COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON THE PRE-CLINICAL EVALUATION OF ANTICANCER MEDICINAL PRODUCTS

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1. INTRODUCTION

1.1 Objectives of the guideline

The purpose of this guideline is to define the preclinical data which are considered obtainable from preclinical studies with respect to pharmacodynamic, pharmacokinetic and toxicological properties of new anticancer drugs and which are considered relevant with respect to Phase I (Human Pharmacology), Phase II (Therapeutic Exploratory) and Phase III (Therapeutic Confirmatory) Clinical Trials and Marketing Applications.

Furthermore, the guideline serves the purpose of avoiding unnecessary tests, thus enabling the promptest possible introduction of newly developed anticancer medicinal products into clinical trials without compromising safety.

This note for guidance should be read in the light of general requirements set by Council Directive 75/318 (EEC) as amended. The applicant should also refer to the Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (CPMP/ICH/286/95).

1.2 Scope of the guideline

The guideline concerns primarily cytotoxic/cytostatic drugs that are presumed to have a direct effect on tumour cells. It focuses on the development of single drug treatment. To support the clinical development of combinations of anticancer drugs, preclinical testing to investigate pharmacodynamic, kinetic and toxicological interactions is encouraged.

The guideline is aimed at formulating recommendations for pharmacodynamic investigations and the requirements for toxicological studies prior to Phase I, II and III Clinical Trials as well as Marketing Applications. As appropriate, additional studies may be required based on the findings of preclinical and clinical studies.

2. CHARACTERISATION OF PRIMARY PHARMACODYNAMICS

Prior to Phase I studies, preliminary characterisation of the mechanism(s) of action, resistance, and schedule dependencies as well as anti-tumour activity in vivo should have been made. As appropriate, these properties should be further investigated in parallel with Phase II and III studies.

2.1 In vitro studies

The primary aims of the in vitro studies are to obtain mechanistic information about the test substance and to characterise the activity profile.

2.1.1 Activity profile and mechanism(s) of action

By determination of the activity of a new drug at different concentrations in an appropriately selected cell panel and identifying IC_{50} concentrations for each cell line, a drug-specific activity profile is obtained. By comparing the profile with that of standard drugs, the activity of the new drug can be classified as similar or unrelated.
If a specific target structure is indicated, cell lines expressing different levels of this structure should be studied, if possible.

The use of well-characterised cell lines as regards genotype and biochemistry is encouraged. The selected test panel should be justified and the following panel should be considered:

- cell lines with different proliferation rates
- cell lines with different growth characteristics (e.g. solid and haematological)
- cell lines expressing general drug sensitivity and general resistance
- cell lines with sub-lines expressing specific resistance pheno/geno types

The use of cell line panels such as those found in the NCI cell line screen, which are well characterised with respect to sensitivity to standard agents, genotype, biochemistry and 'molecular targets', could also be accepted.

2.1.2 Mechanism(s) of resistance

In parallel with the characterisation of the mechanism(s) of action, the corresponding profile with respect to possible mechanism(s) of resistance (e.g. overexpression of P-glycoprotein/multidrug resistance protein/glutathione, changes in topoisomerase I and II) can be obtained.

Observed resistance could be investigated for its circumvention by resistance modulating agents. Investigation of the possible induction of resistance by long-term exposure of cell lines to the new drug and further characterisation of mechanism(s) of resistance are encouraged.

Assessment in the cell test panel of the activity of standard drugs in parallel with that of the new drug is recommended for establishing the existence of possible cross-resistance.

2.1.3 Exposure time and cell-cycle dependency

AUC normalised time dependency of drug activity and studies of cell-cycle- dependency of a new drug are recommended as an aid for the selection of proper dosing schedules. Studies in proliferating as well as non-proliferating cells are encouraged.

2.1.4 Disease-specific activity

The activity profile may be further investigated in fresh tumour samples from patients representing different diagnostic groups utilising justified techniques.

2.2 In vivo studies

The primary aims of in vivo studies are to obtain further information with respect to antitumour activity, therapeutic index and schedule dependency.

Studies in animals are usually carried out in rodents, mainly in mice, giving due consideration, when possible, to likely differences to man in pharmacokinetics/dynamics. The selection of a suitable animal model (including species, strain and tumour type) depends on the properties and proposed therapeutic indications of the anticancer drug and the available information about the response of different tumour cell lines. Anticancer drugs may be tested against xenografts of human cell lines inoculated in immunodeficient mice or tumour cell lines implanted in immunocompetent rodents. The type of tumour cell studied, the tumour load and the progression of the disease (e.g. metastases) in the animal should be considered.
The administration route and dosing regimen should mimic the anticipated clinical treatment schedule as far as possible.

Suitable criteria for the evaluation of efficacy include tumour growth, survival time and degree of remission or cure.

3. EVALUATION OF TOXICITY

The primary aims of the toxicity studies are to

- establish the maximal tolerated dose (MTD based on approximate minimal lethal dose) to be used to define the starting dose in Phase I trials (cf. section 3.3).
- identify effects on vital functions and target organ toxicity in relation to drug exposure and "treatment cycles" to support dose escalation in Phase I studies and duration of therapy.

3.1 Safety pharmacology

For compounds with a novel mechanism of action, an evaluation of safety pharmacology data (e.g. respiratory and cardiovascular effects) should have been made before the initiation of Phase I trials.

3.2 Pharmacokinetic/toxicokinetic studies

The evaluation of limited kinetic parameters, e.g. peak plasma levels and AUC, at doses around the MTD in the animal species used for preclinical studies may facilitate dose escalation during Phase I studies. Further information on ADME in animals should normally be made available prior to Phase II/III studies.

3.3 Single-dose toxicity studies

An assessment of those dose levels at which severe toxic symptoms or death occur (limit dose approach) should be performed in rodents with the administration route and formulation envisaged for clinical use.

A preliminary dose-finding study should be performed to establish an approximate MTD (maximal dose compatible with survival) in mice followed by a study with additional doses and animals to establish the MTD more accurately. The findings should be confirmed in rats to establish whether the relationship between toxicity and surface area is linear. If not, the Phase I starting dose should be based on the most sensitive species.

Dosages and the required number of animals per dose should be determined on the basis of the previous results in such a way that the necessary accuracy will be achieved with a minimum number of animals. The follow-up period of observation for the surviving animals should be at least 14 days.

The MTD, as established from single-dose toxicity studies, should be known prior to Phase I trials. Experience has shown that one tenth of the MTD may be an appropriate starting dose in Phase I studies.

In cases where the rodent species are known to be poor predictors of toxicity in humans e.g. antifolates, or the agent under investigation has a novel mechanism of action, an approximate MTD should be established in a non-rodent species.
3.4 Repeat dose toxicity studies

The dosing schedule should be as similar to the proposed clinical schedule as possible. Particular attention should be paid to critical target organ toxicity and reversibility of toxic effects.

A repeat-dose toxicity study of limited duration (2 to 4 weeks or 1 to 2 cycles) in two rodent species should be performed prior to Phase I studies. For compounds with a novel mechanism of action studies should be performed in a rodent and a non-rodent species.

For Phase II and Phase III trials and for Marketing Applications, repeat-dose toxicity studies should be performed in a rodent and a non-rodent species. Irrespective of daily or intermittent administration in the clinic, the duration of the repeat dose toxicity studies should be at least equal to the duration of the clinical trials, although not longer than 6 months.

3.5 Genotoxicity/Carcinogenicity

Normally, there is no established therapy available for patients eligible for Phase I and II Trials. Therefore, prior to Phase I and II Trials, genotoxicity testing is not required. In vitro genotoxicity tests should have been performed prior to Phase III trials and Marketing Application. Normally, carcinogenicity studies are not required (cf. ICH S1A).

3.6 Toxicity to Reproduction

Studies of toxicity to reproduction are not required since cytotoxic/cytostatic drugs are assumed to cause reproductive disturbances. Pregnant women may nevertheless be treated with these agents and therefore studies elucidating the potential for reproductive toxicity are encouraged.

3.7 Local tolerance

Anticancer drugs can be highly toxic to tissues which come into contact with the product. Prior to Phase I studies, an evaluation of local tolerance relevant to the intended route(s) of clinical administration and user safety of the investigational product should be made. It should be noted that local tolerance testing may be part of other toxicity studies provided that the product is given via the intended clinical route of administration. If the product intended for marketing differs from the investigational product, relevant local tolerance, including paravenous, should be considered prior to Phase III studies and Marketing Applications.