Patterns of sore mouth in outpatients with cancer receiving chemotherapy.

By: Carlton G. Brown, Susan L. Beck, Douglas E. Peterson, Deborah B. McGuire, William N. Dudley and Kathleen H. Mooney

Brown, C.G., S.L. Beck, D.E. Peterson, D.B. McGuire, W.N. Dudley & K H. Mooney. Patterns of sore mouth in outpatients with cancer receiving chemotherapy. *Supportive Care in Cancer*, 2009. 17(4): p. 413-428.

Made available courtesy of Springer Verlag. The original publication is available at www.springerlink.com

*****Reprinted with permission. No further reproduction is authorized without written permission from Springer Verlag. This version of the document is not the version of record. Figures and/or pictures may be missing from this format of the document. *****

Abstract:

Goals

The aims of this secondary data analysis were to (a) categorize patterns in the development, duration, intensity, and resolution of sore mouth (which can be considered a proxy for oral mucositis) severity and distress over two cycles of chemotherapy in cancer outpatients and (b) examine the relationship of demographic (age, gender, marital status, and educational level) and disease characteristics (type of cancer and type of chemotherapy) to specific patterns of sore mouth (SM).

Materials and methods

Visual graphical analysis (VGA) was applied to identify individual patterns of SM severity and distress in 51 outpatients receiving chemotherapy who provided daily reports of sore mouth using a computerized interactive voice response system. The majority were female (n = 41, 8%) with a mean age of 53 (SD = 8.35). Most had breast cancer (68%), and one third received chemotherapy with adriamycin and cyclophosphamide (AC). VGA is a technique in which graphs of individual patients' symptoms are coded for specific individual or group profiles.

Main results

Seven distinct patterns were identified based on variability in onset, duration, and intensity (degree of severity or distress). Chemotherapy agents were significantly associated with patterns of SM. The AC regimen was significantly associated with late onset; however, the intensity did not last long. In contrast, patients receiving R-CHOP were significantly more likely to experience duration intensity (SM after day 15 and a score equal to or greater than a 5 on a 1–10 scale).

Conclusions

VGA revealed symptom patterns often hidden in traditional analysis. Understanding individual variability is important to the design and implementation of future intervention research and clinical care.

Keywords: oral mucositis | chemotherapy | outpatient cancer treatments | cancer patients | cancer outpatients | health sciences

Article:

Introduction

While contemporary cancer therapies can be highly effective in curing or stabilizing the cancer patient, debilitating side effects, such as oral mucositis (OM), continue to compromise delivery of optimal therapeutic regimens. In addition, the toxicities from cancer treatment can affect overall quality of life [12, 15]. Almost 90% of the one million cancer patients treated with chemotherapy in the USA receive these medications on an outpatient basis; thus, OM can be a frequently encountered toxicity in clinical oncology practice [11]. Once patients leave the clinic or physician office, assessment is challenging; thus, OM often goes unreported and untreated.

In spite of an increase in research on OM [13], there are still important gaps in our knowledge for at least three fundamental reasons. First, most longitudinal research of OM has been conducted with inpatients receiving high-dose chemotherapy for blood and marrow stem cell transplantation [6, 7, 18] or with patients receiving radiation therapy [20]. Few studies have included outpatients receiving chemotherapy as participants; thus, little is known about the trajectories and patterns of OM in this population. In one intervention study, Dodd et al. [4] investigated the incidence of chemotherapy-induced OM in outpatients over 3 months; however, daily assessments were not completed and results were reported in aggregate.

Second, only a minimal amount of research has been conducted that examines OM longitudinally over an entire course of chemotherapy regardless of whether chemotherapy was administered on either an outpatient or inpatient basis. In addition, few studies have investigated OM over consecutive cycles of outpatient chemotherapy.

Third, most research studies have used standard analytic approaches with summary statistics to explore changes in OM over time; such approaches may mask some of the clinical variability seen in practice. Several important descriptive and intervention studies have included daily measures of OM using a variety of measures. All of theses studies reported change over time using group level summary statistics such as means and standard deviations at each time point [6, 7, 17, 18]. These studies, all conducted in hematopoietic stem cell transplant settings, revealed group level patterns in which OM peaked after myeloablative therapy and then gradually

recovered as the bone marrow rebounded. However, the use of traditional statistical methods to summarize group change over time may have obscured individual trajectories of change [1].

The incidence of OM depends on the particular antineoplastic treatment regimens and patient-specific characteristics. Anthracycline-based regimens are associated with rates of OM around 1–10%, including those standard regimens for adjuvant treatment in patients with breast cancer (doxorubicin and cyclophosphamide) and regimens for non-Hodgkin's lymphomas (cyclophosphamide, doxorubicin, vincristine, and prednisone) [16]. Further, there is an increased risk of OM when rituximab is added to the above regimens when used in the treatment of breast cancer [16]. When 5-FU (commonly used in colon and some breast cancer regimens) is administered, the rates of grades 3 and 4 OM are greater than 15% [16]. There is no research to explore whether patterns of OM over time are associated with type of regimen.

There is some limited evidence that gender and age may be risk factors for OM. Vokurka et al. [19] reported a higher incidence of chemotherapy-induced OM in females when compared with males. Raber-Durlacher et al. [10] suggested that patients over 50 years of age develop OM that is more severe and has a longer duration. They proposed that this more intense and prolonged OM might be related to a decline in renal function in patients over 50.

The clinical literature has always consistently suggested a typical pattern of OM in patients receiving chemotherapy. Erythema is typically the earliest clinical sign of OM, occurring approximately 4–5 days following chemotherapy administration [12]. Ulcers then develop 7–10 days following chemotherapy, creating marked discomfort for patients, many of whom require opioid medications for pain relief. OM resulting from chemotherapy administration typically lasts 1 week and usually heals within 21 days after administration [12]. Despite these typical characteristics, few studies examine variation in these trajectories within a given cancer patient cohort, particularly in an outpatient setting.

In summary, there are important limitations to existing research, which include a primary focus on inpatient, high-dose chemotherapy populations, the use of traditional statistical analyses that can sometimes obscure individual trajectories of OM, and a limited number of longitudinal studies investigating OM over more than one cycle of chemotherapy. One key reason for these limitations is the impracticality and cost associated with observational studies of OM when outpatients receive their chemotherapy and return to their home setting. This report takes advantage of an innovative approach to studying symptoms on a daily basis using computerized interactive voice technology. We have specifically focused on daily self-reports of sore mouth (SM) severity and distress, a reasonable proxy for OM used by other researchers [6, 7] that is easy for patients to understand and report.

Thus, the aims of this secondary data analysis were to (a) explore and categorize patterns in the development, duration, intensity, and resolution of SM severity and distress over two cycles of chemotherapy in cancer outpatients and (b) describe and explore the relationship of demographic

(age, gender, marital status, and educational level) and disease characteristics (type of cancer and type of chemotherapy) to specific patterns of SM.

Materials and methods

Parent study

A secondary data analysis was performed using visual graphic analysis to investigate individual patterns of SM severity [1]. The analysis was based on data from a multi-site, prospective randomized clinical trial of patients receiving outpatient chemotherapy [8] (NCI R01 CA89474). The purpose of the parent study was to assess the efficacy of telephone-linked care for chemotherapy alerting (TLC-Chemo Alert) in the symptom management of adults receiving chemotherapy for cancer. A total of 223 patients participated in this study.

TLC chemotherapy alerting mechanism was a computer-based communication system that used interactive voice technology to gather and to electronically document cancer patients' daily symptom experience by means of automated telephone conversations. The TLC-Chemo alert technology is a well-validated technology that included standardized patient response formatting. The inclusion and exclusion criteria for the parent study sample are summarized in Table 1. Patients were screened at the end of cycle 1 to confirm that they experienced a symptom that was at least moderate in intensity during their first cycle. Eligible patients who provided informed consent then provided daily data via the TLC system for cycles 2 and 3.

Table 1

Inclusion and exclusion criteria of parent study

Inclusion criteria
Adult (age 18 or over)
Histologic diagnosis of cancer
A life expectancy of at least 6 months
Cognitively able to participate (as verified by the provider team)
At the end of their first cycle of a new course of chemotherapy that was planned for a minimum of 3 cycles
Poorly controlled symptoms during the first cycle of the chemotherapy (based on a phone screening)

Exclusion criteria

Receiving concurrent radiation therapy

Biotherapy only

Initial demographic and clinical variables were collected from participants at the beginning of the study. Patients were instructed to call into TLC each day during cycles 2 and 3 of chemotherapy and to answer a series of questions that focused on the presence/absence of nine symptoms associated with chemotherapy, including SM. Single-item indicators using a standardized approach for each symptom were utilized—such measures are generally used to obtain the subject's perception of particular dimensions of multidimensional concepts or of an overall concept. Because data collection was daily, it was essential to keep the response burden to a minimum. Youngblut and Casper [21] reviewed numerous clinical studies that used single-item indicators including items to measure symptom severity, concluding that there was evidence to support the reliability and validity of single-item indicators. This approach is also commonly applied in numerous multi-symptom inventories including the Memorial Symptom Assessment Scale and the MD Anderson Brief Symptom Inventory [2, 3].

A hallmark symptom of OM is acute pain of the affected oral mucosa; thus, patients often describe OM as a SM. Use of this term allowed patients to report sore mouth via a pre-recorded script. If patients indicated they had a SM, they were asked specific standardized questions about their SM experience, including how they would rate their level of SM severity and distress on a scale of 1 (minimal) to 10 (worst). A distinct advantage of the dataset is that it provided daily data on the symptom experience through two cycles of chemotherapy.

Visual graphic analysis

Visual graphic analysis (VGA) is a technique in which individual patients' symptoms are graphed and inspected for patterns over time [1]. VGA provides researchers with an alternative method to quantitative statistical analysis, as it enables careful inspection of individual variations and patterns of change that can be obscured by traditional parametric statistics. A goal of VGA is to disclose common patterns and to pinpoint individuals whose data do not conform to common trajectories. Of particular interest were questions such as when does a SM first occur, how severe does it become, and how long does it last? These questions were best addressed by VGA. The VGA analysis was performed in five steps as described in detail by Brown et al. [1] and summarized below.

Step 1:

Determining inclusion criteria. The study had two inclusion criteria. First, only those patients who reported three or more episodes of a SM during cycle 2 or cycle 3 of their respective

chemotherapy treatments were included. At least three data points are needed for pattern analysis, and reports of sore mouth for more than one or two times would be most consistent with oral mucositis. Second, chemotherapy treatment was limited to the first 21 days of data within each cycle, thus assuring that all graphical plots were based on the same abscissa. For purposes of this study, a cycle was defined as a 21-day period in which chemotherapy was administered on day 1 and not again for another 20 days.

Step 2:

Managing missing data. “No call” missing data occurred when participants never called into the TLC system or terminated a call. These episodes were categorized as missing data and were displayed on the graph as gaps in the plots. Of the 1,554 days available (74 graphs × 21 days), 225 days were missing (14.5%).

Step 3:

Creating individual visual graphs. Data from each episode of SM severity were charted on individual graphs using Microsoft Excel. Identical axes were used for each respective participant or symptom being plotted. This methodology prevented the visual distortion of scales that can occur with many software packages which automatically expand or contract scales to complete a page or plot area [14].

Step 4:

Identifying specific individual patterns. All graphs were examined to discover any commonalities and differences in the 21-day trajectories of a SM. The word intensity was used to refer to the degree of severity or distress reported. Seven patterns were identified: early Onset (between days 1 and 5); middle onset (between days 6 and 9); late onset (beginning on or after day 10); onset intensity (first response greater than a 5 on 1–10 scale); duration intensity (after day 15 and a SM score equal to or greater than a 5 on a 1–10 scale); late duration (continuing after day 15); and low intensity (no response greater than 4 on a 1–10 scale). Once the patterns were determined, the individual graphs were visually sorted into these seven pattern groups and labeled. It was possible for any single graph to be categorized into more than one pattern group.

Step 5:

Performing validation and verification. Members of the research team reviewed and independently verified coding of each graph. When differences occurred, they were discussed until a consensus was reached.

Data analysis

Data analysis was performed using SPSS (version 11). Multiple analyses using cross-tabulations with chi-square tests were conducted to evaluate whether any differences in demographic or clinical characteristics existed among individuals categorized into each of the seven pattern groups. We collapsed categories to improve the power of the chi-square analyses as appropriate and meaningful, and cell sizes were adequate for the total number of cells included (i.e., at least five per cell). However, in some instances (e.g., type of chemotherapy), inclusion of specific categories was most meaningful even if there were less than five cases in some cells. We recognized that findings are not definitive but may inform future studies

The three onset patterns were combined into a new variable called onset that consisted of three levels (early, middle, and late onset). The other pattern variables (onset intensity, duration intensity, late duration, and low intensity) consisted of two levels, either “yes” (for those assigned to the pattern) or “no” (for those not assigned to the pattern). Demographic variables were collapsed in order to have adequate cell sizes to conduct chi-square tests as follows: gender (male or female), marital status (married or non-married), educational level (high school or college), and income level (0–39,999or40,000 and above). Treatment variables included type of cancer (breast, non-Hodgkin’s lymphoma, or other cancers) and type of chemotherapy [doxorubicin and cyclophosphamide (AC); cyclophosphamide, methotrexate, and flurouracil (CMF); rituximab plus cyclophosphamide, oncovin, doxirubicin, and prednisone (R-CHOP); and other chemotherapies]. An independent-samples t test was conducted to evaluate whether there was a difference in age between those who were and who were not assigned to a certain onset pattern group. Since the variable of onset had three levels (early, middle, and late), analysis of variance (ANOVA) was used to determine differences in age.

Results

Of the 223 study participants, 115 (51%) reported SM at any point in time. Of the 115 patients reporting SM, 51 participants reported three or more days of SM in either the second (n = 45) or third (n = 29) cycle of chemotherapy, yielding74 graphs for analysis. The demographic and clinical characteristics of participants with SM are presented in Table 2. The majority of the participants were female (n = 41, 82%) with a mean age of 53 years (SD = 8.35). Most were

married (68%), with a diagnosis of breast cancer (68%), and receiving chemotherapy of AC (33.3%). Approximately 30% of the participants had some college or trade school education, and approximately 40% reported earning more than $70,000 per year.

Table 2

Characteristics of participants reporting SM ($n = 51$)

Variables	***M***	**SD**	***n***	**Percentage**
Age	53.36	8.35		
Gender				
Male			9	17.6
Female			41	82.0
Missing			1	–
Marital status				
Single			5	10.6
Married			32	68.1
Divorced/widowed			10	21.3
Missing			4	–
Educational level				
High school graduate			9	19.1
Some college			14	29.8
Associates degree			6	12.8

Variables	***M***	**SD**	***n***	**Percentage**
Bachelor’s degree			8	17.0
Postgraduate			10	21.3
Missing			4	–
Income				
$0–19,000			4	10.0
$20,000–49,000			13	32.5
$50,000–69,000			7	17.5
Above $70,000			16	40.0
Missing/refused			11	–
Cancer				
Breast			32	62.7
NHL			5	9.8
Other			10	19.6
Missing			4	–
Chemotherapy				
AC			16	33.3
CMF			6	12.5
Taxol/other			8	16.7

Variables	*M*	SD	*n*	Percentage
RCHOP			4	8.3
Other			14	29.2
Missing			3	–

Aim 1 was to explore and categorize patterns in the development, duration, intensity, and resolution of SM severity and distress over two cycles of chemotherapy in cancer outpatients. By using VGA, plots were categorized into the seven patterns mentioned earlier: early onset (n = 17; see Fig. 1); middle onset (n = 43; see Fig. 2); late onset (n = 14; see Fig. 3); onset intensity (n = 6; Fig. 4); duration intensity (n = 13; see Fig. 5); late duration (n = 19; see Fig. 6); and low intensity (n = 36; see Fig. 7). As noted previously, every participant was sorted into one of the levels of onset (early, middle, and late) and then into any of the other pattern groups that appeared to apply to the data (onset intensity, duration intensity, late duration, or low intensity).

Figures 1-7 are omitted from this formatted document.

A small group of patients (n = 14) presented a pattern of two episodes of SM severity occurring during one cycle of chemotherapy separated by at least 2 days of no SM (see Fig. 8). Because some of the patients reported SM at the onset of a cycle and then again at least 2 days later in the cycle, dates at the end of cycle 2 and the beginning of cycle 3 were verified to ensure that the two episodes were indeed in the same cycle.

Figure 8 is omitted from this formatted document.

VGA analysis of SM distress revealed that in virtually every case, SM distress scores were very similar to those for SM severity (see Fig. 9). Equivalence was verified by computing a daily difference score between severity and distress. Interestingly, of the 1,007 daily difference scores, 97% of the severity and distress scores differed by one or less. Thus, patterns of distress and severity were judged as equivalent.

Figure 9 is omitted from this formatted document.

Aim 2 was to describe and explore the relationship of demographic (age, gender, marital status, and educational level) and disease characteristics (type of cancer and type of chemotherapy) to specific SM patterns. Table 3 presents the statistical results (χ 2 and t) and the significance of relationships between participants' characteristics and patterns of SM. Similar to the patients who reported SM, those patients who did not report SM were mostly female (78%) with a mean

age of 57.8 years (SD = 12.18). The majority of them were Caucasian (92%), married (75%), with a diagnosis of breast cancer (33%), and received AC as treatment.

Table 3

Statistical results (χ^2 and t) and significance of relationships between participant characteristics and patterns of SM ($n = 74$)

Variables	χ^2	***p***	***T***	***p* value**
Onset (early, middle, late)				
Marital status	7.08	0.03	–	–
Gender	2.14	0.34	–	–
Income	4.48	0.28	–	–
Educational level	6.11	0.05	–	–
Cancer	9.03	0.06	–	–
Chemotherapy	24.86	0.00	–	–
Onset intensity				
Age	–	–	−1.65	0.11
Marital status	1.31	0.29	–	–
Gender	1.28	0.26	–	–
Income	3.01	0.08	–	–
Educational level	0.80	0.37	–	–
Cancer	9.48	0.01	–	–

Variables	χ^2	***p***	***T***	***p* value**
Chemotherapy	16.00	0.00	–	–
Duration intensity				
Age	–	–	−0.85	0.40
Marital status	0.45	0.50	–	–
Gender	1.87	0.17	–	–
Income	0.06	0.81	–	–
Educational level	0.00	0.97	–	–
Cancer	9.10	0.01	–	–
Chemotherapy	12.27	0.02	–	–
Late duration				
Age	–	–	−0.75	0.46
Marital status	0.16	0.69	–	–
Gender	1.95	0.16	–	–
Income	0.07	0.79	–	–
Educational level	0.00	0.97	–	–
Cancer	6.42	0.04	–	–
Chemotherapy	7.89	0.10	–	–
Low intensity				

Variables	χ^2	***p***	***T***	***p* value**
Age	–	–	−0.54	0.59
Marital status	1.43	0.23	–	–
Gender	3.55	0.06	–	–
Income	0.52	0.47	–	–
Educational level	0.39	0.53	–	–
Cancer	7.57	0.02	–	–
Chemotherapy	6.84	0.15	–	–

Onset

Table 4 presents the relationship between the significant variables (marital status and chemotherapy type) and the pattern of onset of SM. There was a significant association between marital status coded as married versus not married [single, divorced, or widowed; $\chi 2(2) = 7.08$, $p = 0.03$]. The strength of the relationship between married and non-married was low ($\Phi = 0.32$), although the nature of the association as indicated by adjusted residuals [9] suggested that non-married individuals tended to show early onset more often than married individuals. The results of the chi-square analysis indicated a statistically significant but weak association between those in the early, medium, and late onset and the chemotherapy type they received [$\chi 2(4) = 24.86$, $p = 0.002$, Cramer's $V = 0.42$]. An examination of standardized residuals [9] suggested that patients who received AC (3.7) were more likely to experience late onset SM. Patients who received CMF (2.6) experienced middle onset, and patients who received some of the "other" drugs (2.6) were more likely to experience early onset. There were no significant differences between these three groups (early, middle, and late onset) in gender, educational level, and type of cancer. Further, an ANOVA showed there was no significant difference in age [$F(2,67) = 2.43$, $p = 0.10$] between the three levels of onset.

Table 4

Percentages and adjusted residuals of marital status and chemotherapy type and pattern of onset of SM

	Marital status		**Chemotherapy**				
	Not married	**Married**	**AC**	**CMF**	**Taxol/other**	**RCHOP**	**Other**
Early							
N	10	7	4	0	2	1	10
Percentage	43.5	15.2	17.4	0.0	20.0	16.7	43.5
Adjusted residual	2.6[a]	−2.6[a]	−0.9	−1.7	−0.3	−0.5	2.6[a]
Middle							
N	11	29	9	8	7	3	13
Percentage	47.8	63.0	39.1	100.0	70.0	50.0	56.5
Adjusted residual	−1.2	1.2	−2.1[a]	2.6[a]	0.9	−0.4	−0.1
Late							
N	2	10	10	0	1	2	0
Percentage	8.7	21.7	43.5	0.0	10.0	33.3	0.0
Adjusted residual	−1.3	1.3	3.7[a]	−1.4	−0.8	1	−2.8[a]

[a]Significant adjusted residuals > the absolute value of 2

Onset intensity

Table 5 summarizes the relationships among cancer type, chemotherapy administered, and patterns of SM for onset intensity, duration intensity, late duration, and low intensity. There were no significant differences between those in the onset intensity group and those who were not in the group on marital status, gender, age, income, or educational level. However, a chi-square analysis revealed a statistically significant but weak association between those patients in the onset intensity group and those not in it in terms of cancer diagnosis [$\chi^2(2) = 9.48$, $p = 0.009$, Cramer's $V = 0.37$]. An examination of standardized residuals suggested that patients with non-Hodgkin's lymphoma (NHL, −3.1) were significantly less likely to be sorted into the onset

intensity group. There was a significant association in these two onset intensity groups in terms of the chemotherapy they received [$\chi^2(2) = 16.00$, $p = 0.003$, Cramer's $V = 0.48$]. Those receiving R-CHOP seem to have a different pattern and may be more likely to have onset intensity than women with breast cancer. None of these R-CHOP patients were in the low intensity group. These results must be viewed as tentative because of the number of cells with less than five, which violates the assumption of the analysis.

Table 5

Percentages and adjusted residuals for cancer type and chemotherapy administered and patterns of SM

	Onset intensity			**Duration intensity**			**Late duration**			**Low intensity**		
	No, *n*(%)	**Yes, *n*(%)**	**Residual[a]**	**No, *n*(%)**	**Yes, *n*(%)**	**Residual[a]**	**No, *n*(%)**	**Yes, *n*(%)**	**Residual[a]**	**No, *n*(%)**	**Yes, *n*(%)**	**Residual[a]**
Cancer type												
Breast	42 (66.7)	2 (33.3)	1.6	35 (62.5)	9 (69.2)	0.5	30 (60.0)	14 (73.7)	1.1	25 (71.4)	19 (55.9)	1.3
NHL	5 (7.9)	3 (50.0)	3.1[b]	4 (7.1)	4 (30.8)	2.4[b]	4 (8.0)	4 (21.1)	1.5	6 (17.1)	2 (5.9)	1.5
Other	16 (25.4)	1 (16.7)	0.5	17 (30.4)	0 (0)	2.3[b]	16 (32.0)	1 (5.3)	2.3[b]	4 (11.4)	13 (38.2)	2.6[b]
Chemotherapy												
AC	23 (35.9)	0 (0)	1.8	18 (31.6)	5 (38.5)	0.5	16 (31.4)	7 (36.8)	0.4	11 (31.4)	12 (34.3)	0.3

	Onset intensity			**Duration intensity**			**Late duration**			**Low intensity**		
	No, *n*(%)	**Yes, *n*(%)**	**Residual[a]**	**No, *n*(%)**	**Yes, *n*(%)**	**Residual[a]**	**No, *n*(%)**	**Yes, *n*(%)**	**Residual[a]**	**No, *n*(%)**	**Yes, *n*(%)**	**Residual[a]**
CMF	7 (10.9)	1 (16.7)	0.4	7 (12.3)	1 (7.7)	0.5	5 (9.8)	3 (15.8)	0.7	4 (11.4)	4 (11.4)	0
Taxol/other	9 (14.1)	1 (16.7)	0.2	10 (17.5)	0 (0)	1.6	9 (17.6)	1 (5.3)	1	4 (11.4)	6 (17.1)	0.7
RCHOP	3 (4.7)	3 (50)	3.8[b]	2 (3.5)	4 (30.8)	3.2[b]	2 (3.9)	4 (21.1)	2.3[b]	16 (17.1)	0 (0)	2.6[b]
Other	22 (34.4)	1 (16.7)	0.9	20 (35.1)	3 (23.1)	0.8	19 (37.7)	4 (21.1)	1.3	10 (28.6)	13 (37.1)	0.8

[a]Residual presented as absolute value

[b]Significant adjusted residuals >2

Duration intensity

There were no significant differences between those in the duration intensity group and those who were not on gender, age, marital status, educational level, or income level. There were statistically significant yet weak differences between these two groups in terms of cancer diagnosis [$\chi^2(2) = 9.10$, $p = 0.011$, Cramer's $V = 0.36$] and chemotherapy [$\chi^2(4) = 12.27$, $p = 0.015$, Cramer's $V = 0.41$]. Interestingly, patients with "other" cancers were never sorted into the group that experienced duration intensity. Patients who received R-CHOP (3.2) were significantly more likely to experience duration intensity, but not those patients who received AC (0.5).

Late duration

There were no significant differences between those in the late duration group and those who were not on gender, age, marital status, educational level, income level, and type of chemotherapy administered. There was a statistically significant yet weak association between the late duration and the non-late-duration groups on the type of cancer diagnosis [$\chi^2(2) = 6.42$, $p = 0.040$, Cramer's $V = 0.30$]. Adjusted residuals showed that those patients in the "other" cancer group (2.3) were significantly less likely to experience late duration. In fact, only one patient who experienced late duration had an "other" cancer diagnosis.

Low intensity

Chi-square analysis revealed a statistically significant yet weak association between those patients in the low intensity group and those not in it in terms of cancer diagnosis [$\chi^2(2) = 7.57$, $p = 0.023$, Cramer's $V = 0.33$]. Examination of standardized residuals suggested that patients who were in the "other" cancer diagnosis group (2.6) were significantly more likely to experience low intensity SM. There were no significant differences between those in the low intensity group and those not in it on gender, age, marital status, educational level, income level, and type of chemotherapy administered.

In summary, there were statistically significant differences between the three onset groups by marital status, as non-married patients were more likely to report onset earlier than married patients. Concerning the type of cancer, patients with "other" cancers tended to experience a SM with lower intensity and without duration intensity and/or late duration. Patients with NHL did not experience a SM associated with onset intensity. Concerning the type of chemotherapy administered and patterns of a SM, the following associations between type of chemotherapy and SM patterns were noted:

- AC was significantly associated with late onset, but not duration intensity.
- R-CHOP was significantly associated with duration intensity.
- CMF was significantly associated with middle onset.

- “Other” chemotherapy drugs (fluorouracil, cisplatin) were associated with early onset.

Sore mouth longitudinal daily mean scores

Although mean scores may hide the individual patterns of sore mouth, these data are presented in Fig. 10. Very few studies have presented daily sore mouth severity scores in outpatient populations receiving chemotherapy.

Figure 10 is omitted from this formatted document.

Discussion

Results from this study demonstrated that cancer patients receiving outpatient chemotherapy experience several different patterns of SM severity and distress. A majority of patients (n = 43) experienced middle onset SM occurring sometime between days 6 and 9. This middle onset pattern is commonly witnessed in clinical practice, yet is later than the days 4 to 5 onset that is suggested in the clinical literature. Moreover, middle onset was not the only onset pattern. Some patients reported the early onset of SM within 1–3 days after receiving chemotherapy treatment. Other patients reported a late onset of SM in which the first incidence of SM was not reported until day 10 or later. These findings of early and late onset challenge the usual clinical assumption and observations that most acute mucosal injuries induced by chemotherapy develop within 1 week of drug administration (usually by day 4 or 5) and peaks within 2 weeks [15]. It is likely that these two patterns of onset would have been missed if intermittent measurements common in clinical practice (such as the beginning of chemotherapy and maybe the nadir) and traditional summary statistics were used to conduct the data analysis.

In the next pattern, onset intensity, patients reported their first complaint of a SM as above a score of 5 on a 1–10 scale. This new and unique finding suggests that for some patients, there is not a gradual increase in SM discomfort over a few days. Instead, SM begins in the moderate range without a slow period of development. This pattern is of particular concern because it may be more difficult to assist patients with pain control when SM is moderate to severe at its first appearance. All graphs sorted into the onset intensity category were evaluated to confirm that the days prior to the first response were not missing days (see Fig. 4); in all instances, the days prior were true SM severity ratings of zero as opposed to missing data.

Approximately half of the patients were coded into the low intensity pattern, defined as a severity response never exceeding 4 on a 1–10 scale. This pattern, along with middle onset, are perhaps two of the most common patterns of SM seen in clinical practice, especially in patients

receiving outpatient chemotherapy. Two other patterns included late duration and duration intensity. Approximately one fourth of patients (26%) demonstrated a SM severity response that persisted after day 15 of treatment and was an example of late duration. Other patients (18%) reported a SM after day 15 and rated the SM as being 5 or greater (duration intensity), suggesting that some patients experience a SM lasting well after day 15 and at an intensity higher than 5 on a 1–10 scale. These patients may require more intensive pain intervention.

In addition, during the process of visual graphing, the first author discovered a new pattern of two episodes of SM separated by at least 2 days of no SM (see Fig. 9). This finding represents a unique dynamic that has not been previously described in the literature. Further research using prospective designs is needed to verify if participants actually experience a few days of SM, followed by a few days of no report of a SM, followed by more days of SM. It would be helpful in this instance to use actual measures of OM instead of self-reported SM. If research supports the presence of more than one episode of SM during a cycle, it would be interesting to investigate the correlation of these episodes with potential clinical risk factors such as patient's nadir, infection, renal function, or dehydration. For instance, when a patient experiences two episodes of SM, are those episodes in congruence with the beginning and end of neutropenia or with some other physiologic event? The detection of this unusual pattern would likely have been missed using traditional statistics, thus highlighting the advantages of VGA.

As previously noted, patients in this study had already received one cycle of chemotherapy prior to study entry. Patients had experienced at least one symptom of moderate intensity in order to be included in the study. Some of the participants during cycle 1 also experienced selected associated symptoms such as nausea, difficulty sleeping, and SM. Therefore, patients may have be more acutely aware of a particular symptom, leading them to report symptoms that occurred earlier and/or later and at a higher intensity following chemotherapy. Additionally, VGA may have helped identify a subset of patients who experienced SM differently than previously understood. By investigating patterns of a symptom individually over time, a new understanding of those patterns is presented.

Findings from this secondary analysis suggest that there are levels of variability in patients' patterns of SM. No two patients presented with SM (or other symptoms) in exactly the same manner. These findings challenge health care providers and researchers to think differently about patients experiencing SM because not all patients are alike. Thus, assessment and management procedures need more individualization than previously thought. It is imperative for clinicians and researchers to continue vigilant assessment of SM across the entire treatment period. The timing of assessment is important in studies focusing on SM, since studies that only measure the symptom at day 5 or on a weekly basis might miss important data. Thus, oral assessment should occur more frequently, for longer periods of time after treatment, and on a more consistent, daily schedule. Even self-reports can clue the clinician to the need for a more thorough oral exam for full diagnosis and intervention.

Assessment is a particularly challenging endeavor for outpatients because of their non-availability in between treatments. Clinicians and researchers must think of other innovative techniques to assess outpatients. Assessment tools such as TLC alert or daily questionnaires such as those used by Stiff et al. [18] or Wong et al. [20] that gather information from patients at home might be an answer to meeting this challenge. Another option is to teach patients to do a simple visual inspection of their oral cavity using a simple OM assessment tool and reporting changes in color, ulcerations, etc. It is also important for researchers to report patients' adherence rates to conducting such exams and reporting the results when these daily questionnaires are used by patients to help determine the feasibility of using the questionnaires in research.

In addition, it is beneficial to assess patterns of SM longitudinally over two or more cycles of chemotherapy to get a more accurate picture of any given patient's trajectory. Since clinical factors such as chemotherapy regimens and type of cancer seem more important in relation to patterns of SM, increased focus on surveillance and assessment should be included when patients are treated with antineoplastic agents that have been shown in the literature to cause more severe or unusual patterns of SM [5].

Finally, assessment should include particular patient characteristics such as age, marital status, and educational level. Recall that non-married patients were more likely to report early onset of SM. Further research is needed, but it may be that those patients who receive emotional and physical support report SM later and at a lower severity. Thus, there is a need to include particular patient characteristics in clinical assessment and research.

This study demonstrated significant relationships between particular chemotherapy agents and patterns of OM. Amongst participants from this study, the AC regimen was significantly associated with late onset; however, the duration of the onset was not particularly intense. Quite the opposite, patients receiving RCHOP were significantly more likely to experience duration intensity. Interestingly, both regimens contain doxorubicin and cyclophosphamide, yet only those patients receiving R-CHOP got rituximab. Perhaps, rituximab was responsible for the longer duration and intensity of SM. In an extensive study of OM, Sonis et al. [16] noted that grades 3 and 4 OM were seen in approximately 10% of patients receiving a combination of doxorubicin and cyclophosphamide. The regimen CMF was significantly associated with middle onset, while "other" chemotherapy drugs (flurouracil, cisplatin) tended to cause early onset SM. Future studies should investigate duration, onset, incidence, and intensity of SM in particular chemotherapies. In studies with heterogeneous treatment regimens, it is important to analyze patterns related to treatment.

Another interesting finding was that 97% of participants ranked their daily severity and distress scores within one point or less of each other. There may be at least two reasons why participants rated severity and distress similarly. First, patients may really have felt that severity and distress were very similar. Second, patients may not have understood the conceptual differences between the meaning of the words "severity" and "distress" and may, thus, have viewed them as the same

thing. In future studies, it may be helpful to carefully define the words severity and distress to patients so that they can understand what is being asked.

Limitations

This study was limited by several issues. First, the findings from the study are not generalizable beyond the study sample, which consisted primarily of married Caucasian women with some college education and with a diagnosis of breast cancer. Future research should include increased participation by minorities, men, people from other socioeconomic backgrounds, and people with other cancer diagnoses. We also exclude participants who only reported a sore mouth once or twice; some of these patients may have had OM.

Another limitation was the number of cycles each participant received. All participants received one cycle of chemotherapy before beginning the TLC study; recall data from this cycle were used to determine eligibility. Thus, those who had early onset of SM may have been displaying sustained responses related to their prior experience of a SM in cycle 1 of chemotherapy. Further, it is not known what other clinical interventions occurred during the first cycle of chemotherapy. For instance, a participant who had more intense SM in cycle 1 might have received oral morphine at that time. If this patient continued using oral morphine during cycles 2 and 3, the reported severity and distress could have been less. Because some patients might have received some form of pain medication, the reports are indicative of real life clinical experiences in which some patients may have been treated. Future research should begin in cycle 1 and control for and describe such interventions.

In this secondary analysis, SM was used as a proxy for OM. The assumption was made that a patient receiving chemotherapy who had a complaint of a SM at least three times during a chemotherapy cycle was experiencing OM. However, some patients' SM may have resulted from other causes, such as dental prostheses. Although this dataset had the advantage of providing daily reports from outpatients who are not readily observable, the ideal study would examine this issue using a prospective repeated-measures design that measured OM using a reliable and valid observational approach.

Finally, because of the exploratory nature of VGA, there are limitations in its use. VGA can be a time-intensive procedure and is appropriate for a smaller sample size when resources are limited. In this study, although there was an adequate sample based on estimates of five per cell, some categories yielded cell sizes less than expected and the results cannot be considered definitive. However, this exploratory analysis indicates that trajectories of sore mouth do vary by individual, and differences in trajectory may be related to treatment regimen and/or type of cancer. These findings are important to consider in the design of future studies.

Conclusions

This secondary data analysis provides clinicians and researchers with a technique to visualize the trajectory of a symptom over time. It documents a highly variable pattern of SM in patients receiving chemotherapy. It is important to understand a patient's unique response in order to develop an appropriate assessment and treatment strategy. While health care providers may have witnessed one or many of the patterns of SM in their clinical practice, until now, there has been a lack of actual descriptive research that documented these patterns. Better understanding of the multifaceted problem of SM will ultimately lead to improved interventions to both alleviate and lessen the debilitative effects of OM and allow for the support of patients throughout the entire course of OM, not just when their pain is so intense that they cannot eat or drink or tolerate further cancer therapy. The improved understanding of the complex symptom of mucositis will ultimately improve the overall patient experience and allow patients to receive the chemotherapy they need for a chance at long-term control and cure of their respective cancers.

Acknowledgments

This research was supported in part by the American Cancer Society Doctoral Scholarship #DSCN-03-203-01 and National Cancer Institute, R25 CA093831. The parent study "Telephone-Linked Care for Symptom Management" (K. Mooney, PI) 1 R01 CA89474, funded) was funded by the NCI.

References

Brown CG, McGuire DB, Peterson DE, Beck SL, Mooney K (2007) Visual graphical analysis: a technique to investigate symptom trajectories over time. Nurs Res 56:195–201, doi:10.1097/01.NNR.0000270029.82736.5a

Chang VT, Hwang SS, Feuerman M, Kasimis BS (2000) Symptom and quality of life survey of medical oncology patients at a Veterans Affairs Medical Center: a role for symptom assessment. Cancer 88:1175, doi:10.1002/(SICI)1097-0142(20000301)88:5<1175::AID-CNCR30>3.0.CO;2-N

Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M et al (2000) Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer 89(7):1634–1646, doi:10.1002/1097-0142(20001001)89:7<1634::AID-CNCR29>3.0.CO;2-V

Dodd MJ, Larson PJ, Dibble SL, Miaskowski C, Greenspan D, MacPhail L et al (1996) Randomized clinical trial of clorhexidine versus placebo for prevention for oral mucositis in patients receiving chemotherapy. Oncol Nurs Forum 23:921–927

Elting LS, Cooksley C, Chambers M, Cantor SB, Manzullo E, Rubenstein EB (2003) The burdens of cancer therapy. Clinical and economic outcomes of chemotherapy-induced mucositis. Cancer 98:1531–1539, doi:10.1002/cncr.11671

McGuire DB, Altomonte V, Peterson DE, Wingard JR, Jones RJ, Grochow LB (1993) Patterns of mucositis and pain in patients receiving preparative chemotherapy and bone marrow transplantation. Oncol Nurs Forum 20:1493–1502

McGuire DB, Yeager KA, Dudley WN, Peterson DE, Owen DC, Lin LS et al (1998) Acute oral pain and mucositis in bone marrow transplant and leukemia patients: data from a pilot study. Cancer Nurs 21:385–393, doi:10.1097/00002820-199812000-00002

Mooney KH, Beck SL, Friedman RH, Farzanfar R (2002) Telephone-linked care for cancer symptom monitoring. Cancer Pract 10:147–154, doi:10.1046/j.1523-5394.2002.103006.x

Pett MA (1997) Nonparametric statistics for health care research. Sage, Thousand Oaks, CA

Raber-Durlacher JE, Weijl NI, Abu Saris M, de Koning B, Zwinderman AH, Osanto S (2000) Oral mucositis in patients treated with chemotherapy for solid tumors: a retrospective analysis of 150 cases. Support Care Cancer 8:366–371, doi:10.1007/s005200050004

Roemer J (1999) An end to outpatient chemotherapy? Medicare takes aim at reimbursement. J Natl Cancer Inst 91:1444–1445, doi:10.1093/jnci/91.17.1444

Scully C, Sonis S, Diz PD (2006) Oral mucositis. Oral Dis 12:229–241, doi:10.1111/j.1601-0825.2006.01258.x

Senn HJ (ed) (2006) Mucositis guidelines: achievements and perspectives. Support Care Cancer 14(6)

Singer JD, Willett JB (2003) Applied longitudinal data analysis: modeling change and event occurrence. Oxford University Press, New York

Sonis SS (2004) A biological approach to mucositis. J Support Oncol 2:21–32

Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M et al (2004) Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patient. Cancer 100:1995–2025, doi:10.1002/cncr.20162

Spielberger R, Stiff P, Bensinger W, Gentile T, Weisdorf D, Kewalramani T et al (2004) Palifermin for oral mucositis after intensive therapy for hematologic cancers. N Engl J Med 351:10–18, doi:10.1056/NEJMoa040125

Stiff PJ, Erder H, Bensinger WI, Emmanouilides C, Gentile T, Isitt J et al (2006) Reliability and validity of a patient self-administered daily questionnaire to assess impact of oral mucositis (OM) on pain and daily functioning in patients undergoing autologous hematopoietic stem cell transplantation (HSCT). Bone Marrow Transplant 37:393–401, doi:10.1038/sj.bmt.1705250

Vokurka S, Bystricka E, Koza V, Scudlova J, Pavlicova V, Valentova D et al (2006) Higher incidence of chemotherapy induced oral mucositis in females: a supplement of multivariate analysis to a randomized multicentre study. Support Care Cancer 14:974–976, doi:10.1007/s00520-006-0031-z

Wong PC, Dodd MJ, Miaskowski C, Paul SM, Bank KA, Shiba GH et al (2006) Mucositis pain induced by radiation therapy: prevalence, severity, and use of self-care behaviors. J Pain Symptom Manage 32:27–37, doi:10.1016/j.jpainsymman.2005.12.020

Youngblut JM, Casper GR (1993) Focus on psychometrics: single-item indicators in nursing research. Res Nurs Health 16:459–465, doi:10.1002/nur.4770160106