



Choice of starting dose for molecular targeted agents evaluated in phase I clinical trials

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Aims

- To examine the choice of animal model and toxicology parameters used to select the starting dose (SD) in novel molecular targeted agents (MTA) that underwent phase I studies.
- To compare the SD with the maximum administered dose (MAD) and to calculate the number of dose-escalation steps required to achieve the MAD.
- To analyze if hypothetical higher SD would shorten dose escalation without increasing the risk of toxicity for MTA undergoing phase I evaluations.



Material and Methods

- A total of 62 MTA evaluated in 89 phase I trials were reviewed.
- The search was performed on PUBMED using the generic or trade name of the drug and the proposed target.
- MTA were defined as those agents which target selective molecular pathways with a novel and distinctive mechanism of action from conventional chemotherapeutic agents.
- In order to assure comparability when calculation of dose escalation steps and MAD to SD ratios, we only analyze those studies which were performed using standard 3+3 dose escalation design and where DLT was reached.
- An unsafe trial or agent was arbitrarily defined if $SD = MAD$

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Results

- The SD for 60 of the 89 phase I trials were based on animal data: 30 rodent and 30 non-rodent.
- 30 phase I trials followed a standard 3+3 phase I design.
 - 18 used rodent parameters to determine SD (14 used LD10/MTD and 4 used TDL)
 - 12 used non-rodent parameters (6 used NOAEL, 4 used LD10/MTD and 2 used TDL).
- The median number of dose levels to reach MAD from SD was 6 (range 1-9)
- The median MAD/SD ratio was 6 (1-45) and 9 (2-30) for trials with SD based on rodent and non-rodent data.
- Among 18 trials that used rodent data to derive their SD, 7 trials had hematological DLT and 11 had non-hematological DLT; whereas among 12 trials that used non-rodent data to determine their SD, all but 1 had non-hematological DLT.

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Results

| Starting dose | Number of dose levels to reach MAD from SD | | Number of unsafe trials* | Number of unsafe agents* |
|---------------|--|----------------------------|--------------------------------------|--------------------------------------|
| | Rodents Median (Range) | Non-rodents Median (Range) | Rodents (n=18) vs Non-rodents (n=12) | Rodents (n=15) vs Non-rodents (n=11) |
| 1x | 6 [1-9] | 5 [2-9] | 4 vs 0 | 4 vs 0 |
| 2x | 4 [1-6] | 4 [1-6] | 4 vs 1 | 4 vs 1 |
| 3x | 2 [1-5] | 2.5 [1-4] | 8 vs 3 | 7 vs 3 |

* Considered if SD=MAD

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Conclusions

- Unlike cytotoxic agents, the derivation of SD for MTA is based on different practices using a variety of preclinical parameters.
- No significant differences are observed in the number of dose levels to reach MAD using SD based on rodent versus non-rodent data.
- Rodent seems to better predict hematological than non-hematological toxicity.
- Non-rodent data appear to better predict for a safe human SD than rodent data in phase I trials of MTA.

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