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A Step-by-Step Guide to Calculating Relative Dose Intensity in Solid Tumor Studies

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ABSTRACT

The Relative Dose Intensity (RDI) is an essential parameter used to measure the actual dose over a specific period relative to the planned dose. Calculating RDI in oncology solid - tumor studies is critical for evaluating treatment efficacy and patient outcome. This paper demonstrates a practical application of the RDI formula. Through a solid tumor study as an example, this paper illustrates how to derive each component in the RDI formula and accurately compute RDI, even in complex study conditions. It also talks about resetting the baseline weight for significant weight changes, while keeping the units of the numerator and denominator in the RDI formula consistent with the weight variable. The objective of this paper is to provide a detailed, step-by-step guide for calculating RDI in a solid tumor study, including discussions on scenarios with varying cycle lengths, incomplete cycles, and different units for the actual and planned doses.

INTRODUCTION

In clinical trials, Relative Dose Intensity (RDI) plays a pivotal role in exposure analysis. Understanding RDI is essential in optimizing treatment regimens, assessing patient adherence to planned treatment, and evaluating the therapeutic outcome of a study treatment. RDI is a percentage of observed and planned Dose Intensity (DI). This paper delves into methodologies implemented in oncology solid tumor studies for accurately calculating RDI.

Dose Intensity (DI), defined as the dose delivered over a specified time frame, is frequently regarded as a relevant measure for evaluating the compliance and tolerability of a study drug. Determining DI is relatively straightforward for drugs intended to be administered daily at fixed doses, but it can become quite complicated if the dosing schedule is intermittent. Several complex scenarios in oncology solid-tumor studies are discussed here.

DEFINITION OF EACH COMPONENT OF RDI

Relative Dose Intensity: The relative dose intensity is defined as the ratio of Observed Dose Intensity (ODI) to the Planned Dose Intensity (PDI) per protocol and expressed as a percentage.

$$\boldsymbol{Relative\ Dose\ Intensity(RDI)} = \frac{\boldsymbol{Observed\ Dose\ Intensity\ (ODI)}}{\boldsymbol{Planned\ Dose\ Intensity\ (PDI)}} * \mathbf{100}$$

Planned Dose Intensity: The planned dose intensity refers to the intended amount of a chemotherapy drug administered over a specific time.

$$\boldsymbol{Planned\ Dose\ Intensity\ (PDI)} = \frac{\boldsymbol{Planned\ Total\ Dose}}{\boldsymbol{Planned\ Total\ Duration\ of\ Treatment\ Exposure\ (days)}}$$

Observed Dose Intensity: The observed (actual) dose intensity refers to the actual amount of a chemotherapy drug administered over a specific time.

$$\textbf{\textit{Observed Dose Intensity}}\ (\textbf{\textit{ODI}}) = \frac{\textbf{\textit{Actual Total Dose}}}{\textbf{\textit{Actual Total Duration of Treatment Exposure}}\ (\textbf{\textit{days}})}$$

MODEL STUDY TO INCLUDE SOME OF THE COMPLEX SCENARIOS IN SOLID TUMOR STUDIES

- **Weight changes**: Significant changes from baseline weight in the study will impact on the dose amount administered and needs to be adjusted.
- **Varying cycle lengths**: Cycle length (days) varies depending on the time of dosing in the study to calculate the Total duration of treatment exposure.
- **Incomplete cycles**: Subjects who did not complete the scheduled dose in the cycle window will be considered.
- **Consistent Units**: Ensure consistency of units used for all RDI components to plug in to the formula to calculate accurate results.
- **Different Dose Levels:** If single ARM has different dose levels, we need to calculate for each dose level and combine them and then do the RDI calculations.

An example of a solid tumor study will explain, step-by-step, how to apply the above formula to calculate Relative Dose Intensity (RDI). In the RDI formula, the denominator is the Planned Dose Intensity (PDI). According to the example protocol, TRT-01 is administered at different dose levels during various cycles within a single arm, and each arm has cycles of varying lengths. The formula for calculating PDI is as follows.

$$\textbf{\textit{Planned Dose Intensity}}\ (\textbf{\textit{PDI}}) = \frac{\textbf{\textit{Planned Total Dose}}}{\textbf{\textit{Planned Total Duration of Treatment Exposure}}\ (\textbf{\textit{days}})}$$

Planned Total Dose:

To calculate the planned total dose, we can obtain the dosing regimen and related information from the protocol. The example study has seven arms: **Arm A, Arm B, and Arms 1-5**. We will use the calculation of RDI for TRT-01 study drug as an example.

Dosing Regimen And Dose Levels For Arm A (TRT-01 + TRT-02)

		All Cycle (Cycle length = 28 days)	
Study Drugs	**Dose Levels**	**Day 1**	**Day 15**
TRT-02	1 mg/kg	x	
TRT-01	Dose Level 0: 0.03 mg/kg	x	x
	Dose Level 1: 0.1 mg/kg	x	x
	Dose Level 2: 0.2 mg/kg	x	x
	Dose Level 3: 0.3 mg/kg	x	x

Dosing Regimen And Dose Levels For Arms 1- 4 (TRT-01)

Treatment Arm	Study Drugs	Dose Levels
Arm 1 Cycles 1- 5: 21 days Cycle 6+: 28 days	TRT-01	TRT-01 administered Q3W for Cycles 1 - 5 then Q8W for Cycle 6 and above (every other, 28-day cycle)
Arm 2 Cycles 1 - 5: 21 days Cycles 6+: 28 days	TRT-01	TRT-01 administered Q3W for Cycles 1 - 5 then Q8W for Cycle 6 and above (every other, 28-day cycle)
Arm 3 Cycles 1 - 5: 21 days Cycles 6+: 28 days	TRT-01	TRT-01 administered Q3W for Cycles 1 - 5 then Q8W for Cycle 6 and above (every other, 28-day cycle)
Arm 4 All cycles: 28 days	TRT-01	TRT-01 administered Q2W for Cycles 1 - 6 then Q8W (every other, 28-day cycle) for Cycle 7 and above

Q2W = once every 2 weeks; Q3W = once every 3 weeks.
Q4W = once every 4 weeks; Q8W = once every 8 weeks.

Dosing Regimen and Dose Levels for Arm B and Arm 5 (TRT-01 + TRT-02 + TRT-03)

		Cycle (Cycle length = 28 days)	
Study Drugs	**Does Levels**	**Day 1**	**Day 15**
TRT-02	1 mg/kg		x
TRT-03	500 mg	x	
TRT-01	Dose Level 0: 0.03 mg/kg	x	x
	Dose Level 1: 0.1 mg/kg	x	x
	Dose Level 2: 0.2 mg/kg	x	x
	Dose Level 3: 0.3 mg/kg	x	x

The following formula for planned total doses involves two variables. The dose level has been specified in the protocol, and the planned number of doses for TRT-01 can be calculated.

$$Planned\ Total\ Dose = Planned\ dose * Planned\ number\ of\ doses$$

Planned Number Of Doses For Each Arm

During the calculation, look for cycle completion

Arms A, B and 5

If the last dose was Cycle X, Day 1, then

Planned number of doses = (number of cycles * 2)-1 (subtract 1 if the cycle is incomplete)

If the last dose was Cycle X, Day 15, then

Planned number of doses = number of cycles*2

Example: If the last dose was C4D15 with four complete cycles, that will be eight planned doses. If the last dose was C4D1 (no C4D15 dose, incomplete cycle), then the planned number of doses is seven.

Arms 1, 2, and 3

One dose per cycle for cycles 1-5 and one dose every other cycle for cycle 6+.

If the last dose was Cycle X, and X<=5, then

planned number of doses = number of cycles

If the last dose was Cycle X, and X>5, then

planned number of doses = 5+round up [(number of cycles-5)*0.5]

Arm 4

Two doses per cycle for cycles 1-6 and one dose every other cycle for cycle 7+

If the last dose was Cycle X, and X<=6, then

planned number of doses = number of cycles*2

Planned number of doses = (number of cycles*2)-1 (subtract 1 if the cycle is incomplete)

If the last dose was Cycle X, and X>6, then

planned number of doses=6*2+round up [(number of cycles-6)*0.5]

Planned Dose

The planned dose levels are in units of "mg/kg" in the protocol for this example, while actual doses are in units of "mg", the units should be consistent according to the RDI formula. We can use the weight at baseline to calculate the planned total dose in units of "mg".

$$Planned\ total\ dose = PDL * weight\ BL * Planned\ number\ of\ doses$$

***PDL*: Planned Dose Level in mg/kg, *Weight BL*: Baseline weight in kg.**

Per protocol, baseline weight will be adjusted if it fluctuates by more than 10%. If a subject started at Weight A but dropped to Weight B with a 10% decrease at Dose #5, and then continued to Dose #7 without any further 10% weight fluctuation, the planned total dose would be:

Planned Dose Level (mg/kg) * (Weight A * 4 + Weight B * 3)

Planned Total Duration Of Treatment Exposure (Days):

Arms A, B and 5

Planned total duration of treatment = 14*Planned number of doses (see above)

Arms 1, 2, and 3

According to the dose regimen provided in previous tables, the value of the planned number of doses depends on the cycles that the study drug is received.

If 1<= (planned number of doses) <=5 (last cycle was Cycle X, X<=5),

planned total duration of treatment exposure = 21*(planned number of doses)

If (planned number of doses) >5 (last cycle was Cycle X, X>5),

planned total duration of treatment exposure = (21*5)+(56*(planned number of doses-5))

Arm 4

If 1<= planned number of doses <=12 (last cycle was Cycle X, X<=6),

planned total duration of treatment exposure = 14*(planned number of doses)

If planned number of doses >12 (last cycle was Cycle X, X>6),

planned total duration of treatment exposure = 14*(2*6)+56*(planned number of doses-6*2)

If there are different dose levels within the ARM for dosing regimen, please calculate the planned total dose based on each dose level and combine them to get the total planned dose.

Next, to calculate the Observed Dose Intensity (ODI) for TRT-01. Use SDTM Exposure as collected domain (EC) to get the actual doses and actual duration of treatment exposure.

$$\boldsymbol{Observed\ Dose\ Intensity\ (ODI)} = \frac{\boldsymbol{Actual\ Total\ Dose}}{\boldsymbol{Actual\ Total\ Duration\ of\ Treatment\ exposure\ (days)}}$$

Actual Total Dose:

Actual total doses (ADOSE)= Sum of doses (mg) across all visits per subject in the database

Actual Total Duration Of Treatment Exposure (Days):

Arms A, B, and 5

Actual total duration of treatment exposure (days) = TRTEDT (Date of Last Exposure to Treatment)-TRTSDT (Date of First Exposure to Treatment) +14.

Arms 1, 2, and 3

If 1<= Number of TRT-01 cycles <=5,

Actual total duration of treatment exposure (days) = TRTEDT-TRTSDT+21

If Number of TRT-01 cycles >5,

Actual total duration of treatment exposure (days) = TRTEDT-TRTSDT+56

Arm 4

If 1<= Number of TRT-01 cycles <=6,

Actual total duration of treatment exposure (days) = TRTEDT-TRTSDT+14

If Number of TRT-01 cycles >6,

Actual total duration of treatment exposure (days) = TRTEDT-TRTSDT+56

With the numerator (Observed Dose Intensity, ODI) and the denominator (Planned Dose Intensity, PDI) available, you can now use the formula to calculate the Relative Dose Intensity (RDI).

CONCLUSION

We started with the Relative Dose Intensity (RDI) formula and determined the values that need to be substituted into it one by one, paying attention to whether units are consistent, whether weight is needed, and how the length of cycle changes. Paper discusses some scenarios that can be applied in solid tumors. Understanding and analyzing RDI allows researchers to assess treatment adherence, manage dose modifications, and optimize therapeutic strategies, thereby aiming to improve the overall efficacy of cancer treatments.

REFERENCES

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