ESR Researcher Project: Non-technical Summary

"Statistical methods for phase I/II trials of molecularly targeted agents in oncology"

Part 3: "Impact of time on cumulative toxicities in phase I trials of molecularly targeted agents: A meta-analysis study of the DLT-targett"

Team: Maria-Athina Altzerinakou, Xavier Paoletti

Objective

The purpose of this work is to provide an overview of the risk of severe toxicity per treatment cycle and the cumulative toxicity risk over 6 treatment cycles. We estimated these risks on 26 phase I clinical trials of molecularly targeted agents (MTAs) administered as single agents, from the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI). A complementary objective is to analyze how time can affect severe toxicity occurrence. Using those data, we provide a nomogram that relates various risks of severe toxicity at cycle 1 with what can be expected over up to six cycles of treatment.

Motivation of this project

Phase I trials traditionally report the maximum tolerated dose (MTD), that is defined based on the dose limiting toxicities (DLTs) observed during the first treatment cycle. The MTD and the recommended phase II dose (RP2D) are often associated with 20% to 33% of DLTs in the first cycle (21 or 28 days). However, the development of MTAs in oncology challenges this definition. Recently, the European Medicine Agency (EMA) followed a report from the European Organization for Research and Treatment of Cancer -led DLT-TARGETT group[1] and stated that "in contrast to cytotoxic chemotherapy, MTAs are typically administered continuously and the toxicity profiles tend to differ so that DLTs may occur after multiple cycles of therapy. This is of importance for the RP2D in cases where tolerability and toxicity guide dose selection, and may require alternative strategies with regard to definition of DLT and MTD." This guideline then recommends "Broader DLT definitions with longer DLT observation periods may therefore be relevant to consider. A distinction between cycle 1

acute toxicity, prolonged toxicity impacting on tolerability and late severe toxicity may be informative. Adverse events (AEs) should therefore always be reported by treatment cycle and the RP2D should be based on an integrated assessment of likely adverse reactions[2]". This requirement is even stronger with immune-toxic side effects, for which the median time varies from 5 to 15 weeks, which is beyond the usual DLT assessment period[3]. However, whilst an acceptable rate of acute toxicity is rather well-defined to guide dose-escalation, no reference of an acceptable cumulative and per-cycle rate of toxicity has been provided so far to guide RP2D recommendation. In particular, when 20% of acute toxicity is observed at the MTD, what should we expect over several treatment cycles?

Findings

In this work we have investigated the association of time, i.e. the treatment cycle, with the probability of having a severe toxicity. The probability of having a severe toxicity, for patients treated at the MTD, was 27% in cycle 1 and then it decreases for each successive cycle. At the MTD there was 53% cumulative probability of severe toxicity, at the end of cycle 6, which was a lot higher than the 20%-33% usually targeted in cycle 1 for the determination of the MTD. This number increased to 80%, for doses exceeding the MTD, leading to highly toxic events. At the MTD, non-hematologic toxicities accounted for 35% of the overall cumulative toxicity, whereas hematologic or both non-hematologic and hematologic toxicities accounted for 18%.

Recommendations

For phase I designs we strongly believe that 3-6 cycles should be considered to better refine the identification of the RP2D. Grade 3, 4, or 5 toxicity rates of 20% to 30% on the 1st treatment cycle were associated with 44% to 63% of severe toxicity at the end of the 6th treatment cycle (Table 1). A reasonable cumulative target could be 40%-45% over 6 cycles, so as to avoid undertreating or exposing patients to highly toxic doses. Moreover, we have shown the significance of time effect on the severe toxicity rate (often a reduction in the per-cycle rate of toxicity throughout the treatment). Re-evaluation of the cumulative probability of severe toxicity would fit nicely in the objectives of expansion cohorts that have become quite popular in the last years[4]. Nevertheless, toxicity is only one component of the overall evaluation of the optimal dose. Activity data, pharmacokinetic data or biomarker measurements are also keys to refine the dose to be pushed forward. A careful analysis of all

collected data should improve the design of phase I trials of MTAs and avoid re-evaluation of accepted doses in subsequent phases.

Table 1. Nomogram. Cumulative probability of severe toxicity, assuming that toxicity in the first cycle ranges between 5% and 35%.

Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
0.050	0.078	0.093	0.101	0.105	0.107
0.100	0.157	0.189	0.207	0.217	0.221
0.150	0.235	0.284	0.311	0.326	0.334
0.200	0.311	0.374	0.410	0.430	0.441
0.250	0.384	0.460	0.503	0.527	0.541
0.300	0.455	0.539	0.587	0.615	0.630
0.350	0.522	0.613	0.664	0.693	0.710

References

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2. European Medicines Agency: Draft Guideline on the evaluation of anticancer medicinal products in man. 2016

3. Champiat S, Lambotte O, Barreau E, et al: Management of immune checkpoint blockade dysimmune toxicities: A collaborative position paper. Ann Oncol 27:559–574, 2016

4. Dahlberg SE, Shapiro GI, Clark JW, et al: Evaluation of statistical designs in phase i expansion cohorts: The Dana-Farber/Harvard cancer center experience. J Natl Cancer Inst 106, 2014

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.