STUDY PROTOCOL

Protocol for a randomized study of the efficacy of ibandronic acid plus eldecalcitol in patients with gastric cancer after gastrectomy: A comparative study of different routes of administration of ibandronic acid [version 1; peer review: awaiting peer review]

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Abstract

Background: Patients who undergo gastrectomy for gastric cancer are susceptible to osteoporosis. To prevent a decrease in bone mineral density, an appropriate prophylaxis is considered important to adjust the post-gastrectomy condition. In this study, we will compare two different routes of administration of ibandronic acid (oral or intravenous) plus eldecalcitol as a potentially more suitable treatment for patients at a high risk of fragile fracture.
Protocol: This study protocol describes a randomized, active-controlled, non-blind, single-center, phase II trial. For patients in the investigational arm (Group A), sodium ibandronate hydrate will be administered intravenously once a month with daily oral intake of eldecalcitol; for those in the control arm (Group B), sodium ibandronate hydrate will be administered orally once a month with daily oral intake of eldecalcitol. We will recruit patients aged 20–85 years who have undergone gastrectomy for gastric cancer and are at a risk of fragility fractures. The study will include patients with existing vertebral fractures and/or femoral proximal fractures, or with lumbar and/or proximal femur bone mineral density of less than 80% of the young adult mean. The primary outcome of this study will be the change in lumbar bone mineral density. We will also evaluate the

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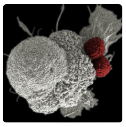
changes in femur bone mineral density, bone metabolism markers, health-related quality of life as evaluated using the EuroQol 5 Dimension (EQ-5D), and digestive symptoms as evaluated using the Gastrointestinal Symptom Rating Scale after 52 weeks of treatment.
Conclusions: We believe that appropriate treatments that are adjusted to the condition of patients after gastrectomy are important for the prevention of bone mineral loss.
Registration: This study was accepted by the Japan Registry of Clinical Trials (jRCT1041200059, November 6, 2021).

Keywords
osteoporosis, gastric cancer, post-gastrectomy, ibandronic acid, eldecalcitol



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Introduction

Patients who have parts of their stomachs removed due to gastric cancer may suffer from low nutrition, impaired calcium absorption, and bone metabolism disorder, which have been reported as post-gastrectomy complications.[1,2] Although oncologic outcomes have improved in terms of long-term survival of patients with gastric cancer,[3] more attention should be paid to maintenance and improvement of quality of life (QOL) of patients. Currently, while more than 10 million people in Japan have osteoporosis and the prevalence of osteoporosis after gastrectomy is reportedly 40%,[4–6] awareness of how to reduce this post-operative risk remains insufficient. Moreover, it has been reported that osteoporosis is likely to occur due to malnutrition associated with nausea and ulceration of the mucosa as a result of anticancer drugs.[7] Thus, the prevention of a possible decrease in bone mineral density, and if necessary, the treatment of osteoporosis, is considered important to prevent future fragile fractures. Moreover, as multi-disciplinary liaison between enterogastric surgeons and physicians who treat osteoporosis does not always occur, some patients do not receive examinations for osteoporosis or appropriate treatments. Better awareness of the risks of osteoporosis is urgently needed for both patients and doctors.[8]

Administration of eldecalcitol, an active vitamin D preparation, is assumed to be effective in compensating for the poor intake of vitamin D after gastrectomy.[9] Furthermore, bisphosphonate is effective against osteoporosis, by inhibiting osteoclast function,[10] and its usefulness has been proven in post-gastrectomy gastric cancer.[11] However, the use of oral bisphosphonates (especially nitrogen-containing alendronate) may induce several adverse events.[12] On the contrary, ibandronic acid, a type of bisphosphonate, has binary administration routes—oral intake and intravenous infusion[13]—but it is not clear which route is suitable for patients with gastric cancer after gastrectomy. Therefore, we aim to examine the efficacy of eldecalcitol and ibandronic acid on bone metabolism in patients in the postoperative stage of gastric cancer, focusing on the usefulness of different ibandronic acid administration routes in this randomized, active-controlled, non-blind, single-center (academic hospital in Japan), phase II trial.

Protocol

Overall study design

This study was approved by the Japan Registry of Clinical Trials (jRCT), approval number jRCT1041200059, on November 6, 2021. The aim of this study is to evaluate the efficacy of different routes of ibandronic acid administration (oral tablets and intravenous injection) on bone mineral density, focusing on the digestive symptoms of patients after gastrectomy. The overall study flow chart is shown in Figure 1. This study protocol follows the SPIRIT guidelines.[29]

We are conducting this trial in accordance with the principles of the Declaration of Helsinki. The Nagoya City University Certified Review Board (CRB4200003) approved this study (deliberation number 2020B003, November 6, 2021). Written informed consent will be obtained from all trial participants by physicians in charge. Physicians and medical institutions involved in this research will cooperate with the monitoring procedure manual and carry out this study in compliance with clinical research methods, related notices, and good clinical practice.

To ensure compliance with the protocol treatment, the attending physicians will ask patients about the medication status at each visit and offer guidance if there is any negligence of medication. The attending physicians will confirm the status of compliance with this study.

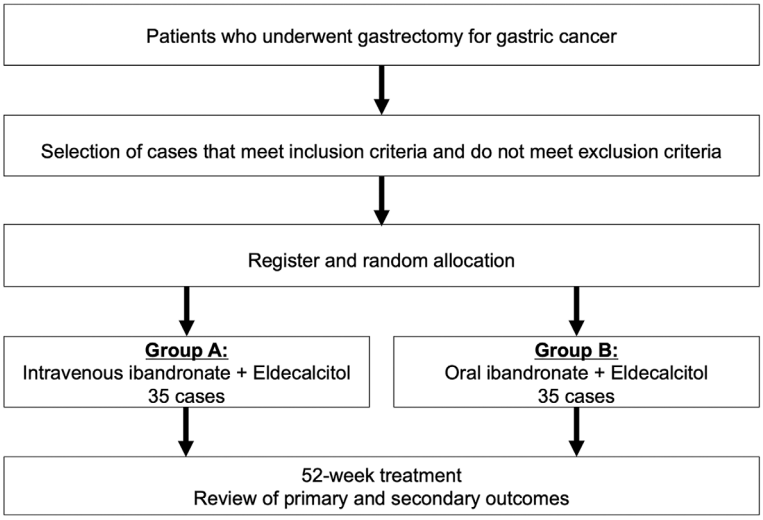

Figure 1. Flow chart of the study protocol.

Drugs

For patients in the investigational arm (group A), sodium ibandronate hydrate (Bonviva® intravenous infusion 1 mg syringe; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) will be administered intravenously once a month with daily oral intake of eldecalcitol (Edirol® Capsule 0.75 μg; Chugai Pharmaceutical Co., Ltd.). For patients in the control arm (Group B), sodium ibandronate hydrate (Bonviva Tablets 100 mg; Chugai Pharmaceutical Co., Ltd.) will be administered orally once a month with a sufficient amount of water (approximately 180 mL) upon waking, with daily oral administration of eldecalcitol. For patients with hypercalcemia (corrected Ca = 10.5 mg/dL or more) identified at the time of registration or administration period, eldecalcitol dose will be reduced to appropriately 0.5 μg daily. Concomitant therapy will be permitted, including palliative and supportive therapies, such as analgesics, antiemetic agents, and anti-vomiting agents, for any symptoms due to primary disease or any adverse events. Additionally, chemotherapy for gastric cancer will be permitted. The usage of bone modulators and calcium/vitamin D supplements will not be permitted.

Patients

We will recruit patients aged 20–85 years who underwent gastrectomy for gastric cancer and are at a risk of fragility fracture. The inclusion criteria will be as follows: i) patients who underwent total or partial gastrectomy for gastric cancer; ii) patients with existing vertebral fractures and/or femoral proximal fractures or with lumbar and/or proximal femur bone mineral density of less than 80% of the young adult mean (YAM); iii) patients with a relatively stable general condition (performance status [PS], 0–2); iv) patients aged ≥20 years and <85 years on the registration date; v) patients with a post-surgery duration of less than six months; and vi) patients with their latest blood test (within 14 days before registration examination) complying with all of the following criteria: white blood cell count ≥ 1,500/μL; platelet count ≥ 100,000/μL; total bilirubin level ≤ 1.5 mg/dL; aspartate aminotransferase level ≤ 100 IU/L; alanine aminotransferase level ≤ 100 IU/L; serum creatinine level ≤ 1.5 mg/dL; and corrected Ca value < 10.5 mg/dL.

The exclusion criteria will be as follows: i) surgical resection extending to organs other than the stomach (*e.g.*, esophagus and pancreas); ii) patients with long-term immobility; iii) pregnant or breastfeeding women; iv) patients with a history or high risk of osteonecrosis of the jaw; v) patients with a history of hypocalcemia; vi) patients with urolithiasis; vii) patients with a history of allergy to the drugs used in this study; viii) patients with distant metastasis (including ascites cytology positive patients) at the time of registration; ix) patients with significant anorexia; x) patients who are being treated for osteoporosis at the time of registration; and xi) patients who are considered inappropriate by the attending physicians.

Randomization

The patient registration center will randomly assign patients to one of two treatment groups. The target number of patients in each group is 35. A computer-generated random sequence, made by Clinical Research Management Center in Nagoya City University Hospital, will be used to allocate a total of 70 patients with no stratification to sequential identification. An independent allocation manager will be responsible for the allocation process, and the allocation list will be concealed an envelope until interventions are assigned.

Target outcomes

The primary outcome of this study is the change in lumbar bone mineral density. Bone mineral density will be measured based on the dual-energy X-ray absorptiometry (DEXA) method. Bone mineral density will be evaluated during the pre-observational period, 24 weeks after the start of medication, and at the time of final observation (52 weeks after the start of medication). In addition, the following secondary assessments will be performed: i) change in femur bone mineral density; ii) change in bone metabolism markers, including tartrate-resistant acid phosphatase 5b (TRACP-5b), total type 1 amino-terminal propeptide (P1NP), and 25OH vitamin D concentration (ELISA method); iii) change in health-related QOL, evaluated using the EuroQol 5 Dimension (EQ-5D)[14] at the start date of medication, 12 weeks after the start of medication, 24 weeks later, and at the time of final observation (after 52 weeks); iv) change in digestive symptoms, evaluated using the Gastrointestinal Symptom Rating Scale (GSRS)[15] at the start date of medication, 12 weeks after the start of medication, 24 weeks later, and at the time of final observation (after 52 weeks); v) presence or absence of fracture events during the medicated period; and vi) medication compliance rate. A total of 13 ibandronic acid doses will be scheduled in both groups over 52 weeks. The actual number of medications/13 will be calculated as the medication compliance rate.

Schedule

In the pre-observation period, medical interviews will be conducted focusing on the patients' backgrounds including sex, age, height, weight, menopausal age, current medication, medical history (presence or absence of past fractures), drinking/smoking history, presence or absence of femoral fractures in their parents, the area of extension of gastrectomy and the length of the remaining stomach, reconstruction techniques after gastrectomy, surgical intervention (open/laparoscopy/robot-guide), presence or absence of gallbladder resection, and presence or absence of post-operative anticancer drugs. In addition, the mineral density of the lumbar spine and femur will be measured using the DEXA

Table 1. Assessment and evaluation schedule.

Stages of the study	Screening and exam description	Registration	0 weeks	4 weeks	12 weeks	24 weeks	52 weeks	4 weeks after discontinuation or cessation of drug administration
Informed consent	○							
Allocation to Group A and Group B		○						
Patient background[a]	○							
Vital signs	○		○	●	●	●	●	●
Bone density measurement (lumbar spine, proximal femur)	○					●	●	
X-ray of the spine	○						●	
Blood test[b]	○		○		●	●	●	
Bone metabolism markers			○		●	●	●	
Administration of research drugs[*]			←	—	—	→		
Checking the proper medication				●	●	●	●	
EQ-5D, GSRS			○		●	●	●	
Checking adverse events[c]				←	—	—	—	→

Abbreviations: EQ-5D, EuroQol 5 Dimension; GSRS, Gastrointestinal Symptom Rating Scale.
○: Items to be recorded before the start of administration of the research and control drugs.
●: Items to be recorded after the start of administration of the research and control drugs.
[a]Collection of information on drugs related to the efficacy or safety of the research drug.
[b]Hematological testing of white blood cell count, red blood cell count, hemoglobin, hematocrit, and platelet count. Testing of alkaline phosphatase, aspartate aminotransferase (glutamate oxalacetate transaminase), alanine aminotransferase (glutamic pyruvic transaminase), lactate dehydrogenase, γ-glutamyl transpeptidase, creatine kinase, total bilirubin, total protein, albumin, urea nitrogen, creatinine, amylase, sodium, potassium, crawl, calcium, and inorganic phosphorus levels, and estimated glomerular filtration rate to confirm the safety of the study.
[c]Adverse events are all unfavorable events regardless of a causal relationship with drugs.
*Delays in the administration of test and control drugs will be acceptable for up to two weeks. If delayed, the observation date will be changed according to the number of days.

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method. Spine radiography will be performed in two directions: front and side in a standing position around the 4th lumbar vertebra and the 9th thoracic vertebra. The alignment of the entire spine and the existing fracture will also be confirmed. After confirming the selection criteria using medical charts and blood tests, the physicians will obtain written informed consent from all trial participants.

On day one of the trial, vital signs, blood test results, bone metabolism markers (TRACP-5b, P1NP, and 25OH vitamin D concentrations (using ELISA)), and physical function (EQ-5D and GSRS) will be examined.

After the start of medication administration, the following will be recorded: vital signs; medication status; the presence of adverse events; presence or absence of new fracture events; blood tests (to determine whether patients comply with the same criteria from the inclusion periods); bone metabolic markers; improvement in physical function evaluation (EQ-5D and GSRS); and bone density measurement (lumbar spine and femur). Subsequently, medical checks for vital signs, compliance with medication, and the presence of adverse events will be performed at 4, 12, 24, and 52 weeks. After the discontinuation of drug administration, observation and investigation will be conducted up to 4 weeks after the date of the last administration of the research drug. If adverse events continue, follow-up and investigation will be continued until recovery from the adverse events (Table 1).

Safety

To evaluate safety, adverse events considered to be related to the research medicine will be monitored. All serious adverse events will be reported from the start of drug administration to the end of the follow-up period, along with the relationship among the type, severity, treatment content, time of expression, and turning point. Adverse events will include all undesirable or unintended symptoms and signs (including abnormalities in laboratory tests). Follow-up investigations will be performed until the disappearance of/or recovery from adverse events. All serious adverse events will be reported to the Certified Review Board by the physicians in charge. The investigators shall promptly and appropriately treat the subjects and record the adverse event, date of onset, severity, and outcome, as well as ascertain the causal relationship of the study drug.

Data collection methods

The data will be collected using a unified Case Report Form, which can be found as *Extended data*[28] and dissemination of the GSRS and EQ-5D charts.

Data management

All individuals involved in this research will properly handle the information of the research subjects and protect the personal information according to the "Act on the Protection of Personal Information." The information of all patients involved in this study will be confidentially handled using the research specific identification code. Only the principal investigator (H.A.) will handle correspondence table between autonyms and anonyms. During the research, related information will be managed using a highly secured offline computer. Quality of the data will be checked during the data monitoring process.

Statistical analysis

Statistical analysis will be performed within six months after data collection and enrollment of the final research participant. As it is predicted that the number of events will not be sufficient to make an early cancellation decision in the middle of registration, an intermediate analysis will not be performed.

The effectiveness of the investigational drugs will be evaluated using the intent-to-treat analysis for all eligible patients. The full analysis set (FAS) will comprise the entire group excluding the following research subjects: patients who do not meet the inclusion criteria, those who meet the exclusion criteria, those who are never administered drugs, and those for whom data are not obtained after the start of research medication. In the FAS, the per-protocol set (PPS) will comprise the entire group excluding the following research subjects: those for whom data on the main evaluation items are not obtained 52 weeks after the start of medication or those with a medication compliance rate of less than 80%. The sample size calculation was based on a previous study,[3] which reported that another bisphosphonate preparation (alendronate internal use) and eldecalcitol increased lumbar bone density by approximately 6% at 12 months after administration compared with an increase of approximately 3% with eldecalcitol alone. We expect the difference between the intravenous infusion and oral intake combined with eldecalcitol will show 1.5% higher lumbar bone mineral density at 52 weeks (set to half of the additional effect of alendronate in the above previous study). The number of patients required to detect this with statistical significance is estimated to be 29 in each group with standard deviation 2%, significance level 5% (bilateral sides), and power 80%. Therefore, the target number of patients in this study is 35 (70 patients in total) in each group with the expectation that several patients will drop out.

To analyze effectiveness in the FAS and PPS, the rate of change in the bone mineral density from before the start of treatment will be calculated with respect to the lumbar bone mineral density at 52 weeks, and a comparison between groups will be performed using a Student's *t*-test. In addition, for the analyses of secondary evaluation items in the FAS and PPS, the rate of change from before the start of treatment will be calculated for bone metabolism markers (TRAPC5b, P1NP), femoral bone mineral density, and QOL (EQ-5D, GSRS) at 52 weeks using a Student's *t*-test for comparison between groups. The frequency of fragile fracture events in each drug group will be calculated, and an intergroup comparison will be performed using a chi-square test.

Only the principal investigator (H.A.) will prepare a correspondence table of the research subject identification code set and only the principal investigator and biostatistician (H.H.) can access the final trial dataset.

Data monitoring
In this clinical study, an independent data monitoring officer (Y.G.) will be assigned. On-site monitoring will be conducted to confirm whether the study is carried out safely and according to the research plan and whether the data are collected reliably. Monitoring will be conducted before the start of the research, during the research (every three months), and at the end of the research. In addition, monitoring will be carried out at the time of registration and when a serious adverse event occurs.

Plans for dissemination
The results of this study will be published in peer-reviewed journals.

Study status
We are currently recruiting patients.

Discussion
The efficacy of ibandronate in vertebral fractures has been demonstrated in patients with postmenopausal osteoporosis. According to the BONE study, oral daily (2.5 mg) and intermittent ibandronate (between-dose interval of >2 months) intake reduced the risk of new morphometric vertebral fractures by 62%.[16] The DIVA study demonstrated the efficacy of intravenous ibandronate as a useful alternative to oral dosing,[17] and intravenous ibandronate was approved in Japan in 2013 after a phase II/III clinical study (the MOVER trial[18]). This study demonstrated the non-inferiority of 1 mg of intravenous ibandronate to risedronate. At three years, the mean relative change in bone mineral density from baseline was 9.0% for the ibandronate group and 7.6% for risedronate groups.[18] Moreover, the rate of first new vertebral fractures was 11.6% in the ibandronate group and 13.2% in the risedronate group. Although the rates of acute-phase reaction were higher in the ibandronate group (11.2% in the ibandronate group vs. 4.9% in the risedronate group), severe gastrointestinal adverse events were lower in the ibandronate group (0.5% in the ibandronate group vs. 2.2% in the risedronate group). The efficacy of monthly oral ibandronate was evaluated by the MOBILE study,[19] which concluded that the monthly intake was at least as effective and well-tolerated as the daily ibandronate regimen in postmenopausal osteoporosis. The MOVEST study[13] involved a randomized trial of 100 mg of monthly oral ibandronate versus 1 mg of monthly intravenous ibandronate in a Japanese population and showed comparable mineral density of the lumbar spine after 12 months of treatment (5.22% [oral] vs. 5.34% [intravenous]). Subsequently, monthly oral ibandronate intake was approved in Japan in 2016. In a real-world setting, a post-marketing observational study of 1,025 Japanese people revealed that 49.7% of the patients were concomitantly prescribed active vitamin D drugs, and preferable results with combined therapy were suggested in terms of bone mineral density at one year (3.54% [ibandronate alone] vs. 5.74%, [ibandronate + eldecalcitol]).[20]

To date, studies have reported that the intake of calcium gluconate,[21] vitamin D,[2] or bisphosphonate[22] is useful after gastrectomy. Despite this, a standard treatment has not been established. In Japan, Segawa *et al.*, reported that osteoporosis was recorded in 29.5% of patients after gastrectomy[23] and reported that being over 70 years of age, weight loss, and chemotherapy were risk factors for osteoporosis. Sugiyama *et al.*, reported that the rate of increase in lumbar bone mineral density was 9.3% at one year when oral alendronate was administered to patients after gastrectomy.[22] Hirota *et al.*, compared minodronate and eldecalcitol in post-operative patients with gastric cancer and the increase in mineral density of the lumbar spine was 4.52% in the minodronate group and 1.72% in the eldecalcitol group.[24] Similarly, Ha *et al.*, compared outcomes of administration of a weekly dose of alendronate (70 mg) + daily elemental calcium (500 mg) with cholecalciferol (1,000 IU) with those of administration of daily elemental calcium (500 mg) with cholecalciferol (100 IU) only. They reported a significantly smaller decrease in mineral density of the lumbar spine in patients who received alendronate and those who did not (-0.28 $\pm$ 5.20 vs. 8.39 $\pm$ 7.41, respectively).[25] Although it is difficult to integrate the results of these studies owing to the varied characteristics of patients after gastrectomy, methodology, and types of investigational drugs, there seem to be consistent positive effects on bone metabolism as a result of osteoporosis prophylaxis.

We should be aware of the disadvantages of bisphosphonate, including acute-phase reaction, general malaise, renal failure, joint pain, gastrointestinal symptoms, hypocalcemia, osteonecrosis of the jaw, and atypical femoral fracture.[26] However, according to the results of the MOVEST study,[13] there were no significant differences in adverse events between the oral intake and intravenous groups except for gastrointestinal symptoms, and we hypothesize that intravenous injection is appropriate for the management of post-gastrectomy patients. Considering the less variable bioavailability of intravenous ibandronate than the highly variable bioavailability of oral ibandronate,[27] especially in patients with malabsorption, a more stable concentration should be assured. In addition, a previous study reported that the completion rate of oral minodronate administration[25] was 77.5% in patients who underwent gastrectomy. This relatively low rate of compliance with drug use should be assessed further.

In conclusion, we plan to conduct a prospective study on the efficacy of ibandronate plus eldecalcitol in patients with gastric cancer after gastrectomy, focusing on different routes of administration. We believe that the results of this trial will conclusively identify a novel strategy for the post-gastrectomy treatment of osteoporosis in patients with gastric cancer.

Data availability

Underlying data

No data are associated with this article.

Extended data

Figshare: case report form.xlsx. https://doi.org/10.6084/m9.figshare.20217278.v3.[28]

Reporting guidelines

Figshare: SPIRIT checklist for 'Protocol for a randomized study of the efficacy of ibandronic acid plus eldecalcitol in patients with gastric cancer after gastrectomy: A comparative study of different routes of administration of ibandronic acid'. https://doi.org/10.6084/m9.figshare.20217338.v1.[29]

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