The Cancer and Leukemia Group B Pharmacology and Experimental Therapeutics Committee: A Historical Perspective

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Abstract

The Chemotherapy Committee of Cancer and Leukemia Group B (CALGB) was established in the mid-1970s to assemble a group of experts in cancer chemotherapy and pharmacology who could advise the CALGB disease committees about the optimal use of drugs in the fight against cancer and to provide quality assurance for the chemotherapy section of CALGB protocols. Chaired initially by Edward Henderson and then David Van Echo, the committee was also the repository of studies in diseases for which CALGB did not have a formal committee, such as testis cancer and sarcoma. In 1990, following the appointment of Richard Schilsky as Chair, the name of the committee was changed to the Pharmacology and Experimental Therapeutics (PET) Committee to reflect a more specific focus and scientific agenda (i.e., studies of chemotherapy pharmacology and development of new agents). Three PET Committee reference pharmacology laboratories (led by Merrill Egorin, Tony Miller, and Mark Ratain) were established to measure drug concentrations in biological fluids and to perform pharmacokinetic analyses. In addition, the PET Committee embarked on a number of multi-institution phase I studies. These phase I studies included studies of special populations, including the first prospective study of an anti-cancer agent (paclitaxel) in patients with hepatic dysfunction. In addition, the Committee studied a number of phase I combinations destined for phase II evaluation in disease-specific committees. Following Dr. Schilsky’s election as CALGB Group Chair in 1994, Mark Ratain took over as Chair of the PET Committee and continued to emphasize population pharmacology as the primary theme of the Committee’s research agenda. In addition, the PET Committee began to develop novel clinical trial designs, including the first completed randomized discontinuation trial of an antineoplastic agent. Most recently, the PET Committee has launched an ambitious research program in pharmacogenetics, facilitated in large part through the recruitment of Howard McLeod as Vice Chair. This area of research is a collaborative effort with the NIH Pharmacogenetics Research Network and has the potential to definitively address the hypothesis that germ line polymorphisms are a significant determinant of the toxicity and efficacy of anticancer therapy. It is anticipated that the results of the current studies will contribute significantly to the goal of individualizing cancer treatment.

Population Pharmacology and Organ Dysfunction Studies

Cancer and Leukemia Group B (CALGB) 8362 was a study led by Robert Capizzi to examine the relationship of the pharmacokinetics of cytarabine to antileukemic activity and host toxicity (1). A total of 342 patients were enrolled in this study over a 5-year period. Of the enrolled patients, 265 patients had samples collected and shipped appropriately, a “success rate” of 77%. As anticipated, there was marked interpatient pharmacokinetic variability, with the coefficient of variation of cytarabine clearance (low-dose continuous infusion) of 52%. Of interest, patients with a higher baseline WBC had faster clearance. However, there was no relationship between pharmacokinetic variability and either antileukemic activity or host toxicity. This study is notable for paving the way for subsequent CALGB population studies. It showed that multicenter cooperative groups, including community oncologists, could conduct complex studies involving collection and processing of pharmacokinetic samples.

The second major population pharmacology study was CALGB 8862, led by Mark Ratain (2). This study involved the topoisomerase II inhibitor amonafide, which was undergoing phase II evaluation in CALGB. This was the first CALGB study to use a limited sampling model, which had been specifically developed for this study, and could estimate the amonafide area under the curve from two blood samples, collected at 45 minutes and 24 hours after a 1-hour infusion of the drug (3). The original hypothesis was that the estimated area under the curve (using this limited sampling model) would correlate with

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the extent of myelosuppression produced by amonafide. Although amonafide did show some activity in breast cancer (4), it was not considered to be of sufficient interest for further development.

However, the CALGB study was remarkable for its demonstration of a striking relationship between pharmacokinetic variability and toxicity. As the protocol was being written, new data emerged, showing that amonafide had an active metabolite N-acetyl-amonafide (5). Therefore, the study also included quantitation of this metabolite (using the same samples), which was a most fortuitous decision. A total of 73 patients were enrolled, 58 (73%) of whom had evaluable plasma samples. In assessing the pharmacokinetic data, the most striking finding was tremendous variability in the N-acetyl-amonafide concentration at 24 hours, ranging from <10 to 1,609 ng/mL. Patients could be classified into two groups, fast and slow acetylators, and, surprisingly, the results indicated that fast acetylators had a lower amonafide clearance than slow acetylators. Thus, fast acetylators had higher plasma concentrations of both amonafide and its active metabolite N-acetyl-amonafide. This seemed to account for the marked variability in myelosuppression observed with this agent, as the median WBC nadir for the fast acetylators was 500/μL, compared with 3,400/μL for the slow acetylators. These results were subsequently confirmed by additional studies at The University of Chicago, which showed that N-acetylation of amonafide could be predicted by caffeine N-acetylation, thus facilitating individualization of this drug’s dosing (6–8). Thus, this study was the CALGB’s first foray into pharmacogenetics, albeit without the use of molecular genotyping.

Most recommendations regarding dosing of anticancer agents in patients with hepatic dysfunction are based on expert opinion rather than data. CALGB 9264, led by Alan Venook, was the first prospective study of toxicity and pharmacokinetics of an anticancer agent in patients with hepatic dysfunction (9). The study included 81 patients with increased aspartate aminotransferase or total bilirubin, stratified into three groups based on liver function tests. Patients were escalated in cohorts, within each group. Paclitaxel was studied on both a 24- and 3-hour infusion schedule, at doses ranging from 50 to 175 mg/m². Toxicity was increased on both schedules, suggesting that dose reduction is indicated for hepatic dysfunction. On the 24-hour infusion schedule, there was no apparent effect of hepatic dysfunction on pharmacokinetics compared with historical controls. Despite the lower doses of paclitaxel, 50% of patients had dose-limiting toxicity on the 24-hour schedule. The explanation for this increased toxicity remains elusive, as it could not be explained by the pharmacokinetic results.

This study spawned an entire program for studying special populations in the CALGB. Subsequent organ dysfunction studies have evaluated the dosing and toxicity of irinotecan, gemcitabine, erlotinib, and sorafenib in patients with organ dysfunction. Indeed, such studies are now routinely requested by the Food and Drug Administration, and a separate working group has been formed by the National Cancer Institute to conduct such studies. Thus, there are now two major multicenter groups conducting these trials: the CALGB Pharmacology and Experimental Therapeutics (PET) Committee and the National Cancer Institute Organ Dysfunction Working Group. Such information is of enormous practical value to clinical oncologists as the initial package insert for new drugs rarely includes definitive dosing recommendations for patients with abnormal organ function.

The second study (CALGB 9565) led by Alan Venook was of gemcitabine (10). This was the first study to incorporate patients with either hepatic or renal dysfunction. A total of 40 patients were studied. There were no apparent alterations in pharmacokinetics, but patients with elevated bilirubin or creatinine had increased susceptibility to toxicity, warranting dose reduction by 20%.

CALGB 9863, also led by Alan Venook, was the third study in organ dysfunction patients conducted by the PET Committee (11). This study was novel in that it included patients with hepatic or renal or bone marrow dysfunction, the latter defined as patients with prior pelvic irradiation. In contrast to previous efforts, hepatic dysfunction was defined based on an elevated conjugated bilirubin, as unconjugated hyperbilirubinemia was already a known risk factor for irinotecan toxicity, reflecting impaired activity of UGT1A1 (12, 13).

A total of 35 patients were enrolled at doses of 115 to 280 mg/m², given every 3 weeks. Patients with elevated direct bilirubin had increased toxicity, associated with decreased irinotecan clearance and metabolism of SN-38. Thus, these patients require a dose reduction of at least 60% (three of five patients treated at 145 mg/m² had dose-limiting toxicity). There was no evidence for increased toxicity (or alterations in pharmacokinetics) in patients with elevated aspartate aminotransferase (but normal bilirubin), decreased renal function, or prior pelvic irradiation.

The most recent study of patients with organ dysfunction was of erlotinib (CALGB 60101, chaired by Tony Miller). A preliminary analysis of the pharmacokinetics of erlotinib in this population suggests that patients with hepatic dysfunction have an ~50% decrease in apparent oral clearance. Notably, these pharmacokinetic findings are consistent with the phase I results of CALGB 60101, as a 50% dose reduction seems necessary to avoid undue toxicity.

The PET Committee has also conducted prospective studies to address the effect of age, ethnicity, and body surface area on the pharmacokinetics and pharmacodynamics of taxanes. CALGB 9762 investigated potential age-related alterations in the pharmacokinetics of paclitaxel (14). This prospective study, which enrolled 133 patients, used a limited sampling schedule to characterize the clearance of paclitaxel in three cohorts of patients (55-64, 65-74, and >75 years old), showed that paclitaxel clearance decreased progressively across the three cohorts, although there was marked interpatient variability within each cohort. Furthermore, the study showed that paclitaxel-induced neutropenia increased progressively across the three cohorts, although this increased neutropenia was not associated with an increase in adverse clinical outcomes, such as fever, antibiotic use, or hospitalizations. In addition to achieving its primary and secondary pharmacokinetic and clinical objectives, this study showed the feasibility of a cooperative group performing pharmacokinetic studies in the elderly, which, like patients with organ dysfunction, is another special population of great interest.

CALGB 9871, which enrolled 109 patients, used a limited sampling strategy to evaluate the hypothesis that known ethnic differences in CYP3A and ABCB1 (also known as P-glycoprotein) would result in ethnic differences in the clearance and toxicity of docetaxel, which is a known substrate for CYP3A and ABCB1. Although no statistically significant differences were shown in the pharmacokinetics of docetaxel or docetaxel-associated neutropenia between African-American and Caucasian patients, this study again showed the ability of a cooperative group to frame a pharmacologically rational hypothesis, design a study to evaluate that hypothesis, implement the logistical requirements to perform the study successfully, and perform the study in a timely fashion.

CALGB 9763 capitalized on the proven pharmacokinetic resources of the PET Committee to evaluate, in a prospective manner, the important question of whether dosing of a chemotherapeutic agent required body surface area–based dosing (15). Thirty-two women received a fixed dose of paclitaxel that was based on the experience of a CALGB phase III study of paclitaxel in women with breast cancer, who had received doses of 175, 210, or 250 mg/m². The clinical data from this study and paclitaxel pharmacokinetic data indicated that fixed dosing of paclitaxel was feasible and could simplify dosing of the drug.

**Phase I Studies**

CALGB 8881, led by Stuart Lichtman, was the first multicenter phase I study conducted by the PET Committee (16). This study of high-dose cyclophosphamide (using granulocyte macrophage colony-stimulating factor in lieu of bone marrow transplantation) was conducted at three institutions: North Shore University Hospital, University of Chicago, and the University of Maryland. A total of 52 patients were studied at cyclophosphamide doses of 1.5 to 6.0 g/m², given as an outpatient every 2 weeks. Total doses up to 18 g/m² were given in a 6-week time span, a dose higher than that used at the time for bone marrow transplant. The study also investigated cyclophosphamide pharmacokinetics at these high doses. This was significant for demonstrating that there was minimal cyclophosphamide-derived alkylating activity at the time of initiating granulocyte macrophage colony-stimulating factor. This study was important to establish that dose-finding studies could be safely conducted in a multi-institutional setting with weekly conference calls among the investigators to review toxicity data and determine whether dose escalation was appropriate.

Subsequently, the PET Committee conducted several phase I studies of topotecan combinations, with an intention to evaluate these further in phase II studies in small cell lung cancer (by the Respiratory Committee). Regimens of topotecan as a 30-minute i.v. infusion on five consecutive days were developed in combination with either cisplatin (17) or paclitaxel (18) on day 1 of a 21-day cycle in patients with advanced solid tumors. When these regimens of topotecan/cisplatin and topotecan/paclitaxel were subsequently tested in a randomized phase II study that also included a standard regimen of cisplatin/paclitaxel, an unacceptably high rate of treatment-related fatal sepsis was encountered in patients with previously untreated, extensive-stage, small cell lung cancer (19). The PET Committee did another phase I study of topotecan as a continuous i.v. infusion for 21 days in combination with cisplatin on days 1, 8, and 15 of a 28-day cycle (20). However, toxicity was still substantial, and this regimen of prolonged infusional topotecan did not seem advantageous compared with the prior schedule of short infusions daily for 5 days.

**Novel Trial Designs**

The PET Committee has had responsibility over the years for studies of diseases not encompassed by the established disease-specific committees. Until recently, renal cell cancer was one such disease. CALGB 9163 (led by Brian Samuels), the first study conducted by the PET Committee for this disease, was aimed at testing the hypothesis that either cyclosporine A or tamoxifen could act as a sensitizer of vinblastine in this disease (21). The study was randomized phase II study of 126 patients (enrolled over 18 months) with metastatic disease. Patients were randomized and then treated with infusional vinblastine alone (the dose varied by arm). The modulating agent was added at tumor progression, or at the end of two cycles, if
disease stabilization had occurred. Unfortunately, there were no partial responses, with or without modulators. However, this study did establish that the CALGB could rapidly conduct studies in metastatic renal cell cancer.

It is now accepted that noncytotoxic agents modulating cell signaling have a role in anticancer therapy, as evidenced by the Food and Drug Administration approval of a number of agents, beginning with imatinib’s approval in 2001 for chronic myelogenous leukemia. Although imatinib’s efficacy was obvious in its phase I study (22), the development of other cell signaling inhibitors has been challenging. Thus, the CALGB PET Committee designed a trial to evaluate whether a new agent may have disease-stabilizing activity, using a novel randomized discontinuation design.

The study design was reported in 2002 and modeled varying effects of a drug on tumor growth (23). The assumption was made that the drug would not cause tumor regressions. This design was implemented (led by Walter Stadler) for the putative antimitastatic agent carboxyaminoimidazole (Fig. 1), which had undergone its preclinical development at the National Cancer Institute (24). Patients with metastatic renal cell cancer were initially treated with carboxyaminoimidazole given as 250 mg daily (orally) for 16 weeks. At the end of the initial treatment, patients underwent reassessment of their disease burden, and those patients with stable disease were randomized (placebo controlled and double blind) to continue or discontinue carboxyaminoimidazole. Patients who progressed after randomization were allowed to be unblinded and offered the opportunity to restart carboxyaminoimidazole if they had been on placebo.

A total of 368 patients were enrolled (over ~18 months). Although only half the patients progressed over the initial 16 weeks, an additional 30% of patients were withdrawn for other reasons. Thus, only 64 patients were randomized, in part because a futility analysis conducted by the Data Safety and Monitoring Committee determined that carboxyaminoimidazole was highly unlikely to show activity using this design. Notably, there were five patients with reported partial responses.

Although this study was negative, it was the first completed randomized discontinuation trial in oncology. More recently, this design has been recognized to have great use for showing activity of agents that do not induce a high rate of partial responses. In particular, the design was used for a phase II trial of sorafenib, which was approved for metastatic renal cancer in December 2005 (25).

### Pharmacogenetics

The use of germ line DNA to assess the risk of toxicity or treatment outcome in individual patients has developed through the analysis of small cohorts of patients from single institutions. However, there is a need for the analysis the predictive power of candidate genetic variants before pharmacogenetics can be integrated into clinical practice. The CALGB PET committee has partnered with the CALGB disease-focused committees to integrate pharmacogenetics into large, randomized, multicenter studies (Table 1). Most of these studies are still accruing patients but have shown that the inclusion of pharmacogenetics elements into the National Cancer Institute cooperative group studies is achievable (currently achieving ~80% participation) and allows the opportunity to develop the data necessary to move genetics from a research tool to a useful part of clinical practice.

### Conclusions

The CALGB PET Committee has had a consistent effect on the field of oncology. Its current efforts are focused on two general areas, pharmacogenetics and pharmacologic issues in special populations. The portfolio of current studies, which emanates from this long and rich history, has the potential to have a transforming effect on the field.

### Table 1. Examples of active clinical trials with embedded PET committee pharmacogenetics studies

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<th>Sample size</th>
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