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Ondansetron rapidly dissolving film for the prophylactic treatment of radiation-induced nausea and vomiting—a pilot study

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ABSTRACT

Introduction The purpose of the present study was to investigate the efficacy of an ondansetron rapidly dissolving film (RDF) in the prophylaxis of radiation-induced nausea and vomiting (RINV). Rapidly dissolving film formulations facilitate drug delivery in circumstances in which swallowing the medication might be difficult for the patient.

Methods Patients undergoing palliative radiotherapy at risk for RINV were prescribed ondansetron RDF 8 mg twice daily while on treatment and were asked to complete a nausea and vomiting–specific daily diary, the Functional Living Index–Emesis (FLIE), and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–C15 Palliative (QLQ-C15-PAL). Patients were categorized as receiving primary or secondary prophylaxis based on whether they had already experienced emetic episodes. "Overall control" was defined as a maximum increase of 2 episodes of nausea or vomiting from baseline. "Acute phase" was defined as the days during radiation until the first day after radiation; "delayed phase" was defined as days 2–10 after radiation.

Results The study accrued 30 patients. Rates of overall control for nausea and for vomiting during the acute phase in the primary prophylaxis group were 88% and 93% respectively; during the delayed phase, they were 73% and 75%. Rates of overall control for nausea and for vomiting during the acute phase in the secondary prophylaxis group were both 100%; during the delayed phase, they were 50%. The number of nausea and vomiting episodes was found to be significantly correlated with the FLIE and QLQ-C15-PAL questionnaires.

Conclusions Ondansetron RDF is effective for the prophylaxis of RINV.

Key Words Radiation-induced nausea and vomiting, prophylaxis, ondansetron, rapidly dissolving film

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INTRODUCTION

Depending on the anatomic site of treatment, radiation-induced nausea and vomiting (RINV) can affect 40%–80% of patients undergoing radiation therapy[1]. Inadequately controlled nausea and vomiting can lead to complications such as dehydration and electrolyte imbalance. Radiation-induced nausea and vomiting can also cause delay or discontinuation of radiation treatment[2–4], which can increase the need for medical care and be burdensome to the medical system[5,6].

Guidelines cooperatively issued by the American Society of Clinical Oncology, the Multinational Association of Supportive Care in Cancer, and the European Society for Medical Oncology recommend a 5-hydroxytryptamine-3 receptor antagonist for the prophylaxis or rescue therapy of RINV in high, moderate, and low emetogenic risk categories[2,7,8]. Ondansetron has been prescribed mainly in its oral pill form[8,9]. In the palliative setting, patients can present with comorbidities such as dysphagia or pre-existing nausea and vomiting from chemotherapy or opioid usage. Those symptoms can lead to difficulty in taking the oral pills.

Rapidly dissolving film (RDF) formulations are a proven technology for systemic delivery of medications. They facilitate drug delivery in circumstances in which swallowing can be difficult for the patient, and they also have potential advantages in patients with pre-existing vomiting, nausea, or both. Ondansetron has been formulated as a dissolvable film (Ondissolve: Takeda Canada, Oakville, ON). In a

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randomized single-dose crossover study comparing ondansetron RDF and an orally disintegrating tablet formulation of ondansetron (Zofran Zydis: Aspen Global, Grand-Baie, Mauritius), it was determined that the formulations were bioequivalent, allowing ondansetron RDF to apply for the same indications that the oral ondansetron formulations serve[10]. Our study examined the efficacy of ondansetron RDF (Ondissolve) in patients at risk of RINV.

METHODS

This prospective pilot trial investigated the efficacy of ondansetron RDF in patients receiving emetogenic radiation.

Eligibility Criteria

Patients were eligible if they were receiving palliative radiotherapy that was being delivered to the abdomen (defined specifically as vertebral levels T10–L3), the pelvis, or both, and that was considered to be of moderate or low emetogenic risk by the cooperative guideline from the American Society of Clinical Oncology, the Multinational Association of Supportive Care in Cancer, and the European Society for Medical Oncology. The radiotherapy had been prescribed for bone or soft-tissue metastases. The study was approved by the hospital research ethics board, and patients gave written informed consent.

Ineligibility Criteria

Patients were ineligible if they were scheduled to receive cranial radiation or chemotherapy during or within 10 days of emetogenic palliative radiotherapy or if they had received cranial radiation therapy within 7 days before commencement of palliative radiotherapy. Patients were not included if a scheduled change to their dose or regimen of corticosteroids or any other medication with antiemetic activity had been made within 48 hours of radiation or within 10 days after completion of radiation. Patients with a Karnofsky performance status less than 40 were also excluded.

Radiotherapy Treatment

Patients received either a single fraction (8 Gy) or multiple fractions (20 Gy in 5 fractions or 30 Gy in 10 fractions) of radiotherapy using simple beam arrangements.

Patient Assessments

Drug Administration

Patients were to take ondansetron RDF (8 mg) twice daily on the day or days of palliative radiotherapy, with the first dose being taken at least 1 hour before treatment and the subsequent dose being taken approximately 6–8 hours later in the day. For patients treated with multiple fractions of radiotherapy, patients were also prescribed ondansetron RDF twice daily for weekends or holidays between treatments. An additional 3-day supply of ondansetron RDF for use on an as-needed basis was given to all patients after radiation treatment.

Data Collection

Patient demographic and medical information including age, performance status, sex, primary cancer site, location (arriving for treatment from hospital or home), systemic therapy, radiation treatment prescribed, any pre-existing nausea and vomiting, and any pre-existing antiemetic medication consumed within 24 hours before treatment were recorded. Patients completed a daily diary for all days (including weekends) during treatment and the 10 days after completion of palliative radiotherapy. The daily diary assessed the patient's average experience of nausea and of vomiting or retching on a 4-point Likert scale ("none," "mild," "moderate," or "severe") for the preceding 24 hours. The number of nausea or vomiting episodes and the use of regular and rescue antiemetic medications were also recorded, including type of medication, dose, and amount taken in the preceding 24 hours.

Definitions

Nausea was defined as a feeling often occurring in the area of the back of the throat to the stomach. It is often described as queasiness with or without an urge to vomit, but might not lead to vomiting. Other ways to describe nausea are "sick to the stomach," "upset stomach," and "feel like I am going to throw up." An episode of nausea was defined a period of nausea with a distinct starting and ending point that could be identified by the patient and that was separated by at least 5 minutes of no nausea.

Vomiting was defined as the forceful expulsion of the contents of the stomach by way of the mouth. Other names used are "throwing up," "puking," "upchucking," and "barfing." An episode of vomiting was defined as a period of vomiting with a distinct starting and ending point, identified by at least 1 occurrence of vomiting or retching and separated from other episodes by a lack of vomiting for at least 5 minutes. Retching was defined as the act of vomiting, but without expulsion of any stomach contents. Common terms for retching include "gagging" and "dry heaving."

Functional Living Index–Emesis

The Functional Living Index–Emesis (FLIE) is an emesis-specific questionnaire with 18 questions answered on a scale of 1–7 (Table I). The FLIE can be divided into nausea- and vomiting-specific questions. A FLIE nausea summary score was determined by totalling the responses to the first 9 questions, and a FLIE vomiting summary score by totalling the responses to the last 9 questions. The FLIE includes 1 question that specifically asks about nausea and 1 that specifically asks about vomiting; the other questions assess how nausea and vomiting are interfering with the patient's daily life. A higher score represents increased symptoms or worse quality of life (QOL). Patients completed the FLIE at baseline and at days 3 and 7 after completion of palliative radiotherapy.

Quality of Life Questionnaire–C15 Palliative

The Quality of Life Questionnaire–C15 Palliative (QLQ-C15-PAL) from the European Organisation for Research and Treatment of Cancer is a shortened QOL questionnaire consisting of 15 questions (Table II) divided into two multi-item functional scales and two multi-item symptom scales. It also includes 5 singular symptom questions and 1 question on overall QOL. Other than the 1 question on overall QOL, which is rated on a scale from 1 ("very poor") to 7 ("excellent"), all other questions are rated on a 1–4 Likert

TABLE I Functional Living Index–Emesis

To be administered at baseline before radiation treatment then day 3 and day 7 following radiation treatment completion Date: _____ Day # _____							
1.	How much nausea have you had in the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
2.	Has nausea affected your ability to maintain usual recreation or leisure activities in the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
3.	Has nausea affected your ability to make a meal or do minor household repairs during the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
4.	How much has nausea affected your ability to enjoy a meal in the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
5.	How much has nausea affected your ability to enjoy liquid refreshment in the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
6.	How much has nausea affected your willingness to see and spend time with family and friends, in the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
7.	Has nausea affected your daily functioning in the past day?						
	1	2	3	4	5	6	7
	Not at all						A great deal
8.	Rate the degree to which your nausea has imposed a hardship on you (personally) in the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
9.	Rate the degree to which your nausea has imposed a hardship on those closest to you in the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
10.	How much vomiting have you had in the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
11.	Has vomiting affected your ability to maintain usual recreation or leisure activities during the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
12.	Has vomiting affected your ability to complete your usual household tasks during the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
13.	How much has vomiting affected your ability to enjoy a meal in the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
14.	How much has vomiting affected your ability to enjoy liquid refreshment in the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
15.	How much has vomiting affected your willingness to see and spend time with friends, in the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
16.	Has vomiting affected your daily functioning during the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
17.	Rate the degree to which your vomiting has imposed a hardship on you (personally) in the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal
18.	Rate the degree to which your vomiting has imposed a hardship on those closest to you in the past 3 days?						
	1	2	3	4	5	6	7
	Not at all						A great deal

TABLE II European Organisation for Research and Treatment Of Cancer Quality of Life Questionnaire–C15 Palliative

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.				
	Not at all	**A little**	**Quite a bit**	**Very much**
1. Do you have any trouble taking a short walk outside the house?	1	2	3	4
2. Do you need to stay in bed or a chair during the day?	1	2	3	4
3. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:				
4. Were you short of breath?	1	2	3	4
5. Have you had pain?	1	2	3	4
6. Have you had trouble sleeping?	1	2	3	4
7. Have you felt weak?	1	2	3	4
8. Have you lacked appetite?	1	2	3	4
9. Have you felt nauseated?	1	2	3	4
10. Have you been constipated?	1	2	3	4
11. Were you tired?	1	2	3	4
12. Did pain interfere with your daily activities?	1	2	3	4
13. Did you feel tense?	1	2	3	4
14. Did you feel depressed?	1	2	3	4
For the following question, please circle the number between 1 and 7 that best applies to you.				
15. How would you rate your overall quality of life during the past week?				
1 2 3 4 5 6 7				
Very poor … Excellent				

scale. A higher score on the functional scales and the overall QOL question represent better functioning; for the symptom items, the opposite is true. Patients completed the QLQ-C15-PAL at baseline and on days 5 and 10 after completion of palliative radiotherapy.

Drug Administration Survey

Patients also completed a 6-question survey that gauged whether they had ever taken medication in the form of an oral disintegrating film (ODF), the length of time required to use the ODF, and any problems or side effects that had been encountered. The questionnaire also addressed whether or why patients would or would not consider using an ODF. Patients were also asked whether they liked using the ODF (Table III).

Primary and Secondary Objectives

The primary objective of the study was to examine the efficacy of ondansetron RDF for the prophylaxis and rescue of acute-phase RINV in patients undergoing single or multiple fractions of low-to-moderate emetogenic palliative radiation therapy. Secondary objectives included efficacy in the delayed phase and QOL outcomes.

Study Definitions

"Acute phase" was defined as the period from the first day of radiotherapy to the first day after radiotherapy completion. "Delayed phase" was days 2 to 10 after radiotherapy. "Combined phase" included both the acute and the delayed phases.

Patients were analyzed in two categories: "primary prophylaxis" (patients with no pre-existing nausea or vomiting) and "secondary prophylaxis" (patients with pre-existing nausea and vomiting or antiemetic use for non-radiation causes).

"Complete control" was defined as no emetic episodes or no increase of emetic episodes (in secondary prophylaxis) and no use of rescue antiemetic medication during and after radiotherapy (acute and delayed phase). "Partial control" was defined as an increase of 2 or fewer emetic episodes from baseline and no use of rescue antiemetic medication during or after radiotherapy (acute or delayed phase). "Uncontrolled" or "failure" was defined as an increase of 3 or more emetic episodes or use of antiemetic rescue medication. "Overall control" was defined as the sum of complete and partial control.

Statistical Analyses

The intention-to-treat (ITT) principle was applied. The analysis excluded 4 patients with incomplete follow-up (because of death and noncompliance); the remaining patients were considered evaluable. Demographic and medical information for ITT patients was summarized as means, medians, standard deviations, and ranges. Complete control, partial

TABLE III Patient drug administration survey (self-complete)

The following questions refer to the oral film that you took.
This drug may help in preventing nausea, vomiting and/or needing rescue medication for these symptoms.

1. Did you complete taking the protocol medication?
   - ❒ Yes
   - ❒ No

   If no, why did you not complete taking the medication?

   _____

   _____

2. Have you ever taken medication in the form of an oral film?
   - ❒ Yes
   - ❒ No

3. How long did it take to use the oral film? (i.e., time from removal of the package until fully dissolved)

   _____minutes

4. Did you encounter any problems with the use of this oral film?
   - ❒ Yes
   - ❒ No

   If yes, what problems did you encounter with the use of this oral film?

   _____

   _____

5. Would you consider using an oral film like this again?
   - ❒ Yes
   - ❒ No

   If yes, what are the reasons?

   _____

   _____

   _____

   If no, what are the reasons? (Check all that apply)
   - ❒ I have/had problems with my mouth
   - ❒ I have dry mouth
   - ❒ I don't like the idea of this oral film
   - ❒ I am concerned about the taste in my mouth
   - ❒ I have previously had a bad experience with using oral films
   - ❒ I am concerned about the effectiveness of oral films
   - ❒ I prefer another route of administration (i.e., oral tablet)
   - ❒ I am concerned about the side effects (If yes, check all below that apply)
     - ❒ I had nausea after using this oral film
     - ❒ I retched (gagged) during or after using this oral film
     - ❒ I vomited after using this oral film
     - ❒ Other reason:

       _____

       _____

6. Overall, I liked using this oral film.
   - ❒ Yes
   - ❒ No

control, and failure were calculated according to study definitions and were summarized for both ITT and evaluable patients by nausea and vomiting and by acute or delayed phase separately.

To search for significant correlations within the FLIE, Spearman correlations between the first question (Q1) and the other nausea questions (Q2–Q9) and between the tenth question (Q10) and the other vomiting questions (Q11–Q18) were determined. The general linear regression model was applied for the FLIE nausea question and the remaining nausea-related questions and for the FLIE vomiting question and the remaining vomiting-related questions. To normalize the distribution, natural-log transformation was applied. A positive coefficient indicates a positive relationship between the nausea or vomiting question and the other nausea-related or vomiting-related items.

Spearman correlations were also determined for the total number of nausea or vomiting episodes during the first 5 days or the last 5 days with the QLQ-C15-PAL domains and with the overall QOL question (Q15) collected on days 5 and 10 respectively. To further determine the relationship of total episodes of nausea or vomiting with the QLQ-C15-PAL domains and with the overall QOL question (using log scale), the general linear model was applied for the count data. Poisson distribution with the log link function was used, and a GENMOD procedure was conducted in the SAS software application (version 9.3 for Windows: SAS Institute, Cary, NC, U.S.A.). Scatterplots of total nausea episodes or total vomiting episodes versus the most significant QLQ-C15-PAL domains during the first 5 days or the last 5 days were performed, with a general linear regression line shown on the plot. Values of p less than 0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Of the 30 patients enrolled (Table IV), 26 (87%) had complete follow-up. Follow-up in the delayed phase was incomplete for 4 patients because of death ($n = 1$) or patient noncompliance ($n = 3$). The mean age of the patients was 71 years, and median Karnofsky performance status was 70. More than half the patients were men ($n = 19$, 63%), and the most common primary cancer sites were prostate (37%), breast (27%), and lung (10%). Most patients were treated with a single fraction of 8 Gy (67%); the remaining 33% of patients were treated with multiple fractions.

Baseline Nausea and Vomiting

Most patients ($n = 26$) did not have pre-existing nausea or vomiting; 2 patients had pre-existing nausea only, and 2 patients had pre-existing nausea and vomiting. Of the latter 2 patients, 1 reported both mild nausea and vomiting, with 1 episode of each symptom in the 24 hours preceding radiation. The other patient reported both nausea and vomiting, with 7 episodes of each symptom in the 24 hours preceding radiation. Of the 2 patients who reported pre-existing nausea, both reported mild nausea, with 2 and 3 episodes of nausea respectively in the 24 hours preceding radiation. Of the 4 non-evaluable patients, 2 had no pre-existing nausea or vomiting, 1 had mild pre-existing nausea only, and 1 had mild pre-existing nausea and vomiting (Table V).

TABLE IV Demographics for the study patients

Variable	Patient group		
	All	Prophylaxis	
		Primary[a]	Secondary[b]
Patients (n)	30	26	4
Age (years)			
Mean	71.3±11.0	71.6±11.7	69.8±5.7
Median	74	74	70
Range	40–91	40–91	63–77
Score on the KPS			
Mean	69.3±14.8	69.2±15.2	70.0±14.1
Median	70	70	75
Range	40–100	40–100	50–80
Sex [n (%)]			
Women	11 (36.67)	10 (38.46)	1 (25.00)
Men	19 (63.33)	16 (61.54)	3 (75.00)
Location [n (%)]			
Home	28 (93.33)	24 (92.31)	4 (100.00)
Hospital	2 (6.67)	2 (7.69)	0
Primary cancer site [n (%)]			
Prostate	11 (36.67)	10 (38.46)	1 (25.00)
Breast	8 (26.67)	8 (30.77)	0
Lung	3 (10.00)	2 (7.69)	1 (25.00)
Bladder	2 (6.67)	2 (7.69)	0
Other	4 (13.33)	3 (11.54)	1 (25.00)
Unknown	2 (6.67)	1 (3.85)	1 (25.00)
Systemic treatment [n (%)]			
None	16 (53.33)	13 (50.00)	3 (75.00)
Chemotherapy	8 (26.67)	7 (26.92)	1 (25.00)
Hormone therapy	4 (13.33)	4 (15.38)	0
Bisphosphonate only	2 (6.67)	2 (7.69)	0
Dose [n (%)]			
8 Gy in 1 fraction	20 (66.67)	16 (61.54)	4 (100.00)
20 Gy in 5 fractions	6 (20.00)	6 (23.08)	0
30 Gy in 10 fractions	4 (13.33)	4 (15.38)	0

[a] No pre-existing emetic episodes.
[b] Pre-existing emetic episodes.
KPS = Karnofsky performance status.

Control of RINV in Acute Phase

Primary Prophylaxis Group

Using ITT analysis, 21 patients (81%) experienced complete control of nausea, 2 (8%) experienced partial control, and 3 patients (12%) had uncontrolled nausea. The overall control rate for nausea was 88%. Control of vomiting was complete in 25 of 28 patients (89%) and partial in 1 patient (4%); 2 patients (7%) experienced uncontrolled vomiting (Table VI). The overall control rate for vomiting was 93%.

Secondary Prophylaxis Group

Of the ITT and evaluable patients, all 4 with pre-existing nausea (100%) experienced complete control of nausea, and the 2 with pre-existing vomiting (100%) experienced complete control of vomiting. The overall control rate

TABLE V Individual patient characteristics and nausea and vomiting response rates

Pt ID	Dose	Fr.	Control of nausea				Control of vomiting			
			Baseline	Acute	Delayed	Combined	Baseline	Acute	Delayed	Combined
1		1	None	Complete	Uncontrolled	Uncontrolled	None	Complete	Uncontrolled	Uncontrolled
2		1	None	Partial	Uncontrolled	Uncontrolled	None	Complete	Uncontrolled	Uncontrolled
3		1	None	Complete	Complete	Complete	None	Complete	Complete	Complete
4		1	Mild (2 eps)	Complete	Complete	Complete	None	Complete	Complete	Complete
5		1	None	Complete	Complete	Complete	None	Complete	Complete	Complete
6	20 Gy	5	None	Uncontrolled	Complete	Uncontrolled	None	Complete	Complete	Complete
7	20 Gy	5	None	Complete	Complete	Complete	None	Complete	Complete	Complete
8		1	None	Complete	Complete	Complete	None	Complete	Complete	Complete
9		1	None	Complete	Complete	Complete	None	Complete	Complete	Complete
10	30 Gy	10	None	Complete	Uncontrolled	Uncontrolled	None	Complete	Uncontrolled	Uncontrolled
11		1	None	Complete	Complete	Complete	None	Complete	Complete	Complete
12		1	None	Partial	Partial	Partial	None	Complete	Complete	Complete
13		1	None	Complete	Complete	Complete	None	Complete	Complete	Complete
14	20 Gy	5	None	Complete	Complete	Complete	None	Complete	Complete	Complete
15	20 Gy	5	None	Complete	Complete	Complete	None	Complete	Complete	Complete
16	30 Gy	10	None	Uncontrolled	Uncontrolled	Uncontrolled	None	Uncontrolled	Uncontrolled	Uncontrolled
17	30 Gy	10	None	Complete	Complete	Complete	None	Complete	Complete	Complete
18		1	None	Complete	Complete	Complete	None	Complete	Complete	Complete
19		1	Mild (3 eps)	Complete	Uncontrolled	Uncontrolled	None	Complete	Uncontrolled	Uncontrolled
20		1	Mild (1 eps)	Complete	Uncontrolled	Uncontrolled	Mild (1 eps)	Complete	Uncontrolled	Uncontrolled
21		1	Severe (7 eps)	Complete	Complete	Complete	Severe (7 eps)	Complete	Complete	Complete
22	20 Gy	5,1	None	Uncontrolled	Uncontrolled	Uncontrolled	None	Partial	Uncontrolled	Uncontrolled
23		1	None	Complete	Complete	Complete	None	Complete	Complete	Complete
24		1	None	Complete	Complete	Complete	None	Complete	Complete	Complete
25		1	None	Uncontrolled	Uncontrolled	Uncontrolled	None	Complete	Complete	Complete
26		1	None	Complete	Complete	Complete	None	Complete	Complete	Complete
27	30 Gy	10	None	Uncontrolled	Uncontrolled	Uncontrolled	None	Uncontrolled	Uncontrolled	Uncontrolled
28		1	None	Complete	Complete	Complete	None	Complete	Complete	Complete
29	20 Gy	5	None	Complete	Complete	Complete	None	Complete	Complete	Complete
30		1	None	Complete	Complete	Complete	None	Complete	Complete	Complete

Pt = patient; Fr. = fractions; eps = episodes.

was therefore 100% for both nausea and vomiting. These 4 patients not only had no increase in their episodes of nausea or vomiting, but also reported no episodes of nausea or vomiting at all during the acute phase. Their pre-existing nausea or emetic episodes were controlled by the ondansetron RDF (Table VI).

Control of RINV in Delayed Phase

Primary Prophylaxis Group

Complete control of nausea was experience by 18 patients, for response rates of 69% and 75% in the ITT and evaluable patient analysis respectively. Partial control was experienced by 1 patient, for a response rate of 4% in ITT analysis; however, this patient was excluded from the evaluable patient analysis. The overall control rate for nausea was therefore 73% and 75% for the ITT and the evaluable patient analysis respectively. Nausea was uncontrolled in 7 ITT patients (27%) and 6 evaluable patients (25%). Complete primary control of vomiting was experienced by 21 ITT patients (75%) and 20 evaluable patients (80%). No patient experienced partial control of vomiting. The overall control rate for vomiting was therefore 75% and 80% for the ITT and the evaluable patient analysis respectively. Vomiting was uncontrolled for 7 ITT patients (25%) and 5 evaluable patients (20%, Table VI).

Secondary Prophylaxis

In the ITT and evaluable patient analyses, 2 patients (50%) experienced complete control of nausea; nausea was uncontrolled in 2 patients (50%). Control of vomiting was complete in 1 patient (50%); vomiting was uncontrolled

TABLE VI Intention-to-treat and evaluable-patient analyses of rates of complete and partial control, by phase

Phase	Symptom	Intention-to-treat [*n*/*N* (%)]						Evaluable patients [*n*/*N* (%)]					
		Primary prophylaxis			Secondary prophylaxis			Secondary prophylaxis			Primary prophylaxis		
		Complete control	Partial control	Uncontrolled	Complete control	Partial control	Uncontrolled	Complete control	Partial control	Uncontrolled	Complete control	Partial control	Uncontrolled
Acute													
	Nausea	21/26 (81)	2/26 (8)	3/26 (12)	4/4 (100)	0 (0)	0 (0)	Same as intention-to-treat analysis because of complete follow-up during this phase					
	Vomiting	25/28 (89)	1/28 (4)	2/28 (7)	2/2 (100)	0 (0)	0 (0)						
Delayed													
	Nausea	18/26 (69)	1/26 (4)	7/26 (27)	2/4 (50)	0/4 (0)	2/4 (50)	2/2 (100)	0/2 (0)	0/2 (0)	18/24 (75)	0/24 (0)	6/24 (25)
	Vomiting	21/28 (75)	0/28 (0)	7/28 (25)	1/2 (50)	0/2 (0)	1/2 (50)	1/1 (100)	0/1 (0)	0/1 (0)	20/25 (80)	0/25 (0)	5/25 (20)
Combined													
	Nausea	17/26 (65)	1/26 (4)	8/26 (31)	2/4 (50)	0/4 (0)	2/4 (50)	2/2 (100)	0/2 (0)	0/2 (0)	17/24 (71)	0/24 (0)	7/24 (29)
	Vomiting	21/28 (75)	0/28 (0)	7/28 (25)	1/2 (50)	0/2 (0)	1/2 (50)	1/1 (100)	0/1 (0)	0/1 (0)	20/25 (80)	0/25 (0)	5/25 (20)

in 1 patient (50%, Table VI). The overall control rates for nausea and vomiting were both 50%.

Control of RINV in Combined Phase

Results for the combined phase can be found in Tables V and VI.

Patient Preference

Of the 26 patients who completed the drug administration survey, 22 (84.6%) reported that they would consider using a RDF formulation again. Of the 4 patients who reported that they would not consider using the oral film, the main reasons were concerns about the taste and having a dry mouth. Most patients reported that using the oral film took approximately 2–3 minutes from time of removal from the package until the dose was fully dissolved in the mouth.

QOL and Impact

With respect to the FLIE, we observed a highly significant positive correlation (Spearman $r \geq 0.65$, $p < 0.0001$) and a highly significant positive relationship ($p < 0.001$) between Q1 (nausea) and the remaining nausea-related items and between Q10 (vomiting) and the remaining vomiting-related items at both day 3 and day 7 (Table VII).

During the first 5 days after radiation, the total number of nausea episodes was highly significantly related to the QLQ-C15-PAL scales for nausea and vomiting ($p < 0.0001$), emotional functioning ($p < 0.0001$), and dyspnea ($p = 0.03$, Table VIII). Patients with higher total number of nausea episodes were more likely to have a higher dyspnea or nausea and vomiting scale, and a lower emotional functioning scale. During the last 5 days after radiation, patients with a higher total number of nausea episodes were more likely to have lower physical ($p = 0.007$) and emotional functioning ($p < 0.0001$) scales and a greater nausea and vomiting ($p < 0.0001$) scale.

During the first 5 days after radiation, the total number of vomiting episodes was again highly significantly related to the QLQ-C15-PAL scales for nausea and vomiting ($p < 0.0001$), emotional functioning ($p < 0.0001$), and physical functioning ($p = 0.001$). Patients with a higher total number of vomiting episodes were more likely to have higher nausea and vomiting scales, and lower physical and emotional functioning scales. During the last 5 days after radiation, patients with a higher total number of vomiting episodes were more likely to have lower physical functioning ($p = 0.0003$) and emotional functioning ($p < 0.0001$) scales, a lower overall QOL scale ($p = 0.03$), or a greater nausea and vomiting scale ($p < 0.0001$). Patients with a higher number of vomiting episodes were also more likely to have lower overall QOL (Table VIII).

Figure 1(A) shows scatterplots of total nausea or vomiting episodes versus the most significant QLQ-C15-PAL domains during the first 5 days. The two domain scales of nausea or vomiting and emotional functioning were highly significantly correlated with nausea and vomiting episodes ($p < 0.0001$). Similarly in Figure 1(B), the total episodes of nausea or vomiting were highly correlated with the scales for physical functioning, nausea or vomiting, and emotional functioning on the QLQ-C15-PAL (all $p < 0.01$).

TABLE VII Spearman correlation and general linear regression analysis between nausea question Q1 and other nausea-related items, and between vomiting question Q10 and other vomiting-related items, on the Functional Living Index–Emesis questionnaire at days 3 and 7

Item (log scale)	At day 3					At day 7				
	Item summary		Spearman correlation		*p* Value[b]	Item summary		Spearman correlation		*p* Value[b]
	Mean[a]	Median	*r*	*p* Value		Mean[a]	Median	*r*	*p* Value	
Between nausea question (Q1)[c] and other nausea-related items										
Q2	1.13±0.43	1	0.84	<0.0001	<0.0001	1.23±0.82	1	0.83	<0.0001	<0.0001
Q3	1.21±0.82	1	0.78	<0.0001	<0.0001	1.19±0.69	1	0.83	<0.0001	<0.0001
Q4	1.40±1.19	1	0.99	<0.0001	<0.0001	1.37±1.01	1	1	<0.0001	<0.0001
Q5	1.17±0.46	1	0.84	<0.0001	<0.0001	1.15±0.60	1	0.65	0.0003	0.0008
Q6	1.10±0.40	1	0.65	0.0001	0.0005	1.19±0.56	1	0.84	<0.0001	<0.0001
Q7	1.13±0.43	1	0.84	<0.0001	<0.0001	1.19±0.56	1	0.84	<0.0001	<0.0001
Q8	1.20±0.55	1	0.83	<0.0001	<0.0001	1.26±0.71	1	1	<0.0001	<0.0001
Q9	1.13±0.51	1	0.65	0.0001	0.0008	1.22±0.80	1	0.71	<0.0001	<0.0001
Between vomiting question (Q10)[c] and other vomiting-related items										
Q11	1.03±0.18	1	0.69	<0.0001	<0.0001	1.19±0.68	1	0.83	<0.0001	<0.0001
Q12	1±0	1	0.69	<0.0001	NA	1.19±0.68	1	0.83	<0.0001	<0.0001
Q13	1.03±0.18	1	0.69	<0.0001	<0.0001	1.30±1.2	1	0.78	<0.0001	0.0003
Q14	1.03±0.18	1	0.69	<0.0001	<0.0001	1.30±1.2	1	0.78	<0.0001	0.0003
Q15	1.03±0.18	1	0.69	<0.0001	<0.0001	1.15 ±0.60	1	0.78	<0.0001	<0.0001
Q16	1.03±0.19	1	0.69	<0.0001	<0.0001	1.19±0.68	1	0.83	<0.0001	<0.0001
Q17	1.07±0.25	1	1	<0.0001	NA	1.19±0.56	1	1	<0.0001	NA
Q18	1.03±0.18	1	0.69	<0.0001	<0.0001	1.12±0.43	1	1	<0.0001	NA

[a] With standard deviation.
[b] Obtained by general linear regression of Q1 or Q10 (log scale) on the other nausea-related (Q2–Q9) or vomiting-related items (Q11–Q18). Each model found all positive coefficients, indicating a positive relationship between outcome and individual items on the Functional Living Index–Emesis. Values of $p < 0.05$ were considered statistically significant.
[c] The mean and median values for the Q1 nausea question were, respectively, 1.24±0.64 and 1 at day 3, and 1.26±0.66 and 1 at day 7. The mean and median values for the Q10 vomiting question were, respectively, 1.07±0.25 and 1 at day 3 and 1.19±0.56 and 1 at day 7.
NA = not available (all Q12 responses were 1 at day 3; responses to Q17 at day 3 were same as the outcome of Q10; and responses to Q18 at day 7 were the same as the outcome of Q10).

DISCUSSION AND CONCLUSIONS

The present study is the first to report the efficacy of ondansetron RDF in RINV. In the primary prophylaxis group, complete and partial control rates for nausea in the acute phase were 81% and 8% respectively; for vomiting, they were 89% and 4%. In the delayed phase, the complete and partial control rates for nausea were 69% and 4% respectively; for vomiting, they were 75% and 0%. In the secondary prophylaxis group, the complete control rates for nausea and vomiting in the acute phase were both 100%. In the delayed phase, the complete and partial control rates for nausea were 50% and 0% respectively; for vomiting, they were 50% and 0%. The lower results for the delayed phase were likely a result of the short half-life of ondansetron RDF (4–6 hours) which was taken mostly during the acute phase.

Use of an ondansetron oral pill for the prophylaxis of RINV in patients has previously been reported[1,11,12]. Our group used the ondansetron 8 mg regular oral formulation for the prophylaxis of RINV and reported a complete control rate of 59% for nausea and 75% for vomiting[1]. In another study by Presutti *et al.*, the reported prophylaxis rate using the regular ondansetron 8 mg oral formulation for nausea during the acute phase was 54% in a single-fraction group and 67% in a multifraction group. For vomiting, the rate was 92% in the single-fraction group and 67% in the multifraction group[12]. In the present study, we observed similar response rates for the prophylaxis of both nausea and vomiting.

The international, multicentre, placebo-controlled, randomized NCIC Clinical Trials Group SC.19 trial (5-hydroxytryptamine-3 receptor antagonist with or without short-course dexamethasone in the prophylaxis of radiation-induced emesis) reported a response rate of 50% for complete control of nausea, 78% for complete control of vomiting, and an overall control rate for vomiting of 91%

TABLE VIII Relationship of total episodes of nausea or vomiting with responses on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–C15 Palliative (C15-PAL)[a]

Variable	Total nausea episodes[b]			Total vomiting episodes[b]			C15-PAL summary	
	Coefficient	SE	*p* Value[c]	Coefficient	SE	*p* Value[c]	Mean	Median
During the first 5 days								
C15-PAL, question 15	–0.187	0.713	0.7925	–0.200	0.821	0.8078	3.86±1.46	4
Pain	–0.058	0.254	0.8192	–0.192	0.250	0.4432	50.6±31.0	50
Dyspnea	**0.690**	**0.325**	**0.0337**	1.371	0.804	0.0880	24.1±25.0	33
Insomnia	0.314	0.217	0.1477	0.306	0.252	0.2241	34.5±33.9	33
Appetite loss	0.405	0.249	0.1033	0.428	0.301	0.1551	36.8±36.0	33
Constipation	–0.073	0.179	0.6813	–0.354	0.254	0.1629	27.6±34.6	0
Overall quality of life	0.053	0.351	0.8796	0.015	0.386	0.9695	47.7±24.3	50
Physical functioning	–0.342	0.178	0.0549	**–0.642**	**0.195**	**0.0010**	49.0±36.2	40
Fatigue	0.677	0.565	0.2305	1.484	0.903	0.1006	54.8±34.4	56
Nausea/vomiting	**0.724**	**0.136**	**<0.0001**	**0.920**	**0.161**	**<0.0001**	5.75±19.0	0
Emotional functioning	**–0.639**	**0.145**	**<0.0001**	**–0.915**	**0.121**	**<0.0001**	69.2±25.8	67
During the last 5 days								
C15-PAL, question 15	–1.579	1.067	0.1389	**–2.704**	**1.338**	**0.0433**	3.85±1.51	4
Pain	–0.063	0.323	0.8459	1.450	0.968	0.1341	49.4±32.5	50
Dyspnea	0.505	0.282	0.0736	1.136	0.616	0.0650	25.9±31.1	33
Insomnia	0.359	0.371	0.3325	0.360	0.411	0.3814	44.4±33.3	33
Appetite loss	0.187	0.234	0.4245	1.142	0.793	0.1498	38.3±36.6	33
Constipation	–0.420	0.274	0.1252	–0.363	0.286	0.2045	27.1±34.6	0
Overall quality of life	–1.142	0.716	0.1106	**–1.849**	**0.873**	**0.0343**	**47.7±24.3**	**50**
Physical functioning	**–0.538**	**0.198**	**0.0066**	**–0.817**	**0.228**	**0.0003**	**49.0±36.2**	**40**
Fatigue	0.492	0.472	0.2973	1.938	1.267	0.1263	54.8±34.4	56
Nausea/vomiting	**0.881**	**0.167**	**<0.0001**	**1.137**	**0.220**	**<0.0001**	**5.75±19.0**	**0**
Emotional functioning	**–0.665**	**0.155**	**<0.0001**	**–0.847**	**0.170**	**<0.0001**	**69.2±25.8**	**67**

[a] Analyzed using a generalized linear model with Poisson distribution and log link function. The independent variable in each case was the symptom or scale score on the C15-PAL (log scale). Boldface type indicates statistically significant results..

[b] The mean and median of the total number of nausea episodes were, respectively, 2.23±5.44 and 0 (range: 0–24) during the first 5 days, and 1.14±3.49 and 0 (range: 0–18) during the last 5 days. The mean and median of the total number of vomiting episodes were, respectively, 0.90±3.19 and 0 (range: 0–17) during the first 5 days, and 1.04±3.68 and 0 (range: 0–19) during the last 5 days.

[c] Values of $p < 0.05$ were considered statistically significant.

SE = standard error.

during the period when patients were taking ondansetron and dexamethasone. The ondansetron-with-placebo arm had lower rates in each category[11]. The present study showed that the efficacy of the RDF formulation was similar to the efficacy of the oral preparation.

Patient preference for medication formulation is important in improving patient compliance and ultimately preventing RINV. In the survey portion of our study, most patients preferred using the film formulation and would use the film again. The patient-reported problems with using the film were mainly taste and the difficulty of dissolving the film if patients had less saliva. Some patients also reported difficulty in removing the film from the packaging.

The main limitation of the study is its small sample size. Most of our patients had no pre-existing nausea and vomiting. Although the results are promising, our findings have to be confirmed in a larger study and perhaps in a randomized trial comparing the ondansetron oral pill formulation with ondansetron RDF in the prophylaxis of RINV. A second limitation is that, because of our inclusion criteria and accrual from an outpatient palliative radiotherapy clinic, the generalizability of the study could be limited: Not all palliative patients referred for radiation are outpatients and would meet criteria such as freedom from chemotherapy or cranial radiation for 7 days before and 10 days after treatment.

In conclusion, ondansetron RDF is effective in the prophylaxis of RINV. However, patients might need to moisten their mouth by drinking water or fluids to allow for better absorption of the ondansetron RDF, because dry mouth limits drug absorption.

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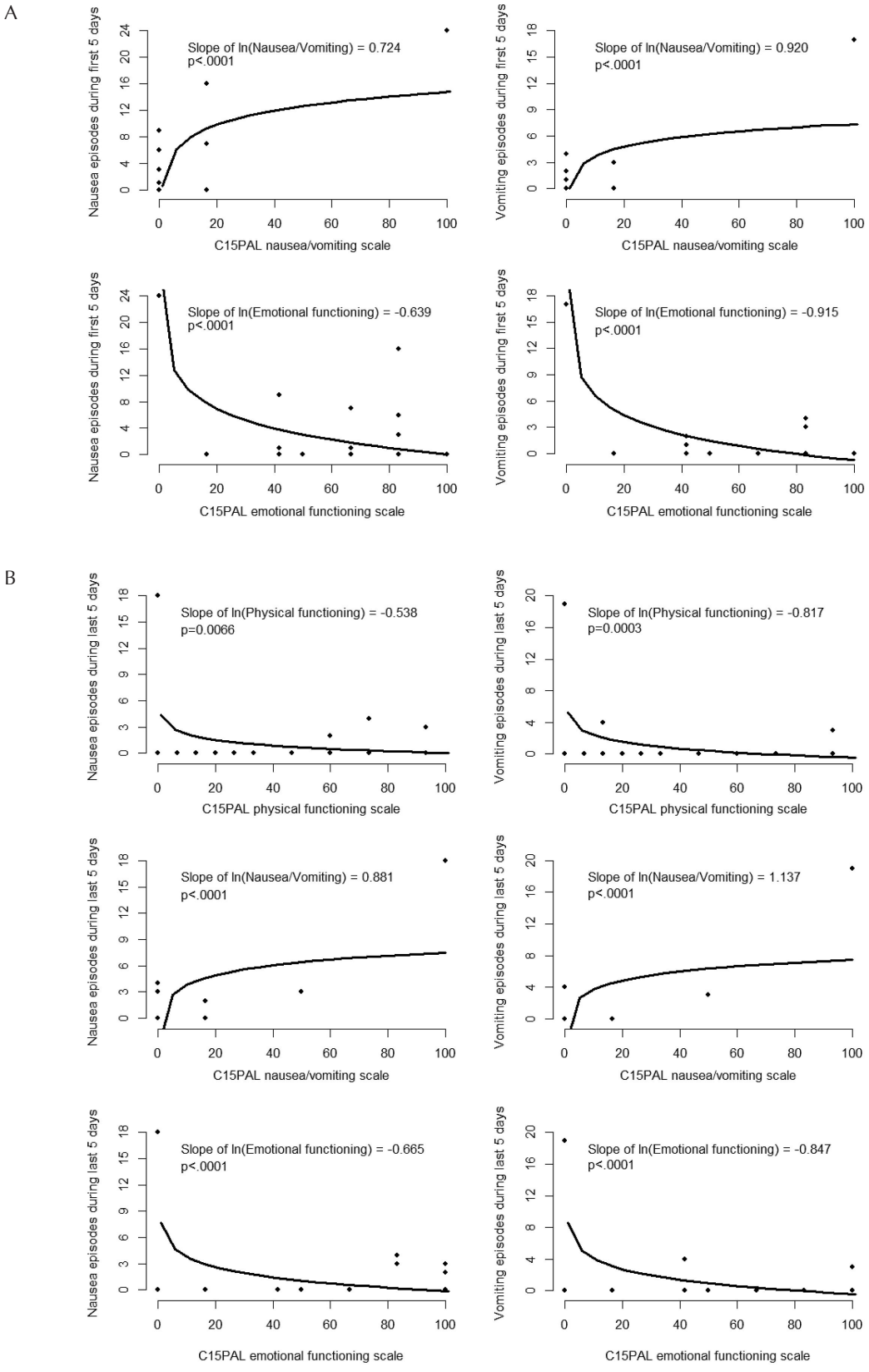

FIGURE 1 Scatterplots with fitted generalized regression lines for total nausea or vomiting episodes (A) during the first 5 days and (B) during the last 5 days, by domain on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–C15 Palliative (C15PAL).

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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