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Randomised comparison of ondansetron plus dexamethasone with dexamethasone alone for the control of delayed cisplatin-induced emesis

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Abstract

The role of 5-hydroxytryptamine$_3$ (HT_3) antagonists in the treatment of delayed emesis is still controversial. To evaluate whether 5-HT_3 antagonists can add to the efficacy of corticosteroids in controlling delayed emesis, we performed a randomised, prospective, open study comparing ondansetron plus dexamethasone with dexamethasone alone in cisplatin-treated patients. 149 cisplatin-naïve patients with lung cancer received at least 60 mg/m^2 of cisplatin and were treated with dexamethasone 32 mg intravenously (i.v.) and granisetron 3 mg i.v. on day 1. Patients were randomly assigned to receive either dexamethasone 16 mg i.v. alone (arm A) or dexamethasone plus ondansetron 8 mg daily (arm B) on days 2–4. None of the efficacy variables related to control of delayed emesis differed significantly between the two arms. In conclusion, there does not appear to be sufficient evidence to support the prolonged use of 5-HT_3 receptor antagonists after 24 h of cisplatin-containing chemotherapy.

Keywords: Delayed emesis; Antiemetics; Cisplatin; Ondansetron; Dexamethasone; 5-HT_3-receptor antagonists

1. Introduction

Nausea and emesis are among the most distressing adverse effects of cancer chemotherapy. The control of nausea and emesis has a remarkable effect on the patient's quality of life and willingness to complete their course of treatment.

Acute emesis after cisplatin administration has been widely studied, and following the introduction of 5-hydroxytryptamine$_3$ (5-HT_3) receptor antagonists, significant advances have been made in its control [1–4]. Furthermore, large multicentre randomised trials have shown that the combination of a 5-HT_3 receptor antagonist plus a corticosteroid is significantly more effective than a 5-HT_3 antagonist alone. In these trials, the combination of a 5-HT_3 receptor antagonist plus a corticosteroid has been shown to yield an approximately 75% (range 58–96%) complete control rate of acute emesis after a high-dose cisplatin-based regimen [5–9].

However, the success achieved in the prevention of acute emesis has not been extended to the control of the delayed emesis induced by cisplatin. Delayed emesis, although less intense than acute emesis, is still a major problem for many patients, and its incidence varies, but can be as high as 80% [10,11]. Since the neuropharmacological mechanism of delayed emesis is not well understood, prevention of this problem has been based on empirical results [12]. In the clinical practice guidelines developed by the American Society of Clinical Oncology (ASCO), a corticosteroid plus metoclopramide or a 5-HT_3 antagonist is recommended for the prevention of delayed emesis [12]. Although the combination of corticosteroid and metoclopramide has been shown to be superior to placebo, and also to dexamethasone alone [11,13], it is controversial whether continuation of a 5-HT_3 antagonist after acute control of emesis prevents the development or reduces the frequency of delayed emesis [14–20,23].

To evaluate the role of a 5-HT_3 antagonist, in particular oral ondansetron, in the prevention of delayed emesis, we planned a single-institution randomised, prospective, open study comparing ondansetron plus

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dexamethasone with dexamethasone alone in cisplatin-treated patients.

2. Patients and methods

2.1. Patient selection

Eligibility criteria included pathologically-confirmed lung cancer, age between 15 and 80 years, performance status of 3 or less according to the Eastern Cooperative Oncology Group (ECOG) scale and chemotherapy including cisplatin at a dose of at least 60 mg/m^2. Patients meeting any of the following criteria were excluded: primary brain tumour or symptomatic brain metastases, prior treatment with cisplatin, presence of nausea and/or vomiting before the cisplatin treatment, current use of corticosteroids, recent changes in the doses of major tranquilisers or sleeping pills habitually used, clinically significant gastrointestinal disease, or evidence of severe uncontrollable diabetes. Written informed consent was obtained from all patients, and the study was approved by the Institutional Review Board of our hospital.

2.2. Treatment protocol

Patients were randomly assigned to receive either dexamethasone alone (arm A) or dexamethasone plus ondansetron (arm B). All the patients received cisplatin treatment (60 or 80 mg/m^2) only on the first day (day 1) of treatment, either alone or in combination with other chemotherapeutic agents. On days 2–4, either no chemotherapy or only agents with low emetogenicity were administered. On day 1, patients received prophylactic treatment with granisetron 3 mg intravenously (i.v.) and dexamethasone 32 mg i.v. in four separate doses (8 mg each). Then patients assigned to treatment arm A received dexamethasone 8 mg i.v. twice daily on days 2–4. The treatment for arm B consisted of oral ondansetron 8 mg daily in the morning on days 2–4, in addition to dexamethasone at the same dose and on the same schedule as arm A. If more than two episodes of severe nausea or vomiting were observed, patients received a standard dose of metoclopramide (10 mg per body i.v. or intramuscularly) or domperidone (60 mg per body suppository). Requirement of any other antiemetic treatment necessitated withdrawal from the study.

2.3. Assessment of efficacy

The protocol-specified primary end-points were complete control of emesis (CCE), defined as no emetic episodes, no use of rescue medication, and no missing data during the 4-day period; complete control of nausea (CCN), defined as no nausea, no use of rescue medication, and no missing data during the 4-day period; and total control of emesis (TCE), defined as no vomiting, no nausea, no use of rescue medication, and no missing data during the 4-day period.

Immediately after randomisation (baseline period) and at the end of each day (days 1–4), all patients were asked to complete a daily diary. These diaries consisted of the number of emetic episodes, the intensity of nausea, their assessment of global satisfaction with the antiemetic treatment, and general mood at that time. Since all the patients were inpatients over the 4-day study period, monitoring by direct observation and interview was also used. An emetic episode was defined as any episode of vomiting or dry retching.

The patients assessed the intensity of nausea according to a graded scale: none, mild (did not interfere with normal daily life), moderate (interfered with normal daily life) and severe (bedridden due to nausea).

Patient's global satisfaction with antiemetic treatment was assessed using the visual analogue scale (VAS). The patient was asked to place a mark on a 100-mm line where 100 mm was 'not at all satisfied' and 0 mm was 'totally satisfied'.

Each patient reported subjective assessment of general mood day-by-day using a five-point face scale from "QOL assessment of cancer patients receiving chemotherapy" reported by Kurihara and colleagues [30].

We plotted the daily VAS score and daily face scale score on a time curve for each patient. The VAS and face scale profiles were then evaluated on the basis of area under curve (AUC) over the 4-day period calculated by trapezoidal summation, and the difference between the baseline score and worst score during the study period.

2.4. Assessment of safety

All adverse events were documented throughout the study period. Vital signs were recorded before and after the administration of the antiemetic or cytostatic therapy. Routine haematological and biochemical tests were performed at the same times. The severity of each adverse event and its relationship to the study treatment was assessed by the investigator.

2.5. Statistical analysis

The sample size was calculated assuming that 40% of patients assigned to arm A, and at least 65% of the patients of arm B would achieve total control of emesis. With type 1 and 2 errors of 5 and 20%, respectively, it was calculated that 61 patients should be included in each arm. To ensure there would be at least 61 patients assessable for analysis, we decided to include 70 patients in each arm.

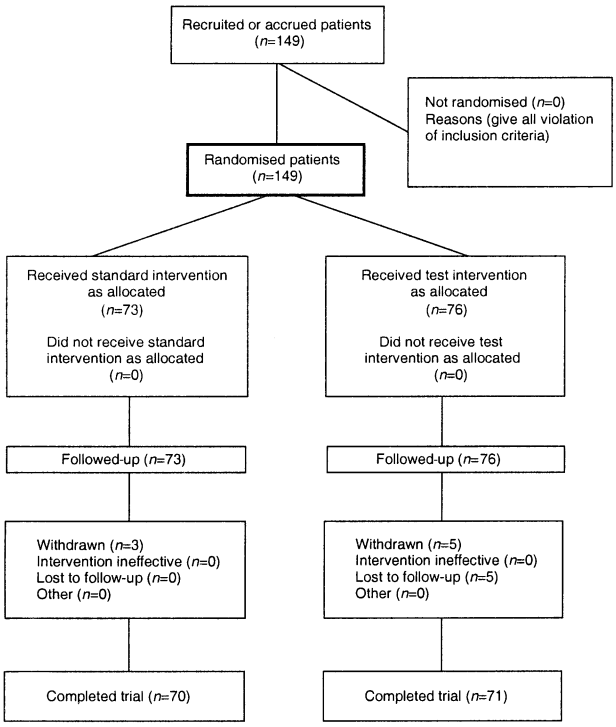

Fig. 1. Flow chart of the progress of patients through the trial (adapted from Ref. [29]).

Analysis of nausea and emesis was performed separately for day 1 (acute emesis) and for each day, from day 2 to day 4, considering the overall results between days 2 and 4 as an evaluation of delayed emesis.

Fisher's Exact test was used to evaluate the balance of prognostic factors between the two groups, and to examine differences in efficacy and the incidence of adverse events. Mann–Whitney's U-test was performed to compare treatment groups with respect to intensity of nausea, global satisfaction with antiemetic treatments, and number of emetic episodes. All P values refer to two-tailed tests, and P values less than 0.05 were considered significant.

3. Results

3.1. Patients' characteristics

A total of 149 patients entered the study, and 141 patients were evaluated for efficacy according to the intention-to-treat principle. 8 were lost to follow-up and excluded from the analysis (Fig. 1). Toxicity was also evaluated in these 141 patients. Of the assessable and eligible patients, 70 received dexamethasone alone (arm A) and 71 received ondansetron plus dexamethasone (arm B) as a maintenance treatment. Treatment groups were well balanced for sex, age, daily alcohol consumption, performance status and for cisplatin dose (Table 1).

3.2. Control of acute emesis (day 1)

Overall, complete control of emesis was observed in 93% and control of nausea was observed in 82% of patients. Between the two randomised groups, no significant differences were observed in the complete control of vomiting (arm A versus arm B; 93% versus 93%), of nausea (84% versus 80%), or of both nausea and vomiting (84% versus 79%). Mean number of emetic episodes (0.1 versus 0.1), mean score of maximum intensity of nausea (0.2 versus 0.3), and the number of

Table 1
Patients' characteristics

	Dexamethasone alone	Ondansetron plus dexamethasone	P value
Number of patients	70	71	
Sex: male/female	55/15	58/13	NS
Median age (years) (range)	65 (40–74)	63 (20–72)	NS
Habitual alcohol intake[a]			
No/Yes	28/37	21/46	NS
Performance status (ECOG)			
0–1/2–3	63/7	66/5	NS
Cisplatin dose (mg/m^2)			
<80	13	14	
$\geqslant 80$	57	57	NS
Histological type			
SCLC/NSCLC	16/54	25/46	NS
Clinical stage			
I-III/IV	44/26	42/29	NS

SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; ECOG, Eastern Co-operative Oncology Group; NS, non significant.
[a], there are missing data in some categories.

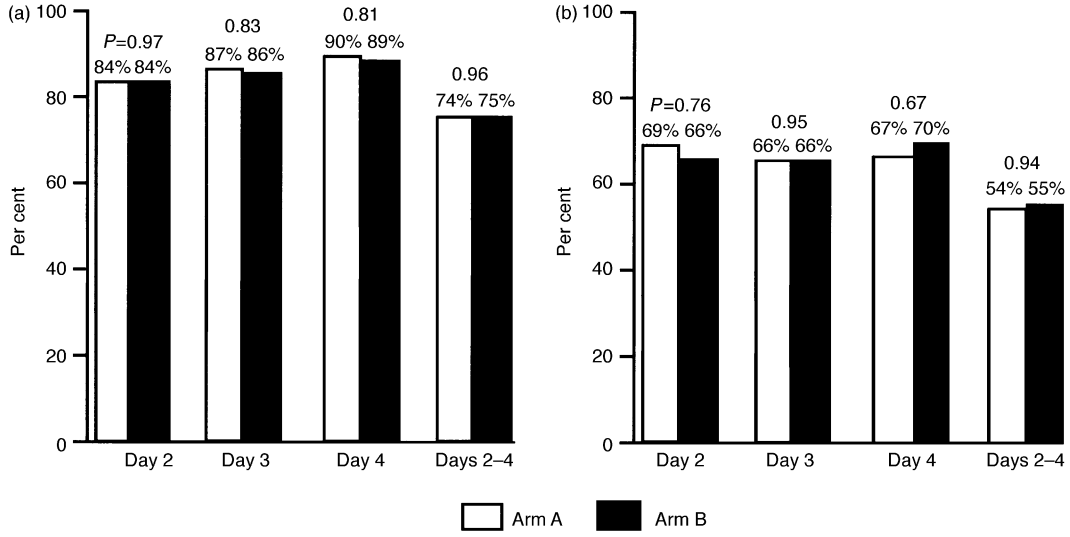

Fig. 2. Percentages of complete control of delayed (a) emesis and (b) nausea.

patients receiving rescue medication (54 versus 55) were nearly identical in the two groups.

3.3. Control of delayed emesis

The percentages of CCE or CCN on a daily basis over days 2–4 are shown in Fig. 2. None of the pairwise treatment comparisons of efficacy revealed a statistically significant difference. We also found no significant difference between the two arms in either total number of vomiting episodes per patient during days 2–4 ($P=0.8716$) or worst grade of nausea intensity during days 2–4 ($P=0.9474$).

As shown in Fig. 3a, TCE rates for the entire study period (days 2–4) were approximately 50%. TCE rates on the individual days and over days 2–4 in the two comparable arms did not differ significantly. Irrespective of the antiemetic treatment received, TCE was achieved in 70 of 115 patients (61%) who did not suffer from emesis on day 1 and in 2 of 26 patients (8%) who suffered from emesis on day 1. This difference was highly significant ($P<0.0001$). In the subgroup of patients who did not suffer from either vomiting or nausea on day 1, there were no significant differences in the TCE rates (Fig. 3c). TCE rates of those who suffered from emesis on day 1 were also similar in the two treatment groups (Fig. 3b).

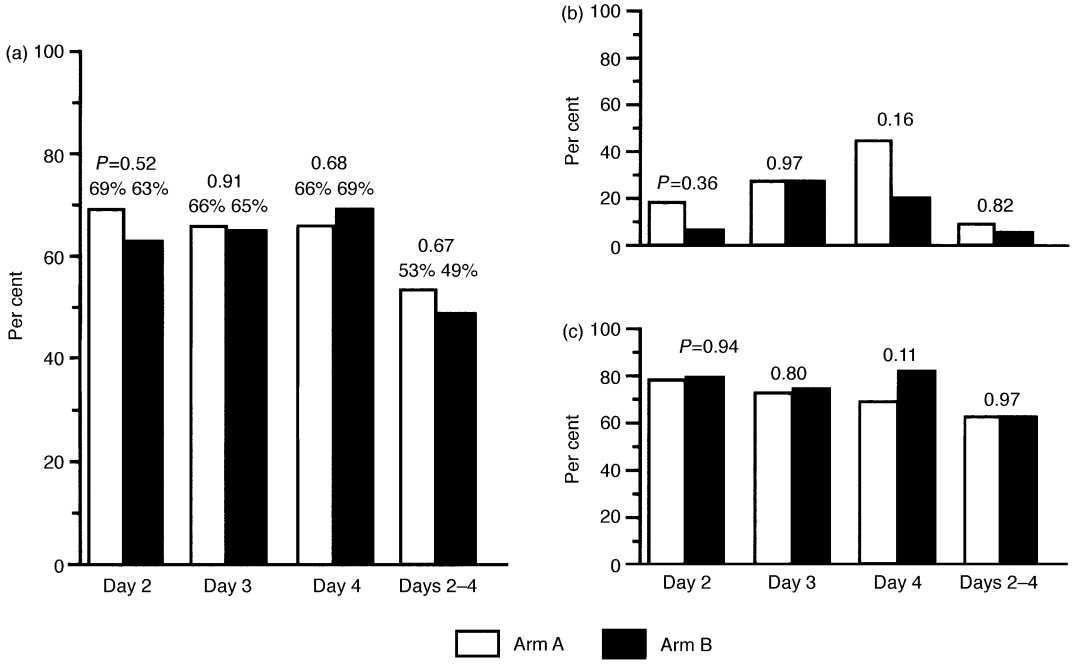

Fig. 3. Total control rates over days 2–4 for delayed emesis among (a) total population, (b) the patients who suffered from emesis on day 1 and (c) the patients who did not suffer from emesis on day 1.

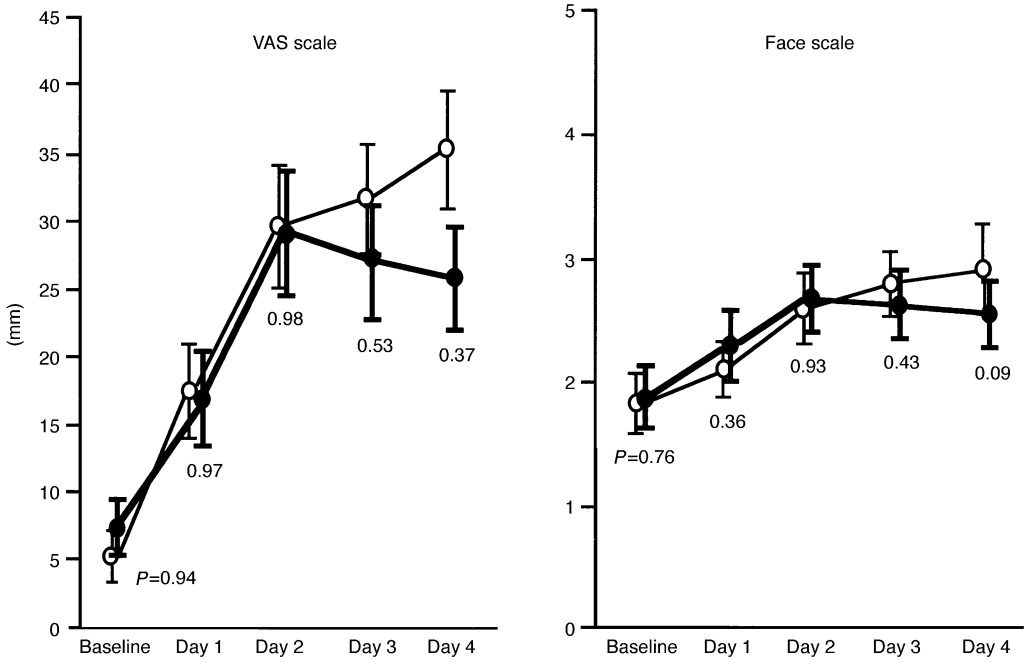

Fig. 4. Visual analogue scale (VAS) and face scale score profile over the study period. Open circles indicate each scale score profile for the patients assigned to arm A and closed circles indicate those for the patients assigned to arm B.

3.4. Patients' global satisfaction

Profiles of the mean daily VAS and face scale scores are shown in Fig. 4. Error bars represent the standard errors. 28 patients were excluded from these analyses because the investigators failed to deliver the questionnaires to 21 of them and because 7 patients stopped filling out the questionnaires halfway through the study period.

There was no difference between the groups in the proportion of patients excluded. No statistically significant differences were recorded between the groups in the VAS or face scale score on any one of days 2–4. When we calculated the AUC over the 4-day period and the difference between baseline and the worst score on these two scales during the study period, no significant differences were found between the two arms (Fig. 4).

Table 2
Adverse events (days 2–4)

	Dexamethasone alone	Ondansetron plus dexamethasone	*P* value
Number of patients	70	71	NS
Adverse effects[a]	Number (%) of patients suffering adverse event		
Headache	9 (13)	4 (6)	NS
Epigastric pain	1 (1)	6 (8)	NS
Rush	9 (13)	7 (10)	NS
Abdominal gas	10 (14)	7 (10)	NS
Constipation	15 (21)	16 (23)	NS
Asthenia	15 (21)	19 (27)	NS
Heartburn	1 (1)	4 (6)	NS
Insomnia	6 (9)	12 (17)	NS
Hot flashes	4 (6)	4 (6)	NS
None	36 (51)	25 (35)	NS

NS, non significant.
[a] All events were grade 1 or 2.

3.5. Safety

No severe or unexpected adverse events were reported. Adverse events of grade 3 or 4 were also not reported. Adverse events of grade 1 or 2 occurred in 34 (49%) of the 70 patients for arm A and in 46 (65%) of 71 for arm B ($P = 0.06$). Epigastric pain, constipation, asthenia, heartburn, and insomnia occurred with greater frequency with arm B (8, 23, 27, 6 and 17%, respectively) compared with arm A (1, 21, 21, 1 and 9%, respectively). However, there were no significant differences in the rates of each adverse event from days 2 to 4 between the two treatment groups (Table 2).

4. Discussion

The combination of a corticosteroid plus a 5-HT_3 antagonist is one of the recommended regimens for cisplatin-induced delayed emesis in the ASCO clinical practice guidelines [12]. Several randomised trials have shown that the addition of corticosteroids to 5-HT_3 antagonists significantly improved the control of delayed emesis [16,21–23].

However, there was very limited data on the efficacy of dexamethasone alone without 5-HT3 antagonists as background therapy [24]. None of the trials comparing

the combination of corticosteroid plus a 5-HT_3 antagonist with corticosteroids alone determined the benefit of adding 5-HT_3 antagonist to corticosteroids in the control of delayed emesis [18–20]. These studies employed granisetron or tropisetron as a 5-HT_3-receptor antagonist.

Although the majority of multiple, randomised studies have demonstrated that the four currently available 5-HT_3 antagonists have equivalent activity against cisplatin-induced acute emesis [25,26], oral ondansetron was the only agent shown to be significantly superior to placebo in the control of delayed emesis [14]. To the best of our knowledge, this is the first study to evaluate whether the combination of oral ondansetron plus dexamethasone is more beneficial than dexamethasone alone in controlling delayed emesis after cisplatin-based chemotherapy.

In this study, however, the addition of oral ondansetron to dexamethasone on days 2 through to 4 after the administration of cisplatin had no discernible effect on the control of delayed emesis. Neither the complete control rate of emesis and/or nausea, nor the total control of emesis or global satisfaction score differed between the two treatment arms.

Although patients were randomised before chemotherapy, all patients received the same treatment on day 1 and underwent randomised treatment only during the delayed phase. Furthermore, on retrospective analysis, the percentages of acute control were similar in the two randomised arms. Taking these findings into account, we could exclude the carry-over effect of control of acute emesis. In addition, the two groups of patients exhibited no significant differences in other known prognostic factors for delayed emesis such as age, sex or alcohol intake.

However, we cannot exclude the possibility that use of an inadequate dose of ondansetron in this study (8 mg daily) resulted in an underestimation of the effect of ondansetron. The reason why significant adverse events due to ondansetron were not observed may also be due to the inadequate dose. In fact, in a study demonstrating clinical benefit of use of a 5-HT_3 antagonist compared with placebo in the control of delayed emesis, patients received ondansetron 8 mg twice daily [14]. In addition, the discrepancy in findings between these two studies may be due in part to differences in the control of acute emesis produced by the different prophylactic regimens on day 1. The percentages of patients with complete control of emesis within 24 h in this study was 93%, compared with 64% in the study by Navari and colleagues [14]. Better control of acute emesis may lead to a lower incidence of delayed emesis, with less opportunity for an improvement in the control of delayed emesis by ondansetron.

The importance of an early control of nausea and vomiting asserted by Roila and colleagues [27] was also confirmed in this study. Significantly more patients were protected from delayed emesis among complete responders to the antiemetic treatment for acute emesis than among non-responders.

Although the dosage of dexamethasone used in both the acute and delayed phase in this study is higher than in other studies [18–20], severe side-effects possibly due to dexamethasone were not seen. Ioannidis and colleagues also showed in their meta-analysis that only one case of haematoemesis attributed to dexamethasone was reported among all their considered studies, although several studies reported increases in hiccups and various gastrointestinal symptoms among patients given dexamethasone [23]. No significant differences in the rates of each adverse event between the two treatment groups were seen in our study, which suggests that the adverse events seen in our study are due in considerable part to dexamethasone.

The results of this study indicate that 5-HT_3 antagonists (in this case, oral ondansetron as a single daily dose of 8 mg) have only a limited effect on delayed emesis, thus supporting the experimental and clinical findings that the two phases of the emetic response involve different mechanisms that may partially overlap [28].

In conclusion, the results of our study do not provide evidence strong enough to support the prolonged use of 5-HT_3-receptor antagonists throughout the delayed phase, at least if adequate antiemetic treatment is given during the acute phase.

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