difference (Table 3). As shown in Fig. 1a, survival was significantly better in patients who underwent a complete resection (R0 disease) as compared to those with incompletely resected tumors (R1 or R2 disease). When we compared patient outcomes between R1 and R2 diseases, there was no significant difference ($p = 0.20$). Great vessel invasion evaluated by pathological examination was detected in 6 (invasion to SVC in 4 and invasion to Aorta in 2) whose survival was significantly worse as compared to that of patients without pathological vessel invasion (Fig. 1b).

Comments

The optimum treatment for advanced thymic tumors remains controversial. Invasion of mediastinal and other intrathoracic structures, including the major blood vessels, pericardium, heart, and lung in stage III disease, as well as dissemination of pleural and pericardial implants in stage IVa and lymph node metastasis in IVb, makes complete resection difficult to achieve [3]. When complete resection cannot be anticipated for the patients without apparent

pleural or pericardial dissemination, extrathoracic lymphogenous metastasis, or distant metastasis after a review of preoperative workup findings, induction therapy is administered. Induction therapy facilitates and increases the amount if surgically resectable material is available by reducing the size of the mass and down-staging the tumor. Furthermore, induction therapy is thought to prevent local and systemic relapse, and provide better assessment of the activity and efficacy of administered drugs. Thus, induction therapy has become the standard approach at several oncological centers for stage III and IV thymic tumors, with good clinical response rates reported [4]. On the other hand, a thymic carcinoma is an uncommon malignancy, thus therapeutic modalities have not been established and induction therapy similar to that for an invasive thymoma is generally applied to increase resectability [5]. The rationale for the addition of radiotherapy to induction chemotherapy is an attempt to enhance the rate of complete resection and the pathologic response compared with induction chemotherapy alone [4]. Whereas definitive radiation therapy is generally used for patients who are not candidates for surgery and radiation doses of 60–66 Gy are recommended to control gross disease [6], the most commonly used dose of radiation for induction therapy may be 40–45 Gy [7]; thus we generally selected 40 Gy as the concurrent radiation dose to avoid high morbidity and mortality rates after concurrent chemoradiation. We previously reported that induction chemoradiotherapy appeared to be useful for enabling complete resection of advanced thymic carcinomas using 40 Gy as the concurrent radiation dose [8, 9]. In the present study, the complete resection rate was 69 % after induction therapy. This good result is important, because complete initial resection was judged to be not feasible in these cases based on the preoperative workup findings. The disadvantages of induction therapy include increased toxicity of combined therapy. No postoperative mortalities occurred after induction therapy followed by surgery in the present cohort. Furthermore, neoadjuvant chemotherapy or chemoradiotherapy results in dense fibrosis involving the structures at the site of infiltration and makes dissection difficult. For this reason, en bloc resection may sometimes be required even in cases where true neoplastic invasion is not histologically proven [10].

Among the present patients, great vessel invasion, as determined by pathological examination findings, was detected in 6. The aorta was the most frequently involved organ, with pathological tumor invasion of the aorta detected in 2. In the others, the tumor was excised from the aortic tunica adventitia by sharp dissection, then an intraoperative pathologic examination showed fibrous change without viable cells, indicating that induction therapy might have down-staged the tumor. These findings also suggested that preoperative CT and MRI can overestimate the degree of aortic invasion. Accurate evaluation of great vessel invasion is an important key for treatment decisions, thus a more accurate preoperative workup method is necessary. The addition of PET–CT to the staging armamentarium may increase the accuracy of preoperative evaluation for patients with great vessel invasion.

Some authors have reported that incomplete surgical resection did not negatively impact long-term survival in cases that received postoperative cisplatin-based therapy [11], whereas other have noted that total resection of a thymic carcinoma significantly increased survival rate [12–14]. The present analysis also demonstrated that patients who received total resection had better prognosis. Based on the previously reported findings, the treatment of locally advanced thymic tumors has changed to an induction strategy with chemotherapy and radiation therapy, followed by complete removal of the tumor. Tseng et al. [13] also reported poor prognosis in patients with tumor invasion of the great vessels. We also showed that survival was significantly worse in patients with pathological great vessel invasion as compared to that of patients without vessel invasion. Of those 6 patients, 4 were not able to achieve complete resection due to positive resected margin in 2 and dissemination in 2, thus incomplete surgical resection might negatively impact survival.

Treatment of patients with pleural dissemination (Masaoka IVa) or metastasis to the lymph nodes is controversial. In the present study, there was no significant difference in prognosis between cases of Masaoka stage III disease and those with stage IV (Table 3), and 2 cases with stage IVb disease were alive at more than 5 years after receiving total resection. Thus, we consider that Masaoka stage IVb disease without a disseminated disease or metastasis to extrathoracic lymph nodes can be included in the operative indication criteria if complete resection is considered possible after induction therapy in preoperative evaluation. Since our goal of treatment for thymic cancer is complete resection, we do not perform surgical debulking as part of the treatment plan. In patients with tumors that appear to be invasive to the great vessels or metastasis to the lymph nodes, a biopsy should be performed prior to the treatment to decide the strategy. We consider that surgical debulking is acceptable for an invasive thymoma, because of the potential for favorable outcome [15]. Thus, all of the patients in the present study had an initial biopsy, which confirmed thymic carcinoma.

Our study has several limitations. Selection for induction treatment was somewhat dependent on the decision of the attending surgeon, oncologist, and radiation oncologist. Treatment was not performed based on a standard protocol, but rather using a domestic institutional formula. To establish a more effective regimen for such induction therapy, multicenter trials are necessary.

Conclusion

Our results showed that complete resection is a prognostic indicator for patients with thymic cancer after multimodality treatment.

Conflict of interest None declared.

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ORIGINAL ARTICLE

Impact of cardiopulmonary complications of lung cancer surgery on long-term outcomes

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Abstract
Purpose The impact of postoperative cardiopulmonary complications on long-term outcomes has not been established. We investigated the effects of acute postoperative cardiopulmonary complications not only on cancer recurrence, but also on cardiovascular or respiratory events in the chronic phase after lung cancer surgery.
Methods From a prospective single-institution database of 496 consecutive patients, who underwent lung cancer surgery between August, 2008 and December, 2011, medical records, including information about cardiovascular or respiratory events and cancer recurrence in the chronic phase (>6 months) after surgery, were analyzed retrospectively. Results were compared between patients with vs. those without postoperative cardiopulmonary complications in the acute phase.
Results Postoperative cardiopulmonary complications were identified in 90 (20 %) patients. There were significantly more cardiovascular or respiratory events in the chronic phase after lung cancer surgery in the patients who had suffered postoperative cardiopulmonary complications in the acute phase than in those who had not (23 vs. 5 %; $p < 0.0001$).
Conclusions Postoperative cardiopulmonary complications in the acute phase were associated with a higher incidence of cardiovascular or respiratory events in the chronic phase after lung cancer surgery.
Clinical trial registration number JPRN-UMIN2370

Keywords Lung cancer surgery · Postoperative complications · Long-term outcome

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Introduction

Surgery is considered the best option for cure in patients with resectable non-small cell lung cancer (NSCLC), but it is still associated with a high complication rate [1, 2]. Postoperative cardiopulmonary complications are a major source of morbidity and mortality in the acute phase after lung cancer surgery. It has been reported that elderly patients and patients with chronic obstructive pulmonary disease (COPD) have an increased risk of postoperative cardiopulmonary complications after lung cancer surgery [3, 4]. Even without surgery, these patients are at risk of suffering cardiovascular events, such as arrhythmias, and respiratory events, such as pneumonia or acute respiratory distress syndrome [5, 6]. Thus, we hypothesized that patients with cardiopulmonary complications in the acute phase after surgery are at increased risk of the development of cardiovascular or respiratory (CVR) events in the chronic phase after surgery.

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B-type natriuretic peptide (BNP) is a useful biomarker for acute heart failure or cardiovascular events and elevated BNP levels have been reported in elderly or COPD patients [5, 7]. We previously reported that elevated preoperative BNP levels were associated with postoperative atrial fibrillation or cardiopulmonary complications after lung cancer surgery in elderly patients [8, 9]. It is possible that patients with elevated BNP levels before surgery have a higher risk not only of cardiopulmonary complications in the acute phase, but also of CVR events in the chronic phase after surgery. However, once the acute phase of surgery has passed, greater attention is generally paid to cancer recurrence because of its associated mortality in the chronic phase. Yet, CVR events in the chronic phase are also important for mortality and quality of life in patients with or without cancer recurrence. The objective of this study was to investigate the effect of postoperative cardiopulmonary complications in the acute phase, not only on cancer recurrence, but also on CVR events in the chronic phase after lung cancer surgery.

Patients and methods

Study design and population

From a prospective single-institution database of 496 consecutive patients who underwent elective pulmonary resection of lung cancer at our institute between August 2008 and December 2011, the medical charts of patients who underwent curative surgery with complete follow-up were analyzed retrospectively. Patients with limited surgery ($n = 32$) and patients who died in the immediate postoperative period ($n = 4$) were excluded from the analysis. Data of the remaining 460 patients were analyzed for the incidence of CVR events or cancer recurrence in the chronic phase (>6 months after surgery) after surgery. Complete preoperative and follow-up data were obtained for all of these patients. This study was performed at the National Hospital Organization Toneyama Hospital. The study protocol was approved by the Institutional Review Board, and all patients provided written, informed consent before participation (trial registration number: JPRN-UMIN2370). Results were compared between patients with vs. those without postoperative cardiopulmonary complications in the acute phase.

Surgical procedure

All patients underwent anterolateral thoracotomy or video-assisted thoracic surgery (VATS). In VATS, three access ports were inserted through 1–2 cm skin incisions in the side of the chest. One of these skin incisions was extended by 4–5 cm, through which the resected lung lobe was removed in a plastic bag without using a rib retractor. When VATS was replaced intraoperatively with open thoracotomy, this was classified as open thoracotomy.

Measurement of serum BNP levels

Serum BNP concentrations were measured using a chemiluminescence enzyme immunoassay (MI02 Shionogi BNP, Shionogi Pharmaceutical, Osaka, Japan) before and 1 month after surgery. The minimum quantity of BNP detectable with this system was 4 pg/mL.

Postoperative cardiopulmonary complications

All patients were followed up prospectively after surgery and complications occurring during the same hospitalization as the index procedure were recorded. We defined cardiopulmonary complications as respiratory complications, including pneumonia, diagnosed by a fever >38 °C, purulent sputum, and abnormal findings on chest X-ray; acute respiratory distress syndrome, diagnosed by a partial pressure of oxygen in arterial blood (PaO_2)/fraction of inspired oxygen (FiO_2) of less than 200 mmHg; respiratory insufficiency requiring tracheostomy; respiratory failure requiring mechanical ventilation; atelectasis with bronchoscopic therapy; and cardiovascular complications, including arrhythmias such as atrial fibrillation, paroxysmal supraventricular tachycardia, and ventricular tachycardia; angina pectoris; myocardial infarction; congestive heart failure; and thromboembolic events. Operative mortality was defined as death within 30 days of surgery.

Postoperative follow-up examinations

All patients were followed up routinely in our institute, at 3-month intervals postoperatively. Each evaluation comprised a physical examination, chest X-ray, and blood tests, including tumor markers. Thoraco-abdominal CT scans were generally performed at 6-month intervals and additional bone scintigraphy and magnetic resonance imaging (MRI) of the brain for the detection of cancer recurrence were performed every year. Positron-emission tomography (PET) using the glucose analog tracer fluorine-18 fluorodeoxyglucose (FDG) could be used as a substitute for bone scintigraphy for assessing distant metastases. In addition to the scheduled examinations, any CVR events occurring during follow-up were recorded for all patients.

Statistical analysis

Data are presented as mean ± standard deviation (SD) or as medians with an interquartile range. Categorical variables

are shown as the percentage of the sample. Comparisons between the groups were assessed by Student's t test or the Mann–Whitney U test for continuous variables and by the χ^2 test or Fisher's exact test for categorical variables. All data were analyzed with SAS for Windows 9.3 (SAS Institute, Cary, NC, USA). P value less than 0.05 were considered to be significant.

Table 1 Postoperative cardiopulmonary complications

Variable	Number of patients (%) ($N = 460$)
All cardiopulmonary complications	90 (20 %)
Cardiovascular complications	76 (17 %)
Atrial fibrillation	63
Paroxysmal supraventricular tachycardia	11
Acute heart failure	1
Acute cerebral infarction	1
Respiratory complications	15 (3 %)
Pneumonia	12
Acute respiratory distress syndrome	3

Results

Subjects

Postoperative cardiopulmonary complications were identified in 90 (20 %) of the 460 patients and are listed in Table 1. One patient had both cardiovascular and respiratory complications. Overall, the most common complications were arrhythmias, especially atrial fibrillation, while pneumonia was the most common respiratory complication.

Table 2 summarizes the characteristics of the patients with vs. those without postoperative cardiopulmonary complications. The mean age of the patients was 68 years (range 19–84 years). There was a significantly higher incidence of advanced age, hypertension, COPD, ischemic heart disease, induction chemotherapy, and thoracotomy (non-VATS procedure) in the group of patients with postoperative cardiopulmonary complications. There were also significantly higher BNP levels before and after surgery among the patients with postoperative cardiopulmonary complications. The median follow-up period was 36 months from surgery (range 24–60 months).

Table 2 Characteristics of patients with vs. those without postoperative cardiopulmonary complications in the acute phase (<1 month) after lung cancer surgery

Variable	With cardiopulmonary complications ($N = 90$)	Without cardiopulmonary complications ($N = 370$)	p value
Age, years	71 (64–75)	67 (60–73)	0.004
Male	61 (68 %)	217 (59 %)	0.112
Comorbidity			
Hypertension	50 (56 %)	146 (40 %)	0.005
Dyslipidemia	28 (31 %)	102 (28 %)	0.473
Diabetes mellitus	17 (19 %)	45 (12 %)	0.087
COPD	33 (37 %)	79 (21 %)	0.001
Ischemic heart disease	10 (11 %)	11 (3 %)	0.003
Preoperative BNP levels (pg/mL)	30 (13–47)	15 (8–24)	<0.0001
Lung cancer stage			0.072
IA	36 (40 %)	191 (52 %)	
IB	23 (26 %)	86 (23 %)	
IIA, IIB	20 (22 %)	46 (12 %)	
IIIA, IIIB	11 (12 %)	47 (13 %)	
Induction chemotherapy	7 (8 %)	10 (3 %)	0.027
VATS procedure	47 (52 %)	270 (73 %)	<0.0001
Mediastinal lymph node dissection	73 (81 %)	311 (84 %)	0.500
Adjuvant chemotherapy	27 (30 %)	101 (27 %)	0.576
Postoperative BNP levels (pg/mL)	21 (13–48)	16 (10–28)	0.035

BNP B-type natriuretic peptide, *COPD* chronic obstructive pulmonary disease, *VATS* video-assisted thoracic surgery

Table 3 Cardiovascular or respiratory events in the chronic phase (>6 months after surgery) and cancer recurrence in patients with vs. those without postoperative cardiopulmonary complications in the acute phase after lung cancer surgery

Variables	With cardiopulmonary complications ($N = 90$)	Without cardiopulmonary complications ($N = 370$)	p value
All cardiovascular or respiratory events	21 (23 %)	18 (5 %)	<0.0001
Cardiovascular events	14 (16 %)	11 (3 %)	<0.0001
Acute heart failure	3	2	
Arrhythmias	7	2	
Coronary artery disease	0	4	
Peripheral vascular disease	2	0	
Cerebrovascular disease	2	3	
Respiratory events	7 (8 %)	7 (2 %)	0.015
Pneumonia	6	6	
Acute respiratory distress syndrome	1	1	
Cancer recurrence	24 (27 %)	72 (19 %)	0.13

Clinical outcome in the chronic phase

There were significantly more CVR events in the chronic phase in the patients with, than in those without, postoperative cardiopulmonary complications in the acute phase (23 vs. 5 %; $p < 0.0001$; Table 3). Among the CVR events, the most common cardiovascular events were arrhythmias, especially atrial fibrillation ($N = 6$). All these patients with atrial fibrillation ($N = 6$) in the chronic phase had experienced transient atrial fibrillation in the acute phase after surgery. Most had recurrent atrial fibrillation for more than 2 years after surgery. The incidence of cardiovascular events in the chronic phase was significantly higher in those who had than in those who had not suffered postoperative cardiopulmonary complications in the acute phase (16 vs. 3 %; $p < 0.0001$). The incidence of respiratory events in the chronic phase was also significantly higher in those who had than in those who had not suffered postoperative cardiopulmonary complications in the acute phase (8 vs. 2 %; $p = 0.015$). Cancer recurrence was seen in 24 (27 %) of the patients with, and 72 (19 %) of the patients without, postoperative cardiopulmonary complications. There was no significant difference in the incidence of cancer recurrence between the patients who had and those who had not suffered postoperative cardiopulmonary complications in the acute phase after surgery. In addition, we performed univariate and multivariate analyses of risk factors for CVR events in the chronic phase (Table 4). Multivariate analysis revealed that postoperative BNP levels and postoperative complications in the acute phase were significant predictors of CVR events in the chronic phase.

Discussion

The findings of this study strongly suggest that patients with postoperative cardiopulmonary complications in the acute phase after lung cancer surgery are at increased risk for CVR events in the chronic phase. Thus, careful follow-up examinations for CVR events are necessary for patients with postoperative complications in the acute phase after lung cancer surgery.

In this study, preoperative and postoperative elevated BNP levels were associated with the incidence of CVR events in the chronic phase following lung cancer surgery. It has been reported that an increased BNP level is associated with advanced age and hypertension [5, 10] and predicts cardiovascular events in a community-based population [5, 11]. It has also been reported that increased BNP levels are associated with pulmonary diseases including not only primary pulmonary hypertension [12] and chronic thromboembolic pulmonary hypertension [13], but also COPD [7, 14]. The common pathway to BNP elevation in these pulmonary diseases seems to be right ventricular (RV) overload. According to some recent studies, patients with RV pressure or volume overload had a leftward shift of the ventricular septum toward the center of the LV cavity [15], resulting in geometric distortion of the left ventricle. Leftward ventricular septal shift in patients with RV overload leads to LV diastolic dysfunction. LV diastolic dysfunction is believed to be a risk factor not only for atrial fibrillation [16] or acute heart failure, but also for COPD [17]. In the present study, all patients with atrial fibrillation ($N = 6$) in the chronic phase experienced transient atrial fibrillation in the acute phase following lung cancer surgery. All of these

Table 4 Univariate and multivariate analyses of factors for cardiovascular or respiratory events in the chronic phase (>6 months after surgery)

Variable	Univariate Odds ratio (95 %CI)	*p* value	Multivariate Odds ratio (95 %CI)	*p* value
Age, years	1.118 (1.059–1.181)	<0.0001	1.049 (0.95–1.159)	0.34
Male	1.423 (0.656–3.088)	0.37		
Hypertension	2.159 (1.036–4.500)	0.04	1.539 (0.376–6.31)	0.55
Dyslipidemia	0.570 (0.228–1.422)	0.23	0.752 (0.143–3.969)	0.74
Diabetes mellitus	0.621 (0.183–2.108)	0.44		
COPD	2.166 (1.017–4.614)	0.045	0.501 (0.103–2.444)	0.39
Ischemic heart disease	1.908 (0.411–8.850)	0.41		
Preoperative BNP levels (pg/mL)	1.016 (1.006–1.026)	0.002	0.956 (0.911–1.003)	0.07
Lung cancer stage				
I vs II	2.213 (0.970–5.052)	0.06	3.479 (0.689–17.569)	0.05
I vs III	1.155 (0.362–3.689)	0.89	1.108 (0.122–10.079)	0.81
Induction chemotherapy	3.058 (0.823–11.365)	0.095	0.591 (0.026–13.415)	0.74
VATS procedure	0.218 (0.103–0.461)	<0.0001	0.468 (0.091–2.412)	0.36
Mediastinal lymph node dissection	0.412 (0.186–0.912)	0.03	0.429 (0.085–2.159)	0.30
Adjuvant chemotherapy	1.165 (0.532–2.553)	0.70		
Postoperative BNP levels (pg/mL)	1.028 (1.011–1.045)	0.001	1.047 (1.008–1.087)	0.02
Postoperative complications	8.256 (3.847–17.72)	<0.0001	5.274 (1.152–24.139)	0.03

BNP B-type natriuretic peptide, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *VATS* video-assisted thoracic surgery

six patients had elevated BNP levels (>30 pg/mL) before and after surgery and four had COPD. LV diastolic dysfunction has been reported to cause mild elevation of BNP levels [18, 19]. We previously reported that LV diastolic dysfunction or elevated BNP levels (>30 pg/mL) before surgery were associated with the incidence of atrial fibrillation in the acute phase after lung cancer surgery [8, 20]. The patients with LV diastolic dysfunction or elevated BNP levels before surgery continued to have LV diastolic dysfunction after surgery, indicating that we should monitor patients with atrial fibrillation in the acute phase after surgery to detect recurrent atrial fibrillation in the chronic phase. In the present study, seven patients suffered respiratory events in the chronic phase after surgery, five of whom had elevated BNP levels (>30 pg/mL) before and after surgery. In summary, elevated BNP levels were associated with both cardiovascular and respiratory events. Therefore, careful follow-up is necessary for patients with elevated BNP levels during both the acute and chronic phases following lung cancer surgery.

To the best of our knowledge, this is the first study to evaluate the effect of postoperative cardiopulmonary complications on long-term outcomes after lung cancer surgery. Serum BNP levels should be measured before surgery and effective prophylactic strategies should be considered for patients with elevated preoperative BNP levels to reduce the incidence of postoperative cardiopulmonary complications and CVR events in the long term. This was a single-institution clinical study, which restricts the generalizability of the results, and the number of patients in the study cohort was relatively small; thus, additional investigations are necessary to define the clinical impact of postoperative cardiopulmonary complications on long-term outcomes for lung cancer patients in the chronic phase.

In conclusion, the results of the present study demonstrated that postoperative cardiopulmonary complications in the acute phase were associated with CVR events in the chronic phase after lung cancer surgery. Patients with postoperative cardiopulmonary complications in the acute phase need to be followed up carefully, not only for cancer recurrence but also for CVR events in the long term.

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ORIGINAL ARTICLE

Atrial natriuretic peptide protects against cisplatin-induced acute kidney injury

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Abstract
Purpose Cisplatin is an effective chemotherapeutic agent used in the treatment of a wide variety of malignancies. Acute kidney injury (AKI) is the major toxicity associated with cisplatin and sometimes necessitates a reduction in dose or discontinuation of treatment. Atrial natriuretic peptide (ANP) is secreted by the heart and exerts a wide range of renoprotective effects, including anti-inflammatory activity. The objective of this study was to investigate the protective effects of ANP on cisplatin-induced AKI in mice.
Methods Mice were randomly divided into three groups: control, cisplatin (20 mg/kg, intraperitoneal)/vehicle treatment, and cisplatin/ANP (1.5 μg/kg/min via osmotic-pump, subcutaneous) treatment. At 72 h after cisplatin injection, serum blood urea nitrogen and creatinine, urine albumin/creatinine, and renal expression of mRNAs encoding tumor necrosis factor-α, interleukin (IL)-1β, IL-6, intercellular adhesion molecule-1, monocyte chemoattractant protein-1, and transforming growth factor (TGF)-β were measured using real-time polymerase chain reaction. Histological changes were also evaluated.
Results ANP treatment significantly attenuated cisplatin-induced increases in serum blood urea nitrogen and creatinine, urine albumin/creatinine, and renal expression of IL-1β, IL-6, intercellular adhesion molecule-1, and monocyte chemoattractant protein-1 mRNAs. Cisplatin-induced renal dysfunction and renal tubular necrosis were thus attenuated by ANP treatment.
Conclusions Our results indicate that ANP exhibits a protective effect against cisplatin-induced AKI in mice. ANP may thus be of value in prophylactic strategies aimed at mitigating the adverse effects associated with chemotherapy agents, including cisplatin.

Keywords Atrial natriuretic peptide · Acute kidney injury · Cisplatin

Introduction

Cisplatin is an effective chemotherapeutic agent used in the treatment of a wide variety of malignancies. Acute kidney injury (AKI) is the major toxicity associated with cisplatin, sometimes necessitating a reduction in dose or discontinuation of treatment [1, 2]. In addition, AKI induced by cisplatin is associated with high morbidity and mortality [1]. Although several therapeutic strategies have been proposed for preventing cisplatin-induced AKI, no specific treatments are currently recommended aside from vigorous hydration with normal saline [3]. Prophylactic management of AKI is therefore an important issue in chemotherapy with agents such as cisplatin.

Atrial natriuretic peptide (ANP) is secreted by the heart and mediates a wide range of biological activities, such

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as diuresis, natriuresis, vasorelaxation, and inhibition of the renin–angiotensin–aldosterone system through binding to the guanylyl cyclase-A (GC-A) receptor [4, 5]. The GC-A receptor is abundantly expressed in the heart, vascular endothelium, and kidney, indicating that the kidney would be one of the primary target organs for treatments using ANP [6]. ANP is also reportedly renoprotective, exhibiting both anti-inflammatory and anti-fibrotic activities [7, 8]. In addition, recent clinical studies reported that ANP treatment has beneficial effects on contrast-induced nephropathy [9], renal function, and postoperative cardiorenal events following cardiac surgery [10]. Therefore, we hypothesized that ANP may inhibit AKI induced by cytotoxic chemotherapy. In the present study, we investigated the protective effects of ANP on cisplatin-induced AKI.

Materials and methods

In vivo studies

Seven-week-old C57BL/6 mice were purchased from Japan SLC, Inc. (Shizuoka, Japan). All animal experiments were performed according to the protocol approved by the Animal Care Ethics Committee of the National Cerebral and Cardiovascular Center Research Institute.

Cisplatin was purchased from Yakult Co. Ltd. (Tokyo, Japan). Mice were randomly divided into three groups: control, cisplatin/vehicle treatment, and cisplatin/ANP treatment. Cisplatin was administered as a single intraperitoneal dose of 20 mg/kg; an identical volume of sterile saline was administered to control mice. One day before cisplatin administration, ANP administration was started using an osmotic mini-pump, as previously reported [11]. ANP was purchased from Peptide Institute (Osaka, Japan). The osmotic mini-pump (Alzet Model 1003D, Duret Corporation, Cupertino, CA), containing either 5 % glucose (vehicle) or ANP in 5 % glucose (delivered at 1.5 μg/kg/min), was implanted subcutaneously under anesthesia in the upper back of each mouse. The ANP dose used had no effect on blood pressure or heart rate in the treated mice (data not shown). Mice were allowed free access to water and standard mouse chow and were killed 24 or 72 h after cisplatin administration, at which time the kidneys were removed and stored at −80 °C until analysis.

Serum and urine analyses

On the day of the killing, mice were deeply anesthetized with inhaled isoflurane and the kidneys and urinary bladder were exposed through a midline abdominal incision. The urinary bladder was emptied by direct compression to obtain a urine sample. Blood samples were collected via the femoral vein and centrifuged (2,000×*g* for 5 min), and the resulting serum samples were stored at −80 °C until analysis. Serum blood urea nitrogen (BUN) and creatinine levels were measured using FUJI DRI-CHEM SLIDE BUN-PIII and CRE-PIII, respectively, with a DRI-CHEM 4000 chemistry analyzer (FUJIFILM Co., Ltd., Tokyo, Japan). Urine protein and creatinine levels were measured by Albuwell M ELISA and Creatinine Companion chemical analysis, respectively (Exocell Inc., Philadelphia, PA).

Histological evaluation of the kidney

Kidneys were fixed with 4 % formaldehyde for 24 h, embedded in paraffin, sectioned at 4 μm, and stained with hematoxylin–eosin (HE) or periodic acid–Schiff (PAS) reagent for histological examination. Tubular damage was assessed microscopically in PAS-stained sections and scored based on the percentage of cortical tubules showing epithelial necrosis as follows: 0, normal; 1, <10 %; 2, 10–25 %; 3, 26–75 %; 4, >75 %. Tubular necrosis was defined as the loss of the proximal tubular brush border, blebbing of apical membranes, tubular epithelial cell detachment from the basement membrane, or intra-luminal aggregation of cells and proteins. Apoptosis in the kidney was assessed by terminal deoxynucleotidyl transferase-mediated uridine triphosphate nick-end labeling (TUNEL) assay using an ApopTag Plus Peroxidase In Situ Apoptosis Detection Kit (Millipore, Bedford, MA) according to the manufacturer's protocol. The number of apoptotic cells in each section was calculated by counting the number of TUNEL-positive cells in ten random, non-overlapping fields per slide at a 400× magnification. Histological and morphometric examinations were performed in a blinded manner.

Quantitative real-time PCR analysis

Total RNA was isolated from the kidneys using an RNeasy Mini Kit (Qiagen, Hilden, Germany) and reverse-transcribed into cDNA using a Quantitect Reverse Transcription Kit (Qiagen). PCR amplification was performed using SYBR Premix Ex Taq (Takara, Siga, Japan). Real-time PCR was performed in a 96-well plate using a Light Cycler 480 System II (Roche Applied Science, Indianapolis, IN) and the following primers: for monocyte chemoattractant protein-1 (MCP-1), sense 5′-GCAGGTGTCCCAAAG AAGCTGTAGT-3′ and antisense 5′-CAGAAGTGCTTG AGGTGGTTGTGGA-3′; for interleukin (IL)-6, sense 5′-CCAGTTGCCTTCTTGGGACTGATG-3′ and antisense 5′-GTAATTAAGCCTCCGACTTGTGAAG-3′; for IL-1β, sense 5′-AGCACCTTCTTTCCCTTCATCTTTG-3′ and antisense 5′-GAGGTGGAGAGCTTTCAGTTCATAT-3′; for tumor necrosis factor-alpha (TNF-α), sense 5′-TGGCC CAGACCCTCACACTCAGATC-3′ and antisense 5′-GCC

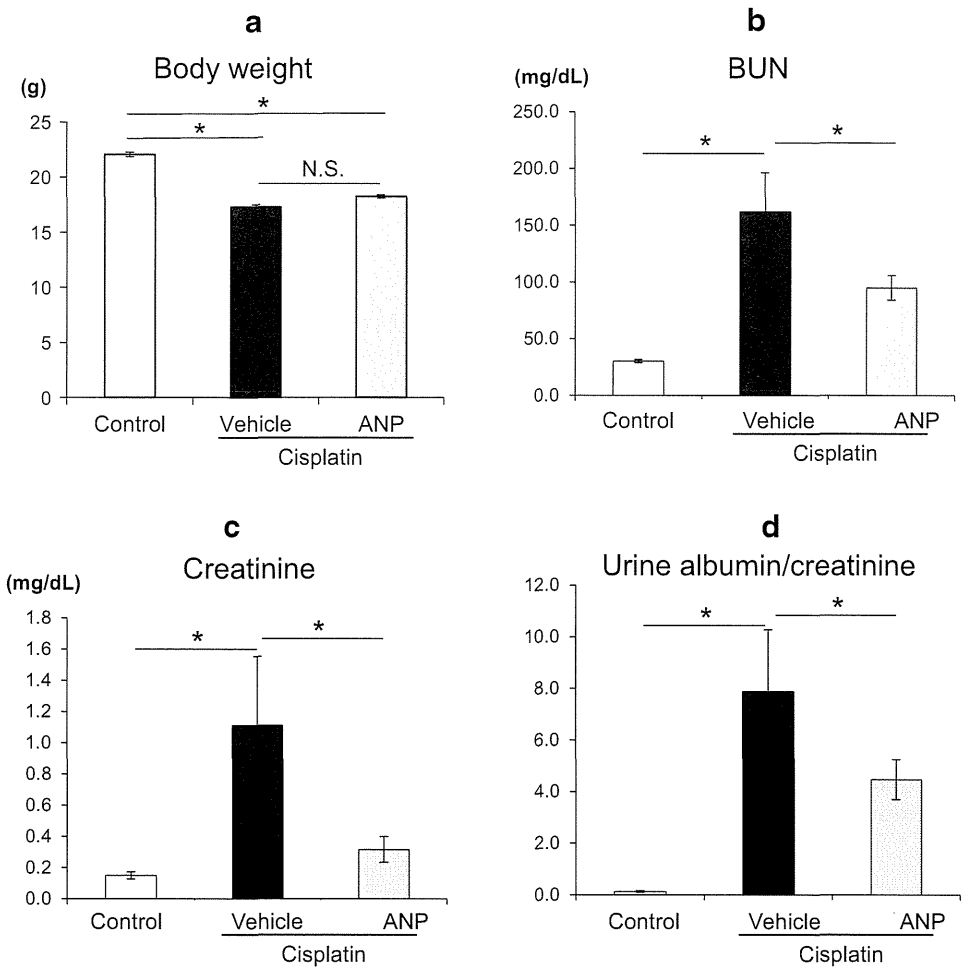

Fig. 1 Body weight (**a**), serum BUN (**b**) and creatinine (**c**), and urine albumin/creatinine (**d**) in each group 3 days after cisplatin administration. Data are expressed as mean ±SE; $n = 5$; $^*P < 0.05$. *N.S.* not significant

TTGTCCCTTGAAGAGAACCTGG-3′; for intercellular adhesion molecule-1 (ICAM-1), sense 5′-GGCAAGAA CCTTACCCTACGCTGCC-3′ and antisense 5′-GTTCAGTG CGGCACGAGAAATTGGC-3′; for transforming growth factor-beta (TGF-β), sense 5′-CAACTACTGCTTCAGCTCC ACAGAG-3′ and antisense 5′-CAAGGACCTTGCTGTA CTGTGTGTC-3′; and for 36B4, sense 5′-TCATTGTGGGA GCAGACAATGTGGG-3′ and antisense 5′-AGGTCCTCCT TGGTGAACACAAAGC-3′. The PCR conditions were as follows: Initial denaturation at 95 °C was followed by 35 cycles of amplification for 15 s at 95 °C and 20 s at 58–62 °C (optimized for each primer pair), with subsequent melting curve analysis, increasing the temperature from 72 to 98 °C. Quantification of gene expression was calculated relative to 36B4, which was used as a housekeeping gene.

Western blot analysis

Kidneys were lysed with RIPA buffer containing protease inhibitors. Total cell lysates were loaded on a 10–20 % gradient gel (10 μg/lane) (Bio-Rad, Hercules, CA) and transferred onto polyvinylidene difluoride membranes (Millipore) after electrophoresis. The following antibodies were used: anti-nuclear factor-kappa B (NF-κB) and anti-pS536-NF-κB (93H1) (both purchased from Cell Signaling Technology, Beverly, MA).

Statistical analysis

Results are presented as mean ±SE. Stimulated samples were compared with controls using the unpaired Student's *t* test. One-way ANOVA followed by the post hoc Tukey's test was used for multiple-group comparisons. A P value <0.05 was considered significant.

Results

ANP inhibits cisplatin-induced AKI

Figure 1 shows the mean body weight, serum BUN and creatinine levels, and urine albumin/creatinine levels for each group. Three days after cisplatin administration, significant weight loss was observed in the vehicle- and ANP-treated

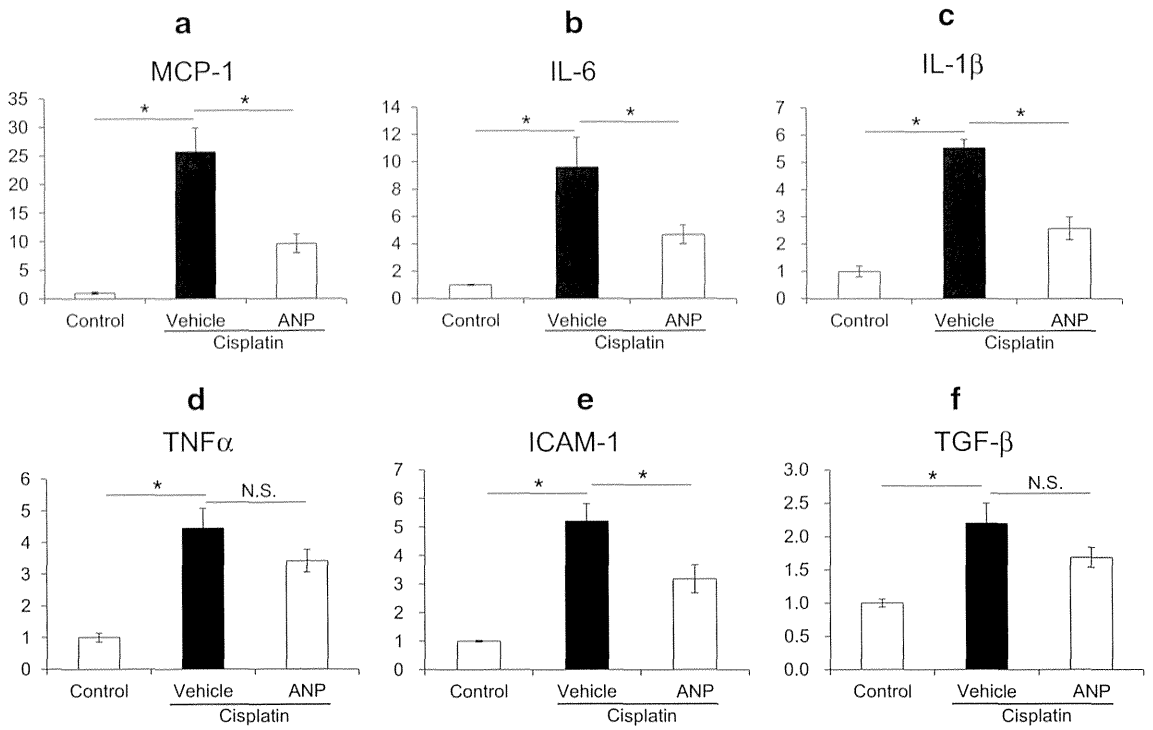

Fig. 2 Relative expression of MCP-1 (**a**), IL-6 (**b**), IL-1β (**c**), TNF-α (**d**), ICAM-1 (**e**), and TGF-β (**f**) mRNAs normalized to that of 36B4 mRNA in each group 3 days after cisplatin administration. Data are expressed as mean ±SE; $n = 5$; $^*P < 0.05$. *N.S.* not significant

groups compared with the control group; however, there was no significant difference in body weight between the vehicle- and ANP-treated groups after cisplatin administration (Fig. 1a). The levels of serum BUN/creatinine and urine albumin/creatinine increased significantly after cisplatin administration, whereas ANP pretreatment significantly attenuated the increase in serum BUN/creatinine and urine albumin/creatinine levels observed after cisplatin administration (Fig. 1b–d). Expression of the genes encoding MCP-1, IL-6, IL-1β, TNF-α, ICAM-1, and TGF-β was significantly upregulated in the kidneys after cisplatin administration, but ANP pretreatment significantly attenuated the upregulated expression of the genes encoding MCP-1, IL-6, IL-1β, and ICAM-1 (Fig. 2). Although expression of the genes encoding TNF-α and TGF-β was lower in the ANP group compared with the vehicle group, the difference was not significant.

ANP protects kidney morphology and function after cisplatin administration

Histological examination of the kidneys of mice treated with vehicle after cisplatin administration revealed more extensive renal tubular injury, including tubular cell necrosis, loss of the brush border membrane, tubular dilatation, and cast formation, compared with the control group (Fig. 3). Compared with vehicle, ANP pretreatment significantly attenuated renal tubular injury in the kidneys resulting from cisplatin administration (Fig. 3a–c). Semi-quantitative assessment of the severity of tubular injury in PAS-stained tissue sections demonstrated significantly more extensive injury in vehicle-treated mice than in control mice. Compared with vehicle, ANP pretreatment significantly attenuated renal injury resulting from cisplatin administration (Fig. 3d). TUNEL analyses revealed significant apoptosis of tubular epithelial cells in cisplatin-treated mice. The extent of tubular epithelial cell necrosis following cisplatin administration was significantly attenuated in mice pretreated with ANP relative to vehicle-treated mice (Fig. 4a–d).

The renoprotective effects of ANP involve NF-κB signaling

Cisplatin-treated mice showed significantly higher levels of phosphorylated NF-κB (pNF-κB) in the kidneys 1 day after cisplatin administration (Fig. 5). Compared with vehicle, ANP pretreatment significantly attenuated the increase in kidney pNF-κB levels associated with cisplatin administration (Fig. 5).

Discussion

In the present study, we demonstrate for the first time that ANP has a prophylactic effect on cisplatin-induced AKI.

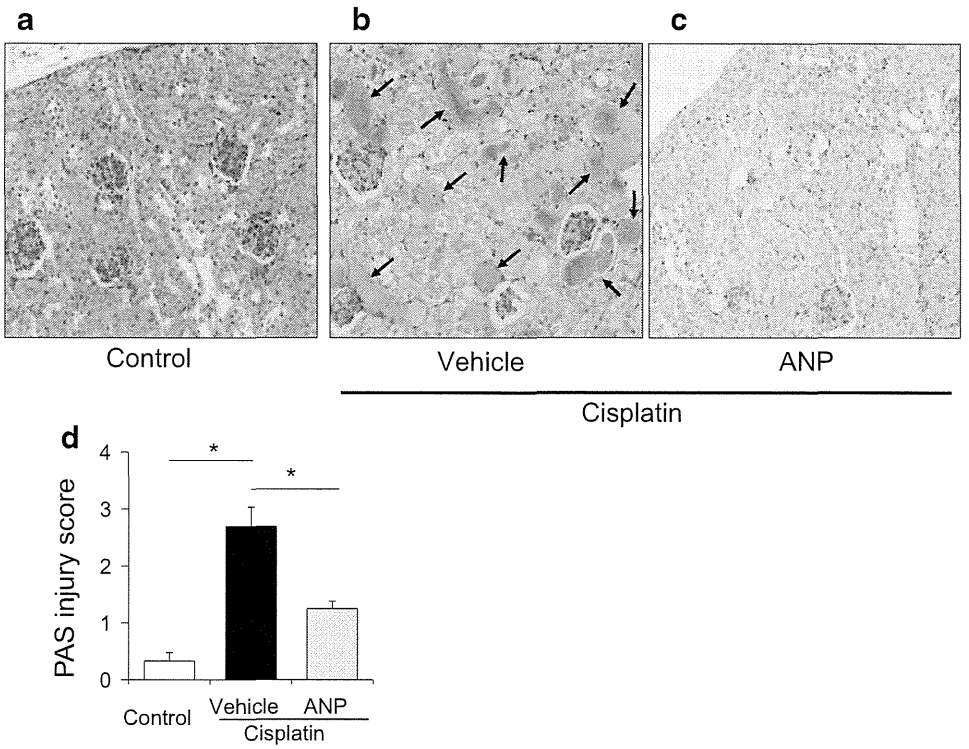

Fig. 3 Effect of ANP on morphology in a mouse model of acute kidney injury induced by cisplatin. Kidney tissue sections from control (**a**), cisplatin/vehicle-treated (**b**), and cisplatin/ANP-treated (**c**) mice were prepared and stained with PAS 3 days after cisplatin administration. Representative images are shown at 400× magnification. *Black arrows* indicate PAS-positive parts. (**d**) Assessment of tubular injury score via PAS staining. Data are expressed as mean ±SE; $n = 5$ per condition; $^*P < 0.05$

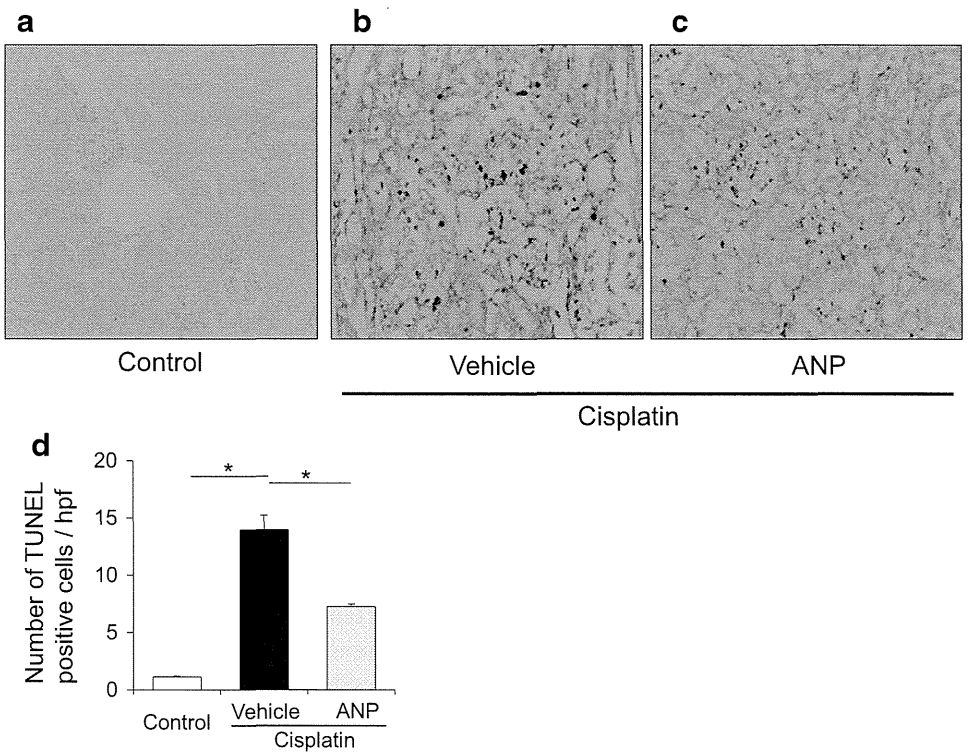

Fig. 4 Effect of ANP on cisplatin-induced apoptosis in a mouse acute kidney injury model. Kidney tissue sections from control (**a**), cisplatin/vehicle-treated (**b**), and cisplatin/ANP-treated (**c**) mice were prepared and evaluated by TUNEL 3 days after cisplatin administration. Representative images are shown at 400× magnification. (**d**) Assessment of apoptotic cells via TUNEL assay. The number of apoptotic cells was counted in 10 high-power field (hpf) and is expressed as mean ±SE; $n = 5$ per condition; $^*P < 0.05$

ANP pretreatment significantly attenuated renal dysfunction and tubular epithelial cell necrosis induced by cisplatin in our mouse model. The present findings indicate that ANP administration is a valuable treatment option to prevent AKI induced by cytotoxic chemotherapy, including that using cisplatin.

Numerous studies have shown that ANP has inhibitory effects against cardiovascular events such as acute heart

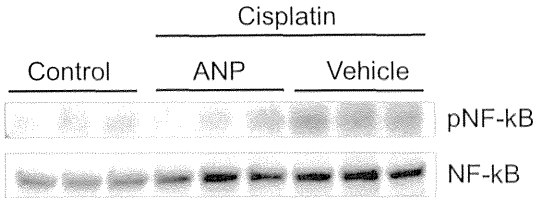

Fig. 5 Effect of ANP on NF-κB signaling in the acute kidney injury model 1 day after cisplatin administration. NF-κB signaling was assessed by immunoblot analysis. Representative images are shown; $n = 5$ per condition

failure and arrhythmias [4, 5]. However, there have been few studies examining the effects of ANP on renal injury and the pathophysiology of renal disease. As the GC-A receptor is abundantly expressed not only in the cardiovascular system but also in the kidney, the kidney could be a primary target organ for ANP [6]. Previous studies have shown that ANP inhibits the growth of mesangial cells, vascular smooth muscle cells, and fibroblasts [12, 13]. Recently, it was reported that ANP inhibits early inflammatory responses and renal fibrosis through NF-κB signaling [7, 8]. More recently, clinical evidence has shown that ANP exerts a much broader range of renoprotective activities [9, 10, 14]. Morikawa et al. [9] reported the results of a prospective randomized controlled trial that showed ANP administration attenuates contrast-induced nephropathy after coronary angiography. In their study protocol, low-dose ANP administration (0.042 μg/kg/min) was started 4–6 h before angiography and continued for 48 h. As a result, the incidence of increases in creatinine of ≥25 % or ≥0.5 mg/dL over baseline was significantly lower in the ANP-treated group than in the control group (3.2 vs. 11.7 %, respectively; $P = 0.015$). Mori et al. [14] reported that low-dose (0.0125 μg/kg/min) ANP treatment reduces the incidence of AKI after aortic arch surgery. In their study protocol, ANP administration was started just before surgery and continued for 24 h postoperatively. As a result, the incidence of AKI was significantly lower in the ANP-treated group than in the placebo-treated group (30 vs. 73 %, respectively; $P = 0.015$). There were no significant differences in mean arterial pressure or number of events of hypotension between the groups. The results of these studies suggest that ANP reduces the incidence of renal events following chemical or surgical injury, without severe side effects.

However, there are some limitations to the efficacy of ANP with respect to attenuating the severity of renal failure. Allgren et al. [15] reported no beneficial effects resulting from ANP treatment with respect to the need for dialysis in patients with acute renal failure. In their study protocol, an excessive dose of ANP (0.2 μg/kg/min) was administered for condition-established patients with acute tubular necrosis due to recent ischemic or nephrotoxic insults. Furthermore, in their study population, ANP-treated patients had significantly lower blood pressure than placebo-treated patients. In another study, it was shown that low-dose ANP (0.02 μg/kg/min) initiated at the start of cardiopulmonary bypass decreases the incidence of post-surgery dialysis for acute renal failure in patients with chronic kidney disease, without significant hypotension [10]. It is possible that hypotension might account for the lack of beneficial effects of ANP treatment on renal function. In addition, it could also be very important that ANP is given as a "pretreatment" prior to any stimulation in order for it to be of benefit. In the present study, we showed that ANP pretreatment significantly attenuates renal dysfunction and the increases in inflammatory cytokine levels in the kidneys in AKI induced by cisplatin, without causing hypotension.

ANP is an endogenous peptide that has been approved for treatment of acute heart failure in Japan, and few patients have suffered severe side effects [16]. Therefore, the clinical safety of ANP has already been established [16]. The observed protective effects of ANP in attenuating AKI as demonstrated in this study may reduce the severity of side effects resulting from cytotoxic chemotherapy agents, including cisplatin.

In this study, the effects of ANP on tumor-bearing mice with or without cisplatin have not been studied. In addition, we examined the effect of ANP on only NF-κB pathway; however, cisplatin-induced kidney injury has been reported to involve various pathways, such as mitochondrial pathway [17]. Therefore, further studies to identify the specific targets affected by ANP are required. After mechanism identification, we want to begin clinical trials examining the use of human ANP for preventing AKI in lung cancer patients undergoing chemotherapy.

In summary, we present the first report that ANP exerts a prophylactic effect on AKI induced by cisplatin. Additional studies are warranted to determine whether these effects can be observed in clinical cases and translated into improved clinical outcomes.

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Conflict of interest All authors have nothing to declare.

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ORIGINAL ARTICLE

Surgery for pulmonary malignancies in patients with a previous history of head and neck squamous cell carcinoma

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Abstract
Purpose To examine the perioperative and long-term outcomes of surgery for malignancies of the lungs in patients with a history of head and neck squamous cell carcinoma (HNSCC) and to evaluate the risk factors associated with postoperative complications.
Methods The data of 39 patients with a history of HNSCC who underwent pulmonary resection were reviewed. The perioperative and long-term outcomes were analyzed.
Results Eight patients (21 %) had difficult airways, and nine patients (23 %) developed postoperative complications. A low body mass index (<18.5), a history of malignancy besides HNSCC and chronic obstructive pulmonary disease were each found to be significantly associated with the development of postoperative complications. The 5-year survival rate of all patients was 80 %.
Conclusions The airway management of patients with a history of HNSCC should be carefully undertaken. Preoperative assessment of their nutritional status and careful prevention of air leakage during surgery are important. Because favorable outcomes can be achieved, aggressive surgical management should be considered for the treatment of pulmonary malignancies in patients with a history of HNSCC.

Keywords Pulmonary metastasis · Lung cancer · Head and neck cancer

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Introduction

Head and neck cancer (HNC) is the fifth most common cancer worldwide [1]. Squamous cell carcinoma is the most common histological type of HNC. It has been reported that distant metastases of head and neck squamous cell carcinoma (HNSCC) occur most frequently in the lungs, followed by the bones and liver [2, 3]. In addition to having a high incidence of pulmonary metastases, patients with a history of HNSCC also have a higher risk of developing primary lung cancer [4, 5]. In this situation, the surgical treatment of pulmonary malignancies, including second and metastatic cancers, in patients with a history of HNSCC is not rare. However, information about the perioperative management of these patients remains limited, and airway problems, such as aspiration pneumonia or intubation difficulties, i.e. a difficult airway, are expected to be problematic.

The aim of this study was to examine the perioperative outcomes of surgery for malignancies of the lungs in patients with a history of HNSCC. In particular, we evaluated the risk factors associated with postoperative