Original research papers

Impact of histamine type-2 receptor antagonists on the anticancer efficacy of gefitinib in patients with non-small cell lung cancer

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ABSTRACT

Purpose

Gefitinib is one of the standard treatments for non-small cell lung cancer (NSCLC) with epidermal growth factor receptor mutations. It has been reported that acid suppressants (AS) decrease the anti-tumor effect of gefitinib by reducing its solubility. AS is sometimes necessary in cancer patients; however, previous reports have not shown the most compatible AS with gefitinib administration in cancer patients. This study was conducted to determine if histamine type-2 receptor antagonists (H2RA) can affect the anti-tumor efficacy of gefitinib.

Methods

Eighty-seven patients with NSCLC who were administered gefitinib were retrospectively investigated. Patients who were co-administered H2RA were compared with non-AS control patients. H2RA was administered once a day at about 3–5 or 8–12 h after gefitinib intake. The primary endpoint of this study was progression-free survival (PFS), and secondary endpoints were overall survival (OS), overall response rate (ORR), and adverse effects.

Results

Median PFS in H2RA group and control group was 8.0 months and 9.0 months,

respectively, with no significant difference (p = 0.82). The incidence of liver dysfunction was significantly less in patients administered H2RA, whereas there were no differences between the two groups with regards to skin toxicity and diarrhea. Multivariate analysis suggested that H2RA co-administration is not a risk factor for worse PFS and OS (hazard ratio of 0.95, 0.86; 95 % confidence interval of 0.60–1.48, 0.52–1.43; p = 0.82 and 0.60, respectively).

Conclusion

This study demonstrated that concomitant administration of H2RA with gefitinib does not affect the efficacy of gefitinib.

Keywords: gefitinib; histamine type-2 receptor antagonists (H2RA); acid suppressants (AS); antacids; EGFR; non-small cell lung cancer

Background

Gefitinib is one of the most prescribed epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in patients with non-small cell lung cancer (NSCLC) [1, 2]. It has been reported that these medicines are more effective than cytotoxic anti-cancer agents in patients with EGFR mutations [1, 2]. EGFR mutations are present in approximately 40–50 percent of lung adenocarcinoma in Japan [3, 4].

Body surface area (BSA) could cause reduced therapeutic response in gefitinib therapy, although previous reports on this have been inconclusive. [5-8]. As the dose of gefitinib is fixed at 250 mg per day, it is likely that the plasma drug level may affect its efficacy.

Acid suppressants (AS) such as proton pump inhibitors (PPI) and histamine type-2 receptor antagonists (H2RA) are prescribed to 33.2–46.3 % of patients with lung cancer [9], causing the intragastric pH to increase from 1 to 4 [10]. A study reported that the blood concentration of gefitinib was reduced by the co-administration of AS; the oral administration of 450 mg ranitidine 13 h and 1 h before a single dose of 250 mg gefitinib to achieve gastric pH > 5 in healthy volunteers resulted in a decrease in area under the concentration-time curve (AUC) and C_{max} by 44 % and 70 %, respectively [11]. It has also been reported that the anti-tumor efficacy of erlotinib is affected by the

co-administration of AS [12]. Moreover, other studies have shown that AS, although not significantly, tends to reduce the anti-tumor effect of EGFR-TKIs [13-15]. PPI has a longer suppressing effect (~24 h) than H2RA (~12 h) [10]; therefore, beside the interval between AS administration and gefitinib intake, the type of AS is another important factor that can influence the efficacy of gefitinib. However, AS definition included both PPI and H2RA, and the co-administration period was defined to be more than 30 % in these reports. Considering these points, the results are still controversial.

In Hokkaido University Hospital, PPI was changed to H2RA as much as possible and the administration time was moved as far away as possible from the administration time of gefitinib in consideration of the blood level of gefitinib.

In this study, we evaluated H2RA influence on the anti-tumor effect of gefitinib and its typical adverse effects such as liver dysfunction, skin disorders (rash, cutaneous dryness, and perionychia), and diarrhea.

Methods

1. Patients

Patients with NSCLC who were administered gefitinib (250 mg per day) from March 2005 to December 2014 were enrolled in this retrospective study. The patients were

divided into two groups: a control group without AS administration from March 2005 to December 2014 and an H2RA group with concurrent administration of gefitinib and H2RA from September 2007 to June 2014. Patients in the H2RA group were educated to take H2RA once a day at 3–5 or 8–12 h after gefitinib administration.

All enrolled patients met the following criteria: (1) aged ≥ 20 years; (2) gefitinib-administration naive; (3) detailed patient information available from medical records; (4) performance status of 0–2; and (5) adequate liver and renal function. Patients whose detailed information on EGFR mutation and co-administered drugs were unavailable, who were co-administered PPI and/or other chemotherapeutic agents other than gefitinib were excluded from the study.

The present study was approved by the Institutional Review Board of the Hokkaido University Hospital (approval number: 019-0226), and was carried out in accordance with the Declaration of Helsinki, and STROBE statement. In view of the retrospective nature of the study, informed consent from the subjects was not necessary.

2. Evaluation of the efficacy and adverse effects of gefitinib

Patient information was obtained from their medical records. The progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and safety of gefitinib treatment were determined. The primary endpoint was PFS, and the secondary

endpoints were OS, ORR, and the adverse effects. OS was calculated from the date of initial treatment of gefitinib until death from any cause or the last follow-up. PFS was defined as the initiation of gefitinib administration until disease progression, death, or the last follow-up. Tumor response was classified as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE), according to the Response Evaluation Criteria in Solid Tumors (version 1.1). Adverse effects caused by gefitinib during the administration period were evaluated in accordance with the Common Terminology Criteria for Adverse Events (version 4.0).

3. Statistical Analysis

The differences in the baseline clinical characteristics between the control and H2RA groups were assessed using Fisher's exact probability test for categorical outcome variables and the Mann-Whitney *U* test for continuous parameters. PFS and OS were analyzed in an intention-to-treat fashion using the Kaplan-Meier method, and the differences between the two groups were compared using the log-rank test. The incidence of adverse effects such as skin toxicity, diarrhea, liver dysfunction, and ORR in the two groups was assessed using Fisher's exact probability test. Univariate and multivariate Cox proportional hazards regression was used to adjust for the effect of H2RA therapy for other clinical variables, including sex, age, BSA, performance status

(PS), smoking history, EGFR mutation status, clinical stage, histology, prior chemotherapy, liver dysfunction (grade 1 or higher of aspartate aminotransferase, alanine aminotransferase, or γ-glutamyl transferase elevation). Variables that showed a significant association in the univariate analysis were considered when building the multivariable model.

All analyses were carried out using JMP version 14.0 statistical software (SAS Institute Inc.). A p value < 0.05 indicated a statistically significant difference.

Results

1. Patient characteristics

A total of 87 patients, with 56 patients in the control group and 31 patients in the H2RA group, were enrolled (Fig. 1). Baseline patient characteristics are shown in Table 1. There were no differences between the groups with regards to sex, age, staging, EGFR mutation status, histology, performance status (PS, ECOG), BSA, smoking history, prior chemotherapy, liver dysfunction (grade 1 or higher aspartate aminotransferase or alanine aminotransferase or γ-glutamyltransferase elevation), and serum creatinine level. The details of concomitant H2RA are shown in Table 2. All patients were administered 10–40 mg famotidine per day.

2. Treatment efficacy

Figure 2 shows Kaplan-Meier plots of PFS and OS of gefitinib treatment. Median PFS in the H2RA group and the control group was 8.0 months (95 % confidence interval (CI), 3.5–13.3 months) and 9.0 months (95 % CI, 7.4–9.8 months; p = 0 .82), respectively, which were not significantly different. Median OS in H2RA group was 29.6 months (95 % CI, 11.3–42.3 months), which was also similar to that in the control group (25.5 months; 95 % CI, 17.4–32.7 months; p = 0.60). The ORR in the H2RA group and that in the control group were also similar (50.0 % vs. 59.3 %, p = 0.48) (supplemental Table 1).

3. Adverse effects

Table 3 shows the adverse effects caused by gefitinib administration. The frequency of skin toxicity tended to be higher in the control group and diarrhea tended to appear more in the H2RA group, without any significant difference. On the other hand, the frequency of all and severe grade of liver dysfunction was significantly less in the H2RA group. We also observed that 28.6 % of the control patients and 25.8 % of patients administered H2RA needed dose reduction (extension of dose interval) due to adverse effects (p = 1.00), and 28.6 % in the control group and 38.7 % in the H2RA group required temporary drug withdrawal (p = 0.35).

4. Association between gefitinib progression-free survival (PFS), overall survival (OS), and histamine type-2 receptor antagonists (H2RA) co-administration

We evaluated the association between patient factors and PFS as well as OS (Table 4). It was suggested that H2RA administration did not affect PFS and OS. In addition, gefitinib administration as well as male sex, poor PS, and primary onset were associated with worse PFS or OS.

Discussion

Chemotherapeutic agents such as molecular target drugs and immune checkpoint inhibitors (ICIs) have been widely developed with advances in anti-cancer therapy, and the use of oral medicines have increased. In pharmacotherapy, drug-drug interactions could pose more problems with oral medicines than with injection drugs. Cancer patients tend to take many drugs due to complications, symptom relief, and supportive care. AS are one of the most prescribed medicines in patients with cancer; however, they can interact with many drugs including anti-cancer agents during absorption, metabolism, and excretion [16-19]. It has been reported that the degree of gefitinib solubility significantly decreases with increase in gastric pH [20]. It has also been shown that the plasma concentration of gefitinib in patients who were co-administered

H2RA twice daily is lower than that in those without H2RA administration [11]. Nakamura et al. reported a relationship between the blood trough level of gefitinib and PFS in patients with advanced NSCLC [21]. Moreover, it has been controversially suggested that the co-administration of AS longer than the defined period of time could reduce EGFR-TKI efficacy, although the optimal time interval and usage are unknown [12-15].

We evaluated the influence of H2RA co-administration at longer intervals from gefitinib intake on its efficacy.

The result showed that PFS, which was defined as the primary endpoint of this study, was not different between patients co-administered H2RA and those in the control group who were not administered AS. In addition, OS and ORR of the two groups were also similar. To the best of our knowledge, this is the first report evaluating the impact of H2RA co-administration on the anti-tumor efficacy of gefitinib monotherapy.

It has been shown that the plasma concentration of gefitinib with H2RA administration twice daily is lower than in patients who have not been administered H2RA [22]. It has also been suggested that the gastric acid suppression effect of H2RA is generally short-term [10], and hence, it is reasonable to administer gefitinib away from H2RA. In this study, H2RA was administered 3–5 h after gefitinib administration in some patients

considering the anacidity or duration of action. The results of the different H2RA usages did not differ (data not shown), and hence, both administration times of H2RA should be acceptable. The results obtained in this study could also provide a reference for the appropriate administration of erlotinib and dacomitinib, which can also be influenced by AS [12, 23].

In previous studies, larger BSA, male sex, primary onset, poor PS, smoking history, non-adenocarcinoma were suggested as risk factors for worse PFS and/or OS [5-8]. The risk factors in this study were similar to those in previous studies, although these reports did not consider the concomitant administration of AS, especially PPI, with gefitinib.

We also evaluated the typical adverse effects caused by gefitinib, such as liver dysfunction, skin toxicity, and diarrhea. Surprisingly, we observed that the frequency and severity of liver dysfunction were significantly less in the H2RA group than in the control group. It has been reported that gefitinib is imported to the liver by organic anion transporting polypeptide (OATP) 2B1 and exported by p-glycoprotein, breast cancer resistance protein (BCRP) [24-26]. It is unknown if H2RA or symptoms which need antacid treatment can affect the regulation or function of these transporters; however, it is possible. We consider that multiple contributing factors, including prior chemotherapy, other co-administered drugs, drug-drug interactions, early administration

of liver supporting medicines, patient's genetic background (such as OATP2B1 or p-glycoprotein, BCRP), patient's background (such as age or lifestyle habits), infection, anti-tumor effect on liver metastasis, in addition to direct H2RA effects on the transporters, might have caused the results; however, they were obtained as a secondary endpoint, and further studies are necessary. In contrast, diarrhea appeared more frequently in the H2RA group, presumably due to dyspepsia by the antacid effect. Diarrhea might cause hypoalbuminemia, hypokalemia, dehydration, and edema, and also decrease drug and nutrition absorption. We should be able to predict its occurrence when gefitinib is co-administered with H2RA.

It has been recognized that citrus or healthy foods which contain rich furanocoumarins inhibit the metabolism of CYP3A4 substrates [11]. If patients consume these foods, food–drug interaction increases the blood concentration level of gefitinib. In addition, it has also been reported that smoking induces CYP1A2 expression, resulting in a reduction in the blood concentration level of erlotinib [27]. Therefore, caution should be taken not only with co-administered medicines but also with regards to lifestyle and habits, and patients should be educated on drug interactions for effective and safe administration of oral anti-cancer agents.

Three patients administered H2RA experienced gastrointestinal dysfunction and changed to PPI, resulting in their exclusion from this study. Digestive symptoms sometimes occur in cancer patients especially those taking non-steroidal anti-inflammatory drugs, and gastric mucosa-protective drugs or misoprostol could be the choices in these cases. If the symptoms are severe, it would be temporarily necessary to change from H2RA to PPI in addition to these medicines, and it could be better to monitor the blood concentration level of gefitinib.

There were some limitations regarding the evaluation of H2RA co-administration on the efficacy of gefitinib. First, this study was retrospective, used a relatively small population of patients, and was conducted at a single institution. Therefore, it is necessary to conduct a large-scale randomized prospective multicenter study to confirm these results and evaluate them thoroughly, especially regarding the secondary endpoints. Second, the retrospective nature of this study indicates uncertainty with regards to the oral intake of the study drugs. Third, we did not evaluate the blood concentration level of gefitinib, unknown factors such as drug–drug interaction or patient background which changes its pharmacokinetics might have affected the results. Fourth, patients in this study were not administered ICIs, and results of the treatment efficacy and safety might differ from the ones when patients were administered ICIs.

Finally, administration doses and times of famotidine were not consistently the same, which could have affected the results. Famotidine plasma levels at the administration times of gefitinib should have been measured for better assessment.

Conclusions

In conclusion, the results of this study indicate that the concomitant administration of H2RA does not affect the efficacy of gefitinib. Further studies by reference to our study regarding other EGFR TKIs, such as erlotinib and dacomitinib, will offer further advances in cancer management.

Declarations

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interest: YS, MK, YT, NS, YS, IK, KI, MS have no conflicts of interest. HD received an honorarium from AstraZeneca for speaking at a symposium.

Ethics approval and consent to participate: All the procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki

declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions:

Designed study: Y.S., Y.T., M.K., N.S., Y.S., I.K., H.D., K.I., and M.S.

Performed research: Y.S.

Analyzed data: Y.S., Y.T., M.K.

Contributed new methods or models: Y.S., Y.T., M.K.

Wrote the paper: Y.S.

All authors have read and approved the manuscript.

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Table 1. Patient characteristics

	Control group (n = 56)	H2RA group (n = 31)	*p* value
Sex (Male/Female)	21/35	18/13	0.08
Median age (range)	64 (51–82)	61 (37–87)	0.16
Staging			
Recurrence	14	10	
Others	42	21	0.47
EGFR mutation status			
Exon 19 deletion	26	17	
Exon 21 L858R	29	14	
Others	1	0	0.78
Histology			
Adenocarcinoma	53	31	
Others	3	0	0.55
Performance status			
0-1	47	26	
2-3	9	5	1.00
BSA (m^2)			
< 1.5	23	8	
≥ 1.5	33	23	0.17
Smoking history			
Current, former-smoker	26	20	
Never smoker	30	11	0.12
Prior chemotherapy			
0	42	20	
≥ 1	14	11	0.33
Liver dysfunction			
Present	15	13	
Absent	41	18	0.16
Serum creatinine			
Median (range)	0.69 (0.40–1.60)	0.70 (0.43–2.13)	0.86

EGFR: epidermal growth factor receptor, BSA: body surface area

Table 2. Characteristics of H2RA administration

	Number of the patients (n = 31)
Famotidine 10 mg, after 3–5 hours from gefitinib administration	1
Famotidine 20 mg, after 3–5 hours from gefitinib administration	9
Famotidine 20 mg, after 8–12 hours from gefitinib administration	8
Famotidine 40 mg, after 3–5 hours from gefitinib administration	13

Table 3. Adverse effects during gefitinib administration period

	Control group (n = 56)	H2RA group (n = 31)	*p* value
Skin toxicity			
All grade	44	20	0.21
Grade 3/4	4	2	1.00
Diarrhea			
All grade	14	14	0.06
Grade 3/4	0	0	-
Liver dysfunction			
All grade	27	4	0.001
Grade 3/4	10	0	0.01

Liver dysfunction was defined as grade 1 or higher of aspartate aminotransferase, alanine aminotransferase, or γ-glutamyl transferase elevation.

Table 4. Univariate and multivariate analyses of variable assessing for impact on PFS and OS

	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Sex								
male/female	1.77 (1.14–2.73)	0.01*	1.94 (1.24–3.82)	< 0.01**	2.09 (1.27–3.40)	< 0.01**	1.88 (1.04–3.51)	0.03*
Age (years)								
≥ 65/< 65	1.24 (0.80–1.91)	0.33	Excluded	-	0.94 (0.58–1.52)	0.81	Excluded	-
BSA (m^2)								
≥ 1.5/< 1.5	1.11 (0.72–1.75)	0.64	Excluded	-	1.68 (1.02–2.84)	0.04*	1.65 (0.83–3.24)	0.15
PS								
2 or more/0-1	2.26 (1.20–3.98)	0.01*	2.59 (1.36–4.64)	< 0.01**	3.38 (1.68–6.31)	< 0.01**	4.83 (2.30–9.57)	< 0.01**
Smoking history								
Yes/No	1.23 (0.80–1.90)	0.35	Excluded	-	1.35 (0.84–2.17)	0.21	Excluded	-
EGFR mutation status								
L858R/Exon19 deletions	0.98 (0.63–1.52)	0.93	Excluded	-	1.28 (0.80–2.06)	0.30	Excluded	-
Clinical stage								
Recurrence/IIIB or IV	0.53 (0.31–0.87)	0.01*	0.54 (0.32–0.89)	0.01*	0.51 (0.28–0.87)	0.01*	0.45 (0.24–0.79)	< 0.01**
Histology								
Ad/Non-Ad	1.19 (0.44–4.87)	0.76	Excluded	-	0.71 (0.26–2.93)	0.59	Excluded	-
Prior chemotherapy								
Present/Absent	1.02 (0.62–1.62)	0.94	Excluded	-	1.19 (0.69–1.98)	0.51	Excluded	-

Liver dysfunction								
Present/Absent	1.32 (0.82–2.07)	0.24	Excluded	-	0.84 (0.48–1.40)	0.51	Excluded	-
H2RA co-administration								
Yes/No	0.95 (0.60–1.48)	0.82	Excluded	-	0.86 (0.52–1.43)	0.60	Excluded	-

Univariate and multivariate Cox proportional hazards regression was used to adjust for the effect of H2RA therapy for other clinical variables, including sex, age, body surface area (BSA), performance status (PS), smoking history, EGFR mutation status, clinical stage, histology, prior chemotherapy, liver dysfunction (grade 1 or higher of aspartate aminotransferase, alanine aminotransferase, or γ-glutamyl transferase elevation). Variables that showed a significant association in the univariate analysis were considered when building the multivariable model.

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; BSA, body surface area; PS, performance status; EGFR, epidermal growth factor receptor; H2RA, histamine type-2 receptor antagonists

*: $p < 0.05$, **: $p < 0.01$

Supplemental Table 1. Overall response rate

	Control group (n = 56)	H2RA group (n = 31)	*p* value
CR	1	1	
PR	31	12	
SD	19	7	
PD	3	6	
NE	2	5	
Response rate	59.3 %	50.0 %	0.48

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease;

NE, not evaluable

Figure 1

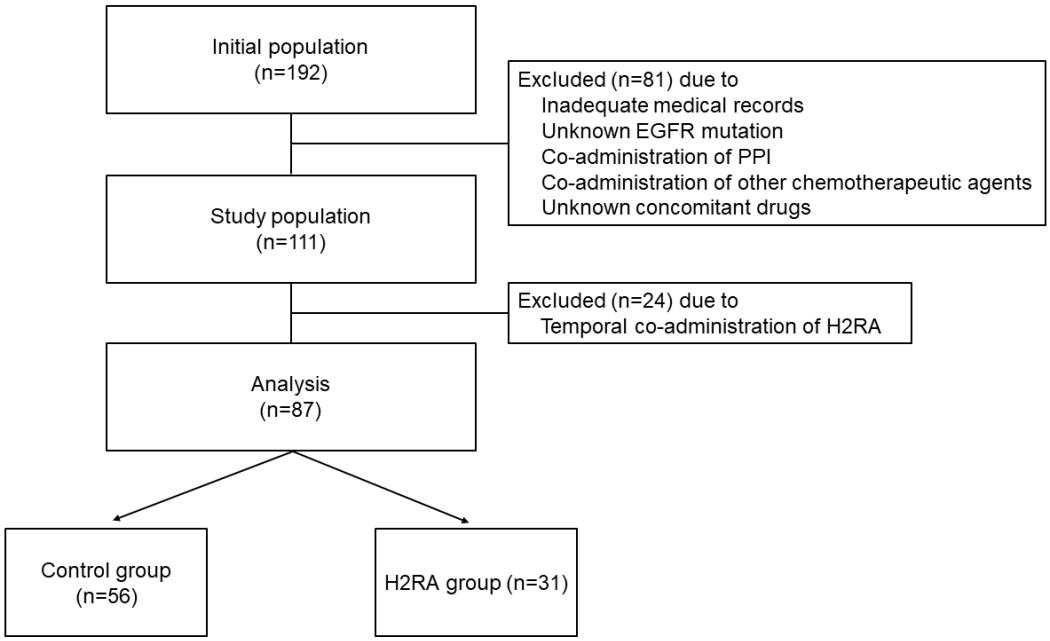

Fig. 1 Consort diagram of this study

Figure 2A

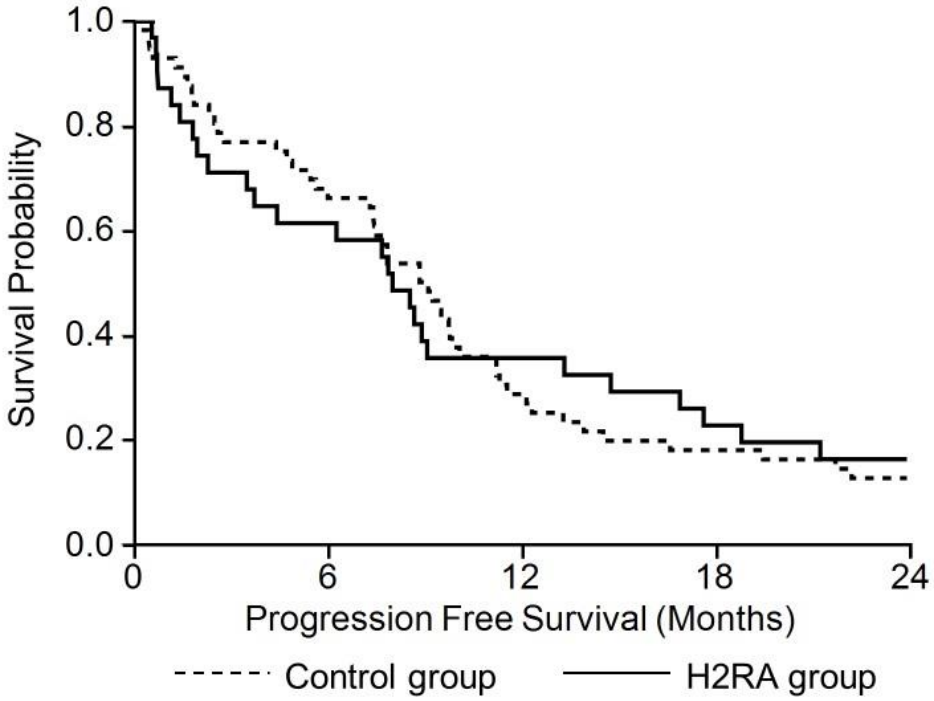

Figure 2B

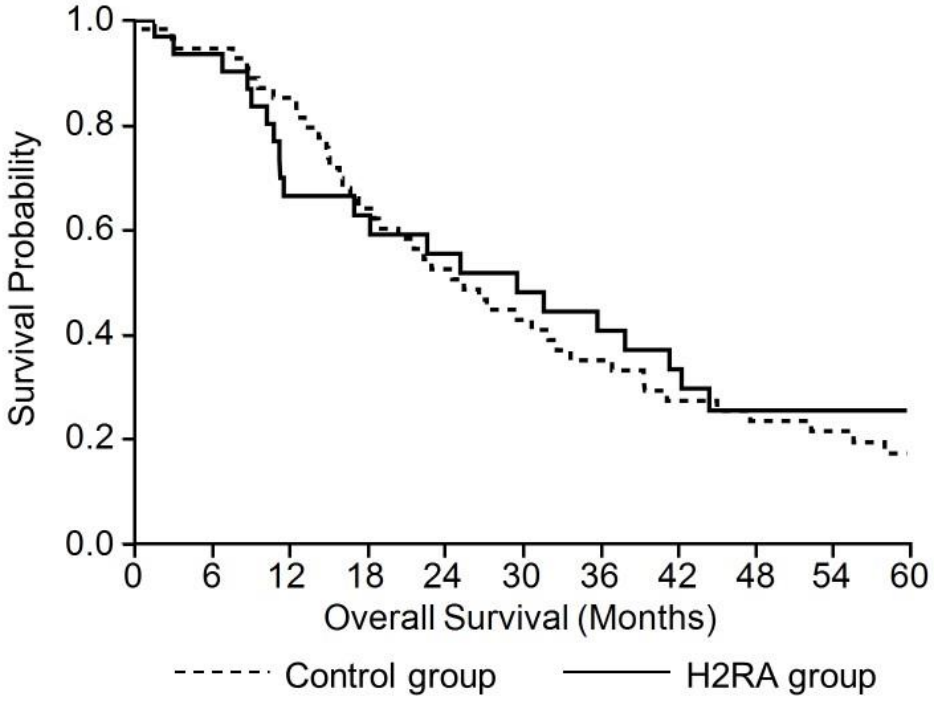

Fig. 2 Kaplan-Meier survival curves of (A) progression-free survival and (B) overall survival