DOI:10.1111/j.1365-2125.2006.02721.x

Editors' view

Cancer pharmacotherapy: 21st century 'magic bullets' and changing paradigms

L. D. Lewis, North American Editor, British Journal of Clinical Pharmacology

Section of Clinical Pharmacology, Department of Medicine, Dartmouth Medical School and Dartmouth-Hitchcock Medical Center, HBox 7506, One Medical Center Drive, Lebanon, New Hampshire 03756, USA; lionel.d.lewis@dartmouth.edu

In this month's issue of the *Journal* we focus on cancer pharmacotherapy. The articles provide insights into the current scientific basis of recently available and potential anti-cancer drugs, and discuss the current and future challenges in using classical cytotoxic[a] and molecularly targeted anti-cancer drugs.

Over the past decade the explosion in new and potential anti-cancer drugs has had its foundation in an increased scientific understanding of the biology of cancer [1]. The current oncology drug pipeline of the pharmaceutical industry contains nearly 400 small molecules and biological modifiers undergoing clinical development [2]. Optimal anti-cancer drug treatment, whether it involves the use of classical cytotoxic agents or novel molecularly targeted anti-cancer drugs, will require oncologists to incorporate into their therapeutic decisions up-to-date knowledge of the factors that contribute to the variability in human drug response [3–6]. The therapeutic armamentarium of 21st century oncologists when compared with that of the earliest physicians, or for that matter with that available in the mid 20th century, has a greater number of drugs, is more complex, uses many multi-drug combinations and continues to expand.

Early descriptions of cancer and its treatment

The Egyptian papyri which are thought to have been written between 3000 and 1500 BC are considered by many to contain the earliest descriptions of human cancer. The Edwin Smith papyrus [7] describes several cases of tumours or ulcers of the breast. The translation of the heiroglyphic inscriptions in the Smith papyrus, by Breasted [8], informs us that Egyptian physicians (known as "swnw" and pronounced *sounou*) had no effective treatments for cancer, but that cauterization was used as a palliative measure. However, the papyrus, does describe surgical removal of superficial tumours, in keeping with current medical practice. The "swnw" also used compounds of barley, pigs ear and other indigenous materials as treatments for cancer of the stomach and the uterus, although their efficacy was poorly defined [8].

A synopsis of the history of cancer pharmacotherapy

The dawn of modern cytotoxic anti-cancer therapy can be traced back to the investigation of the cytotoxic properties of nitrogen mustards by Gilman in 1942 [9]. The dramatic therapeutic success of nitrogen mustard in patients with Hodgkin's disease and lymphosarcoma was initially described by Goodman *et al.* in 1946 [10]. This probably represents one of the first Phase I/Phase II studies reported in the modern medical literature [11]. However, from the mid 1940s into the 1990s the increasing scientific understanding of cancer biology was not paralleled by rapid translation of this knowledge into effective anti-cancer drugs. Nevertheless, during these 50 years there were significant advances in cancer pharmacotherapy [12]. Anti-folate drugs were used to induce remission in children with acute lymphatic leukemia and methotrexate cured patients with choriocarcinoma; 6-mercaptopurine was synthesized; combination chemotherapy was used effectively in acute lymphoblastic leukemia, lymphoma and as adjuvant therapy for

[a]The term cytotoxic when used in this article to describe drugs, indicates drugs that have greater cytocidal than anti-proliferative (cytostatic) effects on cells.

node-positive breast cancer. Many of these advances in anti-cancer drug combination therapy were linked to concomitant advances in laboratory screening and testing of drugs against tumour cell lines, originally begun by the National Cancer Institute in 1955. In the late 1970s cisplatin was synthesized and found to be effective in treating ovarian and testicular cancer. The development of the cisplatin analogue, carboplatin, quickly followed. In addition, following an intensive search for anti-cancer drugs from plant sources, in the 1960s and the 1990s respectively, the clinical utility and efficacy of the vinca alkaloids and the taxanes in treating solid tumours was defined [10].

So into the 21st century, the era of 'molecularly targeted' anti-cancer therapy, which brings to mind Paul Ehrlich's concept of the Zauberkugel, the 'magic bullet' for cancer cells [13]. Ehrlich's concept was developed into the 'selective toxicity' concept by Albert [14], which was particularly appropriate for the cytotoxic anti-cancer drugs. The current focus on molecularly targeted agents that alter cell growth but do not necessarily kill cells directly, points us to more subtle forms of bullet. The first major success of molecularly targeted therapy was imatinib mesylate (Glivec, Gleevec). Imatinib is an ATP mimetic and competitive inhibitor of several cellular ABL-kinases, including the BCR-ABL kinase fusion protein, which is the single molecular mutation that drives cellular proliferation in Philadelphia chromosome-positive chronic myeloid leukemia (CML). But, as is often the case, success brings new challenges, imatinib treatment selects surviving leukemic clones, ultimately producing resistant disease in a number of patients with CML [15].

Early 21st century cancer pharmacotherapy

This issue begins with a series of reviews on anti-cancer drug treatment. Eastman and Perez [16] provide a timely and detailed summary of the cellular pathways that have recently been implicated in the pathogenesis of cancer. These pathways include growth factor receptors on the tumour cell membrane involved in cell proliferation, receptor and non-receptor tyrosine kinases involved in proliferation and growth and cellular kinases involved in the control of cell cycle progression. The authors specifically highlight pathways/molecules that have either in the recent past or may in the future yield novel targeted therapies (for example imatinib, epidermal growth factor receptor tyrosine kinase inhibitors, and Chk I inhibitors). In keeping with current opinion they emphasize the need to stratify the patients who will benefit most from molecularly targeted drugs based on the propensity of an individual's tumour expressing the drug target.

Kummar and colleagues [17] describe how the strategies traditionally used to develop classical cytotoxic anti-cancer drugs may be sub-optimal for molecularly targeted agents, particularly in the early exploratory Phase I and II trials. The determination of the therapeutic anti-cancer drug dose, based on maximum tolerability combined with efficacy based on an objective reduction in tumour burden may not be the best model for such agents. This is because many of the molecularly targeted agents have a wide therapeutic index and inhibit tumour proliferation (cause cytostasis) often without producing a demonstrable cytocidal effect. Instead, early-phase drug development studies of molecularly targeted agents would probably be the most appropriate investigative arena in which to focus on other pharmacodynamic endpoints, such as validated disease biomarkers (while concomitantly defining important concentration–response relationships), and disease stabilization rather than reduction in tumour burden.

Boddy [18] reminds us that there have been developments and innovations in the clinical pharmacology of classical cytotoxic anti-cancer drugs. He correctly draws attention to advances in bioanalytical methods using liquid chromatography–mass spectrometry (LC-MS) to measure drug concentrations in the picogram range; and medical imaging techniques such as PET and magnetic resonance spectroscopy to improve our ability to monitor the effects of drugs on tumours. These methods have guided improved therapeutics for several traditional cytotoxic anti-cancer drugs. Furthermore, Boddy suggests that integrative physiologically based–pharmacokinetic-pharmacodynamic (PB PK-PD) modeling, may further enhance our ability to individualize anti-cancer drug treatment.

Yong *et al.* [19] elucidate in more detail some of the pharmacogenetic issues also mentioned by Boddy [17] regarding the genetic contribution to variability in human anti-cancer drug response. The Chicago group provide a comprehensive synopsis of current studies of the effects of germline polymorphisms in important anti-cancer drug metabolizing enzymes (for example thiopurine methyl transferase; uridine 5'-diphosphate glucuronosyltransferase; dihydropyridine dehydrogenase) and somatic mutations in tumour targets (e.g. polymorphisms in tumour thymidylate synthase activity resulting in altered mRNA stability or protein overexpression which affect 5-fluoro-uracil cytotoxicity; tumour epidermal growth factor receptor tyrosine kinase domain polymorphisms which confers stabilization of the receptor tyrosine kinase inhibitor -target complex).

They emphasize how such genetic variants modulate anti-cancer drug-related toxicity and therapeutic effects, a pivotal issue for all drugs especially those with a narrow therapeutic index.

Population pharmacokinetics of anti-cancer drugs

Several articles in this month's issue of the journal describe studies of different aspects of the population pharmacokinetics of anti-cancer drugs. Ralph *et al.* [20] examine the advantages or disadvantages of internal and external validation of a population pharmacokinetic model of epirubicin. In keeping with what would be predicted in principle, they conclude that internal validation with relatively small numbers of patient is problematic.

Mould *et al.* [21] report a population pharmacokinetic study of 24-hour infusional paclitaxel combined with either cisplatin or doxorubicin in patients with advanced endometrial cancer. They conclude that in these patients paclitaxel AUC was an independent predictor of neutropenia and patient survival. This is the first study to have suggested that paclitaxel exposure predicts survival; it needs confirmation. Docetaxel AUC has been associated with neutropenia but not with survival [22].

Joerger *et al.* [23] describe the population pharmacokinetics of high dose methotrexate in primarily choriocarcinoma and head and neck cancer patients. This study confirmed the published pharmacokinetic parameters for high dose methotrexate. In addition, it suggests that methotrexate and 7-hydroxy methotrexate clearance was reduced in patients who concomitantly received the benzoimidazoles omeprazole or lansoprazole. The mechanism of this drug–drug interaction is probably by inhibition of the ABCG2 drug transporter [24].

Perez-Ruixo *et al.* [25] describe a large population pharmacokinetic study tipifarnib in healthy volunteers and cancer patients. Tipifarnib is a reversible inhibitor of farnesyltransferase, an enzyme that is involved in post-translational protein modification which mediates protein trafficking and activation. This is especially important in malignant cells that overexpress growth signaling molecules such as Rho B, Ras and lamin as is in hematologic malignancies, for which tipifarnib has shown promising activity. They conclude that based on the tipifarnib population pharmacokinetic parameter estimates there is no need to adjust the dose of tipifarnib based on weight or total serum bilirubin in cancer patients.

Widmer *et al.* [26] report a study of the population pharmacokinetics of chronic oral imatinib in 59 patients with chronic myeloid leukemia or gastro intestinal stromal tumours (GIST). Their conclusions confirm earlier studies in leukemia and GIST populations that there was large interindividual variability in imatinib disposition (30–35% CV in Vd/F and CL/F) [27, 28]. They also report that plasma alpha-1 acid glycoprotein (AAG) markedly influenced imatinib disposition, a finding that was predictable, as imatinib is approximately 95% bound by AAG [29, 30]. Based on their data they suggest that therapeutic drug monitoring be used to individualize imatinib treatment.

We endorse the suggestion initially made by Aarons [31], and in this issue by Boddy [18], that pharmacokineticists should consider the appropriate use and potential benefits of more sophisticated integrative PB PK-PD modeling approaches in such studies.

Future challenges in cancer pharmacotherapeutics

The literature on classical anti-cancer drug therapy, its successes and failures, leads one to predict that further successful development and optimal therapeutic use of molecularly targeted anti-cancer drugs will not be easily achieved. But the knowledge base generated over the past 60 years has provided us with several principles that will be applicable to molecularly targeted therapies. First, animal models, while instructive, are poorly predictive of therapeutic efficacy against human cancer and data generated from such studies should be viewed with caution. Secondly, human tumours that respond to drug treatment still contain subclones which, can become drug resistant by a broad array of mechanisms. Therefore the anti-tumour effects of an anti-cancer drug (or drug combination) probably need to be monitored regularly and perhaps modified based on relevant molecular changes identified in the tumour cells over time. Thus, molecular profiling of a patient's tumour before choosing therapy and as a means to define treatment modifications is likely to become the standard of care [32].

With currently available anti-cancer drugs and the molecularly targeted anti-cancer drugs in development there is clearly the potential to change the outcome of a cancer into either cure or a more chronic condition, in marked contrast to the current natural course of the disease, which for many cancer patients is fatal. From an academic perspective perhaps the greatest excitement concerning cancer pharmacotherapy is that in the 21st century novel paradigms for anti-cancer drug treatment are evolving for different cancers. One can envision anti-cancer drug regimens in which initially classical cytotoxic drugs either alone or in combination with molecularly targeted drugs are first used to reduce tumour burden, followed by maintenance treatment with molecularly targeted drugs either alone or in scientifi-

cally individualized combinations. The implication of such therapeutic regimens is that there will always be new therapeutic challenges for clinical pharmacologists in collaboration with oncologists.

In conclusion, with the advent of molecular targeted anti-cancer therapies, it appears that Paul Ehrlich's romantic concept of the 'magic bullet' [12, 33] against tumour cells, which is more than a century old, has been achieved at least for imatinib in chronic myeloid leukemia. With the current large oncology drug pipeline we are at the dawn of an era during which 'magic bullets' may be developed and effectively used to treat a wider spectrum of cancers. Only by undertaking thoughtful studies of the clinical pharmacology of these agents, will molecularly targeted anti-cancer therapy change the natural course of cancer.

References

1 Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. Nat Med 2004; 10: 789–99.
2 PhRMA website: http://www.Phrma.org/files/Cancer%20Survey.pdf. (last accessed 28 May 2006).
3 International HapMap Consortium. A haplotype map of the human genome. Nature 2005; 437: 1299–320.
4 International HapMap Project. http://www.hapmap.org. (last accessed 28 May 2006).
5 O'Shaughnessy KM. HapMap, pharmacogenomics, and the goal of personalized prescribing. Br J Clin Pharmacol 2006; 61: 783–86.
6 Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, Karrison T, Janisch L, Ramirez J, Rudin CM, Vokes EE, Ratain MJ. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004; 22: 1382–8.
7 http://www.s2ortho.com/z-knowledge/pharaonic/medicin... (last accessed: 28 May 2006).
8 Breasted JH. The Edwin Smith surgical papyrus. Chicago: Chicago University Press, 1930.
9 Gilman A. The biological actions and therapeutic applications of the beta-chloroethyl amines and sulfides. Science 1946; 103: 409–36.
10 Goodman LS, Wintrobe MM, Dameshek W, Goodman MJ, Gilman A, McLennan MT. Nitrogen mustard therapy. Use of methyl-bis(beta-chloroethyl)amine hydrochloride and tris(beta-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. JAMA 1946; 132: 126–32.
11 Gilman A. The initial clinical trial of nitrogen mustard. Am J Surg 1963; 105: 574–8.
12 Chabner BA, Roberts TG Jr. Timeline: Chemotherapy and the war on cancer. Nat Rev Cancer 2005; 5: 65–72.
13 Schwartz RS. Paul Ehrlich's magic bullets. N Engl J Med 2004; 350: 1079–80.
14 Albert A. Selective toxicity. Nature 1950; 165 (4184): 12–16.
15 O'Hare T, Corbin AS, Druker BJ. Targeted CML therapy: controlling drug resistance, seeking cure. Curr Opin Genet Dev 2006; 16: 92–9.
16 Eastman A, Perez RP. New targets and challenges in the molecular therapeutics of cancer. Br J Clin Pharmacol 2006; 62: 5–14.
17 Kummar S, Gutierrez M, Doroshow JH, Murgo AJ. Drug development in oncology: classical cytotoxics and molecularly targeted agents. Br J Clin Pharmacol 2006; 62: 15–26.
18 Boddy AV. Recent developments in the clinical pharmacology of classical cytotoxic chemotherapy. Br J Clin Pharmacol 2006; 62: 27–34.
19 Yong WP, Innocenti F, Ratain MJ. The role of pharmacogenetics in cancer therapeutics. Br J Clin Pharmacol 2006; 62: 35–46.
20 Ralph LD, Sandstrom M, Twelves C, Dobbs NA, Thompson AH. Assessment of the validity of a population pharmacokinetic model of epirubicin. Br J Clin Pharmacol 2006; 62: 47–55.
21 Mould DR, Fleming GF, Darcy KM, Spriggs D. Population analysis of a 24-hour paclitaxel infusion in advanced endometrial cancer: a gynecologic oncology group study. Br J Clin Pharmacol 2006; 62: 56–70.
22 Bruno R, Olivares R, Berille J, Chaikin P, Vivier N, Hammershaimb L, Rhodes GR, Rigas JR. Alpha-1-acid glycoprotein as an independent predictor for treatment effects and a prognostic factor of survival in patients with non-small cell lung cancer treated with docetaxel. Clin Cancer Res 2003; 9: 1077–82.
23 Joerger M, Huitema ADR, van den Bongard HJGD, Baas P, Schornagel JH, Schellens JHM, Beijnen JH. Determinants of the elimination of methotrexate and 7-hydroxy-methotrexate following high-dose infusional therapy to cancer patients. Br J Clin Pharmacol 2006; 62: 71–80.
24 Breedveld P, Zelcer N, Pluim D, Sonmezer O, Tibben MM, Beijnen JH, Schinkel AH, van Tellingen O, Borst P, Schellens JH. Mechanism of the pharmacokinetic interaction between methotrexate and benzimidazoles: potential role for breast cancer resistance protein in clinical drug-drug interactions. Cancer Res 2004; 64: 5804–11.
25 Perez-Ruixo JJ, Piotrovskij V, Zhang S, Hayes S, De Porre P, Zannikos P. Population pharmacokinetics of tipifarnib in healthy subjects and adult cancer patients. Br J Clin Pharmacol 2006; 62: 81–96.
26 Widmer N, Decosterd LA, Csajka C, Leyvraz S, Duchosal MA, Rosselet A, Rochat B, Eap CB, Henry H, Biollaz J, Buclin T. Population pharmacokinetics of imatinib and the role of alpha-1-acid glycoprotein. Br J Clin Pharmacol 2006; 62: 97–112.
27 Schmidli H, Peng B, Riviere GJ, Capdeville R, Hensley M, Gathmann I, Bolton AE, Racine-Poon A; IRIS Study Group. Population pharmacokinetics of imatinib mesylate in patients with chronic-phase chronic myeloid leukaemia: results of a phase III study. Br J Clin Pharmacol 2005; 60: 35–44.
28 Judson I, Ma P, Peng B, Verweij J, Racine A, di Paola ED, van Glabbeke M, Dimitrijevic S, Scurr M, Dumez H, van Oosterom A. Imatinib pharmacokinetics in patients with gastrointestinal stromal tumour: a retrospective population pharmacokinetic study over time. EORTC Soft Tissue and Bone Sarcoma Group. Cancer Chemother Pharmacol 2005; 55: 379–86.
29 Kretz O, Weiss HM, Schumacher MM, Gross G. In vitro blood distribution and plasma protein binding of the tyrosine kinase inhibitor imatinib and its active metabolite, CGP74588, in rat, mouse, dog, monkey, healthy humans and patients with acute lymphatic leukaemia. Br J Clin Pharmacol 2004; 58: 212–16.
30 Gambacorti-Passerini C, Zucchetti M, Russo D, Frapolli R, Verga M, Bungaro S, Tornaghi L, Rossi F, Pioltelli P, Pogliani E, Alberti D, Corneo G, D'Incalci M. Alpha1 acid glycoprotein binds to imatinib (STI571) and substantially alters its pharmacokinetics in chronic myeloid leukemia patients. Clin Cancer Res 2003; 9: 625–32.
31 Aarons L. Physiologically based pharmacokinetic modelling: a sound mechanistic basis is needed. Br J Clin Pharmacol 2005; 60: 581–83.
32 Sparano JA, Fazzari MJ, Childs G. Clinical application of molecular profiling in breast cancer. Future Oncol 2005; 1: 485–96.
33 Osieka R. Oncology. Arzneimittelforschung 1997; 47: 1161–65.