Beyond Maximum Grade: Modernizing the Assessment and Reporting of Adverse Events

The Lancet Haematology Commission

NCI Clinical Trials and Translational Research Advisory Committee (CTAC) Meeting
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Gita Thanarajasingam, MD

Assistant Professor of Medicine
Senior Associate Consultant
Division of Hematology
Mayo Clinic
Rochester, MN

DISCLOSURE

Relevant Financial Relationship(s)

None

Off Label Usage

None

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Objectives

- Discuss why traditional approaches to reporting and analyzing adverse events (AEs) are inadequate in the era of modern therapeutics for hematologic malignancies
- Briefly introduce a complementary approaches to adverse event analysis that captures AE time frame and chronic, low grade events
- Define priority areas and tangible solutions for improving AE assessment across the hematologic malignancies as identified by an international commission and recently published in The Lancet Haematology

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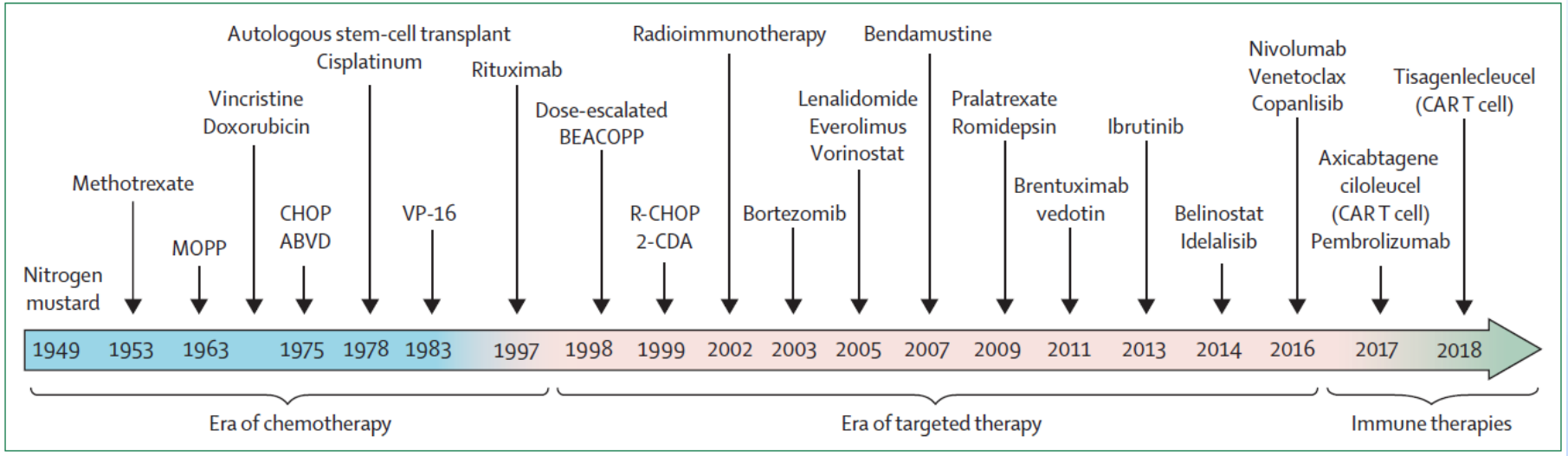
Evolution of therapy of hematologic malignancies

Lymphoma as an exemplar of changing treatment paradigms in hematologic malignancies



Thanarajasingam G, Lancet Haematol, 2018

Current AE reporting for hematology therapies is incomplete

- Does not account for time profile of AEs
  - When will they arise?
  - How long will they last?
  - When will they be the worst?
- Does not capture the impact of chronic, low grade toxicity on the ability to continue treatment
- Does not incorporate patient-reported outcomes (PRO)

Panel 1: Definitions of toxicity relative to drug exposure, by drug category

Acute effects
Develop within a short and defined timeframe; can be transient or reversible or persistent.

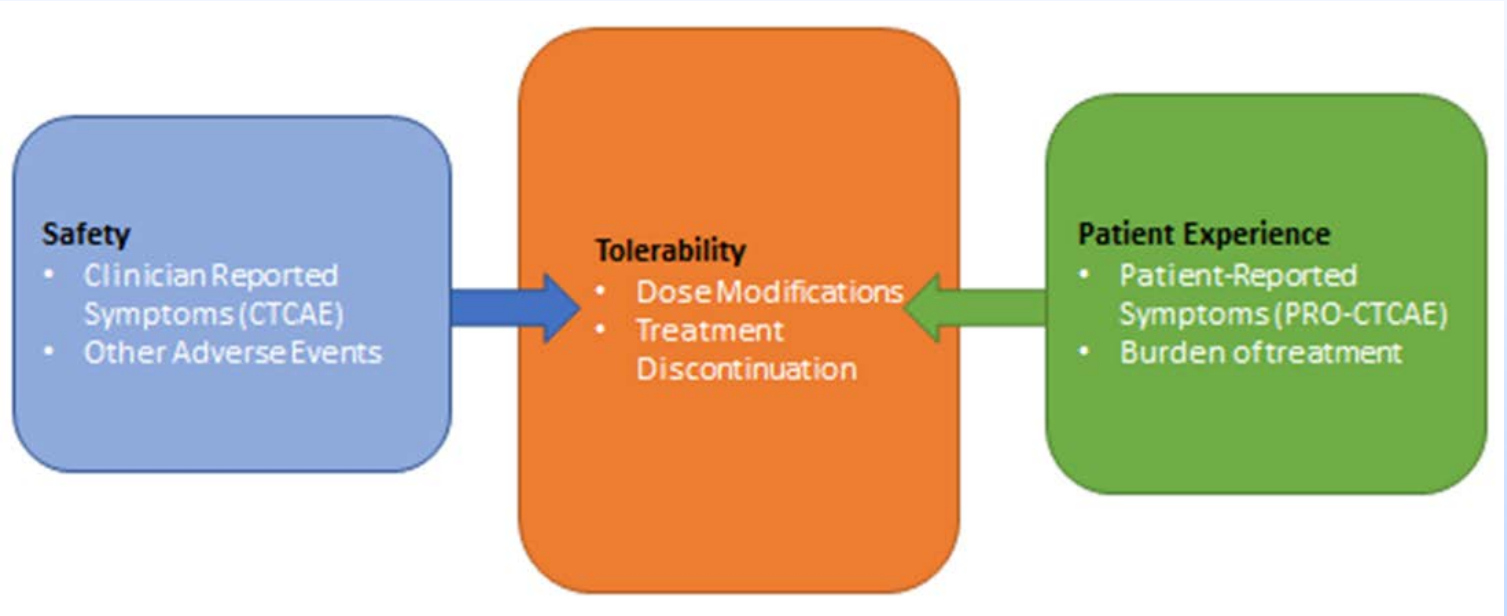
Chronic effects
Develop over time to be a persistent and unremitting, or intermittent and recurring, series of events, extending past a defined interval such as the first cycle of therapy.

Cumulative effects
Develop and increase with repeated exposures to drug (progressive over time).

Late effects
Result in subclinical or asymptomatic physiological changes that do not result in immediate, intermittent, or short-term adverse clinical events, but rather are manifest over an extended timeframe.

Thanarajasingam G. J Natl Cancer Inst 2015. 107(10)
Basch E. N Engl J Med 2013; 369;5:397-400
Carrabou M. Ann Oncol 2016; 27(8)1633-8.
Thanarajasingam G, Lancet Haematol, 2018

Safety, tolerability and the patient experience of AEs in the current landscape of hematology therapies



Slide courtesy of Lori Minasian, MD

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Shortcomings of traditional “maximum grade” reporting: chronic low grade AEs

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

Table 4. Adverse Events Deemed Related to Panobinostat (≥ 10% any grade) As of June 11, 2010

	Any Grade		Grade 3 to 4	
Adverse Event	No.	%	No.	%
Thrombocytopenia	110	85	102	79
Diarrhea	85	66	4	3
Nausea	77	60	1	1
Anemia	49	38	27	21
Fatigue	49	38	12	9

Table 2. Adverse Events during Treatment.*

Event or Abnormality	Grade	
	Any	*no. (%)* ≥3
Diarrhea	54 (43)	16 (13)
Nausea	37 (30)	2 (2)
Fatigue	37 (30)	2 (2)
Cough	36 (29)	0

Chronic low grade diarrhea?

National Cancer Institute. CTCAE v.5.0. Bethesda, MD: US. Department of Health and Human Services; 2009
Younes et al. J Clin Oncol 2012;30:2197-203
Gopal et al. N Engl J Med 2014; 370;11:1008-18.

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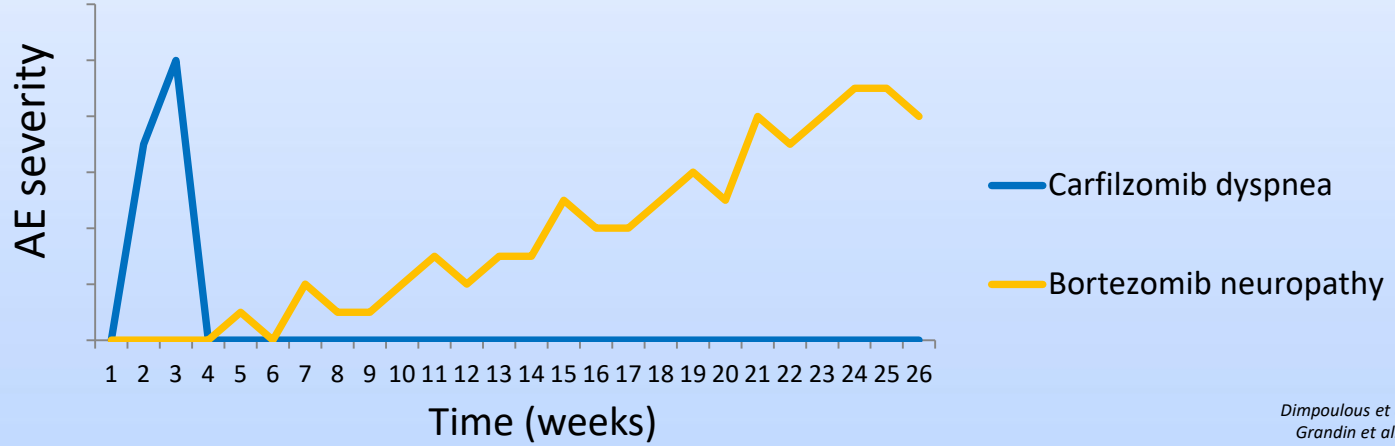
Shortcomings of traditional “maximum grade” reporting: lack of time profile of AEs

Two grade 3+ AEs with similar incidence (maximum grade reporting)

Grade 3 or higher	Carfilzomib + dex (n=463)	Bortezomib + dex (n=456)
Dyspnea	25 **(5%)**	10 (2%)
Peripheral neuropathy	6 (1%)	24 **(5%)**

Conceptual patient AE experience: which is more burdensome?

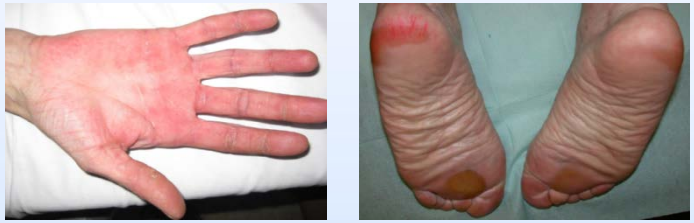


Dimpoulous et al. Lancet Oncol 2016; 17:27-38
Grandin et al. J Cardiac Fail 2015;21:138-144
Siegel et al. Haematologica 2013; 98(11):1753-61

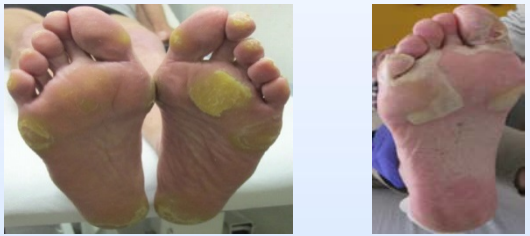
Shortcomings of traditional “maximum grade” reporting: lack of time profile of AEs

Two oral agents that produce a similar AE

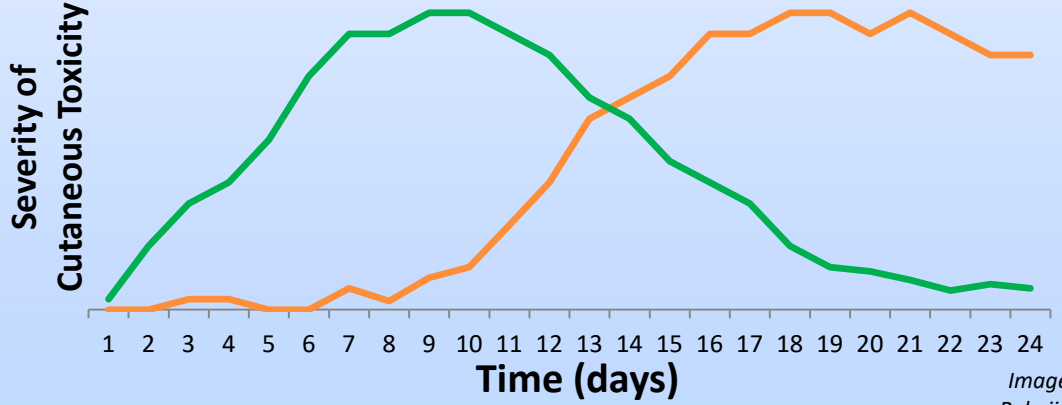
Hand-foot syndrome (**capecitabine**)



Hand-foot skin reaction (**regorafenib**)



Clinical experience of time of AE occurrence: ramifications on AE intervention?



Grothey et al. J Clin Oncol 31, 2013 (suppl; abstr 3637)
Grothey et al. Oncologist 2014;19(6)669-80
Images : McLellan et al. Ann Oncol (2015) 26 (10): 2017-2026.
Bekaii-Saab TS et al. J Clin Oncol. 2018;36(suppl 4S; abstr 611).

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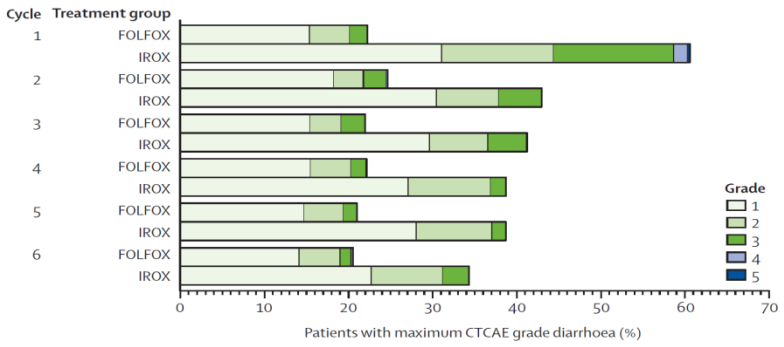
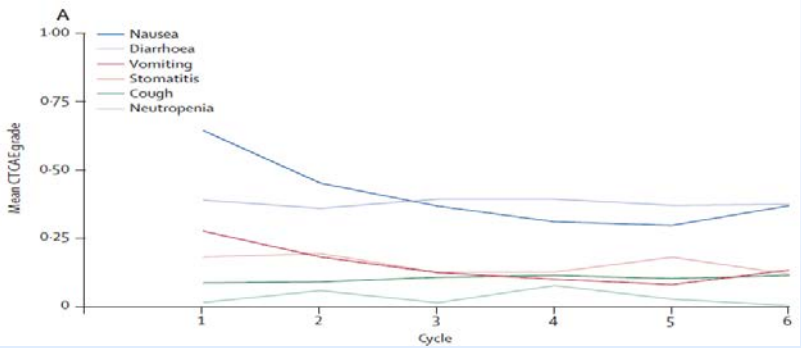
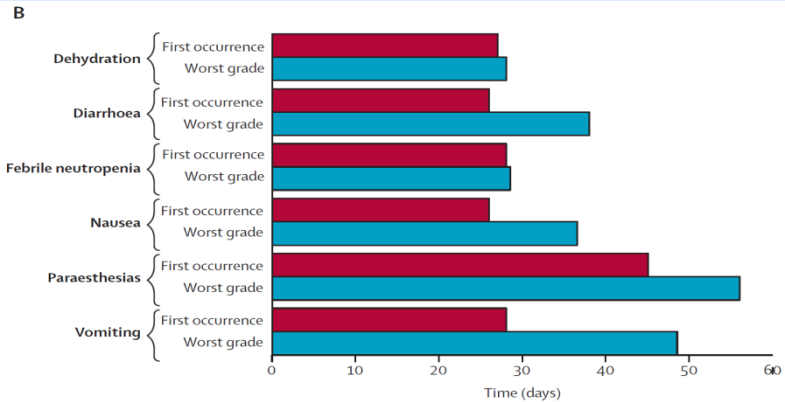
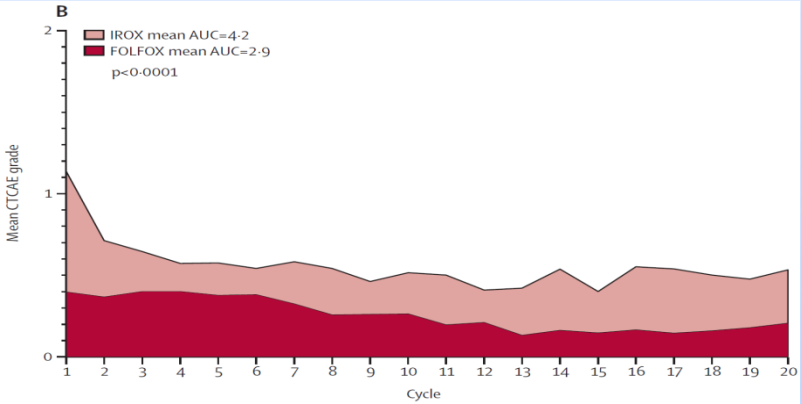
Improving AE analysis: longitudinal analysis
Toxicity over Time (ToxT) approach



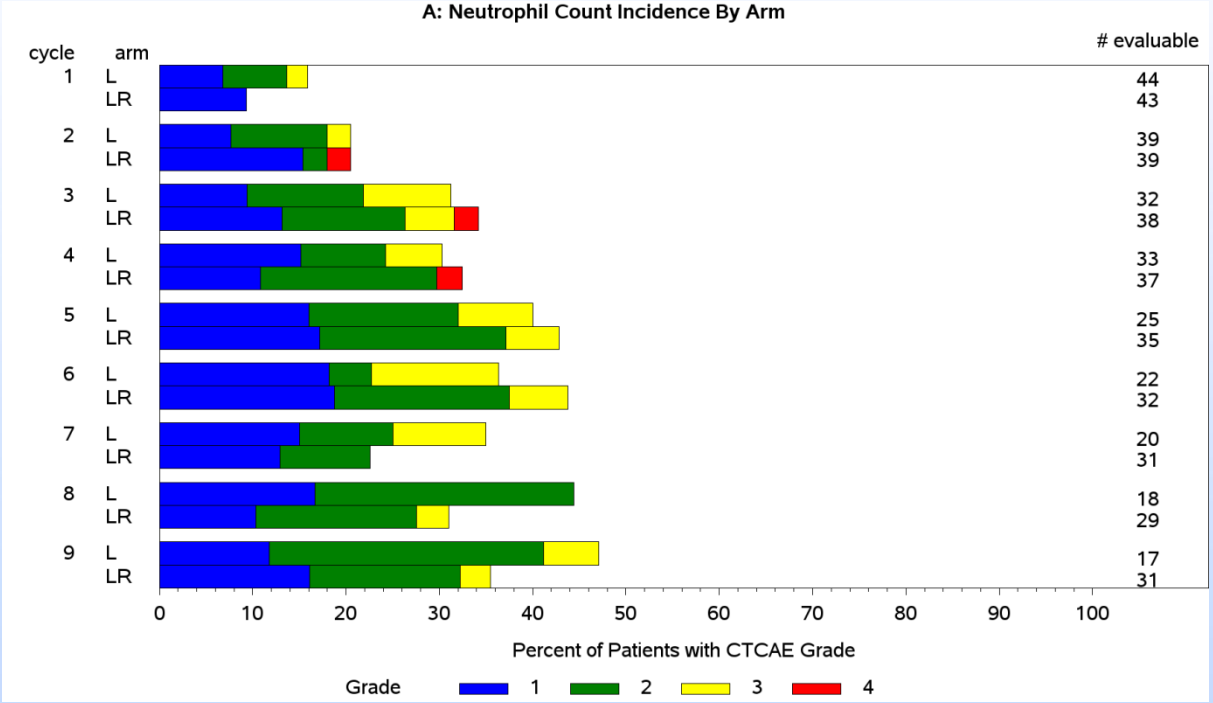






Thanarajasingam G. Lancet Oncol. 2016; 17:663-70

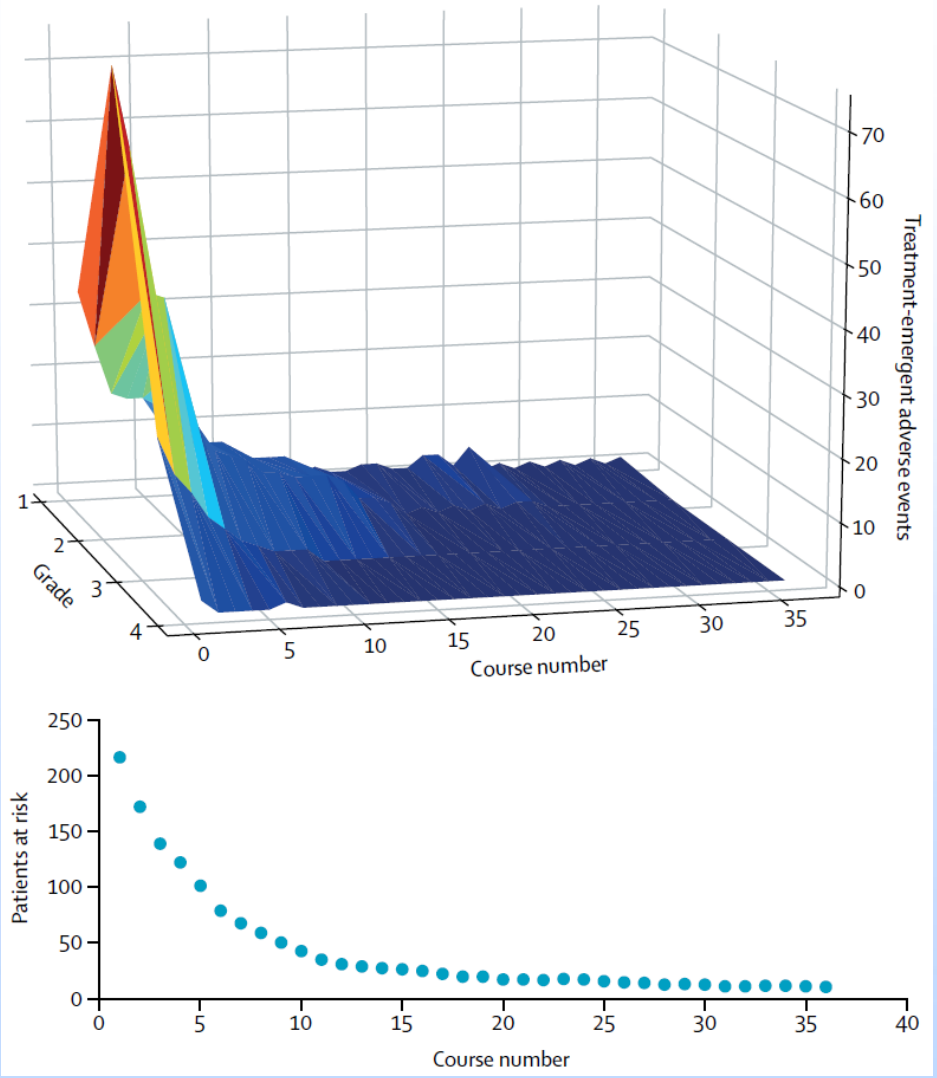
Application in hematology: neutropenia over time on lenalidomide (in CALGB/Alliance 50401)



Thanarajasingam G, Hematological Oncology 2017, 35: 213–215 (abstr)

The NCI Web Reporting Tool

- Displays grade and frequency of one AE in patients from five clinical trials of the combination of two novel agents
- Time-dependent graphical representation
- Aggregate analyses (multiple trials)
- Also represents number at risk (captures patient attrition)



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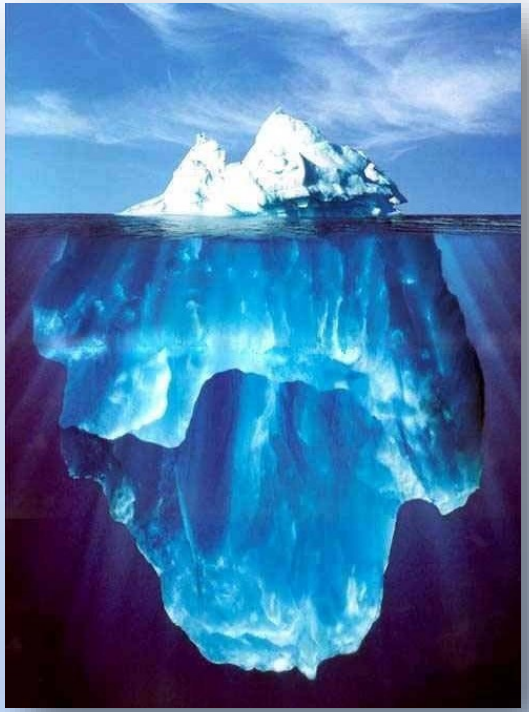
Thanarajasingam G, Lancet Haematol 2018
Adapted from work of S. Percy Ivy, MD and Richard F. Little, MD

Improving AE analysis is only the tip of the iceberg



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Commission on Improving AE Assessment in Haematology

- International collaboration of 40 clinicians, clinical investigators, patient advocates, regulators and biostatisticians to address multi-faceted challenges to AE assessment in haematologic malignancies
- Includes authors from Europe, North America, Asia and Australia
- Individuals representing NCI, US cooperative groups, EORTC, global regulatory agencies (EMA, FDA, PMDA, TGA) involved, among others
- Produced a “call to action” paper with tangible targets and timelines for improvement
- Most issues applicable to all tumor types (not just hematology)

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The Lancet Haematology Commission

Beyond maximum grade: modernising the assessment and reporting of adverse events in haematological malignancies

Gita Thanarajasingam, Lori M Minasian, Frederic Baron, Franco Cavalli, R Angelo De Claro, Amylou C Dueck, Tarec C El-Galaly, Neil Everest, Jan Geissler, Christian Gisselbrecht, John Gribben, Mary Horowitz, S Percy Ivy, Caron A Jacobson, Armand Keating, Paul G Kluetz, Aviva Krauss, Yok Lam Kwong, Richard F Little, Francois-Xavier Mahon, Matthew J Matasar, María-Victoria Mateos, Kristen McCullough, Robert S Miller, Mohamad Mohty, Philippe Moreau, Lindsay M Morton, Sumimasa Nagai, Simon Rule, Jeff Sloan, Pieter Sonneveld, Carrie A Thompson, Kyriaki Tzogani, Flora E van Leeuwen, Galina Velikova, Diego Villa, John R Wingard, Sophie Wintrich, John F Seymour, Thomas M Habermann

- Published June 12, 2018
- Launched with oral presentation sessions at the European Hematology Association Meeting 2018 and at the Karolinska Institute
- Four NCI authors: Lori Minasian MD, Richard F. Little MD, S. Percy Ivy MD, Lindsay M. Morton PhD

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Commission Sections

- Current processes in adverse event assessment: strengths & shortcomings
- Incorporation of PROs in the assessment of adverse events
- Special issues of toxicity from hematopoietic stem cell transplant (HSCT)
- Survivorship and long-term toxicity in hematologic malignancies
- Adverse events in haematologic malignancies and regulatory approval
- Toxicity reporting in hematologic malignancies in the real world setting

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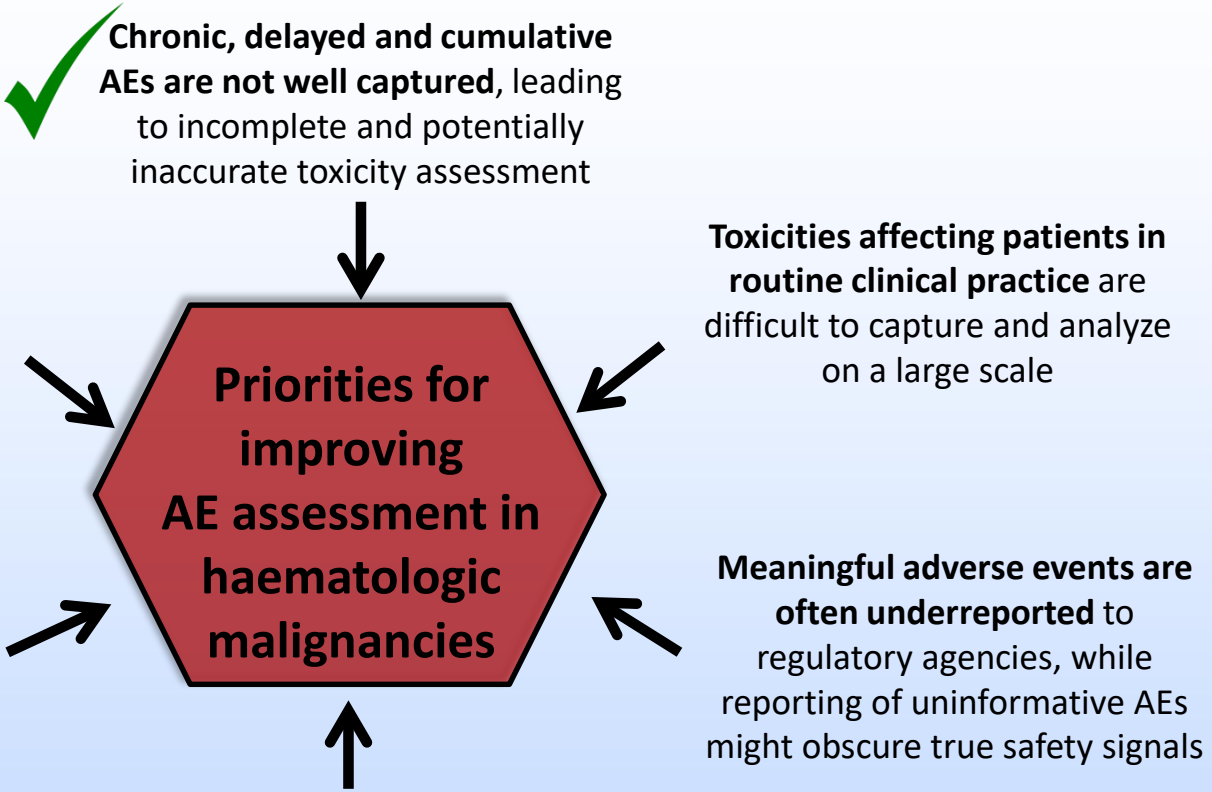
Priority issues



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Challenges in AE analysis: proposed solutions

Priority issue

Chronic, delayed and cumulative adverse events are not well described

Immediate-action solutions (1-5 years)

- Phase 1 trials with longer dose-limiting toxicity (DLT) evaluation periods
- Adaptive designs that span phase I/II
- Development of longitudinal methods for analysis of adverse events

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Inclusion of PROs: proposed solutions

Priority issue

PROs are not a standard part of toxicity assessment

Immediate-action solutions

- Hypothesis-driven PROs in more trials
- Increasing use of PRO-CTCAE and other tools for capturing symptomatic AEs from patients
- Electronic capture of PROs

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AEs in HSCT: proposed solutions

Priority issue

Cumbersome reporting of "expected" AEs in HSCT trials

Immediate-action solutions

- Achieve consensus on "expected" AEs from registry data
- Develop targeted approaches that focus on unique, potentially relevant, or unexpected AEs including drug interactions and neurocognitive effects

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Toxicity assessment in survivors: proposed solutions

Priority issue

Description of cumulative and late toxicities in survivors is inconsistent, inadequate or absent

→

Immediate-action solutions

- Develop infrastructure to collect data for adult survivors (ex. longitudinal patient cohorts)
- Standardize the use and content of survivorship care plans

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Regulatory challenges: proposed solutions

Priority issue

Meaningful AEs are underreported, while reporting of uninformative AEs obscures safety signals

→

Immediate-action solutions

- Electronic submission of simplified adverse event reports
- Better systems for collection and analysis of data obtained from the trial, post-marketing or non-trial setting

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Real world toxicity evaluation: proposed solutions

Priority issue

Toxicities affecting patients in routine clinical practice are difficult to evaluate on a large scale

Immediate-action solutions

- Optimize systematic, objective collection of toxicity data in databases
- Explore real world toxicities using large database systems and real-time analyses from tools such (ex. CancerLinQ)

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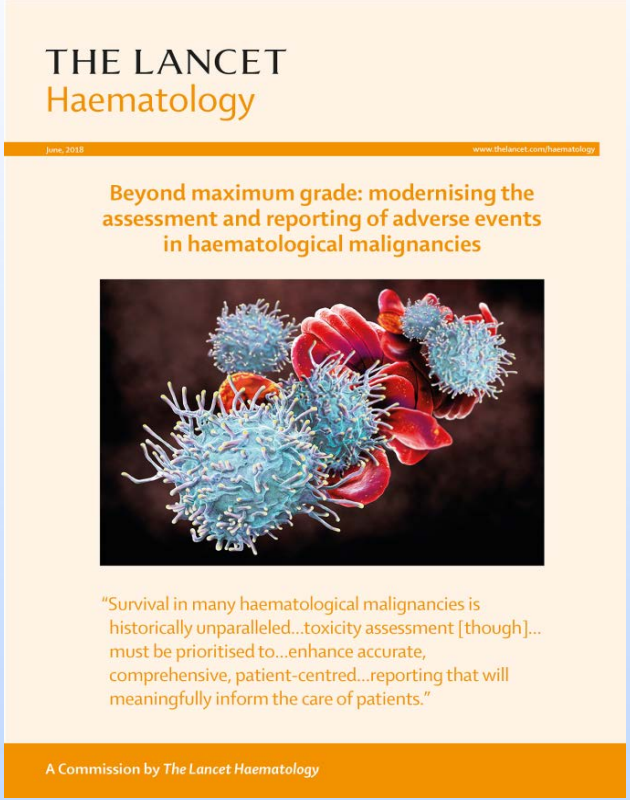
A start to addressing challenges of toxicity assessment

- Will require ongoing global collaboration amongst all stakeholders to drive meaningful change
  - Patient, clinician, clinical investigator, NCI, regulatory agency, cooperative group, and industry input (among others) invaluable
- Ties in well with ongoing NCI activities
- NCI has led the development and use of CTCAE, and is an important stakeholder in going beyond maximum grade



Conclusions

- The conventional “maximum grade” approach to reporting and analyzing adverse events (AEs) is insufficient in the modern treatment landscape of most cancers
- Novel longitudinal approaches may be able to portray additional complementary information on AE time frame and chronic, low grade events that are relevant to tolerability
- As part of a global initiative, we have defined priority areas for improving AE assessment and proposed future directions for improvement across the spectrum of malignancies

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  - Lori Minasian, MD (National Cancer Institute, USA)
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  - Carrie Thompson, MD (Mayo Clinic Rochester, USA)
  - Aviva Krauss, MD (FDA, USA)
  - Tarec El-Galaly, MD (University of Aalborg, Denmark)
- Commission co-authors

  Frederic Baron MD, Franco Cavalli MD, R Angelo De Claro MD, Neil Everest MBBS, Jan Geissler MBA, Christian Gisselbrecht MD, Mary Horowitz MD, Caron Jacobson MD, Paul G Kluetz MD, Yok Lam Kwong MD, Richard F Little MD, Francois-Xavier Mahon MD, Matthew Matasar MD, Kristen McCullough PharmD, Robert S Miller MD, Mohamad Mohty MD, Philippe Moreau MD, Lindsay M Morton PhD, Sumimasa Nagai, MD, Simon Rule MBBS, Kyriaki Tzogani MSc, Flora E. van Leeuwen PhD, Galina Velikova PhD, Diego Villa MD, John R Wingard MD, Sophie Wintrich
- The Lancet Haematology

Patient advocates, patients & their families

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Supplementary slides

- The following slides summarize the priority issues, immediate action solutions and longer term solutions from The Lancet Haematology Commission “Beyond Maximum Grade: Modernising the assessment and reporting of adverse events in haematological malignancies”
- This information is detailed further in the Commission publication (Thanarajasingam G, Lancet Haematol 2018) in Table 6 (page 36)

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The problem in AE analysis and proposed solutions

Priority issue

Chronic, delayed and cumulative adverse events are not well described, leading to incomplete and potentially inaccurate toxicity assessment

Immediate-action solutions (1-5 years)

- Design phase 1 trials with longer dose-limiting toxicity evaluation periods and increase use of adaptive designs that span phase I/II
- Continue to develop, disseminate, validate and apply longitudinal methods for analysis of adverse events

Long-term solutions (5+ years)

- Establish consensus on the best metrics and representations of time-dependent AE data
- Standardize and require use of these metrics and displays in publications and drug labels

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Including PROs and proposed solutions

Priority issue

PROs are not a standard part of toxicity assessment and therefore tolerability of therapies for hematological malignancies from the perspective of the patient is not addressed

Immediate-action solutions (1-5 years)

- Include hypothesis-driven PROs in more hematology trials
- Increase use of PRO-CTCAE and other tools for capturing symptomatic AEs to better inform tolerability assessment of novel drugs
- Facilitate electronic capture of PROs

Long-term solutions (5+ years)

- Identify consensus analytic approaches to convey longitudinal PRO adverse event data
- Complement clinician-graded CTCAE with patient-reported symptomatic AE data
- Standardize these approaches to the analysis of PROs across cancer trials internationally

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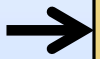
Priorities in improving AE evaluation in HSCT

Priority issue

Cumbersome reporting of the myriad of expected adverse events in the HSCT setting is a barrier to performing clinical trials



Immediate-action solutions (1-5 years)

- Develop consensus on "expected" AEs after HSCT based on registry data
- Define streamlined approaches to capture and analysis of these AEs, with hematologist and transplant input
- Include regulators and industry partners engaged in the conduct of BMT trials in evaluating this system

Long-term solutions (5+ years)

- Develop automated approaches that can recognize data routine captured in medical record as expected toxicity data after HSCT, and also highlight provider attention to unexpected, unique, and potentially relevant AEs

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Priorities in toxicity evaluation in survivors

Priority issue

The description and management of cumulative and late toxicities in survivors of haematological malignancies is inconsistent, inadequate or absent

Immediate-action solutions (1-5 years)

- Develop and support infrastructure to collect data for adult survivors (ex. longitudinal patient cohorts)
- Standardize the use and content of survivorship care plans

Long-term solutions (5+ years)

- Link PRO, delayed, or long term complications of hematological malignancies and a patient's baseline treatment in electronic medical records
- Increase availability of survivorship clinics

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Regulatory challenges and proposed solutions

Priority issue

Meaningful AEs are often underreported to regulatory agencies, while reporting of uninformative AEs might obscure true safety signals

Immediate-action solutions (1-5 years)

- Simplify and make electronic the submission of all adverse event reports
- Develop better systems for collection and analysis of data obtained from the trial, post-marketing or non-trial setting

Long-term solutions (5+ years)

- Attain international regulatory consensus on reduction of uninformative adverse event reports to prioritize relevant toxicity data
- Incorporate patient experience from trial and non-trial data, including real-world evidence, to inform both the pre-marking and post-marketing safety evaluation

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Priorities in toxicity evaluation in real world patients

Priority issue

Toxicities affecting patients with hematological malignancies in routine clinical practice are difficult to capture and analyze on a large scale

Immediate-action solutions (1-5 years)

- Optimize systematic, objective collection of toxicity data in real world databases
- Explore real world toxicities in large groups of patients using large database systems and real-time analyses from tools such as CancerLinQ

Long-term solutions (5+ years)

- Develop electronic health record systems that reliably capture relevant AE (both provider- and PRO) in off study patients with haematologic malignancies
- Leverage these systems to guide AE management and symptom control

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