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Special Paper

Phase II Trials in the EORTC

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The Protocol Review Committee (PRC) has prepared this document in order to clarify the phases of introduction of a new therapeutic agent in the treatment of cancer. Our aim is to define these phases and to make explicit the intentions which lie behind EORTC studies at each stage in the process. The PRC hopes that this will help the Cooperative Groups of the EORTC in developing their protocols for clinical trials carried out under the auspices of the EORTC. This position paper may also assist those undertaking this form of clinical research outside the EORTC. © 1997 Published by Elsevier Science Ltd.

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INTRODUCTION

THE TERM phase II has come to mean many things and to encompass clinical studies of widely differing intentions [1]. Indeed, it is to some extent easier to define phase II as the studies which are carried out following phase I assessment of a new agent but before large-scale assessment as part of a randomised phase III trial. This diversity in intention in phase II studies can lead to confusion in the development of a protocol, especially over the study endpoints and the need for randomisation. By identifying the different purposes of phase II studies, a clearer definition of the process can be obtained and of the design of the studies.

TYPES OF PHASE II STUDIES

When the term was first introduced it was used to describe those studies where a new drug or treatment had passed through phase I testing, its toxicity and schedule were approximately known, and the intention was to study its activity in defined tumour types. Phase I studies now include those studies where a drug of known activity is reassessed with respect to dose or schedule. This may be in combination with other treatment modalities or drugs. The essential feature is that phase I studies are exploratory.

In a phase II study the dose and schedule have been largely determined and the aims are different. In the case of an individual drug it may be: (a) to determine single-agent activity in a given tumour type; (b) to define further the toxicity profile in a larger group of patients; (c) to compare two different schedules of administration; or (d) to determine response rate and toxicity in combination with other drugs or treatments. It is this multiplicity of objectives which sometimes causes difficulty in study design.

When phase II studies have as their objective the study of the response rates and toxicity of a single agent in a defined dose and schedule, the studies are referred to as single-agent phase II studies (Table 1). The aim will be to incorporate an active drug in future treatment strategies, and to subject the agent to further trial as part of a more complex general treatment.

In these studies the principal endpoint which is used to calculate sample size is usually tumour response. 14–40 patients are usually treated depending on the observed response rate. The statistical considerations of sample size are based on those defined by Gehan [2] or Simon [3]. The response to treatment is based on intention to treat in all registered eligible patients, the details of ineligibility being clearly stated. The response rate is not based on patients who have received a defined duration of treatment, although these data should be included in the report. The aim is not to determine if patients benefit in respect to quality of life or survival. Even relatively low response rates (such as those typically seen in non-small cell lung cancer, pancreatic cancer or melanoma) may be of great interest. It is essential not to reject a drug which may have activity, especially in tumour types which are usually drug resistant, i.e. to avoid a false-negative (type II) error. Other essential objectives are the documentation of acute or cumulative side-effects occurring during treatment, and the study may also include pharmacokinetic measurement.

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Table 1. Intentions and terminology of phase II studies

Intention	Proposed terminology
Assessment of activity and/or schedule of a new agent in a defined tumour type	Single-agent phase II study
(a) Assessment of the therapeutic effect of a new agent, in combination with other drugs or modalities	Phase II feasibility study
(b) Assessment of the therapeutic effect of an established active agent in combination with other treatment(s)	Phase II feasibility study

Further stages of assessment of the value of a new drug or treatment are, however, often included under the rubric of phase II studies. A new drug or agent may have shown promising activity, but it is not clear if the level of activity justifies further clinical development, or if the drug can be combined with other agents safely, or if such a combination is active in treatment. It is, at this stage, too soon to judge if the combination is worthy of assessment against a standard treatment in a larger study. The compatibility of the agent with other treatments, such as surgery or radiotherapy, may not be known.

Phase II studies addressing these questions can be generally described as phase II feasibility studies. The terms early and late phase II studies have not been used because they give no insight into the purpose behind the study. In general, feasibility studies fall into the category of what may be called late phase II studies. The agent has promise and the study is the start of the process in which the drug is assessed for its value as part of the generally and widely available treatments of the tumour. Can this treatment strategy be put into practice, and has it the potential to become incorporated into standard treatment? In addition to the assessment of a new drug in combination with other therapies, such studies can be used to gain information on the clinical efficacy and toxicity of variations in dose, timing, fractionation and sequencing of agents in a treatment employing several modalities. The features of these phase II feasibility studies are given in Table 2 and some examples are given in Table 3.

In conducting these feasibility studies, it is often the intention of the investigators, if the treatment appears promising, to move to a randomised comparison with an existing, generally accepted, alternative treatment. In those studies where the new treatment may subsequently be compared with standard therapy there is much to recommend randomised comparison with standard treatment, even at the initial phase II stage. The randomisation between the new regimen and a standard therapy is not carried out in order to make a formal statistical assessment of effectiveness since these studies are too small to allow this. The purpose is to ensure that the response in the control group falls within the generally accepted range of response. In this way a false-negative result, due to chance or patient selection, can be avoided [4]. Additionally, the control group allows an assessment of what is likely to be the difference in response (and survival) in a large-scale trial. This prevents investigators being over-optimistic in designing phase III studies and choosing an inappropriately small sample size. Another advantage to randomisation is that the phase II study can itself be taken forward into a phase III study if, at the end of the study, the investigators decide that the results justify this step. This is an efficient use of time and resources and means that the patients entering the phase II feasibility trial have contributed to the phase III evaluation. It might be argued that a randomised study will take longer to complete, but this is counterbalanced by the more efficient use of results in patients if the study goes forward to a phase III trial. There are of course some situations in which early randomisation is not possible, for example, with toxic and technically demanding treatments or in very rare diseases.

Table 2. Characteristics of phase II feasibility studies

The protocol will often have endpoints additional to tumour response and acute toxicity
The drug or agent will have already been investigated in the tumour type
Radiotherapy or surgery may be part of the protocol
There may be more than one drug in the regimen
There is often another established treatment available to serve as a comparison
The intention is often to develop experience of the activity and toxicity of the regimen prior to undertaking a phase III study

Table 3. Examples of phase II feasibility studies

Combination of a new agent with a well-established drug or drugs in metastatic disease
Novel fractionation or schedule of established agent alone or in combination
Novel strategy such as high-dose therapy with stem cell support, hyperfractionation of radiation, synchronous drug and radiation treatment or use of a chemoprotectant

In phase II feasibility studies, the endpoints may differ depending on the nature of the question being posed. Both response (remission) rate and toxicity may be important in assessing a new intensive cytotoxic induction regimen in, for example, relapsed AML (acute myeloid leukaemia). Response rate and median survival may be of interest in the assessment of a new treatment of extensive small cell lung cancer. Acute toxicity may be an important endpoint for a new drug/radiation combination in oesophageal cancer. New statistical methods for continuously assessing response and toxicity in single-arm studies have been developed [5]. In randomised phase II studies, it may be appropriate to measure quality of life as an endpoint, against the standard treatment, e.g. when palliation or cosmesis are the primary objective of the trial. Compliance with the protocol may be important as an assessment.

Although the PRC encourages the use of randomisation in phase II feasibility studies, such studies can not be converted automatically to phase III trials without a formal assessment at the end of the phase II stage. This phase II protocol will state clearly the endpoints of the trial and these results will be reviewed before a decision is made to move forward to phase III. This larger trial will have a new protocol which may have new endpoints, one of

which will almost always be survival, and appropriate sample size calculations. The eligibility criteria may also be modified as a result of the earlier study and may be less or more restrictive. The case report forms may also be modified at this stage. The expanded study will be formally reviewed by the usual PRC procedures.

New agents such as vaccines, chemoprotectants and cytostatic drugs (such as metalloproteinase inhibitors) will demand new approaches to the design and conduct of phase II studies. The EORTC will in due course prepare position papers on these aspects of therapeutic investigation as the issues become better defined.

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