Under-reporting of harm in clinical trials

Alberto Ocana
Albacete University Hospital
Albacete, Spain

ESMO

Copenhagen, October 10th, 2016

COPENHAGEN 2016 ESMO congress

Disclosures

I do not have any conflict of interest to declare

Outline

- Under-reporting of harm
- Impact of under-reporting of harm
- Possible solutions to mitigate the under-reporting of harm

Under-reporting of harm

- In clinical trials
  - perception of harm in patients vs. physicians
  - reporting of detected harm by physicians
  - updated vs. first report of a clinical trial

- In postmarketing experience or everyday clinical practice
  - patients treated outside of clinical trials have more co-morbidity and are more likely to have toxicity
  - outside clinical trials health care resources may be less abundant

How good are physicians in reporting of harm in clinical trials?

- Physician‘s reporting of symptomatic AEs lacks reliability
  - agreement between different physicians is moderate at best,
- Clinicians under-report the incidence and severity of symptoms compared to reports of patients
- Patient reports better than clinician reflecting the underlying health status

Atkinson et al, Qual Life Res, 2012; Pakhomow et al, Am J Manag Care, 2008
Basch et al, JNCI, 2009

VOLUME 33 · NUMBER 8 · MARCH 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Symptomatic Toxicities Experienced During Anticancer Treatment: Agreement Between Patient and Physician Reporting in Three Randomized Trials

Massimo Di Maio, Ciro Gallo, Natasha B. Leighl, Maria Carmela Piccirillo, Gennaro Daniele,

- Reporting of 6 subjective toxicities was compared for 1090 patients in 3 phase III clinical trials with reports of their physicians

Under-reporting of	Any toxicity	"Very much" toxicity
Anorexia	74%	50%
Nausea	40%	26%
Vomiting	47%	13%
Constipation	69%	44%
Diarrhea	50%	24%
Hair loss	65%	43%

A growing body of evidence shows that physicians under-detect harm in clinical trials

Bias in reporting of end points of efficacy and toxicity in randomized, clinical trials for women with breast cancer

F. E. Vera-Badillo, R. Shapiro, A. Ocana, E. Amir & I. F. Tannock*

Division of Medical Oncology & Hematology, Princess Margaret Hospital and University of Toronto, Toronto, Canada

Ann Oncol, 2013

- Quality of reporting of the primary endpoint (PE) and of toxicity in RCTs of breast cancer assessed
- Of 164 included trials, 33% showed bias in reporting of the PE and 67% in the reporting of toxicity
  - only 32% of articles indicated the frequency of grade 3 and 4 toxicities in the abstract
  - a positive PE was associated with under-reporting of toxicity (OR= 2.0; p=0.044)

Physicians/investigators not only under-detect but also under-report detected harm in clinical trials

Comparison of results between the first and updated reports of RCTs

- 311 initial reports of RCTs, published between 1990-2010 (prostate, breast and lung cancer)
- Of these, 64 (21%) had updated reports
- Independent predictors for an update:
  - prostate cancer site
  - conduct of an interim analysis
  - larger sample size
  - smaller HR (a larger magnitude of effect)

Elimova et al, ASCO 2014

Comparison of results between the first and updated reports of RCTs

	First publication	Updated publication	P - value
HR - primary endpoint	0.71	0.78	0.003
HR - secondary endpoint	0.76	0.82	0.35
Patients with G 1/2 AEs (%) (IQR)	21 (6-42)	23 (8-43)	0.012
Patients with G 3/4 AEs (%) (IQR)	5 (2-9)	6 (2-12)	0.001

Benefit-risk ratio of new anticancer agents may be less favourable according to the updated reports

Ellmova et al. ASCO 2014

From clinical trials to post-marketing experience

(an example: lapatinib)

Randomized clinical trial

Original publication	**Initial drug label**
2006	**2007**

From clinical trials to post-marketing experience

(an example: lapatinib)

Randomized clinical trial

Post-marketing surveillance

active

passive

Original publication

2006

Initial drug label

2007

Labeling revision #2

2007

Labeling revision #12

2015

Added: Black box warning on hepatotoxicity, interstitial lung disease, severe cutaneous reactions

Drugs@FDA

VOLUME 29 · NUMBER 2 · JANUARY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Reporting of Serious Adverse Drug Reactions of Targeted Anticancer Agents in Pivotal Phase III Clinical Trials

Bostjan Seruga, Lynn Sterling, Lisa Wang, and Ian F. Tannock

Updated drug labels
for 12 targeted agents

All Serious ADRs
N=76

Potentially fatal ADRs
N=38

ADR: Adverse Drug Reaction

VOLUME 29 · NUMBER 2 · JANUARY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Reporting of Serious Adverse Drug Reactions of Targeted Anticancer Agents in Pivotal Phase III Clinical Trials

Bostjan Seruga, Lynn Sterling, Lisa Wang, and Ian F. Tannock

Updated drug labels for 12 targeted agents	NOT reported in initial drug labels	NOT reported in pivotal RCTs
All Serious ADRs N=76	49%	39%
Potentially fatal ADRs N=38	58%	39%

ADR: Adverse Drug Reaction; RCT; Randomized Clinical Trial

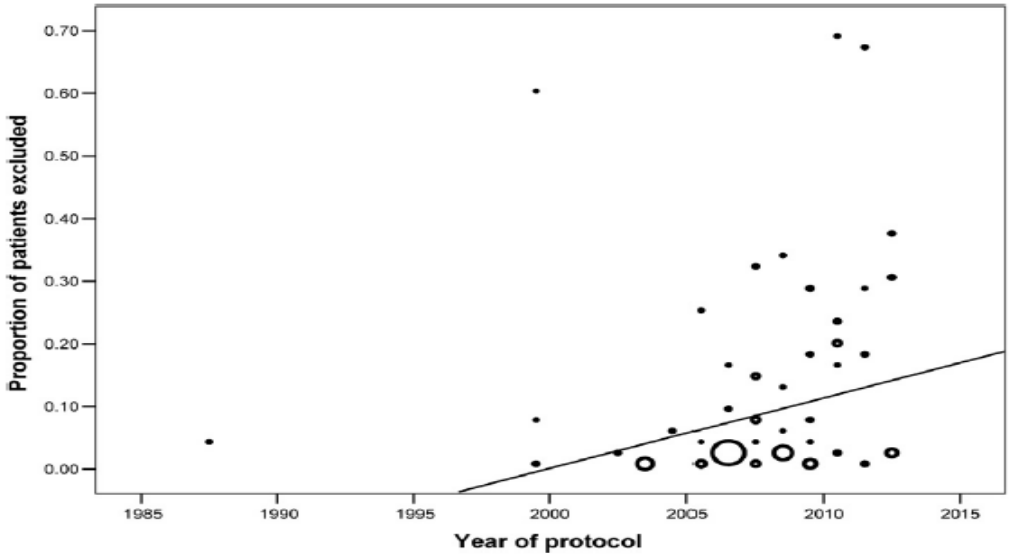
Published reports of pivotal RCTs and initial drug labels contain limited information about serious ADRs

Do participants of clinical trials reflect the real-world population of patients?

Anti-Tumour Treatment

Evolution in the eligibility criteria of randomized controlled trials for systemic cancer therapies

A. Srikanthan [a], F. Vera-Badillo [b], J. Ethier [a], R. Goldstein [a], A.J. Templeton [c], A. Ocana [d], B. Seruga [e], E. Amir [a,*]



COPENHAGEN 2016 ESMO

Translating clinical trials to clinical practice: outcomes of men with metastatic castration resistant prostate cancer treated with docetaxel and prednisone in and out of clinical trials*

Annals of Oncology 24: 2972–2977, 2013
doi:10.1093/annonc/mdt397
Published online 14 October 2013

A. J. Templeton[1], F. E. Vera-Badillo[1], L. Wang[2], M. Attalla[1], P. De Gouveia[1], R. Leibowitz-Amit[1], J. J. Knox[1], M. Moore[1], S. S. Sridhar[1], A. M. Joshua[1], G. R. Pond[3], E. Amir[1] & I. F. Tannock[1]*

Patients treated with 3-weekly docetaxel (2001-2011)	Routine practice N=314	Clinical trials N=43	TAX 327 N=335	p
Median # of cycles	6	8	9.5	< 0.001
Median OS (mo)	13.6	20.4	19.3	< 0.001
Febrile neutropenia	9.6%	0	3%	< 0.001
Death during therapy	4%	0%	3%	ns

A substantial proportion of patients are ineligible for clinical trials and their outcomes are inferior

Impact of under-reporting of harm in clinical trials

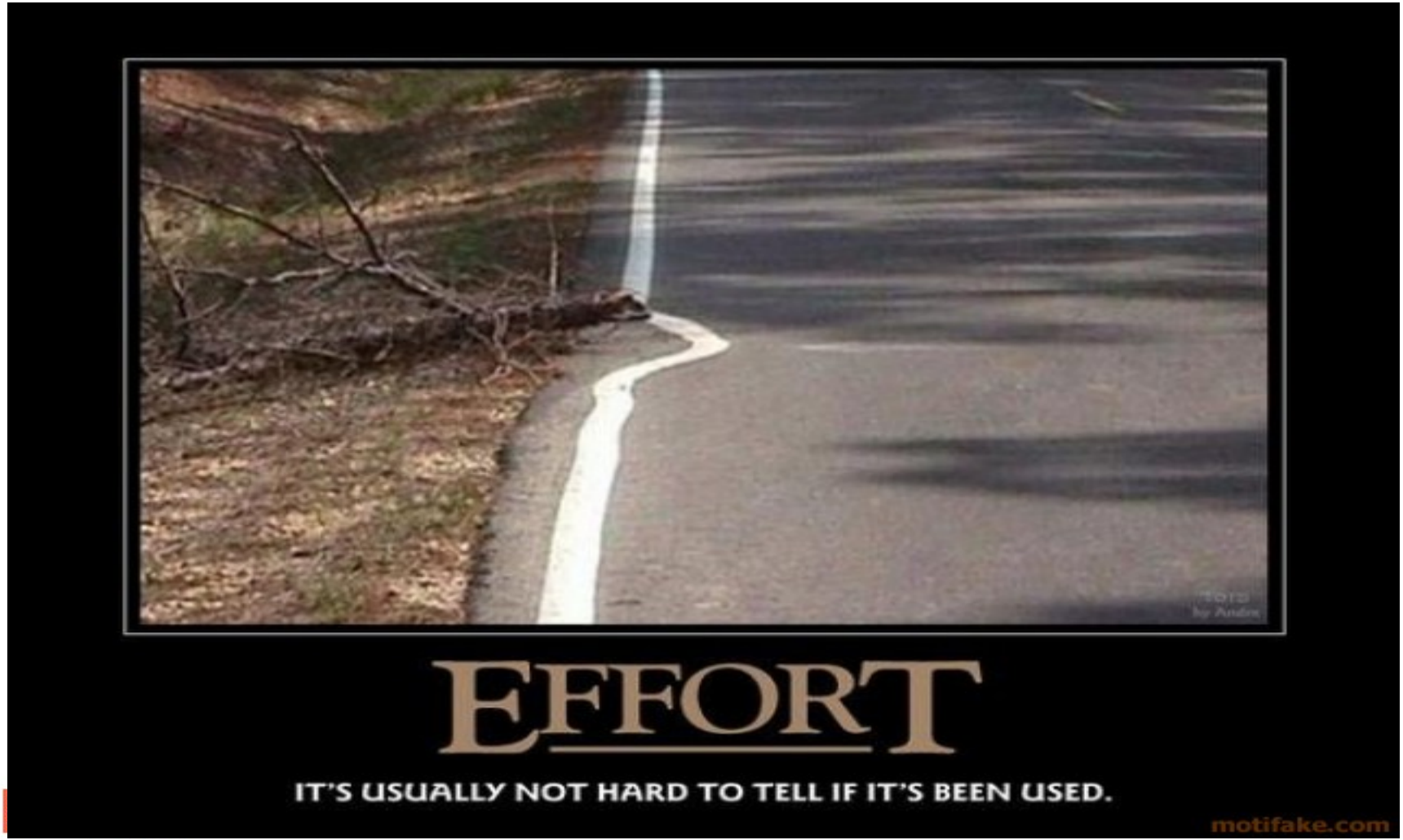
- Patients do not know what symptoms to expect based on prior experience
- Drug developers may have a false impression as to how a drug is tolerated
- Regulators may not have confidence in the fidelity of information about balancing risks and benefits
- Payers cannot accurately predict the utilization of health-care services

Basch et al, JNCI, 2011

What can we do to improve the situation?

- At the level of clinical trials
  - A patient-centered approach to AE reporting in clinical trials: development of the National Cancer Institute‘s Patient Reported version of the CTCAEs (PRO-CTCAE)
  - Presentation of updated reports of clinical trials
  - Conduct of specific trials addressing the unmet needs of protocol ineligible patients
- Post-marketing setting/every-day clinical practice
  - observational population-based outcomes studies

Basch et al, JNCI, 2014


EFFORT
IT'S USUALLY NOT HARD TO TELL IF IT'S BEEN USED.
motifake.com

Conclusions

- In contemporary clinical trials harm is under-detected and under-reported by investigators
- With a current trend to very restrictive eligibility criteria the application of results of clinical trials to everyday practice is seriously compromised
- Oncologists (and journal editors and societies like ESMO and ASCO) need to introduce measures to ensure complete reporting of toxicity to serve our patients better

Acknowledgements

Dr. Bostjan Seruga
Ljubljana, Slovenia

Dr. Arnoud Templeton
St. Gallen, Switzerland

Dr. Ian Tannock
Toronto, Canada

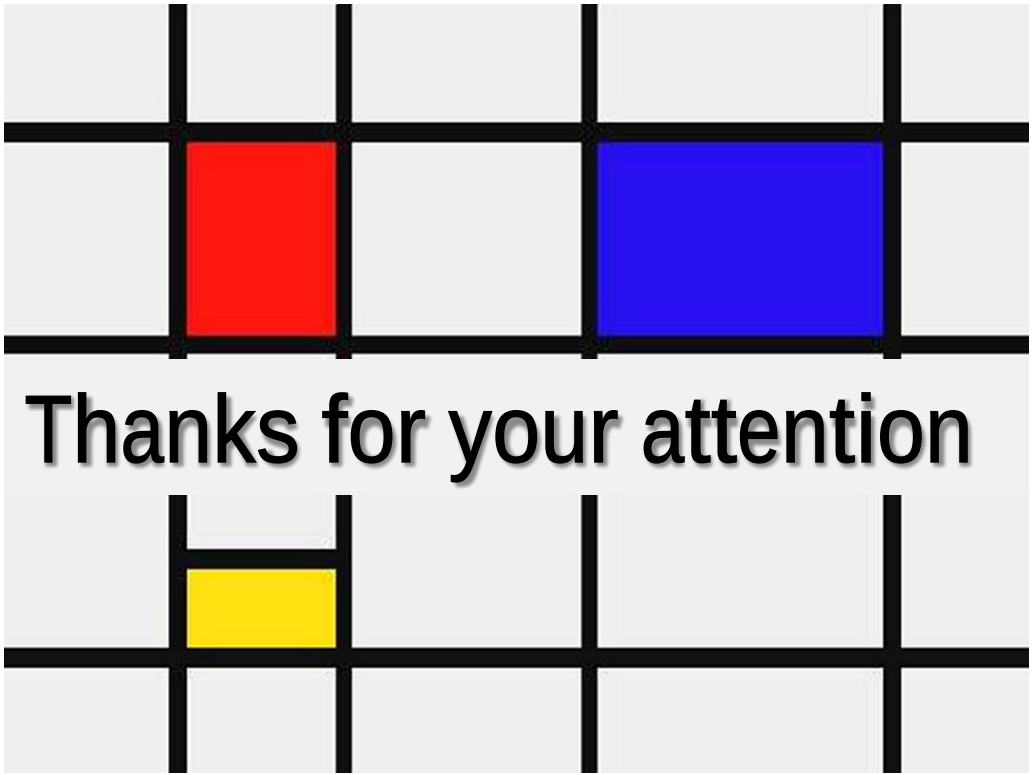
Dr. Elena Elimova
Toronto, Canada

Dr. Amirtha Srikanthan
Toronto, Canada

Dr. Eitan Amir
Toronto, Canada

Dr. Francisco Vera-Badillo
Kingston, Canada

COPENHAGEN 2016 ESMO congress


Thanks for your attention