The challenge of oncology drug dose optimization

An EU regulatory perspective

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The obligatory disclaimer

- **Whatever I say may be my own opinion rather than the position of the EMA, CHMP or the Swedish MPA**

What is required for licensure?

- **“The marketing authorization (MA) shall be refused if (a) the medicinal product is harmful in the normal conditions of use, or (b) that its therapeutic efficacy is lacking or is insufficiently substantiated” (Article 26, directive 2001/83/EC)**
- **Correspondingly, if the benefit/risk (B/R) balance may be deemed positive for the proposed use, the MA should be granted**

What about optimising the dosing regimen?

- There is no formal requirement to establish the "optimal" dosing regimen: we don't deny approval because another, unstudied posology might have had a better B/R
- An "optimal" characterization of the exposure/response (E/R) relation may require the exposure of patients to doses likely to be suboptimal
- The most fundamental regulatory consideration when approving clinical trial applications is study subject safety, rather than optimizing the understanding of E/R

Post-authorisation aspects

- **Post-authorisation commitments to study alternative dosing regimens after EU approvals are not the rule, but do occur (see e.g., Maliepaard et al 2021)**
- **In some cases, medical practice has investigated and/or adopted lower doses than those originally approved according to the SmPC**
- **Such lower doses have been accepted for use in pivotal trials for new agents, if generally used clinically (e.g., bortezomib, capecitabine)**
- **In some cases, insufficient evidence for such dosing regimens accepted by the clinical community, has prevented their regulatory approval**

CHMP Anticancer Guideline on dose selection

- **Distinguishes between “cytotoxic” and “non-cytotoxic” compounds**
- **For cytotoxic compounds, “the basic assumption governing the design of single agent dose and schedule finding trials is that (…) toxicity is an acceptable endpoint”**
- **“The main objective is thus to define dose-limiting toxicities and the dose to bring forward into further trials”**
- **“Maximum Tolerated Dose (MTD), Dose Limiting Toxicity (DLT) and recommended Phase II dose (RP2D) should be identified”**

Anticancer Guideline on ”non-cytotoxic” compounds

- **“This refers to a very heterogeneous group of compounds”**
- **“In contrast to cytotoxic chemotherapy, these compounds are typically administered continuously, and the toxicity profiles tend to differ so that DLTs may occur first after multiple cycles of therapy”**
- **“May require alternative strategies with regard to the definition of DLT and MTD”**

Dose-finding for “molecularly targeted agents”

- **“The dose-finding strategy should not only focus on safety endpoints, but also on determining an optimal (…) dose**
- **This is the dose at which optimal biological response according to a predefined effect marker is achieved.” At this dose, “giving a higher dose does not further improve outcomes**
- ***Examples include escalating doses until a target-mediated biologic pathway is optimally altered or escalating doses until a target becomes saturated with the drug, while minimizing the dose required to achieve this maximum pharmacodynamic effect (thereby aiming to minimize toxicity*)”**

Considerations for protein kinase inhibitors

- With increasing exposure such agents will become less selective, with broader receptor promiscuity and more off-target (receptor) effects
- With lower doses there may be less off-target (receptor) effects
- A rational phase II randomised dose-ranging trial might include a dose defined by target saturation and/or MTD, and a lower dose
- The study objective would be to determine if a lower dose might be similarly active (ORR) or exert smilar PD effects, while exhibiting better tolerability
- Sample size would be decided by the precision in PD marker and safety endpoints required for informed dose selection

Intra-patient dose modification for protein kinase inhibitors

- **It is anticipated that the optimal dose as well as the MTD of an anticancer agent will vary between patients**
- **Most pivotal trials of protein kinase inhibitors investigate a dosing regimen, part of which is a dose reduction scheme**
- **For a variable and frequently significant proportion of patients in pivotal trials, the starting dose of a protein kinase inhibitor is not tolerable, and dose reductions are necessary**

Reflections on intra-patient dose modification

- **A high proportion of patients requiring dose reductions, may not per se indicate that dose selection was wrong, provided that most patients do not need to discontinue therapy**
- **Intra-patient dose reduction may confound the characterization of E/R, as patients requiring dose reductions on average are likely to have higher exposure at a given dose**

Considerations for mAbs (1)

- **For a conventional mAb, no off target (receptor) effects are anticipated**
- **Side effects are anticipated based on lack of tissue selectivity**
- **Presumably, dose-finding should generally ensure that the selected dose yields exposure beyond Emax (on the plateau of the E/R curve) for most or all patients**

Considerations for mAbs (2)

- **Target mediated clearance may correlate with prognostic factors. In such situations, randomised dose-ranging trials may be required to inform an unbiased E/R model**
- **The E/R model is of key importance for subsequent adaptions of the dosing interval, or for bridging from i.v. to s.c.**
- **For antibody-drug conjugates (ADC) and T-cell engagers, concerns may differ**

Questions

- **What safety problems can and can not be addressed by dose titration in the individual patient based on dose reduction schemes, rather than optimized starting dose selection based on randomized dose-comparative trials?**
- **Under what circumstances is a randomized dose-comparative study needed or advisable?**
- **What are appropriate target populations for such studies?**
- **If such a study is advisable, what are the research questions and corresponding study designs and endpoints?**
- **If long term toxicity concerns are key to the dose-comparison, how are these realistically addressed prior to phase III (i.e., what is the required duration of study)?**
- **How do concerns and solutions on dose selection differ between kinase inhibitors, mAbs, ADC, T-cell engagers?**