Cumulative risk of toxicity in phase I trials of targeted therapies: What to expect at the recommended phase II dose?

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Background

The European Medicine Agency stated in a draft Guideline on the evaluation of anticancer medicinal products in man that "*in contrast to cytotoxic chemotherapy, targeted therapies are typically administered continuously and the toxicity profiles tend to differ so that dose limiting toxicities (DLTs) may occur after multiple cycles of therapy. This is of importance for the recommended phase II dose (RP2D) and alternative strategies with regard to definition of DLT and maximum tolerated dose (MTD) might be necessary*".

Objective: We investigated the risk of first-severe toxicity per treatment cycle and the corresponding cumulative incidence (CI) over up to six treatment cycles.

Methods

Trials: 27 phase I trials of single targeted therapies conducted by the National Cancer Institute

Patients: 963 adults with solid tumors or lymphomas and at least 1 cycle of therapy

Information: toxicities per type, treatment cycle, grade, MTD, dose assigned

Analysis: Estimation of the per-cycle risk of severe toxicity and the CI over 6 cycles with the corresponding prediction intervals (PI) using a sequential probit model that estimates the

probability of experiencing an event at time *s* is given that the event did not occur at time *s-1*

$$P(S = s|S > s-1) = 1 - \Phi(a_0 + a_1(s-1)) = 1 - \Phi(s),$$

where $s \in \{1, \dots, k\}$, and k is the total number of treatment cycles. $\Phi(s)$ is the cumulative normal distribution at time s, a_0 the model intercept and a_1 the parameter for the cycle effect.

Results

At the MTD: risk of severe toxicity in **cycle 1** was 27.3% [PI: 22.6% to 32.1%] → **cycle 6** (CI) 52.9% [PI: 43.7% to 61.5%]
Below the MTD: risk of severe toxicity in **cycle 1** was 12.1% [PI: 9.7% to 15.2%] → **cycle 6** (CI) 33.3% [PI: 27% to 40.5%]
Above the MTD: risk of severe toxicity in **cycle 1** was 48.9% [PI: 40.4% to 56.7%] → **cycle 6** (CI) 80.1% [PI: 70.1% to 88.7%]

Figure 1: a) Risk of severe toxicity for patients who are still at risk, for groups of patients treated at doses below, above and at the MTD. b) Cumulative incidence of severe toxicity, for groups of patients treated at doses below, above and at the MTD.

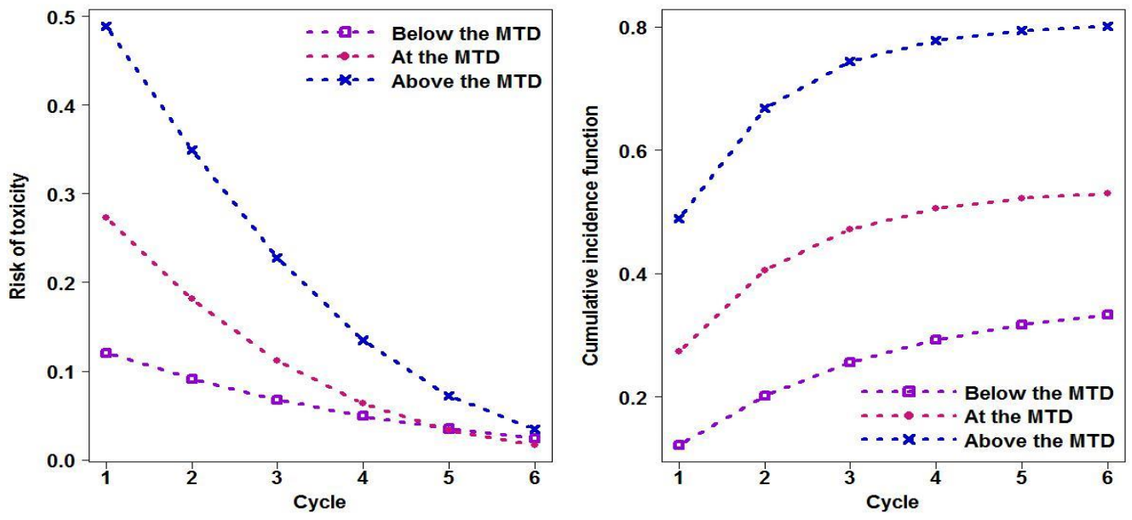

Table 1. Cumulative incidence of severe toxicity, assuming that risk of severe toxicity in the first cycle ranges between 5% and 35%.

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

Conclusion

This is the first study to evaluate the cumulative incidence of toxicity. For patients assigned at the MTD, the CI at cycle 6 reached 53%, which is much higher than the 20%-33% usually targeted for the determination of the MTD and the RP2D.
For future phase I trials for targeted therapies we propose:

1) 3-6 cycles for the RP2D evaluation
2) 40%-45% cumulative target over 6 cycles
3) re-evaluation of CI of toxicity in expansion cohorts

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