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Phase II Studies: Wrong Doses, Wrong Patients?

IN DEFIANCE of recent trends in clinical research, phase II testing of new anticancer agents is still carried out in uncontrolled studies using small numbers of patients. Are current procedures adequate to ensure that the goals of identifying active agents rapidly, accurately and safely are met?

In phase II trials, a defined dose and schedule are tested in specific tumour types. Success or failure at this stage will determine the subsequent future of the drug. In spite of recent advances in our understanding of the underlying genetic processes which cause cancer, the majority of new anticancer drugs currently in development are antiproliferative agents with a relatively small therapeutic index. It is usually necessary to administer such drugs at the maximum tolerated dose (MTD) in order to achieve optimal antitumour activity. Hence, a successful phase II study is critically dependent on the use of an adequate dose and appropriate schedule. Success also depends on careful patient selection.

If known, a knowledge of the mechanism of action of a drug will help to guide the choice of schedule and a good phase I study will help to ensure that an adequate dose is chosen for phase II trial. In the traditional phase I study 3 patients are entered per dose level, dose escalations are performed using a "modified Fibonacci" scheme and the MTD, or "highest safety tolerable dose", is defined [1]. This is generally regarded as that dose causing grade III myelosuppression, diarrhoea, or mucositis or grade II-III renal, hepatic pulmonary, cardiac or neurological toxicity. The dose chosen for phase II study is then usually one dose level below the MTD. If this scheme is used unimaginatively it is possible to recommend a dose for phase II study which is 30–40% lower than the MTD and which has only been administered to 3 patients! Pharmacokinetics can be used to expedite dose escalation and also to correlate drug concentrations at the MTD with those known to be effective against experimental tumours [2, 3]. If such concentrations cannot be achieved in man owing to toxicity then further evaluation is likely to be fruitless. Before determining the phase II dose it is advisable to treat a larger group of patients at just below the MTD in order to determine the degree of interpatient variation in toxicity and pharmacokinetics. The sort of patients available for phase I trials may not tolerate chemotherapy well, especially if they are heavily pretreated, and one may need to consider the option of defining separate MTDs for non-previously treated and heavily pretreated patients. Another approach to the problem of correct dosage is to recommend dose escalation if a predetermined level of toxicity is not observed after the first course. Conversely, dose reductions will, of course, be allowed if toxicity is excessive.

If failure to choose the right dose and schedule can result in a falsely negative phase II study, what about the choice of patients? It is known that previous exposure to cytotoxic drugs and radiotherapy may lead to the induction of drug resistance, in some case due to increased expression of P-glycoprotein or via an increase in glutathione S-transferase activity [4, 5]. Because of the impact of acquired resistance on response rates it would be ideal if one could test new drugs in previously untreated patients. However, there are practical and ethical problems with this approach in disease types where conventional treatment is reasonably effective, at least in terms of short-term symptom control.

For example, metastatic breast cancer is generally regarded as incurable, hence the administration of a new drug prior

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to conventional combination chemotherapy does not involve withholding potentially curative treatment. Therefore, the majority of patients could be treated ethically in phase II studies, particularly if there were good reasons to expect efficacy with a particular agent, such as known activity with similar analogues or if responses had been observed in phase I trials. However, it would clearly be unethical to give experimental treatment to a patient with life-threatening liver or lung disease. Such patients require prompt administration of chemotherapy of known efficacy.

In small cell lung cancer (SCLC) the problem of acquired resistance is clearly illustrated by three of the most active drugs, etoposide, carboplatin and teniposide. Etoposide has been reported to give a response rate of 50% in previously untreated patients [6] compared with 3–9% in patients with previously refractory disease [7, 8].

Carboplatin achieved a response rate of 60% in untreated compared with 19% in previously treated patients [9]. Most strikingly, teniposide has been reported as producing a 90% response rate in previously treated patients [10] compared with 0% following previous chemotherapy [11].

The practice of testing new drugs in previously untreated patients with SCLC has recently become more widely accepted [12], particularly in patients with extensive disease on the grounds that they have little to lose. However, this may be the wrong approach. Take, for example, a phase II study of idarubicin in previously untreated extensive disease patients, in which the response rate was only 14% [13]. This was not unexpected, but of real concern was the finding that these patients subsequently fared badly in spite of switching rapidly to conventional combination chemotherapy. Only 14 of 21 patients were well enough to receive this and only 4 responded giving a median survival of only 6 months. Similarly, in a trial of first-line mitoxantrone in extensive disease none of 15 patients responded to this or second-line conventional therapy giving a median survival of only 2 months [14].

If extensive disease SCLC is not a good testing ground for new agents, what about limited disease? Given the good prognosis with conventional treatment with a median survival of about 1 year and 10% long-term survival, it would seem unethical to withhold combination chemotherapy. However, patients with limited disease SCLC have a much worse prognosis than those with metastatic breast cancer [15]. Furthermore, the majority of patients show evidence of response after one course of treatment. Thus it seems likely that one course of experimental therapy would be sufficient to give an indication of efficacy and would be unlikely to prejudice future treatment.

An alternative approach is the testing of new drugs in patients who have initially responded well to conventional chemotherapy and subsequently relapsed. It is no longer the practice to continue chemotherapy in SCLC beyond 6 months and a recent review confirmed the lack of benefit from maintenance treatment [16]. Patients who relapse off treatment have a good chance of a second response with the same combination, 67% in a study at the Royal Marsden Hospital [17], a finding which has been confirmed by other groups [18]. Survival is nevertheless limited and such patients are entirely suitable for new drug trials.

In ovarian cancer, a similar problem has been identified. In a retrospective study of 5 phase II trials, it was found that treatment-free interval was the most important prognostic factor for response in a multivariate analysis [19]. The impact of differences in this variable may explain the wide variations in response to certain agents, e.g. 0–26% for mitoxantrone as second line therapy for stage III/IV ovarian cancer [20–22]. In ovarian cancer as in SCLC, retreatment with the same chemotherapy may be effective after a reasonable time off treatment. In this case, platinum complex-based chemotherapy may produce a response rate of about 50% after a treatment-free interval of > 12 months [23, 24]. For this reason, phase II studies in ovarian cancer should be performed in patients who have either not received prior treatment or who have previously had a good response to therapy and relapsed after a long, e.g. 12 months, treatment-free interval. Again, there is concern about the possibility that exposure to an ineffective drug may induce resistance to more effective conventional agents and response assessment is a major problem in this disease [25].

One way of addressing this issue might be to use the serum marker CA-125 as an indication of tumour response after only one or two courses [26, 27], in order to gain useful information regarding the potential efficacy of a new drug "up-front" while limiting the potential for inducing resistance to platinum complexes. Similarly, in prostate cancer, prostate specific antigen (PSA) may be used to monitor response in a disease where conventional response criteria are also extremely difficult to obtain [28, 29]. Careful studies are now required to validate the use of such markers as a substitute for objective tumour measurements.

If tumour markers are a useful way of monitoring response, pharmacokinetics should also be considered as an integral part of new drug studies. Unfortunately, few phase II trials incorporate pharmacokinetic measurements but if a drug is showing promise such studies could be extremely useful. For example, if there were large interpatient variations in toxicity these might be explained on the basis of differences in clearance or in the efficiency of metabolic activation. For a drug which is dependent on a particular route of elimination, such as the kidney in the case of carboplatin, variations in renal function, in this case, may result in underdosage as well as overdosage leading to toxicity. Awareness of this problem led Calvert *et al.* [30] to develop a dosage formula for carboplatin based on renal function. Many years after the introduction of etoposide into clinical practice, studies continue regarding its optimum mode of administration and the impact of renal function on clearance has only recently been established [31]. Studies of the relationship between dose and response, or pharmacodynamics, have demonstrated that plasma concentrations may predict response to treatment, e.g. Evans *et al.* [32] showed that children with acute lymphoblastic leukaemia being treated with high-dose methotrexate were three times more likely to relapse if the plateau concentration was < 16 μmol/l. Plunkett *et al.* [33] showed a strong positive correlation between the intracellular concentration the cytarabine metabolite ara-CTP in leukaemic cells and the likelihood of subsequent remission.

Finally, there are concerns about the uncontrolled nature of phase II studies. If one takes the case of refractory tumours such as renal cancer or melanoma, the best single agents have response rates in the order of 15–20%. In such a disease, errors in measuring response and bias due to the inclusion of patients with advanced disease or poor performance status will be particularly important. An example of the inaccuracy of uncontrolled studies is to be found in the large range of reported response rates to single agent 5-fluorouracil in large bowel cancer, 8–85% in one survey [34]. Such differences may variously be due to chance and to differences in patient selection. There is clearly a good case to be made for performing a randomised study between the new treatment and standard therapy since

the patients in the latter group would enable one to monitor the quality of patient selection and minimise reporting bias. This may be particularly important in multicentre trials. Sadly, the majority of phase II studies are negative, perhaps sometimes due to underdosage and poor patient selection. However, if all phase II studies were randomised from the outset the costs would rise considerably and studies would take longer to complete. A reasonable compromise might be to include a randomised control group once significant activity had been demonstrated. The threshold would vary according to tumour type and the efficacy of existing treatment.

In conclusion, there appears to be a need to revise our approach to phase II studies in terms of the determination of the appropriate dose and schedule, the timing of experimental treatment in relation to conventional chemotherapy, definitions of response, incorporation of pharmacokinetics and overall trial design. A degree of flexibility is required to take into account the nature of the drug itself and the problems posed by different disease types. It should always be remembered that the goal of phase II testing is to identify active new agents efficiently and safely. There are reasons for thinking that existing methods are not adequate and that a more imaginative approach is required.

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