European Journal of Cancer 86 (2017) 275–284

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Revisiting the definition of dose-limiting toxicities in paediatric oncology phase I clinical trials: An analysis from the Innovative Therapies for Children with Cancer Consortium

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Received 1 August 2017; accepted 13 September 2017

KEYWORDS
Dose-limiting toxicity;
Recommended phase II dose;
Maximum tolerated dose;
Dose-finding clinical trials;
Early drug development;
Paediatrics;
Oncology

Abstract ***Background:*** Dose-escalation trials aim to identify the maximum tolerated dose and, importantly, the recommended phase II dose (RP2D) and rely on the occurrence of dose-limiting toxicities (DLTs) during the first treatment cycle. Molecularly targeted agents (MTAs) often follow continuous and prolonged administrations, displaying a distinct toxicity profile compared to conventional chemotherapeutics, and classical DLT criteria might not be appropriate to evaluate MTAs' toxicity. We investigated this issue in children.
Methods: The Innovative Therapies for Children with Cancer Consortium (ITCC) phase I trials of novel anticancer agents between 2004 and 2015 were analysed. Data from investigational product, trial design, items defining DLT/RP2D were extracted. A survey on dose-escalation process, DLTs and RP2D definition was conducted among the ITCC clinical trials committee members.
Results: Thirteen phase I trials with 15 dose-escalation cohorts were analysed. They explored 11 MTAs and 2 novel cytotoxics; 12 evaluated DLT during cycle 1. Definition of DLT was

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https://doi.org/10.1016/j.ejca.2017.09.015

heterogeneous: Grade III–IV haematologic toxicities that were transient or asymptomatic and grade III–IV non-haematological toxicities manageable with adequate supportive care were often excluded, whereas some included dose intensity or grade II toxicities into DLT. None of the studies considered delayed toxicity into the RP2D definition.

Conclusion: DLTs should be homogeneously defined across trials, limiting the number of exceptions due to specific toxicities. Dose escalation should still be based on safety data from cycle 1, but delayed and overall toxicities, pharmacokinetic parameters and pharmacodynamic data should be considered to refine the final RP2D. The evaluation of long-term toxicity in the developing child cannot be adequately addressed in early trials.

1. Introduction

The ultimate objective of phase I oncology early-phase clinical trials is to determine the recommended phase II dose (RP2D) of new anticancer drugs. The primary endpoint to define the maximum tolerated dose (MTD) and RP2D has been the proportion of dose-limiting toxicities (DLTs) during a first treatment cycle. DLTs are usually pre-defined as any non-haematologic grade III–IV toxicity, excluding few manageable events or grade IV haematological toxicity [1]. A main difference in paediatric trials had been the allowance of more severe haematological toxicities in children based on their acceptance in front-line protocols [2,3]. This definition had been set up at the time of cytotoxic chemotherapies, frequently administered in a limited number of cycles and with recovery periods. However, the introduction of molecularly targeted agents (MTAs) has challenged this definition due to their distinct mechanisms of action, different toxicity profiles and the frequently continuous and prolonged administration [4], and many aspects of early trial design have to be adapted [5].

Grade III–IV toxicities are usually considered as DLTs, although some manageable toxicities may be excluded, such as nausea/vomiting with insufficient supportive care or agent-specific toxicity that may be considered acceptable [6]. The evaluation of MTAs introduced the consideration of lower grade toxicities interfering with normal life activity [6]. Furthermore, dose-intensity modifications or dosing-delays due to toxicity may also be incorporated into the definition of DLT. No clear consensus exists with regard to the DLT definition in adult phase I trials [7].

Traditionally, DLTs are evaluated during the first cycle. There is increasing evidence of delayed toxicity beyond the first cycle for some MTAs [8]. The DLT-TARGETT group recommended to consider severe toxicity at any cycle for defining the RP2D in adults based on an analysis of the type, grade and duration of toxicities observed in 54 dose-finding trials, enrolling 2084 adults exploring 35 MTAs [9]. An international medical oncologist and statistician expert survey revealed that the majority were in favour of considering a longer DLT assessment period and incorporating specific grade II toxicities into the DLT definition, as well as considering worsening from baseline adverse events and a minimum dose intensity of 70% to refine the definition of the final RP2D [6]. The differential aspects in paediatric drug development compared to adults, mainly safety for developmental organs, pharmacology and trial organisational aspects, make necessary an analysis and consensus about the definition of DLTs in children.

We describe how DLTs have been defined in several paediatric phase I dose-finding clinical trials that run within the Innovative Therapies for Children with Cancer Consortium (ITCC), present results from a survey conducted among the ITCC Clinical Trials Committee (ITCC-CTC) members, and propose modifications of the current DLT and RP2D definitions for paediatric oncology phase I trials. A standard definition of the DLT is mandatory for comparative interpretation and to design efficient combination trials.

2. Material and methods

2.1. Clinical trials and data extraction

All phase I dose-finding trials of MTAs or novel cytotoxic agents for children with solid tumours, which run within the ITCC from 2004 to 2015 were analysed. Trials permitting inclusion of patients with leukaemia besides those with solid tumours were included.

Data extracted from each trial were as follows: agent's mechanism of action, single/combination study, administration route, dosing schedule, dose levels and dose-escalation method. Each MTA was classified based on its presumed target. Dosing schedule was divided depending on the number of dosing days per cycle. All items used to define the DLTs and RP2D were recorded.

2.2. Survey

A survey was conducted among the 11 paediatric haemato-oncologists and the statistician ITCC-CTC members (www.itcc-consortium.org). The questions were adapted from the recommendations elaborated by the DLT-TARGETT group [9]. One specific paediatric