Published in final edited form as:
J Pain Symptom Manage. 2008 April ; 35(4): 381–387. doi:10.1016/j.jpainsymman.2007.05.008.

Effect of a Nausea Expectancy Manipulation on Chemotherapy-Induced Nausea: A University of Rochester Cancer Center Community Clinical Oncology Program Study

Abhay R. Shelke, MD[1], **Joseph A. Roscoe, PhD**[1], **Gary R. Morrow, PhD, MS**[1], **Lauren K. Colman, MD**[2], **Tarit K. Banerjee, MD**[3], and **Jeffrey J. Kirshner, MD**[4]

[1] University of Rochester, James P. Wilmot Cancer, Rochester, NY

[2] Northwest CCOP, Tacoma, WA

[3] Marshfield Clinic Research Foundation CCOP, Marshfield, WI

[4] Hematology-OncologyAssociates of Central NY, Syracuse, NY

Abstract

Several studies have shown that patients' expectancy for the development of nausea following chemotherapy are robust predictors of that treatment-related side effect and some studies have shown that interventions designed to influence expectancies can affect patients' reports of symptoms. In this randomized multicenter Community Clinical Oncology Program (CCOP) trial, we investigated the effect of an expectancy manipulation designed to reduce nausea expectancy on chemotherapy-induced nausea in 358 patients scheduled to receive chemotherapy treatment. Patients in the intervention arm received general cancer-related educational material plus specific information about the efficacy of ondansetron specifically designed to diminish nausea expectancy. Patients in the control arm received only the general cancer-related educational material. Nausea expectancy was assessed both prior to and following the educational intervention. We observed a significant reduction in nausea expectancy in the intervention group ($p = 0.024$) as compared to the control group ($p = 0.34$). In the intervention group, patients' expectations of nausea assessed prior to the intervention correlated significantly with average nausea ($r = .27$, $p = .001$); whereas nausea expectancy assessed following the intervention did not ($r = 0.1$, $p = 0.22$). In our study, the expectancy manipulation reduced patients' reported expectations for the development of nausea but did not reduce occurrence of nausea. Furthermore, post-intervention nausea expectancy compared to pre-intervention expectancy was less predictive of subsequent nausea. Explanations for these findings include the possibility that the expectancy manipulation was not strong enough, and the possibility that changing nausea expectancies does not change occurrence of nausea.

Keywords

Expectations; Nausea Severity; Chemotherapy; Response expectancy

Introduction

Nausea and vomiting (NV) continue to be troublesome and common side-effects of many chemotherapy regimens.[1–5] Although the occurrence and severity of chemotherapy-induced

Correspondence: Abhay R. Shelke, MD, University of Rochester Cancer, Center 601 Elmwood Avenue, Box 704, Rochester, NY 14642, Phone (585) 273-5357, Fax: (585) 461-5601 Abhay_Shelke@urmc.rochester.edu.

NV derive largely from the emetogenic potential of the chemotherapeutic drugs, individual patient characteristics, such as younger age,[6] female gender,[7] previous experience of pregnancy-related nausea,[6,8] and a history of motion sickness,[9] play a role. Even taking all these factors into account, there is great deal of variability both across and within specific chemotherapyregimens with respect to the occurrence and severity of NV. This unexplained variation in NV might reflect differences in multiple factors, including: the prescription and usage of antiemetic agents,[10] psychological factors, such as infusion-related state anxiety, behavioral conditioning, and general" psychological stress." [9,11] Patients' beliefs and expectations about whether they will experience NV from chemotherapy have also been demonstrated to be strong and independent predictors of chemotherapy-related NV.[9,12–16]

In our previous studies, we found a significant relationship between patients' pretreatment expectations for nausea development and their mean postchemotherapy nausea severity[15] and that pretreatment expectations of experiencing chemotherapy-induced nausea make a significant contribution to the development of anticipatory nausea.[17] Recently, we reported that expectancy of nausea assessed in 194 female breast cancer patients before they received their first doxorubicin-based chemotherapy cycle was a strongpredictor of subsequent nausea severity, and in fact, was a stronger predictor than previously reported predictive factors, such as age, nausea during pregnancy, and susceptibility to motion sickness. In that study, expectation of developing nausea as a result of treatment was assessed before treatment by the question: "Before you spoke to your doctor about possible side effects of chemotherapy, what did you think the chances were that you would have severe nausea from your treatments?" The possible responses were "very unlikely," "unlikely," "about even chance," "likely," and "very likely." Patients who believed it was "very likely" that they would experience severe nausea from chemotherapy were five times more likely to have severe nausea than fellow patients who thought its occurrence would be "very unlikely." [16]

Several hypotheses have been offered to explain the relationship between symptom expectancies and subsequent report of symptoms. T he simplest explanation is that the predictive capacity of expectancies derives from the patient's prior experience with factors that cause the symptom. For example, by the time most people reach adulthood, they have a fairly good idea of how susceptible they are to nausea and what circumstances are likely to cause it. Cognitive schemas[18] may also be involved in that expectations of symptoms may exacerbate their intensity and/or frequency because, for an individual expecting a symptom such as nausea, an otherwise ambiguous physiological sensation, such as stomach rumbling, is more likely to be interpreted as nausea than when nausea is not expected. Another possible factor involves what might be called a "Self-Fulfilling Prophecy" (SFP) or "nocebo" effect. SFP is a phenomenon by which belief that a future event will occur contribute to that event actually occurring. SFP plays a powerful role in shaping experiences, and, to the extent that it exists, is causal rather than merelypredictive.[19] As suggested by Kirsch, such beliefs about what is going to happen, termed "response expectancies," can have a direct and unmediated effect on health outcomes.[20] According to this theory, response expectancies for non-volitional outcomes, such as post-surgical pain or post-chemotherapy nausea, are sufficient to cause the expected outcome, and the effect is self-confirming.

Evidence supporting Kirsch's theory is provided by several studies that have altered patients' expectations and achieved mitigation or prevention of subjective symptoms, such as pain[21,22] and nausea.[23–25] Changes in objectively measured outcomes, including reduction in blood loss during surgery[26] and resumption of normal gastrointestinal activity in the postoperative period,[27] have also been observed. A particularly interesting example of how response expectancies affect chemotherapy-related nausea comes from a large multicenter study conducted by our research group examining the efficacy of acustimulation and

acupressure bands as an adjunct to standard antiemetics for nausea control. Seven hundred thirty-nine patients were randomly assigned to three arms: acupressure bands, an acustimulation band, and a no-band control condition. Patients, who were randomized to receive acupressure bands and expected them to be effective, experienced less severe nausea, reported having a higher quality of life (QOL), and also used significantly less antiemetic medication at home compared to those who wore the bands but did not expect them to be effective, and to those in the no band control ($P<0.05$). Conversely, patients receiving the acupressure bands who did not expect them to be effective did not perform differently from the control group on any measure. It appears that the beneficial effect of wearing the acupressure bands on symptom management is due, at least in part, to a placebo/expectancy effect.[28]

The study described herein addresses the question of whether a modest educational intervention designed to reduce patients' nausea expectancies by dispelling misconceptions about chemotherapy-related nausea and building confidence in the efficacy of their antiemetic drug regimen results in less nausea.

Methods

Patients

Chemotherapy-naïve cancer patients scheduled to receive their first treatment with a chemotherapy regimen containing cisplatin, carboplatin, or doxorubicin were enrolled in a multicenter study. Study subjects were patients at 18 private medical oncology practice groups that were grantees of the National Cancer Institute's Community Clinical Oncology Program (CCOP) and were members of the University of Rochester Cancer Center CCOP Research Base between January 12, 1998 and September 25, 2000. All the patients received a standardized dose of ondansetron (Zofran^{R}) with dexamethasone on the day of treatment and whichever antiemetic regimen their treating oncologist prescribed for subsequent days.

Design and Procedure

After signing consent, each patient completed a questionnaire assessing his or her expectations of developing nausea. A computer-generated random numbers table was used to assign patients to one of the two arms: Arm 1 = standard educational materials given to new patients; Arm 2 = the same standard educational materials plus a one-page handout emphasizing how effective ondansetron, a relatively new antiemetic at the time of the study, would likely be in controlling NV. Findings from our previous studies were quoted in the handout indicating that better anti-emetic control is achieved with ondansetron compared to the older anti-emetic medications. Examples of other statements in the handout include: "*Ondanetron is the first of a new class of drug which was created specifically to reduce sickness; During that time it has helped millions of patients receive their chemotherapy without the often debilitating sickness which these drugs can cause; Ondansetron acts like a specific key turning a lock which stops nausea and vomiting.*" After reading the provided information and before the first chemotherapy infusion began, all patients completed the measure of expectations of nausea again.

Expectation of developing nausea was measured using a 5-point Likert scale, anchored at one end by "1" = "I am certain I WILL NOT have nausea," and at the other end by "5" = "I am certain I WILL have nausea." Patients with a score of "4–5" were coded as "expected nausea," whereas patients with a score of "1–3" were coded as "did not expect or were unsure about nausea." Nausea and emesis were measured by a patient report diary which included assessments starting from the treatment day until the fourth day following chemotherapy treatment. During each of these days, patients reported their nausea and

vomiting at four different time points, i.e., morning, afternoon, evening, and night. Occurrence of nausea was categorized into two time frames with acute nausea defined as occurring on the day of treatment and delayed nausea occurring on any of the subsequent four days. The severity of nausea was assessed on a 7-point rating scale anchored at one end by 1 = "not at all nauseated" and at the other end by 7 = "extremely nauseated." A score of "6" or "7" was coded as "severe nausea."

Results

Patient sample

Three hundred and fifty-eight chemotherapy naíve cancer patients were accrued to the study and completed expectancy assessments. Of these 358 patients, 322 (90%) provided evaluable post-treatment nausea assessments. The mean age of the patients was 57.8 years in the control group and 57.4 years in the intervention group. Demographic and clinical characteristics of 322 patients reported on herein are summarized in Table 1.

Intervention Effects

Despite administration of a 5-HT_3 receptor antagonist, approximately 76% (73% control, 79% intervention) of the patients reported nausea following treatment. There was no statistically significant difference between treatment groups, Pearson Chi-Square = 0.19. Overall, one fourth of the patients experienced severe nausea at some point during the 5-day assessment period (25% control, 26% intervention) with no statistically significant difference between groups, Pearson Chi-Square = 0.70. Similarly, the difference in average nausea between the control group (mean = 1.76, s.e. = .076) and the intervention group (mean = 1.86, s.e. = .076) was not significant, p =0.34. Additional analyses examined the effect of the intervention independently on acute and delayed nausea. All analyses comparing either severity or frequency of nausea by treatment group in either time period were non significant, (all, ps > 0.1)

There was a significantly greater reduction in expected nausea in the intervention group (from a mean of 2.95 to a mean of 2.58) compared to the control group (from a mean of 2.96 to a mean of 2.80), p = 0.024. In the intervention group, expectations of nausea assessed prior to the intervention correlated significantly with average nausea (r = .27, p = .001) and with peak nausea (r = .31, p < .001); whereas, nausea expectancy assessed following the intervention did not correlate significantly with either (both, rs < 0.1, ps >0.2). For the control group, both expectancy measurements (assessed before, and after the intervention) correlated significantly with average nausea (first assessment, r = .18, p = .021; second assessment, r = .23, p = .004) and with peak nausea (first assessment, r = .30, p < .001; second assessment, r = .27, p < .001).

Collapsing across study arms, 226 patients at the initial assessment prior to the intervention did not expect nausea or were unsure about whether they would have nausea (i.e. a score of 1 – 3 on the 5-point scale) and 94 patients expected to have nausea (i.e., a score of 4 or 5). Of the 94 patients expecting nausea, 82 (87.2%) reported at least some nausea, and 35 (37.2%) were severely nauseated at some point following the treatment. For the remaining 226 patients, 161 (71.2%) developed nausea and 47 (20.8%) reported severe nausea at some point after treatment. Table 2 contains additional details on study variables.

Discussion

In the present randomized clinical trial using a modest educational intervention prior to first chemotherapy, we were able to reduce patient expectations for subsequent chemotherapy-induced nausea but failed to reduce actual nausea severity or occurrence. It is possible that

the failure of the expectancy manipulation to reduce nausea severity was due to the modest strength (i.e., the confidence with which the outcome is expected) of the expectancy intervention vis-á-vis the potent emetic potential of the chemotherapeutic agents. According to Kirsch, expectancy varies along its two dimensions: the strength of expectancy and the magnitude of the outcome. When a small change is expected with a strong expectancy, there is a greater likelihood that the response will be confirmed compared to when a large change in the response is expected with a weak strength of expectancy.[29] In our study, the expectancy manipulation changed expectations concerning nausea, but it is possible the strength of the expectancy change was not sufficient to reduce chemotherapy-induced nausea–a very difficult undertaking. It is possible that a stronger expectancy manipulation, perhaps one involving the use of audio or video tapes with hypnosis, might have been more effective. The use of audio tape-generated suggestions has been successful in mitigating health outcomes in various studies[22,23] and could potentially work in this situation.

Consistent with many previous reports,[9,12–16] in the present study we observed a strong association between expectations regarding the development of nausea and its subsequent development. Patients who expected nausea compared to those who did not had both more frequent and more severe nausea. It is not clear at this point whether the association between expectations and chemotherapy-induced nausea is merely predictive or may be in some way causal. As mentioned in the introduction, there is some evidence suggesting the latter but nothing conclusive thus far.

Interestingly, we found in the present study that patient expectancy assessed prior to the intervention was a stronger predictor of nausea severity than expectancy measured after the intervention. This is consistent with our previous report that the strongest predictor among expectancy measures was the one that assessed response expectancies for severe nausea held by patients before speaking with an oncologist.[16] The two studies taken together suggest that patients' initial nausea expectancies are more relevant in terms of predicting outcomes than later expectancy formulations, and that modifying these initial expectancies by a modest educational intervention or by information normally received in a cancer clinic may not be sufficient to affect nausea occurrence.

Patients receive information about the possibility of nausea from a variety of sources: their health-care providers, family, friends, and media. Whether or not the information is scientifically derived or validated, it may account for patients' beliefs and expectations about the side effects following chemotherapy. There is a need to refine questionnaires about expectations to further delineate the relative contribution of each of these factors in the formation of nausea expectancy and underline those factors which are significant as well as modifiable. Clearly, there is a need to increase awareness about how the information presented by health-care professionals affects patients' expectations about health outcomes. It may be that more effective nausea management can be obtained by assessing patients' initial nausea expectancies and having clinic staff work to neutralize misconceptions. It may also be a good idea to provide stronger antiemetic medications to patients who hold strong initial expectancies for nausea following treatment.

Acknowledgments

The study was supported by Grant U10CA 37420 from the National Cancer Institute. The authors would also like to thank Dr. Susan Rosenthal for her assistance in editing this article.

References

1. Miller M, Kearney N. Chemotherapy-related nausea and vomiting - past reflections, present practice and future management. Eur J Cancer Care. 2004; 13:71–81.

2. Bovbjerg DH. The continuing problem of post chemotherapy nausea and vomiting: contributions of classical conditioning. Auton Neurosci. 2006; 129:92–98. [PubMed: 16905371]
3. Sun CC, Bodurka DC, Weaver CB, et al. Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. Support Care Cancer. 2005; 13:219–227. [PubMed: 15538640]
4. Grunberg SM, Osoba D, Hesketh PJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicityan update. Support Care Cancer. 2005; 13:80–84. [PubMed: 15599601]
5. Grunberg SM, Deuson RR, Mavros P, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. Cancer. 2004; 100:2261–2268. [PubMed: 15139073]
6. Morrow GR. Methodology in behavioral and psychosocial cancer research. The assessment of nausea and vomiting. Past problems, current issues and suggestions for future research. Cancer. 1984; 53:2267–2280. [PubMed: 6704914]
7. Zook DJ, Yasko JM. Psychologic factors: Their effect on nausea and vomiting experienced by clients receiving chemotherapy. Oncol Nurs Forum. 1983; 10:76–81. [PubMed: 6553910]
8. Jacobsen PB, Bovbjerg DH, Redd WH. Anticipatory anxiety in women receiving chemotherapy for breast cancer. Health Psychol. 1993; 12:469–475. [PubMed: 8293730]
9. Jacobsen PB, Andrykowski MA, Redd WH, et al. Nonpharmacologic factors in the development of posttreatment nausea with adjuvant chemotherapy for breast cancer. Cancer. 1988; 61:379–385. [PubMed: 3334973]
10. Andrykowski M, Garrison J. Prescription and Use of Antiemetics Among Cancer Chemotherapy Outpatients. J Psychosoc Oncol. 1989; 7:141–157.
11. Carey MP, Burish TG. Etiology and treatment of the psychological side effects associated with cancer chemotherapy: A critical review and discussion. Psychol Bull. 1988; 104:307–325. [PubMed: 3062654]
12. Montgomery GH, Tomoyasu N, Bovbjerg DH, et al. Patients' pretreatment expectations of chemotherapy-related nausea are an independent predictor of anticipatory nausea. Annals of Behavioral Medicine. 1998; 20:104–109. [PubMed: 9989316]
13. Montgomery GH, Bovbjerg DH. Specific response expectancies predict anticipatory nausea during chemotherapy for breast cancer. J Consult Clin Psychol. 2001; 69:831–835. [PubMed: 11680560]
14. Olver IN, Taylor AE, Whitford HS. Relationships between patients' pre-treatment expectations of toxicities and post chemotherapy experiences. Psychooncology. 2005; 14:25–33. [PubMed: 15386792]
15. Roscoe JA, Hickok JT, Morrow GR. Patient expectations as predictor of chemotherapy- induced nausea. Annals of Behavioral Medicine. 2000; 22:121–126. [PubMed: 10962704]
16. Roscoe JA, Bushunow P, Morrow GR, et al. Patient expectation is a strong predictor of severe nausea after chemotherapy: A University of Rochester Community Clinical Oncology Program study of patients with breast carcinoma. Cancer. 2004; 101:2701–2708. [PubMed: 15517574]
17. Hickok JT, Roscoe JA, Morrow GR. The role of patients' expectations in the development of anticipatory nausea related to chemotherapy for cancer. J Pain Symptom Manage. 2001; 22:843–850. [PubMed: 11576801]
18. Thorndyke PW, Hayes Roth B. The use of schemata in the acquisition and transfer of knowledge. Cognitive Psychology. 1979; 11:82–106.
19. Eden D, Zuk Y. Seasickness as a self-fulfilling prophecy: Raising self-efficacy to boost performance at sea. J Appl Psychol. 1995; 80:628–635. [PubMed: 7592232]
20. Kirsch I. Response expectancy as a determinant of experience and behavior. Am Psychol. 1985; 40:1189–1202.
21. Egbert LD, Battit GE, Welch CE, et al. Reduction of postoperative pain by encouragement and instruction of patients. N Engl J Med. 1964; 270:825–827. [PubMed: 14108087]
22. Lebovits AH, Twersky R, McEwan B. Intraoperative therapeutic suggestions in day-case surgery: are there benefits for postoperative outcome? Br J Anaesth. 1999; 82:861–866. [PubMed: 10562780]

23. Eberhart LH, Doring HJ, Holzrichter P, et al. Therapeutic suggestions given during neuroleptanaesthesia decrease post-operative nausea and vomiting. European Journal of Anaesthesiology. 1998; 15:446–452. [PubMed: 9699102]

24. Lauder GR, McQuillan PJ, Pickering RM. Psychological adjunct to perioperative antiemesis. Br J Anaesth. 1995; 74:266–270. [PubMed: 7718369]

25. Williams AR, Hind M, Sweeney BP, et al. The incidence and severity of postoperative nausea and vomiting in patients exposed to positive intra-operative suggestions. Anaesthesia. 1994; 49:340–342. [PubMed: 8179147]

26. Bennett HL, Benson MD, Kuiken DA. Preoperative instructions for decreased bleeding during spine surgery. Anesthesiology. 1986; 65:A245.

27. Disbrow EA, Bennett HL, Owings JT. Effect of preoperative suggestion on postoperative gastrointestinal motility. Western Journal of Medicine. 1993; 158:488–492. [PubMed: 8342264]

28. Roscoe JA, Morrow GR, Hickok JT, et al. The efficacy of acupressure and acustimulation wrist bands for the relief of chemotherapy-induced nausea and vomiting: A URCC CCOP multicenter study. J Pain Symptom Manage. 2003; 26:731–742. [PubMed: 12906958]

29. Kirsch, I. How Expectancies Shape Experience. Washington, DC: American Psychological Association; 1999.

Table 1

Demographic and Clinical Characteristics of Patients

Characteristic	Control Group (n=163)	Intervention Group (n=159)
Age		
(mean ± SD)	57.8 ± 13.4	57.4 ± 12.1
Range	28.3 – 91.4	27.4 – 84.3
Gender		
Male	44 (27.0%)	43 (27.0%)
Female	119 (73.0%)	116 (73.0%)
Marital status		
Married	115 (70.6%)	107 (67.3%)
Not currently married	48 (29.4%)	52 (32.7%)
Chemotherapy		
Adriamycin	85 (52.1%)	84 (52.8%)
Carboplatin	56 (34.4%)	50 (31.4%)
Cisplatin	22 (13.5%)	25 (15.7%)

Table 2

Distribution of Nausea Expectancy and Peak and Average Severity of Nausea

Parameters	Control Group (n=163)	Intervention Group (n=159)
Nausea expectancy assessed prior to the intervention		
Patients who did NOT expected nausea or were unsure (Score = 1–3)	115 (71.0%)	111 (70.3%)
Patients with high nausea expectation (Score = 4–5)	47 (29.0%)	47 (29.7%)
Nausea expectancy assessed just before the treatment (i.e. after patient read the education materials)		
Patients who did NOT expect nausea or were unsure (Score = 1–3)	121 (74.7%)	129 (81.6%)
Patients with nausea expectation (Score = 4–5)	41 (25.3%)	29 (18.3%)
Peak nausea severity		
No nausea (Score = 1)	42 (25.9%)	33 (20.8%)
Mild (Score = 2–3)	48 (29.4%)	52 (32.7%)
Moderate (Score = 4–5)	33 (20.2%)	32 (20.1%)
Severe (Score = 6–7)	40 (24.5%)	42 (26.4%)
Average Nausea Severity	Mean =1.76	Mean = 1.86