Clinical Effectiveness of Boron Neutron Capture Therapy for a Recurrent Malignant Peripheral Nerve Sheath Tumor in the Mediastinum

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A 70-year-old woman underwent extirpation of a malignant peripheral nerve sheath tumor, 4.5 × 2.0 cm in size, in the right supraclavicular fossa. Locoregional recurrence was found 10 months after operation (Figure 1). Although one course of systemic chemotherapy using cisplatin (80 mg/m^2 at day 1) and vinorelbine (25 mg/m^2 at days 1 and 8) was given, the recurrent tumor progressed. Because conventional radiotherapy is not effective for malignant peripheral nerve sheath tumor, boron neutron capture therapy (BNCT) was considered based on the subcutaneous mediastinal location. After institutional review board approval and securing the patient's written informed consent, accumulation of p-boronophenylalanine (BPA) in the tumor was confirmed using 18F-BPA positron emission tomography. Using simulation environment for radiation applications software program, fast neutron and γ-ray physical doses, compound biologic effectiveness- and relative biologic effectiveness-weighted doses, were calculated.

The patient underwent two courses of BNCT with an interval of 3 weeks. BPA-fructose was administered intravenously at a dose of 500 mg/kg just before irradiation. For the first course, the epithermal neutron irradiation was performed for 105 minutes. The dose distribution in the tumor ranged from 13.7 to 22.3 Gy-Eq and was 6.0 Gy-Eq to the skin. For the second course, the irradiation time was shortened to 51 minutes, because of the higher epithermal neutron flux. The dose delivered to the tumor ranged from 6.0 to 24.3 Gy-Eq and was 9.7 Gy-Eq to the skin.

Chest computed tomography scan 1 year after BNCT showed that the tumor size decreased from 6.2 × 4.0 cm to 4.6 × 3.2 cm in size (25% reduction), and stable disease was maintained for 24 months (Figure 2). Positron emission tomography-computed tomography 18 months after BNCT showed no uptake of 18F-fluorodeoxy glucose in the residual mass, suggesting no viability (Figure 3). Neuralgia of the right arm improved. Although temporary dysphagia because of an oral mucosa disorder was observed as a side effect, the patient's general quality of life was preserved. There is no evidence of recurrence 2 years after BNCT.

DISCUSSION

When ^{10}Boron absorbs thermal neutrons, α and ^{7}Lithium particles are generated.[1] BNCT selectively injures the tumor cells containing ^{10}Boron; it was suitable in this case with tumor invasion into the neighboring great vessels. Because the peak of thermal neutron flux is 3 cm beneath the tissue surface, its clinical applications have been limited to malignant melanomas and brain tumors. Kato et al.[2] reported its efficacy for head and neck malignancies. The indication was extended to metastatic liver tumor,[3] malignant mesothelioma,[4] and glioblastoma.[5] This is the first case of mediastinal tumor treated with BNCT.

The effect of BNCT is critically dependent on selective accumulation of ^{10}Boron compounds. The tumor/normal tissue ratio of the ^{10}Boron uptake was 2 in this case, while a ratio greater than 2.5 is preferable for selective treatment. BNCT might be a treatment option for subcutaneous mediastinal tumors, which is resistant to conventional irradiation.

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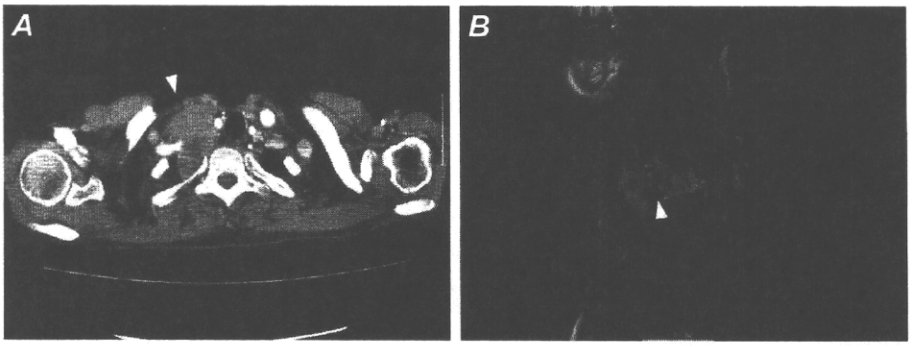

FIGURE 1. Chest computed tomography (CT) scan and magnetic resonance imaging (MRI) showing the recurrent lesion. *A*, Postoperative recurrence, 4.5 × 2.0 cm in size, is seen in the right subclavicular region (arrow head) in the follow-up CT scan 10 months after operation. *B*, Tumor invasion into the right subclavicular artery and brachiocephalic vein is seen (arrow head) in the sagittal view of MRI.

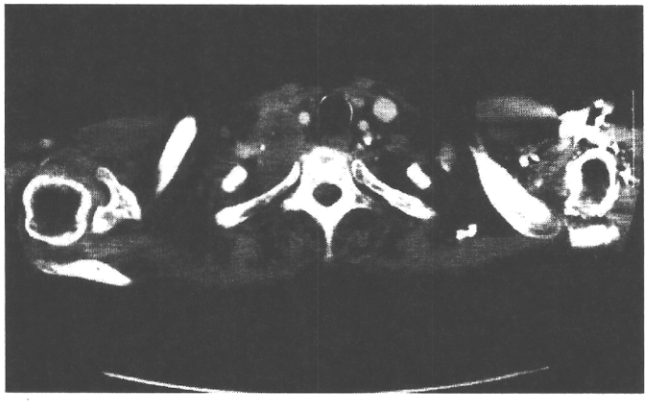

FIGURE 2. Chest computed tomography scan 1 year after boron neutron capture therapy shows shrinkage of the recurrent lesion after chemotherapy from 6.2 × 4.0 cm to 4.6 × 3.2 cm in size (25% reduction).

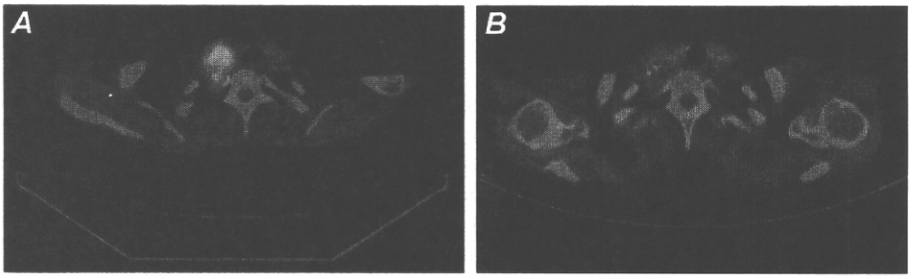

FIGURE 3. FDG-positron emission tomography (PET) shows the remarkable effect of boron neutron capture therapy (BNCT). *A*, PET-computed tomography (CT) before BNCT shows significant tumor uptake. *B*, Although a residual mass is seen, the FDG uptake is reduced to the background level 18 months after BNCT.

加速器中性子源による ホウ素中性子捕捉療法の展望

小野公二ほか

P.1038～1041 参照

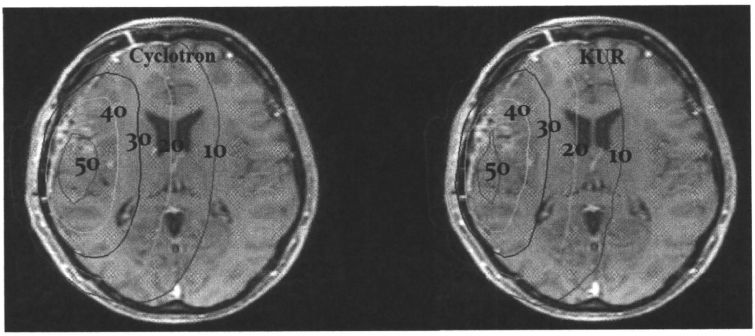

図4　サイクロトロンとＫＵＲでの中性子分布の比較

組織内照射～高線量率を中心に

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P.1056～1059 参照

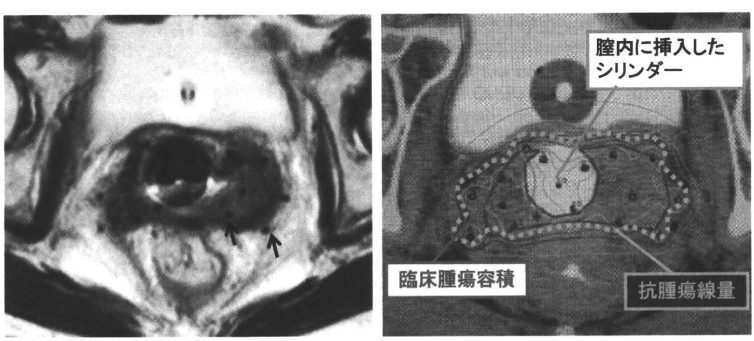

図1　組織内刺入後にCT/MRIを撮影して治療計画を行った高線量率組織内照射の症例　図1a 図1b
a：子宮頸癌T3b症例。MRI：T2強調像。矢印は刺入された治療用アプリケータ。
b：MRIを参考に、CT上に描いた臨床腫瘍容積に、危険臓器に配慮しながら抗腫瘍線量を処方。

加速器中性子源による ホウ素中性子捕捉療法の展望

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はじめに

中性子捕捉療法（NCT：Neutron Capture Therapy）は熱中性子（～0.5eV、平均0.025eV）が原子核と起こす核反応を利用した放射線療法の一種である。ホウ素（Boron、B）の安定同位体^{10}B（天然存在比：19.9%）とは^{10}B（n、α）^{7}Li反応を起こし、その断面積は3,595 barnで^{14}Nとの反応の約2,000倍も大きく、生成粒子の飛程はそれぞれ9μmと4μmで、一般的な細胞の直径よりも短い。ゆえに反応が起こった細胞のみを破壊する（**図1**）。

2粒子は平均LETがおのおの163 keV/μmと210 keV/μmの高LET放射線で、生物効果が大きく酸素増感比は1.0で低酸素腫瘍細胞の破壊にも効果的である。SLDやPLDが大きい腫瘍細胞や休止期腫瘍細胞にも効果が大きい[1]。ホウ素化合物の腫瘍集積性が選択的ならば腫瘍の選択的破壊が可能で、X線抵抗性腫瘍、浸潤性の強い腫瘍や放射線治療歴のある再発腫瘍の治療に応用が可能である。

1960年代末より腫瘍選択性の高いBorocaptate（BSH）とフェニルアラニン誘導体*para*-boronophenylalanine（BPA）の2種のホウ素化合物それぞれと原子炉中性子、あるいはBPAの弱点を補うべく両化合物を同時併用しての臨床研究や基礎研究が行われてきた[2～5]。本稿では京大原子炉実験所での研究を紹介するとともに、現在、臨床試験に向けて準備を進めている加速器中性子源によるNCTを展望する。

原子炉中性子による中性子捕捉療法

1）BNCTに必要な中性子源

熱中性子の水での半価層は15～16 mmで、かつての悪性脳腫瘍BNCTは術中照射であった。現在の熱外中性子（0.6eV～10keV）は生体の原子核と反応し熱中性子に変わるので、表面での熱中性子強度は2～3 cm深部のほぼ1/3であり、皮膚線量を大幅に低減できる。高い中性子強度が必要で、わが国では京大原子炉（KUR）と原研開発機構4号炉（JRR4）が利用されている。

2）対象疾患と症例の選択

わが国での熱外中性子の利用は2001年にKURで開始され、実施例が急増した。再発頭頸部癌[6]、多発肝癌[7, 8]、肺癌[9]と、いずれも世界初の試みを行い、対象を徐々に拡大している。これは京都府立医大と京大原子炉実験所の共同になる^{18}F-BPA PET BNCTシステムによってBPAが悪性腫瘍に広く集積することが明らかになったことと、集積の大まかなT/Nが事前に把握できるようになったためである[10]。

3）悪性神経膠腫

大阪医大脳外科を中心とした脳外科Gとの共同研究を進めているが、診断時からの中央生存期間は17.3～23.0ヵ月に達し[11]、直近のデータの2年生存率は50%を超える。原子炉施設での治療ゆえのバイアスの危険性を排除するため、RTOGの定義に従いRPAの6クラスに症例を分類解析した結果をTMZ併用X線治療の他家報告と比較したが、すべてのクラスでBNCTの方が良好であ

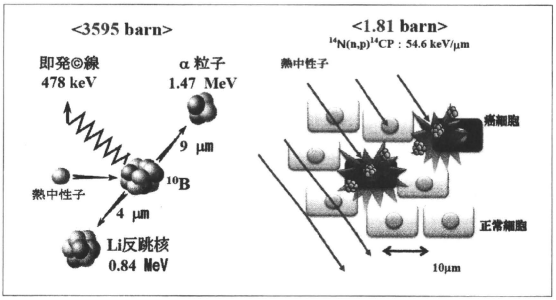

図1　ホウ素中性子捕捉療法による選択的細胞破壊の機序

った。ただ、確実な結論にはさらなる症例の蓄積が必要で、現在、多施設共同研究が進行中である。BNCTではきわめて大きい1回線量を腫瘍に照射できるので、画像上の1次効果は顕著である。その一方で腫瘍の脊髄腔への播種が顕在化し、2年以降の生存率の低下の原因となっている。

4)再発頭頸部癌

再発頭頸部癌を対象に、川崎医大G、大阪大学口腔外科Gなどと共同研究を進めている[6, 12]。世界最初の頭頸部癌のBNCTも京大原子炉で実施された。X線治療を含む標準治療後の再発頭頸部癌においてもほとんどの症例で腫瘍の縮退を示し、治療の奏効率は＞90%である[6]。一般には制御が不可能な再発腫瘍にもかかわらず、腫瘍の完全消失・制御を得た症例もある。他に治療の選択肢がまったくない再発頭頸部癌症例を対象にBNCTを試み、24%の長期生存率を得ている。

加速器中性子源開発

原子炉は十分な実績のある安定した中性子源であり、最近、中国では小型(熱出力30kW)の医療専用炉が建設されてはいるが、一般には原子炉特有の規制、設置場所の選択の不自由などに由来する臨床使用上の制約が非常に大きい。特にわが国ではBNCTがこの制約から解放され、承認された癌治療法へと発展していくためには、小型加速器中性子源の開発が不可欠である。現在、京大原子炉実験所では住友重機械工業株式会社との共同開発になるサイクロトロン中性子源が完成し、臨床試験の開始をめざした諸準備が急ピッチで進んでいる。

1)加速器中性子源の性能と中性子ビームの特性

開発したのは、サイクロトロンで電流量1mAの陽子をエネルギー30MeVまで加速し、Beターゲットに衝突させて発生する中性子を減速し、BNCTに供するBNCT用加速器中性子照射システムである(**図2、3**)。サイクロトロンとしての性能は加速エネルギー30MeV、電流量2mAを達成している。中性子捕捉療法には1mAの電流で十分で、その中性子強度は京大炉の公称強度の1.67倍である(**表1**)。KURが運転を再開した5月28日～9月14日に18件のBNCTを実施したが、その実測中性子強度は6.11～7.28n/cm^2/s、平均は6.78n/cm^2/sなので、実際の強度比較では1.80倍である。原子炉の場合、ウランの燃焼度によって中性子強度が変化するが、加速器は電流が安定していれば中性子強度は変化せず、それらの安定性は確認ずみである。京大炉での中性子照射に要する時間は、ホウ素濃度にもよるが、通常、最長1時間である。同じ線量を与えるとすると、その照射時間は最長33分程度となる。患者とコリメータの接近度など中性子強度以外の要因も患部表

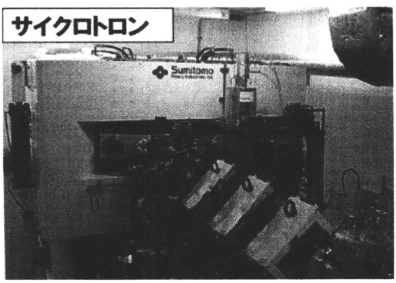

図2　中性子捕捉療法用加速器（サイクロトロン）

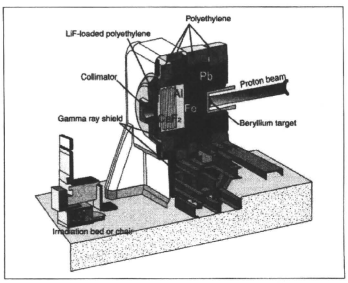

図3　中性子照射システム

表1　KURと加速器中性子のビーム特性比較

	Epi-thermal neutron flux(Φ_{epi}) (n/cm2/s)	Fast neutron dose/Φ_{epi} (Gy/n cm2)	Gamma-ray dose/Φ_{epi} (Gy/n cm2)
KUR (epi-thermal)	7.30E+08	9.10E-13	2.40E-13
Accelerator	**1.22E+09**	5.84E-13	7.75E-14

面の中性子強度に影響するが、加速器中性子照射システムでは京大炉での経験をふまえて接近度が改善できるように設計されているので、さらなる照射時間の短縮が期待できる。熱外中性子あたりの混入高速中性子やγ線の線量も、京大炉より低減されたビームとなっている。

2）中性子ビームの生物特性

臨床試験で目標とする中性子強度が達成され、運転やターゲットの安定性が確認できたので、昨年から培養細胞や担癌および非担癌マウスを用いて中性子ビームの生物特性を把握する研究を実施した。マウスの50%放射線口腔死線量、ヒト株化癌細胞および繊維芽細胞のコロニー形成能によるD_{10}あるいはD_0を指標に加速器中性子ビームのRBEを検索したところ、値は2.2～2.7であった。この値は、原子炉中性子ビームのそれ（3.0）よりもやや小さいが、これは加速器中性子の平均エネルギーが原子炉のそれよりも高いこととよく整合する。

ヒト舌癌細胞SASを移植した担癌ヌードマウスにホウ素化合物を投与し、加速器中性子ビームを照射するとホウ素中性子捕獲反応による明瞭な抗癌効果が確認された。

3）加速器中性子BNCTでの線量分布のシミュレーション

上記の中性子ビームの物理・生物特性をふまえて、本システムでBNCTを実施した場合に予想されるX線等価線量分布のシミュレーションを行った。平均サイズの成人正常脳が受ける最大線量（10Gy-Eq）が等しい条件でKURと性能比較を行うと、大脳正中部の腫瘍線量がKURでは15Gy-Eqであるのに対し、加速器中性子では20Gy-Eqに達する（**図4**）。同じ条件で対側からも中性子を照射すると、サイクロトロン中性子ビームの場合、正中部の合計線量は40Gy-Eqとなる[13]。この線量は臨床研究で目標とするGTVの最低線量であり、抗腫瘍効果の向上を期待させる。全脳に広がった転移性脳腫瘍や対側大脳半球へ進展している

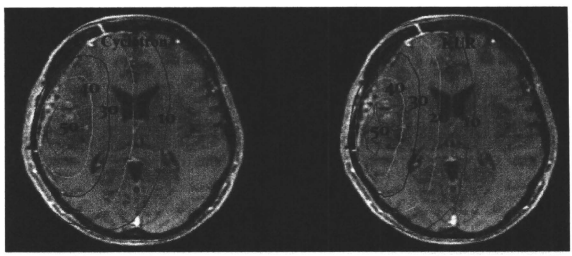

図4　サイクロトロンとKURでの中性子分布の比較　IMAGE PREVIEW 参照

悪性脳腫瘍に対する治療、悪性脳腫瘍で脊髄腔に播種した症例に対する治療も可能になるかもしれない。加えて新規腫瘍に対するいっそうの適応拡大も期待される[14]。また研究炉でのBNCTとは異なり、年間の利用可能時間の大幅な増加によって2～3回の分割BNCTも将来は可能となり、より安全で効果的なBNCTの実現が期待される。

BNCTは、20世紀の癌放射線治療を支配してきたパラダイムを革新し、その高度な選択性によって癌放射線治療を別次元に押し上げる可能性を有する治療である。

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Phase II study of erlotinib plus gemcitabine in Japanese patients with unresectable pancreatic cancer

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Erlotinib combined with gemcitabine has not been evaluated in Japanese patients with unresectable pancreatic cancer. This two-step phase II study assessed the safety and pharmacokinetics of erlotinib 100 mg/day (oral) plus gemcitabine 1000 mg/m^2 (i.v. days 1, 8, 15) in a 28-day cycle in the first step, and efficacy and safety in the second step. The primary end-point was safety. One hundred and seven patients were enrolled (first step, n = 6; second step, n = 101). The most common adverse event was RASH (compiled using the preferred terms rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash) in 93.4% of patients. One treatment-related death occurred. While interstitial lung disease-like events were reported in nine patients (8.5%; grade 1/2/3, 3.8/2.8/1.9%), all patients recovered or improved. The median overall survival, the 1-year survival rate and median progression-free survival were 9.23 months, 33.0% and 3.48 months, respectively. The overall response and disease control rates were 20.3% and 50.0%, respectively. In Japanese patients with unresectable pancreatic cancer, erlotinib plus gemcitabine had acceptable toxicity and efficacy that was not inferior to that seen in Western patients. (*Cancer Sci* 2011; 102: 425–431)

Approximately 232 000 individuals are diagnosed with pancreatic cancer worldwide each year, with an annual death rate estimated at 227 000.[1] In Japan, approximately 22 000 new cases were reported in 2005.[2] Furthermore, data from 2007 show that around 24 000 individuals in Japan died from pancreatic cancer, making this tumor type the fifth leading cause of cancer-related death.[3] The majority of pancreatic cancer cases are diagnosed at an unresectable stage when prognosis is extremely poor.

Current treatment for advanced pancreatic cancer is based on systemic chemotherapy with gemcitabine. Single-agent gemcitabine has been shown to extend median overall survival (OS) to 5.65 months in chemonaïve patients compared with 4.41 months in patients who received fluorouracil.[4] Addition of other cytotoxic agents to gemcitabine has not demonstrated survival benefits over gemcitabine alone.[5–13] The potential of combining gemcitabine with biological agents in patients with advanced pancreatic cancer has also been evaluated in several phase III studies, but these trials failed to show a survival benefit.[14–19]

Epidermal growth factor receptor (EGFR)-mediated signaling is associated with various cellular processes, and the dysregulation of these processes is common in tumorigenesis.[20,21] Furthermore, EGFR is overexpressed in many tumors and its overexpression is often associated with poor prognosis.[22–26] EGFR tyrosine-kinase inhibitors (TKI, such as erlotinib) are used in the treatment of various types of solid tumors.

Erlotinib has demonstrated antitumor activity in pancreatic cell lines[27] and was subsequently assessed as a potential therapeutic agent in pancreatic cancer. In the PA.3 study (n = 569), the risk of death with erlotinib plus gemcitabine was reduced by 18% versus gemcitabine alone (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69–0.99; P = 0.038 after adjustment for stratification factors), with a median OS of 6.24 months *vs* 5.91 months, respectively. Erlotinib plus gemcitabine combination therapy provided significant improvements in the 1-year survival rate (23% *vs* 17%; P = 0.023) and progression-free survival (PFS; HR 0.77; 95% CI, 0.64–0.92; P = 0.004).[28] As a result, this combination was approved for use in pancreatic cancer in many countries.

In Japanese patients with non-small-cell lung cancer (NSCLC), a phase II study has specifically shown that erlotinib monotherapy is well tolerated and has promising antitumor activity.[29] However, there are no data on the use of erlotinib combined with gemcitabine in Japanese patients with pancreatic cancer. This phase II study evaluated the safety and efficacy of erlotinib in combination with gemcitabine in Japanese patients with unresectable locally advanced or metastatic pancreatic cancer.

Methods

Patients. Patients aged 20–80 years with histological/cytological evidence of unresectable locally advanced or metastatic adenocarcinoma/adenosquamous carcinoma of the pancreas were eligible for inclusion in the present study. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, adequate hematological, renal and hepatic function and a life expectancy of at least 2 months. No more than one prior regimen for pancreatic cancer was permitted. Patients who had received prior gemcitabine and/or a TKI were excluded from participation, as were those who had previously been exposed to a human epidermal growth factor receptor 2 (HER2) or EGFR inhibitor. Other key

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Clinical trial registry: JAPIC Clinical Trials Information (see links below). http://rctportal.niph.go.jp/examDetail.php?center=3&center_seq=698 http://www.clinicaltrials.jp/user/cteDetail.jsp?clinicalTrialId=839&language=ja. Trial registration number: JapicCTI-060337.

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exclusion criteria were: symptomatic cerebral metastases; a concurrent lung disorder (such as idiopathic pulmonary fibrosis, interstitial lung disease [ILD] or pneumoconiosis); concurrent or previous drug-induced pneumonia; or a history of radiation to the chest.

The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was obtained from all patients, and the protocol was approved by ethics committees at all participating institutions.

Study design and treatment. This was a phase II, multicentre, open-label, two-step study. In the first step, six patients were enrolled into the study and treated with oral erlotinib 100 mg/day on days 3–28, plus i.v. gemcitabine 1000 mg/m^2 on days 1, 8 and 15 in a 28-day cycle. The starting doses of erlotinib and gemcitabine were chosen in reference to the PA.3 study. Dose-limiting toxicities (DLT) were assessed in these study participants using the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (NCI-CTCAE, National Cancer Institute, Bethesda, MD, USA). Dose-limiting toxicities were defined in conformity to the P1b study as follows:[30] (i) grade 4 decrease (i.e. to <500/mm^3) in neutrophil count >5 days; (ii) grade ≥3 decrease (i.e. to <1000/mm^3) in neutrophil count with associated fever (≥38.5°C); (iii) grade 4 decrease in platelet count (i.e. to <25 000/mm^3); (iv) any grade ILD; (v) grade 4 elevation of alanine transaminase (ALT)/aspartate transaminase (AST) levels, or grade 3 elevation of ALT/AST levels >7 days; (vi) grade ≥3 non-hematological toxicity (excluding rash, hyperglycemia, γ-GTP and events that were judged to be transient/had no effect on study continuation); and (vii) dose-reduction/interruption required due to persistent adverse events (AE), which meant that the second cycle could not be started.

If treatment-related DLT occurred in no more than two of the six patients, transition to the second step of the study was permissible with approval of the Data Safety and Monitoring Committee (DSMC). If DLT occurred in three or more patients, transition to the second step was limited to those cases that were judged to be safe for this study after the DSMC had evaluated the safety data of the patients with a DLT. In the second step, it was planned that 94 patients would be treated with the same dose as the first step. Treatment was continued until disease progression, death, unacceptable toxicity or patient/investigator request.

The primary end-point of the study was safety, with secondary end-points including OS, 1-year survival rate, PFS, overall response rate (ORR), disease control rate (DCR = complete response [CR] + partial response [PR] + stable disease), pharmacokinetics (PK) and correlation of *EGFR* mutation status with outcomes.

Toxicity evaluation. Adverse events were monitored and graded using NCI-CTCAE v3.0. Clinical and laboratory assessments were conducted throughout the study. Adverse events prespecified in the study to be monitored carefully were rash, diarrhea, vomiting, liver dysfunction and ILD-like events. Chest X-ray examination to assess pulmonary toxicity was conducted weekly until week 4 and every 2 weeks thereafter. In addition, chest computed tomography (CT) scan was performed every 4 weeks. The DSMC reviewed the images and clinical data associated with all potential ILD-like events. All ILD-like events were reported to be serious AE (SAE), regardless of the grade.

Efficacy evaluation. The tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) in patients who had at least one measurable target lesion. Tumors were measured using computed tomography (CT) at baseline and on day 22 of every two cycles thereafter. Median PFS, ORR and DCR were estimated by the extramural review. The relationship between efficacy and the severity of RASH (compiled using the preferred terms rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash) was also examined.

Pharmacokinetic evaluation. Pharmacokinetic evaluation of erlotinib and its O-desmethylated metabolite (OSI-420) was performed in the six patients enrolled in the first step of the study. Venous blood samples were taken prior to erlotinib dosing on day 3 and day 8 of cycle 1 at 0.5, 1, 2, 4, 6, 8 and 24 h after erlotinib administration. Samples were also taken prior to gemcitabine infusion on days 1 and 8 at 0.5, 0.75, 1, 1.5, 2.5 and 4.5 h after dosing.

The plasma concentrations of erlotinib, OSI-420 and gemcitabine were measured by liquid chromatography, tandem mass spectrometry (LC-MS-MS). The LC-MS-MS analytical methods have been described previously.[31,32] Derived PK parameters included the maximum plasma drug concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma drug concentration-time curve to the last plasma sample (AUC_{last}), terminal half-life ($t_{½}$) and oral clearance (Cl/F).

Biomarker analysis. *EGFR* mutations were assessed in patients with available tumor tissue specimens, which were formalin fixed and paraffin embedded. Samples were analyzed at a central laboratory where DNA was extracted and exons 18–21 sequenced using a nested PCR.

Statistical analysis. Progression-free survival and OS were estimated using the Kaplan–Meier method in all patients who received at least one dose of the study treatment, with 95% CI for the median duration calculated using Greenwood's formula. The Clopper–Pearson method was used to calculate the 95% CI around the ORR, DCR and AE rate. Multivariate analyses were performed for the occurrence of ILD-like events using the logistic regression model. Baseline characteristics investigated for this analysis included gender, age, lung metastasis, emphysema and various baseline laboratory values. The target enrollment was 100 patients, as this was required to evaluate the safety of erlotinib.

Results

Patient characteristics. Between December 2006 and October 2007, a total of 107 patients were enrolled (first step, $n = 6$; second step, $n = 101$) from 12 institutions (Fig. 1). One patient who enrolled into the second step did not receive treatment due to deterioration in PS prior to the start of treatment. A total of 106 patients were evaluable for safety (safety population, full analysis set).

The patient demographics and baseline characteristics are shown in Table 1. The median age was 62 years (range, 36–78) and 52.8% of patients were male. Almost all patients were chemonaïve (95.3%). The majority (75.5%) of patients had an ECOG PS of 0 and most (83.0%) had metastatic disease. Over half (63.2%) of the patients had a history of current or past smoking.

Toxicity and dose modifications. The median duration of erlotinib exposure was 102.5 days and its median dose intensity was 100.0 mg/day, with the majority of patients (78.3%) receiving more than 90% of the relative dose intensity. The median duration of gemcitabine treatment was 4.0 cycles and its median dose intensity was 688.0 mg/m^2 per week, with approximately half of the patients (51.4%) receiving more than 90% of the relative dose intensity.

As only one patient had a DLT (grade 3 diarrhea) in the first step, the second step of the study was initiated. One hundred and six patients received at least one dose of erlotinib; these patients were assessable for toxicity. Treatment-related AE and treatment-related changes in laboratory values are summarized in Table 2; most of these were mild to moderate in severity. The most frequently reported AE was RASH, which occurred in

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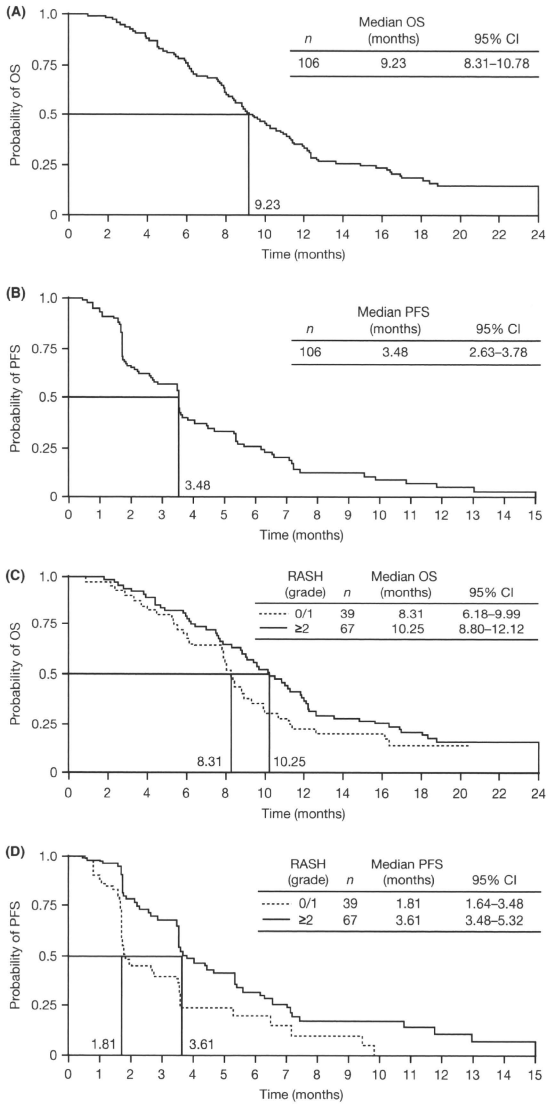

Fig. 1. Kaplan–Meier estimates of (A) overall survival (OS) and (B) progression-free survival (PFS) in the study population (n = 106); (C) OS and (D) PFS according to the severity of RASH (grade ≤1 [n = 39] *vs* grade ≥2 [n = 67]). RASH is a composite of the terms: rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash. CI, confidence interval.

Table 1. Baseline characteristics and demographics (n = 106)

Characteristic	
Median age (range) (years)	62 (36–78)
Gender, n (%)	
Male	56 (52.8)
Female	50 (47.2)
Median bodyweight (range) (kg)	52.3 (33.1–95.0)
Smoking history,† n (%)	
Never smoker	39 (36.8)
Past smoker	37 (34.9)
Current smoker	30 (28.3)
ECOG PS, n (%)	
0	80 (75.5)
1	26 (24.5)
2	0 (0)
Disease status, n (%)	
Metastatic	88 (83.0)
Locally advanced	18 (17.0)
Primary tumor identified, n (%)	92 (86.8)
Primary sites, n (%)	
Head	46 (43.4)
Body and tail	23 (21.7)
Body	22 (20.8)
Tail	10 (9.4)
Other	5 (4.7)‡
Biliary drainage, n (%)	19 (17.9)
Sites of distant metastases, n (%)	
Liver	56 (52.8)
Distant lymph nodes	39 (36.8)
Lung	17 (16.0)
Other	26 (24.5)
Prior lines of therapy, n (%)	
None	101 (95.3)
One regimen	5 (4.7)§
Median CA19–9 (range) (U/mL)	
Median	776 (0–435 000)
Median CEA (range) (ng/mL)	
Median	4.8 (0.6–1100.1)

†Never smoker, never/hardly smoked; past smoker, passage of at least 1 month since stopping smoking (at the time of registration); current smoker, smoked within 1 month (at the time of registration). ‡Whole of pancreas (n = 1); head and body (n = 3); other (n = 1). §Tegafur, gimeracil, oteracil potassium (S-1) (n = 3); 5-fluorouracil plus leucovorin (n = 2). CA 19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; ECOG, Eastern Co-Operative Group.

Table 2. Treatment-related adverse events occurring in >30% of patients treated with erlotinib and gemcitabine (n = 106)

	Any grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Non-hematological			
Rash	78 (73.6)	3 (2.8)	0 (0)
Anorexia	75 (70.8)	15 (14.2)	0 (0)
Pruritus	57 (53.8)	1 (0.9)	0 (0)
Fatigue	56 (52.8)	3 (2.8)	0 (0)
Nausea	56 (52.8)	6 (5.7)	0 (0)
Diarrhea	52 (49.1)	2 (1.9)	0 (0)
Dry skin	49 (46.2)	0 (0)	0 (0)
Stomatitis	38 (35.8)	0 (0)	0 (0)
Pyrexia	32 (30.2)	0 (0)	0 (0)
Hematological			
White blood cell count decreased	85 (80.2)	31 (29.2)	0 (0)
Platelet count decreased	77 (72.6)	9 (8.5)	0 (0)
Hemoglobin decreased	76 (71.7)	13 (12.3)	2 (1.9)
Hematocrit decreased	73 (68.9)	8 (7.5)	0 (0)
Neutrophil decreased	73 (68.9)	32 (30.2)	5 (4.7)
Red blood cell count decreased	72 (67.9)	8 (7.5)	0 (0)
ALT increased	59 (55.7)	10 (9.4)	0 (0)
AST increased	57 (53.8)	4 (3.8)	1 (0.9)
Weight decreased	53 (50.0)	3 (2.8)	0 (0)
Lymphocyte count decreased	46 (43.4)	14 (13.2)	0 (0)
Blood albumin decreased	35 (33.0)	0 (0)	0 (0)
Gamma-glutamyltransferase increased	35 (33.0)	12 (11.3)	1 (0.9)

ALT, alanine amino transferase; AST, aspartate amino transferase.

93.4% of the patients; most cases were mild to moderate in severity (87.7%, grade ≤2; 5.7%, grade ≥3). Other common non-hematological AE included anorexia, pruritus, fatigue, nausea and diarrhea. Most patients experienced some degree of hematological toxicity, with grade 3 or 4 neutropenia (neutrophil decreased), leucopenia (white blood cell count decreased) and anemia (hemoglobin decreased) occurring in 34.9%, 29.2% and 14.2% of patients, respectively. Only one treatment-related death occurred (due to gastrointestinal hemorrhage), which was probably due to arterial bleeding caused by the invasion of the primary tumor into the gastrointestinal tract. Although the likelihood of this event being treatment-related was deemed remote, a causal relationship could not be completely excluded because the event occurred during the study treatment administration period.

Treatment-related SAE were reported in 26 (24.5%) patients. These included nine ILD-like events (8.5%), the majority of which (n = 7) were grade 1–2 in severity. Importantly, all of these nine patients recovered or improved, and four of these patients did so without any treatment for ILD-like events. Other treatment-related SAE were anorexia (3.8%), vomiting, pyrexia and abnormal hepatic function (1.9% each). The baseline characteristics, treatment and outcomes of patients who developed treatment-related ILD-like events during the study are detailed in Table 3. The onset times of ILD-like events ranged from 7 to 187 days after the start of treatment. In these patients, a relatively long survival was observed (from 119 to 568+ days), and five patients received post-study therapy. All of these nine patients were past or current smokers, and six had emphysema at baseline (not detected prior to treatment, but diagnosed at the extramural review by a radiologist in the DSMC). Multivariate analyses were performed for the occurrence of ILD-like events using the logistic regression model and emphysema at baseline was indicated as a risk factor for onset of ILD-like events (odds ratio [95% CI], 12.13 [1.01–145.7]; P = 0.0491).

Adverse events led to erlotinib discontinuation in 30 patients (28.3%) and gemcitabine discontinuation in 27 patients (25.5%). The main reasons for treatment discontinuation were ILD (n = 6) and anorexia (n = 3); no patient discontinued treatment due to RASH or diarrhea. Due to the onset of AE, a total of 65 patients (61.3%) required one or more interruptions of erlotinib (36 patients [34.0%] for longer than seven consecutive days and 17 patients [16.0%] for longer than 14 consecutive days) and 56 patients (52.8%) had one or more skip of gemcitabine. Modifications in the erlotinib or gemcitabine dosage were required in 17 (16.0%) and 11 (10.4%) patients, respectively, due to AE.

Efficacy. The median OS was 9.23 months (95% CI, 8.31–10.78; Fig. 1A) and the 1-year survival rate was 33% (95% CI, 24–42). Median PFS was 3.48 months (95% CI, 2.63–3.78; Fig. 1B). Among the patients evaluable for tumor response (n = 64), the ORR was 20.3% (13/64; 95% CI, 11.3–32.2) and the DCR was 50.0% (95% CI, 37.2–62.8; CR, n = 0; PR, n = 13; stable disease, n = 19).

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Table 3. Characteristics, treatment and outcomes of patients with treatment-related ILD-like events (n = 9)

Event	Gender	Age (years)	Smoking status†	Days on treatment	ILD maximum grade	Suspicious findings of ILD	Steroids	Oxygen	ILD outcome	Presence of emphysema (assessed by radiologist)	Survival outcome (days)	Post-therapy (chemotherapy)
Lymphoid ILD	M	62	Past	82	1	Pyrexia	None	No	Improved	Yes	362	Yes
ILD	M	42	Current	50	3	Pyrexia	Pulse	Yes	Recovered	Yes	517	Yes
Organising pneumonia	M	60	Past	183	2	Respiratory symptoms	None	No	Improved	Yes	568+	Yes
ILD	F	62	Past	113	2	Cough	Oral	No	Recovered	Yes	376	No
ILD	F	74	Past	111	3	Cough, dyspnea	Pulse	Yes	Improved	None	183	No
ILD	M	60	Current	25	1	Pyrexia	Pulse	No	Recovered	None	119	Yes
ILD	M	77	Past	7	1	X-ray	None	No	Recovered	Yes	255	No
ILD	M	55	Past	187	1	CT	None	No	Recovered	Yes	415	No
ILD	F	60	Current	76	2	Cough	Oral	No	Recovered	None	346	Yes

†Past smoker, passage of at least 1 month since stopping smoking (at the time of registration); current smoker, smoked within 1 month (at the time of registration). CT, computed tomography; F, female; ILD, interstitial lung disease; M, male.

The median OS was longer in patients who experienced RASH of grade ≥2 (n = 67) than in those with RASH of grade ≤1 (n = 39) (10.25 months [95% CI, 8.80–12.12] *vs* 8.31 months [95% CI, 6.18–9.99], respectively; Fig. 1C) and the 1-year survival rate was higher (39% [95% CI, 27–50] *vs* 23% [95% CI, 10–36], respectively). Similarly, the median PFS was longer in patients with RASH of grade ≥2 versus those with RASH grade ≤1 (3.61 months [95% CI, 3.48–5.32] *vs* 1.81 months [95% CI, 1.64–3.48]; Fig. 1D). While there was no notable difference in ORR between patients with RASH grade ≥2 and those with grade ≤1 (21.1% [95% CI, 9.6–37.3] *vs* 19.2% [95% CI, 6.6–39.4]), the DCR was higher in those with more severe RASH (60.5% [95% CI, 43.4–76.0] *vs* 34.6% [95% CI, 17.2–55.7]).

Pharmacokinetics. Plasma sampling for PK analyses was performed in all six patients enrolled in the first step. On day 8, the values of C_{max} were 1760 ± 456.9 ng/mL (mean ± SD) for erlotinib, 169.7 ± 64.5 ng/mL for OSI-420 and 22 700 ± 3272.9 ng/mL for gemcitabine. The AUC_{last} was 29 001 ± 6560 h ng/mL, 2748 ± 788 h ng/mL and 10 717 ± 1458 h ng/mL (mean ± SD), respectively. The mean t_{max} was 8.0 h (range, 2.0–23.9 h), 9.0 h (2.0–23.9 h) and 0.51 h (0.45–0.57 h), respectively. Also on day 8, the mean plasma $t_{1/2}$ was 54.92 h (range, 9.25–144.61 h), 32.79 h (10.36–60.46 h), and 0.63 h (0.31–1.14 h), respectively. The Cl/F of erlotinib and gemcitabine showed interindividual variability; the Cl/F on day 8 was 3972.6 ± 772.1 mL/h (mean ± SD; coefficient of variation 19.4%) and 146 580.4 ± 31 101.3 mL/h (21.2%), respectively.

Biomarker analysis. Of the 106 patients enrolled, *EGFR* mutation status was evaluated in 47 patients (44.3%), all of whom had wild-type *EGFR*. The mutation status of the remaining patients was classified as unknown because samples were not available (30.2%), not examined (9.4%) or the results following sequencing were inconclusive (16.0%).

Discussion

This study was designed to initially assess the safety of erlotinib with gemcitabine for Japanese patients with pancreatic cancer, in whom there had been no prior exposure to either drug. As no significant safety concerns were raised in the first step of the study, enrollment of a further 101 patients was performed. Although the incidence of AE in this study was higher than in the PA.3 study, the incidence of grade 3–4 AE was similar.[28] Despite these results, no new AE specific to Japanese patients were observed. As expected, RASH and gastrointestinal events were among the most common AE in this study, and most of these cases were mild to moderate in severity.

Interstitial lung disease-like events were reported in nine patients (8.5%; grade 1/2/3, 3.8/2.8/1.9%) in the current study, while its incidence was reported to be 2.4% in patients treated in the erlotinib plus gemcitabine arm of the PA.3 study.[28] In addition, in Japanese patients with advanced pancreatic cancer, ILD-like events were reported in two (6.1%) of 33 patients treated with gemcitabine plus S-1, and were reported in three (1.1%) of 264 patients with gemcitabine monotherapy, respectively.[33,34] Likewise, the higher incidence of ILD-like events were documented using S-1 or erlotinib in combination with gemcitabine compared with gemcitabine as monotherapy in patients with pancreatic and biliary tract cancer.[35] On another front, outside of Japan, a high incidence of ILD-like events was reported in gemcitabine and paclitaxel combination therapy in patients with NSCLC.[36] From the above information, considering the higher incidence of ILD when gemcitabine is used in combination, an additive effect from such combinations cannot be ruled out.

In NSCLC, Japanese patients have an increased risk of developing ILD-like events when treated with EGFR TKI.[29,37–39] Fatal cases of ILD-like events have been reported following EGFR TKI administration for the treatment of NSCLC.[37–41] Importantly, however, no patients died due to an ILD-like event in this study. Seven patients experienced ILD-like events of grade 1–2 in severity. This may be due to active management of ILD-like cases during the study period. This management included regular and immediate chest X-rays, in addition to diagnosis with CT scans after any early signs and symptoms were observed (e.g. pyrexia, cough or dyspnea), timely discontinuation of the antitumor drugs (as a precautionary measure in case these drugs were associated with the symptoms) and appropriate treatment for the events (including oral/pulse steroids). By appropriately treating the early symptoms of ILD-like events, patients could restart antitumor therapy (chemotherapy: treatment change). In this study, the onset time for ILD-like events varied markedly between patients (7–187 days). It is therefore necessary to monitor the patients throughout the treatment period.

All of the patients who developed ILD in this study were current or past smokers, and smoking status has been shown to be a risk factor for ILD in the NSCLC population.[38] Results from the multivariate analyses in this study suggest that emphysema is also a risk factor for developing ILD; six of the nine

patients with ILD-like events were diagnosed with emphysema at baseline. Although the number of reports of an ILD-like event may have been artificially elevated due to underlying patient baseline characteristics and the active management of ILD-like events, these results demonstrate the need to consider the risk of ILD-like events in Japanese patients treated with TKI. In particular, it is important that chest CT scans are closely checked for the presence of emphysema or comorbid ILD and that pulmonary status is assessed prior to treatment administration.

This study corroborates the results of the combination of gemcitabine and erlotinib shown in the PA.3 study. The median OS in this study of 9.23 months was longer than those reported in trials with gemcitabine alone. In this study, patients who experienced skin toxicity of grade ≥2 had better outcomes than those with less severe toxicity or the overall study population. Retrospective analyses of data from the PA.3 and AViTA studies have found a significant association between the development of skin toxicity and efficacy in patients with pancreatic cancer treated with erlotinib-based therapy, although the precise mechanisms for the association between skin toxicity and effectiveness are unknown.[28,41,42]

Although the presence of mutations in the tyrosine-kinase region of the *EGFR* gene appears to predict a better response to erlotinib in NSCLC,[43,44] this has not yet been evaluated in pancreatic cancer. *EGFR* mutations are very rare in patients with pancreatic cancer;[45–47] indeed in the present study, no *EGFR* mutations were detected. Further work is required to determine whether *EGFR* mutations can be used as predictive markers for improved survival in Japanese patients receiving erlotinib and gemcitabine as treatment for advanced pancreatic cancer.

In conclusion, the present study shows that erlotinib in combination with gemcitabine is generally well tolerated in Japanese patients with advanced pancreatic cancer. This combination is associated with efficacy and survival outcomes, and the results of this study are consistent with the findings of the global PA.3 study.

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Short communication

A case of small undifferentiated intramucosal gastric cancer with lymph node metastasis

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Abstract
Early gastric cancer (EGC) has a favorable prognosis after surgical gastrectomy. For intramucosal EGC with little risk of lymph node metastasis, endoscopic mucosal resection (EMR) is an accepted treatment method. Herein we document a noteworthy case of small undifferentiated gastric cancer with nodal metastasis. A 60-year-old Japanese woman underwent gastrectomy with D2 lymph node dissection for the treatment of EGC in the lower gastric body. Histological examination revealed that signet-ring cell carcinoma was located in approximately one-third of the superficial portion of the mucosal layer, with a tumor size of 13 mm. No lymphatic invasion, venous invasion, or fibrosis was observed in the submucosal layer. This case had nodal metastasis and was finally diagnosed as stage IB (T1N1M0) according to the Japanese Classification of Gastric Carcinoma (JCGC). The patient is alive without recurrence 6 years after treatment.

Key words Early gastric cancer · Lymph node metastasis · Undifferentiated carcinoma

Introduction

Early gastric cancer (EGC) is defined as a gastric cancer localized to the mucosa or submucosa regardless of lymph node metastasis. Radical gastrectomy with regional lymphadenectomy is the gold-standard treatment for patients with EGC [1]. For intramucosal EGC with little risk of lymph node metastasis, endoscopic mucosal resection (EMR) has been accepted as a minimally invasive treatment modality. EMR is generally indicated for intramucosal differentiated adenocarcinoma less than 20 mm in diameter and without ulceration [2, 3]. Recently, several institutions have suggested that the indications for EMR should be expanded to include larger, differentiated intramucosal adenocarcinoma and undifferentiated adenocarcinoma less than 20 mm in diameter and without ulceration.

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Case report

A 60-year-old Japanese woman visited a local hospital because of anorexia and body weight loss, and gastroscopy revealed gastric cancer. She was admitted to our hospital for the treatment of gastric cancer in October 2001. She had no history of malignant disease and no family history of cancer. Upper gastrointestinal endoscopy revealed irregular, depressed mucosa, type 0 IIc in accordance with the *Japanese classification of gastric carcinoma* (JCGC) [4] in the large curvature of the lower gastric body (Fig. 1). The diameter was approximately 1 cm, and there were no ulcer findings. Endoscopic ultrasonography revealed this to be an intramucosal cancer, and computed tomography examination showed no distinct lymph node metastasis. Pathologically, signet-ring cell carcinoma was detected in the biopsy specimen. Laboratory results were within normal limits, and serum carcinoembryonic antigen (CEA) levels were normal. Wedge resection of the stomach with resection of a single lymph node (#4d) was performed in November 2001 (Fig. 2). Histological examination revealed that signet-ring cell carcinoma was located in approximately one-third of the superficial portion of the mucosal layer and that carcinoma cells had not invaded into the muscularis mucosa (Fig. 3A, B). The tumor was 13 mm in size. No lymphatic invasion, venous invasion (immunohistochemical staining with CD34 and D2–40), or ulcer scar was observed in the submucosal layer. Histologically, there was no fibrosis in the submucosal layer and no breakdown of the muscularis mucosa. The resection margin was clear of tumor cells. The single resected lymph node had metastatic cancer cells; these were also signet-ring cell car-

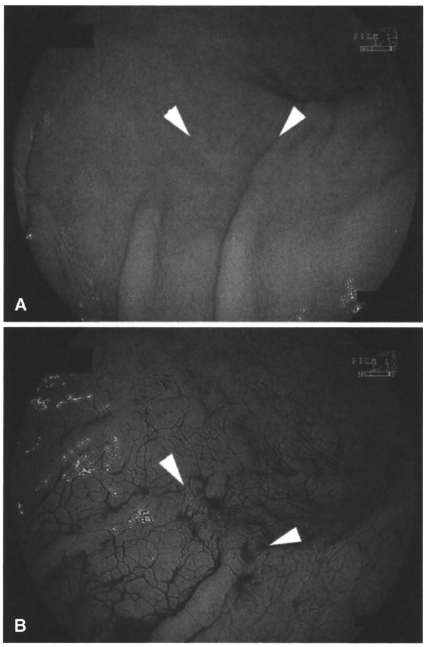

Fig. 1A, B. Gastroscopy revealed a depressed lesion in the large curvature of the lower gastric body (*arrowheads*). There were no ulcer findings, and endoscopic ultrasonography showed that this was an intramucosal cancer. **A** Without dye; **B** dyeing with indigo carmine

cinoma. Immediately, additional distal gastrectomy with D2 lymph node dissection (regional lymph node dissection of all group 1 and group 2 nodes) was performed, with a Billroth-I reconstruction. The gastric body with the first resection scar was histologically examined and there was no cancer lesion. Cancer cell metastasis was detected in nodes #4sb, #4d, and #6 (5/65), and this case was finally diagnosed as stage IB (T1N1M0) according to the JCGC. This patient is alive without recurrence 6 years after treatment.

Discussion

For intramucosal EGC with little risk of lymph node metastasis, EMR is accepted as a minimally invasive treatment modality. Undifferentiated intramucosal EGC is known to be more commonly associated with

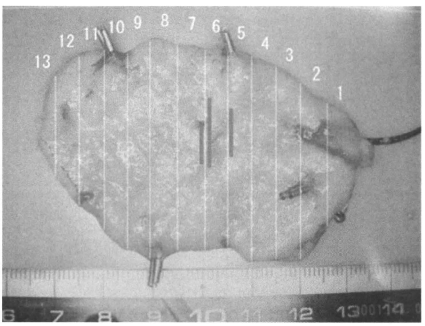

Fig. 2. Surgical specimen from partial gastrectomy. The locations of tumor cells are shown as *bold lines*. The tumor was 13 mm in diameter

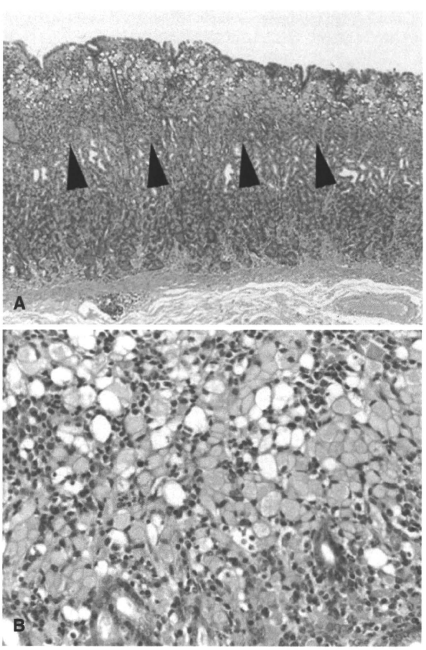

Fig. 3A, B. Histological examination. **A** Signet-ring cell carcinoma was located in approximately one-third of the superficial portion of the mucosal layer, and carcinoma cells had not invaded into the muscularis mucosa. **B** Higher magnification microscopic findings.

lymph node metastasis compared to differentiated intramucosal EGC [5, 6], and the indications for EMR are limited to differentiated intramucosal EGC that is less than 20 mm and without ulceration. Gotoda et al. [3] reported that none of 141 patients with undifferentiated intramucosal EGC less than 20 mm in size without ulceration had lymph node metastasis. The upper limit of the 95% confidence interval was 2.6%, which was considered to be sufficiently large to exclude the possibility of lymph node metastasis. Some predictive factors for lymph node metastasis in undifferentiated EGC have been reported [7–11]. Previously, we retrospectively examined factors predictive of lymph node metastasis in 332 patients with undifferentiated EGC who underwent gastrectomy, including the present patient. Multivariate analysis showed that the presence of lymphatic-vascular involvement was significantly correlated with the incidence of lymph node metastasis [8]. Abe et al. [7] reported that multivariate logistic regression analysis indicated that tumor size and lymphatic involvement were independent risk factors for lymph node metastasis. Abe et al. reported small undifferentiated intramucosal EGC cases with tumors 10, 12, and 20 mm in diameter without ulceration that had lymph node metastasis. These investigators concluded that EMR should not be indicated for undifferentiated EGC more than 10 mm in diameter.

Fewer lymphatic-vascular vessels are present in the mucosal layer than in the submucosal layer. D2-40 immunohistochemical staining has revealed that lymphatic vessels are most densely distributed in the muscularis mucosa layer of the gastric wall [12]. The cancer cells in the patient reported here were located in one-third of the mucosal layer and did not contact the muscularis mucosa. The process of cancer metastasis in this patient is difficult to conjecture. Circulating cancer cells may have played a role, as cancer cells have been identified at the DNA level in the peripheral blood of patients with EGC [13].

The expanded criteria of EMR for undifferentiated EGC are controversial. For further clarification of this issue, prognostic data for patients with undifferentiated EGC treated by EMR are required.

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Short Communication

Clinical Implication of the Antidiuretic Hormone (ADH) Receptor Antagonist Mozavaptan Hydrochloride in Patients with Ectopic ADH Syndrome

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Ectopic antidiuretic hormone syndrome is a medical emergency characterized by dilutional hyponatremia. Clinical effectiveness of the vasopressin V2 receptor antagonist mozavaptan was evaluated in 16 patients. In short-term (7-day) treatment with the drug, serum sodium concentration (mean ± standard deviation) significantly ($P = 0.002$) increased from 122.8 ± 6.7 to 133.3 ± 8.3 mEq/l, and symptoms due to hyponatremia were improved. On the basis of these results, mozavaptan (Physuline®) was approved as an orphan drug for the treatment of the syndrome in 2006 in Japan. During the 43 months following its launch, 100 patients have been treated with the drug; overall clinical effects of the drug were found similar to those of this clinical trial. Clinically, mozavaptan may allow hyponatremic patients to be treated by aggressive cancer chemotherapy with platinum-containing drugs. Moreover, the drug may free patients from strict fluid-intake restrictions and thereby improve their quality of life.

Key words: SIADH – ectopic ADH syndrome – small cell lung carcinoma – hyponatremia – antagonist

INTRODUCTION

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is divided into two categories; one is the ectopic ADH syndrome induced by abnormally secreted ADH (arginine vasopressin) from cancer cells, and another is the morbidity caused by inappropriately secreted ADH from the pituitary gland in various benign diseases. In both situations of SIADH, ADH binds to vasopressin V2 receptors (V2Rs) in renal tubules and thereby increasing water reabsorption. Clinically, SIADH is characterized by elevated fluid retention in the body, resulting in dilutional hyponatremia and subsequent manifestations of various central nervous system (CNS) symptoms.

In the present study, clinical effectiveness of a newly developed vasopressin V2R antagonist was evaluated in patients with ectopic ADH syndrome. This morbidity is frequently observed in patients with small cell lung carcinoma (SCLC) and makes it to be difficult to aggressive cancer chemotherapy with platinum-containing drugs. Patients with SIADH often require severe water restriction, worsening their quality of life.

Mozavaptan, the world's first non-peptide V2R antagonist with aquaretic action, was developed by Otsuka Pharmaceutical, Japan, in 1989 (1). Its potent effect was first demonstrated by clinical pharmacological trials involving healthy adult male subjects in 1992 (2). To understand

whether mozavaptan might play an important role in the treatment of ectopic ADH syndrome, the Ectopic ADH Syndrome Therapeutic Research Group conducted an open-label multicenter clinical trial at Japanese hospitals from December 1994 to December 1997. This paper describes the study results and their implication for mozavaptan's potential usefulness in the treatment of cancer-related ectopic ADH syndrome.

PATIENTS AND METHODS

This open-label, multicenter study protocol was approved by the Institutional Review Board of each participating medical institution prior to its inception; written informed consent was obtained from all patients.

Recruited were inpatients aged 20 to <75 years who had malignant tumors that might cause ectopic ADH syndrome as well as the diagnostic criteria of ectopic ADH syndrome as defined by Bartter and Schwartz (3) such as serum sodium concentration ≤124 mEq/l, persistent urinary sodium excretion, normal renal, adrenal, and thyroid function, and no evidence of edema or dehydration.

Following a ≤2-day placebo administration period during which baseline data were collected, patients were given orally mozavaptan (single 30 mg tablet) once daily for 7 days, or where this was difficult, 3 days was allowed. Fluid restriction was used throughout the study period only for patients in whom it had already begun. Treatment of hyponatremia with demeclocycline, lithium chloride, or urea was not permitted.

The primary endpoint was serum sodium concentration. Blood samples were collected immediately before dosing on each test day. Clinical symptoms associated with hyponatremia such as anorexia, nausea/vomiting, headache, and CNS symptoms were recorded. Urine volume, urinary osmolality, urinary electrolyte (sodium, potassium, chloride) excretion, serum electrolyte (potassium, chloride) concentration, serum osmolality, and plasma ADH concentration were measured. New medical problems or exacerbations of those already existing were reported as adverse events.

In each case, the serum sodium level after the final administration of the study drug was compared with baseline value. The patients are divided into three groups: (i) the serum sodium level is improved to normal range; (ii) the level is still low, but increase is ≥6 mEq/l and (iii) the level is still low, and increase is <6 mEq/l. And mean sodium concentration after the final administration of the study drug was compared with that of baseline value by paired *t*-test.

RESULTS

Sixteen patients [M/F: 10/6; mean age: 63.9 (range: 48–78) years] who received at least one dose of the study drug were included in the efficacy and safety evaluation. All patients received mozavaptan 30 mg once daily for 7 days, except two individuals who received treatment for 3 days.

Underlying diseases were SCLC ($n = 14$), thymic small cell carcinoma ($n = 1$) and cervical cancer ($n = 1$). Fluid intake was restricted in 5 of the 16 patients (Table 1).

Serum sodium concentration (mean ± SD) at the time of diagnosis of the ectopic ADH syndrome was 117.3 ± 4.3 (range: 110–124) mEq/l. Plasma ADH concentration was 4.9 ± 5.8 (median: 2.3; range: 0.4–18.9) pg/ml immediately before treatment.

At baseline and at the end of study, mean serum sodium concentration was 122.8 ± 6.7 and 133.3 ± 8.3 mEq/l, respectively, a statistically significant difference ($P = 0.002$; Fig. 1). Serum sodium concentration increased at 24 h after the first administration of mozavaptan and remained elevated ≤24 h after administration for 7 days. Serum osmolality gradually increased starting from 24 h after first administration till the study end. Cumulative urine volume over 24 h increased on the first treatment day, whereas urine osmolality decreased in the first two treatment days.

A total of 16 patients were evaluated for the serum sodium level. The serum sodium level was improved to normal range in eight patients, still below normal range but increased by at least 6 mEq/l in four patients and increased by <6 mEq/l in four patients (Table 1).

Symptoms associated with ectopic ADH syndrome such as anorexia, nausea/vomiting, headache and CNS symptoms improved or disappeared in seven of eight patients who had at least one of these symptoms at baseline. By symptom, anorexia disappeared in three and improved in two among eight patients who had the symptom at baseline, whereas nausea/vomiting, headache and CNS symptoms disappeared by the completion of treatment in all patients who had at least one of the symptoms at baseline. On the other hand, however, new anorexia and headache developed in one patient each.

Although some patients showed slight increases or decreases of plasma ADH concentration after receiving mozavaptan, overall there were no obvious changes.

There were 35 adverse events in 11 of the 16 patients; none was serious. The most common adverse event was dry mouth developing in five patients. Fifteen adverse drug reactions occurred in six patients (dry mouth, $n = 5$; increased blood potassium, $n = 2$; malaise, increased AST, increased ALT, decreased blood calcium, increased blood lactate dehydrogenase, increased blood urea, decreased appetite and nocturia, $n = 1$ each).

One patient was withdrawn after administration of the study drug for 3 days because of anorexia. After completion of administration of mozavaptan, one cancer-related death occurred 30 days post-treatment (ID 1 in Table 1); the patient had small cell lung cancer, and had myasthenia gravis, diabetes, pneumonia and hypertension. Chemotherapy (carboplatin and etoposide) was given from 146 to 144 days before treatment with mozavaptan, which reduced the tumor size and improved SIADH. However, the chemotherapy was

Table 1. Clinical characteristics of each patient at baseline and changes in serum sodium concentration/clinical symptoms

ID	Sex (M/F)	Age (years)	Disease	Tx duration (days)	Fluid-intake restriction	Data at baseline			Changes in serum sodium concentration (mEq/l)				Clinical symptoms
						Plasma ADH concentration (pg/ml)	Serum osmolality (mOsm/kg)	Urine osmolality (mOsm/kg)	At the time of diagnosis	At baseline	24 h after the first administration	24 h after the last administration	
1	F	64	SCLC	7	Yes	12.5	274	712	115	129	136	139	ANRX improved, NV disappeared, HA disappeared
2	F	64	Thymic SCC	3	Yes	3.3	256	—	110	122	133	140	ANRX improved, NV disappeared, HA disappeared, CNSS disappeared
3	M	54	SCLC	7	Yes	0.8	254	754	115	123	130	139	ANRX disappeared, HA disappeared, CNSS disappeared
4	M	76	SCLC	7	No	2.1	254	657	119	111	121	119	ANRX disappeared, NV disappeared
5	M	65	SCLC	3	Yes	2.4	300	753	121	130	134	142	ANRX developed
6	M	66	SCLC	7	No	18.9	256	461	119	123	—	128	None
7	M	78	SCLC	7	No	0.5	279	590	124	127	128	133	None
8	F	75	SCLC	7	No	0.4	254	465	124	120	125	122	None
9	M	66	SCLC	7	No	7.8	261	492	115	117	123	127	ANRX continued, NV disappeared, HA developed
10	M	48	SCLC	7	Yes	2.1	283	730	110	132	129	127	None
11	M	66	SCLC	7	No	1.4	241	450	116	107	117	130	ANRX disappeared, NV disappeared, HA disappeared, CNSS disappeared
12	F	53	SCLC	7	No	1.5	241	465	117	127	138	148	n/a
13	F	60	SCLC	7	No	2.8	245	406	123	122	128	142	None
14	M	65	SCLC	7	No	5.2	263	370	114	123	130	139	None
15	M	63	SCLC	7	No	15.7	275	755	116	129	133	133	ANRX continued
16	F	60	Cervical cancer	7	No	1.0	268	349	119	123	132	140	ANRX continued, HA disappeared, CNSS disappeared

SCLC, small cell lung carcinoma; Thymic SCC, thymic small cell carcinoma; ANRX, anorexia; NV, nausea/vomiting; HA, headache; CNSS, central nervous system symptom; n/a, not available.