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Article

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Cumulative Toxicity in Targeted Therapies: What to Expect at the Recommended Phase II Dose

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Abstract

Background: In the era of molecularly targeted agents (MTAs), it is recommended to account for toxicity over several cycles to identify the recommended phase II dose (RP2D). We investigated the relationship between the risk of toxicity at cycle 1 and the cumulative incidence of toxicity over subsequent cycles in trials of single MTAs.
Methods: On individual patient data from 26 phase I clinical trials of single MTAs provided by the National Cancer Institute, we estimated the probability of first-severe toxicity per treatment cycle as well as the cumulative incidence at, below, and above the maximum tolerated dose (MTD). Toxicity was further subclassified into nonhematologic and hematologic. A prediction table was developed to estimate the cumulative incidence up to six cycles based on the toxicity rate observed in the first cycle.
Results: Overall, 942 patients were included. For patients treated at the MTD, the probability of first-severe toxicity decreased from 24.8% (95% prediction interval [PI] = 20.3% to 32.9%) to 2.2% (95% PI = 0.1% to 7.7%) from cycle 1 to 6, whereas the cumulative incidence of toxicity reached 51.7% (95% PI = 40.5% to 66.3%) after six cycles. Toxicity rates ranging from 20.0% to 30.0% in the first cycle were associated with 46.8% (95% PI = 39.5% to 54.2%) and 65.8% (95% PI = 57.7% to 73.1%) cumulative incidence after six cycles.
Conclusion: This study examined the risk of severe toxicity over time of single MTAs. The cumulative incidence of toxicity at the MTD was higher than the usually accepted toxicity targets, challenging the definition of the RP2D of MTAs. The prediction table may help calibrate the target rate at the RP2D.

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In phase I clinical trials the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) are often selected as the doses associated with 20% to 33% of dose-limiting toxicities (DLTs) in the first cycle (usually lasting 21 or 28 days). However, the development of molecularly targeted agents (MTAs) in oncology has challenged this definition. Recently, the European Medicine Agency followed a report from the European Organization for Research and Treatment of Cancer (EORTC)-led DLT and Toxicity Assessment Recommendation Group for Early Trials of Targeted Therapies (TARGETT) group (1) and stated in a draft guideline on the evaluation of anticancer medicinal products in man (2):

> 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.

The same 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).

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This requirement is also relevant for immune-toxic side effects, for which the median time varies from 5 to 15 weeks, which is beyond the usual DLT assessment period (3). In 1997, Simon et al. (4) reported the per-cycle and the cumulative risk of severe toxicity on 20 phase I studies of chemotherapeutic agents, but no such information exists regarding the new classes of agents. Although the target rate of acute toxicity for guiding dose escalation is rather well-defined, when it comes to guiding the RP2D recommendation, no such definition of an acceptable cumulative and per-cycle rate of toxicity exists. In particular, when 20% of acute toxicity is observed at the MTD, what cumulative toxicity rate should we expect over several treatment cycles?

The purpose of the present work is to provide an overview of the risk of first-severe toxicity per treatment cycle and of the corresponding cumulative incidence of up to six treatment cycles. The cumulative incidence describes the risk of having a severe toxicity from the beginning of the trial up to a certain time point, if a patient were to be treated up to this time point. We estimated these risks based on 26 phase I clinical trials of MTAs administered as single agents from the Cancer Therapy Evaluation Program (CTEP) of the US National Cancer Institute (NCI). A secondary objective is to document the relation between time-on-treatment and the risk of severe toxicity.

Methods

Trials and Patients' Characteristics

This retrospective analysis included single molecular targeted agent phase I studies that reached the MTD and were carried out within the NCI CTEP. Collected trials dated from 1997 to 2013. All adult patients with solid tumors or lymphomas who received at least one cycle of treatment were eligible for the analysis. Individual patient data was provided to the DLT-TARGETT group. Data management and standardization are described elsewhere (1). Doses were measured in various units across trials. For standardization, doses were divided by the MTD of the corresponding trial, leading to a continuous variable that takes values greater than zero, with 1 indicating patients that were treated to the trial's MTD (Supplementary Methods, available online).

Toxicity Data

All AEs at least potentially related to the treatment that occurred during the first six treatment cycles and that were not present at baseline at the same or higher grade were extracted. Toxicity severity was harmonized across studies using the NCI Common Terminology Criteria of Adverse Events, version 3.0 (5). Severe toxicities (grades 3, 4, or 5) were further divided into hematologic and nonhematologic, according to the Medical Dictionary for Regulatory Activities 15 (6).

Statistical Analysis

A treatment cycle as defined per protocol was used as time unit, irrespectively of the duration in days (Table 1). As DLTs were recorded only for the first treatment cycle, the event of interest was the time-to-first severe toxicity (grades 3, 4 or 5). The probability of having a severe toxicity at each treatment cycle (or per-cycle risk) was estimated for those still at risk at the cycle initiation. The cumulative incidence of severe toxicity of up to six cycles of treatment was estimated using a cumulative probit model (7), with a random effect at the trial level to take into account the variability across trials. All prediction intervals were obtained from the bias-corrected bootstrap technique.

Table 1. Descriptive characteristics of patients (n = 942) from the 26 studies included in the analysis*

Characteristics	No. (%)
Type of agent	
Antiangiogenic agent	2 (7.7)
Antivascular agent	1 (3.8)
CDK inhibitor	2 (7.7)
HDAC inhibitor	3 (11.5)
HSP inhibitor	6 (23.1)
Immunotherapy	3 (11.5)
Monoclonal antibody	3 (11.5)
Proteasome inhibitor	2 (7.7)
Other	4 (15.4)
Administration route	
Intravenous	21 (80.8)
Oral	4 (15.4)
Intraperitoneal	1 (3.9)
Duration of treatment cycle, days	
14	2 (7.7)
21	6 (23.1)
28	15 (57.7)
42	3 (11.5)
Patients per cycle	
Cycle 1	942 (100)
Cycle 2	548 (58.2)
Cycle 3	236 (25.1)
Cycle 4	155 (16.5)
Cycle 5	93 (9.9)
Cycle 6	68 (7.2)
Patients per group of doses	
Below the MTD	490 (52.0)
At the MTD	289 (30.7)
Above the MTD	163 (17.3)

*CDK = cyclin-dependent kinase; HDAC = histone deacetylase; HSP = heat shock proteins; MTD, maximum tolerated dose.

In a first analysis, the per-cycle risk of severe toxicity and the cumulative incidences were estimated separately in patients treated at doses below, above, and at the MTD. Let i and j denote the individual and trial, respectively. The probability of experiencing an event at time s given that the event did not occur at time $s-1$ is given by

$$P(S_{ij} = s | S_{ij} > s-1, \quad U_j) = \Phi\left(a_0 + a_1 c_{i\ (s-1)} + \ U_j\right), \qquad [1]$$

where $c_{i\ (s-1)} \in \{1, \ldots, k$ denotes the cycle and $k = 6$ is the total number of treatment cycles. $\Phi()$ is the cumulative normal distribution, a_0 the model intercept, and a_1 the parameter for the cycle effect. U_j is the random effect on the trial level that follows a normal distribution $U_j \sim N(0, \sigma^2)$ and captures the trial's heterogeneity in terms of overall risk of toxicity. Then, Model 1 was also adjusted on the dose as follows:

$$P(S_{ij} = s | S_{ij} > s-1, \quad U_j) = \Phi\left(a_0 + a_1 c_{i\ (s-1)} + \ a_2 d_i + \ U_j\right), \qquad [2]$$

where d_i is the dose attributed to the i^{th} individual and a_2 the parameter for the dose effect. Model 2 was used to develop a prediction table of the cumulative incidence over six cycles from the risk of severe toxicity observed at cycle 1. For each value of the risk of severe toxicity in the first cycle, the corresponding dose was identified, which in turn provided us with the

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cumulative risk of severe toxicity over two to six cycles of treatment. Both dose and cycle were included as continuous variables after assessment of the model residuals.

To test for statistically significant differences among agents, on the alpha level of 5%, Model 2 was further adjusted on the type of agent (cyclin-dependent kinase [CDK] inhibitor, histone deacetylase [HDAC] inhibitor, immunotherapy, monoclonal antibody, proteasome inhibitor, poly adenosine diphosphate [ADP] ribose polymerase [PARP] inhibitor, and others), and the associated parameters were tested (Supplementary Methods, Model 3, available online).

We conducted an external validation on five independent phase I trials of single MTAs, also provided to the DLT-TARGETT group. Studies with the largest total number of cycles were selected; they covered a broad range of sample sizes (39, 47, 53, 68, and 110 patients). For these studies, we estimated the cumulative incidence of severe toxicity at the MTD using Model 2, and we compared it to the risk of toxicity predicted from the risk at the first cycle, as in the prediction table.

Next, the cumulative incidence of any type of severe toxicity was split into two competing events, time-to-first hematologic and time-to-first nonhematologic severe toxicity using the competing risks framework (8), for the three dose subgroups. For this analysis, whenever both hematologic and nonhematologic toxicities were observed for a patient in the same treatment cycle, the case was classified with hematologic toxicities. Patients who progressed without severe toxicity were censored. The cumulative incidences were not adjusted for the study.

As sensitivity analyses, the analysis was repeated, this time assigning cases when both hematologic and nonhematologic toxicity occurred in the same cycle with nonhematologic toxicities. Additionally, we repeated the main competing risks analysis after exclusion of grade 3 hematologic toxicities from the definition of severe toxicities. All analyses were performed using the Rv3.4.3 software (9).

Results

Trial Characteristics

The 26 eligible trials enrolled a total of 942 patients with solid tumors or lymphomas (Figure 1). Among the trials, two of them (7.7%) tested antiangiogenic agents; one (3.8%), antivascular agents; two (7.7%), CDK inhibitors; three (11.5%), HDAC inhibitors; six (23.1%), heat shock protein (HSP) inhibitors; three (11.5%), immunotherapy; three (11.5%), monoclonal antibodies; two (7.7%), proteasome inhibitors; and four (15.4%), other classes of agents.

Treatment Administration

Of the 942 patients, 58.2% received a second cycle, and 25.1%, 16.5%, 9.9%, and 7.2% received a third to a sixth cycle, respectively (Table 1). A total of 289 patients (30.7%) were assigned to the dose later defined as the trial MTD. Of those 289 patients, 20 (6.9%) received six cycles (Figure 2A). A total of 490 (52%) and 163 patients (17.3%) were treated below and above the MTD, respectively.

Toxicity Outcomes

Over the six treatment cycles, 35.3% of patients had at least one event of severe toxicity. Among these patients, 61.0% had a severe nonhematologic toxicity, 27.3% had a severe hematologic toxicity, and 11.7% had both severe nonhematologic and hematologic toxicities at the same cycle (Figure 2B). Nonhematologic toxicities included 39.0% gastrointestinal disorders, 10.0% general disorders, 7.0% central nervous system disorders, 4.0% dermatological, 3.0% liver, 3.0% glycemia, 3.0% vascular disorders, and others. During cycle 1, 15.1% of patients had a first nonhematologic toxicity, 6.7% a first hematologic toxicity, and 3.5% had both of them; contrary to cycle 6 during which first toxicities of each type were recorded in 1.5% of patients still at risk. Of the overall severe toxicity, 13% were abnormal laboratory values of biological characteristics without clinical symptoms.

Time to First-Severe Toxicity

Figure 3A depicts the per-cycle risk of first-severe toxicity that decreased with treatment cycle. For patients allocated to the MTD, the probability of a severe toxicity at the first treatment cycle was 24.8% (95% prediction interval [PI] = 20.3% to 32.9%), and this number monotonically decreased from 17.1% (95% PI = 13.6% to 23.6%) at cycle 2 to 2.2% (95% PI = 0.1% to 7.7%) at cycle 6 (see Supplementary Table 1 for risk and cumulative incidence, available online). The cumulative incidence of severe toxicity for patients treated at the MTD increased from 24.8% (95% PI = 20.3% to 32.9%) at cycle 1 to 51.7% (95% PI = 40.5% to 66.3%) at cycle 6. Of note, 51.7% represents the risk that would have been observed had patients received six treatment cycles. For patients assigned to doses below the MTD, the cumulative incidence increased from 11.3% (95% PI = 9.5% to 16.4%) to 31.2% (95% PI: 26.1% to 43.7%) and for doses above the MTD from 49.3% (95% PI = 39.6% to 58.1%) to 85.1% (95% PI = 66.8% to 94.2%) (Figure 3B).

The predictions of the cumulative incidence at cycle 6 obtained from the risk at cycle 1 are given in Table 2. Please see Supplementary Table 2 (available online) for parameter estimates. A 5.0% risk of severe toxicity in the first cycle of treatment was associated with a predicted cumulative incidence of 11.5% (95% PI = 9.3% to 14.4%) over six cycles. Most importantly, for the traditionally accepted values of 20% and 30% of severe toxicity in cycle 1, targeted to identify the RP2D, the predicted cumulative incidences at cycle 6 were 46.8% (95% PI = 39.5% to 54.2%) and 65.8% (95% PI = 57.7% to 73.1%), respectively.

Patients treated with HDAC inhibitors and immunotherapy had a statistically significant different risk of severe toxicity compared to those treated with HSP inhibitors (null value not included in the 95% confidence interval [CI]) (Supplementary Table 2, available online for parameter estimates and 95% CIs). Indicatively, the cumulative incidence of severe toxicity for patients treated at the MTD at cycle 6 was 82.6% (95% PI = 69.4% to 90.9%) and 86.2% (95% PI = 67.8% to 95.7%) for HDAC inhibitors and immunotherapy, respectively (data not shown).

Results of the external validation are displayed in Supplementary Figure 1 (available online). Interestingly, the risk of severe toxicity at cycle 1 at the MTD ranged from 7% to 30% covering various situations. For all but one study, the predictions of Table 2 included the actual cumulative incidence of severe toxicity (Supplementary Figure 1A, available online).

Cumulative Incidence of Hematologic and Nonhematologic Severe Toxicity

For patients assigned to the MTD, the cumulative incidence of nonhematologic severe toxicity by the end of cycle 6 was 34.8% (95% PI = 26.6% to 44.1%) and was almost twice as high as that of having hematologic severe toxicity (18.2%, 95% PI = 12.8% to

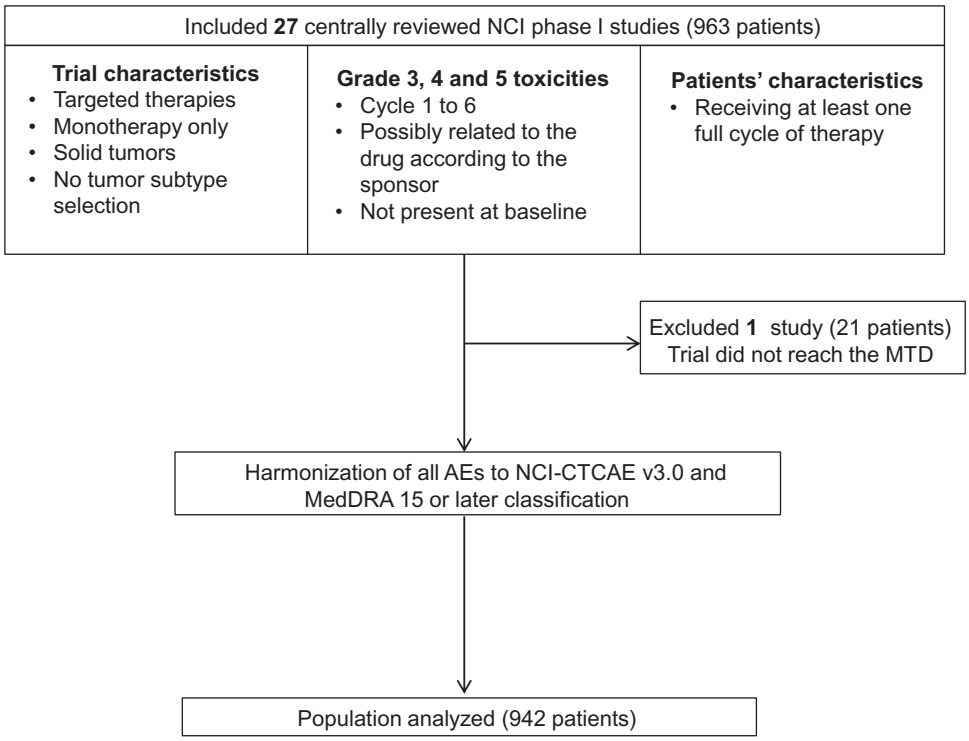

Figure 1. Flowchart of the study. Overview of the study design and trial selection. AE = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; MTD = maximum tolerated dose; NCI = National Cancer Institute; NCICTCAE = NCI Common Terminology Criteria for Adverse Events.

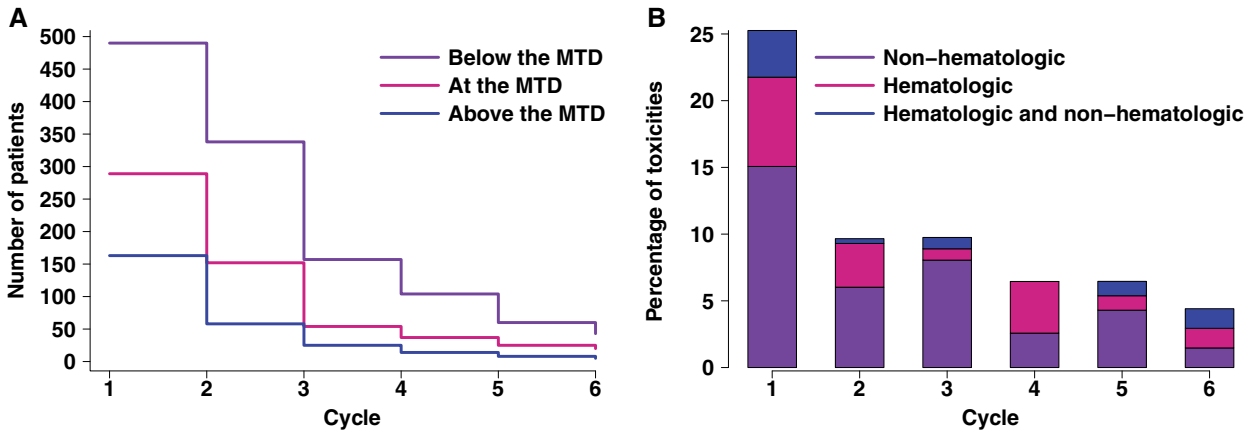

Figure 2. Patient characteristics per dose-subgroup and type of severe toxicity over six treatment cycles. **A**) Number of patients at each treatment cycle, for groups treated at doses below, above, and at the MTD. **B**) Percentage of a first nonhematologic, hematologic, or both hematologic and nonhematologic severe toxicity, over six treatment cycles. Percentages were calculated for patients who were still at risk at cycle initiation. MTD = maximum tolerated dose.

23.9%) (Figure 4B and Supplementary Table 3, available online). Similarly, for patients below the MTD, the cumulative incidence of nonhematologic severe toxicity reached 20.2% (95% PI = 15.2% to 26.1%) versus 13.1% (95% PI = 8.8% to 18.7%) for hematologic toxicity. For patients above the MTD, it reached 45.6% (95% PI = 36.4% to 55.1%) for nonhematologic severe toxicity and 34.2% (95% PI = 24.8% to 44.5%) for hematologic toxicity (Figure 4, A and C).

Reclassification of mixed cases in the group of nonhematologic toxicities led, as expected, to inflation in the cumulative incidence of nonhematologic toxicity (Supplementary Table 4, available online). At the MTD, it reached 39.2% (95% PI = 31.2% to 48.9%) and 13.8% (95% PI = 9.2% to 19.6%) for nonhematologic and hematologic severe toxicity, respectively. Exclusion of grade 3 hematologic toxicities from the definition of severe toxicity led to similar cumulative incidences of any type of toxicity (Supplementary Table 5, available online). However, the cumulative incidences of strictly nonhematologic and hematologic toxicity were higher and lower respectively. At cycle 6, the cumulative incidence of nonhematologic toxicity was six times higher than that of hematologic toxicity.

Discussion

We investigated the association of time-on-treatment—that is, the number of treatment cycles—with the probability of severe

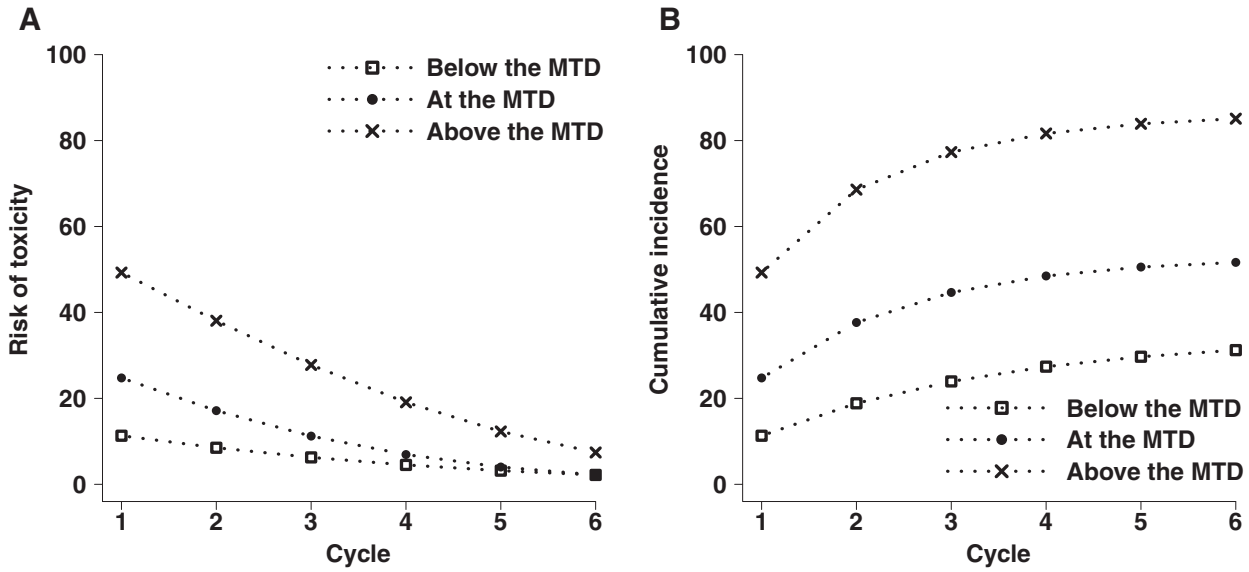

Figure 3. Risk and cumulative incidence of severe toxicity. **A)** Risk of severe toxicity for patients who were still at risk, for the three subgroups of patients treated at doses below, above, and at the maximum tolerated dose (MTD). **B)** Cumulative incidence of severe toxicity, for the three subgroups of patients treated at doses below, above, and at the MTD. The risk and the cumulative incidences were estimated from Model 1. Prediction intervals can be found in Supplementary Table 1 (available online).

Table 2. Cumulative incidence of severe toxicity, assuming that risk of severe toxicity in the first cycle ranges between 5% and 35%*

	Cumulative incidence (95% PI)				
Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
5.0%	8.0 (7.4 to 8.5)	9.7 (8.5 to 10.9)	10.7 (9.0 to 12.5)	11.3 (9.2 to 13.7)	11.5 (9.3 to 14.4)
10.0%	16.0 (15.1 to 16.9)	19.7 (17.6 to 21.7)	21.8 (18.7 to 25.0)	23.1 (19.2 to 27.3)	23.8 (19.4 to 28.9)
15.0%	23.9 (22.6 to 25.1)	29.3 (26.5 to 31.9)	32.6 (28.4 to 36.7)	34.5 (29.2 to 40.0)	35.7 (29.6 to 42.3)
20.0%	31.6 (30.1 to 32.9)	38.5 (35.2 to 41.5)	42.7 (37.7 to 47.4)	45.3 (39.0 to 51.4)	46.8 (39.5 to 54.2)
25.0%	39.0 (37.3 to 40.4)	47.2 (43.5 to 50.4)	52.1 (46.7 to 56.9)	55.1 (48.2 to 61.4)	56.9 (48.9 to 64.5)
30.0%	46.1 (44.2 to 47.6)	55.2 (51.4 to 58.4)	60.6 (55.0 to 65.4)	63.9 (56.9 to 70.0)	65.8 (57.7 to 73.1)
35.0%	52.8 (50.9 to 54.3)	62.6 (58.8 to 65.7)	68.2 (62.8 to 72.7)	71.6 (64.8 to 77.2)	73.6 (65.8 to 80.2)

*Predictions were derived from Model 2. PI = prediction interval.

toxicity. We showed that for patients assigned to the MTD, the probability of having severe toxicity was 24.8% in cycle 1 and the per-cycle risk decreased for each successive cycle. This is in line with results from other studies (10).

At the MTD, the cumulative incidence of severe toxicity by the end of cycle 6 was 51.7%. This risk is much higher than the 20%–33% risk of severe toxicity in cycle 1 usually targeted for the determination of the MTD and the RP2D. Of note, this is a cumulative risk assuming that patients would not stop treatment before cycle 6; the observed risk of toxicity is lower, because a fraction of the phase I patients progresses quite early, and this prevents to observe toxicity. We nevertheless consider that our estimate should match what is likely to be observed in phase II or phase III clinical trials in which patients are more fit and stay longer on treatment. At the MTD, the cumulative incidence of severe toxicity was made of 34.8% risk of exclusively non-hematologic toxicities and of 18.2% risk of hematologic or mixed toxicities. Finally, exclusion of grade 3 hematologic toxicities did not greatly impact the cumulative incidence of severe toxicity.

Many authors have pointed out that delayed and cumulative toxicities of MTAs, resulting from the prolonged administration of these treatments, have a non-negligible impact on the selection of the RP2D (11–13), even though keeping the first cycle of treatment was still relevant to define the MTD. This might be related to the poor prediction of future approved dose levels from phase I and the resulting reevaluation of the MTD in subsequent phases of treatment development (14–16).

The strengths of our study, in addition to the large number of trials and the individual patient data, is the detailed information collected about administered doses, treatment cycles, grades and types of toxicity, and the standardization of practice within the NCI CTEP. Conversely, the fact that the treatments evaluated in the included phase I studies are not from the most recent classes of agents is a limitation of our study. Furthermore, we used a definition of severe toxicity that is probably much broader than the usual definition of dose-limiting toxicity that typically excludes some grade 3 events, such as febrile neutropenia lasting less than 7 days. This may explain the high cumulative incidence of toxicity that we observed in patients treated at doses above the MTD. Finally, we did not account for dose modification during the course of the trial, as the model of toxicity, in terms of cumulative exposure, is largely unknown..

In view of our findings, we consider that for phase I designs the estimate of cumulative toxicity over three to six cycles of

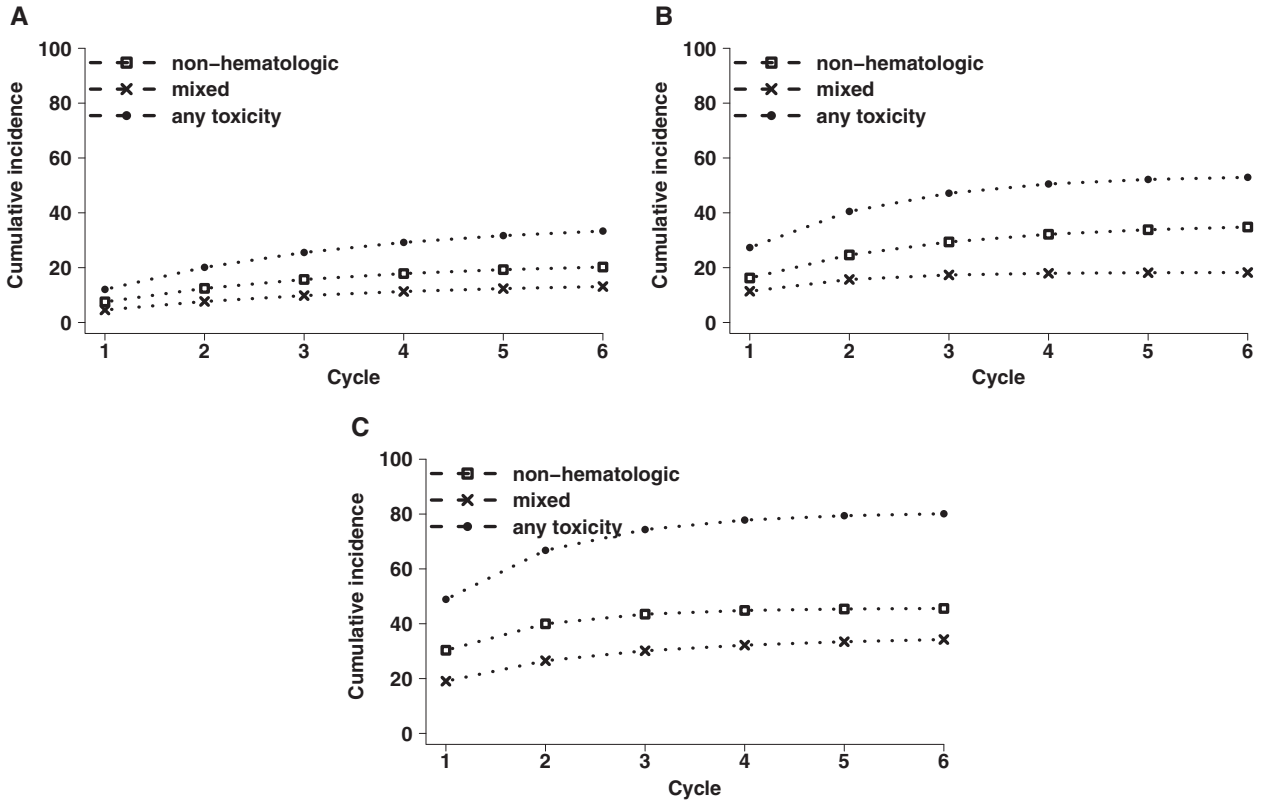

Figure 4. Cumulative incidence of severe toxicity for the competing risks analysis. A) Cumulative incidence of severe toxicity, over six treatment cycles, for patients treated below the maximum tolerated dose (MTD). B) Cumulative incidence of severe toxicity, over six treatment cycles, for patients treated at the MTD. C) Cumulative incidence of severe toxicity, over six treatment cycles, for patients treated above the MTD. Cumulative incidences were estimated for any type of severe toxicity, nonhematologic severe toxicity alone, and hematologic severe toxicity, with or without concomitant nonhematologic toxicity (mixed). Prediction intervals can be found in Supplementary Table 3 (available online).

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treatment (if available) should be considered to more reliably determine the RP2D. In our analysis, the risk of grade 3 to 5 toxicity of 20.0% to 30.0% on the first treatment cycle translated into a cumulative incidence of such events of 46.8% to 65.8% by the end of the sixth treatment cycle. Therefore, we suggest that a reasonable maximum threshold of cumulative risk of severe toxicity over six cycles may be around 40.0% to 45.0%.

We further suggest that reevaluation of the cumulative incidence of severe toxicity should be part of the stated objectives of the now rather popular expansion cohorts (17). Several dose-escalation methods have been proposed that take into account time-on-treatment in the dose-escalation process, such as the time-to-event continual reassessment method (CRM) (18, 19) or the CRM for longitudinal data (20). We also recommend that the definition of DLT should include those persisting grade 2 toxicities that may make patients drop out of the study. However, we recognize that toxicity is only one element of the definition of the optimal dose of a treatment. Pharmacokinetic data or biomarker measurements are also important factors that help refine the dose selected for the next phase of treatment development (21–28). Designs that make use of all collected data should improve the efficiency of phase I trials of MTAs at defining the RP2D and therefore avoid the need to reevaluate accepted doses in subsequent phases (29).

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Notes

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