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Research paper

Pragmatic dose-escalation methods incorporating relative dose intensity assessment for molecularly targeted agents in phase I trials

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ABSTRACT

The recommended phase 2 doses of molecularly targeted agents, determined by using an ordinal dose-finding method that only uses toxicity data at first cycle, may not be optimal. Some researchers have proposed the use of relative dose intensity that can account for late-onset, cumulative, and low-grade toxicities to determine the recommended phase 2 dose (RP2D). In this study, we proposed two dose escalation methods based on the observed relative dose intensities (RDIs) between the pre-specified intervals (cycles) for toxicity evaluation used in combination with DLT evaluation in the first cycle. First, we propose the modified 3 + 3 design that incorporates longitudinal RDI assessment. Second, we propose the sequential assessment method for longitudinal RDI (SARDI) to achieve faster dose escalation compared to that of the modified 3 + 3 design. Simulation studies demonstrated that the SARDI was, in many cases, superior to the ordinal and modified 3 + 3 designs in respect to the selection rate of true RP2D and study period. The two proposed methods could also in some cases decrease the average number of patients enrolled in the trial compared to that of the ordinary 3 + 3 design. Incorporation of the RDI assessment into the 3 + 3 design is not difficult and does not require the use of complex statistical techniques. Therefore, we believe that investigators who routinely use the 3 + 3 design in practice can easily use our proposed methods.

1. Introduction

Phase 1 oncology trials determine the recommended phase 2 dose (RP2D) for further testing [1]. For a cytotoxic agent, the RP2D corresponds to the maximum tolerated dose (MTD), defined as the highest dose administered to patients with clinically acceptable toxicity. The MTD is generally determined based on the dose-limiting toxicity (DLT) observed during the first treatment cycle. Methodologies determining the MTD are roughly categorized into algorithm-based methods, such as the 3 + 3 design [2], and model-based methods, such as the continual reassessment method (CRM) [3]. Both methods determine the MTD based solely on the first treatment cycle toxicity data, although toxicity data after the first cycle and information, such as treatment management changes, are generally recorded in actual trials. Additionally, these methods have been successful for cytotoxic agents, but not for the RP2D of molecularly targeted agents (MTAs) [4] due to their mechanism of action. Although many researchers have developed dose-finding methods that account for non-monotonic patterns in the MTA dose-efficacy curve [5–9], most determine the RP2D using toxicity and efficacy data obtained at the first treatment cycle, similar to the cytotoxic agent dose-finding methods.

Investigators, however, feel that such an RP2D may not be "optimal" for MTA clinical use due to late-onset and/or cumulative toxicity [10–12]. Additionally, some patients develop chronic low-grade toxicity from MTAs during the phase 1 trial period. This eventually warrants dose reduction or drug withholding due to patient intolerance [13,14]. Most of the dose-finding methods for MTA rely largely on the traditional definition of the MTD during cycle 1, and hence, late-onset, cumulative, and low-grade toxicities are discounted and excluded from the MTD determination. These eventually become intolerable, however, and are a major factor in dose reduction or drug withholding after the cycle 1 period, ultimately resulting in insufficient drug exposure.

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Table 1
Data of the first cycle of patient 1 in scenario 1 in Table 3.

Day	1	2	3	4	5	6	7	8	9	10	…	28
Dosage	4	4	4	4	4	4	4	4	4	NA	…	NA
Toxicity grade	1	1	1	1	1	1	1	1	DLT	NA	…	NA

A number of studies have investigated longitudinal toxicity data in phase 1 trials of MTAs [10–12,15]. Typically, they found that the toxicities yielding dose reduction or treatment interruption occur regularly after the first cycle. Additionally, they indicated the utility of longitudinal relative dose intensity (RDI) as a better endpoint to determine RP2D, taking into consideration late-onset, cumulative, and low-grade toxicities. RDI is generally defined as the ratio of the effectively administered to the theoretically administered cumulative dose [16–18]. A higher RDI generally provides a better clinical outcome [19, 20]. The expert consensus is that a threshold of >75% of the intended RDI is acceptable [12]. To our knowledge, no statistical dose-finding approach incorporating the RDI for MTA exists, although several dose-finding methods capable of accounting for late-onset toxicity have been developed [21–25].

In this study, we propose two dose-escalation methods based on longitudinal assessment of the RDI to determine the RP2D of single MTA therapy in phase 1 trials. The proposed methods are based on the dose escalation algorithm using the observed RDIs between the pre-specified intervals (cycles) for toxicity evaluation in combination with the DLT evaluation in the first cycle. First, we propose the modified 3 + 3 design that incorporates the longitudinal RDI assessment, as the 3 + 3 design remains widely used in practice [24]. Second, we propose the sequential assessment method for longitudinal RDI (SARDI) to achieve faster dose escalation compared to that of the modified 3 + 3 design. The operating characteristics of these methods were examined through simulation studies that imitate real phase 1 trial data, and the utility of the proposed methods is discussed.

1.1. Trial setting

In this paper, we model a phase 1 trial where drug administration to each patient occurs through a cycle of daily oral doses. One cycle spans 28 days, but is not limited to this setting. We determine the RP2D based on both the DLT and the RDI observed from the first cycle to the pre-specified Jth ($j = 1, \ldots, J$) cycle. Each patient is treated with the assigned dose level that is determined according to the dose escalation algorithm of the proposed method. During treatment, dose reduction and/or dose interruption is achieved according to the predefined criteria described earlier. The treatment for each patient is continued as long as the DLT is not observed or the trial is not terminated.

1.2. Toxicity

The toxicity observed during the trial is evaluated based on the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) [26] and classified as one of the grades from 0 to 5. In phase 1 oncology trials, DLT is often defined as clinically unacceptable toxicity. Specifically, the pre-specified grade 3 or higher non-hematologic toxicity and grade 4 hematologic toxicity are frequently defined as DLT.

1.3. Dose reduction/interruption

When DLT is observed during the trial, drug administration is discontinued. When toxicities other than DLT are observed, dose reduction or dose interruption is performed depending on the grade observed in actual trials. In this study, the criteria for dose reduction and dose interruption are described below (but not limited to this criterion).

For simplicity, we propose a trial where the dose for the next day is determined depending on the grade of toxicity observed in the current day. In the two proposed methods, the dose level is not changed if grade 1 toxicity was observed. When grades 2–4 are observed, the dose for the next day is reduced to two levels lower than the current dose; however, when the dose can be reduced only by one level, the dose is interrupted (in other words, no dose is administered). When DLT (including grade 5) is observed, administration is terminated.

After dose reduction and interruption, once the toxicity improves to grades 0–1, administration of the assigned dose is resumed. In the simulations described in the Simulation studies section, we assume that the probability of recovery from grade 2 to grades 0–1 is 40% per day, and the probability of recovery from grades 3–4 to grades 0–1 is 20% per day.

1.4. Calculation of relative dose intensity

Here, we provide a method for calculating RDI. At the end of each cycle, for cycle j of patient i, RDI_{ij} $(i = 1, \ldots, n;\ j = 1, \ldots, J)$ is calculated. Let the dosage on day k of cycle j of patient i be x_{ijk} $(k = 1, \ldots, 28)$. We have L assigned doses, d_l ($l = 1, \ldots, L$), giving us $x_{ijk} \in \{d_1, \ldots, d_L\}$. The RDI_{ij} of cycle j of patient i is defined as follows:

$$\mathrm{RDI}_{ij} = \frac{\sum_{k=1}^{28} x_{ijk}}{x_{i11} \times 28}$$

where x_{ij1} is the assigned dose level for patient cycle j of patient i. In the case of dose interruption or termination, we set $x_{ijk} = 0$.

Further, after the completion of the trial, using the RDI_{ij} from the first cycle to the Jth cycle, the mean RDI_i (mRDI_i) of patient i is calculated as:

$$\mathrm{mRDI}_i = \frac{\sum_{j=1}^{J} \mathrm{RDI}_{ij}}{J}$$

For the total number of patients who were administered with assigned dose d_l ($l = 1, \ldots, L$), n_{d_l}, we calculate the population average value ($\mathrm{pRDI}(d_l)$) of the mRDI_i $(i = 1, \cdots, n_{d_l})$ as follows:

$$\mathrm{pRDI}(d_l) = \frac{\sum_{i \in n_{d_l}} \mathrm{mRDI}_i}{n_{d_l}}$$

In the two proposed methods, the dose escalation is employed based on the presence or absence of DLT and $\mathrm{pRDI}(d_l)$ during the trial.

An example of the RDI calculation is described below. For simplicity, suppose that the assigned dosage of 4 mg is administered to patient i ($i = 1, 2, 3, 4, 5, 6$), and the toxicity grades in cycles 1 to 6 are recorded. Suppose that the data of the first cycle of patient 1 are obtained as shown in Table 1. As the trial was terminated on day 9 ($k = 9$) due to DTL for patient 1, the data for day 10 or later are not applicable (NA).

The RDI_{11} of cycle 1 for patient 1 is 0.32 ($= \frac{4 \times 9}{4 \times 28}$). As the trial is terminated in the second and subsequent cycles (i.e., $\mathrm{RDI}_{1j} = 0, j = 2, \ldots, 6$), the mRDI_1 becomes 0.053 (= 0.32/6). Similarly, we calculate the mRDI_i ($i = 2, \ldots, 6$) for patients 2 to 6, and can then obtain the pRDI of the 4 mg dose level. The pRDI defined in this study is unitless, and its value is between 0 and 1. In this example, suppose that the mRDIs for patients 2–6 receiving 4 mg are 0.053, 0.038, 0.381, 0.631, 0.637, and 0.646. The pRDI for 4 mg is then calculated as follows:

$$\mathrm{pRDI}(4\ \mathrm{mg}) = (0.053 + 0.038 + 0.381 + 0.631 + 0.637 + 0.646)/6 = 0.398$$

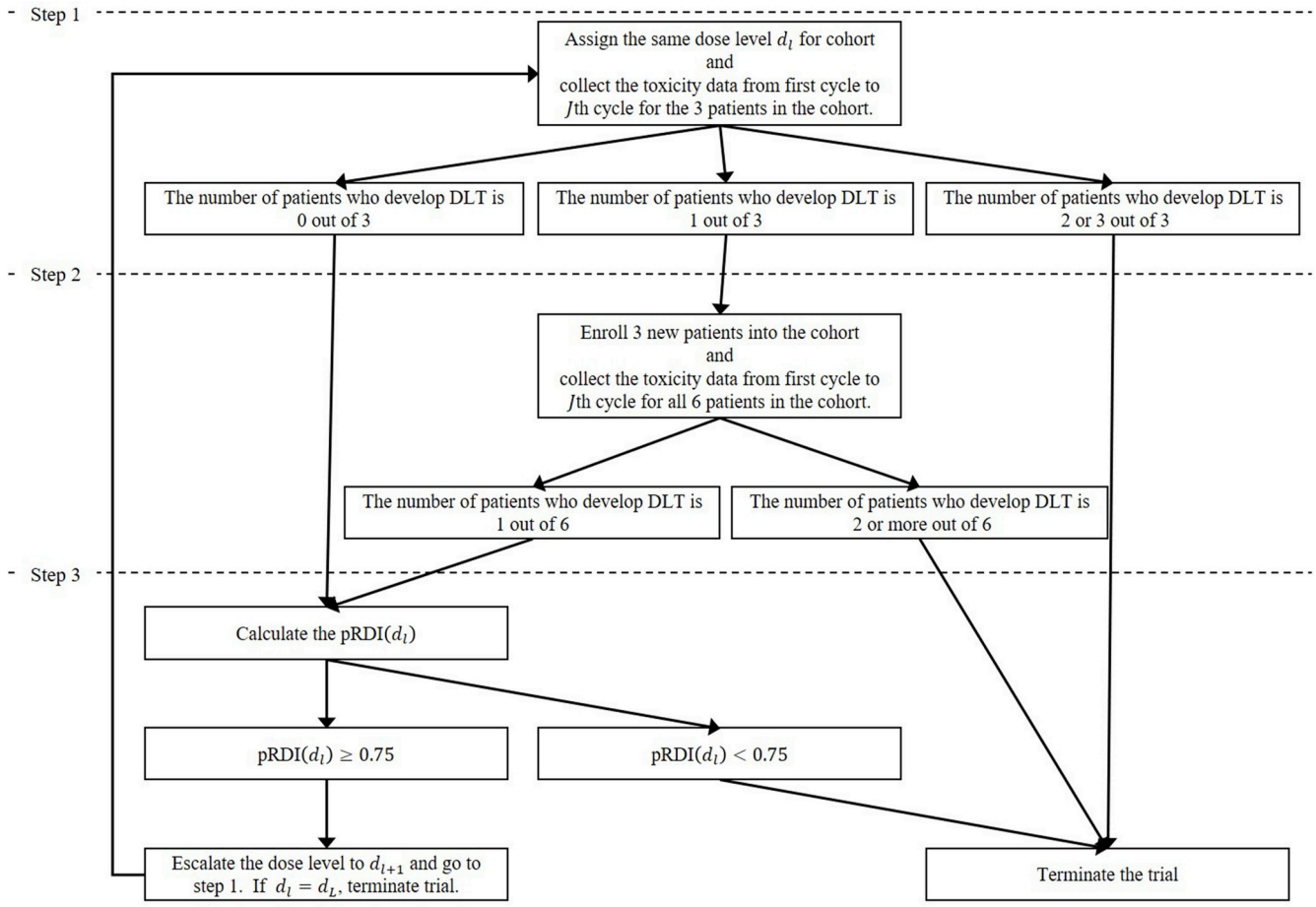

Fig. 1. Flow chart of the 3 + 3 RDI method.

1.5. Proposed dose escalation methods

In this section, we propose two dose escalation algorithms, specifically the modified 3 + 3 design incorporating the RDI assessment (hereafter the "3+3-RDI design") and the SARDI. In both methods, during the trial dose reduction or dose interruption is performed based on the criteria described earlier, and the RP2D is determined based on the pRDI(d_l) upon the completion of the trial.

2. 3+3-RDI design

Here, we propose a method to determine RP2D by incorporating RDI assessment into the 3 + 3 design (Fig. 1). We also provide a schematic of the 3+3-RDI design in appendix Fig. 1

Step 1 The number of patients per cohort is assumed as three, and the same dose level is assigned for each cohort. The lowest dose (d_1) is assigned to the first cohort. For all patients in the cohort, the toxicity data from the first cycle to Jth cycle is collected, unless the DLT occurs earlier or the trial is terminated.

(1A) If the number of patients who develop DLT during the first cycle to the Jth cycle is zero out of three patients, we go directly to step 3.

(1B) If the number of patients who develop DLT during the first cycle to the Jth cycle is one out of three patients, we go to step 2.

(1C) If the number of patients who develop DLT during the first cycle to the Jth cycle is two or more out of the three patients, d_l is determined as an unacceptable toxicity dose and the trial is terminated.

Step 2 We enroll three new patients, assign the same dosage as described in step 1 to the three patients, and we observe the toxicity data from the first cycle to Jth cycle. Out of the six patients, we obtain the number of cases that develop DLT.

(2A) If the number of patients who develop DLT during the first cycle to the Jth cycle is one out of six cases, we go to step 3.

(2B) If the number of patients who develop DLT during the first cycle to the Jth cycle is two or more out of six, d_l is judged as an unacceptable toxicity dose, and the trial is terminated.

Step 3 We calculate the pRDI(d_l) of dose d_l.

(3A) If the condition pRDI(d_l) ≥ 0.75 is satisfied, we escalate the dose assigned to the next cohort of patients to d_{l+1} and proceed to step 1. If $d_l = d_L$, we terminate the trial.

(3B) If the condition pRDI(d_l) ≥ 0.75 is not satisfied, d_l is determined as an unacceptable toxicity dose due to low RDI, and the trial is terminated.

2.1. Sequential assessment of relative dose intensity

The 3+3-RDI design monitors toxicity data until the last patient of the cohort reaches the Jth cycle, unless the DLT occurs earlier or the trial is terminated. Alternatively, we propose the SARDI that enables faster dose escalation compared to the 3+3-RDI design by accounting for the interim pRDI(d_l) during the trials (Fig. 2). We also provide a schematic of the SARDI design in Appendix Fig. 2.

Step 1 The number of patients per cohort is assumed as three, and a dose is assigned for each cohort. The lowest dose (d_1) is assigned to

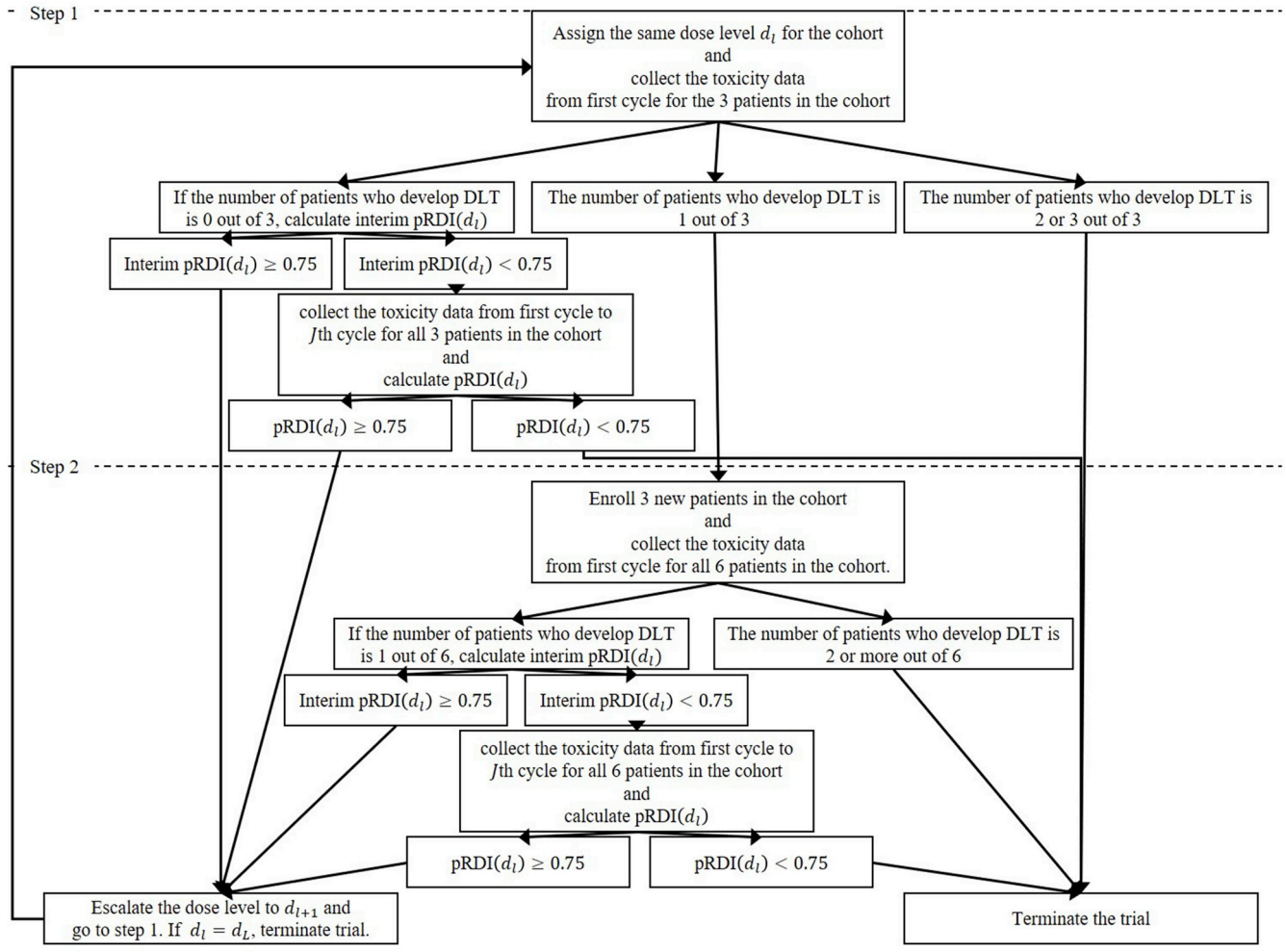

Fig. 2. Flow chart of the SARDI method.

the first cohort. When the toxicity data of the first cycle for the three patients in the cohort are obtained, the interim pRDI(d_l) is calculated.

(1A) If the number of patients who develop DLT is zero out of three and the interim pRDI(d_l) ≥ 0.75 is satisfied, we escalate the dose to d_{l+1} and go back to step 1. If $d_l = d_L$, we terminate the trial. Of note, we collect the toxicity data of the three patients assigned to d_l until the Jth cycle.

(1B) If the number of patients who develop DLT is zero out of three, but the interim pRDI(d_l) ≥ 0.75 is not satisfied, we continue to follow these patients until the Jth cycle. Consequently, if the final pRDI(d_l) that is calculated based on the RDI until the Jth cycle is higher or equal to 0.75, we escalate the dose to d_{l+1} and go back to step 1. If $d_l = d_L$, we terminate the trial. In all other cases, d_l is determined to be an unacceptable toxicity, and the trial is terminated.

(1C) If the number of patients who develop DLT is one out of three, we proceed to step 2. For the remaining two cases, we continue to follow them until the Jth cycle.

(1D) If the number of patients who develop DLT is two or more out of three, d_l is determined to be an unacceptable toxicity, and the trial is terminated.

Step 2 We enroll three new patients and assign the same dose as that assigned in step 1. At the time that toxicity data of the first cycle for the additional three patients are collected, we evaluate the number of patients with DLT out of the total six patients, and we calculate the interim pRDI(d_l) using all the available RDI.

(2A) If the number of patients who develop DLT is one out of six and the interim pRDI(d_l) ≥ 0.75 is satisfied, we escalate the dose to d_{l+1} and go back to step 1. If $d_l = d_L$, we terminate the trial. For the remaining 5 cases, we continue the observation until the Jth cycle.

(2B) If the number of patients who develop DLT is one out of six but the interim pRDI(d_l) ≥ 0.75 is not satisfied, we continue to follow the patients in the cohort until the Jth cycle. Consequently, if the final pRDI(d_l) calculated based on the RDI until the Jth cycle is higher than or equal to 0.75, we escalate the dose to d_{l+1} and go back to step 1. If $d_l = d_L$, we terminate the trial. Otherwise, d_l is determined to be an unacceptable toxicity and the trial is terminated.

(2C) If the number of patients who develop DLT is two or more out of six, d_l is determined as an unacceptable toxicity, and the trial is terminated.

Thus, the SARDI enables more rapid dose escalation compared to that of the 3 + 3 RDI design by accounting for the interim pRDI during the trials. The interim RDI is defined as the pRDI calculated using all the available RDI at that time (i.e., using the $\frac{\sum_{j=1}^{J'} \mathrm{RDI}_{ij}}{J'}$ as mRDI for patient i, where $J' \leq J$). For example, for the first three patients enrolled into the trial, we calculate the interim pRDI(d_1) at the time when the toxicity data of these three patients in the first cycle are obtained. In this case, as the three patients are enrolled with time difference, the observational period J' for each patient is also varied. Therefore, we calculate

Table 2
Probability of toxicity grade.

	Cumulative probability of toxicity at a cycle	Probability of toxicity at a cycle	Probability of toxicity at a day	Cumulative probability of toxicity added subject effect at a cycle	Interval for toxicity grade by day
Grade 0–1	α	α	$\frac{1}{\alpha^{28}}$	$\alpha' = \frac{\exp\left\{\log\left(\frac{\alpha}{1-\alpha}\right)+u_i\right\}}{1+\exp\left\{\log\left(\frac{\alpha}{1-\alpha}\right)+u_i\right\}}$	$\left[0, \alpha', \frac{1}{28}\right]$
Grade 2	β	$\beta-\alpha$	$\frac{1}{\beta^{28}}-\frac{1}{\alpha^{28}}$	$\beta' = \frac{\exp\left\{\log\left(\frac{\beta}{1-\beta}\right)+u_i\right\}}{1+\exp\left\{\log\left(\frac{\beta}{1-\beta}\right)+u_i\right\}}$	$\left[\alpha', \frac{1}{28}, \beta', \frac{1}{28}\right]$
Grade 3–4	γ	$\gamma-\beta$	$\frac{1}{\gamma^{28}}-\frac{1}{\beta^{28}}$	$\gamma' = \frac{\exp\left\{\log\left(\frac{\gamma}{1-\gamma}\right)+u_i\right\}}{1+\exp\left\{\log\left(\frac{\gamma}{1-\gamma}\right)+u_i\right\}}$	$\left[\beta', \frac{1}{28}, \gamma', \frac{1}{28}\right]$
DLT	1	$1-\gamma$	$\frac{1}{1-\gamma^{28}}$	1	$\left[\gamma', \frac{1}{28}, 1\right]$

"interim" pRDI(d_1) in the SARDI. The dose level assigned to the next three patients is determined based on the interim pRDI(d_1). Similarly, at the time that toxicity data of the first cycle for the additional three patients are collected, we also calculate interim pRDI(d_l) for each patient.

2.2. Determination of the recommended phase 2 dose

In both methods, upon the completion of the trial, we calculate the pRDI(d_l) for each dose level using all available data for the enrolled patients. In general, as the RP2D is determined not only by DLT but also by other factors, such as toxicity grades observed during the trial and pharmacokinetics and response data, it is difficult to provide its single common definition. In this study, our aim is to find a dose that can be administered continuously, and we therefore calculate the $d_l \times$ pRDI(d_l) as the average cumulative dose that can be administered. Thereafter, among the doses that satisfy the pRDI(d_l) ≥ 0.75, we select the highest average cumulative dose as the RP2D that provides the highest exposure of the drug.

2.3. Simulation studies

We evaluated the operating characteristics of the two proposed dose-escalation methods through the use of simulation studies. The performance of the conventional 3 + 3 design was compared with the performances of the two proposed methods. Although dose escalation of the 3 + 3 design is often performed in a manner based only the DLT of the first cycle, the RP2D for the 3 + 3 design is determined based on the cumulative dose defined in the previous section in our simulation studies to achieve a fair comparison of the operating characteristics among the three methods.

The administration period is set at a total of six cycles ($j = 1, \ldots, 6$). We also conducted the simulation studies with only one cycle ($J = 1$) to reveal the effects of using the longitudinal RDI data in each method. The number of dosage levels (L) is assumed to be four (or six), and it is supposed that each dose is taken as $d_l = l$ (mg). The maximum sample sizes are 24 and 36 patients for four and six of the dosage levels, respectively, but the actual sample size in each trial could be much smaller since the trial can stop earlier based on the number of DLT

Table 3
Probability of toxicity per cycle ($L = 4$). The true RP2D is shown in bold.

Dose level (mg)	Grade 0-1	Grade 2	Grade 3-4	DLT	Expected pRDI ($J = 6$)	Expected cumulative dose ($J = 6$)	Expected pRDI ($J = 1$)	Expected cumulative dose ($J = 1$)
Scenario 1								
1	0.81	0.14	0.03	0.02	0.91	0.91	0.97	0.97
2	0.74	0.16	0.05	0.05	0.82	**1.64**	0.94	1.89
3	0.67	0.18	0.05	0.10	0.71	2.13	0.92	2.77
4	0.50	0.20	0	0.30	0.43	1.73	0.82	**3.30**
Scenario 2								
1	0.67	0.30	0.02	0.01	0.93	0.93	0.96	0.96
2	0.60	0.32	0.03	0.05	0.81	1.62	0.93	1.86
3	0.56	0.34	0.02	0.08	0.75	**2.24**	0.93	2.78
4	0.49	0.36	0.05	0.10	0.70	2.82	0.92	**3.67**
Scenario 3								
1	0.50	0.30	0.19	0.01	0.89	0.89	0.93	0.93
2	0.30	0.38	0.29	0.03	0.80	1.60	0.88	1.76
3	0.20	0.40	0.35	0.05	0.77	**2.32**	0.89	2.66
4	0.10	0.45	0.36	0.08	0.71	2.86	0.88	**3.50**
Scenario 4								
1	0.90	0.07	0.02	0.01	0.95	0.95	0.98	0.98
2	0.85	0.10	0.03	0.02	0.91	1.83	0.97	1.94
3	0.75	0.17	0.05	0.03	0.88	2.64	0.96	2.89
4	0.60	0.27	0.08	0.05	0.82	**3.28**	0.95	**3.79**
Scenario 5								
1	0.85	0.05	0.05	0.05	0.82	**0.82**	0.95	0.95
2	0.70	0.10	0.05	0.15	0.62	1.24	0.90	**1.79**
3	0.25	0.15	0.10	0.50	0.27	0.82	0.70	2.11
4	0	0.20	0.10	0.70	0.23	0.91	0.51	2.06
Scenario 6								
1	0.85	0.05	0.05	0.05	0.82	**0.82**	0.95	0.95
2	0.10	0.60	0.15	0.15	0.56	1.13	0.79	**1.57**
3	0.25	0.15	0.10	0.50	0.27	0.82	0.70	2.11
4	0	0.20	0.10	0.70	0.23	0.91	0.51	2.06

Table 4
Probability of toxicity per cycle ($L = 6$). The true RP2D is shown in bold.

Dose level (mg)	Grade 0-1	Grade 2	Grade 3-4	DLT	Expected pRDI ($J = 6$)	Expected cumulative dose ($J = 6$)	Expected pRDI ($J = 1$)	Expected cumulative dose ($J = 1$)
Scenario 7								
1	0.89	0.01	0.05	0.05	0.84	**0.84**	0.96	0.96
2	0.80	0.05	0.05	0.10	0.73	1.46	0.93	1.85
3	0.65	0.10	0.05	0.20	0.55	1.65	0.87	2.62
4	0.50	0.15	0.05	0.30	0.42	1.69	0.82	3.29
5	0.35	0.2	0.05	0.40	0.32	1.61	0.77	**3.84**
6	0.20	0.25	0.05	0.50	0.24	1.46	0.71	4.28
Scenario 8								
1	0.20	0.60	0.19	0.01	0.84	0.84	0.87	0.87
2	0.16	0.62	0.19	0.03	0.78	1.55	0.85	1.70
3	0.12	0.64	0.19	0.05	0.76	**2.29**	0.87	2.62
4	0.08	0.66	0.18	0.08	0.71	2.86	0.88	3.51
5	0.04	0.68	0.18	0.10	0.68	3.39	0.87	**4.35**
6	0.00	0.70	0.18	0.12	0.56	3.37	0.73	4.35
Scenario 9								
1	0.95	0.03	0.01	0.01	0.96	0.96	0.99	0.99
2	0.90	0.06	0.03	0.01	0.95	1.90	0.98	1.96
3	0.85	0.09	0.04	0.02	0.92	2.75	0.98	2.93
4	0.80	0.12	0.05	0.03	0.88	3.54	0.97	3.88
5	0.75	0.15	0.06	0.04	0.86	4.28	0.96	4.82
6	0.70	0.18	0.08	0.04	0.85	**5.13**	0.96	**5.79**
Scenario 10								
1	0.38	0.10	0.02	0.50	0.27	0.27	0.71	0.71
2	0.31	0.12	0.02	0.55	0.24	0.47	0.68	1.36
3	0.24	0.14	0.02	0.60	0.20	0.61	0.65	1.95
4	0.17	0.16	0.02	0.65	0.18	0.72	0.62	2.47
5	0.10	0.18	0.02	0.70	0.16	0.79	0.58	2.92
6	0.03	0.20	0.02	0.75	0.14	0.82	0.54	3.26
Scenario 11								
1	0.93	0.01	0.05	0.01	0.95	0.95	0.98	0.98
2	0.89	0.03	0.05	0.03	0.88	1.77	0.97	1.94
3	0.85	0.05	0.05	0.05	0.83	2.49	0.96	2.88
4	0.77	0.10	0.05	0.08	0.76	**3.02**	0.94	3.77
5	0.10	0.75	0.05	0.10	0.69	3.45	0.89	4.45
6	0.03	0.80	0.05	0.12	0.65	3.87	0.87	**5.22**
Scenario 12								
1	0.94	0.01	0.04	0.01	0.95	0.95	0.99	0.99
2	0.90	0.03	0.04	0.03	0.88	**1.77**	0.97	**1.94**
3	0.00	0.20	0.75	0.05	0.48	1.43	0.52	1.57
4	0.00	0.15	0.77	0.08	0.54	2.18	0.63	2.52
5	0.00	0.10	0.80	0.10	0.57	2.84	0.69	3.44
6	0.00	0.05	0.83	0.12	0.56	3.35	0.72	4.33

observed during the trial. The number of patients enrolled in the trial per cycle is assumed to follow a Poisson distribution with a parameter of 1. This corresponds to our assumption that the patient accrual follows a Poisson process with a rate of one patient per month.

For the toxicity probability of each patient, the subject effect is considered. Following the approach used by Paoletti et al. [27], subject effect u_i is assumed to be followed by the normal distribution with mean 0 and variance 0.5. In each cycle, let the cumulative probability of toxicity with grade ≤0–1, ≤2, ≤3–4, DLT (including grade 5) be α, β, γ and 1, respectively. In this context, for example, the relationship between the dose d_l and the probability of grade ≤0–1 can be written as follows:

$$d_l = \log\frac{\alpha}{1-\alpha}$$

By adding the subject effect u_i on the left side of the equation, the cumulative probability of toxicity-added subject effect at a cycle for patient i is obtained as follows:

$$\alpha_i^{'} = \frac{\exp\{d_l + u_i\}}{1+\exp\{d_l + u_i\}} = \frac{\exp\left\{\log\left(\frac{\alpha}{1-\alpha}\right) + u_i\right\}}{1+\exp\left\{\log\left(\frac{\alpha}{1-\alpha}\right) + u_i\right\}}$$

Thus, we determine the toxicity grade for each day using the uniform random variable of the interval [0, 1] (Table 2).

The comparison of operating characteristics was performed using twelve scenarios. Tables 3 and 4 show the probability of toxicity for each grade per cycle (i.e., α, β − α, γ − β, and 1 − γ shown in Table 2) when dose level l is administered for $L = 4$ and $L = 6$, respectively. In the case of dose level 1 in scenario 1 of Table 3, we first specified the cumulative probabilities of toxicity at a cycle with grade ≤0–1, ≤2, ≤3–4, and DLT (including grade 5) as $\alpha = 0.81$, $\beta = 0.95$, $\gamma = 0.98$, and 1.00, respectively. In this case, using the equations shown in Table 2, the probabilities of toxicity at a cycle for grade 0–1, grade 2, grades 3–4, and DLT are calculated by $\alpha = 0.81$, $\beta - \alpha = 0.14$, $\gamma - \beta = 0.03$, and $1 - \gamma = 0.02$, respectively. Using these probabilities, we obtain the other probabilities of toxicity (e.g., the figures of third, fourth, and fifth column in Table 3). Using these probabilities, we calculated the expected pRDI(d_l) and the expected cumulative dose for each dose d_l, that are used to define the true RP2D in each scenario, by generating 10,000 simulated data points. Among the doses satisfying the expected pRDI(d_l) ≥ 0.75, the true RP2D was defined as the highest average cumulative dose.

For each scenario, 1000 simulated trials were performed. In the SARDI, if the DLT rate for all patients at the time of dose escalation is >50%, the trial is terminated. Performance indices included the selection rate of the true RP2D, the average DLT rate, the average number of patients included in the trial, and the average trial period that is defined as the time of first patient in to last patient out (i.e., the average of the total number of cycles in 1000 simulated trials). We also indicated the percentage of patients receiving the true RP2D, under dose, and overdose in each scenario in Appendix Table 1.

Table 5
Summary of the operating characteristics of the three methods for $L = 4$ using $J = 6$ (or 1). The true RP2D is shown in bold.

	$J = 6$				Average DLT rate, %	Average number of patients, n	Average trial period, cycle	$J = 1$				Average DLT rate, %	Average number of patients, n	Average trial period, cycle
	Selection rate of true RP2D, %							Selection rate of true RP2D, %						
	1	2	3	4				1	2	3	4			
Scenario1														
3 + 3	1.5	**7.3**	32.1	58.7	43.1	13.9	13.5	1.5	7.3	32.1	**58.7**	13.1	13.9	13.5
3+3-RDI	35.1	**39.5**	17.4	0.3	30.4	9.6	20.4	1.6	7.3	32.1	**58.5**	13.1	13.9	13.5
SARDI	18.8	**40.7**	34.4	1.6	38.5	12.4	15.7	1.6	7.3	32	**58.6**	13.1	13.9	13.5
Scenario2														
3 + 3	1.1	6.1	**10**	82.8	30.8	13.6	13.1	1.1	6.1	10	**82.8**	7.2	13.6	13.1
3+3-RDI	32.8	40.9	**20**	4.4	26.5	10.4	22.3	1.2	6.1	9.9	**82.7**	7.2	13.5	13.1
SARDI	17.9	29.1	**31.1**	20.9	30.4	13	17.2	1.2	6.1	9.9	**82.7**	7.2	13.6	13.1
Scenario 3														
3 + 3	0.6	2.7	**6.7**	90	22.5	13.4	12.9	0.6	2.7	6.7	**90**	4.7	13.4	12.9
3+3-RDI	23.3	30.4	**27.4**	16	21.5	12	25.6	4.6	3.5	6.4	**84.1**	4.6	12.9	12.5
SARDI	11.1	23	**33.9**	31	23.1	13.6	18.2	4.6	3.5	6.4	**84.1**	4.5	12.9	12.5
Scenario 4														
3 + 3	0.2	1.1	3.2	**95.5**	17.2	13.1	12.7	0.2	1.1	3.2	**95.5**	3.3	13.1	12.7
3+3-RDI	10.8	22.2	28.9	**36.7**	18.4	13	27.5	0.2	1.1	3.2	**95.5**	3.3	13.1	12.7
SARDI	3.4	9.7	27.1	**59.4**	17.8	13.7	18.7	0.2	1.1	3.2	**95.5**	3.3	13.1	12.7
Scenario 5														
3 + 3	**9**	58.9	30.4	0.3	60.7	11.5	11	9	**58.9**	30.4	9	24	11.5	11
3+3-RDI	**57.9**	11.4	0	0	44.6	6.4	13.7	9	**59**	30.2	9	24	11.5	11
SARDI	**53**	25.4	0.5	0	52.8	9	12	9	**58.9**	30.4	9	24	11.5	11
Scenario6														
3 + 3	**20.4**	46.8	31.1	0.3	59.4	11.6	11.1	20.4	**46.8**	31.1	20.4	23.6	11.6	11.1
3+3-RDI	**60.8**	8.5	0	0	43.9	6.5	13.9	24.2	**46.8**	27.3	24.2	22	11	10.6
SARDI	**59.5**	17.8	0.6	0	51.3	9.1	12.1	24.2	**46.8**	27.3	24.2	22	11	10.6

According to the results for $J = 6$ in Table 5, the selection rate of true RP2D for the two proposed methods outperformed the 3 + 3 design by 10–50% in scenarios 1–6. The two proposed methods also tended to select the lower dose level as the RP2D, compared to that selected by the 3 + 3 design. This can be explained by the observation that the dose escalation of the two proposed methods is inherently limited by incorporating the dose escalation criterion of RDI <0.75 during the trial. In terms of selecting the true RP2D, the SARDI also resulted in a better performance than the 3+3-RDI design by approximately 10–20% in scenarios 2 and 3, where the true RP2D is a relatively higher dose level (e.g., dose levels 3 and 4). The average DLT rates of the two proposed methods was lower than that of the 3 + 3 design. The average number of patients enrolled in the trial of the two proposed methods was almost equal to or smaller than that of the 3 + 3 design in scenarios 1–6; however, the trial period of the two proposed methods were larger than that of the 3 + 3 design in scenarios 1–6. The trial period of the SARDI was in competition with the 3 + 3 design in the cases where the true RP2D represented a relatively lower dose (e.g., dose levels 1 and 2). Similar relative relationships among the three methods with respect to each performance index were also observed in the results for $J = 6$ in Table 6. Additionally, in scenario 9 where there was a <5% of DLT probability at all dose levels, the 3 + 3 design tended to rapidly escalate the dose level due to a failure in considering the dose escalation conditions based on the RDI assessment. The proposed two methods occasionally suppressed the dose escalation by the lower RDI caused by the grades 2 and 3–4 toxicities, ultimately yielding a lower selection rate of true RP2D.

Across the 12 scenarios where $J = 6$, the 3 + 3, 3+3-RDI, and SARDI methods demonstrated average selection rates for true RP2D of 28.3%, 39.5%, and 45.8%, respectively. The 3 + 3, 3+3-RDI, and SARDI methods demonstrated average DLT rates of 40.9%, 33.5%, and 37.2%, respectively. The average number of patients enrolled in the trial for the 3 + 3, 3+3-RDI, and SARDI methods were 14.6, 10.0, and 12.3 patients, respectively. The average trial periods for the 3 + 3, 3+3-RDI, SARDI methods were 14.2, 21.0, and 16.1 cycles, respectively.

We also performed the simulation study with $J = 1$ and compared the operating characteristics among the 3 + 3 design, 3 + 3 RDI, and SARDI using the scenarios described in Table 3 for $L = 4$ (or Table 4 for $L = 6$). According to the results for $J = 1$ shown in Tables 5 and 6, in all the scenario other than scenario 12, selection rates for true RP2D (i.e., the highest cumulative dose), average DLT rate, average number of patients, and average trial period were comparable among the three methods. In scenario 12 with a lower probability of DLT for each dose level, the selection rates of true PR2D in the 3 + 3 RDI and SARDI were higher than that of the 3 + 3 design. The reason for this is that the 3 + 3 design escalated the dose level during the trial, as it did not account for the dose reduction due to the grade 2 or grades 3–4 toxicities. Thus, the increased performance of the two proposed designs is due to the incorporation of the toxicity data from all cycles primarily and the RDI data partially in some cases.

3. Discussion

Dose reduction and interruption due to toxicity are often encountered in practice during cancer treatment. This often causes a decrease of the RDI that, in turn, results in reduced drug exposure. To continue treatment until the progression of disease or death, we must identify the dose level that can continuously be administered during treatment. The RDI is one of the better endpoints to accommodate such a requirement, particularly in the dose-finding trial for MTA. The two proposed methods of RDI assessment inherently incorporate the potential efficacy outcome into the dose selection. To our knowledge, this study is the first proposal to incorporate the RDI into the dose-escalation method. These methods, therefore, will provide a basis for future work in RDI-based dose-finding methods. Incorporation of the RDI assessment into the 3 + 3 design is easy, and there is no need to use complex statistical

Table 6
Summary of the operating characteristic of the three methods for $L = 6$ using $J = 6$ (or 1). The true RP2D is shown in bold.

	$J = 6$									$J = 1$								
	Selection rate of true RP2D, %						Average DLT rate, %	Average number of patients, n	Average trial period, cycle	Selection rate of true RP2D, %						Average DLT rate, %	Average number of patients, n	Average trial period, cycle
	1	2	3	4	5	6				1	2	3	4	5	6			
Scenario 7																		
3 + 3	**5.2**	21	31.5	26.6	11.5	2.8	57.4	14.9	14.4	5.2	21	31.5	26.6	**11.5**	2.8	20.1	14.9	14.4
3+3-RDI	**50.2**	18.8	0.9	0	0	0	42.9	6.7	14.5	5.2	21.1	31.4	26.6	**11.5**	2.8	20.1	14.9	14.4
SARDI	**39.2**	33.2	8.7	1.1	0	0	48.6	10.1	13.5	5.2	21	31.5	26.6	**11.5**	2.8	20.1	14.9	14.4
Scenario 8																		
3 + 3	1	2.5	**5.8**	9.6	48.2	32.9	29.8	19.7	19.3	1	2.5	5.8	9.6	**48.2**	32.9	7.3	19.7	19.3
3+3-RDI	24.5	27.9	**24.7**	11.3	4.4	0.1	21.8	12.2	25.9	7.6	3.2	5.4	8.1	**41.1**	28.6	6.8	17.7	17.3
SARDI	10.1	20.7	**24.4**	21.9	17.4	3.6	27.2	16.7	20.7	7.6	3.3	5.4	8.1	**40.8**	28.8	6.8	17.7	17.3
Scenario 9																		
3 + 3	0.2	0.3	1.4	3.7	4.4	**90**	16.8	19.4	18.9	0.2	0.3	1.4	3.7	4.4	**90**	3.6	19.4	18.9
3+3-RDI	6.5	11.4	20.8	22	15.5	**22.5**	17.2	16.9	35.4	0.2	0.3	1.4	3.7	4.4	**90**	3.6	19.4	18.9
SARDI	1.5	4.5	9.6	12.2	18.8	**53**	17.1	19.1	23.9	0.2	0.3	1.4	3.7	4.4	**90**	3.6	19.4	18.9
Scenario 10																		
3 + 3	36.3	6.3	0.4	0.2	0	0	96.5	5	4.6	36.3	6.3	0.4	0.2	0	0	57.2	5	4.6
3+3-RDI	0.1	0	0	0	0	0	95.9	3	4.3	36.3	6.3	0.4	0.2	0	0	57.2	5	4.6
SARDI	0.4	0	0	0	0	0	96.3	3.7	4.8	36.3	6.3	0.4	0.2	0	0	57.2	5	4.6
Scenario 11																		
3 + 3	0.4	2.9	5.5	**13**	12.6	65.6	32.1	19.6	19.1	0.4	2.9	5.5	13	12.6	**65.6**	7.9	19.6	19.1
3+3-RDI	17.5	35.2	28.4	**14.6**	2.7	0.4	24	12.4	26.4	0.5	2.9	5.4	13.1	12.6	**65.5**	7.9	19.6	19.1
SARDI	7.8	17.5	27.7	**26**	14.7	5.8	29	16.3	20.2	0.5	2.9	5.4	13.1	12.6	**65.5**	7.9	19.6	19.1
Scenario 12																		
3 + 3	0.4	**48.6**	1.9	0	0.1	49	25	19.7	19.3	0.4	**48.6**	1.9	0	0.1	49	5.9	19.7	19.3
3+3-RDI	17.8	**80.3**	0.6	0.1	0	0	15.3	10.2	22	0.4	**95.7**	3.6	0.3	0	0	2.5	9.8	9.4
SARDI	12.1	**84**	3.1	0.2	0	0	14	10.7	15.7	0.4	**95.7**	3.7	0.2	0	0	2.5	9.8	9.4

techniques. Given this, we believe that investigators who routinely use the 3 + 3 design in practice can easily use our proposed methods. Simulation studies demonstrated that the SARDI was in many cases superior to the 3+3-RDI design with respect to the selection rate of true RP2D and study period. The proposed methods could also in some cases decrease the average number of patients enrolled in the trial compared to the number of enrolled patients determined by the 3 + 3 design. Additionally, we performed the simulation studies using the actual doses of 1, 2, 4, and 8 for $L = 4$ and 1, 2, 4, 8, 16, and 32 for $L = 6$. Although the expected pRDI and expected cumulative dose for each dose level are altered, the selection rates for true RP2D, average DLT rate, average number of patients, and average trial period in the three methods were almost all identical to those shown in Tables 5 and 6 of the revised manuscript (data not shown).

In this paper, we devised an algorithm-based dose escalation method incorporating the RDI, but we can also easily incorporate the RDI assessment into Bayesian model-based dose-finding methods such as the CRM and the existing dose-finding methods for MTA. Our proposal provides a new perspective on developing dose-finding methods for phase I oncology trials. The development of a dose-finding method for evaluating the longitudinal RDI by using the mixed effect model (or marginal model based on generalized estimating equation) would be warranted for future work.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2019.100489.

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