APPENDIX

The data resulting from the MAP procedure of SAS version 6.07 are postscript files and can be printed by a postscript film plotter, e.g. AGFA matrixpcr. Alternatively, prints are possible with each postscript printer which then transforms the colours to different grey levels.

The files are stored in the public domain of a computer of the German Cancer Research Center (dkfz). They can be received over a network and the file transfer program (ftp). The internet address is ftp.dkfz-heidelberg.de, the user-identification is anonymous, the password is arbitrary and the name of the directory is pub/atlas.

The names of the maps are constructed according to the following rule: it begins with an m, continues with the three-digit ICD-code and ends with an m for male or f for female. The filetype is generally posts (for postscript). Examples: m162m.posts is the postscript file of the lung cancer (ICD 162) map for males, m174f.posts is the file of the breast cancer (ICD 174) map for females.

The maps are only test versions. They do not include a complete legend. Rate levels and ranges of colours can be found in Tables 1 and 2 of this paper. There are four small regions with a 'blackout', where the maps remain uncoloured in all maps. This origins from a technical error in the boundary data and has not been corrected because this map of the old FRG will not be used in future atlas projects which will cover the unified Germany.

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Pharmacokinetics and Cancer Chemotherapy

P. Workman and M.A. Graham

As in all areas of medicine and, indeed, arguably more so than in most other therapeutic disciplines, pharmacokinetic studies are essential to the efficient, safe, state-of-the-art development of new anticancer drugs. Moreover, our emerging understanding of the relationships between pharmacokinetics (the quantitative study of the concentration–time profile of the drug in the body, incorporating absorption, distribution, metabolism and excretion) and pharmacodynamics (the quantitative study of the effects of the drug on the body, including both efficacy and toxicity) is encouraging a more systematic and rigorous analysis of the potential role of pharmacology in the day-to-day management of individual cancer patients. The latest issue of *Cancer Surveys* [1] provides an up-to-date, critical analysis of current developments in the pharmacokinetics of cancer drugs. The contents of the monograph cover three broad subject areas: (1) novel concepts in pharmacokinetics and metabolism in relation to drug development and therapy, including locoregional delivery, (2) pharmacokinetics of a range of drug classes and (3) selected techniques for analytical detection.

Surprisingly, it is 10 years since this specific topic was reviewed in equivalent detail in a dedicated monograph format [2]. During this time, the whole face of anticancer drug discovery and development has changed. Not only are we now dealing with highly innovative and distinct classes of molecules in terms of both mechanism of action and chemical structure—for example, recombinant therapeutic antibodies, cytokines, antisense oligonucleotides, therapeutic genes and signal transduction inhibitors—but we are also deploying an impressive array of new techniques and ideas.

Since the effects of a therapeutic entity in the body are generally a function of its concentration at the molecular site of action (usually a receptor), it now appears obvious to us that a description of the spatio-temporal behaviour of the drug will be helpful, if not essential, in understanding and predicting normal tissue toxicity and tumour response. Given the multiple factors which can cause drug concentrations to vary, even after a fixed dose, it is clearly much more meaningful to talk about drug exposures (usually expressed as the area under the drug concentration against time curve, or as time above a minimum effective level) rather than absolute dose. Ideally, this would be at the molecular locus of action or at least at the tissue level but, most commonly, drug concentrations must be measured in the plasma as a more readily accessible surrogate.

It seems extraordinary in the 1990s that many of our commonly used cancer drugs were introduced with little or no pharmacokinetic experimentation in the modern sense of the term. The crucial importance of pharmacokinetics in the evaluation and use of new therapeutic entities has now become widely accepted by the academic community, pharmaceutical companies and the regulatory authorities alike. The extent to which this thinking has advanced is illustrated by the timely and influential recommendations on opportunities for integration of pharmacokinetics and toxicokinetics in rational drug development, published recently by Peck and colleagues [3]. A central feature of these proposals is the advocacy of concentration–response models in place of the more common dose–response models. Although the extent to which these concepts should be embodied in mandatory requirements for drug registration, as opposed to undergoing detailed evaluation as investigational research tools, remains controversial in some quarters, the scientific good sense of these developing ideas and the growing

Correspondence to P. Workman at the Cancer Research Department, ZENECA Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.
M. A Graham is at the Pharmacokinetics and Drug Metabolism, Sterling Winthrop Research Centre, Willowburn Avenue, Alnwick, Northumberland NE66 2JH, U.K.
Both authors were previously at the CRC Department of Medical Oncology, CRC Beatson Laboratories, University of Glasgow, U.K.
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number of examples of their practical utility have led to their enthusiastic promulgation within the cancer pharmacology community. This edition of *Cancer Surveys* provides many excellent examples of the practical value of pharmacokinetics, but at the same time points out where real limitations exist. It illustrates how pharmacokinetic concepts can play a pivotal role in all phases of the development of a novel therapeutic entity—from discovery, through *in vitro* and *in vivo* efficacy testing, toxicology and early clinical trials to routine clinical use. In the patient, pharmacokinetics provides rapid and rational answers to critical questions such as: How much? How often? How long? By what route? Appropriate resolution of these issues can make the difference between a good drug and a poor one, or indeed having no effective drug at all.

In the introductory chapter, Workman provides a broad overview of the successes, failures and future prospects for pharmacokinetics in both new drug development [4–6] and routine patient care [7–9]. The increasingly important application of pharmacokinetics in the drug discovery process is stressed, given that a major stumbling block is frequently the inability to convert a promising *in vitro* lead into a compound with *in vivo* activity. With its origins in the 1980s [10, 11], but still very much in its infancy, the ability to use computers to predict quantitative structure–pharmacokinetic relationships is seen as having the potential to revolutionise rational drug design in a similar way to the enormous benefits arising from quantitative structure–activity relationship (QSAR) approaches.

In contrast to preclinical and early clinical studies, where the value of pharmacokinetics is beyond doubt, the contribution of measuring blood levels in day-to-day care by busy clinicans is less widely recognised and its broader potential remains to be clarified [7–9]. The gold standard is, of course, methotrexate where the monitoring of circulating drug concentrations can avoid potentially fatal toxicity by guiding leucovorin rescue [12]. More than ever in the current healthcare environment, the potential to expand routine therapeutic drug monitoring across a broader range of agents necessitates a tough, pragmatic approach to such questions as : Can the assays be conducted on a routine basis? Do the measurements affect treatment outcome? Are they cost effective? Will they actually be used by clinical and nursing staff in a busy hospital environment? The foundations from which to build up to answering these key questions are laid by detailed studies which seek to identify the relationship between pharmacokinetics and pharmacodynamics [13–14].

Pharmacokinetics has a particularly distinct contribution to make in phase 1 clinical trials. This is an especially critical time in drug development since it is the period in which the widest range of drug doses will be evaluated. There are particular ethical issues associated with the need to escalate doses as rapidly as possible while at the same time maintaining safety [15,16]. Pharmacokinetics can greatly improve the speed and rationality of this process [4–6]. Graham and Kaye review the area of pharmacokinetics in phase 1, covering both conventional and alternative approaches, including maximally tolerated systemic exposure, continual reassessment and pharmacokinetically guided dose escalation (PGDE). They cite several instances in which PGDE has been especially beneficial (e.g. with 4′-iodo-4′-deoxydoxorubicin [17]). They also point out areas of difficulty: analytical sensitivity (e.g. amphethinile, rhizoxin), non-linear pharmacokinetics (e.g. flavone acetic acid), species differences in plasma protein binding (e.g. antibiotic LL–D49194 α1) and drug metabolism (e.g. 4′-iodo-4′deoxydoxorubicin), and marked interpatient variability in drug clearance (e.g. anthrapyrazole DuP941 [18]).

Of course, pharmacokinetic studies of a new drug must not be abandoned after phase 1. There is a welcome trend towards the conduct of carefully planned pharmacokinetic studies being carried out as part of phase 2 trials. This provides an additional insight into the handling of the drug in a wider patient group, and in particular allows the validation or further development of pharmacokinetic–pharmacodynamic models in a setting where most of the patients receive similar doses and where evidence of tumour response is specifically sought. Kobayashi and colleagues provide an up-to-date review of pharmacokinetic–pharmacodynamic relationships, not only for haematological and non-haematological toxicities but also for therapeutic response. In addition, they describe how such information can then be used to provide the basis for therapeutic drug monitoring and adaptive control of dosing using feedback. This approach is aimed specifically at agents having substantial interpatient variability in addition to the usual low therapeutic index. The objective is to optimise the systemic exposure so as to maximise the probability of a therapeutic response while minimising the risk of toxicity. Although various complex and specialist statistical methods and computer programmes are required in the early stages (Bayesian methods, NONMEM, ADAPT), the use of limited sampling strategies can reduce the discomfort to the patient and at the same time simplify the work in the clinic and in the analytical laboratory. However, Koybayashi and colleagues stress the need for any method entering widespread use to be simple and user-friendly. Although work with numerous established agents, like etoposide and experimental agents such as suramin, is ongoing, the best current example of this approach is the development of the simple dose individualisation formula for carboplatin based on renal function [19, 20].

Much of the variability in drug handling between individuals is genetic in nature, and Boddy and Idle therefore provide an overview of the role of pharmacogenetics in cancer chemotherapy. The importance of polymorphisms for the metabolism of xenobiotics is stressed. Many drugs are metabolised by members of the cytochrome P450 gene superfamily. These include the oxazaphosphorines cyclophosphamide and ifosfamide, the complex biotransformation of which also involves aldehyde dehydrogenase. An established cancer drug for which pharmacogenetics is a predictor of toxicity is mercaptopurine; this agent is a major component of maintenance therapy for childhood acute lymphoblastic leukaemia and is inactivated by the polymorphic enzyme thiopurine methyltransferase [21]. Since it is increasingly feasible to predict patterns of human drug metabolism, for example, using cloned human enzymes expressed in yeast or mammalian cells, it should in the future be possible to 'design out' genetically variable metabolic pathways so that the problem of abnormally slow and rapid metabolisers will be greatly reduced [22].

One way of improving drug delivery to particular tumour sites is to employ locoregional chemotherapy, the pharmacokinetic principles of which are reviewed by Kerr and Los. Particular care must be taken in the choice of agent for locoregional therapy. There is good evidence that, under certain situations, pharmacokinetic advantage can translate into clinical advantage but potential problems include that of tumour bulk.

Although the intention was not to provide a basic textbook of cancer pharmacokinetics (but rather a comprehensive survey of the present status of the subject, assessing current needs, problems and growth areas and highlighting future prospects),

it was felt appropriate to present a series of cutting edge reviews on the pharmacokinetics of various drug classes. Beginning with one of the earliest drug types, Peters and colleagues review the clinical pharmacokinetics of antimetabolites, covering cytidine analogues (including gemcitabine), purine antimetabolites (including fludarabine), methotrexate, 5-fluorouracil and the important topic of biochemical modulation. Likewise, Lind and Ardiet cover alkylating agents for which the problems of chemical reactivity are yielding to modern analytical methods. Platinum complexes are dealt with by Calvert and colleagues. They emphasise platinum–DNA adduct formation, resistance mechanisms and modulation, and current approaches to carboplatin dosing based on the pharmacokinetic–pharmacodynamic approaches mentioned earlier. The pharmacokinetics and metabolism of anthracyclines are elaborated by Robert and Gianni, who highlight locoregional delivery, effects of liver dysfunction and metastasis, pharmacokinetic–pharmacodynamic relationships, the use of carriers and conjugates and the challenges posed by the fascinating and highly potent new morpholino-anthracyclines which undergo metabolic bioactivation [23] and can circumvent multidrug resistance [24]. The topic of epipodophyllotoxins is addressed by McLeod and Evans. Pharmacokinetic–pharmacodynamic insights feature prominently for etoposide and teniposide. New approaches are focussing on multiple fractioned doses and more prolonged infusions which may provide a pharmacokinetic advantage while also taking into account the mode of action against DNA topoisomerase II. Despite the very promising results achieved so far, the optimal schedule for etoposide remains to be resolved. It has been argued that targeting a specific plasma level with the more convenient oral route is not feasible because of the variable absorption of etoposide [25]. However, the problems of solubility, stability and variable pharmacokinetics may be eased by the introduction of the attractive prodrug etoposide phosphate [26]. It is interesting that multiple fractionated oral dosing and prolonged intravenous infusions are under evaluation for a range of carrier drugs and may be of particular relevance to investigational agents with novel mechanisms of action.

In discussing the pharmacokinetics and metabolism of the potent tubulin-binding vinca alkaloids, Rahmani and Zhou illustrate how the introduction of radioimmune assays and very sensitive ELISA methods, developed during the 1980s, have made a major impact in the understanding of the pharmacology of these agents. The oral bioavailability of the lipophilic analogue navelbine provides new scheduling options. Two of the most promising new cytotoxic drugs to show clinical activity in recent years—taxol and taxotere—also target tubulin. These are reviewed by Rowinsky and colleagues, and Bruno and Sanderink, respectively. Issues raised include the relatively undefined metabolic fate of taxol. Ongoing pharmacokinetic–pharmacodynamic studies are likely to be of considerable value in defining the most efficient use of the taxanes, both alone and in combination with other agents.

Increasingly, we are seeing the introduction of a variety of novel therapeutic entities of much larger molecular size than conventional cytotoxic agents. These can pose special challenges, for example, with regard to analytical methodology. Data are now emerging on the pharmacokinetics of antisense and antigene oligonucleotide agents [27], and it may be that uptake of such agents into tissues *in vivo* is not as limiting a factor as was previously supposed. The delivery vehicles used for gene therapy will also be crucial for success [28]. In the present monograph, Cassidy and colleagues review the extremely important topic of high molecular weight anticancer agents by focusing on polymeric and lipid carriers, microparticulate drug delivery systems and antibody-based therapies. The enhanced permeability and retention effect (arising from leaky vasculature combined with poor lymphatic drainage) can promote the accumulation of simple, non-targeted polymers in tumours. Alternatively, the penetration into tumour tissue of targeted antibodies remains sub-optimal, but the molecular features which affect antibody pharmacokinetics are becoming much clearer, as is our understanding of basic tumour physiology and haemodynamics in relation to therapy [29]. Antibody-directed enzyme prodrug therapy is particularly attractive because the liberation of a locally diffusable prodrug at the tumour site provides for bystander killing of those tumour cells which fail to bind the antibody, because of either antigen negativity or molecular weight-limited penetration [30].

Endocrine therapy plays a major role in the systemic treatment of breast, prostate and some gynaecological malignancies. Anti-endocrine agents, typified by tamoxifen in breast cancer, are notable for their less aggressive side-effect profile and broader therapeutic margin than cytotoxic agents. In a sense they provide a paradigm for the expected next generation of drugs which will be designed to inhibit the intracellular signal transduction pathways used by oncogenes and growth factors [31,32]. These will include, for example, tyrosine kinase inhibitors and farnesylation antagonists which are already showing promise in model systems. The pharmacokinetics of the classical anti-endocrine agents are reviewed by Lonning and Lien. It should be noted that, unlike cytotoxic agents, escalation to maximum dose/exposure may well not be appropriate. The availability of a pharmacodynamic measurement of biochemical effect will be extremely useful for dose optimisation. The interesting possibility is raised that tamoxifen resistance may relate to poor tissue levels, perhaps as a result of the production of oestrogenic metabolites in tumour tissue [33].

In their review of pharmacokinetics in the early clinical trials of new drugs, Kaye and colleagues make a timely selection: the promising anthrapyrazole Dup 941 and its cousins Dup 937 and 942; the very interesting topoisomerase 1 inhibitory camptothecin analogues topotecan and CPT-11; the unusual macrocyclic lactone microtubule inhibitor rhizoxin; the polysulphonated napthylurea suramin which binds growth factors; and the bioreductive indoloquinone EO9. Each tells an interesting story, but the authors are critical of the practical contribution made by pharmacokinetic studies in these particular cases, while at the same time stressing the values of continuing pharmacological input as the drugs progress further. The potential importance of measuring the reductive enzyme DT-diaphorase in tumour biopsies as a predictor of EO9 response is stressed [34].

The ongoing development of improved analytical methodology has been a major factor in the growing influence of cancer pharmacokinetics. The ability to measure drugs and metabolites is frequently a problem, particularly for reactive chemicals or highly potent agents such as certain natural products. High performance liquid chromatography (HPLC) and radioimmune assays have been particularly important because of their sensitivity, robustness, comparative ease of use and wide-ranging applicability. Gas chromatography, while giving way to HPLC in many areas, remains useful, as with the oxazaphosphorines and the novel agent ipomeanol. In the present monograph, we have chosen to focus on four techniques with particular significance. Gouyette describes technical advances in mass spectrometry (MS) and explains the power of this tool for

studying the fate of drugs *in vivo*, especially when used in combination with new procedures such as fast atom bombardment and ion spray. The development of HPLC–MS is equally noteworthy when applied to identifying the structure of drugs and their biotransformation products and to study complex macromolecules [35]. In a related review, McKay describes progress with the use of inductively-coupled plasma spectrometry (ICP–MS) for the ultratrace determination of elemental platinum in biological samples. Most researchers have previously used atomic absorption spectrometry or inductively-coupled plasma atomic emission spectrometry (ICPAES) for total platinum determination. ICP–MS has the potential to monitor very prolonged retention, as well as linking to HPLC to analyse individual metabolites and platinum–DNA adducts [36]. Laser ablation methodology has potential for examining spatial distribution of platinum in tissues. Positron-induced X-ray excitation (PIXE) has also been used for this. The ability to analyse cancer drugs in tissue is very important and emerging techniques for this include confocal fluorescence microscopy and electron spectroscopic imaging/electron energy loss spectroscopy (EELS/ESI), as mentioned in the introductory chapter.

An exciting new development that is likely to have a major impact on cancer pharmacology and the conduct of early clinical trials is the ability to monitor tissue distribution of drugs non-invasively. Maxwell shows how nuclear magnetic resonance (NMR) spectroscopy and associated imaging methods allow identification of metabolites *in vivo*, but are rather insensitive, while positron emission tomography (PET) has the opposite characteristics, as described by Tilsey and colleagues. NMR has been used especially for fluorine-containing drugs such as 5-fluorouracil [37] while PET is being applied to a range of novel cancer drugs. Both techniques require expensive specialist facilities but each has important potential to provide pharmacodynamic as well as pharmacokinetic information. Biosensor technology also has exciting potential.

The integration of biochemical and molecular pharmacodynamics with pharmacokinetics is emphasised towards the end of the introductory chapter by Workman. In addition to its importance with the classical cancer drugs acting on conventional types of targets, it will be essential for the rational development of new agents designed to exploit advances in molecular oncology and acting on oncogenes, tumour suppressor genes and related signal transduction pathways [31,32], including apoptosis [38]. As mentioned earlier in this review, such innovative agents may require an especially careful and imaginative choice of dosage regimens. Continuous inhibition of an oncogene function may require long-term, daily administration to maintain active but non-toxic dose levels (but see also [39]). The same will probably be true of agents used for chemoprevention or to inhibit invasion, angiogenesis and metastasis.

A further point raised in the introductory chapter, and worth highlighting here, is the key role of pharmacokinetics as a problem-solving subject [40] which must interact closely with a range of other disciplines [41], and the implications of this for the training and career development of its practitioners. There needs to be an ongoing debate to clarify the optimal roles of pharmacokineticists in different environments—such as academic institutes and universities, hospitals and the pharmaceutical industry—in response to the rapidly changing shape of oncology research, healthcare service provision and regulatory and commercial perspectives. Although pharmacokinetics is essential to all phases of discovery and development, and also to routine therapy in some cases, very different work is involved in the discovery of an orally active signal transduction inhibitor compared to improving the delivery of an immunotoxin or anti-oncogene oligonucleotide versus adaptive dosing with an established cytotoxic agent. There is ample evidence in this edition of *Cancer Surveys* that pharmacokinetics will continue to provide vital support to both routine patient management and the discovery, development and evaluation of innovative, cutting edge therapies.

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European School of Oncology

First Euro-American Forum on Lung Cancer Treatment

P.A. Bunn Jr., N. Van Zandwijk, U. Pastorino, J. Aisner, P. Alberto, R. Arriagada, D. Carney, R. Cornis, C. Dittrich, U. Gatzemeier, R. Ginsberg, F.A. Greco, H.H. Hansen, P. Harper, R. Henriksson, H. Huber, P. Klener, T. LeChevalier, R. Lewensohn, N. Murray, N. Niederle, P. Postmus, R. Rosell, G. Scagliotti, J.P. Sculier, T. Splinter, R. Stahel, M. Symann, N. Thatcher, M. Tonato and A. Turrisi

INTRODUCTION

THE FIRST Euro-American Forum on Lung Cancer Treatment, designed and organised by the European School of Oncology, was held in Vienna, Austria on 9–10 December 1993 with the aim of reviewing the current and future state of the art in lung cancer therapy. The workshop participants, listed above, represented the disciplines of prevention, surgery, radiotherapy and chemotherapy. There was guarded optimism expressed by the participants that recent combined modality therapies had made small improvements in survival. Advances in preventing second malignancies have also occurred. There was optimism that newly available chemoprevention strategies, chemotherapeutic agents, radiation and surgical techniques and biologically based therapies might lead to even further survival gains in the near future. Because most of the survival improvements have occurred in small increments, the need for large prospective randomised trials was emphasised. Rather than stressing pessimism toward lung cancer patients, we should encourage primary care physicians and related specialists to refer patients to specialists with appropriate experience in lung cancer so that optimal care can be delivered. By necessity, this care requires collaborative interactions among the specialities.