High-dose dexamethasone therapy as the initial treatment for idiopathic thrombocytopenic purpura

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High-dose Dexamethasone Therapy as the Initial Treatment for Idiopathic Thrombocytopenic Purpura

running head: HDD Therapy as the Initial Treatment for ITP

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Abstract

There is a controversy which short term high dose dexamethasone therapy (HDD) or standard dose prednisolone therapy as the initial treatment leads to long term efficacy in idiopathic thrombocytopenic purpura (ITP) patients. We conducted a multicenter, prospective trial to determine the efficacy and safety of short-term HDD in ITP patients aged 18-80 years with platelet counts of $<20 \times 10^9$/L, or $<50 \times 10^9$/L and bleeding symptoms.

The primary endpoints are the proportion of complete response (CR) plus partial response (R) on day 180 after the completion of the 46-day HDD.

Twenty-three patients were enrolled. Test for *Helicobacter pylori (H.pylori)* was positive for 6 patients, and negative for 17 patients. In positive patients, 5 were received successful *H.pylori* eradication therapy. The proportion of CR+R was 60.9% (14/23) with 90% confidence interval of 41.7-77.8%. For patients with positive *H.pylori* and successful eradication, proportion of CR+R was 80.0% (4/5). There was one grade 4 adverse event. Although we have enrolled relatively old, severe ITP patients with a median age of 63 years in this study, the efficacy was comparable to the reported clinical trials with HDD therapy.

Key words: idiopathic thrombocytopenic purpura, short-term, high-dose dexamethasone therapy, open-label, single-arm trial

1. Introduction

The first-line therapy for idiopathic thrombocytopenic purpura (ITP) is prednisolone at 1 mg/kg/day continuously for 2-4 weeks, followed by tapering (standard-dose prednisolone therapy) for ITP is widely used worldwide and is recommended in the clinical guidelines [1,2] of several countries. However, the regimen is not based on the results of high-quality, randomized controlled trials (RCTs); it is ultimately empiric therapy. Approximately 80% of ITP patients show some improvement from prednisolone treatment, and the platelet count recovers to $> 100 \times 10^9$/L in 50% of the patients [3,4], and thrombocytopenia often recurs during prednisolone therapy weaning, only 10-20% of patients will be able to discontinue prednisolone with a relapse-free state [5,6], but long-term prednisolone therapy can reduce an individual's quality of life and lead to side effects, such as susceptibility to infections and osteoporosis.

Chen et al. [7] and Mazzucconi et al. [4] reported the effects of short-term, high-dose dexamethasone therapy (HDD) for treating newly diagnosed ITP patients. In a multicenter, prospective trial, Mazzucconi et al. administered 40-mg dexamethasone for 4 days to 95 patients with newly diagnosed ITP, repeated every 2 weeks for a total of 4 courses [4], showing some therapeutic effect in 85.6% of the patients, a progression-free survival rate of 81% after 15 months and no particular side effect.

Mashhadi et al. [8] reported the results of a prospective RCT that examined the effect of one course of either HDD or standard-dose prednisolone, with 30 patients in each group. Significantly better results were observed in the HDD group in terms of both the 3-month complete response (CR) rate (80% vs. 23.3%) and the 6-month CR rate (73.3% vs. 16.7%) without any differences of treatment-related side effects between the two.

In Japan, Sakamoto et al. [9] retrospectively compared 31 patients who received HDD with 69 patients who received standard-dose prednisolone, showing a significantly better treatment response (42.7% vs. 28.4%), significantly better steroid withdrawal rate after 6 months (64.5% vs. 37.7%), respectively, and no differences in toxicity. In contrast, Nakazaki et al. [10] conducted a retrospective study comparing one course of HDD (12 patients), three courses of HDD (5 patients), and standard-dose prednisolone (8 patients), showing a better long-term therapeutic effect in the prednisolone group.

No prospective investigation of HDD for ITP has been reported in Japan. Thus, a multicenter, prospective investigation of the effectiveness and safety of this regimen is essential for the establishment of a standard therapy for ITP.

Clinical trials conducted outside of Japan regarding the use of HDD for ITP patients do not address *Helicobacter pylori* (*H. pylori*) eradication. In Japan, *H. pylori* eradication is emphasized in the treatment of ITP. A clinical reference guide [1] published in 2012 by a team studying coagulopathies as part of the Japanese Ministry of Health, Labour and Welfare's research initiative for treating intractable diseases states that the initial approach to treatment should involve testing for *H. pylori*, with the provision of eradication therapy in positive cases. This recommendation was put forward because clinical trials and other studies had shown that platelet levels rise in approximately 50% of ITP patients who still test positive for *H. pylori* infection after receiving *H. pylori* eradication therapy.

The reference guide published in Japan [1] also recommends eradication therapy in patients with markedly low platelet levels and bleeding symptoms, but only after some therapeutic effect from the treatment has been observed. In clinical practice, patients like the subjects in this trial (platelet count of $<20 \times 10^9$/L, or $<50 \times 10^9$/L with bleeding symptoms) would first have steroids administered. Then, after the demonstration of some therapeutic effect, eradication therapy was initiated based on testing for *H. pylori* infection.

Plasma thrombopoietin (TPO) levels and other markers have been found to be useful in differentiating ITP from other diseases [11].

We conducted a multicenter, prospective trial to determine the efficacy and safety of short-term HDD in ITP patients. Based on the results of some clinical studies [4,7,8], we chose as our primary endpoint the efficacy on day 180 after the completion of the 46-day HDD.

Eradication therapy was administered to patients who tested positive for *H. pylori* after the initiation of treatment, and the safety of this therapeutic approach was investigated.

To confirm the diagnosis of ITP and to investigate the correlation of plasma TPO level and the efficacy of HDD, we examine pre-treatment plasma TPO level.

2. Materials and Methods

2.1. Trial design

This study was a multicenter, open label, single-arm trial.

2.2. Participant

Patients newly diagnosed with ITP and assessed as requiring treatment, from 18 to 80 years old, platelet count of $<20 \times 10^9$/L, or $<50 \times 10^9$/L with bleeding symptoms, and performance status of 0-2 were enrolled[11]. In diagnosis of ITP, ruling out was still dominant. The criteria for thrombocytopenia is a platelet count of $<100 \times 10^9$/L. In ITP, a symptom of anemia caused by persistent bleeding may appear, and coagulation examination shows the normal value. Bone marrow examination was not essential, but positively recommended in elderly people (60 years of age or older) or where myelodysplastic syndrome etc. were suspected. All patients provided written informed consent before enrollment.

2.3. Study settings

The study was approved by the central review board of Japan's National Hospital Organization for clinical trials (H28-0810001). The registration period was from March 2016 to June 2018. The study was registered in the University Hospital Medical Information Network Center (UMIN)-Clinical Trials Registry (CTR) on May 23, 2016 (UMIN 000022415).

2.4. Interventions

High-dose dexamethasone therapy

Three courses of high-dose dexamethasone therapy were administered every 2 weeks. One course consisted of dexamethasone 40 mg orally, administered daily for 4 days, or dexamethasone 33 mg (included in Dexamethasone sodium phosphate 40 mg) intravenously, administered daily for 4 days. The attending physician could decide between oral or intravenous administration. If the patient's platelet count was $<20 \times 10^9$/L after 4 days of the investigational drug, up to 2 mg of dexamethasone may be administered. Patients who exhibit steroid withdrawal symptoms or were deemed to be at high risk for these symptoms may have up to 2 mg of dexamethasone administered. Regardless of the platelet count or other symptoms, weaning should be performed so that dexamethasone administration ends by day 14 after the end of the third course.

Helicobacter pylori eradication therapy

Patients were tested for *H. pylori* at the time of diagnosis. A stool test for *H. pylori* antigen was recommended, but the test selection was left to the discretion of the attending physician. After the beginning of the trial, eradication therapy may be given at any point if a patient was found to be positive for *H. pylori*. This therapy consists of a 7-day course of 3 drugs (amoxicillin 1,500 mg, clarithromycin 400 mg, and a proton pump inhibitor [PPI]) given in 2 divided doses

per day (after breakfast and after dinner). Following this treatment course, the success of the eradication was assessed over the next 4-8 weeks via stool tests for *H. pylori* antigen or the urea breath test. If eradication was unsuccessful, a second round of therapy was administered, replacing clarithromycin with metronidazole (amoxicillin 1,550 mg, metronidazole 500 mg, and PPI), and the effects were again assessed over the next 4-8 weeks.

Antiviral therapy

Patients who test positive for HBs antibodies or hepatitis B core (HBc) antibodies were not be excluded from the trial, but the trial therapy carries a risk of hepatitis B virus (HBV) reactivation. These patients should be monitored for HBV DNA with polymerase chain reaction (PCR) every 1 or 2 months for ≥ 6 months after completing treatment. Patients who test positive should receive aggressive antiviral therapy.

Preventing gastrointestinal ulcers and infections

A gastrointestinal ulcer drug (PPI or H2-blocker) were administered during oral dexamethasone therapy. Anti-tuberculosis drugs, trimethoprim-sulfamethoxazole, antifungal drugs, and antiviral drugs were used to prevent infections at the discretion of the attending physician.

2.5. Outcomes

Response was judged according to criteria by international working group [12]. “Complete response” (CR) is defined as any platelet count of at least 100 $\times 10^9$/L without any bleeding tendency. “Response” (R) is defined as any platelet count between 30 and 100×10^9/L and at least doubling of the baseline count without bleeding symptom. “No response” (NR) is defined as any platelet count lower than 30×10^9/L or less than doubling of the baseline count. Platelet

counts should be confirmed on 2 separate occasions at least 7 days apart when defining CR or R. The response on day 180 was categorized as CR, R, NR, or others. "Others" was chosen when the response was undecidable, prohibited concomitant drugs were used, or prohibited medical treatments were performed after trial treatment.

The primary endpoints were the proportion of responses (CR+R) on day 180 (day 46+180) after the patients complete the high dose dexamethasone therapy (which was completed 46 days after starting treatment). The secondary endpoints were the platelet count on day 46+180 (by response, complete response, and partial response), relapse-free survival, the frequency of adverse events, the frequency of *H. pylori* infection, the bacterial eradication effect, the proportion of complete responses on day 46+180 among the patients without *H. pylori* infection, the proportion of complete responses on day 46+180 among the patients with *H. pylori* infection with eradication/no eradication effect, the relapse-free survival for the patients without *H. pylori* infection, the relapse-free survival for patients with *H. pylori* infection with eradication/no eradication effect, and the adverse events with eradication/no eradication effect.

2.6. Sample size

In a retrospective study performed in Japan, the CR rate after 1 year of prednisolone administration was 28.4% [9]. In a registry in Japan, the proportion of responses (CR+R) at 2 years after diagnosis was 75.0% (114/152) [13]. In a prospective interventional study from Iran, the CR+R rate of the group that received standard steroid treatment was 53.3% (16/30) and 46.7% (14/30) after 6 months and 1 year, respectively [8]. Based on these results, we chose 50% as the threshold proportion of response. The response rate at ≥2 months after the completion of therapy according to the GIMEMA (Gruppo Italiano per le Malattie Ematologiche dell'Adulto) protocol was 83.8% (31/37) in a single-center study and 84.4% (76/90) in a multicenter study [4]. Based on these results, we chose 80% as the expected

proportion of response. The number of patients needed was calculated to be 21 based on binomial proportion with a significance level of 0.05 (one-tailed) and statistical power of 0.90. To account for dropouts, we set the sample size as 25.

2.7. Statistical methods

Proportion of CR+R at 84+180 days and 90% confidence interval (CI) was estimated. For patients with maximum response of CR or R, relapse-free survival was estimated by Kaplan-Meier method. The platelet count on day 46+180 by response, the frequency of *H. pylori* infection, and the bacterial eradication effect were summarized (Table 2). The effect of platelet count, bleeding score, age and TPO to CR+R at 84+180 days was examined by logistic regression. We used the bleeding score defined by Survey on blood coagulation disorders [14]. It was categorized by platelet count (50×10^9/L or more than 100×10^9/L, 20×10^9/L or more and less than 50×10^9/L, and less than 20×10^9/L) and clinical symptoms (no symptom, subcutaneous bleeding, mucosal bleeding, and severe bleeding). Cut off value of TPO was based on the threshold of eltrombopag to response for ITP patients [15]. The frequency of adverse events with eradication/no eradication effect was calculated.

3. Results

Twenty-three patients were registered, and all of them received protocol treatment. One patient who considered as refractory case stopped treatment after course 1. Others completed all courses. *H.pylori* was positive for 6 patients, and negative for 17 patients. In six *H.pylori*-positive patients, 5 were received successful *H.pylori* eradication therapy. (Figure 1). The patient characteristics are shown in Table 1. Five patients were male (21.7%), and Median age was 63. Median platelet count was 7000/μl. Bleeding score were 3 for 2 patients, 4 for 20

patients, and 5 for 1 patient. Median PA-IgG was 297(ng/10^7 cells). Two patients had a history of *H.pylori* eradication. Median (range) TPO concentration was 54.4 (14.2-153.9) pg/ml.

Overall response (CR+R) rate was 82.2% (19/23). Median duration to overall response was 26 days (range: 2-211 days). The response at 46+180 days was shown in Table 2. The proportion of CR+R was 60.9% (14/23) with 41.7-77.8% of 90%CI. For patients without *H.pylori* eradication proportion of CR+R was 55.6% (10/18). For patients with positive *H.pylori* and successful eradication, proportion of CR+R was 80.0% (4/5). One patient with positive *H.pylori* and without eradication therapy, discontinued treatment after one course of HDD, and showed poor prognosis. Relapse free survival (RFS) rate after 12 months was 57.3% in Figure 2. There was no relation between platelet count, bleeding score, age, TPO and response in Table 4.

One case of grade 4 prostate infection, 1 case of grade 3 bronchial infection and 1 case of grade 2 skin infection (Table 3). Grade 4 prostate infection applied to a serious adverse event. This patient aged 75 years and developed a prostate infection on the day after the course 1 had been completed (4 days after the start of treatment). The patient was relieved by the antibiotic treatment. Patients with grade 3 bronchial infection aged 19 years, and developed 9 days after course 1 ended (12 days after the start of treatment). There was 1 case of grade 2 fracture, which had causal relationship with the underlying disease, osteoporosis (Table 3).

4. Discussion

This study was the first to examine the efficacy and safety of simultaneous HDD and *H.pylori* eradication therapy as an interventional study. It is also the first prospective clinical trial to show the efficacy and safety of HDD for ITP in Japan.

Cheng et al. reported 80% response rate was in the prospective trial with one course of HDD for naive ITP patients. The duration of treatment response after 6 months was reported as 50% in the trial. Wei et al. reported no difference for the long-term therapeutic effect between one course of HDD group (40.0%) and standard dose PSL group (41.2%) in the RCT [16].

On the other hand, in the RCT (n = 30) of one-course HDD and standard dose PSL by Mashhadi et al., the response rate after 6 months of treatment was better in one-course HDD group (73%) compared with standard dose PSL group (53%) [8]. However, the patients in HDD group in the study have received long-term maintenance dose of PSL in addition to the 4 day treatment of HDD, which is different from short-term HDD alone.

The multicenter prospective trial using 3-4 courses of HDD for the naive ITP patients show long-term efficacy over 80% in all age groups [4], and for patients over 18 years of age, the effectiveness at 6 months after HDD was 61% [4]. In our study, we have enrolled relatively old, severe ITP patients with a median age of 63 years, the efficacy (60.9%) was comparable to the reported clinical studies with HDD.

In this study, CR+R rate was set at 50% or less at 180 days after treatment with standard dose PSL treatment, referring to the results of conventional PSL treatment in the above mentioned prospective comparative study, retrospective observational research, etc.. However, the proportion of CR+R was 60.9% (14/23) with 41.7-77.8% of 90% CI. In this test result, the usefulness of the HDD could not be shown.

In this trial, HDD and *H.pylori* eradication were performed simultaneously, but no additional safety issue was observed against the HDD alone. CR+R rates at 180 days after the end of treatment was 80% in patients with HDD and *H.pylori* eradication (median age of 74 years and

median platelet count of 12 $\times 10^9$/L), which is a very good result for the severe ITP cases. On the other hand, in cases without eradication, CR+R rate at 180 days was 55.6%. Considering the background of the cases (median age of 59 years and median platelet count of 7 $\times 10^9$/L), the results didn't show lower effectiveness than previous reports.

Six randomized controlled trials of the eradication group and the control group have been reported [17–22]. Among them, two studies for adults are for cases with moderate ITP with a platelet count 30×10^9/L or more and reported CR+R rate as 46.2% [17] and 66.7% [18], relapse rate at 1 year was 33.3% [18]. In our study, more severe ITP cases were enrolled, and the response rate was expected to be lower with *H.pylori* eradication alone. Although patient number is relatively low, these results suggest that this treatment is safe and effective for the *H.pylori*-positive, naive severe ITP patients, from the viewpoint of initial treatment response and long-term effects.

At the time of diagnosis, plasma thrombopoietin (TPO) concentration was measured in 22 of 23 cases, and there were no cases showing abnormally high levels exceeding 300 pg/ml. The thrombopoietin level remains at a mild rise below 300 pg/ml from normal in ITP cases, this result supports that enrolled patients are not thrombocytopenia other than ITP [23]. In this study, the correlation between the plasma TPO concentration at diagnosis and the treatment response of HDD was not observed. Similarly, in treatment of thrombopoietin agonists, it has been reported that there is a correlation between the plasma TPO concentration before treatment and the treatment efficacy [15].

We showed the efficacy and safety of HDD for Japanese patients for the first time. As an initial treatment for ITP, development of a combination drug therapy aiming at prolongation of

treatment-free survival is in progress. So far, the efficacy of dexamethasone high-dose therapy in combination with rituximab and cyclosporine [24] and in combination with eltrombopag [25] has been reported. The results of this study will provide the base data when the study protocol is developed using HDD with rituximab or TPO agonist in Japan.

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Conflict of interest

HN reports grants and personal fees from Janssen Pharmaceutical K. K., Mundipharma K.K., Celgene Corporation, Bayer Yakuhin Ltd., Takeda Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Esai Co., Ltd., Bristol-Myers Squibb, Ono Pharmaceutical Co., Ltd., Gilead Sciences Inc., Zenyaku Kogyo Co., Ltd., AstraZeneca plc., and SymBio Pharmaceuticals Limited, outside the submitted work; grants from Abbvie G.K., Solasia Pharma K.K., HUYA Bioscience International, Otsuka Pharmaceutical Co., Ltd., and IQVIA service Japan K.K., outside the submitted work ; personal fees from Roche Ltd., Sanofi K.K., outside the submitted work. HY reports grants from Astellas, outside the submitted work. AK reports personal fees from Bayer Yakuhin, Ltd. for a member of independent data monitoring committee of clinical trials, outside the submitted work. All other authors have nothing to disclose.

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Author's contribution

KT designed this study and drafted this article. AMS performed data management and monitoring of this study. AK was responsible for the statistical analysis. KT, HN, MK, TY, NY, YH, TI, MS, AY, SY, IT, MO, YS, MH, IY, HY, HI, HI, MN, TH, HI and YK have contributed to data collection and interpretation. All authors wrote and approved the manuscript. KT and HN contributed equally to this study.

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Figure Legends

Figure 1. Flowchart

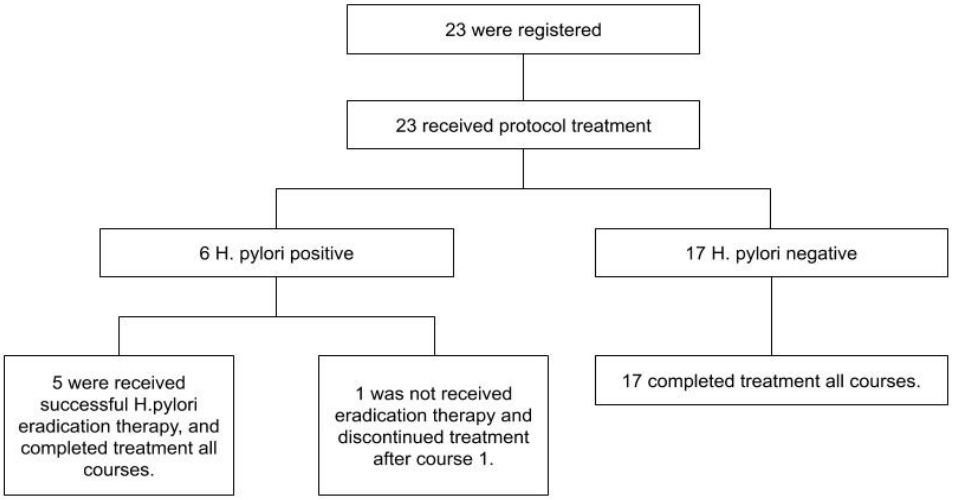
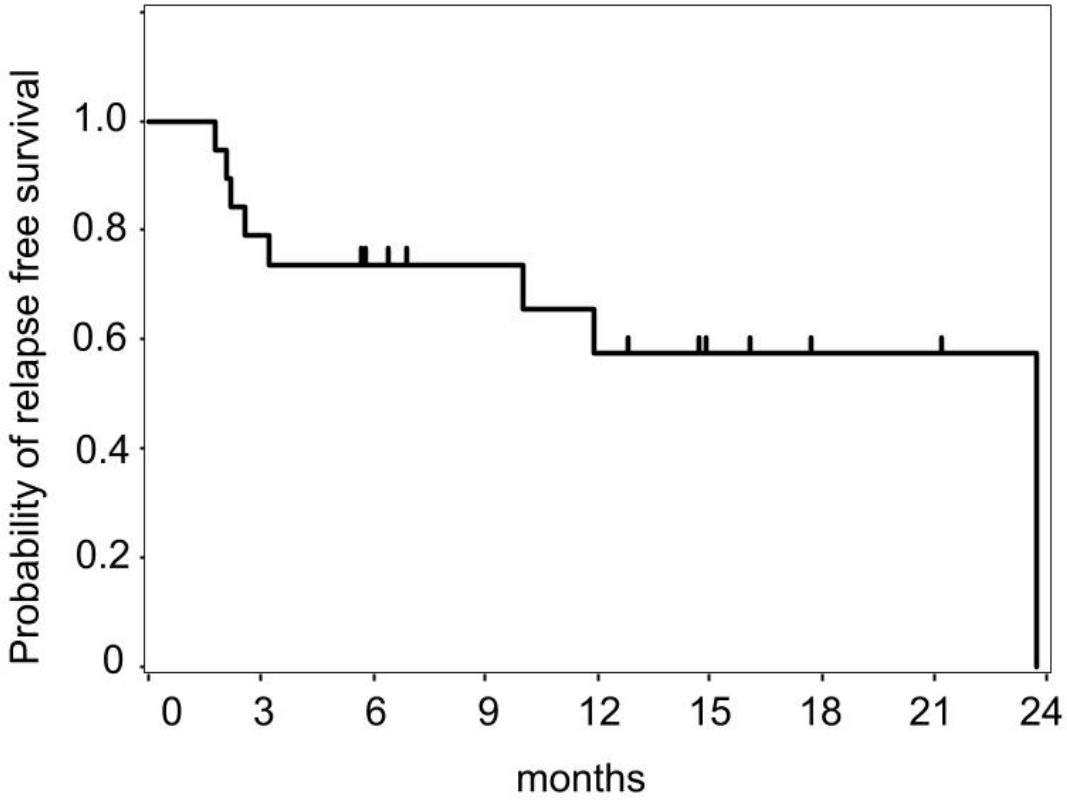


Figure 2. Kaplan-Meier curve for relapse free survival



Tables

Table 1 Patient characteristics

	(n=23)
Male, n(%)	5 (21.7)
Age, median,(range)	63 (18-80)
Platelet counts ($\times 10^9$ / L), median (range)	7 (0.0-40.0)
Bleeding score, n(%)	
3	2 (8.7)
4	20 (87.0)
5	1 (4.3)
PA-IgG (ng/10^7 cells), median(range)	297 (71-1820)
Thrombopoietin concentration (pg/mL), median(range) (n=22)*	54.4 (14.2-153.9)
Antinuclear antibody positive, median(range)	7 (30.4)
H.pylori positive, median(range)	6 (26.1)
Anti-cardiolipin antibody positive, median(range), (n=22)*	2 (8.7)
History of *H.pylori* eradication, median(range)	2 (8.7)

*: It was not investigated for one patient.

Table 2 Response at 46+180 days

	CR n(%)	R n(%)	NR n(%)	Other n(%)	CR+R(%) n(%)	90%CI
Total	12(52.2)	2(8.7)	2(8.7)	7(30.4)	14(60.9)	41.7-77.8
H. pylori						
-	9(52.9)	1(5.9)	2(11.8)	5(29.4)	10(58.8)	-
+, eradication therapy success	3(60.0)	1(20.0)	0(0.0)	1(20.0)	4(80.0)	-
+, eradication therapy not received	0(0.0)	0(0.0)	0(0.0)	1(100)	0(0.0)	-

Table 3 Adverse event until 46 + 180 days by eradication

	eradication		All
	no	yes	
	(N=18)	(N=5)	(N=23)
Bacterial infection			
Prostate infection (grade 4)	0	1	1
Bronchial infection (grade 3)	1	0	1
Virus infection			
Skin infection (grade 2)	0	1	1
AST increased (grade 1)	2	0	2
ALT increased (grade 1)	4	0	4
ALP increased (grade 1)	1	0	1
Bilirubin increased (grade 1)	1	1	2
Fracture (grade 2)*	0	1	1

*: Causal relationship with the underlying disease osteoporosis

Table 4 Response at 46 + 180 days by factors

	CR n(%)	R n(%)	NR n(%)	Other n(%)	CR+PR n(%)	OR (95%CI)
Platelet count						
$<10 \times 10^9$ / L	8(66.7)	0(0.0)	0(0.0)	4(33.3)	8(66.7)	1.67(0.31-9.01)
$\geq 10 \times 10^9$ / L	4(36.4)	2(18.2)	2(18.2)	3(27.3)	6(45.5)	-
Bleeding score						
4,5	11(52.4)	2(9.5)	2(9.5)	6(28.6)	13(61.9)	1.63(0.09-29.78)
3	1(50.0)	0(0.0)	0(0.0)	1(50.0)	1(50.0)	-
Age						
65-	6(54.5)	1(9.1)	0(0.0)	4(36.4)	7(63.6)	1.25(0.23-6.72)
-64	6(50.0)	1(8.3)	2(16.7)	3(25.0)	7(58.3)	-
Thrombopoietin concentration(pg/mL)						
<136	10(50.0)	2(10.0)	1(5.0)	7(35.0)	12(60.0)	*
≥136	2(100)	0	0	0	2(100)	-

*: not calculated

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