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Lymphoma Therapy and Adverse Events

Nursing strategies for thinking critically and acting decisively

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BACKGROUND: Multiple treatment options, combined with disease heterogeneity, have created nursing challenges in the management of adverse events (AEs) during antilymphoma therapy. Testing has revealed that less than half of participating nurses correctly graded peripheral neuropathy and neutropenia related to antilymphoma regimens.

OBJECTIVES: This article identifies nursing challenges in the management of AEs associated with therapy for lymphomas and describes how strategies in critical thinking can help meet those challenges.

METHODS: A comprehensive literature search in oncology nursing, nursing education, and critical thinking was conducted; participant responses to pre- and post-tests at nursing education programs were evaluated; and a roundtable meeting of authors was convened.

FINDINGS: Oncology nurses can cultivate critical thinking skills, practice thinking critically in relation to team members and patients, leverage information from the Patient-Reported Outcomes Common Terminology Criteria for Adverse Events, and manage workflow to allow more opportunity for critical thinking.

KEYWORDS

lymphoma; adverse events; critical thinking; communication; nursing assessment

DIGITAL OBJECT IDENTIFIER

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THERAPY FOR LYMPHOMAS HAS CHANGED MARKEDLY in recent years (National Comprehensive Cancer Network [NCCN], 2016c, 2016d). Treatment of B-cell lymphomas has been enhanced by rituximab (Rituxan[®]) immunotherapy; novel targeted therapies, such as bortezomib (Velcade[®]), lenalidomide (Revlimid[®]), and idelalisib (Zydelig[®]); bendamustine (Treanda[®]) chemotherapy; and other innovations (Coiffier et al., 2002; Fowler et al., 2011, 2014; NCCN, 2016d; Rummel et al., 2013). Patients with T-cell lymphomas may now receive histone deacetylase inhibitors and other targeted agents (Duvic et al., 2009). For patients with Hodgkin lymphoma (HL), although chemotherapy remains the standard of care, targeted therapies and immunotherapies may also be indicated as second-line treatment (Ansell et al., 2013; Johnston et al., 2010; Moskowitz et al., 2015).

A growing number of treatment options, combined with the heterogeneity of HL and non-Hodgkin lymphoma (NHL), have created nursing challenges in the management of adverse events (AEs). Nurses are the most trusted health-care team members (Newport, 2012). This puts the oncology nurse in a strong position to assess toxicities with the highest level of patient input, to gather information about overall distress related to the toxicities, and to learn how the toxicities are impacting the patient's routine activities and daily quality of life. Nurses are called on to identify a host of AEs in a wide variety of regimens, and differentiate these AEs from complex lymphoma symptom patterns. Nurses must then grade each AE accurately, and determine which of the multiple antilymphoma drugs in the regimen may have caused the AE. Finally, nurses must collaborate with the interdisciplinary care team to recommend whether to adjust therapy based on the grade and description of the AE, distress level, and impact on quality of life. The recommendation from nurses is essential to help the patient and clinical team come to a shared decision on therapy adjustment.

These activities require nurses to think critically and act decisively by conducting a logical and systematic analysis to determine AE grade, deciding on a recommendation for intervention, and communicating persuasively to the interdisciplinary team, the patient, and the caregiver (Brenner, Hughes, &

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Sutphen, 2008). This skill set is not limited to lymphoma; it applies across all types of malignancies. Lymphoma treatment, because it encompasses so many regimens and virtually all types of AEs, provides an optimal model for AE management across cancer care. The problems and solutions presented in this article are applicable to lymphomas but certainly extend beyond lymphoma to other cancers (see Appendix A).

Nurses can access a number of valuable resources to enhance their knowledge and competency regarding the assessment and management of AEs. Among these are guidelines from the NCCN (2016a, 2016b) on supportive care and the Oncology Nursing Society's ([ONS's], 2016) Putting Evidence Into Practice resources. An overview of all lymphoma treatment toxicities is beyond the scope of this article but can be found in McFadden, Poniatowski, and Temple's (2006) *Contemporary Issues in Lymphoma: A Nursing Perspective* and, for more recently introduced regimens, in NCCN (2016c, 2016d) guidelines for NHL and HL.

Challenges

Lymphoma treatment options are so vast that virtually every possible AE may occur. For example, hematologic toxicities that include anemia, neutropenia, and thrombocytopenia are common to cytotoxic drugs and molecularly targeted agents. IV doxorubicin (Adriamycin[®]), cyclophosphamide (Cytosan[®]), oral lenalidomide, and numerous other drugs may produce grade 3–4 neutropenia (Baxter Healthcare, 2010; Celgene Corporation, 2015; Pfizer Laboratories, 2015) Peripheral neuropathy may occur with drugs as diverse as bortezomib (Velcade[®]), vincristine (Oncovin[®]), carboplatin (Paraplatin[®]), brentuximab vedotin (Adcetris[®]), alemtuzumab (Lemtrada[®]), and many more (Genzyme Corporation, 2014; Grisold, Cavaletti, & Windebank, 2012; Millennium Pharmaceuticals, Inc., 2015; Seattle Genetics, 2015). Serious mucocutaneous reactions are associated with a range of drugs—from the antibody rituximab to cytotoxic therapy like bendamustine (Genentech, 2014; Teva Pharmaceuticals, 2015). Fatigue and gastrointestinal (GI) effects are ubiquitous reactions to anticancer therapy (NCCN, 2016a, 2016b), and some injectable drugs, notably antibodies, carry high risk for hypersensitivity infusion reactions (Genentech, 2014; Genzyme Corporation, 2014). Older chemotherapy drugs, which are still heavily relied upon in current regimens, are characterized by potentially severe and dose-limiting GI, mucosal, and hematologic AEs.

Because antilymphoma therapy often relies on drug combinations (see Figures 1 and 2), additive or synergistic toxicity of drugs in the regimen may occur. The introduction of novel agents into combinations may produce new interactions or toxicities that will not be fully understood without more clinical experience. The potential exacerbation of toxicities in combination therapy complicates the already intricate set of AEs in antilymphoma therapy. In addition, various lymphomas have disease-related symptom patterns that mimic treatment-related

symptoms. For example, pruritus and fatigue may occur in HL and B-cell NHLs, and anemia in diffuse large B-cell lymphoma (NCCN, 2016c, 2016d).

In this complex setting, inaccurate grading of AEs, uncertainty or errors in decisions to adjust therapy, and ineffective team communication represent significant hurdles to effective care (Cirillo et al., 2009; Schulmeister, 2006). Unfavorable outcomes can result, including risks to patient safety (e.g., toxicities graded inaccurately low) and less-optimal treatment efficacy (e.g., drugs are withheld because of inaccurate high grades on AEs or miscommunication of grade). These hurdles contribute to conditions that impede critical thinking in nursing practice.

FIGURE 1.
HODGKIN LYMPHOMA AGENTS

APPROVED AGENTS

- Bleomycin
- Brentuximab vedotin
- Carmustine
- Chlorambucil
- Cyclophosphamide
- Dacarbazine
- Doxorubicin hydrochloride
- Lomustine
- Mechlorethamine
- Pralatrexate
- Prednisone
- Procarbazine hydrochloride
- Rituximab
- Romidepsin
- Vinblastine sulfate
- Vincristine sulfate
- Vorinostat

COMBINATIONS

- *ABVE-PC*—doxorubicin hydrochloride, bleomycin sulfate, vincristine sulfate, etoposide, prednisone, cyclophosphamide
- *BEACOPP*—bleomycin sulfate, etoposide phosphate, doxorubicin hydrochloride plus COPP
- *COPP*—cyclophosphamide, vincristine, procarbazine, prednisone
- *COPP-ABV*—COPP plus doxorubicin hydrochloride, bleomycin sulfate, vinblastine sulfate
- *ICE*—ifosfamide, carboplatin, etoposide
- *MOPP*—mechlorethamine hydrochloride, vincristine sulfate, procarbazine hydrochloride, prednisone
- *OEPA*—vincristine sulfate, etoposide, prednisone, doxorubicin hydrochloride
- *OPPA*—vincristine sulfate, prednisone, procarbazine hydrochloride, doxorubicin hydrochloride
- *Stanford V*—mechlorethamine, doxorubicin hydrochloride, vinblastine sulfate, vincristine sulfate, bleomycin sulfate, etoposide phosphate, prednisone
- *VAMP*—vincristine sulfate, doxorubicin hydrochloride, methotrexate, prednisone

Note. Combinations may contain additional chemotherapy drugs in long use for many types of cancer.

Note. Based on information from National Comprehensive Cancer Network, 2016c.

FIGURE 2.
NON-HODGKIN LYMPHOMA AGENTS

APPROVED AGENTS

- Alemtuzumab
- Belinostat
- Bendamustine hydrochloride
- Bleomycin
- Bortezomib
- Brentuximab vedotin
- Carmustine
- Chlorambucil
- Cyclophosphamide
- Denileukin difitox
- Dexamethasone
- Doxorubicin hydrochloride
- Ibrutinib
- Idelalisib
- Interferon
- Lenalidomide
- Liposomal cytarabine
- Mechlorethamine hydrochloride
- Methotrexate
- Nivolumab
- Plerixafor

COMBINATIONS

- *ABVD*—doxorubicin, bleomycin, vinblastine, dacarbazine
- *ABVE*—doxorubicin, bleomycin, vincristine, etoposide
- *BR*—bendamustine, rituximab
- *CHOP*—cyclophosphamide, doxorubicin, vincristine, prednisone
- *COPP*—cyclophosphamide, vincristine, procarbazine, prednisone
- *CVP*—cyclophosphamide, vincristine, prednisone
- *EPOCH*—etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin
- *ESHAP*—etoposide, methylprednisolone, cytarabine, cisplatin
- *Hyper-CVAD*—cyclophosphamide, vincristine, doxorubicin, dexamethasone
- *ICE*—ifosfamide, carboplatin, etoposide
- *R-CHOP*—rituximab plus CHOP
- *R-CVP*—rituximab plus CVP
- *R-EPOCH*—rituximab plus EPOCH

Note. Combinations may contain additional chemotherapy drugs in long use for many types of cancer.
Note. Based on information from National Comprehensive Cancer Network, 2016d.

Grading

During lymphoma treatment, nurses confront the documented challenge of AE grading during assessment and care (Cirillo et al., 2009; Schulmeister, 2006; Trotti, Colevas, Setser, & Basch, 2007). Grading inaccuracy can lead to clinical deficits, including underestimation of toxicity and the potential for avoidable risk, as well as overestimation of toxicity, leading to unnecessary dose reduction or therapy termination. Grading of many AEs include impact on quality of life, so that the nurse, by making this quality-of-life assessment, is among the most strongly positioned healthcare team member to evaluate and report this critical consideration.

Participant responses during 10 nursing education programs, conducted at ONS Chapters, revealed gaps in grading knowledge among nurses (Rogers, 2015). An author of the current article (AG) served as a faculty member for these programs. Program

participants were presented with six cases and were informed that the cases pertained to peripheral neuropathy, neutropenia, or infusion reactions. They were asked to identify the symptom or AE, grade it, and, if appropriate, provide treatment options for that toxicity and grade. Participant responses were analyzed by an advisor to this article, Barbara Rogers, CRNP, MN, AOCN®, ANP-BC. Responses revealed that only a minority of participating nurses could correctly grade the severity of two common AEs in lymphoma therapy—peripheral neuropathy and neutropenia. In another activity, a higher proportion of participants could correctly grade infusion reactions, but their ability to grade accurately was far from universal for this potentially serious AE (see Table 1).

In a blinded survey (Cirillo et al., 2009), nurses graded AEs more accurately than physicians via the well-established criteria of the Common Terminology Criteria for Adverse Events (CTCAE) (see Table 2). In the study, accuracy was measured by the key parameter of patient-clinician agreement (Cirillo et al., 2009; National Cancer Institute [NCI], 2010; Pakhomov, Jacobsen, Chute, & Roger, 2008). However, better accuracy did not always mean higher nurse accuracy. Nurse-patient agreement in the grading of sensory neuropathy, mucositis, and asthenia was 65% or less by kappa coefficient (KC) (defined as the percentage by which agreement exceeds that expected by chance). Nurse-patient agreement was higher for GI AEs (range = 74%_{KC} to 85%_{KC}) (Cirillo et al., 2009).

Although nurses may exhibit a skill gap in grading AEs, they display much less of a gap in the identification of AEs. In pre- and post-testing during the ONS Chapters education programs, more than 91% of nurses correctly identified peripheral neuropathy, neutropenia, and infusion reaction related to lymphoma treatment. In addition, survey data show patient-nurse agreement of 75%_{KC} or greater for identification of six treatment-emergent AEs—asthenia, nausea, mucositis, sensory neuropathy, constipation, and diarrhea—all of which may occur during one or more forms of lymphoma therapy (Cirillo et al., 2009).

Barriers to Grading

Undeniably, grading of AEs is difficult. A nurse engaged in grading is engaged in an analytic process that demands high-level critical thinking. Several aspects, however, conspire to impair the nurse’s ability to think critically during grading. The first arises from the CTCAE itself, which has the potential for incomplete reporting (Trotti et al., 2007). CTCAE is clinician-centric rather than patient-centric; it does not capture patient self-report of AEs, severity, or impact. Instead, the CTCAE captures the clinician’s analysis of laboratory-based events (e.g., blood counts), events observable on examination (e.g., tremor), and symptomatic events (e.g., nausea) (Basch et al., 2014; Trotti et al., 2007). However, accruing evidence has shown that patient self-reports of toxicity are a better gauge of health status than clinician reports, and that clinicians underreport the severity of AEs in comparison

TABLE 1.
ACCURACY OF GRADING OF LYMPHOMA THERAPY
ADVERSE EVENTS BY NURSE

ADVERSE EVENT CASES	CORRECT PRETEST GRADING			CORRECT POST-TEST GRADING		
	n	N	%	n	N	%
Peripheral neuropathy in a 65-year-old receiving R-CHOP for DLBCL	30	130	23	49	176	28
Neutropenia in a 25-year-old receiving ABVD for HL	46	110	42	37	137	27
Neutropenia in a 40-year-old receiving BR for FL	47	107	44	66	138	48
Infusion reaction in a 70-year-old receiving weekly rituximab for FL	59	115	51	107	160	67
Infusion reaction in an 83-year-old receiving weekly rituximab for FL	65	114	57	98	156	63

ABVD—doxorubicin, bleomycin, vinblastine, dacarbazine; BR—bendamustine, rituximab; DLBCL—diffuse large B-cell lymphoma; FL—follicular lymphoma; HL—Hodgkin lymphoma; R-CHOP—rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
Note. Participating nurses completed pre- and post-testing for educational evaluation.
Note. Based on information from Rogers, 2015.

to patients (Basch et al., 2006, 2009, 2014; Brunner et al., 2011; Dueck et al., 2015; Pakhomov et al., 2008; Quinten et al., 2011). In other words, the CTCAE may fail to provide the evidence needed for patient–clinician agreement on AEs, a key measure of grading validity (Pakhomov et al., 2008). In addition, CTCAE criteria, although in widespread use for decades, have never been formally validated (Trotti et al., 2007), further compromising CTCAE evidence on the severity of AEs. Because evidence is the input for the critical thinking process, attaining the output of accurate grading can be difficult with the current CTCAE.

Another aspect that impedes critical thinking in grading AEs resides in the language of the CTCAE. Grading verbiage has changed between CTCAE version 3.0 (NCI, 2006) and the current version 4.03 (NCI, 2010). Different clinicians may use different terminology depending on the version with which they were trained, leading to inconsistent critical analyses. This problem has been documented for hypersensitivity infusion reactions (DeMoor et al., 2011). A review of 222 cases of hypersensitivity infusion reactions found that different versions of the grading system led to inconsistencies in grading and clinician response to the reaction in about 50% of cases (DeMoor et al., 2011).

The significant weaknesses in the CTCAE has prompted action by the NCI. To overcome the incompleteness and lack of validation, the NCI has spearheaded the development of the

Patient-Reported Outcomes CTCAE (PRO-CTCAE) for use in clinical trials (Basch et al., 2014; Brunner et al., 2011). Although the PRO-CTCAE has not been adapted for use in community clinical practice, its validation study did include patients with lymphoma (Basch et al., 2014), and its implementation in the research setting is instructive for all oncology practitioners.

An additional problem in AE grading is the disjunction between nursing workflow and the critical reasoning process needed for grading. The nursing day offers little time for this process. An observational study revealed that frequent task switching and unpredictable demands characterize the nursing workflow (Cornell et al., 2010; Cornell, Riordan, Townsend-Gervis, & Mobley, 2011). For example, in an observational study, 68% of nurse tasks on a pediatric oncology unit were one minute or less in duration (Cornell et al., 2011). As a result, nurses rarely encounter the conditions—such as workflow control and uninterrupted time—needed for critical thinking (Cornell et al., 2010, 2011).

Another issue of concern is nurse visibility and involvement in the care of patients with lymphoma. The less present and visible nurses are, the less they are able to gather reports, histories, and other evidence regarding patients' AEs. Sustaining a nursing presence requires greater effort than ever because more oral cancer therapies taken by the patient at home have been introduced for the treatment of lymphomas (Yagasaki & Komatsu, 2013). Telephonic assessment is useful for triage of patients and identification of severe AEs but requires experienced clinicians to conduct interviews and supplementation with face-to-face assessments during scheduled office visits (Kondo et al., 2015; Towle, 2009).

TABLE 2.
COMMON TERMINOLOGY CRITERIA FOR ADVERSE
EVENTS

GRADE	DESCRIPTION
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADLs) ^a
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADLs ^b
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

^a Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, or managing money.

^b Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

Note. From Common Terminology Criteria for Adverse Events [v.4.03], by National Cancer Institute Cancer Therapy Evaluation Program, 2010. Retrieved from http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Lastly, the specific nature of critical thinking itself within the discipline of nursing can pose problems. Experts in critical thinking in nursing suggest that, for the nurse, critical thinking occurs within social relationships that involve the patient, caregiver, and multidisciplinary care team. To think critically in any context, including the grading of an AE, presupposes insightful, collegial dialogue and shared observation; the nurse cannot make a critical analysis in isolation (Brenner et al., 2008; Raymond-Seniuk & Profetto-McGrath, 2011). This raises a question: In a day full of interruptions and task switching, how can nurses find the time to exchange ideas with others?

Decision Making

Shared decision making is currently a key model in oncology practice (Clark, Nelson, Valerio, Gong, Taylor-Fishwick, & Fletcher, 2009; Frerichs, Hahlweg, Müller, Adis, & Scholl, 2016). Across the interprofessional team and between clinicians and patients, shared decision making is an empowering partnership in care (Clark et al., 2009). When a clinician shares decision making with a patient, three supportive roles appear to be most important: help the patient understand the issue being decided, listen to the patient's concerns, and include in discussions what matters most to the issue (Elwyn et al., 2012; Katz, Belkora, & Elwyn, 2014).

COMMENTARY ON GRADING ADVERSE EVENTS (AEs)

Deborah Watkins Bruner, RN, PhD, FAAN (Advisor)

We have to realize that the [Common Terminology Criteria for Adverse Events (CTCAE)] has never been validated. So, we actually don't expect that if two clinicians graded an AE, there would be inter-grader reliability. It is also important for nurses to know everything that is—and isn't—in the CTCAE. There is no entry for neutropenia in the CTCAE, only entries for febrile neutropenia and neutrophil count decreased. But prescribing information for antilymphoma therapies may require adjusting dose for grades of neutropenia. Nurses have to recognize this disjunction.

Nina Wagner-Johnston, MD (Author)

In many lymphoma subtypes, our goal from the outset is cure. That means we want high dose intensity. We don't want to be reducing or holding the dose for toxicity if it isn't necessary. That's why getting an accurate grade and description of an AE is so important. It's also why we need good communication of the grade and description of the AE, to ensure that any dose modifications are based on vetted, analyzed evidence.

Amy Goodrich, MSN, CRNP (Author)

CTCAE grading has flaws, but it still enhances communication between clinicians by giving us a similar language. But you don't just call a physician and say "grade 2 toxicity" and then drop it. You have to explain that toxicity, its features, and why it is important to manage it in this patient.

“Nurses have cited a lack of critical thinking as one of the top five most likely causes of nursing errors.”

Shared decision making may be impeded by limitations to critical thought. For example, some patients are reluctant to share decision making because they engage in “counterfactual thinking,” meaning that they may anticipate feeling regret or self-recrimination if they share in a decision, like stopping a particular drug related to AEs and then, months or years later, experience disease progression (Katz et al., 2014). When nurses have difficulty recognizing and analyzing such reasoning, they may be unable to fully empower the patient as a decision maker.

Within the context of shared decision making, the nurse may be called on to offer evidence, in the form of AE grading and narrative description, with critical consideration of quality of life and distress related to the AE. With this information, the nurse helps the patient participate in the decision to hold treatment or reduce the dose. With systemic therapies, the development of a toxicity and establishing its grade typically determines the decision to continue, reduce, or hold treatment. For example, the decision to reduce bortezomib dose from 1.3 mg/m² to 1 mg/m² in mantle-cell lymphoma requires precision in grading. If a patient has grade 1 neuropathy with no impact on quality of life and no pain, then no bortezomib dose adjustment is required. However, grade 2 neuropathy with pain (with limitations on instrumental activities of daily living) and grade 3 neuropathy (limitations on self-care activities of daily living) require holding bortezomib until the neurologic toxicity resolves (Millennium Pharmaceuticals, Inc., 2015; NCI, 2010). Misgrading could produce dosing or treatment error.

Medication errors are not uncommon, including giving the wrong dose and giving a dose after a discontinuation order (Ford, Killebrew, Fugitt, Jacobsen, & Prystas, 2006). Nurses attribute errors to factors that unfavorably influence critical thinking (Cornell et al., 2010, 2011), such as adding tasks to the workload, chaos in the work environment, being swamped or overwhelmed, emotional responses, and a loss of focus (Roth, Wieck, Fountain, & Haas, 2015; Valiee, Peyrovi, & Nasrabadi, 2014). Of note, nurses themselves have cited a lack of critical thinking as one of the top five most likely causes of nursing errors in the hospital (Roth et al., 2015).

Communication

Even when AEs are graded accurately, communication of the grade and recommended approaches can pose challenges. Barriers to effective communication may result from deficits in critical thinking relevant to managing AEs in lymphoma. These deficits include the following:

- Lack of reasoning across relationships—an inability to understand, anticipate, and compensate for the types of errors that may occur between patient report, upload to the medical record, interpretation and CTCAE grading, and subsequent team discussion. These errors can include gaps in communication; loss of shared interpretation of symptoms among professionals, patients, and caregivers (link loss); and recording and documentation errors (Basch et al., 2005) (see Figure 3).
- Problems in evidence processing—keeping up with new toxicities when a novel therapy or regimen is introduced in the already complex care of lymphoma (e.g., diarrhea and cough with idelalisib in follicular lymphoma) is challenging (Coutré et al., 2015).
- Using a terse or incomplete narrative to describe an AE, which does not take into account the listener’s need for evidence—for example, communicating grade only by the number, rather than also describing its clinical features. An example of this would be writing or saying only “grade 3 fatigue” with lenalidomide without providing information on the patient’s inability to find relief with rest, specific limitations in daily activities, and how well the patient is coping (Celgene Corporation, 2015;

NCI, 2010); incomplete narrative also means that a nurse may not have documented the details needed to trigger accurate grading.

- Lack of curiosity and self-reflection limits the ability to ask questions, solicit feedback, and identify misunderstandings.

Improving Practice: Tools for Thinking Critically and Acting Decisively

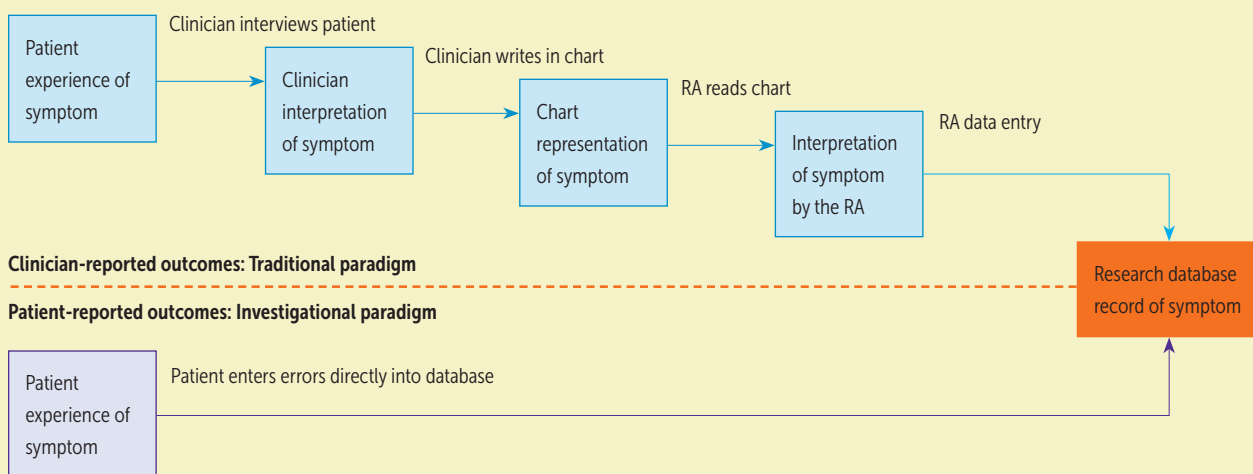
The nursing community has been an important contributor in education to improve critical thinking (Delibovi, 2015). Oncology nurses can use the guidance of nurse educators to enhance critical thinking to improve accuracy in the grading of AEs, to increase precision and confidence in recommendations for the adjustment of therapy, and to communicate recommended approaches clearly and convincingly to aid in the process of shared decision making.

Cultivating Critical Thinking Skills

The nursing literature has identified several important skills for critical thinking among nurses (Brenner et al., 2008; Papanasiou, Kleisaris, Fradelos, Kakou, & Kourkouta, 2014; Papp et al., 2014; Phelps et al., 2009; Raymond-Seniuk & Profetto-McGrath, 2011):

- Flexibility—the ability to remain curious, to ask questions, to stay alert for unexpected circumstances, and to alter preconceived notions on the basis of observations
- Willingness to analyze situations and statements deeply

FIGURE 3. POTENTIAL REDUCTION OF LINK LOSS AND DATA ENTRY ERRORS WITH DIRECT COLLECTION OF PATIENT-REPORTED SYMPTOM



RA—research assistant

Note. From “Patient Online Self-Reporting of Toxicity Symptoms During Chemotherapy,” by E. Basch, D. Artz, D. Dulko, K. Scher, P. Sabbatini, M. Hensley, . . . D. Schrag, 2005, *Journal of Clinical Oncology*, 23, p. 3553. Copyright 2005 by American Society of Clinical Oncology. Reprinted with permission.

- A systematic and orderly approach to all decision making, including a consistent methodology and use of evidence to support decisions
- A focus on problem solving
- The ability to expect, understand, and embrace differences in perspective between oneself and other people
- Self-reflectiveness and the ability to admit error and uncertainty.

These skills are highly relevant to best practices in the process of AE grading, decision making, and communicating in antilymphoma therapy (see Figure 4). For example, even a simple best practice, such as comparing a blood count or a report of neuropathy to the actual text of the CTCAE, cannot be fully actualized without critical thinking. The reason is that patient data and best practices qualify as what nurse educators term “messy information” (Rowles, Morgan, Burns, & Merchant, 2013). Patient data can be scattered, fragmented, or incomplete. Best practices may be gathered from various potentially conflicting sources, such as cancer center memos, published guidelines, first-person articles by experts, facility medical directors, and even third-party payors.

FIGURE 4.
SELECTED BEST PRACTICES IN ADVERSE EVENT (AE) GRADING, DOSE ADJUSTMENT, AND COMMUNICATION

- Recognize that errors can occur; anticipate that identification and grading of AEs can be difficult, particularly in complex lymphoma regimens.
- Obtain patient self-reports of symptoms at every interaction, using formal assessment tools when available; document self-reports carefully (including patient’s reports verbatim).
- Use outreach methods to sustain nursing visibility, particularly in patients taking oral antilymphoma therapies at home; methods include telephonic follow-up, email, and patient web portals.
- Routinely review AE sections of prescribing information for all agents that the patient receives.
- Consult Common Terminology Criteria for Adverse Events (CTCAE) regularly to harmonize documentation with standard grading terminology; post in the nurse’s station or wherever documentation takes place.
- Compare laboratory results and patient reports to the actual entry in the CTCAE; do not rely on memory of the CTCAE when grading, particularly for numeric criteria, such as neutrophil counts.
- Write or verbalize for the team a clear, full, narrative description, along with CTCAE grade, of every AE that may need intervention.
- Never give or accept verbal orders for dose adjustments; make written orders standard.
- Double check dose modifications and supportive care decisions with pharmacy.

Note. Based on information from Basch et al., 2009; Jacobsen et al., 2009; Schulmeister, 2006; Yagasaki & Komatsu, 2013.

Often, no guidance may exist on how to apply a best practice to a particular patient scenario.

What should be done, for instance, if a patient reports trouble buttoning his shirt, but is unable to answer most of the symptom-focused questions on the cancer center’s peripheral neuropathy assessment tool? To solve this problem, a nurse might analyze the patient’s report deeply, reach out once more to the patient for additional evidence of neuropathy, and try to understand the difference between the clinical perspective and the patient’s perspective on his symptoms—three of the critical thinking skills cited earlier in this article. Therefore, to follow best practices, critical thinking is required to assimilate and use the messy information pertinent to each case (Rowles et al., 2013).

Critical Thinking in Relationship

Considering the perspectives of others is a particularly meaningful part of the nursing skill set (Papp et al., 2014; Raymond-Seniuk & Profetto-McGrath, 2011). Part of the definition of a *challenged thinker*, a nurse who struggles to think critically, is resistance to consideration of others’ perspectives (Papp et al., 2014). The effort to “think in relationship” has profound and positive effects on communication regarding AEs and adjustment of therapy. When explaining an AE or recommending a dose adjustment, it matters who receives the explanation or recommendation. Depending on prior experience, healthcare professionals, patients, and caregivers may have different levels of familiarity with grading schema. Therefore, when communicating with different individuals, the nurse cannot assume that writing or saying “grade 3 sensory neuropathy” will be sufficient. To take into account others’ perspectives, a statement of the grade should be accompanied by a narrative description of the AE that include features, such as onset, location, and duration; conditions that worsen or alleviate the AE; the nature of the symptoms; severity; and interference with quality of life. Nurses may even want to create a template or reminder to include these features that functions as a verbal or written script for communication. Scripting is a technique borrowed from successful nursing education for critical thinking (Su & Juestel, 2010), and it may be a useful tool in clinical practice as well.

In antilymphoma therapy, a key aspect of the patient–nurse relationship, nursing presence, has become more challenging. Challenges to nurse visibility stem from the growing number of oral, self-administered therapies available (Yagasaki & Komatsu, 2013), including approved therapies such as lenalidomide (mantle-cell lymphoma), vorinostat (cutaneous T-cell lymphoma), idelalisib (follicular lymphoma, small lymphocytic lymphoma), and others (Celgene Corporation, 2015; Gilead Sciences, 2014; Merck Sharp & Dohme Co., 2015). When patients receive oral antilymphoma therapy, “thinking in relationship” is an important nursing skill that involves understanding the perspective of the patient at home. This patient may be hesitant to make a call to report an AE, may forget the importance of watching for AEs, or

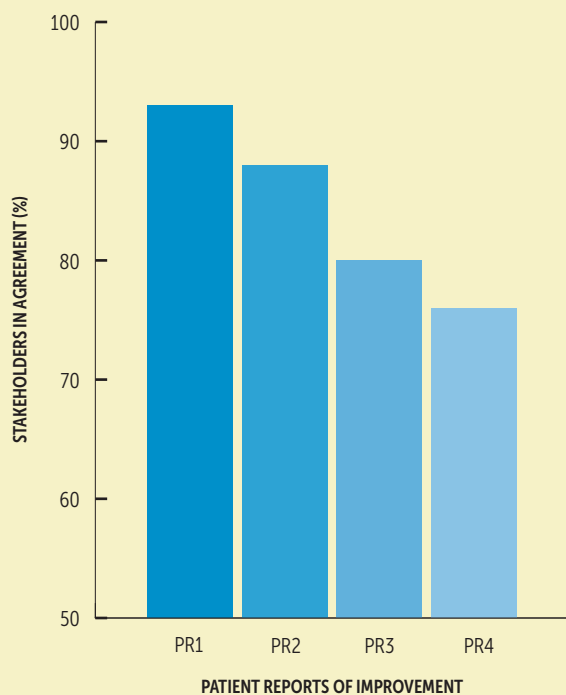
may generally feel more distant from the nurse. Understanding the patient's perspective in such cases can prompt nurses to make more frequent and vigorous outreach by phone or email or on the occasion of a visit to the cancer center.

Leverage Learning From the PRO-CTCAE

The patient-centric PRO-CTCAE has been shown to be valid, reliable, and responsive, indicating that its patient-centeredness is an asset (Dueck et al., 2015). It also is designed to help minimize communication gaps, link loss, and problems in recording error (Basch et al., 2005, 2014). PRO-CTCAE use is gaining momentum in the clinical trial setting, but is not yet widely used in clinical care.

Questions posed to patients via the PRO-CTCAE were designed with three features: plain language terminology for the symptom; a focus on eliciting frequency, severity, and interference

FIGURE 5.
PRO-CTCAE STAKEHOLDERS RATING
OF PATIENT-REPORTED OUTCOMES IN
ADVERSE EVENT ASSESSMENT (N = 727)



PR1—useful to improve understanding of patient experience; PR2—improved completeness of symptom data collection; PR3—improved accuracy of symptom data collection; PR4—improved efficiency of symptom data collection; PRO-CTCAE—Patient-Reported Outcomes Common Terminology Criteria for Adverse Events

Note. Based on information from Brunner et al., 2011.

IMPLICATIONS FOR PRACTICE

- Understand that a growing number of treatment options, combined with the heterogeneity of Hodgkin and non-Hodgkin lymphomas, have created nursing challenges in the management of adverse events (AEs).
- Prepare for challenges regarding accurate grading, shared decision making in the adjustment of therapy based on grade, and communication of action plans to the interdisciplinary team and the patient.
- Meet these challenges by developing critical thinking skills, thinking in relation to recognize the perspectives of others, leveraging information from patient-reported outcomes for AEs, and managing workflow to facilitate critical thinking.

with activity from the patient; and a mechanism to gather the recall period for the symptom (Basch et al., 2014). Sample question formats include: “In the past, how OFTEN did you have [symptom]?”; “In the past, what was the SEVERITY of your [symptom] at its worst?”; “In the past, how much did [symptom] INTERFERE with your usual or daily activities?” (Basch et al., 2014, p. 1). Data have shown a strong consensus among key stakeholders in the implementation of the PRO-CTCAE that including patient reporting of adverse symptoms would be useful for improving understanding of the patient experience in a cancer clinical trial (Brunner et al., 2011). In addition, a high proportion of stakeholders endorsed administration of PRO-CTCAE clinical trials to improve completeness, accuracy, and efficiency of AE data collection (Brunner et al., 2011) (see Figure 5). These findings may suggest that nurses in community clinical practice may gather better input for critical analysis of CTCAE grade by asking patients to describe their own experience of frequency, severity, and interference with an AE, potentially leading to more accurate grading.

Manage Workflow

Chaos and task switching are part of the nursing day, but they are not conducive to the critical thinking needed for accurate grading, confident decision making on the adjustment of therapy, and well-organized communication (Cornell et al., 2010, 2011). Interventions to improve workflow may have a positive impact on critical thinking (Cornell et al., 2011). These include methods that nurses can deploy themselves, such as seeking out education on time and workflow management, delegation of routine or repetitive tasks to non-nursing staff, and more skillful and systematic use of technology (Cornell et al., 2011). Other methods must be championed at the institutional level, such as workflow evaluation and redesign, implementation of better software systems, and reallocation of duties (Cornell et al., 2011).

Conclusion

In antilymphoma therapy, proper management of AEs is essential to good clinical outcomes. The response to AEs cannot be optimal without precise grading of toxicities, adjustment of therapy based on grade and AE description, and effective interdisciplinary and patient-clinician communication. Building

nursing competency in these areas requires development of critical thinking, which enables nurses to implement best practices decisively and appropriately in each clinical case.

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APPENDIX A.

CASE STUDY: CRITICAL THINKING SKILLS AND METHODS FOR ORAL MUCOSITIS

SETTING

K.L. is an oncology nurse in a suburban group practice with an infusion center. The patient, M.G., is a 60-year-old man newly diagnosed with follicular lymphoma who is receiving six planned cycles of bendamustine and rituximab (BR).

PERSPECTIVE TAKING, LEVERAGING THE PRO-CTCAE

M.G. said that he hates to bother people with his problems. Because K.L. considers M.G.'s perspective, she always asks him specific questions about symptoms while reassuring him that his problems are important to the team. During a call three days before the last of M.G.'s six BR cycles, K.L.'s question, "Are you feeling anything that interferes with your daily life?" prompts M.G. to say that his mouth is so sore that he does not want to eat and cannot eat anything crunchy. More discussion reveals a symptom pattern commensurate with oral mucositis (stomatitis). K.L. asks M.G. to come in for an examination, and she and the physician document visible redness and a small sore on the tongue. K.L. asks the physician and another nurse on the team to confirm orders for self-care (ice chips, soft food) and topical treatment.

SYSTEMATIC APPROACH TO SHARED DECISION MAKING AND WORKFLOW MANAGEMENT

In preparation for a team meeting, K.L. uses her 20 minutes of daily planning time, which she specifically requested from her employers, to chart the information on M.G.'s reported symptoms. She compares her learnings to the CTCAE and determines that she needs more information: (a) the nature of mouth irritation with rituximab versus bendamustine and (b) how much mouth pain, on a scale of 1–10, M.G. is experiencing. K.L. checks the prescribing information for the two drugs and telephones M.G. to obtain his numeric pain rating.

PERSPECTIVE TAKING, FOCUS ON PROBLEM SOLVING, WILLINGNESS TO ANALYZE DEEPLY

Several others at the meeting, including M.G.'s physician and the practice manager, need more information than just the CTCAE grade. For this reason, K.L. has notes for a narrative description:

- Based on phone interviews, M.G. has grade 3 oral mucositis, graded in this way because of interference with oral food intake and pain of moderate to severe intensity, measured as 6 on a 10-point pain scale.
- Symptoms have been present and increasing gradually for four weeks.
- The most likely cause is bendamustine chemotherapy, but rituximab can cause mucocutaneous reactions as well.

The physician notes that the prescribing information for bendamustine regarding stomatitis does not specify when to hold or decrease the dose for this AE. Another nurse on the team, as well as the practice manager, share this experience: In another case of grade 3 oral mucositis where the patient was very far along in bendamustine treatment, the team gave the final cycle of the chemotherapy with no dose reduction while continuing to provide self-care methods and topical treatment to control the pain and irritation. The team decides to recommend this approach, and K.L. discusses it with M.G. when he arrives for his treatment. K.L., in concert with the physician, presents the team's reasoning process and supporting evidence. M.G. expresses a wish not to hold the last dose chemotherapy; he wants to complete his cycles and notes that self-care in the past few days has already helped. M.G. shares in the decision to go ahead with the last cycle of BR.

FLEXIBILITY AND ABILITY TO ADMIT UNCERTAINTY

After the treatment, M.G.'s physician contacts K.L. and the practice manager to offer a caveat: Because rituximab has not been completely ruled out as a cause, M.G.'s symptom pattern should be followed telephonically for a number of weeks after this last BR treatment. This is recommended because mucocutaneous reactions to rituximab can signal serious adverse events, such as Stevens-Johnson syndrome, and require discontinuation. K.L. agrees to provide this follow up.

PRO-CTCAE—Patient-Reported Outcomes Common Terminology Criteria for Adverse Events

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