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ARTICLE

Clinical Study

The added value of H_2 antagonists in premedication regimens during paclitaxel treatment

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BACKGROUND: Ranitidine, a histamine 2 blocker, is the standard of care to prevent hypersensitivity reactions (HSRs) caused by paclitaxel infusion. However, the added value of ranitidine in this premedication regimen is controversial. Therefore, we compared the incidence of HSRs during paclitaxel treatment between a standard regimen including ranitidine and a regimen without ranitidine.

METHODS: This prospective, pre–post interventional, non-inferiority study compared the standard premedication regimen ($N = 183$) with dexamethasone, clemastine and ranitidine with a premedication regimen without ranitidine ($N = 183$). The primary outcome was the incidence of HSR grade ≥3. Non-inferiority was determined by checking whether the upper bound of the two-sided 90% confidence interval (CI) for the difference in HSR rates excluded the +6% non-inferiority margin.

RESULTS: In both the pre-intervention (with ranitidine) and post-intervention (without ranitidine) group 183 patients were included. The incidence of HSR grade ≥3 was 4.4% ($N = 8$) in the pre-intervention group and 1.6% ($N = 3$) in the post-intervention group: difference −2.7% (90% CI: −6.2 to 0.1).

CONCLUSIONS: As the upper boundary of the 90% CI does not exceed the predefined non-inferiority margin of +6%, it can be concluded that a premedication regimen without ranitidine is non-inferior to a premedication regimen with ranitidine.

CLINICAL TRIAL REGISTRATION: www.trialregister.nl; NL8173.

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BACKGROUND

Paclitaxel is one of the most commonly used anti-cancer drugs worldwide. It is effective for the treatment of several malignancies, including breast, lung, ovarian, head and neck, and oesophageal cancer. However, due to its hydrophobic properties, paclitaxel must be emulsified in Cremophor-EL (polyethoxylated castor oil and ethanol), which frequently leads to hypersensitivity reactions (HSRs) during paclitaxel infusion.[1] HSRs during paclitaxel infusion can range from mild erythematous rashes to life-threatening anaphylaxis.[2] To prevent HSRs, premedication regimens were introduced as the standard of care during paclitaxel treatment and generally consists of the corticosteroid dexamethasone combined with a histamine 1 (H_1) receptor antagonist (e.g. clemastine or diphenhydramine) and the histamine 2 (H_2) receptor antagonist ranitidine.[3,4] Without premedication regimens, HSRs were seen in 25–42% of all patients using paclitaxel.[5,6] Since the introduction of premedication regimens as the standard of care, the incidence of HSRs during paclitaxel infusion was significantly decreased, but nevertheless occur in ~20% of all patients in the range from mild to death. Severe HSRs during paclitaxel infusion, defined as grade ≥3 (as per Common Terminology Criteria for Adverse Events; CTCAE version 4.03) occur in ~4% of all patients despite premedication.[7–12] In addition, studies show that ~97% of all HSRs present within the first 10 min from the start of infusion during the first or second paclitaxel cycle.[12–15]

Ranitidine is primarily registered for the treatment of gastroduodenal reflux and ulcer disease. The use of an H_2 antagonist in the standard of care premedication regimen for paclitaxel was based on the standard regimen used for preventing HSRs during the use of urographic radiocontrast media.[16] It was believed that blockade of both the H_1 and the H_2 receptors decreased the proportion of patients who experienced an allergic reaction. However, the efficacy in preventing paclitaxel-associated HSRs has never been thoroughly studied and is therefore controversial. The use of an H_2 antagonist (cimetidine) during paclitaxel infusions was first described during a phase 1 trial by Wiernik et al.,[17] but the efficacy in the prevention of HSRs was not assessed. Moreover, it has been shown that cimetidine or ranitidine is not effective in the prevention of HSRs.[18–20] In addition, earlier reports showed that ranitidine itself can cause side effects such as abnormal liver enzyme levels, nausea, vomiting, skin rash and HSRs. Ranitidine-induced HSRs occur in 0.7% of all ranitidine infusions.[21,22] Despite these findings the use of an H_2 antagonist during paclitaxel infusion is still recommended as standard premedication to

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prevent paclitaxel-induced HSRs. Therefore, we aimed to determine the added value of ranitidine in preventing clinically relevant HSRs by comparing the standard premedication regimen with ranitidine to an experimental premedication regimen without ranitidine.

METHODS

Study design

A single-centre, prospective, pre–post interventional, non-inferiority study was conducted at the Erasmus MC Cancer Institute in Rotterdam, the Netherlands. All paclitaxel-naive patients aged ≥18 years within the outpatient department who planned to receive their first cycle of paclitaxel for systemic cancer treatment were enrolled in the study. From October 2018 until 19 April 2019, patients received a premedication regimen with ranitidine. Between 19 April 2019 and December 2019, a second group of patients was included; they received a premedication regimen without ranitidine. Paclitaxel could be part of a combination regimen or given as monotherapy in either a weekly or 3-weekly cycle.

The standard premedication regimen with ranitidine was compared to an experimental premedication regimen without ranitidine. Patients in the pre-intervention group received the standard premedication regimen consisting of dexamethasone (10 mg intravenously (IV)), clemastine (2 mg IV) and ranitidine (50 mg IV). Patients in the post-interventional group received the experimental premedication regimen without the H_2 antagonist ranitidine. Patients in both groups were followed for a minimum of two cycles and a maximum of six cycles of paclitaxel infusions if no HSR would occur or until the occurrence of the first HSR within the first six cycles. During each infusion of paclitaxel, the occurrence of HSRs, defined as an immunological response to paclitaxel corresponding with CTCAE grade from 1 (minimal) to 5 (death), version 4.03, was registered.[7] In case an HSR occurred, patients were treated according to local standards. The primary endpoint was the incidence of HSRs grade ≥3 during paclitaxel treatment.

Secondary objectives were to determine and compare the severity (any grade) of paclitaxel-induced HSR; to determine the number of paclitaxel dosages until the first HSR occurrence (any grade) and to determine the cumulative dose of paclitaxel at the moment of HSR occurrence, all with and without ranitidine. All included patients gave informed consent. The study was approved by the medical ethical board of the Erasmus MC and registered at the Dutch trial registry (www.trialregister.nl; number NL8173).

Statistical analysis

Considering previous studies, 4% of all patients in both treatment groups were expected to experience an HSR grade ≥3.[8,10,11,13] A non-inferiority margin of the difference between the incidence was set at 6% (the HSR rates in the group without ranitidine should be no worse than 6% more than the rate in the group receiving ranitidine). A sample size of 366 (thus 183 patients per group) would be sufficient to confer 90% power at the one-sided significance level of 0.05 using a binomial test.[23]

A closed test procedure was applied to the primary outcome. First, the incidence of patients who experienced an HSR grade ≥3 for both groups, the difference between these incidences and the associated two-sided 90% confidence interval (CI) for the difference was estimated. Non-inferiority of leaving out ranitidine compared to treatment with ranitidine was accepted if the upper bound of the two-sided 90% CI (equal to one-sided 95% CI) around the estimated difference in the primary endpoint lied <6%. Similar analyses were performed for any grade HSR. Furthermore, for both clinically relevant, defined as CTCAE grade ≥3, and any grade HSRs univariate and multivariate logistic regression analysis were considered if the number of events was sufficient to perform multivariate analyses (i.e. if at least 20 events (HSRs) had occurred). If possible, variables that were significant in the univariate analysis were considered for the multivariate analysis. In addition, the severity of paclitaxel-induced HSR was tabulated by study period and the exact χ^2 test for trend was used to compare study periods. The mean cumulative dose of paclitaxel received was computed for the cycles that were given before the one where HSR emerged and divided over the body surface, shown per group and per HSR grade. Data were analysed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp, Armonk, NY) and R.[24]

RESULTS

Of 366 included patients, 183 patients received ranitidine (pre-intervention) as part of their paclitaxel premedication regimen and 183 patients did not receive ranitidine (post-intervention). The median age was 61 years (range 26–86 years) and 60.4% of all patients were women (Table 1). Most patients were diagnosed with oesophageal (42.1%), breast (32.5%), lung (8.7%) and uterine cervical cancer (7.9%). Of all patients, 18.6% had ≥1 previously registered (non-paclitaxel) medication allergy before entering the study.

Clinically relevant HSR grade ≥3 occurred in eight patients (4.4%) in the pre-interventional group with ranitidine compared to three patients (1.6%) in the post-interventional group without ranitidine (Table 2). The absolute risk difference between the two groups was −2.7% (90% CI: −6.2 to 0.1). Hence, non-inferiority was shown. Given the low number of events (<20 events (HSRs)), no additional logistic regression analyses were performed on this outcome.

HSR (any grade) during paclitaxel infusion occurred in 37 (20%) in the pre-interventional group with ranitidine and 22 (12%) in the post-interventional group without ranitidine (Fig. 1). Regarding the comparison of—any grade—HSRs, a regimen without ranitidine showed to be non-inferior to the pre-intervention regimen with ranitidine (difference −8.2%, 95% CI −15.0 to −1.4, $p = 0.046$). The severity of HSRs, the number of paclitaxel dosages and time to first HSR occurrence did not differ between the groups (Table 2).[9]

Univariate logistic regression analyses showed that besides 'ranitidine premedication' versus 'no ranitidine premedication' ($p = 0.035$), sex ($p = 0.034$) and tumour type ($p = 0.003$) were also significantly related to HSR any grade. However, as sex could explain the differences in tumour type (a lower percentage of patients with breast cancer were included and thus fewer women were included) and no rationale could be given for the relation between tumour type and HSR, the multivariate analysis was performed with sex and 'ranitidine premedication' versus 'no ranitidine premedication'.[8,10–13,25–27] In the multivariate analysis 'ranitidine premedication' versus 'no ranitidine premedication' ($p = 0.043$) and sex ($p = 0.042$) remained statistically significant (Table 3) and thus showed that patients who were treated without ranitidine and males were at lower risk for developing an HSR any grade. Detailed clinical characteristics are described of patients with HSRs grade ≥3 during paclitaxel infusions in the groups with and without ranitidine in Table 4.

DISCUSSION

To our knowledge, this is the first study that prospectively investigated the added value of ranitidine as part of the standard of care premedication regimens in preventing paclitaxel-induced HSRs. This study showed that a premedication regimen without ranitidine is non-inferior to the standard premedication regimen with ranitidine in preventing clinically relevant paclitaxel-induced HSRs.

Based on a literature and data study conducted at the Erasmus MC, we expected an incidence of HSRs any grade of ~20% and of

Table 1. Patient characteristics.

	Pre-intervention group with ranitidine ($N = 183$)	Post-intervention group without ranitidine ($N = 183$)	*P* value
Age (years), median (IQR1–3)	61 (51–70)	61 (51–70)	0.608[a]
Sex: *N* (%)			
Female	115 (62.8)	106 (57.9)	0.336[b]
Male	68 (37.2)	77 (42.1)	
Tumour type: *N* (%)			
Uterine cervical	20 (10.9)	9 (4.9)	<0.001[c]
Lung	3 (1.6)	29 (15.8)	
Breast	60 (32.8)	59 (32.2)	
Ovarian	10 (5.5)	2 (1.1)	
Oesophageal	78 (42.6)	76 (41.5)	
Endometrial	5 (2.7)	4 (2.2)	
Others	7 (3.8)[d]	4 (2.2)[e]	
Allergies			
Registered medication allergies[f], *N* (%)	37 (20.2)	31 (16.9)	0.420[b]
If medication allergies, mean number[g], median (IQR1–3, max)	1 (1–2, 5)	1 (1–2, 3)	0.243[a]
Registered food allergies[f], *N* (%)	3 (1.6)	3 (1.6)	1.000[b]
Co-medication with effect on allergy symptoms, excluding chemotherapy-related medication: *N* (%)			
Corticosteroids[h]	18 (9.8)	18 (9.8)	1.000[b]
Beta blockers[i]	20 (10.9)	26 (14.2)	0.344[b]
Immunomodulatory agents[j]	2 (1.1)	0	0.499[c]
Anti-histamines[k]	9 (4.9)	9 (4.9)	1.000[b]

P-values belong to groups (thus: *P*-value <0.0001 belongs to all tumor types, not only to uterine cervical).
[a]Mann–Whitney *U* test.
[b]χ^2 test.
[c]Fisher's exact test.
[d]Oropharynx, vaginal cancer, angiosarcoma, gastric cancer 3× and rectal cancer.
[e]Thymus, prostate cancer, angiosarcoma and Merkel cell carcinoma.
[f]Registered in electronic patient's registration. Concerns all registered medication or food allergies before the start of the first paclitaxel administration.
[g]Applicable to patients where at least one medication allergy was registered in the electronic patients registration before the start of the first paclitaxel administration.
[h]Corticosteroids: Beclometasone, betamethasone, budesonide, cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone and triamcinolonacetonide.
[i]Beta blockers: acebutolol, atenolol, bisoprolol, carvedilol, celiprolol, esmolol, labetalol, landiolol, metoprolol, nebivolol, pindolol and propranolol.
[j]Immunomodulatory agents: abatacept, adalimumab, alemtuzumab, anakinra, apremilast, aurothiobarnsteenzuur, azathioprine, baricitinib, basiliximab, belatacept, belimumab, benralizumab, brodalumab, canakinumab, certolizumab pegol, cyclosporine, dupilumab, eculizumab, everolimus, etanercept, fingolimod, glatirameer, golimumab, guselkumab, hydroxychloroquine, infliximab, interferon alfa 2a, interferon beta 1a, interferon beta 1b, interferon gamma 1b, ixekizumab, leflunomide, mepolizumab, mycofenolzuur, natalizumab, ocrelizumab, omalizumab, peginterferon alfa 2a, peginterferon beta 1a, pimecrolimus, pirfenidon, reslizumab, risankizumab, ropeginterferon alfa 2b, sarilumab, secukinumab, sirolimus, tacrolimus, temsirolimus, teriflunomide, thymocytenimmunoglobuline, tildrakizumab, tocilizumab, tofacitinib, ustekinumab and vedolizumab.
[k]Anti-histamines: acrivastine, alimemazine, azelastine, cetirizine, chloorcyclizine, cinnarizine, clemastine, cyclizine, desloratadine, dimetindeen, ebastine, emedastine, fexofenadine, hydroxyzine, ketotifen, levocabastine, levocetirizine, loratadine, meclozine, mizolastine, olopatadine, oxomemazine, promethazine, rupatadine and tripelennamine.

Table 2. Characteristics of occurred hypersensitivity reactions.

	Pre-intervention group with ranitidine ($N = 183$)	Post-intervention group without ranitidine ($N = 183$)	*P* value
Patients with HSR (any grade): *N*	37	22	
HSR per grade[a]: *N* (%)			
Grade 1	4 (10.8)	1 (4.5)	0.825[b]
Grade 2	25 (67.6)	18 (81.8)	
Grade 3	6 (16.2)	3 (13.6)	
Grade 4	2 (5.4)	0 (0)	
Grade 5	0 (0)	0 (0)	
Occurrence of HSR during: *N* (%)			
Cycle 1	13 (35.1)	8 (36.4)	0.811[b]
Cycle 2	15 (40.5)	7 (31.8)	
Cycle 3	5 (13.5)	6 (27.3)	
Cycle 4	2 (5.4)	1 (4.5)	
Cycle 5	1 (2.7)	0 (0)	
Cycle 6	1 (2.7)	0 (0)	
Occurrence of first symptoms, no. of minutes after start of paclitaxel infusion: *N* (%)			
0–5 min	23 (62.1)	13 (59.1)	1.000[b]
5–15 min	10 (27.0)	8 (36.4)	
15–60 min	3 (8.1)	1 (4.5)	
60–120 min	0 (0)	0 (0)	
>120 min	0 (0)	0 (0)	
Unknown	1 (2.7)	0 (0)	
Cumulative dose of paclitaxel at the time of occurrence of HSR (mg/m^2)[c]: median (Q1–Q3)			
HSR grade 1	0 (0–74.5)	0 (N/A: $N = 1$)	NA
HSR grade 2	163.0 (0–184.9)	51.4 (0–120.4)	
HSR grade 3	87.2 (0–175.7)	0 (0–0)[d]	
HSR grade 4	0 (0–0)[d]	NA	
HSR grade 5	NA	NA	

HSR hypersensitivity reaction, *NA* not applicable.
P-values belong to groups (thus: *P*-value 0.825 belongs to grade 1 til grade 5, not only grade 1; *P*-value 0.811 belongs to cycle 1 to cycle 6, not only cycle 1; *P*-value 1.000 belongs to all occurences, not only to 0–5 min).
[a]CTCAE v4.03.[7]
[b]χ^2 test for trend.
[c]Cumulative dose in mg/m^2 administered in the cycles before the cycle in which the paclitaxel-induced HSR occurs.
[d]Cumulative dose of 0 since HSR occurred during the first paclitaxel administration.

clinically relevant HSRs (grade ≥ 3) of ~4% during paclitaxel infusion in the patient population with ranitidine.[3,11,25,26,28] In the RANISTOP study, we found incidences of HSRs and clinically relevant HSRs consistent with these findings. The lower incidence of HSRs in the post-interventional group without ranitidine may be partially explained by the fact that ranitidine itself may cause HSRs.[2]

The strengths of this study are the prospective study design and the broad inclusion criteria. These factors increase the representativeness of the data and the results are more likely to reflect daily clinical practice. The main limitation of this study was the non-randomised design. A non-randomised pre–post interventional trial design was chosen because of clinical feasibility for the sake of time and money. Moreover, as patients in this study received regular paclitaxel-based therapy with only a subtle change ('ranitidine premedication' versus 'no ranitidine premedication') in the pre–post regimen, respectively, there were concerns about receiving the assigned treatment. Statistical analysis showed that there were no significant differences observed in patient

characteristics between the group with ranitidine and the group without ranitidine, except for tumour type. In the group without ranitidine, a significantly higher percentage of lung cancer patients were seen, but this difference can be attributed to an increasing number of NSCLC patients being treated with paclitaxel (in combination with carboplatin, bevacizumab and atezolizumab) as part of a novel treatment option. As a result, a lower number of patients with gynaecologic tumours were seen in the group without ranitidine. However, the literature showed that tumour type was not associated with an increased risk of paclitaxel-induced HSR.[10,11,15] Hence, we believe that the difference in HSR incidence between the groups with and without ranitidine is attributable to the removal of ranitidine. Besides, a relatively large non-inferiority margin of +6% was chosen in this study in order to set feasible goals in the number of patients within a specific timeframe. A non-inferiority margin of +6% fits within the large variety of paclitaxel-induced HSR incidences seen in the literature.[8,10,11,13] In addition, earlier reports showed that ranitidine itself can cause HSRs, which would result in a decrease in HSR incidence for the group without ranitidine. Moreover, as the upper bound of the two-sided 90% CI for the difference in HSR rates was only +0.1%, the large margin did not affect the conclusions of this study. In this study, a differentiation between HSRs to ranitidine or paclitaxel or a second chemotherapeutic agent was not included as most HSRs occurred within the first 15 min after starting the paclitaxel infusion and could almost certainly be attributed to paclitaxel (and not to second chemotherapeutic agents in the regimen).[12–15] However, an additional in-depth assessment of known HSRs (e.g. through an allergological test) would be an interesting addition to similar studies in the future to discriminate between HSRs to paclitaxel and ranitidine.

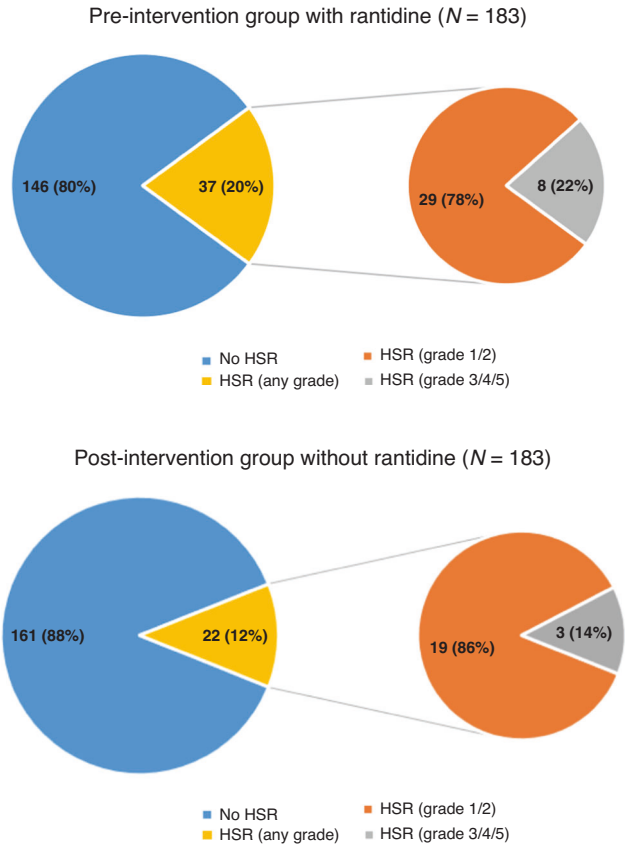

Fig. 1 Distribution of patients. Patients who experienced a hypersensitivity reaction (HSR) in the pre-intervention group with ranitidine and the post-intervention group without ranitidine. Data are presented as *N* (%).

During this study, a worldwide recall of ranitidine was issued. This event has made the conclusions of this study even more relevant as this study provides confirmation that ranitidine can be safely omitted from the premedication regimen during paclitaxel infusion and that an alternative is not necessary for preventing HSRs. Therefore, it should be considered to remove ranitidine from the paclitaxel labels and guidelines addressing the prevention of paclitaxel-induced HSR.

In times of increasing healthcare costs and increasing workload, the appropriate use of drugs is becoming more important. In the Netherlands, each year over 26,000 paclitaxel infusions are given to patients, resulting in the same amount of unnecessary ranitidine injections. The total costs of ranitidine per patient might be relatively low, but considering the high number of patients who receive ranitidine, this will inevitably result in a major reduction in healthcare costs. But probably more important is the time saving and effort saving through less pharmacy technician and nursing time and patient benefits such as shorter infusion time and fewer medication risks.

Table 3. Univariate and multivariate analysis.

	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Ranitidine (without vs. with)	0.54 (0.30–0.96)	0.035	0.55 (0.31–0.98)	0.043
Age (continuous)	0.99 (0.97–1.01)	0.259		
Sex (male vs. female)	0.51 (0.28–0.95)	0.034	0.525 (0.28–0.98)	0.042
Tumour type		0.003		
Lung vs. gynaecological[a]	0.18 (0.05–0.69)	0.012		
Breast vs. gynaecological[a]	0.30 (0.14–0.64)	0.002		
Oesophageal vs. gynaecological[a]	0.25 (0.12–0.53)	<0.001		
Other vs. gynaecological[a]	0.40 (0.08–2.03)	0.266		
Co-medication[b] (yes vs. no)	0.78 (0.37–1.46)	0.381		
Other previous medication allergies (yes vs. no)	1.63 (0.85–3.15)	0.143		

OR odds ratio.
[a]Uterine cervical, ovarian and endometrial carcinoma.
[b]Co-medication with effect on allergy symptoms, excluding chemotherapy-related medication: corticosteroids, beta blockers, immunomodulators and/or antihistamines.

Table 4. Detailed characteristics of patients with HSRs grade ≥3 during paclitaxel infusions, RANISTOP study.

	With/without ranitidine	Tumour type	Age (years)	HSR occurred during cycle no.	Dose (mg/m^2)	Absolute dose (mg)	Symptoms	HSR grade[a]	Time after start infusion until start symptoms (min)
1	With ranitidine	Cervix	49	1	175	300	Shortness of breath, cyanose, back pain, muscle pain, urticaria	4	0–5
2	With ranitidine	Oesophagus	68	1	50	100	Back pain, vomiting, syncope, ECG changes	4	5–15
3	With ranitidine	Cervix	48	2	90	150	Shivering, abdominal pain, facial flushing	3	5–15
4	With ranitidine	Breast	69	2	80	150	Hypertension, flushing	3	0–5
5	With ranitidine	Ovary	62	2	175	350	Flushing, hypotension, dizziness, nausea	3	5–15
6	With ranitidine	Ovary	70	2	175	300	Abdominal pain, back pain, dyspnoea, flushing, hypotension	3	0–5
7	With ranitidine	Cervix	57	1	90	130	Shortness of breath	3	5–15
8	With ranitidine	Breast	55	1	80	150	Shortness of breath, bronchospasm, chest pain	3	15–60
9	Without ranitidine	Oesophagus	78	3	100	200	Chest pain, flushing, hypertension	3	0–5
10	Without ranitidine	Lung	61	1	200	400	Chest pain, flushing, back pain	3	5–15
11	Without ranitidine	Lung	66	1	200	350	Tachycardia, hypertension, red tingling hands	3	15–60

[a]CTCAE v4.

This study shows that premedication regimens during anti-cancer treatment should be evaluated more critically. Their recommended use might not always be evidence-based and therefore may not be effective. Thus, more research is needed on the effectiveness, safety and proper dose of other premedication and co-medication drugs during anti-cancer therapy.

In conclusion, this study showed that a premedication regimen without ranitidine was non-inferior compared to a premedication regimen with ranitidine in preventing HSRs during paclitaxel infusion. The recent worldwide recall and subsequent shortages of ranitidine have made the conclusions of this study even more relevant as this study provides confirmation that ranitidine can be safely omitted from paclitaxel regimens and that an alternative is not necessary for preventing HSRs.

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AUTHOR CONTRIBUTIONS

R.W.F.v.L. conceived the study. J.M.C., L.v.D., E.O.-d.H., P.M.L.A.v.d.B., R.H.J.M. and R. W.F.v.L. contributed to study design. J.M.C., L.v.D. and E.O.-d.H. had a role in data analysis. J.M.C. and L.v.D. wrote the first draft of the manuscript and contributed to data collection. All authors had a role in the interpretation of the results and critically reviewed the manuscript. J.M.C., L.v.D. and E.O.-d.H. contributed to data preparation and analysis. All authors agreed with the decision to submit for publication.

ADDITIONAL INFORMATION

Ethics approval and consent to participate This study was approved by the medical ethical board of the Erasmus MC, reference number MEC-2018-1499. All included patients gave informed consent. This study was performed in accordance with the Declaration of Helsinki.

Data availability All data supporting the findings of this study are available within the article and its information files and from the corresponding author upon reasonable request.

Competing interests R.H.J.M. reports research grants from Astellas, Bayer, Boehringer-Ingelheim, Cristal Therapeutics, Pfizer, Prostakan, Roche and Pamgene. Personal fees from Novartis and Servier; all outside the submitted work. R.W.F.v.L. reports research grants from Astellas, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Servier and Roche. Personal fees from Roche, Pfizer and Sanofi; all outside the submitted work. All other authors declare no potential competing interests.

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