Application of Distance Matrices to Define Associations Between Acute Toxicities in Colorectal Cancer Patients Receiving Chemotherapy

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BACKGROUND. Colorectal cancer patients undergoing chemotherapy (CT) are likely to experience multiple concurrent toxicities that, rather than appearing singularly, may be associated with one another. Graphic and tabular representations of distance matrices were used to identify associations between toxicities and to define the strengths of these relations.

METHODS. Using a standardized data collection tool, electronic medical charts of 300 consecutive patients receiving either the combination of leucovorin, 5-fluorouracil (5-FU), and oxaliplatin (FOLFOX); the combination of leucovorin, 5-FU, and irinotecan (FOLFIRI); or 5-FU) were retrospectively reviewed to record baseline demographic and clinical information. Treatment-related toxicities were recorded using National Cancer Institute Common Toxicity Criteria during the first cycle of CT. Using a distance matrix approach, an analysis of CT-induced toxicity associations was elaborated.

RESULTS. The graphic analysis, in which associations between toxicities were represented as links, identified 6 major hubs (fever, dehydration, fatigue, anorexia, pain, and weight loss), defined as central nodes with more connections than expected by chance. These were highly linked with minor nodes and provided evidence suggesting the existence of symptom clusters associated with CT-induced toxicities.

CONCLUSIONS. The application of distance matrix analyses to define CT-induced toxicity associations is new. The technique was effective in defining the global landscape of the binary relations among toxicities associated with Cycle 1 therapy. The coherent clinical picture emerging from the network provides a strong suggestion that the toxicities in each cluster share a common pathobiologic basis, which may provide an opportunity for intervention. These findings could become useful for the early prediction of co-occurring toxicities and, in the future, as a phenotyping framework for the pharmacogenomic analysis of individual responses to chemotherapy. ***Cancer* 2008;112:284–92.** © *2007 American Cancer Society.*

KEYWORDS: toxicity, chemotherapy, colorectal cancer, distance matrix.

Treatment-related toxicities are common among patients being treated with cancer chemotherapy. Not only do toxicities create pain and distress, they also adversely impact quality of life and patient tolerance of cancer treatment.[1,2] Many contribute either directly or indirectly to increased morbidity or mortality. Furthermore, they are significant drivers of healthcare costs by increasing the need for supportive care.[3,4] Despite an awareness that toxicities rarely occur independent of each other, the majority of research in supportive cancer care has focused only on individual symptoms, such as fatigue,[5] mucositis,[6] anxiety or alopecia,[7] nausea/vomiting,[8]

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hematologic toxicity,[9] or pain.[10] This paradigm is currently shifting to the study of symptom clusters,[11–13] most of which have been defined using conventional hierarchical analysis.

Clustering symptom distress is now recognized as important and measurable in cancer patients. The scale developed at the University of Texas M. D. Anderson Cancer Center[14] and validated in many countries and patient populations has been used to document the nature and frequency of symptom clusters. In a retrospective review of 1000 cancer patients admitted for palliative care, each patient was reported to have a median of 11 symptoms,[15] whereas other series reported a median of 13 symptoms.[16] In many cases, the analyses of symptoms have been performed in patients well beyond the completion of their treatment, and have been attributed to the chronic effects of their disease burden.

In contrast, chemotherapy-induced toxicity symptoms would be expected to be more acute and to occur within days or weeks of the administration of drug, as well as be mechanistically attributable to the induction of biologic pathways that result in direct tissue injury (as in mucositis) or the secondary effects of increased levels of mediators such as proinflammatory cytokines (fatigue). Alternatively, it is conceivable that the products of tumor cell destruction are themselves capable of inducing inflammatory pathways and thereby indirectly evoking symptoms. Clues to the common mechanistic underpinnings of toxicities could be better defined by studying the patterns and groupings in which toxicities occur.

To our knowledge, relatively little has been published to date regarding toxicity complexes among patients being treated for colorectal cancer. Studies have mainly focused on cancer-associated symptoms, rather than those specifically associated with treatment.

The current study was designed to define relations between chemotherapy-induced toxicities reported in colorectal cancer patients using a novel approach that may be less confining and more comprehensive than conventional hierarchical analysis. We developed a graphic and tabular model based on distance matrices in which nodes represent random variables and arcs or arrows define stochastic dependencies quantified by probability distributions.

MATERIALS AND METHODS

Population and Data Collection

To assess the correlations between treatment-related toxicities, we performed a retrospective medical record review of consecutive patients undergoing treatment with chemotherapy for colorectal cancer at the Dana Farber Cancer Institute, Boston, Massachusetts. The local Institutional Review Board reviewed and approved the protocol and the study was conducted in accordance with the Declaration of Helsinki.

An initial study cohort of predetermined size (n = 800) was identified by a comprehensive computer search of all patients with International Classification of Diseases (ICD-9) codes for colorectal cancer treated at the Dana Farber Cancer Institute. From the initial population, 300 patients were enrolled in the analysis in reverse chronologic order, starting from December 31, 2005 and proceeding backward in time until target enrollment was achieved. Patients were eligible for inclusion if they were age $\geq$18 years at the time of diagnosis, had a pathology-confirmed diagnosis of colorectal cancer, and if they underwent at least 1 cycle of conventional chemotherapy.

A standardized data collection tool was developed to record demographic data, habits, clinical and tumor characteristics, and treatment-related information. Toxicities were defined by standard National Cancer Institute Common Toxicity Criteria (NCI CTC; version 2.0 or 3.0) and recorded as being present if a grade of $\geq$1 was noted in the medical record at any time during the first treatment cycle.

Construction of the Distance Matrix Network

To assess binary relations we used a network of associations that was constructed by comparing, for each pair of toxicities, the probability $p(A \leftrightarrow B \mid \Delta)$ that the 2 toxicities A and B are associated given the data Δ with the probability $p(A \perp B \mid \Delta)$ that the 2 toxicities are independent given the data. The probabilities $p(A \leftrightarrow B \mid \Delta)$ and $p(A \perp B \mid \Delta)$ are proportional to the probabilities of the data given the model of association, $p(\Delta \mid A \leftrightarrow B)$ and $p(\Delta \mid A \perp B)$, respectively, known as marginal likelihoods and, for the case of a discrete variable, it is computed in closed form. In this study, the marginal likelihood was corrected by the standard penalty for model complexity known as Bayesian Information Criterion (BIC).

The measure of strength of association between 2 toxicities in this article is known as Bayes Factor and it is computed as the ratio between the model of association and the model of independence:

$$BF = \frac{p(A \leftrightarrow B \mid \Delta)}{p(A \perp B \mid \Delta)}$$

which represents how many times the model of association is more probable than the model of inde-

TABLE 1
Baseline Characteristics of Study Population

	No. (%)
No. of patients	300 (100)
Sex	
Female	144 (48.0)
Male	156 (52.0)
Race	
White	275 (91.7)
African American	18 (6.0)
Asian	6 (2.0)
Other	1 (0.3)
Age at diagnosis, y	
18–45	49 (16.3)
45–64	176 (58.7)
≥65	75 (25.0)
Smoking status	
Nonsmoker	141 (47.0)
Previous smoker	111 (37.0)
Actual smoker	48 (16.0)
1–10 packs/y	68
11–20 packs/y	49
> 20 packs/y	42
Alcohol use	
None	72 (24.0)
Social	151 (51.3)
Regular	62 (20.7)
Heavy	15 (5.0)
Comorbidities	
≥1 comorbidity	118 (39.3)
Hypertension	74
Cardiovascular disease	43
Diabetes	36
Gastrointestinal disease	25
Renal disease	13
Other	9
Stage of the disease	
HR stage II or stage III	103 (34.3)
Stage IV	197 (65.7)
Regimen	
Oxaliplatin based	146 (48.7)
Irinotecan based	78 (26)
Monotherapy with iv/oral 5-FU	76 (25.3)

HR indicates high risk; iv, intravenous; 5-FU, 5-fluorouracil.

pendence for each pairwise comparison. A Bayes factor > 1 demonstrates some evidence of association and a Bayes factor > 3 supports strong evidence of an association, whereas a Bayes factor > 7 provides decisive evidence in favor of association.[17]

RESULTS

Of the 300 consecutive colorectal cancer patients included in this review, the majority received chemotherapy with palliative intent for the treatment of advanced disease. The demographic characteristics of the study population are summarized in Table 1. Approximately half the patients were female. The overwhelming majority were white and age > 45 years, although the mean age at diagnosis was younger than is usually reported. Nearly half of the patients were past or present smokers and approximately 25% were regular or heavy alcohol drinkers. Approximately 40% of patients had at least 1 comorbidity, of which hypertension was the most common. Thirty-six patients (12%) had a history of diabetes mellitus.

With respect to disease setting, 103 patients (34%) were treated with adjuvant intent for high-risk stage II or stage III disease and the remaining 197 (66%) were treated for stage IV metastatic disease for palliation (graded according to the Tumor, Node, Metastasis Staging System, 5th and 6th edition). Patients received 1 of 3 primary treatment regimens: an oxaliplatin-based regimen (in which the platinum compound was either given with continuous infusion of 5-fluorouracil [5-FU] or with capecitabine), an irinotecan-based regimen (in which irinotecan was given in association with either intravenous 5-FU or capecitabine), or monotherapy with 5-FU (either oral or by infusion). Although some patients also received an antiangiogeneic agent (bevacizumab) or an epidermal growth factor receptor inhibitor (either cetuximab or erlotinib), the number was small because these drugs were in limited use, exclusive of clinical trials, before 2004.

Toxicities

Greater than 96% of study patients experienced at least 1 type of toxicity during their first cycle of chemotherapy and most patients experienced more than 2 different toxicities (Table 2). Regardless of the grade, only 20% of the study population reported ≤2 toxicities. Remarkably, > 6 toxicities were noted in approximately one-third of the subjects.

Toxicities were reported by NCI CTC criteria and, for the purpose of this study, placed into 83 categories based on patient reporting during and at the conclusion of Cycle 1 (Table 2). All patients received their planned Cycle 1 treatment. Three were compelled to discontinue subsequent treatment because of toxicity. There were no toxicity-related deaths. Fourteen patients (5.3%) had toxicity-associated hospitalizations during or immediately after Cycle 1 due to infection with febrile neutropenia and/or gastrointestinal toxicity (nausea, diarrhea, and/or vomiting) combined with dehydration. The median duration of hospitalization was 3 days (range, 1–14 days).

From the original platform of 83 different toxicities, we selected for analysis those (n = 25) that occurred with a frequency of at least 5% (Table 3). The most frequently reported toxicities were nausea

TABLE 2
Comprehensive Distribution of Cycle Toxicities as Defined by NCI-CTC Criteria

Type of toxicity	No. (%)	Type of toxicity	No. (%)
Immune system		Memory impairment	1 (0.3)
Autoimmune reaction	0 (0)	Motor neuropathy	2 (0.7)
Allergic reaction	2 (0.7)	Dizziness	3 (1.0)
Arthritis	2 (0.7)	Ataxia	3 (1.0)
Eye and ear		Depression	18 (6.0)
Hearing loss	0 (0)	Anxiety	24 (8.0)
Nystagmus	0 (0)	Insomnia	24 (8.0)
Otitis	1 (0.3)	Sensory neuropathy	67 (22.3)
Tinnitus	3 (1)	Genitourinary	
Loss of vision	6 (2)	Erectile dysfunction	1 (0.3)
Cardiac and vascular		Urinary retention	2 (0.7)
Ischemia	0 (0)	Urinary incontinence	6 (2.0)
Cardiac ischemia	1 (0.3)	Vaginal problems	7 (2.3)
Arrhythmia	2 (0.7)	Cystitis	14 (14.7)
Thrombosis or embolism	4 (1.3)	Respiratory	
Hypotension	7 (2.3)	Bronchospasm	0 (0)
Hypertension	9 (3)	Pleural effusion	0 (0)
Hemorrhage or bleeding	16 (5.3)	Wheezing	0 (0)
Palpitation	35 (11.7)	Hiccups	3 (1.0)
Dermatologic		Cough	13 (4.3)
Nail changes	3 (1)	Dyspnea	24 (8.0)
Wound complication	10 (3.3)	Infection	
Skin pigmentation, HFS	31 (10.3)	Febrile neutropenia	8 (2.7)
Dry skin	26 (8.7)	Infection	19 (6.3)
Pruritus, itching	35 (11.7)	Gastrointestinal	
Rash	38 (12.7)	Colitis	0 (0)
Constitutional		Esophagitis	0 (0)
Weight gain	1 (0.3)	Ascities	1 (0.3)
Hoarseness	1 (0.3)	Belching	1 (0.3)
Hot flushes	3 (1)	Enteritis	2 (0.7)
Edema	6 (2.0)	Dental problem	3 (1.0)
Sweating	9 (3)	Gastritis	3 (1.0)
Chills	14 (4.7)	Dysphagia	5 (1.7)
Hair loss	14 (4.7)	Proctitis	5 (1.7)
Weight loss	22 (7.3)	Incontinence	9 (3.0)
Insomnia	24 (8)	Dry mouth	14 (4.7)
Weakness	24 (8)	Constipation	19 (6.3)
Fever	42 (14)	Taste alteration	20 (6.7)
Pain	53 (17.7)	Heartburn or dyspepsia	30 (10.0)
Fatigue	166 (55.3)	Dehydration	32 (10.7)
Neurologic		Distension, bloating	50 (16.7)
Sleep disorders	0 (0)	Vomiting	65 (21.7)
Psychosis	0 (0)	Mucositis	74 (24.7)
Seizures	0 (0)	Anorexia	75 (25.0)
Speech impairment	0 (0)	Diarrhea	150 (50.0)
Syncope	0 (0)	Nausea	170 (56.7)
Cognitive disturbance	1 (0.3)		

NCI-CTC indicates National Cancer Institute Common Toxicity Criteria; HFS, hand-foot syndrome reaction.

(n = 170; 56.7%), fatigue (n = 165; 55%), and diarrhea (n = 150; 50%).

When we incorporated possible clinical risk factors into the model, no associations were found between reported toxicities and patient sex, age, race, comorbidities, or habits (Table 3). However, we noted a correlation ($P < .05$) between the development of specific toxicities and the type of chemotherapy. For example, all patients (n = 67) who developed sensory neurotoxicity received an oxaliplatin-based regimen, and the same treatment was more frequently associated with the development of pain than the irinotecan-based regimen or monochemotherapy.

TABLE 3
Frequency of the 25 Most Frequent Toxicities by Potential Risk Factors

	No.	%	Female	%	Comorbidities	%	Tobacco use	%	Alcohol	%	Age < 65 y	%	Stage IV	%	Ox	%	Irinotecan	%	5-FU	%
Palpitation	35	11.7	18	51.4	15	42.9	16	45.7	25	71.4	26	74.3	35	100.0	15	42.9	9	25.7	11	31.4
Hemorrhage, bleeding	16	5.3	8	50.0	7	43.8	8	50.0	11	68.8	12	75.0	9	56.3	9	56.3	3	18.8	4	25.0
Skin pigmentation	31	10.3	13	41.9	18	58.1	27	87.1	14	45.2	26	83.9	22	71.0	15	48.4	5	16.1	11	35.5
Dry skin	25	8.3	13	52.0	10	40.0	14	56.0	21	84.0	18	72.0	17	68.0	13	52.0	6	24.0	6	24.0
Pruritus	34	11.3	12	35.3	19	55.9	18	52.9	24	70.6	27	79.4	27	79.4	19	55.9	8	23.5	7	20.6
Rash	37	12.3	19	51.4	12	32.4	30	81.1	30	81.1	26	70.3	33	89.2	23	62.2	10	27.0	4	10.8
Pain	52	17.3	22	42.3	20	38.5	41	78.8	41	78.8	42	80.8	43	82.7	29	55.8	11	21.2	12	23.1
Fatigue	165	55.0	77	46.7	66	40.0	93	56.4	134	81.2	130	78.8	118	71.5	81	49.1	44	26.7	40	24.2
Fever	41	13.7	20	48.8	19	46.3	26	63.4	32	78.0	32	78.0	32	78.0	20	48.8	14	34.1	7	17.1
Insomnia	24	8.0	14	58.3	10	41.7	14	58.3	19	79.2	21	87.5	17	70.8	9	37.5	9	37.5	6	25.0
Weight loss	21	7.0	7	33.3	12	57.1	13	61.9	17	81.0	17	81.0	18	85.7	9	42.9	7	33.3	5	23.8
Weakness	23	7.7	8	34.8	9	39.1	10	43.5	19	82.6	16	69.6	18	78.3	9	39.1	9	39.1	5	21.7
Sensory neuropathy	67	22.3	32	47.8	23	34.3	35	52.2	52	77.6	54	80.6	42	62.7	67	100.0	0	0.0	0	0.0
Anorexia	75	25.0	39	52.0	23	30.7	39	52.0	20	26.7	56	74.7	58	77.3	36	48.0	21	28.0	18	24.0
Constipation	19	6.3	11	57.9	8	42.1	6	31.6	14	73.7	16	84.2	15	78.9	8	42.1	7	36.8	4	21.1
Dehydration	32	10.7	19	59.4	10	31.3	21	65.6	25	78.1	22	68.8	25	78.1	12	37.5	12	37.5	8	25.0
Diarrhea	150	50.0	75	50.0	58	38.7	76	50.7	112	74.7	113	75.3	95	63.3	65	43.3	42	28.0	43	28.7
Bloating	50	16.7	23	46.0	27	54.0	27	54.0	36	72.0	35	70.0	28	56.0	18	36.0	15	30.0	17	34.0
Dyspepsia	30	10.0	14	46.7	13	43.3	17	56.7	19	63.3	25	83.3	22	73.3	14	46.7	9	30.0	7	23.3
Mucositis	74	24.7	40	54.1	28	37.8	35	47.3	13	17.6	48	64.9	44	59.5	30	40.5	16	21.6	28	37.8
Nausea	170	56.7	91	53.5	75	44.1	90	52.9	123	72.4	139	81.8	112	65.9	73	42.9	50	29.4	47	27.6
Vomiting	65	21.7	31	47.7	21	32.3	41	63.1	47	72.3	57	87.7	20	30.8	31	47.7	18	27.7	16	24.6
Taste alteration	20	6.7	9	45.0	9	45.0	16	80.0	19	95.0	15	75.0	8	40.0	7	35.0	7	35.0	6	30.0
Dyspnea	24	8.0	15	62.5	10	41.7	15	62.5	20	83.3	19	79.2	2	8.3	15	62.5	6	25.0	3	12.5
Infection	19	6.3	10	52.6	7	36.8	5	26.3	10	52.6	16	84.2	12	63.2	9	47.4	2	10.5	8	42.1
Anxiety	24	8.0	16	66.7	10	41.7	15	62.5	16	66.7	6	25.0	8	33.3	13	54.2	3	12.5	8	33.3
Depression	18	6.0	11	61.1	9	50.0	10	55.6	13	72.2	10	55.6	13	72.2	9	50.0	4	22.2	5	27.8

Ox indicates oxaliplatin-based regimen; 5-FU, 5-fluorouracil.

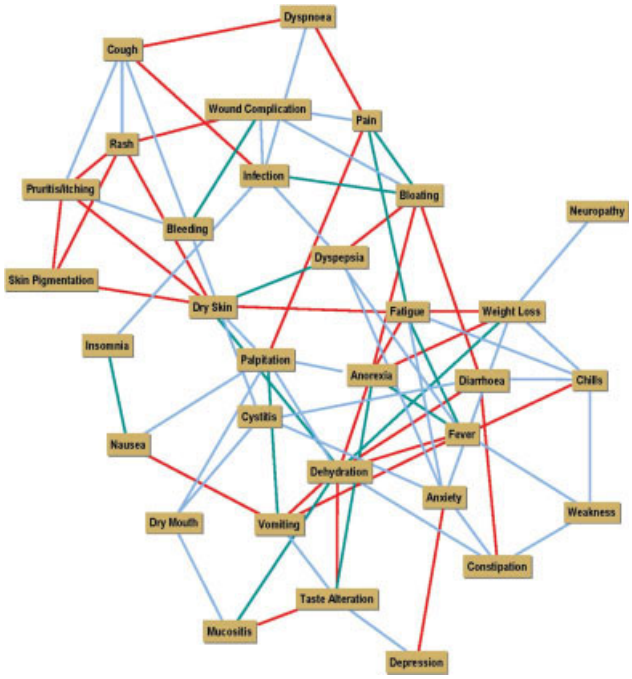

FIGURE 1. Network developed by a Bayesian analytical approach showing associations between cycle 1 toxicities. Strong links, implying an association between 2 different toxicities that was at least 7 times more probable than the possibility that those toxicities were unrelated, are represented as red lines. Weaker links, defined as the probability of an association between 2 toxicities is 3 to 7 times higher than the probability of their not being associated, is represented by a blue line, and association links of <3 are seen as green lines.

Using a Bayesian analytical approach, we developed graphs that defined strong and weak toxicity associations based on probability tests of association (Fig. 1). A strong link implies that the association between 2 different toxicities was at least 7 times more probable than the possibility for those toxicities to be unrelated, or the possibility of either to be represented as independent. In the same way, a weak link was defined if the probability of association between 2 toxicities was between 3 and 7 times higher than the probability that they are not associated. In the network in Figure 1 associations with a Bayes factor > 3 but <7 are colored in blue, whereas associations with a Bayes factor > 7 are colored in red. The matrix in Figure 2 labels in red the associations with a Bayes factor > 7, with blue the associations between 3 and 7, with green the associations with a Bayes factor between 1 and 3, and in white the lack of association.

Using this technique, we defined 6 principal toxicities as major nodes or hubs because they had at least 5 strong connections with other toxicities: fever, dehydration, fatigue, anorexia, pain, and weight loss. Each major node was connected to at least 2 other major nodes, with the exception of pain, which was connected with fatigue only. In agreement with other work,[18,19] we found a strong association between fatigue and pain.

We also found consecutive associations between toxicities. Two groupings clustered around gastrointestinal symptoms: a first cluster consisted of fatigue, anorexia, dehydration, nausea, and vomiting; a second linked anorexia and dehydration with taste alteration, mucositis, and dry mouth. A dermatologic grouping was defined by connections between dry skin, skin pigmentation/hand-foot syndrome reaction (HFS), rash, and itching, which was also connected to wound complication toxicity. Finally, we noticed strong connections between pulmonary symptoms such as cough, dyspnea, and infection. Chills, weight loss, and weakness were all connected with fever.

DISCUSSION

The basis for, and definition of, toxicity clustering remains to be elucidated despite the applications of several analytic approaches. In nononcology settings, when symptoms have been grouped, it has often been done intuitively rather then empirically. Physical symptoms are commonly dissociated from cognitive and affective symptoms. Previous studies have suggested that ≥ 3 symptoms, occurring at the same time, might be considered a cluster,[12,20,21] and several studies demonstrated correlations (tight, close, or frail) between clusters.[22,23] There has been growing awareness that common biologic mechanisms may underlie or contribute to simultaneously reported symptoms[24] and there is clinical evidence that symptoms grouped in a cluster may share a common biologic mechanism.[25]

However, although symptom clusters have been useful in creating diagnostic criteria for many nonmalignant diseases, the process that leads to symptom cluster definitions in oncology is much more complicated. In fact, the symptoms reported could be related to the cancer, to the treatment, to a concomitant illness, or to a combination of these factors. It is also possible that a symptom causes a cascade of other symptoms or that an interaction between key symptoms exists. These relations could lead to an increasing number of functional disturbances,[26] both in the patients receiving chemotherapy treatment and in terminally ill patients.[27]

Consequently, we reasoned that a comparison of various treatment-related toxicities at a more interactive level was highly desirable. Effectively, toxicities

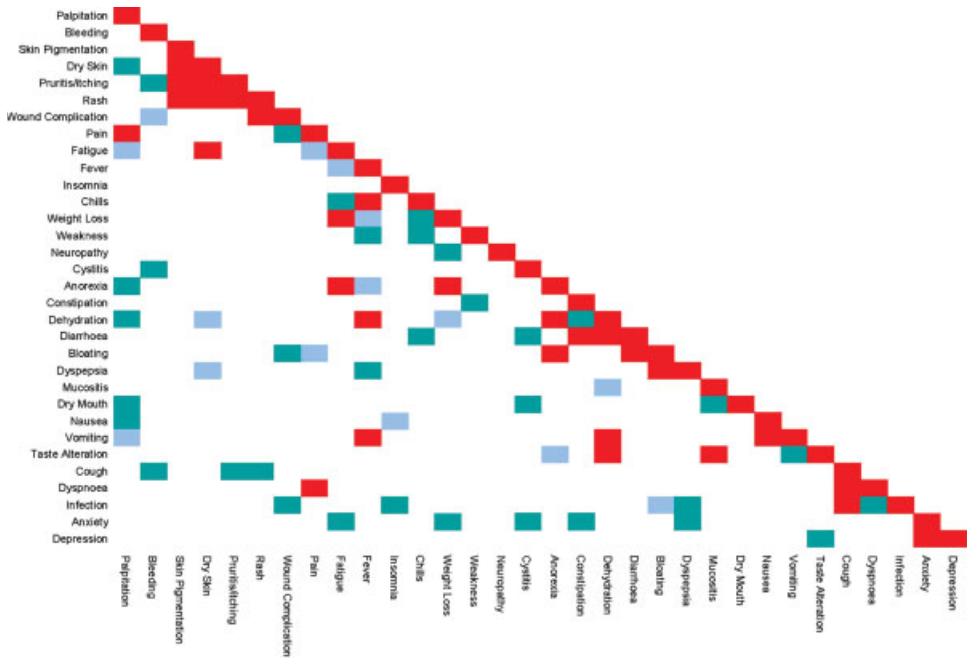

FIGURE 2. Matrix demonstrating toxicity associations. The matrix is read in a manner similar to a distance matrix found in street atlases. Associations in which the Bayes factor is >7 are labeled in red. Blue indicates associations between 3 and 7, and green depicts associations with a Bayes factor between 1 and 3. Those areas in white indicate a lack of any association.

are likely to appear, accumulate, peak, and remain or dissipate at predictable timepoints throughout the treatment cycle. For this reason, we recorded all toxicities reported by nurses and/or physicians during the entire cycle. We focused our analysis on the first treatment cycle to eliminate confounders such as palliative or therapeutic interventions that might be introduced in subsequent cycles.

We found a high frequency of reported toxicities. Fatigue and diarrhea were the most common. Interestingly, we did not find any correlations between the patients' demographic factors or comorbidities and toxicity development. This may be related to the relatively small number of cases analyzed, because other studies report that sex and comorbidities may affect toxicity patterns.[28] As expected, we found a strong correlation between the specific type of toxicity and the chemotherapy regimen given. For example, neurologic symptoms were correlated with exposure to oxaliplatin, whereas the development of cutaneous rash or dermatitis was observed in patients receiving an EGFR-inhibitor. Some of the clusters have been previously suggested,[23] such as a gastrointestinal and a pulmonary association of symptoms.

Description of symptom clusters in cancer patients is not new. Conventional studies used a Pearson correlation coefficient or standard hierarchical analysis with a squared Euclidean method to establish the strength of correlations between different symptoms, or to calculate distances between symptom items.[22] The application of a hierarchical analysis describes the correlation of a specific symptom with another toxicity. A problem with this approach is that hierarchical clustering clusters toxicities into a single structure so that each toxicity can be assigned to 1 cluster only. In contrast, the graphical approach adopted in this study allows a toxicity to be shared by several clusters and, in so doing, identifies toxicities that play a central role in connecting different clusters. In network theory, these highly connected nodes in the network are termed *hubs* and represent a point of contact between alternative clusters, which would not be identifiable by hierarchical analysis.

Herein, we propose a new method to report those correlations, utilizing weak and strong linkages in a Bayesian analytical approach, which offers some specific advantages, as it defines symptom clustering in a dynamic, multidimensional, and comprehensive way that reflects the clinical situation. Rather than analyze only the closest symptom to a specific toxicity, Bayesian methodology depicts multiple associations and relations among toxicities by the application of distance matrices. Effectively, the use of the Bayesian methodology provides the opportu-

nity to discover and define patterns of relations among many concurrent symptoms. Thus, we were able to find 6 key points defined as major connectors, which were linked to at least 5 other lymph nodes. The connections between different toxicities, expressed as a line in the graphs, are not intended to depict causal relations, even if a bilateral causality is possible, as the association between toxicities was interpreted as stochastic variables (either positive or negative). Nonetheless, it could be hypothesized that when 2 toxicities are related a causal connection does exist.

The graphic representation of the network helped us to identify the existence of interesting consecutive associations among toxicities. Two groups of toxicities focused on are gastrointestinal toxicities. The first consisted of fatigue, anorexia, dehydration, nausea, and vomiting, and the second was comprised of anorexia and dehydration with taste alteration, mucositis, and dry mouth. A dermatologic grouping of dry skin, skin pigmentation/HFS, rash, and itching and a pulmonary-focused cluster of cough, dyspnea, and infection suggest both physiologic and mechanistic commonality. Chills, weight loss, and weakness were all connected with fever.

It is interesting to note that we noted a lack of direct associations between some toxicities that have often been unquestionably linked. For example, we found that fever and infection do not have an uninterrupted link in our graphic model. Rather, although correlations between these toxicities are present, the route from one is not direct. This finding is, in fact, consistent with the clinical frequency of fever in the absence of documented infection or neutropenia. In our study population, of the 42 cases of fever identified in patients' medical records, only 11 had fever linked to infection, and 34 had no mention of neutropenia. The nondirectional nature of the network does not address the issue of a causal dependency between associated toxicities, but it identifies relations that could be the subject of further, more detailed analysis, including the determination of their directionality. It is also possible that some of the toxicity associations found in our study population might be different for other cancer regimens. For example, among patients being treated with radiation therapy for cancers of the head and neck, a strong, direct link between oral mucositis and pain would appear inevitable. This raises the question of the ubiquity of toxicity symptom clusters across different cancer diagnoses and treatments, and implies that toxicity associations may vary.

The findings of the current study demonstrate that the application of distance matrices using a Bayesian analytical approach provided a comprehensive picture of toxicity clustering among patients receiving chemotherapy for the treatment of colorectal cancer. This technique provides the opportunity to define the strength of the associations between toxicities, which could reflect common biologic underpinnings. On a clinical level, such a method may provide a basis for the identification of prophylactic and targeted interventions.

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