Definition of dose-limiting toxicity in phase I cancer clinical trials of molecularly targeted agents

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<th>Name</th>
<th>Department</th>
<th>Hospital</th>
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</tr>
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<tbody>
<tr>
<td>Christophe Le Tourneau</td>
<td>Medical Oncology</td>
<td>Institut Curie</td>
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<td>France</td>
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<td>Albiruni A.R. Razak</td>
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<td>Canada</td>
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<td>Australia</td>
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<td>France</td>
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<td>Véronique Diéras</td>
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<td>Institut Curie</td>
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<td>France</td>
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<tr>
<td>Patricia Tresca</td>
<td>Medical Oncology</td>
<td>Institut Curie</td>
<td>Paris</td>
<td>France</td>
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<tr>
<td>Xavier Paoletti</td>
<td>Biostatistics</td>
<td>Institut Curie</td>
<td>Paris</td>
<td>France</td>
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March 7th, 2011 – TAT meeting – Paris
Conflicts of interest

• None to disclose
Introduction

• Assessment of dose-limiting toxicity (DLT) and establishment of the maximum tolerated dose (MTD) constitute the primary endpoint of phase I cancer trials

• Guidelines for the use and reporting of endpoints in phase II/III randomized trials (CONSORT)

• No consensus on the definition of DLT in phase I trials

Begg. JAMA 1996;276:637-9
• Necessity for **standardization** of the definition of DLT in phase I trials?
• Question raised during the 9\textsuperscript{th} NCI/EORTC New Drug Development Symposium in Amsterdam in 1996
• Recommendation was to try standardizing the definition of DLT
• Time of **cytotoxic** agents

Introduction

- Molecularly targeted agents (MTA) display different toxicity profiles
- Efficacy of these agents may not increase with dose
- The **recommended phase II dose** is still largely based on the determination of the MTD and therefore on the assessment of DLT

Postel-Vinay. *BJC* 2009;100:1373-8
Objective

To evaluate how DLT are defined in phase I cancer clinical trials of MTA administered as single agents published over the last decade.
Methods

Selection of trials:

- MTA
- Immunotherapeutics and hormone therapies were excluded
- PO or IV administration
General results

SCOPUS search from January 1\textsuperscript{st}, 2000 to April 18\textsuperscript{th}, 2010
\rightarrow 2,151 references identified

131 phase I cancer clinical trials of molecularly targeted agents

Study of the 131 references

155 phase I cancer clinical trials

Identification of 24 additional references
Items used to define DLTs

Definition of DLT

Items
Items used to define DLTs
Items used to define DLTs
Items used to define DLTs

NON-HEMATOLOGIC
47 categories
Items used to define DLTs

ORGAN-SPECIFIC ITEMS
46 categories
Severity of toxicity

Definition of DLT

Items

Severity
Severity of toxicity

- NCI CTCAE $\geq$G2
- NCI CTCAE $\geq$G3
- NCI CTCAE $\geq$G4
- Not a DLT
- Other classification/threshold
- Not specified
Severity of toxicity

- Non-hematologic items

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**Non-hematologic, nos**

- G2
- G3
- G4
- Not a DLT
- Other
- Not specified

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**Organ-specific items (all)**

- >G2
- >G3
- >G4
- Not a DLT
- Other
- Not specified
Severity of toxicity

- **Organ-specific items**

- **Vomiting**
  - >G2
  - >G3
  - >G4
  - Not a DLT
  - Other
  - Not specified

- **QTc prolongation**
  - >G2
  - >G3
  - >G4
  - Not a DLT
  - Other
  - Not specified

- **Hypersensitivity reaction**
  - >G2
  - >G3
  - >G4
  - Not a DLT
  - Other
  - Not specified

- **Neurotoxicity**
  - >G2
  - >G3
  - >G4
  - Not a DLT
  - Other
  - Not specified
Duration of toxicity

Definition of DLT

- Severity
- Duration

Items
Duration of toxicity

Definition of DLT

Severity

Duration

13%

Items
Reversibility of toxicity

Definition of DLT

- Items
- Severity
- Duration
- Reversibility
Reversibility of toxicity

Definition of DLT

- Items
- Severity
- Duration
- Reversibility

12%
Treatment delay

Definition of DLT

- Items
- Severity
- Duration
- Reversibility
- Treatment delay
Definition of DLT

Items

Severity

Duration

Reversibility

Treatment delay

19%
Dose-intensity reduction

Definition of DLT

- Items
- Severity
- Duration
- Reversibility
- Treatment delay
- Dose-intensity reduction
Dose-intensity reduction

- Definition of DLT
  - Items
  - Severity
  - Duration
  - Reversibility
  - Treatment delay

Dose-intensity reduction: 8%
Influencing factors

Definition of DLT

- Items
- Severity
- Duration
- Reversibility
- Dose-intensity reduction
- Treatment delay
- Route
- Schedule
- Recovery time
- Dose escalation
- First-in-human
- Class of agent
Influencing factors

- Definition of DLT
- Items
- Severity
- Duration
- Reversibility

Factors:
- Dose-intensity reduction
- Treatment delay

Outcomes:
- Schedule
- Recovery time
Final definition of DLTs

METHODS

Initial definition of DLT

Occurrence of DLT

Final definition of DLT

RESULTS
Final definition of DLTs

Proportion of discrepancies between the initial and the final definition of DLT = 25%
Summary

• **Heterogeneity** of the definition of DLT
• Definition of DLT depends on **drug schedule**
• High rate of **discrepancies** between the initial and the final definition of DLT
Recommendations

Definition of DLT

- DLT assessment period
- Severity - absolute - relative to baseline
- Duration - where relevant - grade-specific?
- Reversibility - where relevant - grade-specific?
- Treatment delay
- Dose-intensity reduction