Operating Characteristics of Restrictions on Skipping Dose Level for Adaptive Dose-Finding Method in Two-Agent Phase I Trials

Akihiro Hirakawa* and Shigeyuki Matsui*

*1 Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Aichi 466-8560, Japan
*2 Department of Biostatistics, Nagoya University Graduate School of Medicine, Aichi 466-8550, Japan
e-mail: hirakawa@med.nagoya-u.ac.jp

The model-based dose-finding method for the combination of two agents consists of the following three components: 1) dose-toxicity model, 2) start-up dose allocation rule before model-based dose-finding stage, and 3) restriction on skipping dose levels in the dose-finding algorithm. Although many authors have developed flexible dose-toxicity models as well as the start-up dose allocation rule, the restriction on skipping dose levels during the trial, has not been adequately studied. In this paper, we propose a new restriction that permits the dropping of dose combinations with toxicity probabilities that are expected to be statistically high, during the trial. We also compared the operating characteristics of the proposed strategy with those of conventional restrictions using simulation studies. Based on the results of the simulation studies, we were able to determine the performance of these strategies and provide some recommendations for their uses.

Key words: combination of two agents, dose-finding method, phase I trial, oncology.

1. Introduction

The main purpose of phase I trials in oncology is to determine the maximum tolerated dose (MTD), which is defined as the highest dose that can be administered to patients with acceptable toxicity. The Bayesian model-based dose-finding methods have been developed by many researchers to determine the MTD in single-agent phase I trials. In particular, the continual reassessment method developed by O’Quigley et al. (1990) is a prototype of these methods, and in recent years, use of the two-agent combination trial has increased. In the two-agent combination phase I trial, it is necessary to determine the MTD combinations (MTDCs) of the two agents among all the possible dose combinations.

Thall et al. (2003) proposed a six-parameter model for the toxicity probabilities of the
dose combinations and a toxicity equivalence contour for two-agent combinations. Conaway et al. (2004) determined the simple and partial orders of the toxicity probabilities by defining the nodal and non-nodal parameters. Wang and Ivanova (2005) proposed a logistic-type regression for dose combinations that used the doses of the two agents as the covariates. A Bayesian adaptive design based on latent $2 \times 2$ tables (Yin and Yuan, 2009a) and a copula-type model (Yin and Yuan, 2009b) have also been developed for two agents. Braun and Wang (2010) proposed a hierarchical Bayesian model to determine the toxicity probability of the combination of two agents. Wages et al. (2011a) developed a design based on the notion that there are pairs of dose combinations for which the ordering of the probabilities of toxicity cannot be known a priori, resulting in a partial order.

The above mentioned Bayesian model-based dose-finding method for a combination of two agents consists of the following three components; 1) dose-toxicity model, 2) start-up dose allocation rule before the model-based dose-finding stage, and 3) restriction on skipping dose levels in the dose-finding algorithm. Many authors have developed flexible dose-toxicity models for determining the dose-toxicity relationship based on the Bayesian manner. This flexible model is also based on the start-up dose allocation rule that is applied before the model-based dose-finding in order to stabilize the estimation of the parameter for the assumed dose-toxicity model. However, the restriction on skipping dose levels in the model-based dose-finding stage, has not been adequately studied.

Wang and Ivanova (2005) proposed restricting dose escalation or de-escalation to one dose level of change only, and not permitting progression in diagonal direction (corresponding to simultaneous escalation or de-escalation of both agents) based on the results of simulation studies. Yin and Yuan (2009a, 2009b) and Hirakawa et al. (2013) also used the same restriction in their dose-finding methods. Braun and Wang (2010) proposed the restriction of dose escalation or de-escalation to one dose level of change only, but allowed a simultaneous escalation or de-escalation of both agents. In contrast, Wages et al. (2010a, 2010b) incorporated no restriction on skipping dose levels.

The common aspect of these restrictions is that all the dose combinations have the possibility of being allocated to the next cohort of patients throughout the trial. However, it may be more effective to drop the dose combination with a possible high risk of toxicity if we identify such dose combinations during the trial. In order to accommodate this requirement, we propose a new restriction that allows the dropping of dose combinations with toxicity probabilities that are expected to be high based on the toxicity data at the time, during the trial. We also compared the operating characteristics of the proposed restriction with those of conventional strategies using simulation studies. Based on the results of simulation studies, we evaluated the performance of these strategies and provided some recommendations for their use.

This article is organized in the following manner. We briefly described the components of
the model-based dose-finding method for the combination of two agents and introduced the dose-toxicity model and the start-up dose allocation rule used in this study in Section 2. In Section 3, we described the two restrictions on skipping dose levels and subsequently proposed dose-dropping strategies for the dose-finding method for two-agent combination trials. We compared the operating characteristics of the proposed strategy and the existing restrictions in Section 4, and finally discussed some of our findings and projections in Section 5.

2. Dose-toxicity models and the start-up dose allocation rules

The dose-toxicity model is a statistical model that adequately captures the dose-toxicity relationship whenever a combination of two agents is administered. Several researchers have proposed useful models to accommodate the possible synergistic (or antagonistic) effects of the combination of two agents on toxicity, including a logistic-type model (Wang and Ivanova, 2005), the Clayton and Gumbel’s copula-type models (Yin and Yuan, 2009a), and a shrinkage logistic model with an interaction term (Hirakawa et al., 2013). We here describe the two dose-toxicity models, although other models can also be applied in practice.

2.1 Clayton and Gumbel copulas

We introduced the Clayton and Gumbel copula models proposed by Yin and Yuan (2009b). Let $p_j$ and $q_k$ be the pre-specified toxicity probabilities corresponding to $A_j (j = 1, \ldots, J)$ and $B_k (k = 1, \ldots, K)$, respectively, and $p_j^\alpha$ and $q_k^\beta$ be the true probabilities of the toxicity of agents $A$ and $B$, respectively, where $\alpha > 0$ and $\beta > 0$ are unknown parameters. Let the true probability of the toxicity of combination $(A_j, B_k)$ be denoted as $\pi_{jk}$. The Clayton and Gumbel copula models are given as:

$$
\pi_{jk} = 1 - \left\{ \left( 1 - p_j^\alpha \right)^{-\gamma} + \left( 1 - q_k^\beta \right)^{-\gamma} - 1 \right\}^{-1/\gamma}
$$

and

$$
\pi_{jk} = 1 - \exp\left\{ -\left\{ -\log\left( 1 - p_j^\alpha \right) \right\}^{1/\gamma} + \left\{ -\log\left( 1 - q_k^\beta \right) \right\}^{1/\gamma} \right\},
$$

respectively, where the parameter $\gamma > 0$ characterizes the interaction of the two agents. Applying one of the copula models to the data obtained at a particular time, the posterior distribution is obtained by the following formula,

$$
f(\alpha, \beta, \gamma \mid \text{Data}) \propto L(\alpha, \beta, \gamma \mid \text{Data}) f(\alpha) f(\beta) f(\gamma)
$$

where $L(\alpha, \beta, \gamma \mid \text{Data})$ is the likelihood function of the model while $f(\alpha)$, $f(\beta)$, and $f(\gamma)$ are the prior distributions, respectively. After the start-up dose allocation stage (introduced in the next section), we updated the posterior distributions of the unknown parameters (i.e., $\alpha, \beta, \gamma$) using the Gibbs sampling algorithm and allocated the dose combination with an estimated posterior probability of toxicity $\hat{\pi}_{jk}$ close to the target level ($\phi$) to the next cohort of patients.
2.2 Start-up dose allocation stage

The start-up dose allocation rule is applied, until the required amount of data is obtained. This is introduced to stabilize the estimation of the parameters of the assumed dose-toxicity model. For example, the start-up dose allocation rule in the Bayesian dose-finding method is often continued until the first sign of toxicity is observed. In this section, we introduced the two start-up allocation rules proposed by Yin and Yuan (2009b) and Wages et al. (2011b). We first introduced the rule of Yin and Yuan (2009b), termed the YY’s rule with the following specifications: 1) treat patients along the vertical dose escalation in the order of \((A_1, B_1), (A_1, B_2), \cdots\) until the first DLT is observed, 2) after that, treat patients along the horizontal dose escalation in the order of \((A_2, B_1), (A_3, B_1), \cdots\) until the first DLT is observed. The rule of Wages et al. (2010b) termed the WCO’s rule, begins with the division of the dose combination matrix to several groups in the diagonals of the combination matrix. For example, in the \(4 \times 4\) dose combination matrix, seven groups are generated. The trial begins with the lowest combination \((A_1, B_1);\) first group) and in the absence of toxicity, escalates to the second group \((A_1, B_2)\) or \((A_2, B_1)\). In this step, if the second cohort is allocated to \((A_1, B_2)\), then we automatically allocate the third cohort to \((A_2, B_1)\). That is, we sample without making any replacements from the dose combinations available until all available dose combinations in that group are tested as long as no toxicities occur.

3. Proposed restriction of dose-dropping strategy

After obtaining the data in the start-up dose allocation stage, the dose-finding algorithm subsequently determines the dose combination to be allocated to the next cohort. This determination is achieved using the posterior probability estimated on the basis of the assumed dose-toxicity model while keeping a pre-specified restriction on skipping dose levels. In this section, we introduced the widely used two restrictions on skipping dose levels and subsequently propose the dose-dropping strategy.

3.1 Existing restrictions on skipping dose levels

Yin and Yuan (2009b) and Hirakawa et al. (2013) argue that moving from the current dose \((A_j, B_k)\) to \((A_{j+1}, B_{k+1})\), which entails increasing the doses of both agents, possibly exposes the patients to a higher risk of toxicity. Therefore, they proposed the restriction of dose escalation or de-escalation to one dose level of change only while also prohibiting a move along the diagonal direction (corresponding to simultaneous escalation or de-escalation of both agents, Restriction 1). This implies that at the current dose combination \((A_j, B_k)\), the next cohort of patients would be allocated to the adjacent dose combination in the set;

\[
S_1 = \{(j - 1, k), (j + 1, k), (j, k), (j, k + 1), (j, k - 1), (j + 1, k - 1), (j - 1, k + 1)\}.
\]

Conversely, Braun and Wang (2010) proposed the restriction of dose escalation or de-escalation to one dose level of change only, but allowed a simultaneous escalation or de-escalation.
Restrictions on Skipping Dose Level for Dose-Finding Method

3.2 Proposed dose-dropping strategy

Here, we proposed the dose-dropping strategy as a new restriction on skipping dose levels. Specifically, the proposed restriction allows us to drop the dose combination with a possible high toxicity risk during the trial using the following strategy. After applying a start-up rule, we can then obtain the values of $\hat{\pi}_{jk}$ based on the assumed dose-toxicity model (i.e., Clayton or Gumbel copula model in this paper). For all $J \times K$ dose combinations, we can then determine whether the $\Pr(\hat{\pi}_{jk} > \phi)$ is higher than the prespecified dose-dropping probability ($\Psi_{\text{drop}}$), and also whether the cumulative number of patients allocated to the dose combination $N_{jk}$ is more than or equal to the prespecified value of $N_{\text{drop}}$, that is;

$$\Pr(\hat{\pi}_{jk} > \phi) > \Psi_{\text{drop}} \text{ and } N_{jk} \geq N_{\text{drop}}.$$ 

Notably, we include the criterion of $N_{jk} \geq N_{\text{drop}}$ to address the issue that the estimate posterior probability ($\hat{\pi}_{jk}$) is possibly biased if the cumulative number of patients allocated to the dose combination $(A_j, B_k)$ is too few. If the dose combination $(A_j, B_k)$ satisfies these criteria, then it is dropped from that point on in the study. Then, among the remaining dose combinations, we would allocate the next cohort of patients to the dose combination with the average posterior estimate $\hat{\pi}_{jk}$ closest to the target toxicity probability $\phi$ without a restriction on skipping dose levels. The reasonable values of $\Psi_{\text{drop}}$ and $N_{\text{drop}}$ for the planned trial should be determined based on the simulation studies.

In addition, we also devised other dose-dropping strategies in this study and examined their operating characteristics. The specific restrictions included; 1) the proposed dose-dropping strategy is started following the enrollment of half of the prespecified maximum patients, and 2) reinstatement of dose combinations that were once dropped during the trial is allowed. However, we found that the operating characteristics of these methods were similar to or worse than that of the above-mentioned dose-dropping strategy.

4. Simulation studies

4.1 Simulation setting

We evaluated the operating characteristics of the proposed method by simulating 10 scenarios using $4 \times 4$ and $4 \times 3$ dose combination matrices with different positions and number of true MTDCs as shown in Table 1. The target toxicity probability that is clinically allowed ($\phi$) was set at 0.3. The maximum sample size ($N_{\text{max}}$) was set at 30. Each simulation consisted of 1,000 trials. In the simulation studies, we used the Clayton and Gumbel copula models and applied Jpn J Biomet Vol.36, No.1, 2015
Table 1. Ten scenarios for a two-agent combination trial with the target probability of toxicity 0.3 (true or acceptable MTDCs are in boldface)

|       | Scenario 1 | Scenario 6 |
|-------|------------|------------|
|       | B = 1  | 2  | 3  | 4  | B = 1  | 2  | 3  |
| A = 1 | 0.05  | 0.15 | 0.20 | **0.30** | 0.01  | 0.05 | 0.20 |
| 2     | 0.15  | 0.25 | **0.30** | 0.40  | 0.05  | 0.25 | **0.30** |
| 3     | 0.20  | **0.30** | 0.50 | 0.55 | 0.20  | **0.30** | 0.40 |
| 4     | **0.30** | 0.40 | 0.55 | 0.60 | **0.30** | 0.40 | 0.60 |
|       | Scenario 2 | Scenario 7 |
| 1     | 0.10  | 0.20 | **0.30** | 0.40  | 0.10  | 0.20 | **0.30** |
| 2     | 0.20  | 0.40 | 0.45 | 0.50  | 0.20  | 0.35 | 0.45 |
| 3     | **0.30** | 0.45 | 0.50 | 0.60  | **0.30** | 0.45 | 0.50 |
| 4     | 0.40  | 0.50 | 0.60 | 0.70  | 0.45  | 0.50 | 0.50 |
|       | Scenario 3 | Scenario 8 |
| 1     | 0.01  | 0.05 | 0.10 | 0.20  | 0.01  | 0.05 | 0.15 |
| 2     | 0.05  | 0.10 | 0.20 | **0.30** | 0.05  | 0.20 | **0.30** |
| 3     | 0.10  | **0.30** | 0.40 | 0.45  | **0.30** | 0.60 | 0.70 |
| 4     | 0.40  | 0.40 | 0.45 | 0.50  | 0.60  | 0.70 | 0.80 |
|       | Scenario 4 | Scenario 9 |
| 1     | 0.05  | 0.10 | 0.20 | 0.40  | 0.05  | 0.25 | 0.45 |
| 2     | 0.10  | 0.15 | **0.30** | 0.45  | 0.20  | 0.45 | 0.55 |
| 3     | 0.20  | 0.25 | 0.40 | 0.55  | **0.30** | 0.55 | 0.70 |
| 4     | 0.35  | 0.40 | 0.50 | 0.60  | 0.55  | 0.80 | 0.80 |
|       | Scenario 5 | Scenario 10 |
| 1     | 0.01  | 0.05 | 0.10 | 0.40  | 0.05  | 0.10 | 0.15 |
| 2     | 0.05  | 0.10 | 0.20 | 0.50  | **0.28** | **0.30** | 0.45 |
| 3     | 0.15  | **0.28** | **0.30** | 0.60 | **0.30** | **0.32** | 0.50 |
| 4     | 0.20  | **0.30** | **0.32** | 0.70 | 0.40  | 0.50 | 0.60 |

the YY’s and WCO’s start-up dose-allocation rules. In each method, the values of $p_j$ were set at 0.1, 0.2, and 0.3 for $J = 3$ and 0.075, 0.15, 0.225, and 0.3 for $J = 4$. The same values were set for $q_k$, and we assumed a gamma distribution with a mean of 1 and variance of 0.5 for $\alpha$ and $\beta$. In addition, we assumed a mean of 1 and variance of 1000 for $\gamma$ since the prior distribution and the cohort size of patients was set at one. We also discontinued the trial for safety reasons when the average posterior estimate of toxicity for the lowest dose combination ($A_1, B_1$) was more than 0.8.

We compared the operating characteristics of the proposed dose-dropping strategy with those of the non-restriction and restrictions 1 and 2. In the proposed restriction, we used the convenient values of 0.3, 0.5, and 0.7 for the $\Psi_{\text{drop}}$ and 2 and 3 for the $N_{\text{drop}}$. We summarized the selection rates for the true MTDCs and unacceptable toxicity dose combinations (UTDCs), which is defined as the dose combination with a true toxicity probability higher than the target level of $\phi = 0.3$. We also summarized the selection rates for the average number of patients allocated to true MTDCs and the overall percentage of observed toxicities.
4.2 Summary of simulation results

Table 2 shows the recommendation rates for the true MTDCs of the proposed and existing restrictions. The results of the analysis using the Clayton model and YY’s start-up rule revealed that the proposed dose-dropping strategies provided high recommendation rates for the true

| Table 2. Recommendation rates for true (or acceptable) MTDCs |
|-------------------------------------------------------------|
| **Scenario = 1 2 3 4 5 6 7 8 9 10** |
| **Clayton model using YY’s start rule** |
| No | 36 | 28 | 28 | 13 | 39 | 40 | 27 | 42 | 12 | 48 |
| Restriction 1 | 37 | 25 | 26 | 16 | 42 | 39 | 25 | 39 | 12 | 53 |
| Restriction 2 | 38 | 24 | 29 | 14 | 45 | 40 | 26 | 41 | 12 | 54 |
| Proposed ($\psi_{\text{drop}} = 0.3, n_{\text{drop}} = 2$) | 35 | 24 | 28 | 13 | 43 | 40 | 19 | 41 | 12 | 45 |
| Proposed ($\psi_{\text{drop}} = 0.3, n_{\text{drop}} = 3$) | 38 | 28 | 24 | 14 | 41 | 39 | 26 | 43 | 11 | 46 |
| Proposed ($\psi_{\text{drop}} = 0.5, n_{\text{drop}} = 2$) | 35 | 25 | 28 | 13 | 46 | 41 | 23 | 38 | 12 | 45 |
| Proposed ($\psi_{\text{drop}} = 0.5, n_{\text{drop}} = 3$) | 38 | 25 | 26 | 13 | 40 | 41 | 25 | 44 | 10 | 48 |
| Proposed ($\psi_{\text{drop}} = 0.7, n_{\text{drop}} = 2$) | 37 | 26 | 26 | 13 | 40 | 42 | 23 | 39 | 12 | 48 |
| Proposed ($\psi_{\text{drop}} = 0.7, n_{\text{drop}} = 3$) | 38 | 26 | 27 | 12 | 39 | 42 | 26 | 42 | 12 | 51 |
| **Clayton model using WCO’s start rule** |
| No | 40 | 29 | 27 | 15 | 41 | 43 | 24 | 43 | 12 | 53 |
| Restriction 1 | 37 | 23 | 29 | 16 | 45 | 41 | 23 | 39 | 11 | 57 |
| Restriction 2 | 41 | 22 | 25 | 13 | 45 | 42 | 21 | 43 | 12 | 57 |
| Proposed ($\psi_{\text{drop}} = 0.3, n_{\text{drop}} = 2$) | 42 | 24 | 26 | 10 | 45 | 47 | 26 | 33 | 13 | 43 |
| Proposed ($\psi_{\text{drop}} = 0.3, n_{\text{drop}} = 3$) | 40 | 29 | 25 | 12 | 46 | 40 | 27 | 40 | 11 | 46 |
| Proposed ($\psi_{\text{drop}} = 0.5, n_{\text{drop}} = 2$) | 39 | 25 | 25 | 12 | 47 | 43 | 26 | 36 | 12 | 43 |
| Proposed ($\psi_{\text{drop}} = 0.5, n_{\text{drop}} = 3$) | 36 | 29 | 24 | 14 | 42 | 40 | 25 | 43 | 13 | 51 |
| Proposed ($\psi_{\text{drop}} = 0.7, n_{\text{drop}} = 2$) | 41 | 27 | 27 | 12 | 43 | 41 | 24 | 42 | 14 | 49 |
| Proposed ($\psi_{\text{drop}} = 0.7, n_{\text{drop}} = 3$) | 44 | 23 | 23 | 14 | 43 | 41 | 26 | 43 | 13 | 52 |
| **Gumbel model using YY’s start rule** |
| No | 32 | 23 | 24 | 11 | 39 | 40 | 27 | 45 | 11 | 48 |
| Restriction 1 | 34 | 21 | 25 | 12 | 47 | 38 | 21 | 42 | 11 | 52 |
| Restriction 2 | 38 | 23 | 22 | 12 | 47 | 37 | 21 | 43 | 11 | 54 |
| Proposed ($\psi_{\text{drop}} = 0.3, n_{\text{drop}} = 2$) | 33 | 21 | 24 | 11 | 45 | 38 | 19 | 42 | 12 | 44 |
| Proposed ($\psi_{\text{drop}} = 0.3, n_{\text{drop}} = 3$) | 35 | 25 | 24 | 12 | 38 | 35 | 25 | 45 | 12 | 46 |
| Proposed ($\psi_{\text{drop}} = 0.5, n_{\text{drop}} = 2$) | 32 | 22 | 23 | 12 | 42 | 40 | 20 | 42 | 12 | 43 |
| Proposed ($\psi_{\text{drop}} = 0.5, n_{\text{drop}} = 3$) | 34 | 24 | 22 | 12 | 40 | 38 | 22 | 43 | 11 | 45 |
| Proposed ($\psi_{\text{drop}} = 0.7, n_{\text{drop}} = 2$) | 31 | 25 | 22 | 15 | 39 | 37 | 20 | 42 | 11 | 47 |
| Proposed ($\psi_{\text{drop}} = 0.7, n_{\text{drop}} = 3$) | 35 | 23 | 21 | 13 | 42 | 40 | 23 | 45 | 9 | 46 |
| **Gumbel model using WCO’s start rule** |
| No | 32 | 23 | 24 | 11 | 39 | 40 | 27 | 45 | 11 | 48 |
| Restriction 1 | 34 | 21 | 25 | 12 | 47 | 38 | 21 | 42 | 11 | 52 |
| Restriction 2 | 38 | 23 | 22 | 12 | 47 | 37 | 21 | 43 | 11 | 54 |
| Proposed ($\psi_{\text{drop}} = 0.3, n_{\text{drop}} = 2$) | 33 | 21 | 24 | 11 | 45 | 38 | 19 | 42 | 12 | 44 |
| Proposed ($\psi_{\text{drop}} = 0.3, n_{\text{drop}} = 3$) | 35 | 25 | 24 | 12 | 38 | 35 | 25 | 45 | 12 | 46 |
| Proposed ($\psi_{\text{drop}} = 0.5, n_{\text{drop}} = 2$) | 32 | 22 | 23 | 12 | 42 | 40 | 20 | 42 | 12 | 43 |
| Proposed ($\psi_{\text{drop}} = 0.5, n_{\text{drop}} = 3$) | 34 | 24 | 22 | 12 | 40 | 38 | 22 | 43 | 11 | 45 |
| Proposed ($\psi_{\text{drop}} = 0.7, n_{\text{drop}} = 2$) | 31 | 25 | 22 | 15 | 39 | 37 | 20 | 42 | 11 | 47 |
| Proposed ($\psi_{\text{drop}} = 0.7, n_{\text{drop}} = 3$) | 35 | 23 | 21 | 13 | 42 | 40 | 23 | 45 | 9 | 46 |
MTDCs of 1–5% in several cases, compared with the three restriction strategies. However, there were no combinations of values of $\Psi_{\text{drop}}$ and $N_{\text{drop}}$ that consistently improved the recommendation rates for the true MTDC more than the three restriction strategies. The similar relationships discovered between the proposed and existing restrictions were also evident in the

Table 3. Recommendation rates for UTDCs

| Restriction | Scenario = 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|-------------|--------------|---|---|---|---|---|---|---|---|----|
| No          | 23           | 35 | 45 | 40 | 27 | 29 | 36 | 21 | 70  | 31 |
| Restriction 1 | 22           | 34 | 44 | 37 | 25 | 31 | 37 | 22 | 67  | 29 |
| Restriction 2 | 21           | 36 | 44 | 39 | 23 | 30 | 36 | 20 | 68  | 28 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 2$) | 23           | 37 | 42 | 38 | 22 | 31 | 38 | 21 | 68  | 31 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 3$) | 22           | 34 | 45 | 38 | 24 | 31 | 37 | 20 | 75  | 31 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 2$) | 24           | 35 | 43 | 37 | 21 | 29 | 37 | 23 | 68  | 32 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 3$) | 22           | 35 | 45 | 40 | 27 | 30 | 36 | 18 | 74  | 31 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 2$) | 23           | 34 | 44 | 39 | 25 | 29 | 37 | 21 | 70  | 31 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 3$) | 22           | 36 | 44 | 40 | 26 | 29 | 36 | 20 | 70  | 29 |
| Clayton model using WCO’s start rule |
| No          | 23           | 33 | 44 | 41 | 25 | 26 | 37 | 17 | 63  | 25 |
| Restriction 1 | 22           | 36 | 43 | 38 | 23 | 27 | 38 | 18 | 63  | 21 |
| Restriction 2 | 21           | 38 | 46 | 40 | 21 | 25 | 39 | 18 | 63  | 23 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 2$) | 22           | 36 | 41 | 45 | 20 | 18 | 34 | 16 | 68  | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 3$) | 24           | 34 | 43 | 41 | 24 | 28 | 35 | 17 | 70  | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 2$) | 24           | 36 | 44 | 42 | 19 | 23 | 34 | 16 | 68  | 26 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 3$) | 24           | 36 | 45 | 42 | 24 | 28 | 37 | 14 | 67  | 23 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 2$) | 22           | 36 | 44 | 44 | 24 | 28 | 36 | 15 | 65  | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 3$) | 20           | 37 | 45 | 40 | 23 | 26 | 37 | 18 | 66  | 25 |
| Clayton model using YY’s start rule |
| No          | 25           | 38 | 43 | 40 | 26 | 29 | 35 | 21 | 66  | 31 |
| Restriction 1 | 25           | 39 | 44 | 41 | 22 | 29 | 39 | 22 | 68  | 29 |
| Restriction 2 | 23           | 37 | 46 | 41 | 22 | 30 | 40 | 22 | 67  | 27 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 2$) | 24           | 37 | 44 | 38 | 21 | 28 | 36 | 21 | 69  | 30 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 3$) | 24           | 35 | 44 | 40 | 26 | 30 | 37 | 20 | 70  | 31 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 2$) | 26           | 36 | 44 | 39 | 22 | 29 | 37 | 23 | 67  | 30 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 3$) | 24           | 39 | 45 | 41 | 26 | 31 | 39 | 21 | 70  | 32 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 2$) | 25           | 33 | 44 | 37 | 25 | 32 | 39 | 21 | 67  | 31 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 3$) | 24           | 37 | 45 | 41 | 25 | 29 | 38 | 21 | 70  | 32 |
| Gumbel model using YY’s start rule |
| No          | 24           | 36 | 44 | 40 | 25 | 25 | 36 | 14 | 55  | 23 |
| Restriction 1 | 23           | 36 | 44 | 38 | 23 | 23 | 35 | 16 | 57  | 21 |
| Restriction 2 | 25           | 36 | 45 | 38 | 23 | 25 | 36 | 18 | 55  | 21 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 2$) | 28           | 37 | 43 | 43 | 22 | 25 | 33 | 19 | 64  | 24 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 3$) | 26           | 39 | 46 | 41 | 25 | 29 | 41 | 18 | 67  | 29 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 2$) | 25           | 41 | 45 | 44 | 21 | 25 | 37 | 18 | 67  | 23 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 3$) | 22           | 39 | 44 | 42 | 25 | 28 | 41 | 19 | 67  | 28 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 2$) | 24           | 38 | 45 | 42 | 24 | 28 | 36 | 17 | 66  | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 3$) | 23           | 40 | 45 | 43 | 24 | 29 | 36 | 18 | 66  | 28 |

Jpn J Biomet Vol. 36, No. 1, 2015
remaining three combination cases of dose-toxicity models and start-up rules. In scenarios 1, 2, 6, and 7, the proposed restriction appeared to improve the recommendation rates for the true MTDCs, compared with those of the other scenarios. In scenarios 4 and 10, the benefit of incorporating the dose-dropping strategy, was not demonstrated.

Table 4. Average number of patients allocated to true MTDCs

| Restriction | Scenario = 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|-------------|--------------|---|---|---|---|---|---|---|---|----|
| No          | 11           | 6 | 4 | 2 | 6 | 9 | 8 | 7 | 3 | 10 |
| Restriction 1 | 10           | 6 | 4 | 2 | 7 | 8 | 7 | 7 | 3 | 11 |
| Restriction 2 | 10           | 6 | 4 | 2 | 7 | 9 | 7 | 7 | 3 | 11 |
| Proposed (Ψ_{drop} = 0.3, N_{drop} = 2) | 10 | 6 | 4 | 2 | 6 | 9 | 7 | 7 | 3 | 10 |
| Proposed (Ψ_{drop} = 0.3, N_{drop} = 3) | 10 | 6 | 4 | 2 | 6 | 9 | 8 | 7 | 3 | 10 |
| Proposed (Ψ_{drop} = 0.5, N_{drop} = 2) | 10 | 6 | 4 | 2 | 6 | 9 | 8 | 7 | 3 | 10 |
| Proposed (Ψ_{drop} = 0.5, N_{drop} = 3) | 11 | 6 | 4 | 2 | 6 | 9 | 8 | 7 | 3 | 10 |
| Proposed (Ψ_{drop} = 0.7, N_{drop} = 2) | 11 | 6 | 4 | 2 | 6 | 8 | 8 | 7 | 3 | 10 |
| Proposed (Ψ_{drop} = 0.7, N_{drop} = 3) | 11 | 6 | 4 | 2 | 6 | 9 | 8 | 7 | 3 | 10 |
| Clayton model using YY’s start rule |
| No | 9 | 6 | 5 | 3 | 9 | 9 | 6 | 9 | 3 | 13 |
| Restriction 1 | 9 | 6 | 5 | 3 | 9 | 9 | 6 | 8 | 3 | 14 |
| Restriction 2 | 9 | 6 | 5 | 3 | 9 | 9 | 6 | 8 | 3 | 14 |
| Proposed (Ψ_{drop} = 0.3, N_{drop} = 2) | 9 | 6 | 5 | 3 | 9 | 9 | 6 | 9 | 3 | 12 |
| Proposed (Ψ_{drop} = 0.3, N_{drop} = 3) | 9 | 6 | 5 | 3 | 9 | 9 | 6 | 9 | 3 | 13 |
| Proposed (Ψ_{drop} = 0.5, N_{drop} = 2) | 9 | 6 | 5 | 3 | 9 | 9 | 6 | 9 | 3 | 12 |
| Proposed (Ψ_{drop} = 0.5, N_{drop} = 3) | 9 | 6 | 5 | 3 | 9 | 9 | 6 | 9 | 3 | 13 |
| Proposed (Ψ_{drop} = 0.7, N_{drop} = 2) | 9 | 6 | 5 | 3 | 8 | 9 | 6 | 9 | 3 | 12 |
| Proposed (Ψ_{drop} = 0.7, N_{drop} = 3) | 9 | 6 | 5 | 3 | 9 | 9 | 6 | 9 | 3 | 13 |
| Clayton model using WCO’s start rule |
| No | 10 | 6 | 3 | 2 | 6 | 8 | 8 | 7 | 3 | 10 |
| Restriction 1 | 10 | 5 | 4 | 2 | 8 | 8 | 7 | 7 | 3 | 11 |
| Restriction 2 | 10 | 5 | 4 | 2 | 8 | 8 | 7 | 7 | 3 | 11 |
| Proposed (Ψ_{drop} = 0.3, N_{drop} = 2) | 10 | 6 | 4 | 2 | 6 | 8 | 7 | 7 | 3 | 10 |
| Proposed (Ψ_{drop} = 0.3, N_{drop} = 3) | 10 | 6 | 3 | 2 | 6 | 8 | 7 | 7 | 3 | 10 |
| Proposed (Ψ_{drop} = 0.5, N_{drop} = 2) | 10 | 6 | 3 | 2 | 6 | 8 | 7 | 7 | 3 | 9 |
| Proposed (Ψ_{drop} = 0.5, N_{drop} = 3) | 10 | 6 | 3 | 2 | 6 | 8 | 7 | 7 | 3 | 10 |
| Proposed (Ψ_{drop} = 0.7, N_{drop} = 2) | 10 | 6 | 3 | 2 | 6 | 8 | 7 | 7 | 3 | 10 |
| Proposed (Ψ_{drop} = 0.7, N_{drop} = 3) | 10 | 6 | 3 | 2 | 6 | 8 | 7 | 7 | 3 | 10 |
| Gumbel model using YY’s start rule |
| No | 8 | 6 | 4 | 2 | 8 | 8 | 6 | 9 | 3 | 13 |
| Restriction 1 | 8 | 6 | 5 | 3 | 8 | 8 | 6 | 9 | 3 | 14 |
| Restriction 2 | 8 | 6 | 5 | 3 | 8 | 8 | 6 | 9 | 3 | 14 |
| Proposed (Ψ_{drop} = 0.3, N_{drop} = 2) | 8 | 6 | 4 | 2 | 8 | 8 | 6 | 8 | 3 | 12 |
| Proposed (Ψ_{drop} = 0.3, N_{drop} = 3) | 8 | 6 | 4 | 2 | 8 | 8 | 6 | 9 | 3 | 12 |
| Proposed (Ψ_{drop} = 0.5, N_{drop} = 2) | 8 | 6 | 4 | 2 | 8 | 8 | 6 | 8 | 3 | 12 |
| Proposed (Ψ_{drop} = 0.5, N_{drop} = 3) | 8 | 6 | 4 | 2 | 8 | 8 | 6 | 9 | 3 | 12 |
| Proposed (Ψ_{drop} = 0.7, N_{drop} = 2) | 8 | 6 | 4 | 2 | 8 | 8 | 6 | 8 | 3 | 12 |
| Proposed (Ψ_{drop} = 0.7, N_{drop} = 3) | 8 | 6 | 4 | 2 | 8 | 8 | 6 | 9 | 3 | 12 |
The remaining indices of the recommendation rates for the UTDCs, the average number of patients allocated to the true MTDCs, and the overall percentage of observed toxicities are shown in Tables 3–5, respectively. The operating characteristics of the indices of the proposed restriction were quite similar to those of the existing restrictions. We also calculated the drop

| Table 5. Overall percentage of observed toxicities |
|--------------------------------------------------|
| Restriction | Scenario = 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Clayon model using YY’s start rule | | | | | | | | | | |
| No | 26 | 28 | 25 | 26 | 25 | 25 | 27 | 26 | 26 | 26 |
| Restriction 1 | 26 | 28 | 25 | 26 | 25 | 25 | 27 | 26 | 26 | 26 |
| Restriction 2 | 26 | 28 | 25 | 26 | 25 | 25 | 27 | 26 | 26 | 26 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 2$) | 26 | 28 | 25 | 26 | 25 | 25 | 27 | 26 | 26 | 26 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 3$) | 26 | 29 | 25 | 26 | 25 | 24 | 28 | 26 | 26 | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 2$) | 26 | 29 | 25 | 26 | 25 | 25 | 28 | 26 | 25 | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 3$) | 26 | 29 | 25 | 26 | 25 | 25 | 28 | 26 | 25 | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 2$) | 26 | 29 | 25 | 26 | 25 | 25 | 28 | 26 | 25 | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 3$) | 26 | 29 | 25 | 26 | 25 | 25 | 28 | 26 | 25 | 25 |

| Clayon model using WCO’s start rule | | | | | | | | | | |
| No | 27 | 29 | 26 | 27 | 26 | 26 | 28 | 26 | 28 | 27 |
| Restriction 1 | 27 | 29 | 26 | 27 | 26 | 27 | 28 | 28 | 28 | 28 |
| Restriction 2 | 27 | 29 | 26 | 27 | 26 | 27 | 28 | 28 | 28 | 28 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 2$) | 27 | 29 | 26 | 27 | 26 | 26 | 29 | 27 | 27 | 27 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 3$) | 27 | 29 | 26 | 27 | 26 | 26 | 28 | 28 | 27 | 27 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 2$) | 27 | 29 | 26 | 27 | 26 | 26 | 29 | 27 | 27 | 27 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 3$) | 27 | 29 | 26 | 27 | 26 | 26 | 28 | 28 | 27 | 27 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 2$) | 27 | 29 | 26 | 27 | 26 | 26 | 29 | 28 | 27 | 27 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 3$) | 27 | 29 | 26 | 27 | 26 | 26 | 28 | 28 | 27 | 27 |

| Gumbel model using YY’s start rule | | | | | | | | | | |
| No | 26 | 28 | 24 | 26 | 24 | 24 | 27 | 25 | 25 | 25 |
| Restriction 1 | 26 | 28 | 24 | 26 | 24 | 25 | 28 | 26 | 25 | 25 |
| Restriction 2 | 26 | 28 | 24 | 26 | 25 | 25 | 28 | 26 | 25 | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 2$) | 26 | 29 | 24 | 26 | 24 | 24 | 28 | 25 | 25 | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 3$) | 26 | 29 | 24 | 26 | 24 | 24 | 28 | 25 | 25 | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 2$) | 26 | 29 | 24 | 26 | 24 | 24 | 28 | 25 | 25 | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 3$) | 26 | 29 | 24 | 26 | 25 | 24 | 28 | 25 | 25 | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 2$) | 26 | 29 | 24 | 26 | 25 | 24 | 28 | 26 | 25 | 25 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 3$) | 26 | 28 | 24 | 26 | 24 | 26 | 28 | 26 | 25 | 25 |

| Gumbel model using WCO’s start rule | | | | | | | | | | |
| No | 26 | 28 | 24 | 26 | 24 | 24 | 27 | 25 | 25 | 25 |
| Restriction 1 | 26 | 28 | 24 | 26 | 24 | 25 | 28 | 26 | 27 | 27 |
| Restriction 2 | 26 | 28 | 24 | 26 | 25 | 25 | 28 | 26 | 27 | 27 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 2$) | 26 | 29 | 24 | 26 | 24 | 24 | 29 | 26 | 27 | 27 |
| Proposed ($\Psi_{\text{drop}} = 0.3, N_{\text{drop}} = 3$) | 26 | 29 | 24 | 26 | 24 | 24 | 28 | 26 | 27 | 27 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 2$) | 26 | 29 | 24 | 26 | 24 | 25 | 29 | 26 | 27 | 27 |
| Proposed ($\Psi_{\text{drop}} = 0.5, N_{\text{drop}} = 3$) | 26 | 28 | 24 | 26 | 25 | 28 | 26 | 27 | 27 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 2$) | 26 | 29 | 24 | 26 | 24 | 25 | 28 | 26 | 27 | 27 |
| Proposed ($\Psi_{\text{drop}} = 0.7, N_{\text{drop}} = 3$) | 26 | 28 | 24 | 26 | 25 | 25 | 28 | 26 | 27 | 27 |
rate for each dose combination (see Web Tables 1 and 2). We observed that the drop rates for $N_{\text{drop}} = 2$ were higher than for $N_{\text{drop}} = 3$. The remarkable association between the drop rates for the unacceptable toxicity dose combinations and the recommendation rates for the true MTDCs (grey color and bold font, respectively, Web Tables 1 and 2) were not found in the scenarios we selected.

5. Discussion

In this paper, we proposed a dose-dropping strategy for the dose-finding method for the combination of two agents. In addition, we also compared the operating characteristics of the proposed strategy with those of the existing restrictions using the simulation studies. In the simulation studies, the impact of the dose-dropping criteria ($\Psi_{\text{drop}}$ and $N_{\text{drop}}$) was also evaluated.

Our simulation studies demonstrated that overall performances of the proposed strategy were similar to those of the other three restrictions on average. This is because that the proposed strategy drops the dose combination with a possible high risk of toxicity, but the dose-finding method using the Restrictions 1 and 2 also avoids allocating the cohort of patients to such dose combinations. This indicated that the operating characteristics between the proposed strategy and the conventional restrictions may essentially be same in the dose-finding methods for combination of two agents. Thus, although we can use the different restriction that combines the Restriction 1 (or 2) and the proposed strategy, it would not be expected to make any further improvement of the performances. We also conducted the simulation studies using sample size of 48; however, the relative relationships of the operating characteristics among the restrictions remained about the same (data not shown). Nevertheless, there were some findings from the results of simulation studies. We found that the proposed strategy improved the recommendation rates for the true MTDCs by 1–5% in some cases and performed relatively well, under scenarios with true MTD combinations that existed in the diagonal direction of the dose combination matrix (Scenarios 1, 2, 6, and 7). Therefore, the proposed dose-dropping strategy is a feasible alternative for the restriction on skipping dose levels, for adaptive dose-finding methods in two-agent phase I trials. Interestingly, we observed that removing the restriction on skipping dose levels did not compound the recommendation rates for UTDCs in our simulation studies, which was noteworthy. Many authors have incorporated a restriction on skipping dose levels in their dose-finding methods, but may occasionally prefer to not apply it.

Despite many adaptive dose-finding methods that have been developed, researchers have not focused on the restrictions on skipping dose levels. The restrictions we evaluated varied depending on the dose-toxicity model, start-up dose allocation rule, and toxicity scenario. Our results should be useful in selecting suitable restrictions for skipping dose levels in the dose-finding method.
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