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Development of fast dissolving oral film containing dexamethasone as an antiemetic medication: Clinical usefulness

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ABSTRACT

We developed a fast dissolving oral film containing 4 mg dexamethasone and examined the clinical effect of the film as the antiemetic by a randomized controlled crossover study in breast cancer patients receiving a combination chemotherapy with anthracycline and cyclophosphamide, a highly emetogenic chemotherapy. The film was prepared as reported previously using microcrystalline cellulose, polyethylene glycol, hypromellose, polysorbate 80 and 5% low substituted hydroxypropylcellulose as base materials. The uniformity of the film was shown by the relative standard deviation of 2.7% and acceptance value of 5.9% by the Japanese Pharmacopoeia. Patients were administered with 8 mg dexamethasone as oral film or tablet on days 2–4 after chemotherapy in addition to the standard antiemetic medication. The rates of complete protection from vomiting during acute and delayed phases were not different between film-treated group and tablet-treated group. The time course of the complete protection from nausea or vomiting during 0–120 h was also similar between the two groups. Patient's impressions on the oral acceptability in respect of the taste and ease in taking were significantly better for film than for tablet. Therefore, the present fast dissolving oral film containing dexamethasone seems to be potentially useful as an antiemetic agent in patients receiving highly emetogenic chemotherapy.

1. Introduction

Outcomes from cancer chemotherapy have been greatly improved during recent years due to the development of novel chemotherapeutic agents. However, the occurrence of a number of serious adverse events associated with cancer chemotherapy still often impairs patient's quality of life, which leads to a discontinuation or cessation of the chemotherapy. de Boer-Dennert et al. (1997) reported that nausea and vomiting are the most distressing adverse events that patients reported during cancer chemotherapy. Therefore, prophylactic medication against chemotherapy-induced nausea and vomiting (CINV) is requisite before cancer chemotherapy, particularly in patients receiving highly or moderately emetogenic chemotherapy.

The combination chemotherapy of anthracycline and cyclophosphamide for breast cancer is classified into a highly emetogenic chemotherapy according to the clinical practice guidelines for antiemesis developed by the American Society of Clinical Oncology (ASCO) (Kris et al., 2006; Basch et al., 2011) and the National Comprehensive Cancer Network (NCCN) (2011). For prevention of CINV in patients receiving a highly emetogenic chemotherapy, premedication with a combination of three drugs, including 5-HT_3 antagonist, aprepitant (125 mg orally) and dexamethasone (DEX, 12 mg intravenously), on day 1, followed by the administration of oral aprepitant (80 mg/day) on days 2–3, and oral DEX (8 mg/day) on days 2–4 are recommended. However, in Japan, the standard formulation of oral DEX is limited to a tablet containing 0.5 mg DEX, which may cause a reduction in medication compliance due to the necessity of taking a large amount.

A fast dissolving oral film has been successfully used to deliver medicines to patients having difficulty in swallowing, those with oral pain due to mucositis or after oral surgery, or those with nausea. Several film preparations have been developed for analgesics such as ketrolac (Al-Hezaimi et al., 2011) or fentanyl (Vasisht et al., 2010; Finn et al., 2011), the antiemetic agent prochlorperazine (Nishimura et al., 2009) and Ca^{2+} channel antagonist verapamil (Kunte and Tandale, 2010). We recently developed a

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fast dissolving oral thin film containing uniform content of DEX, the size of which is 2 cm × 2 cm and 0.1 mm in thickness (Shimoda et al., 2009). This film shows an excellent stability and solubility stored even under tough conditions of high temperature and high humidity. Moreover, the pharmacokinetic parameters of DEX determined in rats after oral application of the film are very similar to those obtained after oral administration of the same dose of DEX suspension (Shimoda et al., 2009).

In the present study, a randomized controlled crossover study comparing the antiemetic effect of DEX film with that of DEX tablet was carried out in breast cancer patients receiving a highly emetogenic chemotherapy in the outpatient cancer chemotherapy clinic. Moreover, patient's impression on the oral acceptability of the film formulation in respect of the taste and amount was surveyed by questionnaire.

2. Materials and methods

2.1. Materials

Dexamethasone and ethyl-p-hydroxybenzoate were obtained from Nacalai Tesque (Kyoto, Japan). Microcrystalline cellulose (Asahikasei Co. Ltd., Tokyo, Japan), polyethylene glycol (Sanyo Chemical Industries, Ltd., Kyoto), polysorbate 80 (Nichiyu Co., Ltd., Tokyo), 5% low substituted hydroxypropylcellulose (L-HPC) and hydroxypropylmethyl cellulose (hypromellose) (Shin-Etsu Chemical Co., Ltd., Tokyo) were used as film base materials.

Thaumatin (0.4%) and sucralose (1.3%) were added as sweeteners.

2.2. Preparation of oral film

The constituents of the basic materials were microcrystalline cellulose (57%), polyethylene glycol (15%), hypromellose (7.4%), polysorbate 80 (5.4%) and 5% L-HPC (1.3%). The bases of the film preparation were mixed and fragrance ingredients were included, then the mixture was coated onto plastic film to prepare thin film, then dried by heating. The resultant film was cut into the four square of 2 cm × 2 cm in size, in which 4 mg dexamethasone was included.

2.3. Uniformity of dosage units of the preparation

The uniformity of dosage units of the oral film preparation was tested using 20 preparations, and the content of dexamethasone was determined by HPLC with spectrometric detection. The acceptance value (AV) of the preparation is less than 15%, according to the JP15. AV for JP15 was calculated according to the following Eq. (1):

$$\mathrm{AV} = |M - X| + ks \quad (1)$$

where M is label claim (100%), X is the average (%) of individual contents, k is the acceptability constant (2.2), s is the standard deviation.

In USP27, the contents of major component in the preparation should be within a range between 85% and 115% and the relative standard deviation should be less than or equal to 6.0%.

2.4. Subjects

Twenty breast cancer patients receiving the first and second courses of epirubicin/cyclophosphamide combination chemotherapy during June 2010 and August 2011 were enrolled on the present clinical study. They were randomly assigned to receive DEX film or DEX tablet on days 2–4 at the first course of the chemotherapy.

Table 1
Patient characteristics.

	DEX tablet	DEX film
Age	55.5(41–70)	
Height (cm)	155.8 ± 5.7	
Body weight (kg)	56.3 ± 15.4	
Serum creatinine (mg/dL)	0.53 ± 0.07	0.54 ± 0.10
Aspartate aminotransferase (IU/L)	18.6 ± 5.3	19.9 ± 6.0
Alanin aminotransferase (IU/L)	18.4 ± 11.0	19.2 ± 11.8
White blood cells (/mm^3)	3,934 ± 1,425	4,015 ± 1,895
Hemoglobin (g/L)	11.8 ± 1.5	12.0 ± 1.5
Platelet (10^4/mm^3)	23.0 ± 8.8	24.4 ± 8.2
Dose of anticancer drugs (mg/m^2)		
Epirubicin	88 ± 9	88 ± 7
Cyclophosphamide	581 ± 58	585 ± 47

Data represent the mean ± SD of 20 patients. Figures in parenthesis is the range of age. No statistically significant differences existed between the two groups.

A crossover study was carried out, in which patients administered with DEX film at the first chemotherapy course received DEX tablet at the second chemotherapy course, and vice versa. The exclusion criteria were age under 18-year-old, use of emetogenic drugs such as opioid analgesics, having experience of previous chemotherapy, and having organic disorders accompanying nausea and vomiting. Patient characteristics were shown in Table 1. The present clinical study was carried out in accordance with the guidelines for the care for human study adopted by the ethics committee of the Gifu Graduate School of Medicine (approved number of the institutional review board: 20–128), and notified by the Japanese government.

2.5. Chemotherapy

Patients were injected by intravenous infusion with epirubicin (90 mg/m^2 over 15 min), followed by intravenous infusion with cyclophosphamide (900 mg/m^2 over 30 min) at the outpatient cancer chemotherapy clinic of Gifu University hospital. Chemotherapy was carried out every 21 days.

2.6. Antiemetic medication

For prevention of CINV, patients received a combination of intravenous granisetron (3 mg), intravenous DEX (12 mg) and oral aprepitant (125 mg) 30 min before chemotherapy, followed by oral aprepitant (80 mg/day) on days 2–3, and oral DEX (8 mg/day) either in a form of film (4 mg/piece) or tablet (0.5 mg) on days 2–4.

2.7. Assessment of emetic control

Patients were handed with a form of self-reported symptom diary, in which patients check the symptom and severity of adverse reactions every day at home. The primary endpoint was the complete protection from vomiting during delayed phase (24–120 h). The time course of the complete protection from nausea and vomiting was the secondary endpoint. Complete protection from nausea and vomiting during acute phase (0–24 h) was also compared. Data were obtained from the self-reported symptom diary and a medical interview.

The incidence and the extent of other adverse reactions such as constipation and hematological toxicities, including leucopenia, thrombocytopenia and anemia, were checked from the self-reported diary and laboratory data.

2.8. Survey of oral acceptability of oral dissolving film formulation by questionnaire

Patient's impression on the availability of DEX-containing tablet and oral film was monitored in respect of the taste, amount, and

ease in taking. The size, thickness and solubility regarding the film formulation were also checked. A self-check sheet, in which each item is scored on a three-point scale (1: bad, 2: medium, 3: good), was distributed to patients on the first visit to the cancer chemotherapy clinic, and recovered on the next visit.

2.9. Statistical analyses

Data were analyzed using Statistics Program for Social Science (SPSS X, version 11) for Windows (SPSS Inc., Chicago, IL). Data were statistically compared between the two groups using paired test for parametric data, and Wilcoxon signed-rank test or McNemar test for non-parametric paired sample data. *P* values of less than 0.05 were regarded as statistical significance.

3. Results

3.1. Uniformity of dosage units of oral film preparation

Fig. 1 shows the boxplots for the weight, absolute and relative content of DEX in 20 preparations. The weight (mg) of the film was 19.5 ± 0.6 (mean ± SD), while the absolute content (mg) and relative content (%) of DEX were 3.98 ± 0.11 and 99.6 ± 2.7, respectively. The relative standard deviation (%RSD) in respect of the DEX content was 2.7%, indicating that the preparation met the criteria of USP specification for drug content (<6.0%) (Hill et al., 2009). Moreover, AV was 5.9%, a value that was within a limit (15%) of uniformity of dosage units for Japanese Pharmacopoeia 15.

3.2. Comparison of antiemetic effect between DEX tablet and DEX film

The present fast dissolving oral film containing 4 mg DEX met the criteria of AV in the dosage uniformity test for JP15 and USP specification. In addition, DEX content in the film was found to be stable for at least 24 weeks after preparation (Shimoda et al., 2009). Therefore, the film formulation was applied to cancer patients receiving a highly emetogenic chemotherapy for evaluation of practical usability as an antiemetic agent. Complete protection from vomiting during 24–120 h after chemotherapy was similar (95%) between DEX film group and DEX tablet group (Fig. 2A). As shown in Fig. 2B, the minimal rate of complete protection from nausea during 24–120 h was 55% for film group and 60% for tablet group (relative risk: 1.125, 95% confidence intervals: 0.546–2.318, $P = 1.000$ by McNemar test). The minimal rate of complete protection from vomiting during 24–120 h was similar (95%) between the two groups. On the other hand, patients with no episodes of vomiting during acute phase (0–24 h) was 90% (18/20 patients) for film group and 95% (19/20 patients) for tablet group. Patients with no nausea during acute phase was also similar between the two groups (80%).

3.3. Results of questionnaire about oral acceptability of DEX film

The results from questionnaire indicated that the score of the taste was similar between the film formulation and tablet, thereby suggesting that the bitterness of DEX was acceptable by inclusion of cocoa flavor into basic materials of the film (Fig. 3). In addition, the scores in respect of the amount and the ease in taking were significantly ($P < 0.01$) higher in the film formulation than in tablet. The solubility of the film in the oral cavity, thickness of the film and size were all satisfactory in score ranging from 2.5 to 2.7.

Table 2
Comparison of the incidence of constipation and hematologic adverse events between patients administered with DEX tablet and those with DEX film.

	DEX tablet	DEX film	*P* value
Constipation			
Grade 1	45 (9/20)	40 (8/20)	
Grade 2	0	0	
Grade 3	0	0	
Grade 4	0	0	
All grades	45 (9/20)	40 (8/20)	1.000
Leucopenia			
Grade 1	0	5 (1/20)	
Grade 2	5 (1/20)	10 (2/20)	
Grade 3	15 (3/20)	35 (7/20)	
Grade 4	25 (5/20)	15 (3/20)	
Grade > 2	45 (9/20)	60 (12/20)	0.250
Anemia			
Grade 1	10 (2/20)	30 (6/20)	
Grade 2	20 (4/20)	10 (2/20)	
Grade 3	0	0	
Grade 4	0	0	
Grade > 2	20 (4/20)	10 (2/20)	0.625
Thrombocytopenia			
Grade 0	16	14	
Grade 1	20 (4/20)	25 (5/20)	
Grade 2	0	5 (1/20)	
Grade 3	0	0	
Grade 4	0	0	
All grades	20 (4/20)	30 (6/20)	0.688

Data were statistically compared using McNemar test.

3.4. Comparison of incidence of other adverse reactions between DEX tablet and DEX film

Other adverse reaction that occurred with high frequency was a constipation, although the symptom was mild and in all cases of grade 1 according to the common toxicology criteria for adverse events (CTCAE) version 4.0 (Table 2). There was no significant difference in the incidence of constipation between the two groups ($P = 1.000$ by McNemar test).

On the other hand, moderate to severe hematological toxicities were observed in both groups, in which leucopenia (grade > 2) occurred in 60% of patients receiving film and 45% of those receiving tablet ($P = 0.250$ by McNemar test), anemia (grade > 2) appeared in 10% in film group and 20% in tablet group ($P = 0.625$), and thrombocytopenia (any grades) in 30% in film group and 20% in tablet group ($P = 0.688$). There were no significant differences in the incidence of hematological toxicities between the two groups.

4. Discussion

We developed a novel fast dissolving oral film containing 4 mg DEX. This formulation is small in size (2 cm × 2 cm) and 100-μm in thickness, and dissolved rapidly after application to the oral cavity. The test for the uniformity of the dosage unit of the film preparation showed that the %RSD was 2.7% and AV was 5.9%, values within a range of criteria specified by USP and JP. Moreover, we previously reported in rats that the pharmacokinetic parameters obtained after application of the film formulation to the oral cavity are very similar to those calculated after oral administration of the same dose of DEX suspension (Shimoda et al., 2009). The commercially-available dexamethasone tablet is uncoated tablet, thus dexamethasone is absorbed from gastrointestinal tract immediately after oral intake. The present oral film is dissolved immediately after oral application and swallowed with a drop of water. Although we have not yet determined the pharmacokinetics of DEX from oral film in patients, it is likely that the pharmacokinetics of dexamethasone are similar between the present oral film

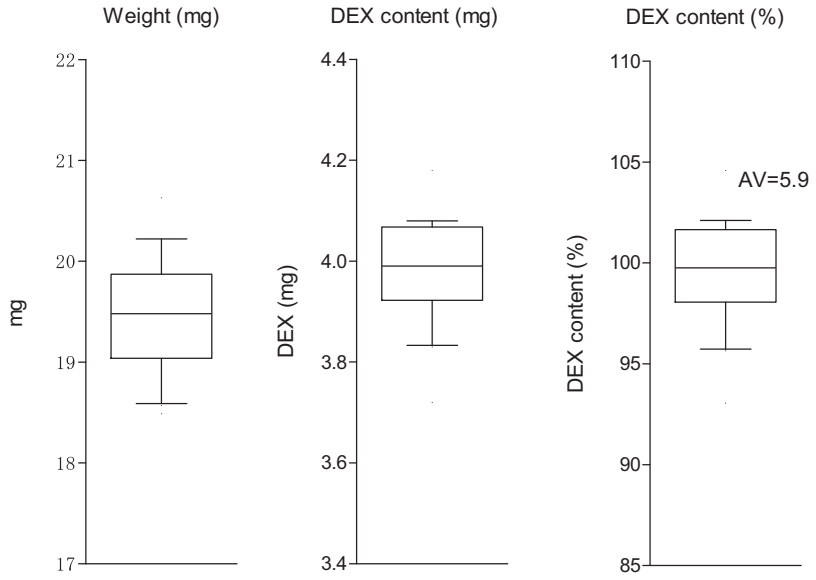

Fig. 1. Box plots showing variation of film weight, absolute and relative DEX contents in 20 fast dissolving oral films containing 4 mg DEX. The film of 100-μm thickness was cut into pieces of 2 cm × 2 cm in size. The content of DEX in each film preparation was determined by HPLC with spectrometric detection. The acceptance value (AV) of the preparation was 5.9%, a value that is within the limit (15%) defined by the 15th edition of the Japanese Pharmacopoeia (JP).

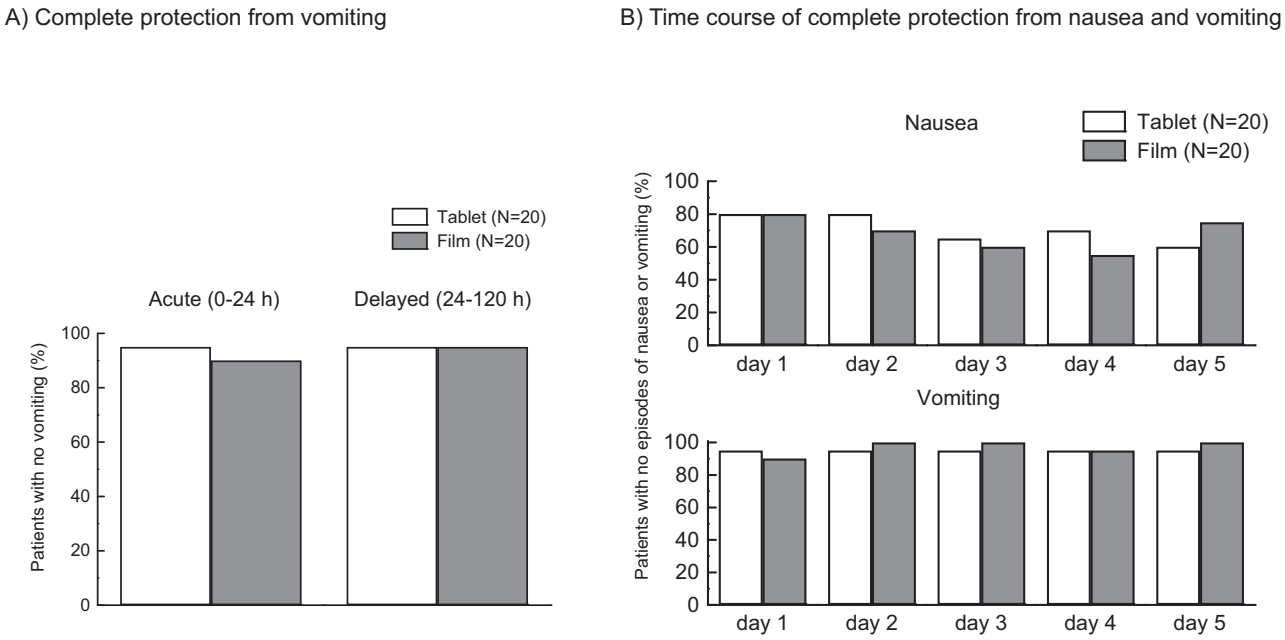

Fig. 2. Comparison of the complete protection from vomiting (A) and time course of the complete protection from nausea and vomiting (B) between DEX tablet formulation and orally-dissolving DEX film formulation in breast cancer patients receiving epirubicin/cyclophosphamide combination chemotherapy in outpatient cancer chemotherapy clinic. For antiemetic medication, all patients received intravenous granisetron (3 mg), intravenous DEX (12 mg) and oral aprepitant (125 mg) on day 1, 30 min before chemotherapy, followed by oral aprepitant (80 mg/day) on days 2 and 3, and oral DEX (8 mg/day) in either tablet or film form on days 2–4. Complete protection from nausea and vomiting was defined as no nausea and no vomiting, respectively, during acute (0–24 h) and delayed (24–120 h) periods.

and tablet. Taken together, the present film formulation may be clinically applicable.

However, without addition of flavor or other ingredients, the film had a drawback in taste such as bitterness derived from DEX. Several flavors, including ginger and citrus flavors, were tested but failed to apply to clinical use because of the presence of bitter taste. Ultimately, the addition of cocoa flavor with sweeteners was found to successfully mask the bitterness of DEX

Using this film formulation, the antiemetic effect and oral acceptability were evaluated in patients receiving a combination chemotherapy with epirubicin and cyclophosphamide for the therapy of breast cancer in the outpatient cancer chemotherapy clinic. This chemotherapy regimen is classified into a highly emetogenic chemotherapy according to the guidelines developed by ASCO (Basch et al., 2011) and NCCN (2011) but regarded as a moderately emetogenic chemotherapy based on the MASCC guideline (Roila et al., 2010). The antiemetic regimen for epirubicin/cyclophosphamide chemotherapy recommended by ASCO and NCCN includes a combination of 5-HT_3 antagonist, aprepitant and DEX on day 1, followed by aprepitant on days 2–3, and DEX on days 2–4 (Basch et al., 2011), while the antiemetic medication recommended by MASCC is a combination of palonosetron,

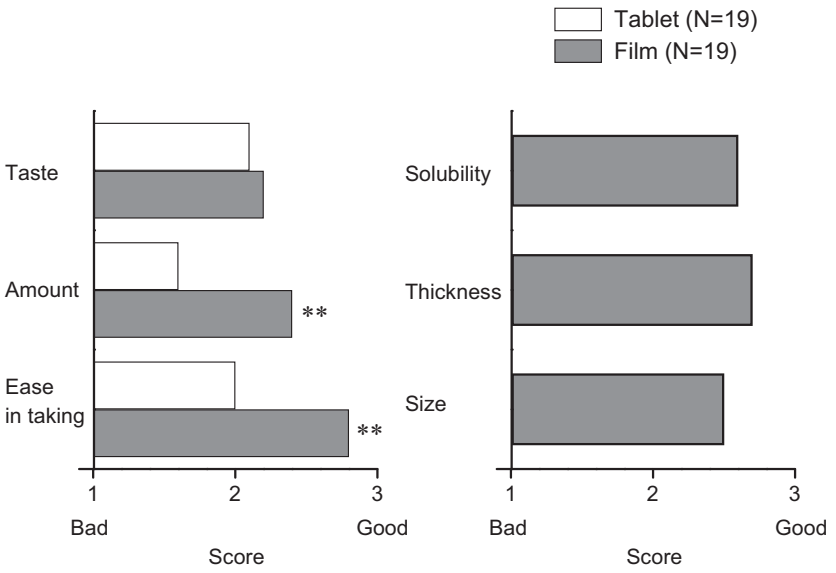

Fig. 3. Results from questionnaire about oral acceptability of the oral dissolving DEX film in comparison with DEX tablet. $^{**}P < 0.01$ by Wilcoxon signed-rank test.

a 5-HT_3 antagonist with a long half-life (Grunberg and Koeller, 2003), aprepitant and DEX on day 1, followed by aprepitant on days 2 and 3 (Roila et al., 2010).

It has been demonstrated that DEX alone is partially effective for prevention of acute and delayed emesis in patients who received a high dose of cisplatin (Kris et al., 1989; Ioannidis et al., 2000) but highly effective against acute as well as delayed emesis, when used in combination with the 5-HT_3 receptor antagonist (Lofters et al., 1997; Garcia-del-Muro et al., 1998). Olver et al. (1996) reported by a multicenter randomized controlled study in cisplatin-treated patients that the complete protection from nausea and vomiting during delayed phase are improved from 27% to 45% and from 32% to 49%, respectively, after addition of DEX to ondansetron treatment. Roila et al. (1991) also reported that the complete protection from nausea and vomiting are improved by 23% and 27%, respectively, by the addition of DEX to ondansetron. In patients receiving moderately emetogenic chemotherapy, addition of DEX to ondansetron significantly increases the rate of complete response (no vomiting and no rescue treatment) during delayed phase by 16% (from 65% to 81%) (Kirchner et al., 1997). Therefore, it is important to prescribe DEX for prevention of delayed emetic episodes. In the present study, the antiemetic regimen was determined according to the guidelines of ASCO and NCCN. The dose of DEX on days 2–4 was 8 mg/day orally. In Japan, the product specification of DEX tablet consists of only 0.5 mg tablet, therefore, patients have no choice but to take 16 pieces of DEX tablets in a day for 3 days. Although 20 patients received tablet formulation in the present study showed a complete medication compliance, patients receiving highly emetogenic chemotherapy often complain an impairment of emetic control due to a reduction of medication compliance. In this respect, it is likely that the film formulation is superior to tablet for maintaining an excellent medication compliance, since the present questionnaire indicated that oral acceptability of film was significantly greater in respect of the amount and ease in intake than that of tablet.

In the present study, the rate of complete protection from vomiting during acute phase was not significantly different between film-treated group (90%) and tablet-treated group (95%). The rate of complete protection from vomiting during delayed phase in film-treated group was the same (95%) as that in tablet-treated groups. Moreover, the time course of the complete protection from nausea or vomiting was similar between the two groups, in which the minimal rate of complete protection was 60% for nausea and 95% for vomiting in tablet group, while those were 55% for nausea and 90% for vomiting in film group. These data, taken together, suggested that there was no significant difference in the antiemetic effect between tablet and film. The rates of complete protection from vomiting obtained from the present study were similar to those reported by Grunberg et al. (2009) who showed in 41 breast cancer patients receiving anthracycline/cyclophosphamide chemotherapy that the rates of complete protection from vomiting are 100% and 95% during acute and delayed phases, respectively, while complete protection of nausea is only 32%, after a single-day three-drug regimen of palonosetron, dexamethasoneand and aprepitant. The high rate of complete protection from nausea observed in the present study may be due to the addition of DEX on days 2–4 in the present study but not in their study. Celio et al. (2011) reported that the addition of DEX on days 2 and 3 to the standard antiemetic regimen (palonosetron and DEX on day 1) increases the rate of complete response during delayed phase by 19% in patients receiving anthracycline/cyclophosphamide chemotherapy.

Concerning the oral acceptability of the film, patients reported in questionnaire that the film formulation is superior to the tablet with respect to the amount and ease in taking. Few patients complained the bitter taste of the film formulation. Moreover, the film formulation had no problem in the solubility in oral cavity, size or thickness.

In conclusion, we prepared a novel fast dissolving oral film containing DEX and examined the antiemetic effect and oral acceptability of the film. The complete protection from vomiting during delayed phase and the time course of the complete protection from nausea or vomiting were similar between the two groups. The oral acceptability of the film was superior to tablet in the amount and ease in taking. Therefore, the present fast dissolving oral film is considered to be successfully applicable to the prophylactic medication against chemotherapy-induced delayed nausea and vomiting.

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