



ORIGINAL RESEARCH PAPER

Oncology

A PERSPECTIVE ON THE DEVELOPMENT OF TOLERANCE, TOXICITY AND RESPONSE TOOL IN LOCAL (MARATHI) LANGUAGE TO ASSESS PATIENT REPORTED OUTCOMES POST CHEMOTHERAPY

KEY WORDS: chemotherapy; patient reported outcomes; language; tolerance, toxicity and response tool

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ABSTRACT

Patient-reported outcomes (PROs) may provide benefits over clinician-reported outcomes by improving patient-clinician communication, providing information about subtle symptoms beyond those typically reported by the staff. The chemotherapy induced toxicity is a subjective matter and requires real-time reporting, which is not feasible in a resource limited country such as India, where the majority of the patients belong to rural areas and are treated at centers far away from their hometowns. Language barrier is a major hindrance in accurate reporting of chemotherapy side effects. For those patients with Limited English Proficiency (LEP), we need an assessment tool in the local language. In India, for the assessment of chemotherapy related toxicities, tolerance and patient satisfactoriness, we need a local language-based patient generated assessment. Hence, we devised a format for reporting of chemotherapy side effects, as well as the tolerance and response assessments in Marathi language to encourage our patients to actively participate, analyze and assess their tolerance, toxicity of chemotherapy and response of the treatment given. Hence, our tolerance, toxicity and response questionnaire tool developed in Marathi language may help the patients from Maharashtra, especially from the rural areas and who do not understand the English language, for self-reporting of the treatment effects. The current article is a perspective of the authors written to inspire other oncologists in Maharashtra to come up with better and bigger data on the optimal evaluation and management of chemotherapy related side effects, which may improve the health-related quality of the life of cancer patients.

INTRODUCTION

Traditionally, the reporting of chemotherapy induced toxicity is done by clinicians or investigators.¹ Tracking of symptoms related to treatment toxicity, even in trial setting is inefficient and complex. The difficulty in reporting treatment toxicities has led many clinicians to opt for patient-reported outcomes (PROs), which represents an alternative paradigm² helping capture patients' symptoms including their physical and social functioning along with their emotional well-being, providing an overall assessment on the patients' quality of life.¹

Patient-reported outcomes may provide benefits over clinician-reported outcomes by improving patient-clinician communication, providing information about subtle symptoms beyond those typically reported by the staff.³ The advent of PRO measurement may facilitate the strengthening evaluation of treatment toxicities, particularly symptomatic, in the clinical setting.⁴ The reporting of toxicity and response should be in real time, and there can be recall bias⁵ if these are measured after a significant time gap. Hence, early detection and real time reporting⁶ of side effects becomes very important. It is imperative that such information should be patient generated to avoid investigator bias. Also, it may increase efficiency and accuracy by eliminating the need for clinician to abstract symptoms from the posthoc medical records.

The chemotherapy induced toxicity is a subjective matter and requires real-time reporting,⁴ which is not feasible in a resource limited country such as India, where the majority of the patients belong to rural areas and are treated at centers far away from their hometowns. Patients may have to commute a significant distance to report any treatment side effects. Most of the times, they report only serious side effects, ignoring the milder ones. India is a multi-linguistic nation, and a large proportion of Indian population is not well versed with the English language. Language barrier is a major hindrance in accurate reporting of chemotherapy side effects.⁴ For those patients with Limited English Proficiency (LEP), we need an assessment tool in the local language.⁷ In India, we experience more LEP in rural as compared to urban centers.

Local language is the best way of communication and is also the most reliable one. In India, for the assessment of chemotherapy related toxicities, tolerance and patient satisfactoriness, we need a local language-based patient generated assessment. These assessments will help the regulator to perfectly gauge toxicities of chemotherapy in India. It will also help the physician to make proper changes in chemotherapy protocols⁸ so that the toxicities are managed when they manifest subtly.

This will prevent burden on health care industry to manage grave side effects of chemotherapy if they are not monitored meticulously. Proactive management of chemotherapy toxicity is being studied to manage these toxicities effectively.⁹

Hence, we devised a format for reporting of chemotherapy side effects based on common terminology criteria for reporting of adverse events (CTCAE), as well as the tolerance and response assessments in Marathi language to encourage our patients to actively participate, analyze and assess their tolerance, toxicity of chemotherapy and response of the treatment given.

Our questionnaire can also help in assessing geriatric assessment for chemotherapy, which includes questions based on nutritional status and cognitive assessment.¹⁰ Our questionnaire includes three main sections – tolerance, toxicity and response (Figure 1).

Tolerance

The current approaches to mitigate chemotherapy side effects are generally not effective in managing the long-term sequelae or may cause other side effects often leading to a diminished patient's quality of life.¹¹

Hence, Nurgali and colleagues have suggested to look for new tools that can effectively improve tolerance and reduce the sequelae of chemotherapy.¹¹ In our questionnaire, we have included few criteria that have been used to evaluate the activities of daily living (ADL) and cognition skills as a measure of tolerance (Table I).¹²⁻¹⁴



मुक्ता कॅन्सर क्लिनिक

Quality, Care, Commitment...

डॉ. मुकुंद अरविंद घरोटे तीर्थरूप बंगला, डेक्कन पेट्रोल पंपाजवळ, सुंदरबन कॉलनी, माघ सेक्टर, नवीन नाशिक - ४२२००९, फोन : ८७५८०५२७७४		कागदपत्र क्र. : DR.MAG/FORM/IPD/Diag पेशंटचे नाव: _____ सायकल क्र. _____ केमी प्रोटोकॉल : _____ लिंग: _____, वय: _____, कन्सलटंट : डॉ. मुकुंद घरोटे			
सहनशीलता, दुष्परिणाम चाचणी पत्र					
सहनशीलता					
स्वतःचे काम	कोणतीही गरज न लागणे	गरज लागणे	दोन पेक्षा अधिक गरज लागणे	शेरा	गुण
जेवण करणे					
परसाकडे जाणे					
कपडे घालणे					
औषध घेणे					
पैशांचा व्यवहार					
जिना घडणे					
वैयक्तिक काळजी					
				एकूण सहनशीलता	
दुष्परिणाम					
पांढऱ्या पेशी कमी होणे	ग्रेड १ १५०० पेक्षा कमी	ग्रेड २ १००० ते १५००	ग्रेड ३ १००० पेक्षा कमी	ग्रेड ४ ५०० पेक्षा कमी	गुण
ताप			१०१ पेक्षा अधिक किंवा १००.४ (तशाभरणपेक्षा जास्त)	गंभीर स्वरूपाचा ताप	
मळमळ	भूक न लागणे	वजन कमी होणे, शरीरातील पाणी कमी होणे, कुपोषित होणे	सलाईनची गरज भासणे	गंभीर स्वरूप	
वांत्वा / उलट्या	दिवसातून एकदा	दोन ते पाच वेळा	६ पेक्षा अधिक किंवा सलाईनची गरज भासणे	गंभीर स्वरूप	
तोंड येणे	तोंडातील आतले आवरण लाल पडणे	तुरळक चांदा (अल्सर) पडणे	मोठा चांदा, त्यावर पांढरे आवरण परत येणे, रक्त निघणे	गंभीर स्वरूपाचा रक्तस्राव होणे, त्वचा काळी पडणे	
जुलाब	४ पेक्षा कमी वेळा	२ ते ६ वेळा	७ पेक्षा अधिक वेळा व सलाईनची गरज भासणे	गंभीर स्वरूप	
अंलर्जी	त्वचा काही वेळापुरती लाल होणे	औषधाची गरज भासणे	वारंवार अंलर्जी होणे	गंभीर स्वरूप	
त्वचा		सलाईन लावलेल्या जागेच्या ठिकाणी स्वचा लाल पडणे, सूज येणे, सलत वेदना	चांदा / त्वचा काळी पडणे	गंभीर स्वरूप	
थकवा	विश्रांती घेतल्यावर थकवा कमी होणे	विश्रांती घेऊनही थकवा कमी न होणे	विश्रांती घेऊनही थकवा कमी न होणे व दैनंदिन काम करू न शकणे		
केस गळणे	केस तुरळक गळणे	केस पूर्णपणे गळणे			
मुंया येणे व तत्सम		काहीही त्रास नसणे व उपचाराची गरज न भासणे	थोडा त्रास जाणवणे व दैनंदिन कामाला व्यत्यय येणे, दैनंदिन कामाला दुसऱ्याची गरज भासणे	गंभीर स्वरूप	
				एकूण दुष्परिणाम	
परिणाम (व्यक्तीशः रुग्णाने भरणे)					
तक्रारी	वाढणे / कमी होणे	वाढणे	२५% (-१)	५०% (-२)	निकालले गुण
		कमी होणे	५०% (+१)	५०% (+२) पेक्षा जास्त	
सूज	वाढणे / कमी होणे	वाढणे	२५% (-१)	५०% (-२)	
		कमी होणे	५०% (+१)	५०% (+२) पेक्षा जास्त	
सातत्य		कानाच्या पाळीसारखी नरम पडणे	नाकाच्या शेंड्यासारखी कडक होणे	हाडासारखी कडक	
जीवनमान	वाढणे / कमी होणे	वाढणे	२५% (+१)	५०% (+२)	
		कमी होणे	५०% (-१)	५०% (-२) पेक्षा जास्त	
पोषण स्तर	वाढ / साखळे	थोडे कुपोषण	अधिक कुपोषण	सर्वाधिक कुपोषण	
वजन	वाढ	१०% पेक्षा अधिक	२०% पेक्षा अधिक	३०% पेक्षा अधिक	
	घट	१०% पेक्षा कमी	२०% पेक्षा कमी	३०% पेक्षा कमी	
वेदनेची तीव्रता	वेदना न होणे	थोडी वेदना होणे	असह्य वेदना होणे	सर्वाधिक गंभीर स्वरूपाची वेदना	
				एकूण प्रतिसाद	
अनुवादकाचे घोषणापत्र (लागू असल्यास) वापरलेली भाषा : _____ या फॉर्ममधील मजकूर, रुग्ण आणि डॉक्टर यांच्यामधील संभाषण मी अचूकपणे अनुवादीत केले आहे, हे मी मानतो.					
रुग्णाचे / नातेवाईकाचे नाव (रुग्णाशी नाते) : _____				(सही व तारीख) (सही व तारीख)	
गुण	सहनशक्ती: (बांगला/बरा/वाईट)	विषाच्या तीव्रतेचे प्रमाण (सौम्य/मध्यम/तीव्र)	प्रतिसाद (बांगला/बरा/वाईट)	एकूण टीटीआर गुण (सहनशक्ती + प्रतिसाद - विषाच्या तीव्रतेचे प्रमाण)	
कृतीकार्यक्रम :					
निष्कर्ष / शेरा					
वैद्यकीय कर्तारगतज्ज्ञाने तपासले. डॉक्टरांचे नाव : डॉ. मुकुंद अरविंद घरोटे					
					सही व तारीख

Figure 1. The tolerance, toxicity and response form in Marathi

Table I. Assessment of tolerance by 7 questions pertaining to ADL and IADL¹²⁻¹⁴

Question	Score	Remarks
1. Feeding yourself	2-if no help needed 1-if help needed, if no one available to help then score would be 1	Gives a brief idea about distal muscles and hand eye co-ordination, gives a hint of neuropathy
2. Going to toilet	2-if no help needed 1-if help needed, if no one available to help then score would be 1	Helps in gauging bladder and bowel control as well as gives a brief assessment of autonomic neuropathy
3. Getting dressed	2-if no help needed	Requires fine muscle and hand eye co-

	1-if help needed, if no one available to help then score would be 1	ordination
4. Taking medicine	2-if no help needed 1-if help needed, if no one available to help then score would be 1	Gives a brief assessment of cognitive function
5. Managing money (paying bills etc)	2-if no help needed 1-if help needed, if no one available to help then score would be 1	Gives a brief assessment of cognitive function
6. Climbing stairs	2-if no help needed 1-if help needed, if no one available to help then score would be 1	Requires proximal muscles and gives a subtle assessment of myopathy – post steroid
7. Personal care	2-if no help needed 1-if help needed, if no one available to help then score would be 1	Gives a brief assessment of cognitive function

ADL, activities of daily living; IADL, instrumental activities of daily living

The cognitive impairment (dubbed “chemobrain” by cancer survivors) includes a range of difficulties like subtle changes in memory, concentration, and executive function that can emerge in the weeks during cancer treatment and months after its completion.¹⁵

These changes can be analyzed by asking questions on tolerance, which includes handling money, as money matters, need the highest cognitive skill. Another question would be ‘Did they remember taking medicine?’. With these 2 questions, a brief assessment on cognitive impairment can be made.

Toxicity

The common terminology criteria for reporting of adverse events (CTCAE) was introduced to uniformly report chemotherapy side effects. The National Cancer Institute (NCI) has devised the PRO-CTCAE for cancer studies, which has 124 items representing 78 symptomatic toxicities and incorporates patient perspectives on these toxicities.¹⁶ In our questionnaire, the toxicity evaluations were made according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Table II).

The most common side effects such as chemotherapy induced (CI) peripheral neuropathy (CIPN), CI nausea and vomiting (CINV), CI diarrhea (CID), CI constipation (CIC) and pain require subjective assessments.¹¹ Hence, PROs can help in analyzing these side effects and help in better management.¹²

Table II. Toxicity assessments according to CTCAE

Toxicity	Score				Remarks
	Grade				
	1	2	3	4	
Neutropenia	1500	1000-1500	500-1000	<500	ANC helps in assessing marrow toxicity
Febrile neutropenia	Not applicable	Not applicable	ANC <1000 and single episode of fever >101° fr, or 100.4° fr lasting for >1 hour	Life threatening consequences, urgent intervention needed	Febrile neutropenia assessment according to CTCAE
Nausea	Loss of appetite without alteration in bowel habit	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral calorific or fluid intake. IV fluids, tube feedings, or TPN indicated	Life threatening consequences	Assessment according to CTCAE

Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours, IV fluids indicated	>6 episodes in 24 hours, IV fluids or TPN indicated	Life threatening consequences	Assessment according to CTCAE
Stomatitis / Oral ulcers	Erythema of the mucosa	Patchy ulcerations or Pseudomembranes	Confluent ulcerations or Pseudomembranes, bleeding with minor trauma	Tissue necrosis, significant spontaneous bleeding, life threatening consequences	Assessment according to CTCAE
Diarrhea	Increase of <4 stools per day over baseline, mild increase in ostomy output compared with baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated. Moderate increase in ostomy output compared with baseline not interfering with ADL	Increase of >7 stools per day over baseline, incontinence, IV fluids, hospitalization, severe increase in ostomy output	Life threatening consequences i.e. hemodynamic collapse	Assessment according to CTCAE
Allergic reactions	Transient flushing or rash, drug fever <38oC, intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment, e.g. antihistamines	Prolonged recurrence of symptoms following initial improvement, hospitalization required for clinical sequelae, i.e. renal impairment	Life threatening consequences, urgent intervention indicated	Assessment according to CTCAE
Extravasation	Not applicable	Erythema with associated symptoms (e.g. edema, pain, induration, phlebitis)	Ulceration or necrosis, severe tissue damage, operative intervention indicated	Life threatening consequences, urgent intervention indicated	Assessment according to CTCAE
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest and limiting instrumental ADL	Fatigue not relieved by rest and limiting self-care ADL	Not applicable	Assessment according to CTCAE
Hair loss	Thinning or patchy	Complete	Not applicable	Not applicable	Assessment according to CTCAE

Peripheral motor neuropathy	Asymptomatic; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Assessment according to CTCAE
Peripheral sensory neuropathy	Asymptomatic, loss of deep tendon reflexes or parasthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Assessment according to CTCAE

ADL, Activities of Daily Living; ANC, absolute neutrophil count; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; TPN, total parenteral nutrition.

Response

The PROs and clinician assessments may have a certain level of discordance.¹⁷ The FACT-taxane trial highlighted that symptom relief and disease condition improvement had more importance than the toxicity endured from the patient's perspective.

This study underscores the importance of symptom relief and its gradation, so as to help the patient understand the degree of disease control at the cost of toxicity.¹⁸ Hence, we have included response criteria in our questionnaire.¹⁹⁻²² Also, the PRO assessment of bone pain intensity will help improving the use of bisphosphonate in reducing pain intensity.¹³

Hence, a segment on pain alleviation was added with assessment of the level of pain control in the local language (Table III). Our questionnaire includes a scale analogous to verbal response scale (VRS) and gauges pain in 4 grades ranging from mild to very severe / intolerable pain.

Table III. Response assessment¹⁹⁻²²

Response (subjective)	Scores in brackets			Remarks
	Increased	25% (-1)	50% (-2)	
Existing complaints	Decreased	50% (1)	>50% (2)	In order to maintain sensitivity, even if 25% subjective increment in complaints were considered as failure of response and 50% decrement in complaints was considered as good response. Not before: new complaints are considered as progression unless proven otherwise
	Increased	25% (-1)	50% (-2)	
Swelling	Decreased	50% (1)	>50% (2)	In order to maintain sensitivity, even if 25% subjective increment in complaints were considered as failure of response and 50% decrement in complaints was considered as good response
	Increased	25% (-1)	50% (-2)	
Consistency of lump	Soft (like earlobe)	Firm (like tip of nose)	Hard (like bones)	This helps in patient evaluating response to chemotherapy, especially in head and neck malignancy
Quality of life	Better or improved	Same as before	Worse than before	This is used as a tool in palliative chemotherapy

Nutritional status	Mild malnutrition	Moderate malnutrition	Severe malnutrition	This helps in assessing nutritional requirement, in gastrointestinal malignancy and head and neck malignancy	
Weight	gain	Up to 2 kg	2-5 kg	>5 kg	Steroid side effects monitoring / fluid overload in APML
	Loss	Up to 2 kg	2-5 kg	>5 kg	Brief assessment of poor nutrition
Opioid tolerance	No need of opioid (+2)/ Twice in a day needed (+1)	3-4 times in a day (-1)	No significant relief with maximum dose of opioids (-2)	Helps in evaluating opioid dependence due to pain, in palliative subset, bony pain and effects of chemotherapy/radiation therapy can be evaluated	
Pain scale	No pain (+2)	Mild pain (hurts little bit) (+1)/ Moderate pain (more pain) (-1)	Severe pain (Worst pain) (-2)	Helps in evaluating effect on pain, in palliative subset, bony pain and effects of chemotherapy/radiation therapy can be evaluated	

APML, acute promyelocytic leukemia.

We have initiated administering this tolerance, toxicity and response questionnaire for reporting of chemotherapy effects by cancer patients at our center, Mukta Cancer Clinic, Nashik, India. We have planned to register 300 patients in this study, out of which, 150 have already been enrolled. The questionnaire would be filled by the patients based on their real time experience regarding tolerance, toxicity and response to the particular chemotherapy treatment. If the patient does not understand Marathi language or is not able to respond to a particular question, then a translator is provided for their help. This form involves the patient in evaluating the chemotherapy side effects in their own language. All the responses are recorded for analysis and based on that appropriate supportive treatment are added to the chemotherapy regimens, as required. The doses of chemotherapy agents are changed only in palliative intent of treatment and when the toxicity is reported as grade 3 or 4. We are still enrolling patients in this pilot study to evaluate the effectiveness of this new tool, and the results of the study will be presented separately.

There is a growing body of evidence that suggest that patient reported questionnaire developed in languages beyond English may facilitate patient's self-reporting of the side effects. The PRO-CTCAE Spanish Translation and Linguistic Validation Study Group translated the 124 items of PRO-CTCAE into the Spanish language through multiple back and forth translations. The authors successfully administered the new language PRO-CTCAE tool in 109 participants and demonstrated that it was comprehensive and equivalent to the English version.²³ Furthermore, researchers from other countries have also successfully administered German,²⁴ Danish,²⁵ and Dutch²⁶ versions of PRO-CTCAE. These data indicate that the tools developed in local languages to measure PRO-CTCAE can be a feasible option, particularly in a patient who finds difficulty to respond in the English language. Hence, our tolerance, toxicity and response questionnaire tool developed in Marathi language may help the patients from Maharashtra, especially from the rural areas and who do not understand the English language, for self-reporting of the treatment effects. The current article is a perspective of the authors written to inspire other oncologists in Maharashtra to come up with better and bigger data on the optimal evaluation and management of chemotherapy related side effects, which may improve the health-related quality of the life of cancer patients.

Overall, the PRO assessments may help improve the quality of health care and nursing.²⁷ The PROs may be useful in providing a more complete and accurate information in doctor-patient relationship, improving the quality of dialogue and detecting otherwise undetected symptoms or needs, but this assumption requires testing in more robust studies.²⁸ The use of PROs in the local language can prove to be beneficial for both patients as well as physicians. It may help in recognizing newer side effects, assessing patient tolerance and treatment responses more accurately. The subjective assessment of side effects such as CIPN and PRCI (patient reported cognitive impairment) can be better assessed by such questionnaire translated in the local language.²⁹ However, a large scale study is needed to prove the importance of PROs in local language to better understand tolerance, toxicity and response profile of chemotherapy agents.

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