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Toxicity-induced modification of treatment (TIMT): what's in a name?

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ABSTRACT

Severe treatment-induced toxicities can have clinical consequences such as hospitalization or treatment modifications, which in its turn may deteriorate prognosis of cancer patients. Identification of determinants of treatment-induced toxicities is essential to develop strategies that promote therapy compliance and enhance quality of life. Whereas toxicities are systematically recorded and graded per protocol in most clinical trials, observational studies often depend on retrospective data collection from medical records collected as standard care. Existing population-based or patient cohorts are a valuable source of information, even when relying on retrospective data collection, but comparisons across studies are hampered by lack of a uniform definition for toxicity outcomes. We propose a new standardized approach to summarize toxicities in observational studies that rely on medical records for outcome assessment. We recommend the term "toxicity-induced modification of treatment" (TIMT) to cover all toxicities that are responsible for changes in a planned treatment schedule. We define a TIMT as either: i) a dose reduction, ii) temporary interruption, iii) discontinuation of therapy, or iv) an unanticipated switch to another regimen, as a result of treatment-induced toxicities and not due to progressive disease. This definition will provide clinically relevant information, especially when data on specific adverse events and Common Terminology Criteria for Adverse Events (CTCAE) grades are not uniformly available. Implementation of this definition empowers comparisons across studies, facilitates communication between clinicians and researchers and will allow new research questions in this active field of research.

Keywords: toxicity, definition, treatment modification, body composition, determinants, cancer

CURRENT PERSPECTIVES

"Two monologues do not make a dialogue." – *Jeff Daly*. The importance of successful communication is explicitly recognized in clinical and scientific fields, especially when working at the interface of disciplines (1). Talking the same language, or at least understanding each other languages, facilitates efficient communication. One particular field of research where we increasingly recognize confusion and lack of uniform definitions for study outcomes, is related to identification of determinants of treatment-induced toxicities in cancer patients.

Most systemic cancer treatments come at the expense of adverse events. Severe, acute toxicities inevitably have clinical consequences such as hospitalization or modification of the treatment schedule, which in its turn may deteriorate prognosis (2, 3). Moreover, some toxicities can persist far beyond active treatment and can impact, to a greater or lesser extent, quality of life and the ability to function of cancer patients (4, 5).

Assessment of toxicity profiles is an important aspect of clinical trials initiated for the evaluation of new anticancer drugs. The widely adopted Common Terminology Criteria for Adverse Events (CTCAE), developed by the US National Cancer Institute, are often used for identification and characterization of toxicities. Clinical phase I studies aim to identify the maximum tolerated dose (MTD) or the recommended phase II dose (RPTD) of the agent or regimen under study and commonly apply the CTCAE classification. In these dose escalation studies, the dose-limiting toxicities (DLTs) determine at which dose a drug is not tolerable and safe anymore. The adverse events determining the DLT are often defined as CTCAE grade 3–5 toxicities during cycle 1 (6) or the first 21 or 28 days of treatment and are prospectively scored, although definitions are extremely heterogeneous (7) and may depend on the schedule and type of drug (e.g. traditional chemotherapeutic versus molecular targeted agents) (8). Although primarily developed for clinical cancer trials, CTCAE criteria are also commonly applied in routine clinical care to evaluate treatment-induced toxicities in cancer patients undergoing treatment.

Determinants of treatment-induced toxicities in cancer patients

So far, management of acute toxicities largely depends on supportive pharmacotherapeutic approaches, including for example antiemetics, colony-stimulating factors, antibiotics and anti-motility agents for diarrhea. These drugs have been proven to efficiently treat a variety of acute adverse events, however, for various other toxicities no clear consensus about efficient management has been reached, yet (9, 10). One particular example is acute severe chemotherapy-induced peripheral neuropathy, which cannot be effectively treated and is therefore a major reason for dose reduction or premature discontinuation of chemotherapy. Exact causes and predictors of toxicities are largely unknown and variations in toxicity profiles between patients seem to be driven by clinical, genetic, physiological as well as nutritional and other lifestyle factors (11).

Evidence is accumulating that nutrition and lifestyle are associated with risk of toxicities during and after systemic cancer therapy. Knowledge in this emerging field of research is fueled by advanced technologies that allow integration and efficient use of routinely collected clinical data. The role of body composition, assessed through clinically available computed tomography (CT) scans, is perhaps the most powerful example of efficient use of clinical data (12). A lower lean mass and sarcopenia or sarcopenic obesity, referring to depletion of skeletal muscle mass with or without loss of fat mass, have been associated with an increased risk of toxicities in a variety of studies among cancer patients receiving chemotherapy, molecular targeted therapy, and immunotherapy (13). The consistency of these findings highlights the relevance and urgency of this promising area of research, and has also resulted in growing interest in other nutritional or lifestyle factors as determinants of treatment-induced toxicities (14, 15).

New avenues for potential nutritional or lifestyle interventions that can help to mitigate treatment-induced toxicities will come from observational studies. Given the wealth of information available through existing population-based or patient cohorts, various modifiable nutrition and lifestyle exposures can be studied in relation to risk of toxicities in cancer patients. To date, body composition is again the most striking example

showing the elegance of efficient use of data from patient cohorts. However, also other exposures are increasingly being explored. For example, the association between circulating levels of folate and related biomarkers in patients receiving cytotoxic anti-folate therapies, such as methotrexate or 5-fluorouracil, got attention (16). The recent advances in medical oncology, and particularly the introduction of molecular targeted agents and immunotherapy, even provide novel possibilities to further explore and expand this emerging and active field of research.

Lack of a uniform definition for toxicity in observational studies

Currently, a uniform and feasible definition for toxicity outcomes in observational studies is lacking and different criteria have been used across different studies, which raises the question whether we all speak the same language in this context. Ideally, occurrence and severity of toxicities are prospectively scored in a systematic way by using well-defined criteria, such as the CTCAE classification. Functional, clinical or laboratory tests can complement these grading systems with relevant information regarding specific treatment-related symptoms. Also, patient-reported outcomes assessed through validated questionnaires or digital applications are increasingly considered of crucial importance and should be recognized as such in clinical care as well as research dedicated to toxicity outcomes (17, 18).

As described above, especially in studies with treatment efficiency and safety profiles as primary outcomes, such as phase I-IV clinical trials, detailed data on CTCAE grades or patient-reported outcomes are commonly available. However, in these clinical trials comprehensive data on nutritional and lifestyle factors are usually not collected. Detailed exposure data, such as food frequency questionnaires, physical activity measures, other lifestyle characteristics or body composition data, are available in various large-scale cohort studies (e.g. (19-21)). These studies mainly rely on retrospective review of medical records. In most clinical centers standardized collection of toxicity data by using CTCAE criteria is not part of routine clinical care, leading to variation in registration of toxicities within and between centers.

This inconsistency can be nicely illustrated by the aforementioned studies focusing on body composition in relation to toxicities, as these studies cover various types of cancer, different treatment strategies and it comprises a substantial number of studies. As can be seen in **Table 1**, many studies conducted so far also used the term DLT to collectively describe any treatment modifications, with or without consideration of severe adverse events (CTCAE grade ≥3). In these instances, treatment modifications commonly refer to a temporary interruption (delay), dose reduction or permanent discontinuation of therapy due to adverse effects. It should be noted that use of the term DLT or equivalents is not limited to studies focusing on body composition, but has also been applied in relation to other exposures such as nutritional status and resting energy expenditure (22, 23).

In our opinion, the term DLT is confusing in this context as treatment modifications do not necessarily refer to the concept of DLTs as classically used in medical oncology. In contrast to the clinical phase I dose escalation studies, most studies focusing on nutritional and lifestyle determinants of toxicity in population-based or patient cohorts are not primarily designed or meant to study increasing doses of drugs in subsequent groups of patients. Instead, associations between the exposures of interest and toxicities in a representative group of patients receiving standard care will provide relevant information on determinants of toxicities. Use of the term DLT outside the scope of clinical phase I-IV trials is therefore causing confusion, especially since heterogeneous definitions are used across different studies.

Toxicity-induced modification of treatment (TIMT): a new and uniform definition

Given the controversies about the term DLT used in observational studies, we propose a new definition to collectively summarize toxicities in studies that rely on retrospective review of medical records for outcome assessment. We recommend to use the term toxicity-induced modification of treatment (TIMT) to cover any toxicity that is responsible for changes in the treatment schedule. This definition will provide clinically relevant information, especially when data on specific adverse events and CTCAE grades are not uniformly available. As part of the TIMT definition, we recommend inclusion of the

previously mentioned treatment modifications, i.e. a reduction of the dose, a delay, or a premature discontinuation of the therapy (**Table 2**). Furthermore, we propose to add an unanticipated switch in regimes as one of the criteria for a TIMT. Switching from one regime to another is usually a consequence of limited tolerance and experienced toxicities in the patients. One particular example is the common switch from CAPOX to capecitabine monotherapy in case of severe neurotoxicity (24). Naturally, switches that are planned, such as the sequential regimes or combinations with non-cytotoxic drugs, are not considered as TIMT. Also modifications not resulting from toxicities, such as requested interruptions because of holidays or other personal circumstances, should not be considered as a TIMT. Ideally, TIMTs should be evaluated during the entire phase of active treatment, and monitoring of time (in days or cycles) to occurrence of the first TIMT can provide additional information. For studies evaluating determinants of toxicities of modern classes of anticancer drugs, such as targeted agents that are administered for a prolonged time, or checkpoint-inhibitors for which specific immune-related adverse events can be expected, the TIMT definition is also suitable as a primary outcome, whilst additional criteria may be used based on the specific research questions addressed.

Concluding remarks and perspectives

To facilitate research on potential determinants of treatment-induced toxicity in cancer patients, we propose the term toxicity-induced modification of treatment (TIMT) to define outcomes in observational studies within population-based or patients cohorts. Especially studies that rely on retrospective data collection from medical records as part of standard care may benefit from this uniform definition that also favors comparisons between studies. In our opinion, one of the strengths of the TIMT definition is that clinical consequences (i.e. modifications of treatment) are considered independent of the (CTCAE) grade of toxicities. One limitation of the grading systems for symptom severity is that low-grade chronic toxicities are often neglected, whilst these toxicities may seriously impact quality of life of the patient, especially in the context of modern treatment strategies that are administered continuously and for a prolonged time (25). Indeed, low-grade toxicities can result in

substantial treatment modifications especially in patients receiving targeted therapy (26), whereas patients with high-grade toxicities may be able to complete or continue therapy (27), indicating that grades of toxicities are not linked to clinical consequences at all times. This pattern is also inherent to individual tolerance of toxicities and perception by patients as well as physicians (28). In view of this, the TIMT definition is different from the CTCAE criteria as it solitarily focuses on toxicities with clinical consequences, and hence may have important implications for prognosis of the patient (2, 3). Naturally, adequate and essential data on specific adverse events and their severity, either physician- or patient-reported, can provide complementary information in these type of studies whenever available.

Given the existence of various well-described patient cohorts with valuable information on nutrition, lifestyle and other modifiable factors, future studies may expand their view and benefit from clinically available data by studying the association between various exposures and TIMT. As the TIMT definition can be easily applied in heterogeneous patient populations receiving standard care across different centers, also patients with rare cancers can and should be considered in future studies. Needless to say is that the advances in medical oncology, including introduction of molecular targeted therapy and immunotherapy, provide even more exciting opportunities for this research field. Exposures that warrant further attention include, but are not limited to smoking, energy intake, protein intake, alcohol consumption, biomarkers of dietary intake (e.g. folate, vitamin D) and inflammation (e.g. cytokines), dietary supplements and physical activity. In this context and by using clinically available data, one can even look beyond the traditional exposures and explore other fascinating areas such as microbiota composition (29), genetic variants (30) and metabolites (31) in relation to toxicity-induced modification of treatment. That’s in a name!

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Conflict of interest statement

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REFERENCES

1. Potter JD. At the interfaces of epidemiology, genetics and genomics. Nat Rev Genet 2001;2(2):142-7.

2. Morris M, Platell C, Fritschi L, Iacopetta B. Failure to complete adjuvant chemotherapy is associated with adverse survival in stage III colon cancer patients. Br J Cancer 2007;96(5):701-7.

3. Budman DR, Berry DA, Cirrincione CT, Henderson IC, Wood WC, Weiss RB, et al. Dose and Dose Intensity as Determinants of Outcome in the Adjuvant Treatment of Breast Cancer. JNCI: Journal of the National Cancer Institute 1998;90(16):1205-1211.

4. Mols F, Beijers T, Lemmens V, Hurk CJvd, Vreugdenhil G, Poll-Franse LVvd. Chemotherapy-Induced Neuropathy and Its Association With Quality of Life Among 2- to 11-Year Colorectal Cancer Survivors: Results From the Population-Based PROFILES Registry. Journal of Clinical Oncology 2013;31(21):2699-2707.

5. Schmielau J, Rick O, Reuss-Borst M, Kalusche-Bontemps EM, Steimann M. Rehabilitation of Cancer Survivors with Long-Term Toxicities. Oncology Research and Treatment 2017;40(12):764-771.

6. Postel-Vinay S, Collette L, Paoletti X, Rizzo E, Massard C, Olmos D, et al. Towards new methods for the determination of dose limiting toxicities and the assessment of the recommended dose for further studies of molecularly targeted agents – Dose-Limiting Toxicity and Toxicity Assessment Recommendation Group for Early Trials of Targeted therapies, an European Organisation for Research and Treatment of Cancer-led study. European Journal of Cancer 2014;50(12):2040-2049.

7. Le Tourneau C, Razak ARA, Gan HK, Pop S, Diéras V, Tresca P, et al. Heterogeneity in the definition of dose-limiting toxicity in phase I cancer clinical trials of molecularly targeted agents: A review of the literature. European Journal of Cancer 2011;47(10):1468-1475.

8. Eisenhauer EA, O'Dwyer PJ, Christian M, Humphrey JS. Phase I Clinical Trial Design in Cancer Drug Development. Journal of Clinical Oncology 2000;18(3):684-684.

9. Cinausero M, Aprile G, Ermacora P, Basile D, Vitale MG, Fanotto V, et al. New Frontiers in the Pathobiology and Treatment of Cancer Regimen-Related Mucosal Injury. Frontiers in Pharmacology 2017;8:354.

10. Lotfi-Jam K, Carey M, Jefford M, Schofield P, Charleson C, Aranda S. Nonpharmacologic strategies for managing common chemotherapy adverse effects: a systematic review. J Clin Oncol 2008;26(34):5618-29.

11. Tejpar S, Yan P, Piessevaux H, Dietrich D, Brauchli P, Klingbiel D, et al. Clinical and pharmacogenetic determinants of 5-fluorouracyl/leucovorin/irinotecan toxicity: Results of the PETACC-3 trial. Eur J Cancer 2018;99:66-77.

12. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008;33(5):997-1006.

13. Kazemi-Bajestani SMR, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Seminars in Cell & Developmental Biology 2016;54(Supplement C):2-10.

14. O'Flanagan CH, Smith LA, McDonell SB, Hursting SD. When less may be more: calorie restriction and response to cancer therapy. BMC Medicine 2017;15:106.

15. Wedlake L, Shaw C, McNair H, Lalji A, Mohammed K, Klopper T, et al. Randomized controlled trial of dietary fiber for the prevention of radiation-induced gastrointestinal toxicity during pelvic radiotherapy. Am J Clin Nutr 2017;106(3):849-857.

16. Yan M, Ho C, Winquist E, Jonker D, Rayson D, Stitt L, et al. Pretreatment Serum Folate Levels and Toxicity/Efficacy in Colorectal Cancer Patients Treated With 5-Fluorouracil and Folinic Acid. Clin Colorectal Cancer 2016;15(4):369-376.e3.

17. Snyder CF, Aaronson NK, Choucair AK, Elliott TE, Greenhalgh J, Halyard MY, et al. Implementing patient-reported outcomes assessment in clinical practice: a review of the options and considerations. Quality of Life Research 2012;21(8):1305-1314.

18. Basch E, Dueck AC, Rogak LJ, Minasian LM, Kelly WK, O'Mara AM, et al. Feasibility Assessment of Patient Reporting of Symptomatic Adverse Events in Multicenter Cancer Clinical Trials. JAMA Oncol 2017;3(8):1043-1050.

19. Winkels RM, Heine-Broring RC, van Zutphen M, van Harten-Gerritsen S, Kok DE, van Duijnhoven FJ, et al. The COLON study: Colorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that may influence colorectal tumour recurrence, survival and quality of life. BMC Cancer 2014;14:374.

20. Kwan ML, Ambrosone CB, Lee MM, Barlow J, Krathwohl SE, Ergas IJ, et al. The Pathways Study: a prospective study of breast cancer survivorship within Kaiser Permanente Northern California. Cancer Causes Control 2008;19(10):1065-76.

21. Bueno-de-Mesquita HB, Gonzalez CA. Main hypotheses on diet and cancer investigated in the EPIC Study. European Prospective Investigation into Cancer and Nutrition. Eur J Cancer Prev 1997;6(2):107-17.

22. Jouinot A, Vazeille C, Durand JP, Huillard O, Boudou-Rouquette P, Coriat R, et al. Resting energy expenditure in the risk assessment of anticancer treatments. Clin Nutr 2017.

23. Arrieta O, De la Torre-Vallejo M, Lopez-Macias D, Orta D, Turcott J, Macedo-Perez EO, et al. Nutritional Status, Body Surface, and Low Lean Body Mass/Body Mass Index Are Related to Dose Reduction and Severe Gastrointestinal Toxicity Induced by Afatinib in Patients With Non-Small Cell Lung Cancer. Oncologist 2015;20(8):967-74.

24. Banach M, Juranek JK, Zygulska AL. Chemotherapy-induced neuropathies—a growing problem for patients and health care providers. Brain and Behavior 2017;7(1):e00558.

25. Seruga B, Templeton AJ, Badillo FEV, Ocana A, Amir E, Tannock IF. Under-reporting of harm in clinical trials. The Lancet Oncology 2016;17(5):e209-e219.

26. Castellanos EH, Chen SC, Drexler H, Horn L. Making the Grade: The Impact of Low-Grade Toxicities on Patient Preference for Treatment With Novel Agents. J Natl Compr Canc Netw 2015;13(12):1490-5.

27. Ewer MS, Suter TM, Lenihan DJ, Niculescu L, Breazna A, Demetri GD, et al. Cardiovascular events among 1090 cancer patients treated with sunitinib, interferon, or placebo: A comprehensive adjudicated database analysis demonstrating clinically meaningful reversibility of cardiac events. European Journal of Cancer 2014;50(12):2162-2170.

28. Bayo J, Prieto B, Rivera F. Comparison of Doctors' and Breast Cancer Patients' Perceptions of Docetaxel, Epirubicin, and Cyclophosphamide (TEC) Toxicity. Breast J 2016;22(3):293-302.

29. Roy S, Trinchieri G. Microbiota: a key orchestrator of cancer therapy. Nat Rev Cancer 2017;17(5):271-285.

30. Giacomini KM, Yee SW, Mushiroda T, Weinshilboum RM, Ratain MJ, Kubo M. Genome-wide association studies of drug response and toxicity: an opportunity for genome medicine. Nat Rev Drug Discov 2017;16(1):1.

31. Rattner J, Bathe OF. Monitoring for Response to Antineoplastic Drugs: The Potential of a Metabolomic Approach. Metabolites 2017;7(4).

Table 1: An overview of studies describing the association between body composition and treatment-induced toxicities

Study[a]	PMID	Toxicity outcome (definition)	Criteria	Type of cancer	No of patients	Treatment
Mir, 2012	22666367	DLT	any toxicities leading to a dose reduction, temporary or permanent discontinuation of therapy	advanced hepatocellular carcinoma	n=40	targeted therapy (sorafenib)
Huillard, 2013	23462722	early DLT	any toxicity leading to dose reduction, temporary or permanent discontinuation in the first cycle (i.e. 6 weeks)	metastatic renal cell cancer	n=61	targeted therapy (sunitinib)
Tan, 2015	25498359	DLT	toxicity leading to postponement of treatment, a drug dose reduction or definitive interruption of drug administration	locally advanced esophago-gastric cancer	n=89	neoadjuvant chemotherapy
Ali, 2016	26814378	DLT	dose reductions or termination of therapy in the first 4 cycles	colorectal cancer	n=80	chemotherapy (FOLFOX)
Cushen, 2016	28531567	DLT	any grade ≥ 3 toxicity leading to dose reduction, temporary or permanent discontinuation of therapy	metastatic castrate resistant prostate cancer	n=63	chemotherapy (docetaxel)
Cespedes Feliciano, 2017	28881381	1. early discontinuation 2. treatment delay 3. dose reduction	1. < 6 cycles or switch to another regimen 2. ≥ 3 days later than recommendations from guideline 3. relative dose intensity (RDI) < 0.70	stage II – III colon cancer	n=533	chemotherapy (FOLFOX)
Shachar, 2017	28143874	treatment-related toxicity	any and specific grade 3-4 toxicities or dose reductions, treatment delays and hospitalizations	stage I-III breast cancer	n=151	chemotherapy (taxane-based)
Shachar, 2017	27489287	"any adverse event"	hospitalization, grade 3–4 toxicity, dose reductions, or dose delay	metastatic breast cancer	n=40	chemotherapy (taxane-based)
Palmela, 2017	28337365	DLT	any grade 3 or 4 toxicity associated with physician-ordered dose reduction or termination of therapy.	locally advanced gastric cancer	n=48	neoadjuvant chemotherapy
Murimwa, 2017	29184684	acute toxicity	grade ≥3 toxicity within 3 months of radiotherapy	locally advanced esophageal cancer	n=56	chemoradiation
Wendrich, 2017	28688687	CDLT	any toxicity resulting in dose-reduction of ≥50%, postponement of ≥4 days or a definite termination of chemotherapy after the first or second cycle of therapy	locally advanced head and neck squamous cell carcinoma	n=112	radiochemotherapy
Cushen, 2017	24685884	DLT	any toxicity leading to dose reduction, temporary or permanent discontinuation of therapy. Primary analysis compares rates of grade 3-4 toxicity, dose delays, dose reductions, and combinations as DLT	metastatic renal cell carcinoma	n=55	targeted therapy (sunitinib)
Daly, 2017	28072766	DLT and high-grade (3-4) adverse events	any dose delays or early cessation of treatment as a result of significant toxicity (grades 3–4) during 4 cycles	metastatic melanoma	n=84	immunotherapy (ipilimumab)

[a] This table present various studies focusing on body composition and toxicity outcomes to highlight the heterogeneity in definitions for toxicity, but does not provide a comprehensive literature review. Only studies with retrospective data collection from medical records are presented. These studies are acknowledged and referenced by their PubMed identifier (PMID). Studies based on clinical trials or data collection per protocol are not included in this table. Body composition includes measures of muscle (area / mass / index / gauge), fat (area / mass), intramuscular fat and sarcopenia or sarcopenic obesity in these studies. Abbreviations: CDLT; chemotherapy dose-limiting toxicity, DLT; dose-limiting toxicity, FOLFOX; chemotherapeutic regimen containing leucovorin, 5-fluorouracil and oxaliplatin, RDI; relative dose intensity.

Table 2: Proposed definition and criteria for toxicity outcomes in observational studies

Proposed term	**Toxicity-induced modification of treatment (TIMT)**
Including	- Dose reduction - Interruption / delay of therapy - Discontinuation of therapy - Switch to an alternative regimen[a]
Excluding[b]	- Discontinuation of therapy because of progressive disease - Interruption / delay of therapy because of non-clinical reasons[c] - Switch to another regimen per protocol (e.g. sequential regimens)

[a] referring to an unanticipated switch to another regimen which is resulting from severe toxicities experienced by the patient. [b] these events should not be scored as a toxicity-induced modification of treatment (TIMT). [c] reasons not primarily related to treatment e.g. holiday / birthday.