

EORTC Guidelines for Phase I Trials with Single Agents in Adults

EORTC New Drug Development Committee*

INTRODUCTION

PHASE I trials are designed to determine the maximum tolerated dose (MTD) of a drug for a specified mode of administration, to characterize the most frequent toxic effects and to define the dose-limiting toxicities [1, 2].

The MTD is the highest dose which can be safely administered to a patient, i.e. producing acceptable, manageable and reversible toxicity of WHO grade II-III (see Appendix III). MTD varies according to the prognostic factors for toxicity not only with regard to prior therapy (chemotherapy and/or radiation) and performance status, but also with the type of disease, age of the patient, availability of supportive care and occasionally with impaired function of excretory organs. MTD is needed to perform phase II trials at the highest safe dose (i.e. near MTD) in order to obtain a reliable estimation of the clinical effectiveness of a new agent. It is therefore of the utmost importance that dose recommendations emanating from phase I trials be based on patients with a drug tolerance similar to those expected to enter the phase II trials.

All patients accrued in phase I trials must have a histologically confirmed diagnosis of cancer which is not amenable to established forms of treatment. For these subjects, for whom no specific antineoplastic therapy may be recommended, the phase I trial might be beneficial since the new drugs selected for the study have been chosen because of their expected antitumor activity.

In principle, patients with unfavorable pre-treatment characteristics may be entered at the initiation of phase I studies. Lack of toxicity for a given dose in these high-risk patients is an important outcome when considering the magnitude of the increment of the dose for the next step. Early on in phase I trials, factors producing drug-

related toxicity will be progressively identified and become exclusion criteria for higher doses. Also, investigators will be inclined to administer higher doses to patients with less prior therapy so that at the end of the study it might be difficult to identify the population at risk. The recommended dose for phase II trials, which is often one step below the MTD, needs to be qualified with regard to the type of patients to be investigated in the phase II study. It is advisable to treat at least five subjects with well-defined and similar prognostic factors for toxicity at the recommended dose before starting the phase II trial. Any hints of antitumor activity are important for further studies and must be described. Responses must be defined according to standard criteria [3, 4].

These guidelines form the core of a phase I investigation with new conventional therapeutic agents. Adjustments and additional requirements may be needed in the light of special experimental findings and for particular classes of compounds.

THE PROTOCOL

Table 1 displays the sections to be addressed in the elaboration of a phase I study. Each entry in the table must be thoroughly considered by the investigator.

Objectives and background

This section covers the following items *with references* (details can be put in appendices):

Table 1. Phase I master protocol

I.	Objectives and background
II.	Eligibility and exclusion of patients
III.	Treatment
IV.	Number of patients per dose level
V.	Study parameters and serial observations
VI.	Termination of the study
VII.	Tumor response
VIII.	Records
IX.	References
Appendix I.	Performance status
Appendix II.	Surface area as a function of weight and height
Appendix III.	WHO grading of toxicity
Appendix IV, V	As needed

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*This paper was prepared by M. Rozenzweig, M. Staquet, H. H. Hansen, H. M. Pinedo, J. G. McVie, J. P. Armand, Y. Kenis, B. W. Fox, K. Harrap and L. M. van Putten.

- (i) the rationale to undertake the study. It must be explained why the drug is of interest. In the case of an analog, its differences from the parent compound must be discussed;
- (ii) the chemical structure of the drugs with names, synonyms and code number, if any;
- (iii) relevant chemical, physical, pharmacological, toxicological, pharmaceutical and screening data;
- (iv) a description of the results of other clinical studies if available, as well as a list of expected toxicities;
- (v) details of the formulation, its stability (shelf, in infusions), conditions of storage, precautions for handling the drug.

Eligibility and exclusion of patients

All the following criteria must be met to enter patients in phase I trials:

- (i) histologically confirmed diagnosis of a solid tumor no longer amenable to established forms of treatment;
- (ii) between 18 and 75 yr of age;
- (iii) a performance status less than 3 (ECOG-Zubrod scale; see Appendix I);
- (iv) normal hepatic and renal function;
- (v) $WBC \geq 4000/mm^3$ and platelets $\geq 100,000/mm^3$;
- (vi) informed consent;
- (vii) life expectancy of more than 9–12 weeks.

The following are excluded:

- (i) patients treated previously with the same drug;
- (ii) patients who have received cancer therapy during the last 4 weeks. Longer intervals may be needed when delayed toxicity is expected, e.g. 6 weeks for nitrosoureas or mitomycin C;
- (iii) pregnant women;
- (iv) patients with intercurrent complications;
- (v) patients with major organ dysfunction in a site of known or assumed toxic effects (e.g. cardiac toxicity);
- (vi) patients with psychotic disorders.

Treatment

Drug administration. Route and duration must be specified as well as special instructions (such as “to be taken on an empty stomach”, incompatibility with other drugs, duration of infusion, nature and volume of fluids). The drug must never be mixed with other compounds.

Schedule. The relevance of animal data to patients with regard to schedule dependence in mice has not been established to date. Information on mechanism of action, cell cycle specificity and preclinical pharmacokinetics are sometimes used to select a schedule but the empirical approach remains frequent.

It is usual to start the trial with a single bolus

intravenous dose repeated every 3–4 weeks (or after recovery from toxicity). If delayed toxicity is found, the time interval to retreatment will be appropriately lengthened in subsequent courses.

It is generally desirable to explore more than one dose schedule of drug administration (e.g. 5 days administration, weekly schedule). This is particularly the case when non-hematologic dose-limiting factors are predominant (e.g. CNS toxic effects). Occasionally there is some rationale from the preclinical models to perform the phase I by continuous infusion.

Doses. Drug doses are expressed in mg/m^2 body surface area (Appendix II).

Starting dose. If there is no prior experience in humans, the starting dose can be based on 1/10 of the LD_{10} (in mg/m^2) in the mouse [5]. Prior verification that this dose is not lethal or life-threatening in another species such as rats or dogs is necessary.

Subsequent doses. The sequence of dose escalations will use increments from 100% in the beginning to 20–25% of the previous dose at the end of the trial. Low increments will be preferred if non-hematological toxic effects are expected to be dose-limiting.

When the maximum tolerated dose is reached in poor-risk patients, entry at higher dose levels will be limited to a more favorable selection of patients with respect to performance status, prior therapy and life expectancy.

Retreatment in individual patients. Patients should be scheduled to receive at least two courses of therapy.

Eligibility criteria must also be met for retreatment with regard to performance status and intercurrent complications, as well as hematological, hepatic and renal functions.

If toxicity does occur, the patient may be retreated, upon recovery, at the same dose level or at preceding dose levels depending upon the tolerance exhibited in the previous course.

If there is no significant toxicity, the patient should be retreated at the same dose level. Using a higher dose in the same patient may be considered as experience at this higher dose is accumulating in other patients.

Retreatment at different doses must be excluded in the final analysis of the dose-response relationship. In the presence of cumulative toxicity, this analysis must take into account the number of retreatments per patient per dose level.

Those patients who show objective tumor response should be kept on treatment as long as there is no tumor progression, with adjustment of drug dose as indicated.

Follow-up and discontinuation of treatment. Treatment should be discontinued if disease

progression occurs after two courses or after four weeks of treatment, whichever is longer. In other cases medication should be interrupted when this is regarded to be in the best interest of the patient. Patients will be followed until recovery from all toxic effects. At non-toxic doses the patient must be followed for at least 4 weeks after the last drug dose, longer in case of actual or expected delayed toxicity.

Number of patients per dose level

A minimum of three patients and four courses of therapy are requested at each non-toxic or subtoxic level. When overt toxicity is observed, at least five patients should be entered at each dose level.

At a given dose level, at least 1 week should pass between the entry of the first and the next two patients. At least 3 weeks should pass before entry of further patients into the next higher dose level. More prolonged intervals between treatments and large experience at the preceding dose level may be needed when delayed, cumulative or potentially dangerous toxicities are expected.

Past experience shows that the MTD will be found with 15-30 patients. Generally, such a study should not exceed 6-8 months. Exploration of additional schedules will usually require 10-20 additional patients per schedule.

Study parameters and serial observations

A detailed history and complete physical examination, including measurement of tumor lesions and laboratory tests, must be obtained prior to study. Table 2 summarizes the minimal follow-up requirements for evaluating the individual toxic effects. Other parameters and the need for an increased frequency of the determinations may be required, depending on the animal toxicology and the general requirements for the clinical management of the patients. Autopsy data will be recorded whenever available (if death occurs during the trial).

Table 2. Laboratory tests for phase I trials to be performed prior to therapy and repeated as indicated

Height
Weight
Hgb
WBC and platelets
Diff. and retic.
Chemistries (Ca, Na, K, uric acid, creatinine, bilirubin, total protein, albumin, glucose, PTT, alk. phos., SGPT)
Urinalysis
Stool guaiac
ECG
Bone marrow biopsy*
Chest films
Others as indicated

*Optional.

Termination of the study

The phase I study will be terminated when the maximally tolerated dose is established for ambulatory patients. Doses must be recommended for phase II trials in both good- and poor-risk patients. Risk categories are based primarily on performance status and prior therapy; they may be further defined according to specific findings in the phase I trial. Provisions should also be provided for adequate follow-up in subsequent trials.

Tumor response

Responses will be defined according to standard criteria [3,4] and documented by all available means.

Records

A sample of the forms to be used during the study must be appended.

References

All published material relevant to the study must be referenced adequately. Non-published data should be appended.

REFERENCES

1. Rozencweig M, Dodion P, Nicaise C, Piccart M, Kenis Y. Approach to phase I trials in cancer patients. In: Cortés-Funes H, Rozencweig M, eds. *New Approaches in Cancer Therapy*. New York, Raven Press, 1982, 1-13.
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4. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, 47, 207-214.
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