We would like to add a note of caution here when planning aggressive programs of chemotherapy for children with high risk neuroblastoma. The patient population must be defined carefully if such a regimen runs the risk of incurring fatal toxicity. A protocol that accepts children over the age of 1 year with stage III and IV neuroblastoma, without further definition, could include a certain number—admittedly small—who have an excellent prognosis. Many prognostic factors based on biologic standards have been described. These include elevated serum levels of LDH, ferritin, neuronspecific enolase and *p*-glycoprotein; genetic abnormalities such as *N*-Myc amplification, ploidy, and l–p deletion; and the histologic grade of the primary tumour. We have found that the combination of age, stage, serum ferritin, and histologic grade clearly define a prognostic index with 93% confidence limits [1].

Until survival rates improve, we reluctantly must err on the side of aggressive therapies, so that more children, on balance, are cured, and not focus too much on the side effects of treatment. In Philadelphia we are trying to combine different modalities to increase cell kill, but to some extent reduce the toxicity. For example, we have substituted thiotepa for melphalan, and included granulocyte–monocyte cell-stimulating factor (GM-CSF) in the post-transplant period. Since instituting this regimen, we have had one toxic death in 20 patients and so far have no apparent decrease in efficacy.

It is obvious there is a need for a continuing search for the correct balance of treatments that can destroy the disease and not the patient.

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Learning from Cl-941 about Pharmacokinetically Guided Dose Escalation

OVER THE past 6 years, strategies for phase I trials have been profoundly revised. The revision stems from the original contribution of Collins and co-workers in 1986, who proposed that preclinical pharmacokinetic data should be used to guide phase I studies [1]. This proposal was aimed at correcting some inherent problems that severely limited the conventional approach of such investigations.

Due to the narrow therapeutic index of most anticancer agents, the initial clinical evaluation of a new drug in oncology is traditionally aimed at definition of the maximum tolerated dose (MTD). Unfortunately, the MTD cannot be predicted on the basis of toxic doses in animals [2]. Furthermore, the short-term and long-term toxicity of anticancer agents is potentially so severe that the MTD must be defined in patients instead of healthy volunteers. With regard to safety, the traditional design of phase I trials in oncology required the selection of non-toxic doses for starting human testing (usually 1/10th of the mouse LD_{10} [1, 2]), and the use of empirical dose escalation to minimise the risk of major drug-related morbidity or mortality while approaching the MTD. Inherent in this strategy is an unpredictable length of the escalation process, and the ethical problem that many patients are exposed to ineffective suboptimal doses [1]. Lengthy phase I trials have been, and still are, very frequent [1, 3], adding to the ethical burden of investigators, to the delay of evaluation of new therapies and to the deception of "informed" patients who consent to experimental treatments only because they hope to benefit from them.

The starting point of Collins and colleagues' proposal was the pharmacodynamic hypothesis that equal toxicity corresponded with equal drug concentrations. More specifically, the pharmacodynamic concept meant that the dose-limiting toxicity quantitatively correlated with, and could be predicted by plasma drug concentrations in different species. The practical implication was that investigators could know the end-point of phase I trials from preclinical studies before starting to test in man [1]. With the exception of the antimetabolites, retrospective analyses confirmed that even large discrepancies between the mouse LD_{10} and the human MTD were compensated for when plasma drug exposure, expressed in terms of area under the concentration vs. time curve (AUC), was compared in the two species at these doses [1, 4, 5]. Having shown that pharmacokinetic variation was a major reason for inter-species differences in maximally tolerated doses, Collins *et al.* proposed that investigators set the AUC at the mouse LD_{10} as the target of human testing at which the MTD should correspond, and determine the size of the dose escalation steps by measuring how far the patient AUC at a safe entry dose was from the target AUC [1].

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In principle, on-study pharmacokinetic control of the escalation would allow safe reduction of the number of doses required to define the MTD, thus decreasing the number of patients exposed to suboptimal doses and hastening the evaluation of new therapies. This pharmacological approach was termed pharmacokinetically guided dose escalation (PGDE), and was greeted as a major contribution. The Pharmacology and Molecular Mechanisms (PAMM) group of the EORTC emphasised some potential problems, particularly in connection with assay sensitivity to detect drug concentration at 1/10th of the LD_{10}, linearity of the pharmacokinetics and inter-species differences in plasma protein binding and drug metabolism [4]. The analysis generated a detailed set of rules for PGDE, and underlined the need for prospective evaluation of the concept [4].

In *The European Journal of Cancer*, Foster and co-workers describe the prospective evaluation of PGDE in a phase I trial of the new anthrapyrazole Cl-941 [6]. The study is important for several reasons. Most notably, Cl-941 met all the requirements to expect successful implementation of PGDE. The phase I study was preceded by exhaustive preclinical investigation [7] that addressed all the potential problems of the approach highlighted by the PAMM group [4], and ruled out possible interference in the application of PGDE. In this respect, the study is the most thoroughly planned investigation of the approach. Yet, PGDE could not be applied because of large inter-patient variability of AUC at the entry dose [6]. The variability was so large that the investigators applied an escalation scheme even more cautious than the traditional Fibonacci scale. As a result, the trial took more dose steps and more patients than the conventional approach would have required [6].

At first glance, the case of Cl-941 should be cited as evidence against the usefulness of PGDE. Such a conclusion would be wrong and misleading. A closer analysis of the work by Foster *et al.* shows that there is more to PGDE than simply faster dose escalations. Greater safety in drug administration by better informed investigators was proposed as an added advantage of the pharmacological approach [3]. Indeed, for Cl-941, the choice of very cautious escalation was based on the observation of clinical pharmacokinetic variability, and on the preclinical demonstration that pharmacokinetics deviated from linearity at the highest doses tested in mice [7]. Although the study retrospectively showed that inter-patient AUC variation did not have a major impact on toxicity, a bolder escalation than the one selected would have required administration of doses higher than the MTD. In view of the steep dose–toxicity profile of Cl-941 in mice (LD_{10} = 20 mg/kg; LD_{50} = 22 mg/kg [7]), such use could have been detrimental. It is to the credit of the investigators that they took at face value the wealth of pharmacological information on Cl-941, as it is to the credit of PGDE that these data were collected and interpreted so early in the process of the drug's clinical development.

The study by Foster *et al.* is indeed an example of a pharmacologically guided phase I study. Furthermore, in view of the preliminary evidence that Cl-941 is very active in breast cancer patients [8], the available pharmaitlogical data could be of value in planning future studies. For instance, Foster and colleagues suggest that Cl-941 may be a good candidate for use at high doses in combination with haematopoietic growth factors. Knowledge that leukopenia is the common dose-limiting toxicity in mice and men, and that the relation between dose and toxicity is steep in mice would suggest that further dose escalations should be performed with addition of growth factors and possibly with cryopreserved bone marrow rescue, while continuously monitoring drug blood levels to check for linear pharmacokinetics.

Another aspect that should be strongly emphasised is that the study confirmed the validity of the original pharmacodynamic hypothesis of PGDE by showing that the AUC of Cl-941 at the MTD was almost identical to the AUC at mouse LD_{10} [6, 7]. The fact that the central assumption of PGDE withstood prospective analysis despite the problems encountered with Cl-941 should not be dismissed as a minor achievement. So far, only a few other trials have attempted prospective evaluation of PGDE [9–11]. In two instances, on-study corrections of problems with assay sensitivity [11] and with inter-species differences in metabolism [9] translated into successful but minor savings of escalation steps. Together with the inter-patient variability that slowed the evaluation of Cl-941, these problems had been anticipated as potential limiting factors by the PAMM group [4]. The fact that the problems were largely solved without detracting from the original pharmacodynamic assumption is only a reason to refine PGDE further and expand its prospective evaluation.

The experience with Cl-941 agents shows that phase I studies should be pharmacologically more than pharmacokinetically-guided, and that PGDE should not be considered a standard recipe for all drugs. In the selection of drugs for future studies, the need to adapt the clinical investigation to the unique characteristics of individual agents will justify even more exhaustive preclinical investigations than already indicated [1, 4]. For instance, the specific problem of AUC variability raised by the Cl-941 case is common to many anticancer agents. As suggested [6], the issue could be addressed in terms of inter-individual variations in preclinical studies in large animals, and the information used to plan human testing. Another area of refinement, that points to even more precise answers to the problem of variability, should consider means to define less empirical criteria for selecting the size of dose escalations [3]. The size could be tailored to individual drugs or classes of drugs by measuring and taking into account the relation between plasma drug exposure and severity of the dose-limiting toxicity in experimental animals. Such a strategy could ultimately be extended to plan phase I studies in which AUC instead of dose is escalated. Such a development of PGDE is not out of reach. Tools to deal with pharmacokinetic variability, to individualise doses and to achieve uniform AUCs and uniform effects are available and successfully applied [12, 13]. The same group of investigators who approached the clinical and pharmacological development of CI-941 recently showed that AUC escalation of carboplatin is feasible and potentially useful [14]. Furthermore, in this issue of *The European Journal of Cancer* another important paper supports the role of pharmacokinetically guided dosing of anticancer agents [15]. In a straightforward and attractively simple work, Ploin and co-workers show that, also in the case of melphalan, the known variability of hematological side-effects can largely be attributed to plasma AUC variability (p. 1311). Most importantly, from a practical point of view, they also show that melphalan AUC can be successfully escalated in a controlled way, and standardised in individual patients by referring to the plasma drug exposure measured after administration of a non-toxic test dose [15]. The ability to fully control melphalan administration in individual patients, and to normalise the pharmacologic effects thus only waits for a more precise definition of the pharmacokinetic/pharmacodynamic relationship in a larger patient population to identify the optimal plasma AUC. This achievement extends to an old, but still very important

alkylator the concept of pharmacokinetically guided dosing, and is another important piece of evidence supporting the validity and the potential value of the basic pharmacodynamic assumption of PGDE.

In conclusion, the prospective evaluation of Cl-941 and a few other drugs is giving support and momentum to the concepts of PGDE, defining areas where refinements are needed, generating new ideas, and expanding the role of clinical drug monitoring in the development and the use of anticancer agents. The goal of faster, safer and more rational clinical development of new drugs in oncology is more realistic today than six years ago, and should be pursued as one of the greatest opportunities of experimental drug therapy.

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Assessing the Quality of Life of Patients in Cancer Clinical Trials: Common Problems and Common Sense Solutions

"THE ABILITY to simplify means to eliminate the unnecessary so that the necessary can speak."

Hans Hoffman

"Simplification makes action possible in the face of overwhelming complexity; it also increases the odds of being wrong."

Michael Patton

IN RECENT years there has been growing interest on the part of individual investigators, funding agencies and regulatory bodies in broadening the scope of evaluation parameters employed in clinical research in oncology to include assessment of the impact of the disease and treatment on the functional, psychological and social health of the individual. Such quality of life investigations have played a prominent role in recent prospective, randomised trials of breast conserving therapy in operable breast cancer [1], intermittent vs. continuous chemotherapy in advanced breast cancer [2], and limb-sparing procedures in soft-tissue sarcoma [3]. Yet, clinical trial-based quality of life investigations remain the exception rather than the rule. In the past, the major obstacle to carrying out such studies was the lack of consensus on how quality of life should be defined, and the absence of valid and reliable quality of life instruments. While it would be overly optimistic to suggest that these conceptual and measurement issues have been entirely resolved, a great deal of progress has been made in developing psychometrically robust questionnaires for assessing the quality of life of chronic disease patients, in general, and cancer patients, in particular [4].

Much less attention has been paid to the myriad of practical and logistical problems surrounding the collection of quality of life data in cancer clinical trials. Yet, it is such implementation issues that may currently represent the most significant barrier to successful quality of life studies [5]. The extent to which practical problems encountered in quality of life investigations can result in unacceptable levels of missing data and patient loss to follow-up has been illustrated in several recent clinical trials in metastatic lung cancer [6, 7] and prostate cancer [8]. In all three of these studies, where quality of life was a central

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