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Defining dose-limiting toxicity for phase 1 trials of molecularly targeted agents: Results of a DLT-TARGETT international survey

Xavier Paoletti [a,*], Christophe Le Tourneau [b], Jaap Verweij [c], Lillian L. Siu [d], Lesley Seymour [e], Sophie Postel-Vinay [j,k], Laurence Collette [f], Elisa Rizzo [f], Percy Ivy [g], David Olmos [h], Christophe Massard [j,k], Denis Lacombe [f], Stan B. Kaye [i], Jean-Charles Soria [j,k]

[a] *Institut Curie, Biostatistics dpt & INSERM U900, Paris, France*
[b] *Institut Curie, Medical Oncology dpt & INSERM U900, Paris, France*
[c] *Erasmus University MC, Department of Medical Oncology, Rotterdam, The Netherlands*
[d] *Princess Margaret Hospital, Toronto, Canada*
[e] *National Cancer Institute of Canada Clinical Trials Group & Queen's University, Kingston, Canada*
[f] *European Organisation for Research and Treatment of Cancer Headquarter, Brussels, Belgium*
[g] *National Cancer Institute and Cancer Therapy Evaluation Program, Rockville, USA*
[h] *Prostate Cancer Clinical Research Unit, Clinical Research Programme Spanish National Cancer Research Centre (CNIO), Madrid, Spain*
[i] *Royal Marsden Hospital/Institute for Cancer Research, Drug Development Unit, Sutton, UK*
[j] *Gustave Roussy Cancer Campus, DITEP (Département d'Innovations Thérapeutiques et Essais Précoces), Villejuif, France*
[k] *Université Paris-Sud XI, Orsay, France*

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Abstract ***Introduction:*** It is increasingly clear that definitions of dose-limiting toxicity (DLT) established for phase 1 trials of cytotoxic agents are not suitable for molecularly targeted agents because of specific toxicity profiles. An international survey collected expertise on the definition of DLT, as part of an initiative aimed at presenting new guidelines for phase 1 trials of targeted agents.

Methods: A 15-question survey was sent to corresponding authors of phase 1 reports. Questions involved: duration of the DLT assessment period, incorporation of specific grade 1 (G1) or G2 toxicity and their minimum duration to qualify as DLT, exclusion of specific G3 and inclusion of dose modification/delay.

* *Corresponding author:* Address: Biostatistics dpt & INSERM U900, Institut Curie, 26 rue d'Ulm, 75005 Paris, France. Tel.: +33 1 56 24 56 47; fax: +33 1 40 20 10 40.
E-mail address: xavier.paoletti@curie.fr (X. Paoletti).

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Results: Among the 400 investigators contacted, 93 replied of whom 65 completed the questionnaires. A total of 87% opted for an extended DLT assessment period beyond cycle 1, with the proviso not to delay patient accrual. Reanalysis at the end of the study of all safety data was proposed in order to recommend the phase 2 dose. Most respondents (92%) suggested including dose modification in the definition of DLT when dose intensity was decreased to 70%. Whilst moderate toxicity was deemed relevant by 70%, the G1/2 toxicities selected to define DLT however varied.

Conclusion: The majority of experts favoured a longer DLT assessment period as well as incorporation of specific G2 toxicities into the DLT definition. However, no clear consensus existed on a re-definition of DLT. Therefore analyses of a large international data warehouse were also used to develop guidelines presented in a companion paper.

1. Introduction

The main objectives of phase 1 trials are to identify the toxicity profile and the optimal dose of the agent for further studies. The latter is complicated due to the usually limited anti-tumour activity observed in the very advanced disease stage of patients treated in early phase trials. It is therefore common practice to use the maximum tolerated dose (MTD) to define the optimal dose. The MTD itself is determined by dose-limiting toxicity (DLT), i.e. toxicity-severity that limits the possibility to treat a patient at the planned dose. DLT is traditionally defined as any grade 3–4 non-haematological or grade 4 haematological toxicity at least possibly related to the treatment, occurring during the first cycle of treatment. Some adjustments to this definition have been widely accepted, such as febrile neutropenia, or neutropenia grade 4 lasting more than 7 days or abnormal laboratory values rated as a DLT only in the presence of clinical symptoms.

However, the classical definition of DLT for cytotoxic agents raises concerns in phase 1 trials of molecularly targeted agents (MTA) because of their specific toxicity profiles [1] and often continuous and oral administration. For instance, we recently reported that 50% of patients receiving MTAs experienced their worst toxicity after cycle 1 [2]. Others reported the possible impact of moderate and even mild but longer lasting side-effects on the tolerability of an agent [3]. For instance, treatment induced grade 2 diarrhoea or facial cutaneous rashes are largely incompatible with social life and markedly decrease quality of life. In turn, these side-effects may have direct consequences on compliance and can result in poor clinical treatment adherence even for very active drugs such as imatinib in GIST [4] or tamoxifen in breast cancer [5].

A review of published dose finding trials of monotherapy MTA [6] revealed that 25% of studies reported some NCI CTCAE grade 2 toxicities as DLT. About 10% of the reviewed trials also introduced dose reductions or the inability to timely start a new cycle of treatment due to treatment-related toxicity into the definition of DLT. A marked heterogeneity was observed within the side-effects integrated in the definition of DLT. More than 54 different 'organ-specific items' were identified but most of them were applied in a very low frequency. Finally, 25% of these trials modified the definition of the main end-point during the conduct of the trial.

How should DLT be re-defined in the era of MTAs? Although the toxicity profile and DLT identified in each trial are specific to each agent/schedule/administration, there should be some common definition or consensus of what is considered to be tolerable or not. Variations in the definition of DLT make comparison of phase 1 reports inconsistent and create heterogeneity in the definition of the recommended dose for phase 2 studies (RP2D). Standardising the evaluation criteria in phase 1 trials of MTA appears desirable in line with what has been done for phase 2 trials [7] as well as for phase 3 trials for several tumour types [8].

In order to gain further insight into existing opinions on DLT for MTA phase 1 trials and to inform a major initiative, aimed at providing new recommendations for the conduct and analysis of phase 1 trials of MTAs [9], an international survey was performed by the European Organisation for Research and Treatment of Cancer (EORTC)-led DLT-TARGETT research group.

2. Methods

A 15-question electronic survey was developed to investigate four possible components of the definition of dose-limiting toxicity: (a) incorporation of lower grade 1 or 2 side-effects and their minimum duration to qualify as DLT, (b) duration of the DLT assessment period, (c) inclusion of dose modification or dose delay into the definition of DLT and (d) inclusion of the assessment of symptoms at baseline to evaluate worsening of side-effects and not only their absolute grade. Considering the potential impact of dosing schedule on treatment administration, we asked the respondents to consider two scenarios: continuous daily oral administration and 1-day intravenous dosing every three weeks. For each set of questions, there was an open text field for comments. The questionnaire was reviewed and tested by J-C.S., C.L.T., D.L., S.K. and J.V. (supplementary material).