

LESSONS LEARNT FROM THE DEVELOPMENT OF CYTOTOXICS AND PERSPECTIVES

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DISCLOSURES

- Nicolas Penel has reported no conflicts of interest
- Yazid Belkacemi has reported no conflicts of interest
- Emilano Calvo has reported no conflicts of interest
- Fatima Cardoso has reported conducting research sponsored by and participating in Advisory Boards for: Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline (GSK), Macrogenics, Merck-Sharp, Merus BV, Mylan, Novartis, Pfizer, Pierre-Fabre, Roche, Sanofi and Teva.
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DEVELOPMENT OF CYTOTOXICS AND PERSPECTIVES



Phase I trials

Phase II trials

Phase III trials

Conclusions



DOSE-ESCALATING PHASE I (1/3)

Overview

- The primary objective of Phase I trials is to identify a dose and schedule for subsequent studies (Recommended Phase II Dose [RP2D])
- Most Phase I trials assessing cytotoxics are designed as dose-escalating Phase I trials
- This is an exploratory step to assess the dose/toxicity relationship. This implies also a hypothetical dose/activity relationship
- Most Phase I trials define maximal tolerated dose and RP2D on the basis of a relatively short assessment timeframe (**1 or 2 cycle[s]**)
- Most dose-limiting toxicities are haematological **and gastrointestinal** toxicities (easily standardisable)



DOSE-ESCALATING PHASE I (2/3)

Limits

Dose–activity relationship rarely established

Late or cumulative toxicities are not caught because of short assessment timeframe during traditional Phase I trials

Recommended Phase II Dose [RP2D] rarely integrates pharmacological data (no strong evidence supporting the use of standardised dose by amount of drug/m²)



DOSE-ESCALATING PHASE I (3/3)

Perspectives

Current Phase I trials with cytotoxic agents are becoming rare (apart from **antibody drugs conjugates**)

Phase I trials of cytotoxic drugs in combination with molecularly-targeted therapy or immunotherapy are becoming more frequent

Use of more sophisticated study designs:

- Continual reassessment designs instead of classical 3+3
- Extend the timeframe for assessing occurrence of dose-limiting toxicities
- Better integration of PK data in design (pharmacologically-guided dose escalation)



PHASE II TRIALS (1/3)

Overview

The primary objective of Phase II trials is to screen whether the drug under study has sufficient anti-tumour activity warranting further study in a defined population

Tumour shrinkage remains a good marker of drug activity for cytotoxic agents

RECIST 1.1-based criteria (best objective response rate, progression-free survival/rate at a certain time point [the latter provided that the study is randomised or there is objective progression before study entry, respectively] are well-accepted primary endpoints of Phase II trials assessing cytotoxic agents

Definition of level of activity (P1) and level of inactivity (P0) usually based on **previous experience**

In most cases, predominant toxicities are haematological or **gastrointestinal**, that are easily documented, graded and reported (for example, NCI-CT AE V4.0)



PHASE II TRIALS (2/3)

Limits

Tumour shrinkage is rare or difficult to document in some clinical settings (e.g. sarcomas) and requires the use of time-dependent primary endpoints, such as progression-free survival rates at fixed time points

Most cytotoxics are developed to be administered intravenously

Traditionally, the development of the drug starts in patients with advanced disease and after failure of **standard treatments**

Selection of patients (eligibility criteria) and design (stratification, for instance) rarely take into account mechanisms of action of the drug, known resistance mechanisms or putative predictive factors

Sometimes, statistical assumption, sample size calculation and decision rules are based on sparse data that **may** jeopardise the trial



PHASE II TRIALS (3/3)

Perspectives

Randomisation is of the **utmost** importance. **The comparator** is useful to assess the internal bias of the trial and then verify that the statistical assumption is valid

Stratification according to known prognostic/predictive factor is useful to limit the tumour/patient heterogeneity

Integration of patient-reported outcomes, especially in **randomised Phase II trials**, is useful to **assess the clinical benefit** beyond tumour shrinkage

Collection of tumour tissue (from solid lesions or from blood for circulating tumour cells or ctDNA) during the study is necessary to better explore **potential** predictive factors or factors underlying resistance (**often** post-hoc analysis)



PHASE III TRIALS (1/3)

Overview

By definition, this confirmatory step requires randomised trials

The primary objective is the assessment of efficacy (clinical benefit) in terms of improved overall survival or a better quality of life. By default, surrogate endpoints are used, such as **disease/ progression-free survival**

This requires comparison with:

- Accepted/approved standard of care
- Physician choice (limited list of regimens, in cases where there is absence of standard of care or presence of multiple standard of care regimens)
- Rarely placebo, in cases where there is no established standard comparator

If possible, using blinding to avoid subjectivity in efficacy/safety assessment

The magnitude of the clinical benefit has to be clinically relevant; e.g. as defined in the ESMO Magnitude of Clinical Benefit Scale



PHASE III TRIALS (2/3)

Issues

Overall survival (OS) is the less debatable endpoint; nevertheless, this endpoint could be **challenged by post-trial treatments and the duration before events occur (in particular for studies conducted in the perioperative setting)**

Disease/progression-free survival or time to progression are debatable with respect to their surrogacy, since the correlation OS/PFS, OS/DFS or OS/TTP has **rarely and variably been demonstrated in solid tumour (except for DFS/OS in stage II/III colorectal cancer)**

Recent cytotoxics failed to demonstrate clinical advantages compared with well-established standards of care, since the superiority of a novel drug is more and more difficult to achieve

Eligibility criteria frequently do not fit the characteristics of the majority of patients seen in daily life, **rendering it difficult to interpret the real value of a new drug in real-life practice**



PHASE III TRIALS (3/3)

Perspectives

Explore new areas:

- Rare cancers
- Elderly patients, children, patients with comorbidity

Eligibility criteria should be broadened with respect to comorbidities, organ function, comedication, etc, to better fit the characteristics of patients in daily clinical practice

Integrate quality of life and patient-reported endpoints in the assessments (think beyond PFS)

Integrate predictive factors to better select the target population

Integrate cost-effectiveness approaches

Design studies that can detect clinically relevant differences. The ESMO Magnitude of Clinical Benefit Scale can help with this



CONCLUSIONS

- Single-agent, dose-escalating Phase I trials assessing novel cytotoxic agents are becoming rare
- Phase II trials are traditionally based on tumour shrinkage or progression-free survival at a fixed time point
- Phase III should be designed to detect clinically relevant differences (e.g. using the ESMO Magnitude of Clinical Benefit Scale)



THANK YOU!