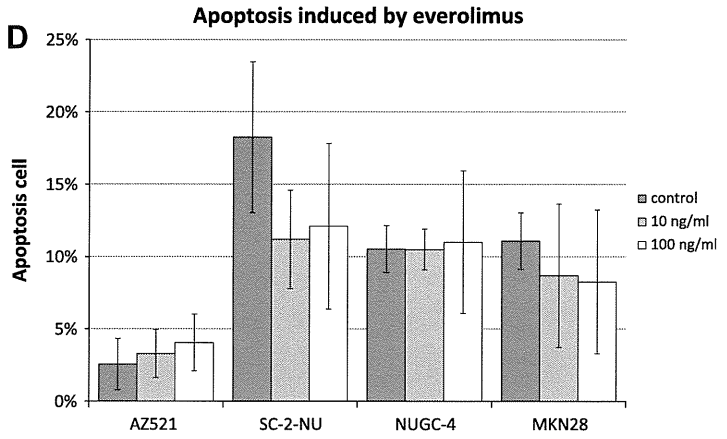


Fig. 1. (*continued*)

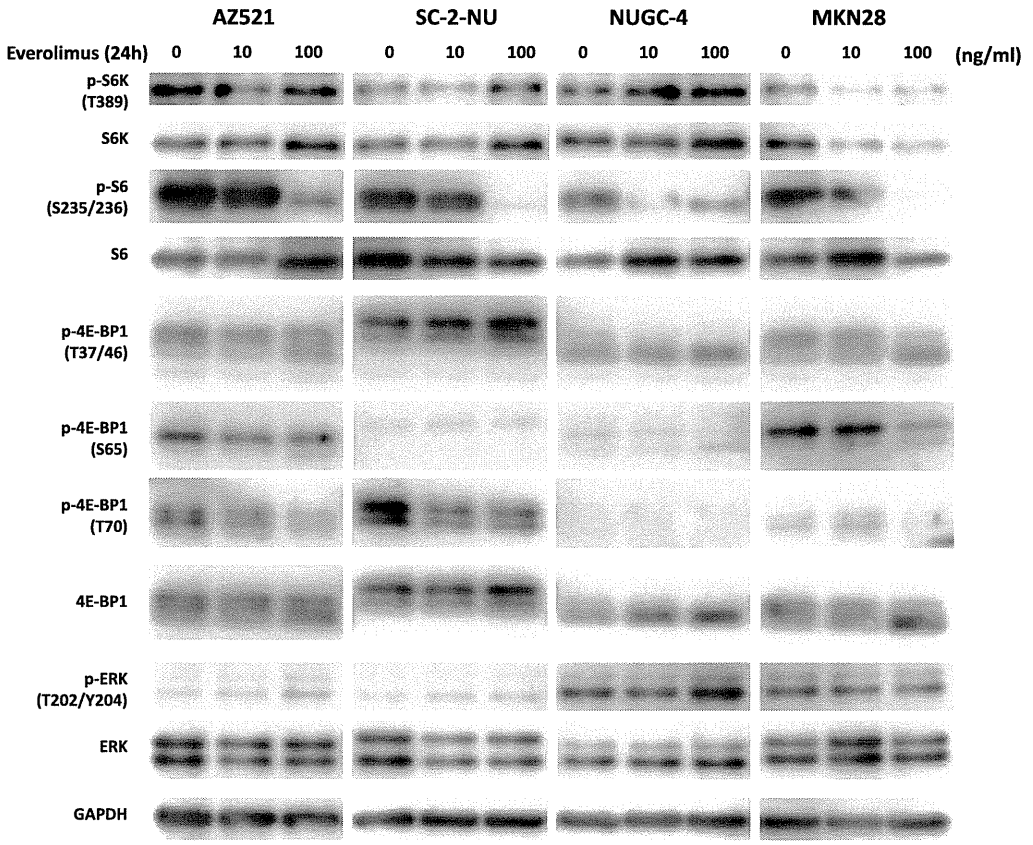


Fig. 2. Activity of ERK and downstream molecule of mTOR pathway. AZ521, SC-2-NU, NUGC-4 and MKN28 cells were treated with 10 and 100 ng/ml everolimus for 24 h. Cells were harvested and subjected to western blotting with antibody against indicated proteins.

3.4. Effects of everolimus on the growth of phospho-4E-BP1-overexpressing cell and phospho-ERK overexpressing cell in vivo

To verify the *in vitro* results under *in vivo* conditions, SC-2-NU (higher 4E-BP1 phosphorylation and lower ERK phosphorylation) and NUGC-4 (lower 4E-BP1 phosphorylation and higher ERK phosphorylation) cells were implanted subcutaneously into nude mice. The tumor-bearing mice were treated with everolimus 5 days a week for 4 weeks, and the tumor size was measured 3 times a week. After 2 weeks of treatment, everolimus significantly inhibited the growth of tumors derived from both cell lines (Fig. 4). Everolimus more powerfully inhibited tumor growth in SC-2-NU cells (79% decrease) than in NUGC-4 cells (26% decrease). The results showed that everolimus indeed was more effective against the everolimus-sensitive cells in the xenograft model.

Xenograft tumor tissue samples were lysed and subjected to western blotting to analyze the phosphorylation levels of 4E-BP1 (T37/46, T70). As observed by the immunohistochemical staining, the phosphorylation of 4E-BP1 (T37/46, T70) was higher in SC-2-NU than in NUGC-4 in western blotting analysis (Fig. 5A). Immunohistochemical analysis of tumor tissue samples showed higher expression of p-4E-BP1 (T37/46) in SC-2-NU than in NUGC-4 (Fig. 5B), though the levels of p-4E-BP1 (T37/46) were not decreased by everolimus treatment. We could not obtain a reliable

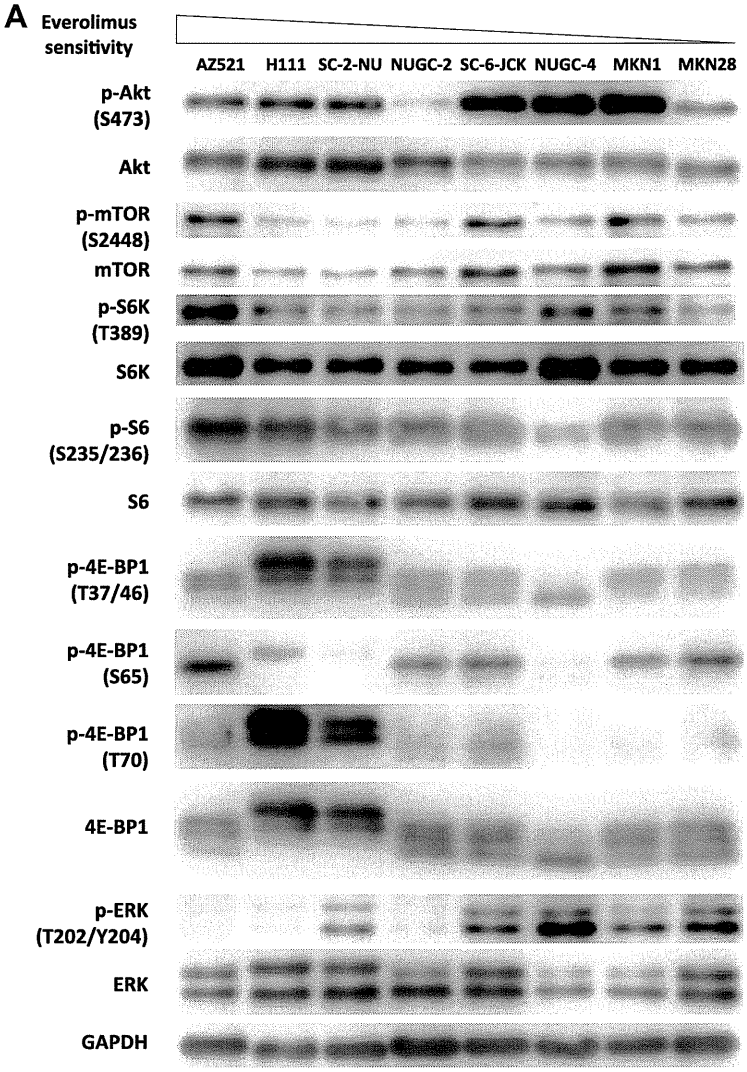


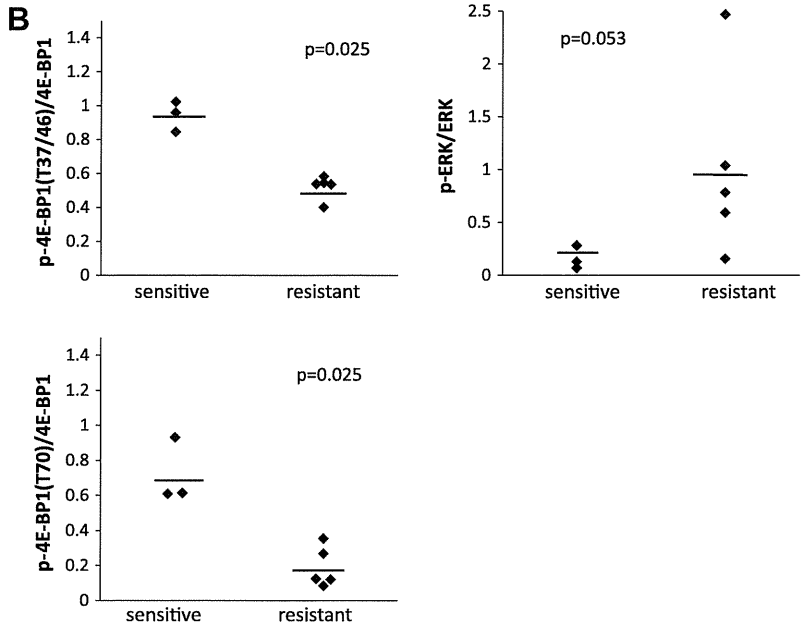
Fig. 3. Comparison of basal activity of ERK and mTOR signal-related molecules among eight different cells. (A) Eight non-treated human gastric cancer cells were seeded and incubated overnight. Cells were harvested and subjected to western blotting with antibody against indicated antibodies. (B) The ratio of the strength of phospho-protein to total protein was quantified and shown. Each bar represents the mean ratio. Sensitive: 3 everolimus-sensitive cell lines (AZ521, H111 and SC-2-NU), Resistant: 5 everolimus-resistant cell lines (NUGC-2, SC-6-JCK, NUGC-4, MKN1 and MKN28).

result regarding the p-4E-BP1 (T70) expression level, because a high-quality antibody for immunohistochemical analysis was not available.

4. Discussion

As in a previous study [29], the results of the present investigation suggested that the anti-proliferative efficacy of everolimus depends on the type of cell line. It is considered that inhibiting mTOR pathway results in G1 phase arrest and inhibition of S phase initiation [23], and that the anti-proliferative effect of everolimus is induced not by cell apoptosis or cell death, but by cell-cycle inhibition [25,29–31]. In our study, everolimus treatment did not lead to induction of cell apoptosis and cell death, even in cell lines that are sensitive to everolimus. Everolimus reduced the phosphorylation of S6 and 4E-BP1 (T70), but did not inhibit the phosphorylation of S6K. These effects on the mTOR signaling pathway were not associated with the sensitivity to everolimus. The Ras/MEK pathway, which is acknowledged to contribute to growth and proliferation of cancer, is a competitive pathway known to be activated by inhibiting the mTOR pathway [32]. Since the interaction between these two pathways might be why an inhibitory effect of everolimus on phosphorylation of S6 and 4E-BP1 did not lead to suppression of cell proliferation, we investigated the effect of everolimus on ERK, the target protein of the Ras/MEK pathway. However, everolimus did not activate Ras/MEK pathway in most cell lines.

To examine in further detail the relation between the basal activity of signaling pathways related to cell proliferation and the sensitivity to everolimus, we investigated phosphorylation levels of the mTOR and Ras/MEK pathway components. The results showed that the phosphorylation of 4E-BP1 (T37/46) and 4E-BP1 (T70) were significantly enhanced in everolimus-sensitive cell lines. 4E-BP1 is a key protein of mTOR pathway but its function remains unclear. Dowling et al. [33] reported that 4E-BP1 mediated cell proliferation and S6K, another key protein of mTOR pathway, regulated cell size, and when 4E-BP1 was knocked down, the anti-proliferative effect of everolimus was decreased. In line with this report, our results suggested that downregulation of 4E-BP1 reduced the impact of mTOR on cell proliferation, resulting in the attenuated effect of everolimus. On the other hand, since



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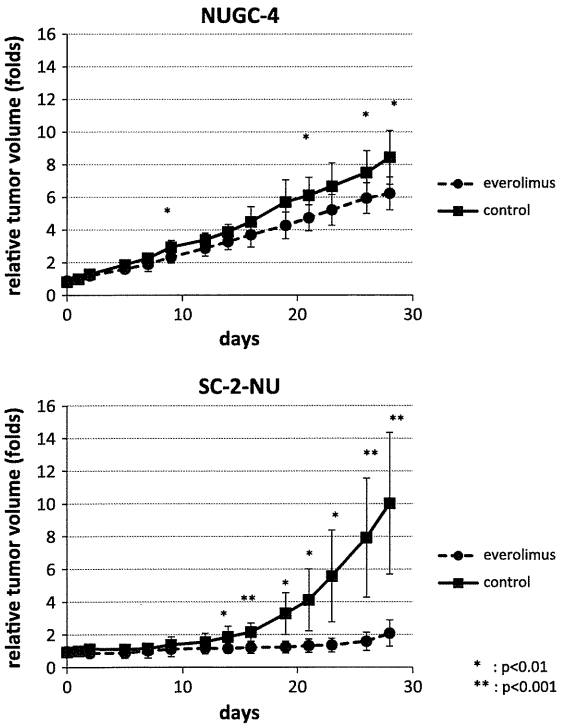

Fig. 4. Everolimus inhibitory effects on gastric cancer cells *in vivo*. Tumor growth was assessed in control and everolimus-treated nude mice bearing s.c. NUGC-4 and s.c. SC-2-NU xenograft for 28 days, and the tumor volume measured. Tumor volume is expressed as the mean fold increase over time. Data represents mean ± SEM ($n = 8$). $^{*}p < 0.01$, $^{**}p < 0.001$.

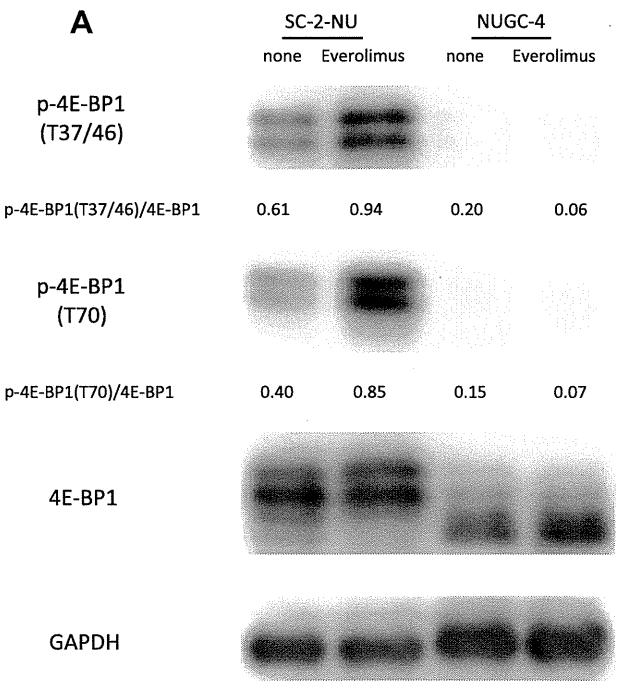

Fig. 5. Phospho-4E-BP1 expression in subcutaneous xenograft tumor. SC-2-NU (everolimus-sensitive cells) or NUGC-4 (everolimus-resistant cells) were subcutaneously injected into nude mice. Tumor tissue sections in xenograft were harvested after 28 days treatment with either a placebo or everolimus. (A) Tumor cells in xenograft were subjected to western blotting with anti-phospho-4E-BP1 (T37/46, T70) antibody. The ratio of phospho-4E-BP1 to total 4E-BP1 was quantified and shown just below p-4E-BP1 panels. (B) Immunohistochemical staining of phospho-4E-BP1 (T37/46) was assessed. Left and right panels show unstained and stained tissue sections, respectively.

phosphorylation of ERK tended to be stronger in everolimus-resistant cells, the basal level of p-ERK could be used as an additional marker predicting everolimus sensitivity.

One of our hypotheses is that the dominant action of Ras/MEK pathway including that of ERK over mTOR pathway in cell proliferation, results in the insufficient anti-tumor effect of everolimus and the resistant properties of these cells. Although more research is needed to clarify the reason for the difference between everolimus-sensitive cells and everolimus-resistant cells, it is suggested that combination therapy with everolimus and other drugs like Ras/MEK inhibitor could improve the anti-tumor effect.

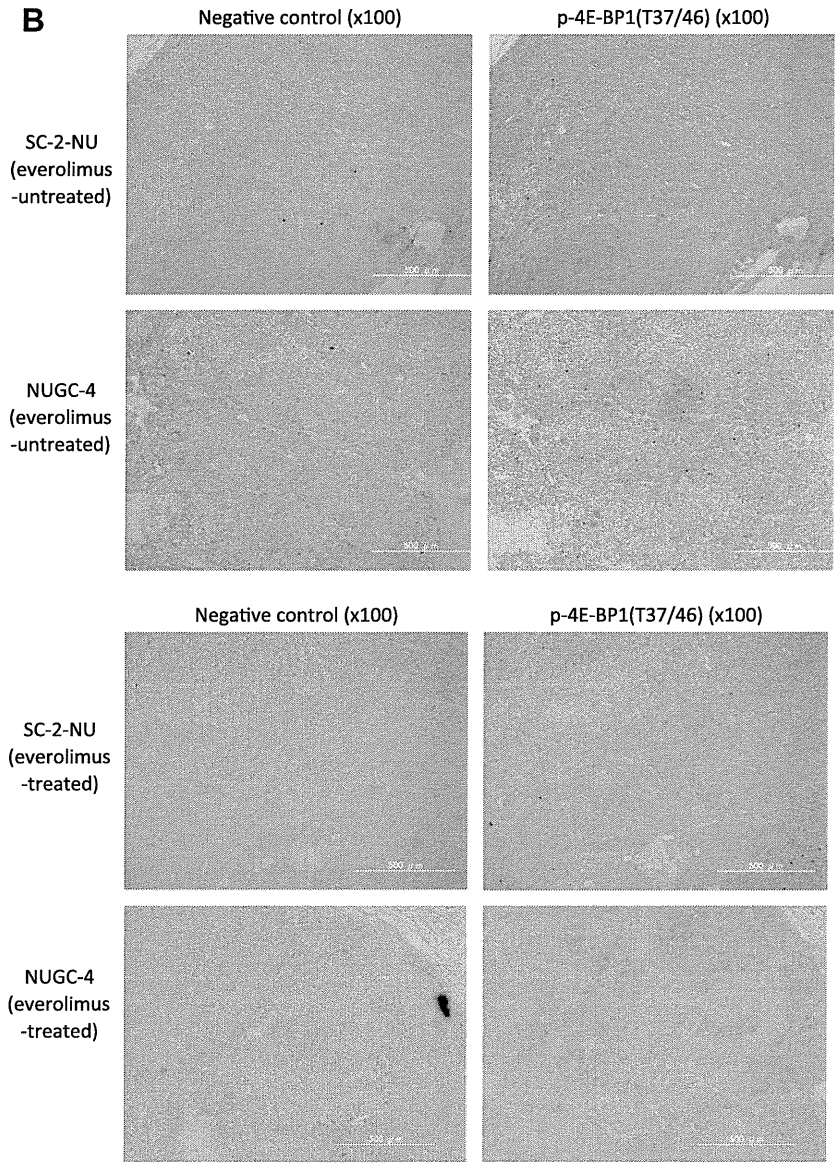

Fig. 5. (*continued*)

Similar to the *in vitro* examination, everolimus had a more powerful anti-tumor effect in SC-2-NU, an everolimus-sensitive cell line, than in NUGC-4, an everolimus-resistant cell line, in a subcutaneous xenograft model. Immunohistochemical staining showed that the phosphorylation of 4E-BP1 (T37/46) was stronger in SC-2-NU than in NUGC-4. From these results, the sensitivity to everolimus could be predicted by examining the phosphorylation of 4E-BP1 (T37/46). However, we obtained the intriguing finding that everolimus treatment did not actually decrease the phosphorylation of 4E-BP1 (T37/46), which corresponds with a previous study on rapamycin [34]. 4E-BP1 phosphorylation events at T37/46 reportedly exist without mTORC1 or mTORC2 expression, which indicates the existence of a potential third mTOR complex [35,36]. As the full phosphorylation of four sites (T37, T46, S65 and T70) in 4E-BP1 is required for the release of eIF4E and promotion of cell cycle [34], the dephosphorylation of 4E-BP1 at T70 alone by everolimus would be enough to prevent cell proliferation even when other 4E-BP1 sites (including T37/46) are still phosphorylated. Therefore, strong expression of phosphorylation at T37/46 of 4E-BP1 might mean that cell proliferation properties are highly dependent on mTOR signaling pathway via mTORC1, C2 and others, which could create a high susceptibility to everolimus. *In vitro* experiment demonstrated that everolimus reduced the phosphorylation of 4E-BP1 (T70). In contrast, p-4E-BP1 (T70) was enhanced in SC2-NU by everolimus treatment in the xenograft model. Initial inhibition of 4E-BP1 phosphorylation by mTOR inhibitor has reportedly been recovered within 6 h [37], although time course of effect would be dependent on cell type and condition. It is also speculated that the properties of cancer cells might be changed by everolimus treatment for 28 days, because long-term suppression of signaling pathway could incidentally cause the activation of another pathway such as Akt [38], which may be responsible for acquired resistance to such a pathway targeted drug. Taken together, the sensitivity to everolimus (i.e., inhibitory effect on cell proliferation) may be ascribed not to the capability to inhibit mTOR pathway, but to be the proliferation properties of cells; that is, the dominant cell growth pathway would be mTOR or others such as Ras/MEK.

The phase II trial of the everolimus effect on gastric cancer showed an overall disease control rate (DCR) of 56%, but an objective response rate of 0%. This suggests that the major benefit of everolimus in clinical use is disease stabilization, not tumor

shrinkage. Looking back on past clinical trials of molecular-targeted agents, effects on gastric cancer, the ToGA study with biomarker-based patient selection showed prolonged overall survival [39], whereas the AVAGAST study, in which all patients were registered without established biomarkers, failed to show significant increases in progression-free survival (PFS) and overall response rate [40]. It seems likely, therefore, that a biomarker to predict an anti-tumor effect of everolimus is clinically important. A previous study [41] reported that the high expression of phosphorylated S6 (S240/244) was associated with higher DCR and PFS, but further clinical trials and analyses were deemed necessary. The proposal of a novel candidate of the biomarker predicting effects of everolimus is timely. In conclusion, the phosphorylation status of 4E-BP1 might predict sensitivity to everolimus in gastric cancer. Thus, close evaluation of this biomarker in the tumor tissues and selecting patients accordingly may indeed help improve the efficacy of everolimus treatment for gastric cancer. Further studies using clinical samples are warranted.

Acknowledgements

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Clinical Trial Note

Effect of Daikenchuto (TJ-100) on Postoperative Bowel Motility and on Prevention of Paralytic Ileus after Pancreaticoduodenectomy: A Multicenter, Randomized, Placebo-controlled Phase II Trial (The JAPAN-PD Study)

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We conducted a multicenter, randomized, controlled trial in patients with pancreaticoduodenectomy to investigate the efficacy of Daikenchuto (TJ-100), which is a Kampo medicine (traditional Japanese herbal medicine), for its effect on postoperative bowel motility and for prevention of postoperative paralytic ileus. This clinical trial primarily evaluates the co-primary endpoints: (i) the incidence rate of postoperative paralytic ileus lasting over 72 h after surgery and (ii) time to having the first postoperative passage of flatus. The secondary endpoints are the incidence of postoperative paralytic ileus in cases that combined with/without enteral alimentation, QOL assessment by the Gastrointestinal Symptom Rating Scale (GSRS) Score (Japanese Version) and visual analogue scale, the change ratio of abdominal circumference, the incidence of postoperative complication, the number of postoperative hospital days, the incidence of surgical site infection and the incidence of postoperative small bowel obstruction within 2 years after surgery. Two hundred and twenty patients are required in the study (110 patients per group).

Key words: pancreaticoduodenectomy – Japanese herbal medicine (TJ-100) – postoperative paralytic ileus – surgical site infection

INTRODUCTION

Pancreaticoduodenectomy (PD) is one of the most extensive surgical procedures with high incidence of morbidity for patients with periampullary disease. Improved surgical skills and modern perioperative care reduced the mortality rate, but there is still a high morbidity rate, which remains about 40–50% (1, 2). In these days, several investigators have reported that a fast-track program reduced the incidence of morbidity and the postoperative hospital days in PD (3, 4). To keep normal state of the digestive function is an essential factor affecting the recovery of postoperative paralytic ileus in the fast-track program. Daikenchuto (TJ-100), which is a traditional Japanese herbal medicine, has been used for the prevention and treatment of postoperative ileus in Japan (5, 6). TJ-100 extract powder (Tsumura & Co., Tokyo, Japan) is manufactured as an aqueous extract containing

2.2% Japanese pepper, 5.6% processed ginger, 3.3% ginseng and 88.9% maltose syrup powder. To date, there has been no prospective study investigating the effect on the normalization of bowel peristalsis after PD. Therefore, we have started a multicenter, randomized, placebo-controlled phase II trial of TJ-100 to evaluate its efficacy for supporting postoperative bowl motility and preventing postoperative paralytic ileus after PD.

PROTOCOL DIGEST OF THE STUDY

Objective

Postoperative paralytic ileus after surgery for intraperitoneal organ is one of the common complications (>90% in many series) and recognized as an inevitable response to intraperitoneal surgery (7–9). The JAPAN-PD study is a multicenter, randomized, double-blinded, placebo-controlled, phase II trial, and planned to implement for patients with periampullary tumors (extrahepatic bile duct tumor, tumors of ampulla of Vater and duodenal tumor) and pancreatic tumors (pancreatic cancer, intraductal papillary mucinous neoplasm of the pancreas, pancreatic endocrine tumor and pancreatic neuroendocrine tumor) of the head of pancreas who are expected to undergo PD to investigate an enhancement effect of the bowel motility and the prevention effect of TJ-100 for postoperative paralytic ileus after PD.

Resources

A research grant from a non-profit organization: epidemiological and clinical Research Information Network (ECRIN).

Endpoints

This clinical trial primarily evaluates the co-primary endpoints: (i) the incidence rate of postoperative paralytic ileus lasting over 72 h after surgery and (ii) the time to having the first postoperative passage of flatus. In this study, the postoperative paralytic ileus is defined as the delay of the first postoperative flatus for over 72 h (3.0 days) after surgery (7–9), or the status requires some intervention of treatment for ileus. Every 12 h are counted as 0.5 postoperative day and 24 h as 1.0 postoperative day. The secondary endpoints are the incidence of postoperative paralytic ileus in cases that combined with/without enteral alimentation, QOL assessment by the GSRS Score (Japanese Version) and visual analogue scale about abdominal pain and abdominal distention, the change ratio of abdominal circumference on postoperative day 3 and operative day just after surgery, the incidence of postoperative complication, the number of postoperative hospital days, the incidence of surgical site infection and the incidence of postoperative small bowel obstruction within 2 years after surgery.

Eligibility Criteria

Inclusion Criteria

(i) Patients with periampullary tumors (extrahepatic bile duct tumor, tumors of ampulla of Vater and duodenal tumor) and pancreatic tumors (pancreatic cancer, intraductal papillary mucinous neoplasm of the pancreas, pancreatic endocrine tumor and pancreatic neuroendocrine tumor) of the head of the pancreas who are scheduled to undergo PD.
(ii) Age of at least 20 years and older at the time of registration.
(iii) All patients provided written informed consent before initiation of study-related procedures.

Exclusion Criteria

(i) Clinically problematic cardiac disease.
(ii) Liver cirrhosis or active hepatitis.
(iii) Severe pulmonary disease (interstitial pneumonia, pulmonary fibrosis, pulmonary emphysema etc.).
(iv) Chronic renal failure requiring hemodialysis.
(v) Other malignant disease that can influence the adverse effect.
(vi) Patients with tumors requiring resection of colon.
(vii) Patients who are expected to have severe intra-abdominal adhesion due to past surgical history or past peritonitis history.
(viii) Patients who had used gastrointestinal prokinetic medication, antipsychotic medication or antidepressants.
(ix) Patients who had used Japanese herbal (Kampo) medicines within 4 weeks before registration.
(x) Pregnant or lactating women.
(xi) Any other medical condition that makes the patient unsuitable for including into the study according to the opinion of the investigator.

Registration

An eligibility report form is sent to the registration center at ECRIN. Eligible patients are centrally randomized to either Arm A (TJ-100) or Arm B (placebo) using primary disease, the presence of preoperative therapy, the presence of pylorus ring in the remnant stomach and the institution as balancing variables. Information regarding the necessary follow-up tests is then sent from the registration center at ECRIN.

Treatment Methods

ARM A

In the TJ-100 group, TJ-100 at a dose of 5 g was administered orally as a solution three times daily immediately before meals or every 8 h for 17 consecutive days (15 g/day from preoperative day 3 to postoperative day 14). On the operative day (only once immediately after operation) and

postoperative day 1, TJ-100 were administered as a diluent via enteral feeding tube (10 Fr), which terminates in jejunum to prevent aspiration pneumonia.

ARM B

In the placebo group, placebo at a dose of 5 g was administered orally as a solution three times daily immediately before meals or every 8 h for 17 consecutive days (15 g/day from preoperative day 3 to postoperative day 14). On the operative day (only once immediately after operation) and postoperative day 1, placebo were administered as a diluent via enteral feeding tube (10 Fr), which terminates in jejunum to prevent aspiration pneumonia.

Criteria of Dose Reduction and Discontinuation of the Protocol Treatment

In cases where Grade 2 postoperative diarrhea or other clinical adverse effects (CTCAE version 4.0 criteria) are observed, the patient will be administered reduced dose of the test drug to a dose of 2.5 g, and in case where Grade 3 postoperative diarrhea or other clinical adverse effects (CTCAE version 4.0 criteria) are observed, the protocol treatment will be immediately discontinued.

Data Collection

Data will be collected prospectively for all patients including history, physical examination, laboratory data, pathologic examination, perioperative clinical information and complications.

Study Design and Statistical Analysis

This clinical trial primarily evaluates the co-primary endpoints: (i) the incidence rate of postoperative paralytic ileus for over 72 h after surgery and (ii) the time to have the first postoperative passage of flatus. The multiplicity issue (inflation of the type I error) due to analyzing two endpoints is dealt with using the Bonferroni method. That is, the significance levels for both tests are set at 2.5% to control the overall type I error rate. The sample size was calculated on the basis that the incidence rate of postoperative paralytic ileus for 72 h after surgery was expected to be 90% for the placebo group. In case the effect of reducing the incidence of postoperative paralytic ileus is assumed to be 20% for the TJ-100 group (that is, incidence rate = 70%), the least number of patients to provide the 85% power necessary to confirm the superiority of a group was calculated to be 94 per group for a two-sided 2.5% significance level test. Furthermore, given the number of patients, 84% statistical power is retained to prove the superiority in terms of time to occurrence of postoperative paralytic ileus for the hazard ratio of 0.62. The significance level for this inference is also set at 2.5%. Taking exclusion from analysis of about 15% into account, the number of patients to be accrued was set at 110 per treatment arm (220 in total). The first primary endpoint, incidence rate of postoperative paralytic ileus for 72 h after surgery, will be compared between the two treatment groups using the χ^2 test. The second primary endpoint, time to having the first postoperative passage of flatus, will be analyzed by constructing Kaplan–Meier curves as time-to-event plots. Differences between the curves are tested for significance using log-rank statistics.

PARTICIPATING INSTITUTIONS

Eleven leading Japanese institutions and hospitals (all of them are high volume center in pancreatic surgery) for PD are participating in this trial.

Funding

A research grant from a non-profit organization ECRIN.

Conflict of interest statement

None declared.

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CASE REPORT

Fatal hypermagnesemia induced by preoperative colon preparation in an elderly woman: report of a case

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Abstract An 85-year-old woman with rectal carcinoma was referred to our hospital for surgical treatment. She had a history of constipation treated with oral magnesium oxide. She received 34 g of magnesium citrate (Magcolol P®) orally for 2 days as a mechanical bowel preparation prior to the operation. Just before the operation, she suddenly developed nausea, vomiting, and cyanosis and went into cardiac arrest. Despite support by mechanical ventilation, dopamine, dobutamine, and norepinephrine, she exhibited repeated bradycardia that was nearly fatal and required temporary pacing. The following day, her laboratory tests revealed marked hypermagnesemia (14.3 mg/dL). After a hemodialysis session, she recovered dramatically and all vasopressors were withdrawn. We conclude that preoperative mechanical bowel preparation with magnesium-containing cathartics can cause fatal hypermagnesemia in elderly patients even if their renal function is normal.

Keywords Hypermagnesemia · Dialysis · Preoperative preparation · Rectum carcinoma · Magnesium citrate

Introduction

Hypermagnesemia is a rare complication caused by intravenous or oral administration of magnesium (Mg) as an antacid, cathartic, or antiarrhythmic; however, when the serum Mg concentration exceeds 9 mg/dL, potentially fatal symptoms can occur such as severe bradycardia, cardiac arrest, paralysis, and respiratory failure [1]. Although symptomatic hypermagnesemia usually occurs in patients with renal dysfunction, people with normal renal function can develop Mg toxicity after therapeutic doses of Mg-containing medications [1–4]. Here, we report the case of a patient who developed fatal hypermagnesemia after mechanical bowel preparation for surgery.

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Case report

An 85-year-old woman suffering from constipation underwent a colonoscopy. After several examinations, she was diagnosed with non-obstructive rectal carcinoma and referred to our hospital for surgical treatment (Fig. 1). She had a history of long-term constipation but had achieved a regular defecation habit via treatment with a daily 1 g oral dose of magnesium oxide and 24 mg of sennoside. She also had a history of abdominal artery aneurysm, cerebral infarction, and femoral fracture. Her renal function was normal (Cr, 0.46 mg/dL; eGFR, 94 mL/min 1.73 m^2). For preoperative mechanical bowel preparation, she received a daily oral dose of 34 g magnesium citrate (Magcolol P®; Horii Pharmaceutical Ind. Ltd, Osaka, Japan) in 500 mL of water containing 2,710 mg of Mg. Although she had a loose stool passage after the first dose, the accumulation of remnant feces was suspicious. She received a total of 68 g of magnesium citrate slowly over 2 days and produced soft bowel movements. On the morning of the operation day (day 1), she vomited and went into shock and was transferred to the intensive care unit. She did not have a heart murmur, but lung crackles were audible from her right chest. Her abdomen was hard and distended, and bowel sounds were diminished. Her deep tendon reflexes were

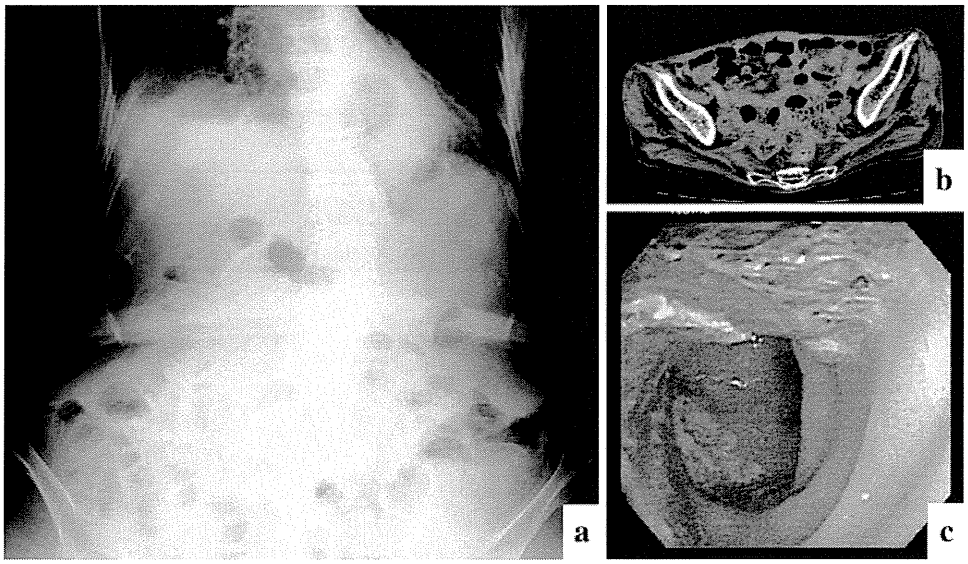

Fig. 1 **a** Preoperative radiograph showing no signs of bowel obstruction. **b** Bowel distension was not detected on abdominal computed tomography. **c** Colonoscopy revealed carcinoma located in the rectosigmoid portion

absent. Radiography showed consolidation in the right lung, indicating aspiration pneumonia, and massive air in the small bowel, suggesting paralytic ileus. Considering ileus and aspiration pneumonia, she was then intubated and supported by mechanical ventilation. To maintain stable hemodynamics, a 10 μg/kg min dopamine drip infusion was started. However, bradycardia occurred repeatedly, and the electrocardiogram showed sinus arrest with junctional escape rhythm. After recovery from cardiac arrest by chest compression, additional administration of dobutamine and norepinephrine was necessary to improve her hemodynamics. Protracted bradycardia required temporary cardiac pacing, and laboratory data showed elevated inflammatory reactions and a decreased anion gap (Table 1). On day 2, the patient showed marked hypermagnesemia (14.3 mg/dL), which strongly suggested that hypermagnesemia was the cause of her refractory bradycardia and cardiac arrest. Although urinary Mg level (232.1 mg/dL) and the Mg excretion fraction (52.4 %) indicated adequate clearance ability, we decided to perform hemodialysis aiming for rapid recovery from severe symptoms. During the hemodialysis session, her hemodynamics dramatically stabilized, and dopamine, dobutamine, and norepinephrine were rapidly withdrawn (Fig. 2). After a single 4-h session of hemodialysis, her serum Mg level decreased to 5.3 mg/dL, and she was returned to the surgery ward on day 9. On day 45, she underwent a laparoscopic low anterior resection with preparation by sodium picosulfate. She had a good postoperative course and was discharged on day 63 without any major medical problems. Interestingly, her serum calcium level was not decreased despite an abnormally high Mg level, and her intact parathyroid hormone (PTH) level remained high even after normalization of Mg and calcium (Table 1). Further examination by ultrasonography and methoxyisobutylisonitrile scintigraphy revealed an adenoma of the parathyroid gland and hyperparathyroidism. However, we did not perform any invasive surgical procedures for her parathyroid adenoma because of her normal calcium level and her age.

Table 1 Laboratory tests

	Day 1	Day 2	Day 3	Day 9	3 months later
WBC (/μL)	21,600	7,600	4,900	5,300	3,900
Neutrophils (%)	65.9	76.9	77.5	62.0	75.2
Na (mEq/L)	138	142	142	143	142
K (mEq/L)	2.9	4.3	3.8	3.9	3.6
Cl (mEq/L)	100	103	108	109	110
Ca (mg/dL)	–	10.2	9.6	10.4	9.5
Alb (g/dL)	3.2	3.5	2.9	2.6	2.6
Mg (mg/dL)	–	14.3	5.3	1.7	1.9
FEMg (%)	–	52.4	–	–	3.9
BUN (mg/dL)	22.0	34.8	18.6	17.0	13.4
Cr (mg/dL)	0.46	0.84	0.71	0.42	0.4
CRP (mg/dL)	0.8	10.4	17.8	1.6	2.9
iPTH (pg/mL)	–	87	–	–	77
pH	7.417	7.608	7.466	–	–
PaO_2 (mmHg)	32.0	110	144	–	–
$PaCO_2$ (mmHg)	57.9	24.7	37.4	–	–
HCO_3 (mEq/L)	36.6	28.1	26.6	–	–
AG (mEq/L)	1.4	10.9	7.4	–	–
Urinary Mg (mg/dL)	–	232.1	–	–	14.4

Discussion

We examined a case of severe hypermagnesemia despite normal renal function. The patient showed severe bradycardia refractory to medical therapy, which thus required

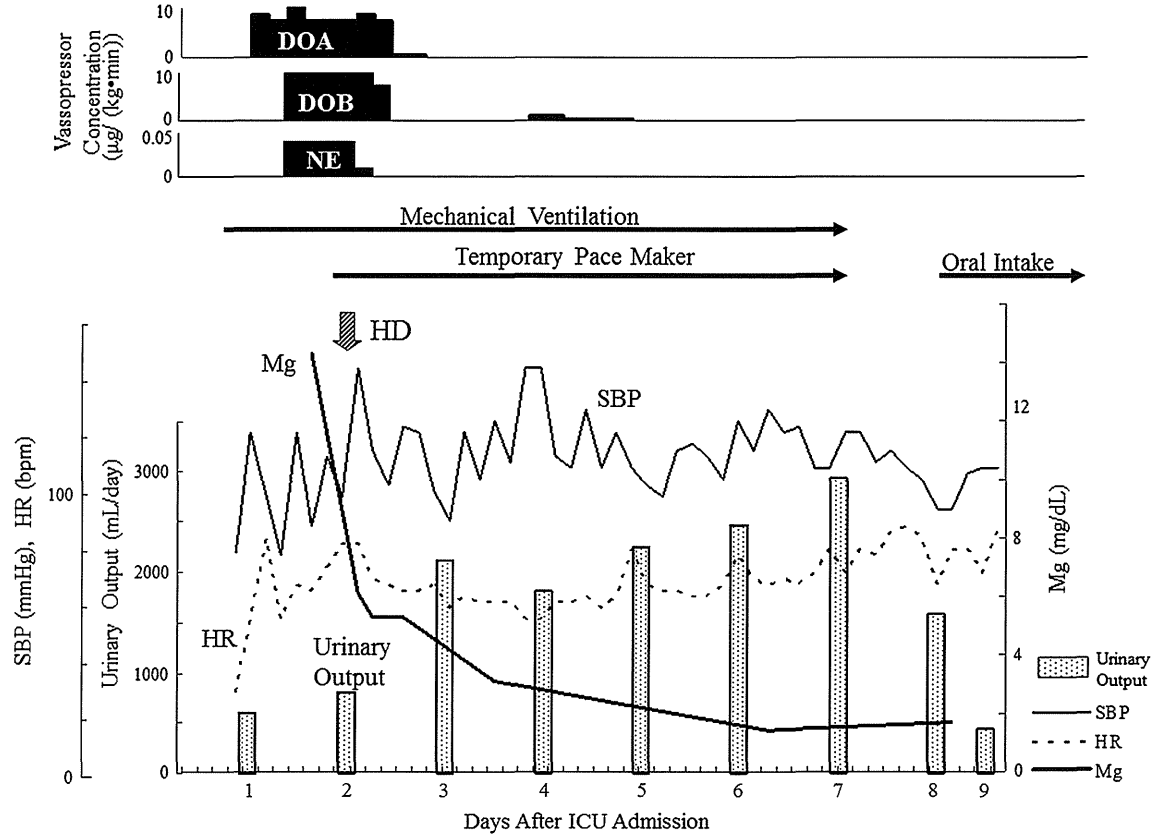

Fig. 2 Clinical course of the patient. *SBP* systolic blood pressure, *HR* heart rate, *Mg* magnesium, *HD* hemodialysis, *DOA* dopamine, *DOB* dobutamine, *NA* norepinephrine, *ICU* intensive care unit

temporary pacing; however, she dramatically recovered by hemodialysis.

Mg is the second most abundant intracellular cation with 67 % of the total body stores found in bone, 31 % found in intracellular spaces, and only 2 % found in extracellular regions. Disorders resulting in Mg elevation include acute renal failure, chronic renal failure, Addison disease, hyperparathyroidism, and familial hypocalciuric hypercalsemia. Lithium administration also causes an increase in Mg levels.

Mg is absorbed through the small intestine by passive paracellular transport through Claudin-16/19 and by active transcellular transport through TRPM6 [5]; the former is thought to be dominant. In a patient with constipation, increasing Mg absorption may cause hypermagnesemia. High levels of extracellular Mg inhibit acetylcholine release from the neuromuscular end-plate and thereby cause paralysis of smooth muscles, resulting in intestinal ileus. Furthermore, elevated intrabowel pressure can promote Mg absorption, creating a vicious cycle. The necessity of preoperative mechanical bowel preparation is still controversial, although it is commonly used in Japan to prevent postoperative infection or anastomotic leak. The cathartics we used contained 5,420 mg of Mg, and although this was an appropriate dose increase recommended by the pharmaceutical manufacturer, it could cause life-threatening hypermagnesemia for patients at high risk for increased absorption or for decreased excretion of Mg. A periodic examination of serum Mg level is necessary when Mg-containing agents are administered for a long time even if these agents are administered at a routine dosage level.

The kidneys are primarily responsible for the excretion of Mg. The mechanism of renal handling of filtered Mg is similar to that of the intestine and involves passive paracellular transport in the proximal tubule (approximately 20 %) and in the thick ascending limb of the loop of Henle (approximately 70 %), as well as active transcellular transport in the distal convoluted tubule (approximately 10 %) [4]. The rate of decline in serum Mg concentration has been reported to follow a logarithmic decay pattern if renal function is normal [5]. The elderly are at a risk for Mg toxicity as kidney function declines with age [11]. Older persons with hypermagnesemia are likely to develop reduced blood flow leading to a prerenal type of renal dysfunction, which creates a vicious cycle. In our case, the patient's renal Mg excretion was remarkably increased with a Mg excretion fraction of 52.4 % (normal value

Table 2 Literature review

References	Age/sex	Clinical examination			Baseline disease	Mg load		Symptom				
		Serum Mg (mg/dL)	Serum Cr (mg/dL)	eGFR (mL/min 1.73 m^2)		Mg quantity	Cause	Vomiting	Abdominal pain	Bradycardia	Hypotension	Somnolence
Schelling [12]	81/F	21.2	1.8	20	AAA COPD	1 g	Operation	+	+	+	+	
Onishi [13]	89/M	12.6	1.1	47	Unilateral kidney	2.7 g	Colonoscopy	+	+		+	+
Weber [14]	77/F	10.3	1.5	25	COPD (theophylline intake)	1.3 g	Treatment for theophylline toxicity					+
McLaughlin [15]	42/F	9.1	0.9	51	Schizophrenia ileus	4.6 g	Constipation	+	+		+	
Kontani [4]	76/F	16.6	1.4	21	Constipation	2.7 g	Constipation		+		+	+
Fung [3]	69/F	16.2	1.7	22	Constipation	24 g	Constipation					
Kikuchi [16]	79/F	11.4	1.3	29	Constipation	0.5 g/day + 2.7 g	Colonoscopy		+	+	+	+
Golzarian [17]	67/F	8.1	2.6	13	Constipation	3 g	Constipation	+				
Weber [14]	61/F	6.9	0.6	60	COPD (theophylline intake)	55 g	Treatment for theophylline toxicity				+	+
Golzarian [17]	65/F	5.1	1	41	Constipation	5 g	Constipation	+	+			
Our case	85/F	14.3	0.5	89	Constipation	0.5 g/day + 5.4 g	Regular intake + operation	+		+	+	+

References	Age/sex	Symptom					Therapy						Outcome
		Absent deep tendon reflexes	Respiratory depression	Paralysis	Complete heart block	Cardiac arrest	Calcium administration	High-volume infusion	Hemodialysis	Mechanical ventilation	Vasopressor	Pacing	
Schelling [12]	81/F						+	+	+				Dead
Onishi [13]	89/M		+			+	+	+			+	+	Dead
Weber [14]	77/F						+	+		+	+		Dead
McLaughlin [15]	42/F					+	+	+		+	+		Dead
Kontani [4]	76/F		+			+		+		+	+	+	Alive
Fung [3]	69/F			+	+			+		+			Alive
Kikuchi [16]	79/F						+	+	+	+	+		Alive
Golzarian [17]	67/F							+					Alive
Weber [14]	61/F						+	+		+	+		Alive
Golzarian [17]	65/F		+					+					Alive
Our case	85/F	+	+		+	+		+	+	+	+	+	Alive

AAA abdominal aortic aneurysm, *COPD* chronic obstructive pulmonary disease

3–5 %), indicating that her renal function was normal and her kidney was unlikely to be the cause of the hypermagnesemia. However, PTH, which affects renal Mg reabsorption and is discussed later in this paper, may have contributed to her onset of hypermagnesemia.

To date, there is no hormone known to primarily regulate serum Mg concentration. However, Mg homeostasis is influenced by many factors including PTH, vitamin D, antidiuretic hormone, 17β-estradiol, glucagon, acid–base status, FK506, cyclosporine, diuretics, epithelial growth factor, the anticancer agent cetuximab, and receptors for activated C-kinase 1 [6]. PTH is thought to activate TRPM6 and thereby increase renal Mg reabsorption from the distal convoluted tubule [6]. In this case, autonomously secreted PTH from a benign adenoma increased both calcium and Mg absorption in the thick ascending limb [7]. Furthermore, metabolic alkalosis caused by the absorption of citric acid contained in magnesium citrate may have also decreased renal Mg excretion in the distal tubule. Administered citric acid is metabolized to bicarbonate in the liver [8]. Acute and chronic metabolic alkalosis may have consistently led to a decrease in urinary Mg excretion [8]. Hyperparathyroidism and metabolic alkalosis, which were observed in this case, might have caused the patient's pathogenesis despite her normal renal function. Our case is unique because although there have been several reports of fatal hypermagnesemia, here we have demonstrated a possible association between hyperparathyroidism and the development of fatal hypermagnesemia. Clinical manifestations of hypermagnesemia vary according to the serum Mg concentration. Hypotension, nausea, vomiting, facial flushing, urinary retention, and ileus occur at levels ranging from 5–8 mg/dL, while the absence of deep tendon reflexes and somnolence occur at 9–12 mg/dL. Respiratory depression, paralysis, and complete heart block occur at levels >15 mg/dL, and cardiac arrest occurs in asystole at levels >20 mg/dL [1, 4]. Although details of the inhibitory effect of Mg on cardiac function have not been fully elucidated, several mechanisms have been suggested, including inhibition of norepinephrine release by sympathetic postganglionic nerves [1] and blocking of calcium and potassium channels [9].

This case exhibited typical manifestations of severe hypermagnesemia; however, we did not recognize these manifestations until day 2. Indeed, the incidence of hypermagnesemia as identified based on physician-initiated requests is reported to be approximately 13 % because most symptoms of hypermagnesemia are nonspecific, and serum Mg is not routinely measured [10]. In our patient, considering her elevated renal Mg excretion, hypermagnesemia would have recovered spontaneously within several days without hemodialysis. In cases such as this, hypermagnesemia would never be diagnosed if not suspected. In our case, severe bradycardia was a prominent feature of hypermagnesemia. Additionally, a decreased serum anion gap indicated an increase in unmeasured cations such as calcium and Mg.

Treatments for hypermagnesemia include high-dose calcium administration, Mg washout via high-volume normal saline infusion, and administration of a loop diuretic and hemodialysis. Loop diuresis inhibits tubular reabsorption of Mg in the thick ascending limb of Henle's loop. Hemodialysis is extremely effective in cases with severe symptoms or renal failure. The expected change in serum Mg level after a 3- to 4-h dialysis session is approximately one-third to one-half between the dialysate Mg concentration and the predialysis ultrafilterable serum Mg [11]. In our patient, serum Mg decreased from 14.2 to 5.3 mg/dL; in fact, her hemodynamics improved remarkably during (rather than after) the hemodialysis session.

We searched the term 'hypermagnesemia' in English literature published between 1989 and 2011 by using the National Library of Medicine's PubMed database (http://www.pubmed.gov) [3, 4, 12–17] and found 10 cases in addition to our case which are summarized in Table 2. Almost all the patients were elderly and had insufficient renal function. Some cases showed extremely high serum Mg levels, and 4 cases succumbed to death. Kontani et al. [4] suggested that severe hypermagnesemia could occur even in the absence of pre-existing renal dysfunction, particularly if the patient is elderly.

In conclusion, Mg-containing preoperative preparations may lead to the development of hypermagnesemia even in patients with normal renal function. Although hypermagnesemia requires early diagnosis and a rapid response, it is often diagnosed only when the condition is severe. The monitoring of serum Mg concentration and/or the serum anion gap before and after the administration of Mg-containing cathartics would be useful for avoiding life-threatening hypermagnesemia. Mg-free cathartics are the ideal choice of mechanical bowel preparations for patients with renal dysfunction, severe constipation, or a long-term history of Mg-containing treatment.

Conflict of interest The authors declare that they have no conflict of interest.

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●特　集●　術前化学療法の新展開

大腸癌に対する術前化学療法

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Neoadjuvant Chemotherapy for Colorectal Cancer: Takeo Sato, Masanori Naito, Atsushi Ikeda, Naoto Ogura, Hirohisa Miura, Atsuko Tsutsui, Takatoshi Nakamura and Masahiko Watanabe (*Dept. of Surgery, Kitasato University School of Medicine*)

Summary

Surgery continues to play an important role in the curative treatment of gastrointestinal cancer. Recently, considerable progress has been made in chemotherapy and radiotherapy. In particular, chemotherapy with FOLFIRI and FOLFOX has prolonged survival in patients with colorectal cancer. Molecular-targeted agents have also enhanced the effectiveness of chemotherapy. However, radical resection offers the potential for a cure and is unsurpassed by any other treatments. Nonetheless, further improvement in survival is unlikely to be achieved by surgery alone. Studying how treatment regimens highly effective against unresectable or recurrent colorectal cancer can be adapted to patients with resectable disease is thus an important issue. **Key words**: Advanced colorectal cancer, Neoadjuvant chemoradiation therapy, Neoadjuvant chemotherapy, **Corresponding author**: Takeo Sato, Department of Surgery, Kitasato University School of Medicine, 2-1-1 Asamizodai, Minami-ku, Sagamihara, Kanagawa 252-0304, Japan

要旨　消化器癌の根治的治療は未だに外科治療である。近年，化学療法や放射線療法は格段の進歩を遂げた。特に，大腸癌の化学療法はFOLFIRI，FOLFOX療法らの多剤併用化学療法によって生存期間の延長をもたらした。さらに，分子標的薬の出現により治療効果の上乗せがもたらされた。しかし，治癒をもたらす治療は根治的切除であり，これを凌駕することはない。一方，手術治療のみでのこれ以上の生存率の向上も困難である。このため，切除不能・再発大腸癌で高い治療効果のある治療法を切除可能な症例へいかに応用できるかが課題となる。

はじめに

消化器癌の根治的治療は未だに外科治療であるが，化学療法，放射線療法も格段の進歩を遂げた。特に，切除不能・転移再発大腸癌に対する化学療法は，1990年代後半から持続5-FU療法にcamptothecin（CPT-11）や，oxaliplatin（L-OHP）を加えたFOLFIRI療法，FOLFOX療法らの多剤併用化学療法によって生存期間の延長をもたらした。さらに，分子標的薬である抗VEGF抗体治療薬bevacizumab，抗EGFR抗体治療薬cetuximabやpanitumumabも実臨床で投与できるようになり，治療効果の上乗せがもたらされた。しかし，治癒をもたらす治療は根治的切除のみである。大腸癌に対する外科的治療の根治性は，腫瘍の占居部位や進行度で異なる。拡大手術か縮小手術を行うか，患者のquality of life（QOL）か根治性をとるか，正しい術式選択をすることが重要である。

大腸癌の外科治療は，他の消化器癌と比べても大きな役割を果たしている。原発巣だけでなく，転移巣も切除することで治癒が望めるからである。しかし，肝切除を行った後の約50～60%で再発を認める。手術のみでのこれ以上の生存率の向上は困難であり，このため，切除不能・再発大腸癌で高い治療効果のある治療法を切除可能な症例へいかに応用できるかが課題となる。

本稿では，大腸癌の術前治療を中心とした補助化学療法の現状と今後について述べる。

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表 1 Neo-adjuvant Tx or Conversion Tx？

Neo-adjuvant Tx: 手術が“大”前提
Conversion Tx: 治療手段の変更
化学療法の効果により，
手術が可能となった場合！

Ⅰ．補助療法

術後補助療法は，大腸癌治療ガイドライン[1]では以下のように記されている。R0 切除が行われた症例に対して，再発を抑制し予後を改善する目的で，術後に実施される全身化学療法である。治癒切除手術が行われた癌に対する補助化学療法の評価は，再発が確認されるまでの無再発生存期間（disease free survival: DFS）と生存期間（overall survival: OS）を指標として行われる。すなわち，術後補助化学療法は手術単独治療に毒性を加える治療のため，安全かつ統計学的にも十分な全生存期間の上乗せ効果が得られるものでなければならない。

結腸癌の「術後」補助化学療法の全生存期間への上乗せ効果は証明されている。特に，MOSAIC Trial[2]や NSABP C-07[3]，NO16968 試験[4,5]などの L-OHP を用いた化学療法が，5-FU/LV 療法に上乗せ効果があることが報告されている。一方，進行直腸癌の治療では，生存率の向上のみならず，独特の再発形式である局所再発のコントロールが重要な課題であるが，「術後」補助化学療法のエビデンスは本邦で行われた N・SAS-CC[6]の UFT 単独 1 年投与のみである。これは，欧米では手術＋化学放射線療法が標準治療と位置付けされているためと考える。しかし，術前・術後化学放射線療法では局所コントロールには優れているものの，生存率の向上に寄与する報告は乏しい。また，転移巣切除に関しての後の補助療法に関する大規模臨床試験の報告は皆無である。

1．術前化学療法と conversion therapy（表 1）

「術前」補助化学療法を定義する上で，「術後」補助化学療法の理論を規範として考えると，R0 切除を行うことが可能な症例に対して再発を抑制し，予後を改善する目的で術前に実施される全身化学療法となる。術前補助化学療法は手術前に毒性を加える治療のため，安全かつ統計学的にも十分な DFS，OS の上乗せ効果が得られ，また手術が安全に行われるものでなければならない。

一方，conversion therapy とは化学療法や（化学）放射線療法により切除不能癌を縮小して，手術に治療方法を変更することを指す。手術を予定していた症例の治療方法を化学療法に変更する場合も conversion therapy となるが，一般的には前者のみを指す。化学療法のみでは根治することは困難であるが，手術に治療方法を変更することによって根治の可能性が得られる。腫瘍学的切除不能の定義は侃侃諤諤されており，議論が分かれるが図 1 のように技術的切除不能癌やボーダーライン症例が conversion therapy の対象となる。

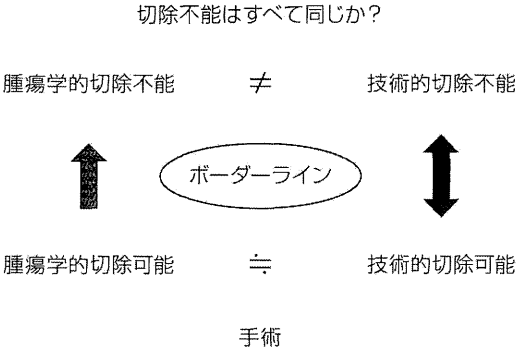

図 1 どのような治療戦略をとるか

Ⅱ．原発巣に対する化学（放射線）療法

1．結腸癌

結腸癌では，根治切除後の補助化学療法の上乗せ効果は多くの臨床試験で証明されてきた。近年では，Stage Ⅲ結腸癌症例で新規抗癌剤である L-OHP を用いた FOLFOX 療法[2]，FLOX 療法[3]，XELOX 療法[4,5]がいずれも術後補助療法において L-OHP が全生存率への上乗せ効果があることが明らかになった。しかし一方で，切除不能・再発癌で用いられる分子標的薬である抗 VEGF 抗体薬[7-9]，抗 EGFR 抗体薬[10]は上乗せ効果をもたらさなかった。

結腸癌切除可能症例における術前化学療法の意義は明らかではない。しかし，他臓器浸潤や高度リンパ節転移を伴う結腸癌の予後は不良である。また，十二指腸や膵頭部浸潤を伴う上行結腸癌の場合も，拡大手術により切除は可能となることもあるが，膵頭十二指腸切除術などの侵襲は大きい。これらの予後不良症例や拡大手術を要する症例で，術前補助療法を行うことにより，患者の予後や QOL の向上に貢献する可能性もある。原発巣に対する化学療法の効果に関するデータは乏しいが，Schrag らが直腸癌において術前の FOLFOX＋bevacizumab 療法で完全奏効（pathological complete response: pCR）が 27%という報告をした[11]。高い抗腫瘍効果は予後向上に貢献する可能性は示唆される。しかし，現状では明らかなエビデンスはなく，R0 切除がもっとも重要であることに異論はないであろう。

2．直腸癌

補助療法としての放射線療法には，術前または術後に行う外照射と術中直接照射がある。術中照射は，局所再発の原因である外科的剝離断端陽性例や不足例での局所制御を目的としている。電子線照射を施行することが多

いが，高線量率小線源を用いることもある[12,13]。使用される電子線のエネルギーは腫瘍の深さにより選択する。術中照射は外科的剝離面や遺残腫瘍部位を直視下に照射することができる。さらに，小腸や膀胱などの正常臓器の防護が可能であるが，管理および照射施設の問題から行える施設が限られる。

一方，術前・術後照射に関しては，各々利点と欠点がある。術前照射に関しては，原発巣の縮小により括約筋温存手術の適応の拡大し得る可能性がある。また，腫瘍への供給血管が切離されていないため，化学療法の腫瘍・リンパ節への接触が多く，化学療法の効果が多く得られる可能性がある。さらに，手術による生体の侵襲がないため，治療コンプライアンスが高いことや化学療法後に検体を摘出するため，化学療法の奏効が病理学的に診断でき，感受性試験となる可能性があるなどの利点があげられる。欠点としては，治療期間が長期化（手術までの期間が長期化）する。他臓器に微小転移が存在すると，照射・化学療法による免疫力の低下が惹起され，転移巣が増大する可能性がある。また，術後の合併症の危険性が高まる可能性がある。さらには，over diagnosisによるover therapyをしている可能性があることがあげられる。一方，術後照射群は術中所見・切除検体による正確な病期診断が可能で，治療症例を限定できる利点がある。欠点としては，術中操作による骨盤腔内へ落ち込んだ小腸に放射線を照射する可能性や手術侵襲後の治療のため，治療コンプライアンスが低下する可能性がある。

局所進行直腸癌に対する補助化学療法は，欧米を中心に多くの臨床試験が行われている。しかし，5-FU系抗癌剤を併用した化学放射線療法が主流になっているが，標準治療とされるレジメンはない。Swedish Rectal Cancer Trialでは，術前化学放射線療法が生存率の向上に寄与することが報告されたが[14]，その他の大規模臨床試験での追報告はみられない。一方，Guillemらは術前化学放射線療法でCRまたはCRに近い効果の得られた症例の予後がよいことを報告した[15]。

近年では，治療効果を高めるために術前化学放射線療法の内容が工夫され種々の報告がみられるようになった。

1990年のNIHの提言以降，直腸局所進行大腸癌の欧米での標準治療は化学放射線療法と手術療法の併用である。本邦では手術の治療成績がよいことから，化学放射線療法の検討が行われていないのが現状である。手術治療のRCTであるJCOG 0212，TME vs TME＋側方郭清の治療成績の結果が待たれるが，今後本邦でも補助化学放射線療法に関する大規模なRCTが行われることが望まれる。

Ⅲ．転移巣に対する術前化学療法

1．切除可能に対する術前化学療法（補助）

治癒的な肝切除が施行された症例でも，残肝再発が41～49%，次いで肺転移が20～30%であると報告されている[16]。このため，術前や術後に化学療法を施行して，残肝再発や肝外再発の抑制を試みてきた。しかし，現状では生存期間の延長を有意に延長させた報告はない。このようななかで，FOLFOX4を術前・術後に投与するEORTC 40983試験が行われた[17]。対象は転移個数が1～4個の治癒切除可能な症例で，手術単独群と術前・術後化学療法群とのRCTである。この結果は，intention-to-treat（ITT）解析では有意差は認めなかったが，適格例，切除例では，FOLFOX4投与群で3年無増悪生存期間（progression free survival: PFS）が36.2%で手術単独群（28.1%）よりも有意に高く，FOLFOX4群が生存期間の延長に寄与する可能性が示された。しかし，ITT解析では有意なPFSの差がなく，術後早期再発となる可能性がある化学療法中の他臓器転移出現例は肝切除適応から外れていること，FOLFOX4の完遂率の低さ（71.3%）などなどの批判的な意見も多く，解釈が難しい。しかし，欧米では術前・術後ともに補助化学療法のエビデンスが構築されていないものの，術前・術後の補助化学療法を推奨している。

切除可能症例での術前化学療法の利点は，腫瘍縮小によるR0手術の可能性や微小転移の抑制，生体内における化学療法の感受性の評価可能などが考えられる。一方，欠点としては転移巣以外の正常な組織への毒性，これに派生する合併症など，化学療法不応症例の腫瘍増大などが考えられる。治療中に腫瘍個数が増加する症例は，手術でも転移巣のコントロールが困難なことも多いが，切除の時期を逸した可能性も考えなくてはならない。

現状では，治癒し得る治療法は手術のみであり，術前補助化学療法に関して綿密に計画された臨床試験としては行うべきである。

2．切除不能・ボーダーラインに対する術前化学療法（conversion therapy）

大腸癌の肝転移の切除不能症例は，全身化学療法が第一治療選択となる。大腸癌の肝転移が切除可能か否かは，転移巣の大きさと分布，主要脈管浸潤の有無，残肝ボリューム，コントロール不能な肝外転移の有無，患者の全身状態，肝機能などによって決定されるが，施設間や外科医間でも見解は分かれる。さらに，系統的切除を行うことが多い欧米と部分切除を駆使する本邦では，術式に関して相違がある。したがって，切除の可否に関して

も，欧米と本邦では若干のずれが生じる。近年では全身化学療法の進歩により，化学療法後に手術可能となり，初診時切除不能症例でも，さらなる長期生存症例や根治症例も経験するようになった。CPT-11やL-OHP，分子標的薬を用いることにより11～37%で切除が可能になると報告されている[18-24]。

conversion therapyによって生存期間の延長が認められ，欧米でも注目を浴びるようになったのはCRYSTAL試験の結果によると考えられる。同試験ではFOLFIRIにcetuximabを併用することで，肝転移のR0切除率が4.5%から9.8%に[25]，OPUS試験でも*KRAS*野生型患者にFOLFOXとcetuximabを併用することでR0切除率が4.1%から9.8%へと[26]，いずれも2倍以上に増加している。切除不能な肝転移を有する大腸癌患者111例を対象にしたCELIM試験[24]では，術前化学療法としてcetuximabをFOLFOX6またはFOLFIRIと併用した場合の奏効率および治療後の肝転移巣の切除率を第Ⅱ相無作為化試験により比較検討した。奏効率はFOLFOX6群，FOLFIRI群ともに同等に良好で68% vs 57%，R0切除率はFOLFOX6群38%，FOLFIRI群30%であった。FOLFOXやFOLFIRIといった標準的化学療法レジメンにcetuximabを併用することで良好な奏効率が得られ，肝転移巣切除の可能性が高まることが示された。この試験を行ったFolprechtらにより，奏効率が上がるほど切除率が高くなる[27]ことも報告されている。一方，FOLFOXまたはXELOXに対するbevacizumabの上乗せ効果を検討したNO16966試験[28]では，奏効率におけるbevacizumabの上乗せ効果は示されなかった。しかし，技術的に切除不能な肝限局転移症例を対象にしたBOXER試験[29]では，XELOX＋bevacizumab療法を検討したところ，33%（10/30例）が切除可能になったと報告されている。また，L-OHPベースのレジメンではいわゆるblue liver（類洞拡張）が懸念されるが，bevacizumabの併用によりblue liverが抑制される[30]という報告もある。

手術を何時行うかについての明らかな見解はない。しかし，6コース以上の化学療法により肝切除後の合併症リスクが増加することが報告されていることから[31,32]，治療効果の発現までの期間が約2～3か月[33]ということも考慮して4～6コース終了時点で適切な評価を行い，可能であれば肝切除を行うことが望ましいと考える（図2）。また，bevacizumabは血管新生抑制剤という性質上，術後合併症の増加などが懸念されたが，臨床試験では有意な上昇は認めていない[34,35]。肝切除までは半減期の2倍の約5～8週とした臨床試験が多い[34-36]。

現状では，どの化学療法剤，分子標的薬剤がconversion therapyに最も適しているかは明らかではない。したがって，患者状態，腫瘍状態を適切に評価して，治療方法を決定することが望ましい。

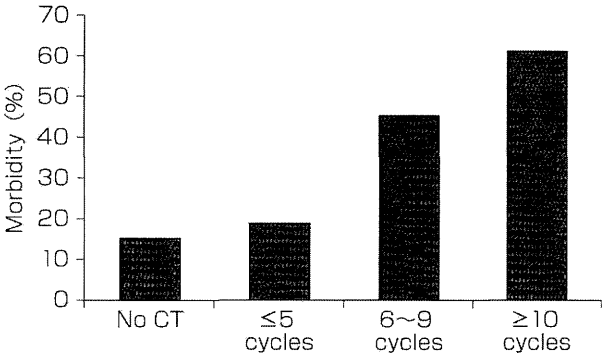

図2 化学療法治療コース数と合併症[31]

おわりに

大腸癌化学療法の効果が認められるようになってから，まだ10年も経過していない。このため，まだ多くの可能性があるが，わかっていないことも多い。術後補助療法におけるL-OHPレジメンへの分子標的薬の上乗せ効果がないことは，われわれへの一つのサジェスチョンである。術前補助化学療法に関するエビデンスもまだ乏しく，今後のデータの蓄積が極めて重要である。現状でわかっていないclinical questionの解消が，今後の新しい治療戦略につながると考えられる。

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