原田　これだけ情報がアベイラブルになってくると，患者が医師を選ぶ傾向が見られます。その結果，外科医が癌化学療法に関しては，内科医に任せるという役割分担が顕著になってきているようです。

西條　こういった専門医の認定条件を満たすために，臨床腫瘍学会ではどのような努力をしているのでしょうか。大江先生，現在，どういう状況なのでしょうか。

大江　法人格の所有という条件を満たしていませんでしたが，NPO法人の申請を平成16年8月にしました。会員数は既に1,000名を超えていますし，医師も今現在8割を超えています。会員名簿に関しては，多分，1，2年内には発行することが可能だと思います。

西條　欠落しているのは法人格ということですが，取得はそれ程難しくはないのですか。

福岡　難しくないと思います。アメリカの学会は，ほとんどがNPO法人であると聞いています。日本では東京都が，呼吸器内視鏡学会と世界気管支学会という2つの学会をNPO法人にしました。NPO法人を取得するということは，学会としては趣旨に合っているんじゃないかと思います。

原田　中間法人というのもありますが，取得は早く取れますが，税金がかかります。その点からしてもNPO法人の方がいいですね。

福岡　社団法人や財団法人は相当な財産が要求されますからね。

西條　今年度から第3次対癌10カ年総合戦略が始まりまして，臨床腫瘍専門医の育成を政策課題として目指しています。やはり，知識を身につけるということ，実地の技術を身につけるということ，この両方が必要です。暫定指導医の存在する全がん協に属する病院・特定機能病院が臨床腫瘍学会とタイアップすることによって，3年後あるいは5年後に臨床腫瘍専門医が実際に出てくるという状況になるでしょう。

大江　私が平成16年度から開始された厚生労働科学研究費補助金がん臨床研究事業による「効果的かつ効率的ながん専門医の育成方法に関する研究」班を担当させていただくことになりました。

専門医の育成で一番考え違いをしていけないことは，「専門医と名前のついた医者」を増やす事が専門医の育成ではないと言うことです。現在，抗がん剤を使っている医者にただ「専門医」と名前をつけてもまったく意味がありません。本当に能力のある「専門医」を育成することが重要です。その為には，卒前から一貫した臨床腫瘍学の教育をすることが必要と思います。また，一部の施設を除いては現在の卒後教育も十分ではありません。特に，臓器別の教育体制から横断的な臨床腫瘍学の教育体制へ改革する必要があると思います。急な改革は難しいかもしれませんが，手術の片手間に化学療法を行なっている現状も改める必要があります。50人の手術をして50人の化学療法をする医者が100人いるよりも，100人の手術をする医者50人と100人の化学療法をする医者50人がいたほうが遥かに効率的で，それぞれのレベルも向上します。

このようなことを念頭に，研究班としての成果がだせればと思っております。

● がん治療学会の専門医との差

西條　がん治療学会でも癌治療専門医というのを認定されているそうですが，臨床腫瘍専門医と質的な差というのはありますか。

福岡　がん治療学会というのは，内科・外科・放射線科・婦人科といった幅広い専門分野の集まりで，横断的な外科系の会員が多い学会です。だから，その中で癌治療全体の専門医というのを一元化するということは，なかなか難しいのではないでしょうか。特に薬物療法に関する専門医を認定するということは，がん治療学会としてはかなり難しいと思います。

がん治療学会は全体の癌治療のレベルの，ボトムを上げるという役割があると思います。

やはり，癌薬物療法の専門医を増やしていくという意味では，それに特化したものをつくるということが重要ではないかと思います。我が国にメディカルオンコロジストがいないというのはやはり，困ったことだと思います。そういう点で，かなりレベルの高い専門医をつくるということを臨床腫瘍学会としては目指していきたいと思っています。

西條　がん治療学会の大半は外科の先生の集まりですので外科の先生がやられる化学療法を正当化するような専門医制度という気がしますね。本末転倒してい

Nonmyeloablative Allogeneic Stem Cell Transplantation for Patients With Unresectable Pancreatic Cancer

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Objectives: To clarify whether nonmyeloablative allogeneic stem cell transplantation (NST) can produce the graft versus tumor (GVT) effect in patients with pancreatic cancer.

Methods: A pilot trial of NST was conducted in 5 patients with unresectable pancreatic cancer. Preparative conditioning consisted of administration of 60 mg/kg cyclophosphamide on days 6 and 7 before transplantation, followed by 25 mg fludarabine per square meter of body surface on each of the last 5 days prior to transplantation. Cyclosporine was started 4 days before transplantation. Peripheral blood stem cells from the patients' HLA-identical siblings were transfused into the patients.

Results: Complete donor T-cell chimerism in peripheral blood was obtained in 4 patients on day 15 after transplantation. NST resulted in tumor reduction in 2 patients as determined by CT, decreasing levels of tumor markers in 2 patients, pain relief in 2 patients, and a decrease in pleural fluid in 1 patient. Two patients developed acute graft versus host disease (GVHD) of grade II or III and 2 had chronic GVHD involving skin and/or liver. Administration of immunosuppressive drugs for the treatment of GVHD resulted in the elevation of tumor marker levels.

Conclusion: These findings are the first to suggest that NST induces a GVT effect on pancreatic cancer.

Key Words: nonmyeloablative allogeneic stem cell transplantation, pancreatic cancer, graft versus tumor effect, graft versus host disease, tumor regression, chimerism

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The prognosis of patients with pancreatic cancer treated with conventional therapeutic modalities is extremely poor, and thus a novel modality is being actively sought for the treatment of this disease. Allogeneic stem cell transplantation has proved to have a potent antitumor effect not only in patients with hematological malignancies[1] but also in those with solid malignancies.[2,3] In a study of nonmyeloablative allogeneic peripheral blood stem cell transplantation (NST) for solid malignancies, Childs et al[4,5] reported the successful treatment of metastatic renal cell carcinoma and clinically demonstrated the presence of the graft versus tumor effect, known as the GVT effect. However, the GVT effect in patients with pancreatic cancer is unknown. Here, we describe the results of a pilot trial of NST in 5 patients with unresectable pancreatic cancer.

PATIENTS AND METHODS

All 5 patients were diagnosed with unresectable pancreatic cancer by abdominal CT scans and angiographies, which demonstrated major vascular invasion. Four patients had metastatic disease (patients 2, 3, 4, and 5), and 1 patient had locally advanced unresectable disease (patient 1) (Table 1). Two patients had multiple liver metastases (patients 2 and 3), 2 had subclavicular lymph node metastases (patients 4 and 5), 1 had bone metastasis (patient 5), and 1 had pleural metastasis (patient 4) on CT. All 5 tumors were confirmed histologically as adenocarcinoma by needle biopsy (patients 1, 2, and 3) or operative biopsy (patients 4 and 5). The CEA and CA19-9 levels were high in all but patient 1. Patients 2, 3, 4, and 5 were administered gemcitabine as chemotherapy. Patients 2 and 4 initially responded to the therapy with stable disease, but the tumor then began to progress again. Patients 3 and 4 underwent gastrojejunostomy for duodenal obstruction by the pancreatic cancer.

All patients accepted the protocol approved by the ethics committee of Tokyo Metropolitan Komagome Hospital, Japan, and full informed consent was obtained in writing.

Preparative conditioning consisted of intravenous infusion of 60 mg cyclophosphamide per kilogram of body weight on days 6 and 7 before transplantation, followed by an intravenous infusion of 25 mg fludarabine per square meter of body surface area on each of the last 5 days prior to transplantation. Cyclosporine was started 4 days before transplantation at a dose of 3 mg/kg daily.

Peripheral blood stem cell allografts were collected from HLA-identical siblings on day 5 of G-CSF administration.

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TABLE 1. Characteristics and Results of Pancreatic Cancer Patients Undergoing NST

Patient No.	Age/ Gender	Metastases	Prior Therapy	Histology	GVHD Acute	GVHD Chronic	GVT Effect	Response Clinical Effects	Response CA-19-9 (U/mL) Pre-NST	Response CA-19-9 (U/mL) Post-NST	Outcome
1	59 F	None	None	Adenocarcinoma	None	Extensive	+	80% Tumor reduction, pain relief	2.7	2.5	Dead (d 349)
2	40 M	Liver	Gemcitabine	Adenocarcinoma	Grade III, liver, gut	Extensive	+	40% Tumor reduction, pain relief	2744	228	Dead (d 156)
3	68 M	Liver	Gemcitabine	Adenocarcinoma	None	—	None	Progressive disease	21,396	26,060	Dead (d 52)
4	61 F	Pleura, lymphnodes	Bypass operation, gemcitabine	Adenocarcinoma	None	None	+	Decreased pleural fluid	39.4	23.2	Dead (d 172)
5	63 M	Bone, lymphnodes	Bypass operation, gemcitabine	Adenocarcinoma	Grade II, gut	—	None	Progressive disease	45,825	100,289	Dead (d 87)

On day 0, allografts from HLA-identical siblings were transfused into the patients.

Donor chimerism was examined by polymerase chain reaction assay of microsatellite regions (PCR assay).

RESULTS

The chimerism determined by PCR assay on days 15 and 30 is shown in Table 2. More than 90% T-cell donor chimerism in peripheral blood was obtained on day 15 in patients 1, 2, 4, and 5, and 100% was obtained in those patients on day 30 after transplantation. Complete donor myeloid chimerism was obtained in patients 1 and 4 who survived for >100 days after transplantation. Table 1 shows the characteristics, results, and course of the pancreatic cancer patients undergoing NST. Acute GVHD occurred in patient 2 (grade III with liver and gut) and patient 5 (grade II with gut). Patients 1 and 2 had chronic extensive GVDH in the skin >120 days after transplantation.

In patients 1 and 2, CT showed tumor reduction, and both experienced pain relief, as described in the following case report. Pleural fluid due to the pancreatic cancer decreased in patient 4 on day 150. Patients 3 and 5 showed progressive disease.

TABLE 2. Percentage of Donor Chimerism After NST

Patient No.	Day 15 T Cell	Day 15 Myeloid Cell	Day 30 T Cell	Day 30 Myeloid Cell	Day 100 T Cell	Day 100 Myeloid Cell
1	92	40	100	43	100	100
2	95	23	100	23	*	*
3	42	1	73	28	*	*
4	94	93	100	84	100	100
5	98	83	100	72	*	*

*Not examined.

The levels of tumor markers (CEA and CA19-9) decreased in patient 2 on day 30 and patient 4 on day 150. No change in tumor marker levels was observed in patients 1, 3, and 5.

Patients 2, 3, 4, and 5 died of progression of pancreatic cancer on days 156, 52, 172, and 87, respectively, while patient 1 died of a syndrome suggestive of cerebral hemorrhage on day 349.

CASE REPORT

Two patients who responded to NST are described.

Patient 1

A 59-year-old woman was admitted to our hospital due to increasingly severe abdominal and back pain of 1-month duration and body weight loss. Abdominal CT revealed a heterogeneously enhanced 10 × 8.0-cm mass, with an irregular low-density area (Fig. 1A), and angiography demonstrated major vascular invasion. Fine needle aspiration biopsy of the tumor confirmed adenocarcinoma (Fig. 2). Based on these findings, the patient was diagnosed with pancreatic tumor, and although the tumor appeared not to be a typical pancreatic duct cell cancer, it definitely arose from the pancreatic tissue itself as shown on CT and angiography. We deemed the tumor unresectable due to the major vascular invasion by the cancer.

Pretransplantation conditioning consisted of 60 mg/kg cyclophosphamide intravenously on days −7 and −6 and 25 mg/m^2 fludarabine intravenously from days −5 to −1. Cyclosporine was started on day −2. Her HLA-identical sister (HLA-A24, B52, B55, DR15, DR9) was given 10 μg/kg granulocyte colony-stimulating factor (G-CSF) subcutaneously daily for 5 days, and a mobilized peripheral blood stem cell allograft was collected by leukapheresis on the day 5 and day 6 of G-CSF

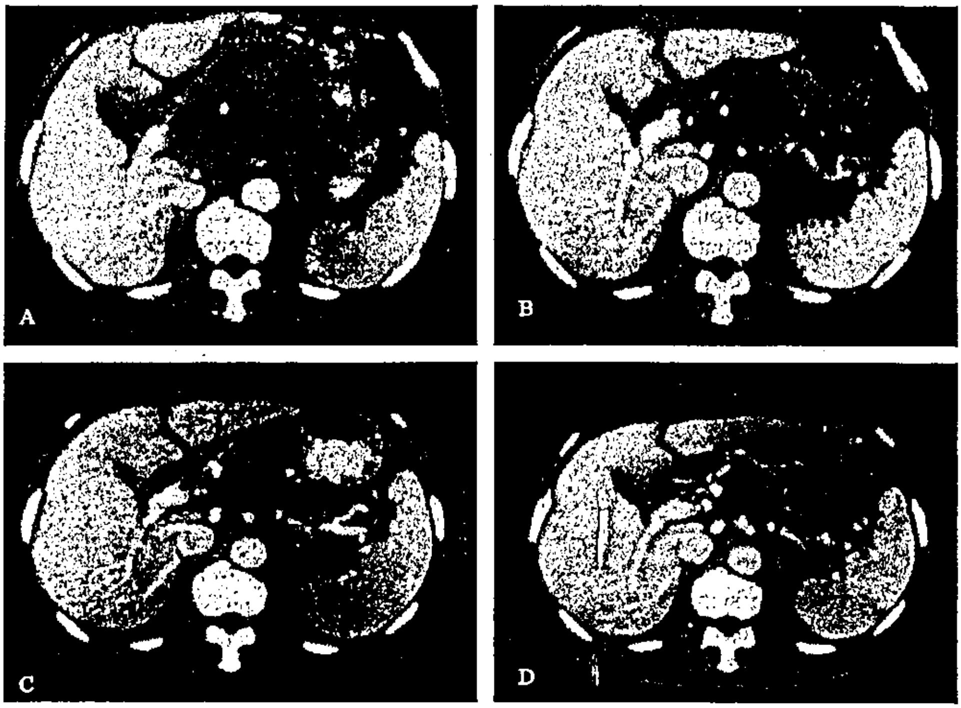

FIGURE 1. CT scan of the pancreatic tumor in patient 1. A: Heterogeneously enhanced 10.0 × 8.0-cm tumor located in the body and head of the pancreas before NST. B: The tumor was reduced 60% in size 30 days after NST; C: 75% reduced on day 100; D: 80% reduced on day 180 after NST.

administration. On day 0 and day +1, a total of 6.01×10^6 CD34+ cells/kg from her sister were transfused into the patient. Successful engraftment was achieved on day +6. Complete T-cell chimerism occurred by day +21, as determined by PCR assay.

Surprisingly, the patient's severe abdominal pain rapidly disappeared within 10 days, and consequently the morphine was stopped. In addition, the palpable upper abdominal tumor disappeared within 2 weeks. Abdominal CT revealed an impressive reduction in posttherapy pancreatic tumor diameter,

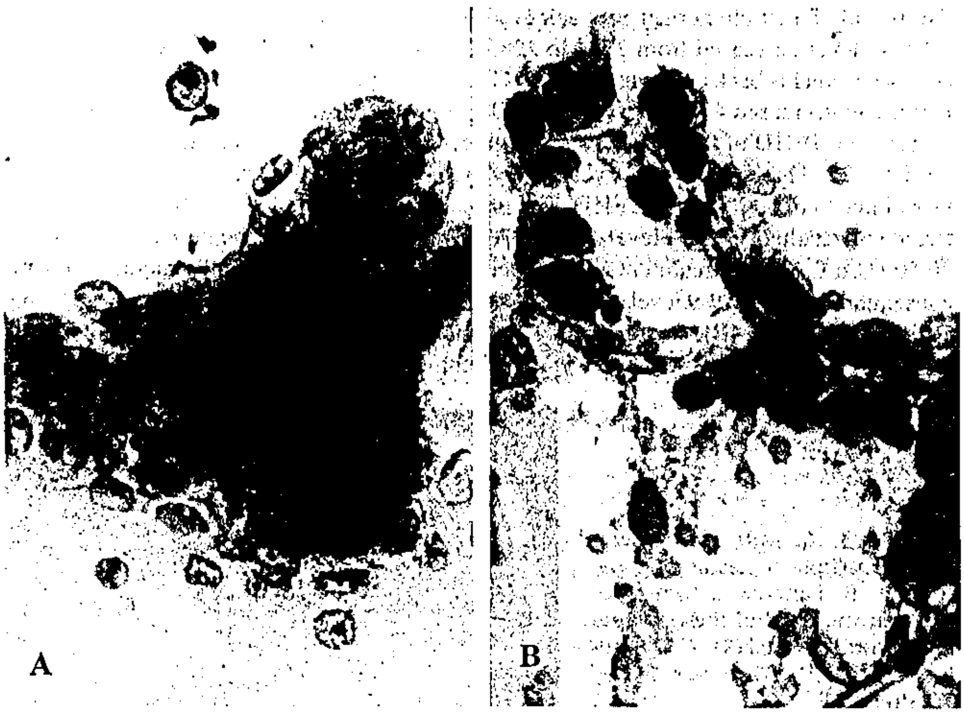

FIGURE 2. A: Epithelial malignant cells taken by needle biopsy from the pancreatic tumor in patient 1. B: The tumor cells forming adenomatous structures were considered adenocarcinoma.

which dropped from 10.0 to 6.5 cm (representative of a 60% reduction) on day +30 (Fig. 1B) to 5.0 cm (representative of a 75% reduction) on day +100 (Fig. 1C) and to 4.5 cm (representative of a 80% reduction) on day +180 (Fig. 1D).

Her posttransplantation course was uneventful, and no symptoms of acute GVHD were noted. The patient was discharged from our hospital on day 60 after NST. Cyclosporine was tapered and discontinued on day +100.

She subsequently developed extensive chronic GVHD of the skin on day +120 and was given corticosteroid ointment at the outpatient clinic. Complete myeloid chimerism was observed, almost at the same time. Cyclosporine treatment was started again on day +190 due to progression of the chronic GVHD of the liver. Although the GVHD had improved by this treatment, the pancreatic tumor had grown slightly by day +220. Thus, cyclosporine was stopped on day +230. Soon after the cyclosporine had been stopped, the tumor regressed again.

On day +348, she became unconscious and convulsed suddenly, showing symptoms suggestive of cerebral hemorrhage. She died on day +349 after NST. Unfortunately, an autopsy was unable to be performed.

Patient 2

A 40-year-old man was admitted to our hospital due to severe back pain and jaundice. MRI or CT revealed multiple liver metastases (Fig. 3A) and pancreas head cancer invading the duodenum (Fig. 3B). His CEA was 25 ng/mL and CA19-9 was 20,089 U/mL. The patient received 3 cycles of chemotherapy with gemcitabine. Transient regression was observed, but the tumor soon began progressing again.

NST was performed from his HLA-identical brother on day 0. Full T-cell chimerism was achieved on day +14. His CA19-9 level decreased from 2744 to 228 U/mL on day +30 (Fig. 4A), and his back pain was relieved. CT revealed that the tumor had decreased 40% in size on day +30 (Fig. 3C). However, acute GVHD of the liver and gut of grade III developed on day +25. The patient was given methylprednisolone and tacrolimus to treat the acute GVHD. The immunosuppressive treatment resulted in the elevation of CA19-9 from 228 to 20,509 U/mL. Steroid treatment was stopped on day +105, and consequently the CA19-9 level again decreased from 20,509 to 10,394 U/mL (Fig. 4B), suggesting the presence of the GVT effect. However, the pancreatic cancer and liver metastasis began to progress from day +130, and the patient died of progressive disease on day +156.

DISCUSSION

Allogeneic stem cell transplantation in the treatment of leukemia has proved to be a potent immune-mediated antileukemia effect [graft versus leukemia (GVL) effect].[1] Stem cells transplanted to the recipient from an HLA-identical donor proliferate and differentiate into T cells in the patient, and these recognize the patient's tissues as "not-self" and eliminate the "not-self" cells. These immunologic reactions produce a graft versus leukemia effect, which brings about leukemia regression and also sometimes produces GVHD. However, whether such an immune-mediated effect was induced in patients with solid tumors has been unclear. Eibl et al[2] and Ueno et al[3] reported a GVT effect in breast cancer patients treated with marrow ablative allogeneic transplantation. In 1999, Childs et al[4,5] reported that nonmyeloablative allogeneic stem cell transplantation induced sustained regression of metastatic renal cell carcinoma in patients who had no response to conventional treatment. However, the existence of the GVT effect of allogeneic stem cell transplantation in patients with pancreatic cancer is as yet unknown.

Myeloablation and immunosuppression have been considered to be the 2 major requirements of preparative conditioning for successful engraftment of stem cells into bone marrow. However, recent studies have established that immunosuppression is the more important of the 2 and that myeloablation, including strong anticancer agents or total body irradiation, is unnecessary for engraftment.[6,7] Thus, nonmyeloablative stem cell transplantation is developing into a method free from severe adverse effects for transplantation.

We performed a pilot trial of nonmyeloablative allogeneic stem cell transplantation in patients with unresectable pancreatic cancer refractory to conventional treatment options.

In our trial, patient 1 showed remarkable regression of the tumor and pain relief. There have been no reports that the small amount of chemotherapeutic agents used in our conditioning regimen (60 mg/kg cyclophosphamide × 2, 25 mg/m^2 fludarabine × 5) are efficacious for pancreatic tumor. Moreover, the tumor consistently decreased in size until day +190,

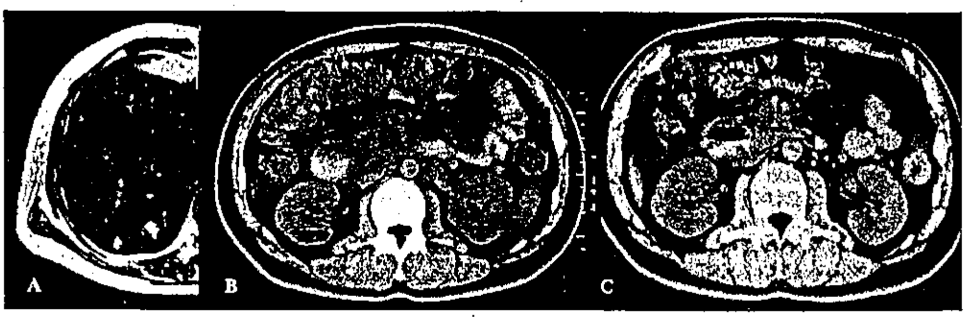

FIGURE 3. A: MRI of the liver shows multiple metastases in patient 2. B: Pancreatic tumor located in the head of the pancreas in patient 2 before NST. C: The tumor decreased 40% in size on day 30 after NST.

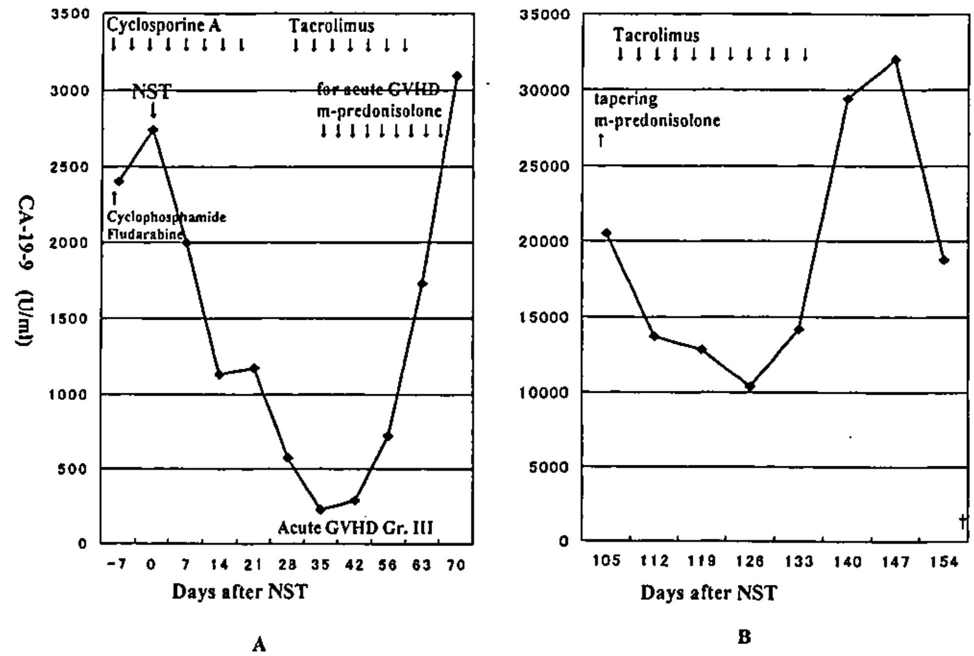

FIGURE 4. CA19-9 levels relative to posttransplantation days and interventions in patient 2. A: NST resulted in decreased levels of CA19-9. B: After tapering methylprednisolone, elevated CA19-9 level decreased.

when cyclosporine treatment was started again due to progression of the chronic GVHD. Subsequently, the pancreatic tumor grew slightly after administration of the cyclosporine, and soon after the drug was stopped, the tumor regressed again. Thus, the continuous regression of the tumor following NST and the changes in tumor size produced by immunosuppressive cyclosporine suggest that the GVT effect was produced by NST in this patient with unresectable pancreatic cancer. Unfortunately, the patient died, probably of a cerebral hemorrhage, but it was not possible to perform an autopsy. We, however, presume that the cerebral hemorrhage was caused by the chronic GVHD. Nonetheless, this may be the first case of the GVT effect on pancreatic cancer.

Patient 2 experienced pain relief, tumor reduction, and changes in the levels of tumor markers. These findings also suggest the presence of the GVT effect on pancreatic cancer.

Patient 4 survived under stable disease conditions until day +250, exhibiting decreased cancerous pleural fluid due to pancreatic cancer and a decreased level of CA19-9. We also believe this to represent the GVT effect.

T-cell chimerism persisted in all patients from the beginning of tumor regression. Notably, the GVT effect occurred only after T-cell chimerism had become complete.

Two of the 5 patients undergoing NST developed acute grade II or III GVHD. GVHD did not always occur in all patients who developed the GVT effect in our trial; patients 1 and 4 did not have acute GVHD when their disease regressed. The antigens of the donor cells that mediated the GVT effects and acute GVHD are the focus of future investigation.

In conclusion, the results of our pilot clinical trial suggest that NST induces the GVT effect in pancreatic cancer, just as in renal cell carcinoma, as demonstrated by Childs.[4,5] NST might represent a new treatment modality for intractable pancreatic cancer. However, we should emphasize that our study was very small and allogeneic stem cell transplantation can cause the substantial and sometimes fatal adverse effects of GVHD. Moreover, since GVT effects are usually delayed after NST, careful selection of pancreatic cancer patients for similar trials is warranted because death from early disease progression has previously been shown to limit this approach in metastatic renal cell carcinoma patients.[5]

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Randomised phase II study of docetaxel/cisplatin *vs* docetaxel/irinotecan in advanced non-small-cell lung cancer: a West Japan Thoracic Oncology Group Study (WJTOG9803)

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Docetaxel plus cisplatin and docetaxel plus irinotecan are active and well-tolerated chemotherapy regimens for advanced non-small-cell lung cancer (NSCLC). A randomised phase II study compared their efficacy and toxicity in 108 patients with stage IIIb/IV NSCLC, who were randomised to receive docetaxel 60 mg m^{-2} and cisplatin 80 mg m^{-2} on day 1 (DC; $n=51$), or docetaxel 60 mg m^{-2} on day 8 and irinotecan 60 mg m^{-2} on day 1 and 8 (DI; $n=57$) every 3 weeks. Response rates were 37% for DC and 32% for DI patients. Median survival times and 1- and 2-year survival rates were 50 weeks (95% confidence interval: 34–78 weeks), 47 and 25% for DC, and 46 weeks (95% confidence interval: 37–54 weeks), 40 and 18% for DI, respectively. The progression-free survival time was 20 weeks (95% confidence interval: 14–25 weeks) with DC and 18 (95% confidence interval: 12–22 weeks) with DI. Significantly more DI than DC patients had grade 4 leucopenia and neutropenia ($P<0.01$); more DC patients had grade $\geqslant 2$ thrombocytopenia ($P<0.01$). Nausea and vomiting was more pronounced with DC ($P<0.01$); diarrhoea was more common with DI ($P=0.01$). Three treatment-related deaths occurred in DC patients. In conclusion, although the DI and DC regimens had different toxicity profiles, there was no significant difference in survival.
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Keywords: combination chemotherapy; doublets; irinotecan; cisplatin; docetaxel; non-small-cell lung cancer; carboplatin

Unfortunately, non-small-cell lung cancer (NSCLC) is a member of the group of neoplastic diseases that is relatively chemoresistant. Recent meta-analyses show that cisplatin-based chemotherapy improves survival (Non-Small Cell Lung Cancer Collaborative Group, 1995), and it is considered a standard treatment for NSCLC. Most cisplatin-based regimens have substantial toxicities that require close monitoring and supportive care. Thus, there is a need to develop active and less toxic chemotherapy regimens that include new active compounds with novel mechanisms of action.

In the 1990s, several new, active therapies with single-agent response rates of 15–30% became available for NSCLC, including irinotecan, docetaxel, paclitaxel, vinorelbine, and gemcitabine. Because irinotecan and docetaxel were approved for NSCLC earlier than the other drugs in Japan, development of regimens containing irinotecan or docetaxel is more advanced. Docetaxel 60 mg m^{-2} showed good antitumour activity against advanced NSCLC (Kunitoh *et al*, 1996), and the combination of docetaxel plus cisplatin (DC) is one of the most effective regimens for advanced NSCLC (Rodriguez *et al*, 2001; Schiller *et al*, 2002). Studies in Japan included a phase II study in which DC yielded a response rate of 42% (Okamoto *et al*, 2002), and a phase III study in which DC was associated with better survival than the vindesine and cisplatin (VC) combination (Kubota *et al*, 2002).

Irinotecan demonstrated activity similar to that of VC in stage IIIb/IV NSCLC (Negoro *et al*, 2003), and significant longer overall survival time than VC in stage IV NSCLC (Fukuoka *et al*, 2000). We reported a phase I study of docetaxel plus irinotecan (DI) in patients with advanced NSCLC, in which a promising response rate of 48% and the median survival time of 48 weeks were achieved with acceptable toxicities (Masuda *et al*, 2000). Thus, DI appeared to be a promising non-cisplatin-containing regimen.

Based on the above findings, we conducted a randomised trial of DC *vs* DI in patients with advanced NSCLC to compare the respective response rates, survival data, and toxicity profiles of the two regimens. This was a multicentred phase II study.

PATIENTS AND METHODS

Patients

Patients enrolled in this trial had histologically or cytologically confirmed stage IIIb or IV NSCLC. Patients with stage IIIb disease who were not candidates for thoracic radiation and patients with stage IV disease were eligible if they had not received previous therapy, had measurable disease, and had a life expectancy of at least 3 months. Additional entry criteria were age $\geqslant$20 years, performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale, adequate bone marrow function (leucocyte

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count 4000–12 000 μl^{-1}, haemoglobin concentration $\geqslant 9.5\,g\,dl^{-1}$ platelet count $\geqslant 100\,000\,\mu l^{-1}$), kidney function (creatinine $\leqslant$ upper limit of normal, 24-h creatinine clearance $\geqslant 60\,ml\,min^{-1}$), liver function (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leqslant 2.0$ times the upper limit of normal, total bilirubin $\leqslant 1.5\,mg\,dl^{-1}$), and pulmonary function ($PaO_2 \geqslant 60$ torr). Patients with active concomitant or a recent (<3 years) history of any malignancy, symptomatic brain metastases, past history of drug allergy reactions, complication by interstitial pneumonia, watery diarrhoea, ileus, treatment with nonsteroidal anti-inflammatory drugs, or other serious complications, such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus or hypertension, massive pleural effusion or ascites, or serious active infection were excluded. All patients gave written informed consent, and the institutional review board for human experimentation approved the protocol.

Study evaluations

Pretreatment studies included a complete medical history and physical examination, chest X-ray, electrocardiography, computed tomography (CT) scan of the brain and chest, CT or ultrasound examination of the abdomen, and bone scintigraphy. Blood and blood chemistry studies included complete blood cell count, liver function test, serum electrolytes, serum creatinine, and blood urea nitrogen. Chest X-ray, blood and blood chemistry analyses, and urinalysis were repeated weekly.

Randomisation and treatment schedule

Patients were randomly assigned to receive the DC regimen or the DI regimen by a minimisation method using stage (IIIB/IV) and treatment institution. The DC regimen was consisting of docetaxel 60 mg m^{-2} on day 1 and cisplatin 80 mg m^{-2} on day 1, and the DI regimen was consisting of docetaxel 60 mg m^{-2} as a 60-min intravenous infusion on day 8 and irinotecan 60 mg m^{-2} as a 90-min intravenous infusion on days 1 and 8 (Figure 1). Both regimens were repeated every 3 weeks. Participating researchers at each institution decided the amount of fluid replacement and the type of antiemetic therapy to administer. Standard antiemetic treatment in the DC arm consisted of 5-HT$_3$ receptor antagonist plus 16 mg dexamethasone intravenously on day 1, before cisplatin administration. In the DI arm, standard antiemetic treatment consisted of 5-HT$_3$ receptor antagonist intravenously before chemotherapy administration on days 1 and 8. Patients received at least two treatment cycles, and those with a complete or partial response after two cycles had treatment continued until there was evidence of disease progression, intolerable toxicity, or patient refusal.

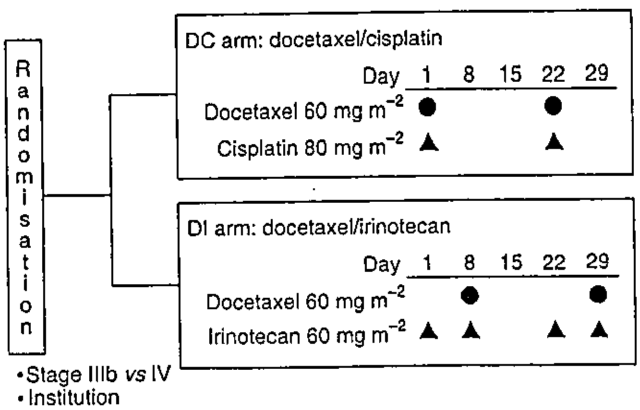

Figure 1 *Treatment schema*: after stratification by stage and institution, enrolled patients were randomly allocated to receive docetaxel plus cisplatin (DC) or docetaxel plus irinotecan (DI).

Dose modifications

Toxicity assessment was based on the National Cancer Institute-Common Toxicity Criteria version 2.0. Dose levels and treatment schedule were modified to avoid severe adverse effects. Patients receiving DI had the day-8 docetaxel and irinotecan doses postponed to day 15 if any of the following toxicities was present on day 8: leucocyte count $<3000\,\mu l^{-1}$, platelet count $<100\,000\,\mu l^{-1}$ diarrhoea consisting of bloody or watery stools, or increased to two or more diarrhoea within 24 h, abdominal pain rated mild or worse, hepatic toxicity $\geqslant$grade 3, or fever >38°C. If these toxicities occurred on day 15 after skipping the day-8 treatment, DI was stopped in that course.

Patients could receive the next treatment course only if the following criteria were met: leucocyte count $\geqslant 4000\,\mu l^{-1}$, platelet count $\geqslant 100\,000\,\mu l^{-1}$ AST/ALT <2.0 times the upper limit of normal, total bilirubin $\leqslant 1.5\,mg\,dl^{-1}$ serum creatinine $\leqslant$ the upper limit of normal, ECOG PS$\leqslant$2, neurotoxicity $\leqslant$grade 1, no diarrhoea or oedema. However, if more than 6 weeks passed before these criteria were satisfied, the patient was removed from the study.

Dose modification criteria for each drug are shown in Table 1. If, during the previous course, grade 4 leucopenia, grade 4 neutropenia lasting $\geqslant$3 days, or grade 4 thrombocytopenia had occurred, doses of all drugs were reduced by 10 mg m^{-2}. Doses of both cisplatin and docetaxel were reduced by 10 mg m^{-2} in subsequent cycles if chemotherapy induced grade $\geqslant$2 neurotoxicity. Moreover, dose of docetaxel was reduced by 10 mg m^{-2} if grade $\geqslant$2 hepatic toxicity or grade $\geqslant$3 stomatitis had occurred. Dose of cisplatin was reduced by 20 /mg/m^2 if grade $\geqslant$2 renal toxicity occurred. Dose of irinotecan was reduced by 5 mg m^{-2} if grade $\geqslant$2 hepatic toxicity had occurred and by 10 mg m^{-2} if grade $\geqslant$2 diarrhoea or cancellation of day-8 treatment had occurred.

Evaluation of response and survival

Tumour response was classified according to World Health Organization (WHO) criteria (World Health Organization, 1979). Complete response was defined as complete disappearance of all measurable and assessable disease for at least 4 weeks, Partial response was a $\geqslant$50% decrease in the sum of the products of the two IL largest perpendicular diameters of all measurable tumours lasting at least 4 weeks and without appearance of any new lesions. No change was defined as a <50% decrease or a <25% increase of tumor lesions for at least 4 weeks with no new lesions.

Table 1 Dose modification criteria

Toxicities in previous cycle	Decrease in docetaxel dose (mg/m^{-2})	Decrease in cisplatin dose (mg/m^{-2})	Decrease in irinotecan dose (mg/m^{-2})
Grade 4 neutropenia lasting $\geqslant$3 days, leucopenia or thrombocytopenia	10	10	10
Grade $\geqslant$2 neurotoxicity	10	10	—
Grade $\geqslant$2 renal toxicity	—	20	—
Grade $\geqslant$2 hepatic toxicity	10	—	5
Grade $\geqslant$3 stomatitis	10	—	—
Grade $\geqslant$2 diarrhoea	—	—	10
Cancellation of day-8 treatment	—	—	10

Progressive disease was defined as development of new-lesions or a 25% increase in the sum of the products of the two largest perpendicular diameters of all measurable tumors. Duration of response in patients who achieved complete or partial response was measured from the start of treatment to the date of disease progression.

Statistical methods

Results of this study were evaluated to determine whether the docetaxel plus irinotecan combination warranted further assessment in a phase III trial. Thus, this study was designed to conduct two randomised phase II studies concurrently. We calculated the number of patients required for each of the two studies based on the Fleming's single-stage procedure (Fleming, 1982). In both studies, we set response rates of 40% as target activity level and 20% as the lowest level of interest with a power of 0.9 at a one-sided significance level of 0.05. As a result, a total of 100 qualified patients were to be enrolled, with 50 patients in each treatment arm. The primary objective was to estimate the response rate to both regimens, particularly to irinotecan plus docetaxel.

Overall survival and progression-free survival were analysed by the Kaplan–Meier method. The overall survival was measured from study entry to death. The progression-free survival was measured from study entry until the day of the first evidence of disease progression. If the disease had not progressed by the time of this analysis, progression-free survival was considered censored at the time of the analysis. All comparisons between patient characteristics, response rates, and toxicity incidences were performed by Pearson's χ^2 contingency table analysis.

RESULTS

Patient characteristics

From October 1998 to August 1999, 108 patients were assigned to receive DC ($n=51$) or DI ($n=57$). Baseline patient characteristics according to treatment arm are shown in Table 2. Patients were well balanced between the two treatment arms in terms of gender, age, performance status, disease stage, and histologic subtypes. There were 23% stage IIIb patients and 74% had adenocarcinoma. All patients were included in the survival evaluation, and all were assessable for antitumor efficacy and toxicity.

Treatment delivery

Patients in both treatment arms received a median of two treatment courses. Two or more courses were delivered to 72.5 and 71.9%, and four courses to 17.6 and 19.1% of patients in the DC and DI arms, respectively. Differences between arms in the number of chemotherapy courses administered were not statistically significant.

Table 2 Baseline patient characteristics

		Docetaxel/ cisplatin	Docetaxel/ irinotecan	χ^2 text
No. of patients		51	57	
Gender	Male/female	37/14	38/19	$P=0.537$
Age (years)	Median	62	60	
	Range	39–74	42–77	
PS	0/1	15/36	15/42	$P=0.830$
Histology	Adenocarcinoma	36	44	$P=0.520$
	Squamous cell carcinoma	13	9	
	Others	2	4	
Disease stage	IIIb/IV	11/40	14/43	$P=0.820$
Brain metastasis	(+)/(−)	4/47	11/46	$P=0.086$

PS = performance status.

Response to treatment and survival

There were no complete responses. In the DC arm, 19 patients had partial responses for an overall response rate of 37% (Table 3). Among DI patients, 18 had partial responses for an overall response rate of 32%. The difference in response rate between arms was not significant ($P=0.55$). Progressive disease was noted in twice as many DI (25%) than DC (12%) patients. Early deaths within 3 months of treatment initiation occurred in 10% ($n=5$) of DC and 5% ($n=3$) of DI patients. The early deaths were treatment-related (three patients, all in the DC arm) or due to disease progression (five patients).

Overall and progression-free survival curves for the two treatment arms are shown in Figures 2 and 3. The median progression-free survival time was 20 weeks (95% confidence interval: 14–25 weeks) in the DC arm vs 18 weeks (95% confidence interval: 12–22 weeks) in the DI arm. Median survival times, 1-year survival rates, and 2-year survival rates were 50 weeks (95% confidence interval 34–78 weeks), 47 and 25%, respectively, in the DC arm, and 46 weeks (95% confidence interval: 37–54 weeks), 40 and 18%, respectively, in the DI arm. No significant differences were noted between groups in progression-free survival ($P=0.33$) or overall survival ($P=0.50$), although there were trends toward higher 1-year and 2-year survival rates in the DC.

Table 3 Overall response to docetaxel/cisplatin (DC) or docetaxel/irinotecan (DI) in patients with stages IIIb/IV non-small-cell lung cancer

Response	DC ($n=51$) No. pts	DI ($n=67$) No. pts
Complete response	0	0
Partial response	19	18
No change	23	25
Progressive disease	6	14
NE (TRD)	3	0
Response rate	37.3%*	31.6%*
95% Confidence intervals	24.1–51.9%	19.9–45.2%

pts = patients; NE = not evaluable; TRD = treatment-related death. *$P=0.55$.

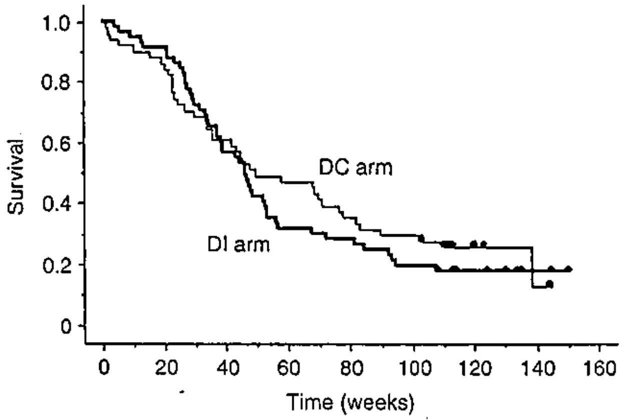

Figure 2 Overall survival according to treatment group, calculated by Kaplan–Meier method. Median survival times were 50 weeks for DC (docetaxel plus cisplatin) and 46 weeks for DI (docetaxel plus irinotecan). $P=0.50$ between treatment groups.

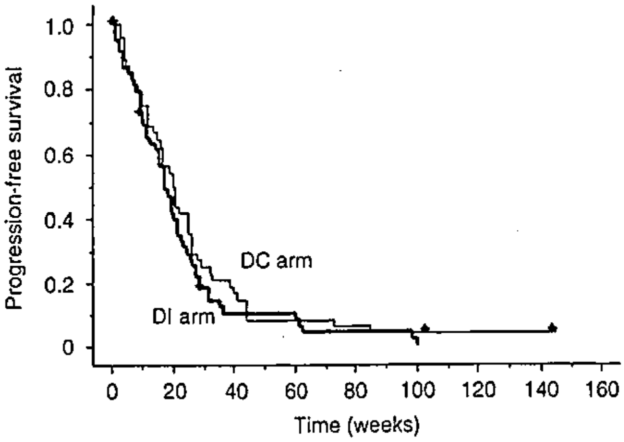

Figure 3 Progression-free survival according to treatment group, calculated by Kaplan–Meier method. Median progression-free survival times were 20 weeks for DC (docetaxel plus cisplatin) and 18 weeks for DI (docetaxel plus irinotecan). P = 0.33 between treatment groups.

Table 4 Haematologic toxicity: maximum toxicity grade in any course

	Docetaxel/ cisplatin (% pts)			Docetaxel/ irinotecan (% pts)		
Toxicity/grade	**2**	**3**	**4**	**2**	**3**	**4**
Leucopenia*	31	43	4	26	40	16
Neutropenia*	10	31	43	4	23	61
Anaemia	47	10	2	46	7	0
Thrombocytopenia**	10	4	0	0	0	0
Febrile neutropenia		20			28	

pts = patients. *$P<0.01$ for grade 4; **$P<0.01$ for the sum of grades 2 and 3.

Second-line chemotherapy was administered to 61 patients (24 DC and 37 DI patients). A total of 22 patients in the DI group received cisplatin-based second-line chemotherapy and five had partial responses to this treatment (overall response rate, 23%). In particular, nine patients were subsequently treated with vinorelbine containing regimen and three patients had a partial response. Only two patients in the DC group received an irinotecan-containing regimen, one of whom had a partial response. Concerning as second-line chest irradiation, 8 patients in the DC group and 13 patients the DI group received.

Toxicity

Haematologic and nonhaematologic toxicities are listed in Tables 4 and 5. Grade 4 leucopenia and neutropenia occurred in a significantly higher percentage of DI than DC patients (leucopenia 16 *vs* 4%, $P<0.01$; neutropenia 61 *vs* 43%, $P<0.01$). On the other hand, there was a higher rate of grade ⩾2 thrombocytopenia in the DC than in the DI arm (14 *vs* 0%, $P<0.01$). Rates of anaemia (decrease in haemoglobin) and febrile neutropenia were similar in both groups.

Nonhaematologic toxicities including grade ⩾2 nausea (88 *vs* 51%, $P<0.01$), vomiting (39 *vs* 14%, $P<0.01$), and renal toxicity (increased serum creatinine; 12 *vs* 2%, $P<0.01$) were significantly more prevalent in the DC than in the DI arm, respectively. On the other hand, grade ⩾2 diarrhoea occurred significantly more often in DI than in DC patients (24 *vs* 42%, $P=0.01$). Other nonhaematologic toxicities, such as hepatic toxicity and peripheral neuropathy, were mild and occurred with similar frequency in both groups.

Table 5 Nonhaematologic toxicity: maximum toxicity grade in any course

	Docetaxel/ cisplatin (% pts)			Docetaxel/ irinotecan (% pts)		
Toxicity/grade	**2**	**3**	**4**	**2**	**3**	**4**
Diarrhoea*	18	6	0	26	12	4
Nausea*	53	33	0	33	18	0
Vomiting**	33	2	4	14	0	0
Peripheral neuropathy	2	0	0	2	0	0
AST increase	8	2	2	7	0	2
ALT increase	14	4	0	9	2	2
ALP increase	8	2	0	4	0	0
Creatinine increase*	10	0	2	0	0	2

pts = patients; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase. *$P<0.01$ for the sum of grades 2, 3, and 4; **$P=0.01$ for the sum of grades 2, 3, and 4.

There were three treatment-related deaths in the DC arm, which were due to febrile neutropenia and sepsis (one of these patients also developed perforation of the oesophagus). No treatment-related deaths occurred in the DI arm. The difference in incidence of treatment-related deaths was not significant.

DISCUSSION

Results of this randomised phase II study showed that the doublet chemotherapy regimens DC and DI had comparable activity in patients with advanced NSCLC. A primary goal of this study was to determine whether the DI combination should be studied in the phase III setting. Although there were no differences between DI and DC – a third-generation cisplatin-containing regimen – in overall and progression-free survival, patients who received DI tended to have lower 1-year and 2-year survival rates. Furthermore, overall toxicity was not reduced in the DI arm compared with the DC arm. Leucopenia and neutropenia were the major toxicities in both groups. As expected, emesis and renal toxicity were more prevalent in patients receiving DC, and diarrhoea occurred more frequently with DI.

Cisplatin has played a prominent role in the treatment of NSCLC, despite a relatively unimpressive single-agent response rate and a relatively severe toxicity profile. In 1995, the Non-Small Cell Lung Cancer Collaborative Group published a pivotal meta-analysis of chemotherapy in lung cancer and demonstrated the advantage of cisplatin-based regimens over best supportive care (Non-Small Cell Lung Cancer Collaborative Group, 1995). In the 1990s, third-generation chemotherapeutic agents, including paclitaxel, docetaxel, vinorelbine, gemcitabine and irinotecan, were shown to have higher response rates often coupled with fewer adverse effects (no renal toxicity, no massive dehydration, less emesis, etc.) than cisplatin. For example, single-agent paclitaxel (Ranson *et al*, 2000), docetaxel (Roszkowski *et al*, 2000), or vinorelbine (The Elderly Lung Cancer Vinorelbine Italian Study Group, 1999) significantly improved survival compared with best supportive care in patients with advanced NSCLC. Studies of single-agent gemcitabine (Perng *et al*, 1997) or irinotecan (Negoro *et al*, 2003) demonstrated a survival benefit comparable to that of second-generation chemotherapy regimens (cisplatin plus vindesine, cisplatin plus etoposide). Based on the above results, we thought that combination chemotherapy consisting of third-generation agents might improve outcome for patients with advanced NSCLC.

Only one published study compared cisplatin-based and noncisplatin-based regimens that included third-generation agents. Georgoulias *et al* (2001) conducted a randomised study of cisplatin plus docetaxel (CD) *vs* gemcitabine plus docetaxel (GD) in 441 advanced NSCLC patients. The noncisplatin regimen provided a comparable response rate (CD 32.4%, GD 30.2%) and median survival time (CD 10 months, GD 9.5 months) but with less toxicity. The authors stated that the non-cisplatin GD regimen would likely be more acceptable to patients based on convenience of administration. However, several randomized trials reported at recent international meetings showed slightly shorter survival times with noncisplatin compared with cisplatin-based combinations. Preliminary results of the EORTC-Lung Cancer Group phase III study of cisplatin plus paclitaxel *vs* cisplatin plus gemcitabine *vs* paclitaxel plus gemcitabine in 480 patients with advanced NSCLC revealed superior overall survival and progression-free survival with the cisplatin-based regimens (Van Meerbeeck *et al*, 2001). Moreover, in a recent Italian–Canadian intergroup study of 501 patients comparing gemcitabine plus vinorelbine with cisplatin plus vinorelbine or gemcitabine, the noncisplatin regimen provided only short-term and sporadic advantages in some quality-of-life components, but there were no significant differences in overall and progression-free survival (Gridelli *et al*, 2002).

The best known noncisplatin platinum-based chemotherapy regimen is the paclitaxel plus carboplatin doublet. A Southwest Oncology Group study compared vinorelbine plus cisplatin with paclitaxel plus carboplatin. No differences in the overall survival or quality of life were noted between the two treatment groups, but toxicity rates were significantly lower in patients who received paclitaxel plus carboplatin (Chen *et al*, 2002). Results of a recent ECOG randomised phase III trial evaluating four platinum-based chemotherapy regimens showed no significant differences in the overall survival, while the paclitaxel plus carboplatin combination was less toxic than cisplatin-based chemotherapy (Schiller *et al*, 2002). Based on these findings, the paclitaxel plus carboplatin regimen is considered a standard therapy for previously untreated patients with advanced NSCLC, with activity comparable to that of cisplatin-based regimens and better tolerability.

The utility of doublet regimens containing third-generation chemotherapeutic agents for advanced NSCLC thus needs to be evaluated against the paclitaxel plus carboplatin combination, and several such studies were reported or are ongoing. The Hellenic Cooperative Oncology Group is conducting a phase III randomised study of paclitaxel plus carboplatin *vs* paclitaxel plus gemcitabine, and final results indicate comparable activity, toxicity and total cost of the two regimens in patients with inoperable NSCLC (Kosmidis *et al*, 2002). The Taiwan group conducted a similar study and found that paclitaxel plus carboplatin and paclitaxel plus gemcitabine had similar efficacy in the treatment of NSCLC, but that paclitaxel plus carboplatin was more cost-effective (Chen *et al*, 2002).

As mentioned in the introductory paragraphs, we conducted a phase I study of docetaxel plus irinotecan (DI) in patients with advanced NSCLC, and had a promising response rate of 48% and median survival time of 48 weeks (Masuda *et al*, 2000). Although we recommended docetaxel 50 mg m^{-2} on day 1 plus irinotecan 50 mg m^{-2} on days 1, 8, and 15 in the phase I study, more than half of patients could not receive irinotecan on day 15 because of haematologic toxicities. Accordingly, the day-15 irinotecan dose was omitted and the day-2 docetaxel dose moved to day 8 and increased from 50 to 60 mg m^{-2} in this randomised phase II trial.

It has been reported that second-line chemotherapy compared with best supportive care may increase the overall survival in patients with advanced NSCLC, and more studies in this regard are needed. In a recent study in which patients received cisplatin-based chemotherapy followed by docetaxel or supportive care alone, the median survival was significantly longer in the docetaxel-treated patients (Shepherd *et al*, 2000). In our study, 52% of patients were treated with second-line chemotherapy. Of these, 19 (33%) DI patients received cisplatin-based second-line chemotherapy, five of whom (26%) responded. Thus, cisplatin-based chemotherapy is capable of exerting antitumour activity in patients who have relapsed after having received noncisplatin-containing regimens.

Only two patients in the DC group received an irinotecan-containing regimen, one of whom had a partial response. As there were only two patients, we cannot judge whether irinotecan-containing regimen is effective for the patients after having received cisplatin-containing regimen.

In conclusion, docetaxel plus irinotecan combinations may be reasonable treatment options for NSCLC patients who cannot tolerate cisplatin. However, as there was no significant difference in the overall survival and no reduction in overall toxicity, DI has not improved on results obtained with DC. Thus, we will not select docetaxel/irinotecan as the experimental regimen in the next phase III study of first-line treatment of advanced NSCLC.

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Effect of re-treatment with gefitinib ('Iressa', ZD1839) after acquisition of resistance

A 70-year-old man with adenocarcinoma of the lung developed pulmonary metastases 7 months after middle and lower lobectomy of the right lung in October 1998. He received four courses of first-line chemotherapy with docetaxel/irinotecan from June to September 1999. The best response was stable disease and, after 6 months of treatment, there was evidence of progressive disease with increase in size and number of pulmonary metastases. Therefore, we recommended enrollment in a phase I study of gefitinib ('Iressa') [1], an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor.

The patient began to take gefitinib 700 mg/day in March 2000. Remarkable tumor regression was immediately achieved in April 2000 (Figure 1). This response lasted for 18 months. However, pulmonary metastases again developed (considered to be progressive disease), and gefitinib was discontinued in October 2001. The patient received a combination of nedaplatin, a second-generation platinum complex with high antitumor activity against non-small-cell lung cancer [2], and gemcitabine in November 2001. Significant tumor regression was achieved, and a total of six courses from November to April 2002 were administered. Pulmonary metastases progressed again and pulmonary effusion developed in August 2002. Although progressed, he had few symptoms, and was considered to have a performance status of 0. We planned to use a chemotherapy regimen that had not previously been used for this patient, but instead commenced re-treatment with gefitinib at the patient's request on September 3, 2002 (gefitinib 250 mg/day had by this time been approved for use in Japan). One month later, a significant response had been achieved (Figure 1).

This is an interesting case in which acquired resistance to gefitinib could be overcome. There are some possible explanations. First, resistance to gefitinib might naturally change over time, but there is no report of this so far. Secondly, because platinum-based cytotoxic chemotherapy was administered after the first treatment with gefitinib, the proportion of sensitive or resistant cells might have been modified. Thirdly, treatment with cytotoxic chemotherapy might produce genetic changes in EGFR or other unknown associated genes that regulate resistance to gefitinib. Saltz et al. reported that a combination of the EGFR inhibitor cetuximab (C225) and irinotecan produced a 22.5% partial response in patients with irinotecan-refractory colorectal cancer with high EGFR expression [3]. In contrast to that report, cytotoxic agents have the possibility of modifying resistance to cytostatic agents. Recently, two large phase III studies to compare concurrent use of conventional platinum-based chemotherapy (carboplatin/paclitaxel or cisplatin/gemcitabine) and gefitinib with conventional chemotherapy alone were reported [4, 5]. No differences in overall survival were found. These results suggested that gefitinib and chemotherapy may be targeting the same cells with the possibility of overlapping activity. If cytotoxic agents altered sensitivity to gefitinib by genetic modification, chemotherapy followed by gefitinib might be superior to concurrent use. Gefitinib is a very promising agent, but little knowledge is available concerning the types of cases for which gefitinib should be administered, or how gefitinib should be combined with conventional cytotoxic agents. Further investigations are needed to answer these questions.

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A

B

C

D

Figure 1. A 70-year-old man with adenocarcinoma of the lung. CT scan before treatment of gefitinib (**A**), after initiation of treatment (**B**), before re-treatment (**C**) and after initiation of re-treatment (**D**).

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Combination phase I study of nedaplatin and gemcitabine for advanced non-small-cell lung cancer

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To establish the toxicities and maximum tolerated dose (MTD) of nedaplatin with gemcitabine, and to observe their antitumour activity, we conducted a combination phase I study in advanced non-small-cell lung cancer (NSCLC). Patients received nedaplatin ($60-100\,mg\,m^{-2}$ given intravenously over 90 min) on day 1, and gemcitabine ($800-1000\,mg\,m^{-2}$ given intravenously over 30 min) on days 1, 8, every 3 weeks. In total, 20 patients with locally advanced or metastatic NSCLC who received no prior chemotherapy or one previous chemotherapy regimen were enrolled. The most frequent toxicities were neutropenia and thrombocytopenia; nonhaematological toxicities were generally mild. Three out of six patients experienced dose-limiting toxicities (neutropenia, thrombocytopenia and delayed anaemia) at dose level 4, $100\,mg\,m^{-2}$ nedaplatin with $1000\,mg\,m^{-2}$ gemcitabine, which was regarded as the MTD. There were three partial responses, for an overall response rate of 16.7%. The median survival time and 1-year survival rate were 9.1 months and 34.1%, respectively. This combination is well tolerated and active for advanced NSCLC. The recommended dose is $80\,mg\,m^{-2}$ nedaplatin with $1000\,mg\,m^{-2}$ gemcitabine. This combination chemotherapy warrants a phase II study and further evaluation in prospective randomised trials with cisplatin- or carboplatin-based combinations as first-line chemotherapy for advanced NSCLC.
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Based on the results of a meta-analysis (Non-Small Cell Lung Cancer Collaborative Group, 1995), cisplatin-based chemotherapy is considered the best available therapy for patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC). Although several new agents with novel mechanisms and significant activity against NSCLC have been introduced, such as taxanes, gemcitabine and vinorelbine, any of these agents used in combination with a platinum agent provide equivalent survival improvement (Kelly *et al*, 2001; Schiller *et al*, 2002; Fossella *et al*, 2003). The prognosis of advanced NSCLC patients who receive cisplatin-based chemotherapy is still poor, and the renal and gastrointestinal toxicities caused by cisplatin often limit its clinical use. Therefore, development of different treatment strategies is necessary.

Nedaplatin is a second-generation platinum derivative that has shown equivalent antitumour activity and lower toxicity – less nausea, and lower nephrotoxicity and neurotoxicity – than cisplatin (Kameyama *et al*, 1990; Ota *et al*, 1992). A phase I study demonstrated the maximum tolerated dose (MTD) and the recommended dose (RD) for phase II studies of nedaplatin was 120 and $100\,mg\,m^{-2}$, respectively, and the dose-limiting toxicity (DLT) was thrombocytopenia (Ota *et al*, 1992). Two independent phase II studies of nedaplatin for NSCLC showed response rates of 14.7 and 20.5%, respectively, and 16.7 and 12.5% with the patients who had received chemotherapy previously (Fukuda *et al*, 1990; Furuse *et al*, 1992a). Based on these promising results, a randomised study of nedaplatin–vindesine *vs* cisplatin–vindesine was conducted for previously untreated NSCLC patients in Japan and indicated that nedaplatin-based chemotherapy yielded similar response rates and overall survival (Furuse *et al*, 1992b). Leucopenia, renal toxicities and gastrointestinal toxicities were more frequent in the cisplatin–vindesine arm, while thrombocytopenia was more frequent in the nedaplatin–vindesine arm.

Gemcitabine, an analogue of deoxycytidine, is a pyrimidine antimetabolite, that shows a reproducible response rates of >20% with a median survival time of 9 months, offering a quality of life benefit in comparison with best supportive care (Abratt *et al*, 1994; Anderson *et al*, 1994; Gatzemeier *et al*, 1996; Anderson *et al*, 2000). The main toxicity of gemcitabine is mild-to-moderate myelosuppression. The combination of gemcitabine and cisplatin showed synergistic effects in preclinical studies because gemcitabine inhibited the repair of DNA damage caused by cisplatin (Bergman *et al*, 1996), and achieved high response rates along with improvements in median survival time in clinical setting (Sandler *et al*, 2000; Schiller *et al*, 2002; Alberola *et al*, 2003).

Recently, carboplatin has attracted attention ahead of nedaplatin because it has similar activity to cisplatin with fewer nonhaematological toxicities. The available data suggest that carboplatin–paclitaxel or carboplatin–gemcitabine should be considered among standard regimen for advanced NSCLC (Kelly *et al*, 2001; Grigorescu *et al*, 2002; Rudd *et al*, 2002; Schiller *et al*, 2002).

It seems that nedaplatin has activity and toxicity profiles similar to those of carboplatin, although no randomised trial has not been done to allow direct comparison (Fukuda *et al*, 1990; Furuse *et al*,

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1992a; Ota *et al*, 1992). Moreover, Matsumoto *et al* (2001) demonstrated that the combination of nedaplatin and gemcitabine resulted in enhanced inhibition of tumour growth *in vivo* and the antitumour efficacy of the combination was superior to that of cisplatin-gemcitabine or carboplatin-gemcitabine. Based on the results of a preclinical study, we designed the present phase I study of the efficacy of the combination of nedaplatin and gemcitabine for advanced NSCLC. The purpose of this study was to establish the toxicities and MTD of this combination, to determine the RD for phase II studies, and to observe their antitumour activity.

PATIENTS AND METHODS

Patient eligibility

Patients with histologic or cytologic confirmation of locally advanced or metastatic NSCLC who received either no prior chemotherapy or one previous chemotherapy regimen were eligible. The eligibility criteria were as follows; (1) measurable lesions; (2) age $\leqslant 75$ years; (3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1; (4) adequate organ function (a white blood count (WBC) $\geqslant 4000\,\mu l^{-1}$, a neutrophil count $\geqslant 2000\,\mu l^{-1}$, a platelet count $\geqslant 100\,000\,\mu l^{-1}$, a haemoglobin count $\geqslant 9.5\,g\,dl^{-1}$, serum total bilirubin $\leqslant 1.5\,mg\,dl^{-1}$, serum transaminase $\leqslant 2\times$ upper normal limits, a serum creatinine $\leqslant$ upper normal limits, blood urea nitrogen (BUN) $\leqslant 25\,mg\,dl^{-1}$, $PaO_2 \geqslant 60$ mmHg or $SpO_2 \geqslant 90\%$]; and (5) normal electrocardiogram (ECG). At least 4 weeks must have passed after the completion of previous therapy and the patients had to have recovered from the toxic effects of previous therapy. The exclusion criteria consisted of pulmonary fibrosis or interstitial pneumonitis with symptoms or apparent abnormalities on chest X-ray, massive pleural effusion or ascites, acute inflammation, pregnancy, lactation, symptomatic brain metastases, active concurrent malignancies, severe drug allergies, severe heart disease, cerebrovascular disease, uncontrollable diabetes mellitus or hypertension, severe infection, active peptic ulcer, ileus, paralysis intestinal, diarrhoea and jaundice. This study was performed at Kinki University School of Medicine and was approved by the Institutional Review Board. Written informed consent was obtained from all patients. This study was conducted in accordance with Declaration of Helsinki.

Pretreatment and follow-up studies

Prior to entry, a complete history was taken and physical examination including age, height, weight, performance status, histological diagnosis, tumour stage, contents of previous treatment and presence of a complication was performed. The pretreatment laboratory investigations included a complete blood cell count, differential WBC count, platelet count, serum electrolytes, total protein, albumin, total bilirubin, transaminase, alkaline phosphatase, lactate dehydrogenase, BUN, creatinine, creatinine clearance and urinalysis. After the initiation of therapy, a complete blood cell count with a differential WBC count was performed at least twice a week. Blood chemistry profiles and chest X-ray films were obtained weekly. The lesion measurements were performed during at least every second course. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 and tumour responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Therasse *et al*, 2000). Time to progression was measured from the date of registration to the date of first progression or death from any cause. Survival time was also measured from the date of registration to the date of death or latest follow-up, and was calculated using the Kaplan-Meier method (Kaplan and Meier, 1958).

Drug administration and dose escalation

The treatment schedule included nedaplatin, diluted with 500 ml of normal saline, given intravenously over 90 min on day 1, and gemcitabine with 100 ml of normal saline, given intravenously over 30 min after the completion of nedaplatin infusion on days 1 and 8, every 3 weeks. All patients were allowed to receive antiemetics with dexamethasone and granisetron, and post-therapy hydration with 1000 ml of normal saline. Granulocyte colony-stimulating factor (G-CSF) prophylaxis was not administered. Doses of gemcitabine on day 8 were given if the WBC count was $>2000\,\mu l^{-1}$ and/or the platelet count was $>750\,000\,\mu l^{-1}$, and/or allergic reaction, fever, elevation of transaminase and pneumonitis were less than grade 2, and/or the other nonhaematological toxicities were less than grade 3. The subsequent courses were withheld until the toxic levels returned to those specified in the eligibility criteria. The doses of both drugs were decreased by one dose level if DLTs occurred. In the case of the initial dose level, the doses of nedaplatin and gemcitabine were reduced by 20 and 200 mg m^{-2}, respectively.

Dose escalations were performed as listed in Table 1. Intrapatient dose escalation was not allowed. At least three patients were treated at each dose level, and three additional patients were entered at the same dose level if DLT was observed in one of the first three patients. The MTD was defined as the dose level at which more than two of three patients, or three of six patients experienced DLT. The definition of DLT was as follows: (1) grade 4 leukopenia, (2) grade 4 neutropenia for more than 4 days, (3) thrombocytopenia $<20\,000\,\mu l^{-1}$, (4) grade 3 febrile neutropenia, (5) grade 3 nonhaematologic toxicity except for nausea/vomiting, (6) delay of administration of gemcitabine on day 8 over a week for toxicities.

RESULTS

Between August 2001 and February 2003, 20 patients were enrolled in this study. The total and the median number of courses were 56 and 3 (range 1-6), respectively. The patients' characteristics are shown in Table 2. The majority of patients had a PS of 1. There

Table 1 Dose-escalation schema

Dose level	Nedaplatin dose (mg m^{-2})	Gemcitabine dose (mg m^{-2})	No. of patients (courses)
1	60	800	3 (8)
2	80	800	3 (10)
3	80	1000	8 (18)
4	100	1000	6 (20)

Table 2 Patients' characteristics

No. of patients		20
Age, years	Median	63.5
	Range	36-74
Sex	Male/female	17/3
Performance status	0/1	5/15
Histology	Adeno/squamous	13/7
Stage	IIIB/IV	4/16
Prior therapy	None	5
	Surgery	5
	Radiation	6
	Chemotherapy	14
	CDDP-based	3
	CBDCA-based	4
	Nonplatinum	4
	UFT	2
	Gefitinin	1

Clinical

were five previously untreated patients (level 3, two patients; level 4, three patients) and 15 (75%) previously treated patients. Of the previously treated patients, five had received prior surgery, five had prior radiotherapy, and 14 had prior chemotherapy. Seven had received platinum-based chemotherapy (cisplatin, three patients; carboplatin, four patients), and four a nonplatinum regimen. Responses to previous chemotherapy included partial response in five patients, stable disease in seven, progressive disease in one, and not evaluable in one. The median interval from previous treatment was 16 weeks (range 4–92.5 weeks). Out of 20 patients, 18 were assessable for toxicity and response. Two patients at level 3 were excluded from the toxicity and response evaluation because they had refused this study after registration.

Toxicities

The haematological and nonhaematological toxicities observed during the first course are shown in Tables 3 and 4, respectively. The most frequent toxicities observed in the first cycle were neutropenia and thrombocytopenia (Table 3). One-third of the patients had grade 3 thrombocytopenia, and one patient received a platelet transfusion during the first course. Three patients had grade 4 neutropenia for no longer than 4 days. The nadir for neutropenia and thrombocytopenia occurred on day 15 (median, range 5–18), and on day 15 (median, range 8–18), respectively. Nonhaematological toxicities generally were mild because none of the patients had experienced more than grade 3 in the first course (Table 4). The major toxicities following all courses are listed in Table 5. Grade 3 thrombocytopenia occurred in 16 out of 56 courses, and three patients received platelet transfusion (one patient at level 1, one at level 3 and one at level 4). However, no patient had haemorrhagic complications. The most frequent nonhaematological toxicities were elevation of transaminase activity, nausea and appetite loss, but all were mild. One previously untreated patient at level 3 experienced grade 3 pneumonitis after the fifth course, probably induced by this treatment, and the patient's condition improved after the administration of steroid. There was no treatment-related death. One of the 18 patients at level 4 underwent dose reduction after the first course due to neutropenia, and two patients at level 3 did not receive gemcitabine on day 8 because they had neutropenia, thrombocytopenia and high transaminase activity. Delays in the commencement of subsequent courses occurred in 11 courses, and the median length of the delay before starting the subsequent course was 21 days (21–35 days).

MTD and DLTs

At levels 1 and 2, none of the patients had developed a DLT. Haematological and nonhaematological toxicities were generally mild at these levels, although one patient had grade 3 thrombocytopenia at level 1. At level 3, two of six assessable patients had developed DLTs. Both could not receive their scheduled dose of gemcitabine on day 8 because they had neutropenia, thrombocytopenia and high transaminase activity. At level 4, three of six patients had developed DLTs. One patient received G-CSF for neutropenia, not lasting more than 4 days, which was considered as the DLT. Another patient required a platelet infusion because of thrombocytopenia $<20\,000\,\mu l^{-1}$. The third patient could not receive the second course due to the delayed anaemia, also considered as DLT. Therefore, dose level 4, 100 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine was regarded as the MTD. The recommended dose level for further phase II study was determined to be 80 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine (dose level 3 in this study).

Response and survival

There were three partial responses, for an overall response rate of 16.7%. As for squamous cell carcinoma, only one out of seven

Table 3 Haematological toxicity following first course of nedaplatin and gemcitabine

		WBC grade					ANC grade					plt grade					Hb grade				
Dose level	No. of patients	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	3	0	2	1	0	0	0	1	2	0	0	0	1	1	1	0	0	2	1	0	0
2	3	1	0	2	0	0	1	0	1	1	0	0	3	0	0	0	0	1	2	0	0
3	6	1	1	2	1	0	2	0	0	3	1	1	2	1	2	0	3	3	0	0	0
4	6	1	0	3	2	0	0	0	3	1	2	0	2	1	3	0	0	3	3	0	0

Table 4 Nonhaematological toxicity following first course of nedaplatin and gemcitabine

		Nausea grade					Vomiting grade					Fatigue grade					Transaminase grade				
Dose level	No. of patients	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	3	3	0	0	0	0	3	0	0	0	0	2	1	0	0	0	3	0	0	0	0
2	3	1	1	1	0	0	3	0	0	0	0	1	2	0	0	0	1	2	0	0	0
3	6	2	3	1	0	0	5	1	0	0	0	4	2	0	0	0	3	1	2	0	0
4	6	2	2	2	0	0	6	0	0	0	0	6	0	0	0	0	1	5	0	0	0

		Infection grade					Fever grade					Appetite loss grade					Constipation grade				
Dose level	No. of patients	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	3	3	0	0	0	0	3	0	0	0	0	3	0	0	0	0	3	0	0	0	0
2	3	2	0	1	0	0	2	1	0	0	0	1	2	0	0	0	3	0	0	0	0
3	6	6	0	0	0	0	6	0	0	0	0	2	4	0	0	0	4	2	0	0	0
4	6	4	0	2	0	0	6	0	0	0	0	2	4	0	0	0	4	2	0	0	0

Table 5 Toxicities following all courses of nedaplatin and gemcitabine (56)

	Grade			
	1	2	3	4
WBC	13	26	10	0
ANC	15	15	13	3
Hb	24	27	1	0
Plt	22	14	16	0
Nausea	17	4	0	0
Vomiting	6	0	0	0
Appetite loss	21	0	0	0
Fatigue	15	0	0	0
Constipation	6	7	0	0
Transaminase	27	5	0	0
Neuropathy	5	0	0	0
Pneumonitis	0	0	1	0
Fever	1	0	0	0
Infection	0	3	1	0

patients had a partial response. The median progression-free survival time was 5.1 months. The median survival time and 1-year survival rate were 9.1 months and 34.1%, respectively. Out of 15 patients who had received prior treatment, two (13.3%) achieved a partial response, and there was no clear relationship between responses to previous treatment and responses to this regimen. For previously treated patients, the median survival time and 1-year survival rate were 9.2 months and 40.3%, respectively. Among five previously untreated patients, one (20%) achieved a partial response and the median survival time and 1-year survival rate were 12.0 months and 50.0%, respectively.

DISCUSSION

Many recent randomised clinical trials have shown that the combinations of cisplatin with one of the new agents, such as gemcitabine, taxanes or vinorelbine, is the standard therapy for patients with locally advanced or metastatic NSCLC (Non-Small Cell Lung Cancer Collaborative Group, 1995; Kelly *et al*, 2001; Schiller *et al*, 2002; Fossella *et al*, 2003). As it is known that cisplatin strongly promotes nephrotoxicity, neurotoxicity and gastrointestinal toxicity, second-generation platinum-containing compounds including carboplatin have attracted attention. Based on several randomised trials that have shown that the combination of carboplatin with paclitaxel produces similar response rates and overall survival with a more favourable toxicity profile than the combination of cisplatin with new agents (Kelly *et al*, 2001; Scagliotti *et al*, 2002; Schiller *et al*, 2002), combined therapy of carboplatin and paclitaxel is considered to be a standard therapy. More recently, the combination of carboplatin with gemcitabine has become attractive as a therapy for advanced NSCLC. Some randomised studies have indicated that carboplatin-gemcitabine regimen offers equivalent median survival compared with cisplatin-gemcitabine or mitomycin-vinblastine-cisplatin /mitomycin-ifosfamide-cisplatin (Danson *et al*, 2003; Zatloukal *et al*, 2003), and results in significant improvements in overall survival over those for gemcitabine alone or the older cisplatin-containing regimens (Grigorescu *et al*, 2002; Rudd *et al*, 2002; Sederholm, 2002). However, neutropenia and thrombocytopenia were more common in carboplatin-gemcitabine regimens than others; thrombocytopenia was particularly common.

Like carboplatin, nedaplatin is also a second-generation platinum derivative that appears to have a similar mechanism and toxicity profile to carboplatin, although direct comparison has not been performed. Moreover, *in vivo* study suggested that nedaplatin-gemcitabine resulted in more enhanced inhibition of tumour growth than cisplatin-gemcitabine or carboplatin-gemcitabine. These results prompted us to investigate nedaplatin-based combinations and to conduct this phase I study.

With respect to toxicities, the most frequent toxicities were haematological toxicities, especially neutropenia and thrombocytopenia. Eight of 18 patients (44.4%) developed more than grade 3 neutropenia after the first courses, and after 16 out of 56 (28.6%) courses overall. On the other hand, six out of 16 patients (37.5%) developed grade 3 thrombocytopenia after the first courses, and after 16 out of 56 courses (37.5%) overall. However, patients required platelet transfusions during only three courses. In addition, one previously untreated patient developed drug-related pneumonitis, which improved with the administration of steroid, at level 3 after the fifth course.

Overall, the toxicities of the combination of nedaplatin with gemcitabine were generally mild and this combination chemotherapy is both well tolerated and active against advanced NSCLC.

The overall response rate of 16.7%, the median survival time of 9.1 months, and 1-year survival rate of 34.1% in this study were quite acceptable because most patients had been given prior chemotherapy. As evaluation of antitumour activity was not a primary objective, and our patient population was small and heterogeneous, we are unable to draw definitive conclusions about the activity of this regimen. Currently, it is still controversial whether novel platinum compounds such as carboplatin and nedaplatin could replace cisplatin for the treatment of advanced NSCLC. However, when not only antitumour activity but also palliation are the main goals of treatment, these new platinum compounds might play a useful role because of their favourable toxicity profile. Therefore, nedaplatin-gemcitabine warrants a phase II study, and further evaluation in prospective randomised trials with cisplatin- or carboplatin-based combinations as a first-line chemotherapy for advanced NSCLC in order to investigate whether nedaplatin could replace cisplatin or carboplatin.

In conclusion, the combination of nedaplatin with gemcitabine is well tolerated and active for advanced NSCLC. The MTD and recommended dose level are 100 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine and 80 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine, respectively.

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Retrospective analysis of the predictive factors associated with the response and survival benefit of gefitinib in patients with advanced non-small-cell lung cancer

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Summary

Background: The purpose of the study was to identify the potential predictive features associated with the response and survival benefit of gefitinib administration. We have retrospectively reviewed data of all patients who received a single regimen of gefitinib in our institution from August 1998 until July 2003.

Methods: Overall 101 patients with non-small-cell lung cancer (NSCLC) who have received a single use of gefitinib were analyzed. Potential factors associated with the response of gefitinib included smoking index, gender, histology, performance status (PS), number of pre-treatments, age and stage. Univariate analysis was performed for these strata by Fisher's exact test and multivariate analysis was then performed using the logistic regression model.

Results: The overall response rate was 19.8%. Univariate analysis revealed that significant predictive factors were associated with the response for 'adenocarcinoma', 'female', 'good PS' (0—1) and 'non-smoker' categories. Multivariate analysis limited the predictive factors associated with the response for 'female' ($P = 0.0032$), 'good PS' ($P < 0.02$) and 'non-smoker' ($P = 0.0417$). In survival analyses, 'female' ($P < 0.005$), 'good PS' ($P < 0.0001$), and a low level of the smoking index ($P < 0.05$) indicated significantly prolonged survival. Response and survival data in elderly patients were equivalent to those in younger patients. Adverse events (AEs) were generally mild and were almost always skin reactions and diarrhea. Interstitial lung disease (ILD) occurred in 4% of the group under observation.

Conclusions: Gefitinib provided clinical benefit for the following factors 'female', 'good PS' and 'non-smoker'. A low smoking index is reported as a novel predictive prognostic factor following a single regimen of gefitinib.

Abbreviations: NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; IDEAL-1, Iressa dose evaluated advanced lung cancer-1; PS, performance status; NCI-CTC, National Cancer Institute-Common Toxicity Criteria; INTACT-1, Iressa NSCLC trial assessing combination treatment-1; INTACT-2, Iressa NSCLC trial assessing combination treatment-2

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