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Tomorrow's Cancer Treatments Today: The First 50 Years of the Cancer and Leukemia Group B

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Abstract

Members of the Cancer and Leukemia Group B have been striving to improve cancer therapies for more than 50 years. The organization began in the mid 1950s as a multi-institutional collaboration between investigators at the National Cancer Institute, Roswell Park Memorial Institute, and the Children's Hospital in Buffalo New York. In 1956 it was officially designated as the Acute Leukemia Group B (ALGB) and for most of its first decade focused largely on leukemia research. Reflecting an expansion of its research portfolio during the 1960s and 70s, the name was changed in 1976 to Cancer and Leukemia Group B (CALGB). Currently the organization has hundreds of members including nurses, clinical research associates, statisticians, physicians, translational scientists, and an administrative staff from a nationwide network of academic and community based organizations and medical practices. Disease areas within the scope of CALGB research include hematologic malignancies, as well as breast, gastro-intestinal, genito-urinary, and respiratory cancers. Modality expertise includes quality of life, medical oncology, surgery, radiation oncology, pathology, imaging, oncology nursing, health outcomes, geriatrics, biostatistics, data management, and an extensive array of correlative sciences. Some of the major accomplishments of CALGB investigators and the patients participating in CALGB research as critical and committed partners will be reviewed in this manuscript.

Introduction

In 1955 Drs. James Holland, Emil Frei III, Richard Silver, and colleagues initiated the first multi-institutional, randomized, controlled trial of multi-agent chemotherapy for management of patients with acute leukemia. The protocol document was rudimentary by today's standards, lacking a formal statistical section, and was open to a very heterogeneous population of patients. However there were clearly specified study objectives, inclusion and exclusion criteria, pre-treatment testing, central morphology review, and defined response criteria. Patients were stratified by selected features – leukemia type, prior therapy, and age

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– and randomly assigned to either an intermittent or continuous schedule of methotrexate combined with a fixed schedule of 6-mercaptopurine.¹ This study, when reported in 1958², demonstrated prolonged survival among responding patients treated with continuous methotrexate and marked the beginning of five decades of important research results emanating from CALGB. In a follow-up study activated in 1959, the same investigators demonstrated the survival benefit of prolonged chemotherapy “maintenance” following remission induction in childhood ALL.

Hematologic Malignancy Milestones

Investigators from the Leukemia Committee of CALGB developed the framework for current therapy of patients with acute myeloid leukemia.³ In a large, prospective, randomized trial the group members demonstrated the efficacy of “7 + 3” (a seven day continuous infusion of cytosine arabinoside and administration of divided doses of daunorubicin on days 1–3) as induction therapy.⁴ Subsequent trials failed to show significant additional benefit for doubling the dose (200 mg/m²/day versus 100 mg/m²/day)⁵ or extending the duration of the cytosine arabinoside to 10 days rather than 7 days, changing the anthracycline from daunorubicin to doxorubicin,⁶ or adding a third drug (6 thioguanine) to the induction regimen. In a phase III trial initiated in the mid 1980s, Leukemia Committee investigators demonstrated the feasibility and efficacy of intensification of therapy utilizing high dose cytosine arabinoside for patients achieving initial complete remission.⁷ The overall approach defined by this series of studies has remained a durable standard of care for the large majority of patients with a new diagnosis of acute myeloid leukemia. Similarly in adult patients with ALL, a CALGB trial initiated in the mid 1970s produced a substantial increase in complete response rate by the addition of an anthracycline to a vincristine-prednisone regimen.⁸

In a paradigm shifting collaboration with a cadre of innovative translational scientists, Leukemia Committee studies moved beyond “simple” morphologic definitions of leukemia subgroups and demonstrated the prognostic and predictive impact of cytogenetic and molecular genetic characteristics of the blasts cells in individual patients with acute leukemia. The high potential for cure of core-binding factor type AML (characterized by the cytogenetic translocation t8;21), the intermediate prognosis of a normal karyotype, and the profoundly unfavorable implications of other cytogenetic abnormalities were defined in CALGB studies.^{9,10} In CALGB led randomized phase III trials enrolling only patients with acute promyelocytic leukemia (defined by t15;17), a dramatic improvement in survival resulted from the addition of all-trans retinoic acid (ATRA) during both induction and consolidation therapy.^{11,12} More recently, in another CALGB led intergroup trial, the use of arsenic trioxide during consolidation has produced additional survival benefit.¹³

CALGB investigators have also made important contributions to current therapy for patients with chronic leukemias. The significant progression free survival benefit of using fludarabine during first-line therapy in patients with CLL was first demonstrated in a randomized phase III US intergroup trial coordinated by CALGB.¹⁴ Since this work was reported, nearly all CLL studies have incorporated fludarabine as a component of induction therapy and fludarabine has become a standard of care for initial therapy of CLL.

Clinical management of patients with myelodysplastic syndromes has traditionally focused on palliation of the clinical symptoms associated with progressive marrow failure and conversion to AML. In a landmark phase III CALGB trial of best supportive care (BSC) compared to BSC plus the demethylating agent 5-azacytidine, the active treatment produced a significant delay in time to conversion to AML and an overall survival benefit.¹⁵ A companion study demonstrated marked improvement in quality of life for patients receiving

active treatment.¹⁶ These data led directly to the Food and Drug Administration approval of 5-azacytidine as the first effective treatment addressing the underlying disease process and ushered in an era of improving outlook for many patients with MDS.

In the 1970s, both MOPP and ABVD were considered potentially curative strategies for individuals diagnosed with advanced Hodgkin's disease. Based on concerns about intrinsic and evolving drug resistance and cumulative organ toxicity, alternating MOPP and ABVD regimens also became a popular curative approach. The optimum treatment strategy from among these options was defined by CALGB Lymphoma Committee investigators in a sequence of randomized phase III studies. The first study directly compared MOPP, ABVD, and an alternating approach.¹⁷ Both anthracycline arms were superior in complete response rate and recurrence free survival compared to MOPP while producing less toxicity. In a subsequent trial ABVD was compared to a MOPP/ABV "hybrid". Efficacy was similar for the two regimens but toxicity favored the ABVD alone approach.¹⁸ These two studies clearly established ABVD as the evidence based standard chemotherapy program for patients with a new diagnosis of advanced Hodgkin's disease.

Solid Tumor Program Milestones

CALGB investigators participate in four solid tumor disease committees – Breast cancer,¹⁹ Genito-urinary²⁰ malignancies (bladder, prostate, and renal), Gastrointestinal cancers²¹ (currently esophagus, stomach, colon, rectum, and pancreas) and Respiratory²² (mesothelioma, non-small cell, and small cell lung cancer) cancers. The breast and respiratory programs began around 1970 while the GI and GU programs were initiated in the early 1980s. All disease committees are fully multimodal with stable biostatistical leadership and integrated participation of radiation oncology and surgical oncology specialists, imaging specialists, pathologists, translational scientists as well as liaisons from all other standing modality committees. Involvement of young investigators developing careers in clinical investigation and translational science has been particularly valued and encouraged.

Breast Cancer

The most widely recognized accomplishments of the CALGB Breast Committee are in the area of adjuvant therapy. In the mid 1980s the committee began to explore different doses, durations, schedules and sequences of adjuvant chemotherapy in patients with completely resected, node positive disease. In CALGB 8541, a total of 1572 women were randomized to receive 4 cycles of a low dose ("300/30/300") cyclophosphamide, Adriamycin, 5-fluorouracil (CAF) regimen, 4 cycles of a higher dose CAF program ("600/60/600"), or 6 cycles of an intermediate dose regimen ("450/45/450"). The total doses delivered in arms two and three were equivalent but dose intensity was higher in regimen two. The findings were pivotal: 1) the low dose regimen was significantly inferior to the other two arms; 2) the high-dose CAF regimen produced the best overall outcome suggesting a role for dose intensity in addition to the total dose of drug delivered; and 3) the benefit of the high dose CAF regimen was more evident in patients with Her2 expressing tumors.^{23,24}

In the follow up phase III study, CALGB 9344, the CALGB evaluated the impact of 1) a further escalation of doxorubicin dose (at 60, 75, or 90 mg/m²/cycle) during the 4 "standard" cycles of adjuvant "AC" chemotherapy, and 2) the addition of paclitaxel at 175 mg/m²/3hours Q 3 weeks x 4 cycles after completion of AC.²⁵ While the escalation of doxorubicin dose failed to demonstrate a disease-free or overall survival benefit for higher doses, the addition of 4 cycles of paclitaxel to the AC produced improvements in both disease free and overall survival when compared to AC x 4 alone. This study was used as the basis for FDA approval of paclitaxel in the adjuvant setting. Important correlative science studies subsequently demonstrated that the benefit of adding paclitaxel was largely

confined to women with ER negative and Her2 positive tumors.²⁶ At the same time, other CALGB studies involving women with metastatic breast cancer showed no significant response or survival advantage for administering paclitaxel at a dose of 210 mg/m² or 250 mg/m² compared to 175 mg/m² when a three-hour infusion Q 3 weeks was utilized.²⁷

The third in this sequence of phase III adjuvant trials led by the CALGB Breast Committee explored the concept of “dose dense chemotherapy”. This strategy, based on laboratory and modeling studies done by CALGB investigators, involved giving full doses of adjuvant therapy at a shortened time interval, i.e., cycling therapy every 2 weeks rather than every 3 weeks. In study CALGB 9741 the regimens were standard AC followed by paclitaxel with each regimen given either every 3 weeks (standard) or every 2 weeks (dose dense). The total number of cycles was the same in each arm. In this trial involving over 3000 patients, disease-free survival was statistically significantly improved using the dose dense schedule, with the most dramatic impact among women with hormone receptor negative tumors.²⁸ Interestingly, sequential dose-dense therapy was as efficacious as the combination therapy.

A critically important trial of high dose chemotherapy and stem cell transplant for patients with high risk (10 or more positive axillary nodes), completely resected, breast cancer was carried out by a consortium of Breast Committee, Radiation Oncology Committee, and Transplant Committee investigators. This trial studied patients with stage II–IIIA breast cancer and 10 positive axillary nodes. All patients were assigned to receive 3 cycles of adjuvant CAF followed by re-staging, an additional cycle of CAF and randomization to either autologous transplant supported high dose chemotherapy [cyclophosphamide, BCNU, cisplatin] or the same agents given at intermediate doses that did not require stem cell support. Following chemotherapy, all patients remaining on study were given chest wall radiation. Those with hormone receptor positive disease were prescribed five years of tamoxifen maintenance. As was the case with other contemporaneous studies of adjuvant high dose chemotherapy for patients with resected breast cancer, this trial failed to demonstrate a survival advantage for the high dose approach.²⁹ Treatment related death rates were 9% overall in the group undergoing transplant and reached 15% in transplanted patients over age 50.³⁰

Thoracic Malignancies

The portfolio of the CALGB Respiratory Committee includes work in the areas of mesothelioma, small-cell, and non small cell lung cancer.²² The mesothelioma work has focused on drug discovery, testing a variety of cytotoxic agents and, more recently, oral small molecule receptor tyrosine kinase inhibitors. Analysis of the wealth of phase II data generated from these studies led to the development of a widely used prognostic index, the Herndon index, for assessing the prognostic characteristics of patients entering mesothelioma trials.³¹

CALGB research accomplishments in both small cell lung and non-small cell lung cancer have emerged from multidisciplinary collaborations, a hallmark of Respiratory Committee activities. In the 1980s, CALGB investigators were the first to report phase III data demonstrating a significant survival benefit for concurrent chemoradiotherapy compared to chemotherapy alone for initial management of patients with limited stage small cell lung cancer (LD-SCLC).³² Over the ensuing two decades improved staging and supportive care strategies have enhanced the survival of patients with a new diagnosis of LD-SCLC. In addition, data from an ECOG phase III trial testing concurrent chemotherapy plus radiation to a total dose of 45 Gy given once or twice per day have shown an overall survival benefit for the “45 Gy BID” approach.³³ During this period CALGB investigators demonstrated that a once per day radiation dose to 70Gy, given concurrent with radiation, is feasible and

associated with very favorable overall survival rates.³⁴ The current Intergroup trial that compares 45 Gy twice daily to 66 – 70 Gy given on a daily schedule concurrent with chemotherapy is under the leadership of CALGB investigators.

CALGB Respiratory Committee contributions to therapy for patients with non-small cell lung cancer also focus on multi-modality management. The seminal contributions of the Committee began with CALGB 8433, a randomized phase III trial of induction chemotherapy followed by standard full dose radiation compared to radiation therapy alone in patients with locally advanced (stage III) disease.³⁵ The design employed two cycles of full dose combination chemotherapy both to control potential micro-metastatic disease and to shrink the bulk of intrathoracic tumor prior to definitive radiation. It reflected the growing awareness that there are at least two competing risks for recurrence or death in this cancer patient population – persistent intrathoracic tumor and microscopic dissemination. The results of 8433 and subsequent trials have revealed that the central nervous system is a third independent site for treatment failure and will likely require prophylactic management once control of disease in the other two sites is maximized.³⁶

In CALGB 8433 the committee restricted the population eligible for enrollment to patients with excellent performance status (PS 0 – 1), limited extent of stage III disease (no supraclavicular adenopathy), and minimal weight loss in order to optimize the opportunity to demonstrate a survival advantage for the induction chemotherapy. In taking this tack, the Committee was one of the first to use a “phenotypic enrichment” strategy to maximize treatment effect. The theory was to include only patients with minimal amounts of micro-metastatic disease whose metastatic tumor might be eradicated with just a short course of induction chemotherapy. Further, it was hypothesized that patients with more favorable prognostic features might actually be free of micrometastases. In that case the potential to increase cure would come from the ability of the induction chemotherapy to reduce the intrathoracic tumor bulk and facilitate radiation sterilization of the remaining tumor.

The use of a short course of induction chemotherapy prior to definitive radiation produced a dramatic and statistically significant improvement in overall survival. The results from CALGB 8433 were emerging at a time when group sequential methods for monitoring clinical trials were in their infancy.³⁷ However, the trial statistician used this approach to recommend to the study team and the Respiratory Committee that accrual to the trial should be stopped prior to reaching the target initially set for the trial. The Committee accepted this recommendation and reported the results at an ASCO plenary session in 1987³⁸ and in the New England Journal of Medicine in 1990.³⁵ This was initially regarded as a very provocative trial, requiring replication. The results of 8433, together with similar findings from French investigators³⁹ and the positive results of a confirmatory US Intergroup trial⁴⁰ established the use of chemotherapy and radiation as the new benchmark for management of fit patients with locally advanced non-small cell lung cancer.

Recent CALGB studies in the treatment of stage III NSCLC have been part of a concerted worldwide effort. Following up on the benefit of induction chemotherapy, the Respiratory Committee studied the addition of more chemotherapy, i.e., single agent carboplatin concurrent with radiation, to the induction regimen. The additional chemotherapy, given concurrently with radiation, failed to further improve outcomes.⁴¹ However other investigators have shown that giving immediate, concurrent, full dose, doublet chemotherapy and radiation is more effective than the CALGB 8433 strategy of sequential full dose induction followed by radiation.⁴² Most recently Respiratory Committee investigators completed and reported a phase III trial comparing full dose induction chemotherapy (paclitaxel and carboplatin), followed by radiation and concurrent weekly radiosensitizing [paclitaxel-carboplatin] chemotherapy or the concurrent sensitizing

chemotherapy and radiation alone.⁴³ The outcome was disappointing on two counts. First, there was no significant benefit for the use of full-dose induction chemotherapy and then combined modality treatment compared to the concurrent therapy alone. Second, the outcome was poor for patients on both study arms. These findings have led the Respiratory Committee to re-evaluate its program in locally advanced NSCLC. Thus, the Committee's current phase II trial is evaluating a new chemotherapy doublet (carboplatin and pemetrexed) and the inclusion of an anti-EGFR monoclonal antibody along with radiation.

In the mid-1990s the Committee implemented a straightforward test of 4 cycles of adjuvant paclitaxel and carboplatin versus observation for patients with pathologic stage IB disease. Multiple correlative science studies were included. The interim results suggesting a major, statistically significant survival advantage for the use of adjuvant chemotherapy were reported at ASCO in 2004.⁴⁴ The more mature results, presented at ASCO in 2006,⁴⁵ failed to show a sustained survival advantage. An unplanned assessment of the effect of adjuvant treatment among patients with different size tumors suggested that adjuvant chemotherapy might benefit patients with a tumor size greater than 4 cm. The current US Intergroup adjuvant therapy trial in resected NSCLC, led by the Eastern Cooperative Oncology Group, incorporates findings from the CALGB trial by including stage IB patients with tumors greater than 4 cm in diameter.

In advanced NSCLC the Respiratory Committee has focused largely on drug discovery. However, two significant phase III studies warrant mention. In the late 1980s, the Committee began the first randomized phase III, cooperative group trial of a complementary therapy agent, hydrazine sulfate, added to chemotherapy compared to chemotherapy alone in a previously untreated group of NSCLC patients with metastatic disease but good performance status.⁴⁶ The results were clear; there was no therapeutic advantage but increased neurologic toxicity in the patients assigned to the chemotherapy + hydrazine sulfate arm. A subsequent phase III trial tested the role of an active single chemotherapy agent (paclitaxel) compared to a full dose combination (paclitaxel + carboplatin) in previously untreated patients with advanced NSCLC.⁴⁷ The study population was prospectively stratified by age (< 70, > 70) and by PS (<2 vs. 2). There was a significant increase in response rate for the combination but no improvement in overall survival. The combination was well tolerated in both the older patients and those with PS 2. Overall survival was significantly improved in the PS 2 patients treated with the chemotherapy doublet. These results defined combination chemotherapy as a standard first-line approach to PS 2 patients with advanced NSCLC

Gastrointestinal Cancer

The GI Cancer Committee of CALGB began its work in the late 1980s, largely as a partner in GI intergroup programs active at that time. From the outset the Committee emphasized multimodality initiatives including surgery, radiation therapy, chemotherapy, pathologic evaluation, and correlative science. As an example, the CALGB GI Committee led the first intergroup trial of sphincter-sparing surgical therapy for patients with low stage rectal cancer.⁴⁸ This strategy was practicable and very effective in patients with low T1 rectal lesions. In patients with stage T2 disease, sphincter-sparing complete surgical resections were achieved routinely but despite the addition of post-operative radiation and chemotherapy, rates of local failure were higher than expected or acceptable. An additional contribution of the committee in the area of rectal cancer was a collaboration with the North Central Cancer Treatment Group (NCCTG) to compare bolus 5FU with continuous infusion 5FU combined with radiation as loco-regional consolidation after complete resection in patients with locally-advanced rectal adenocarcinoma.⁴⁹ This work demonstrated a

significant advantage for continuous infusion 5FU and provided a standard of care that remains in use today.

GI Committee members have also been important contributors to the development of adjuvant therapy studies in patients with completely resected colon cancer that have been performed by the GI Intergroup. Soon after the Committee's founding, CALGB led the Intergroup trial (CALGB 8896) that demonstrated that the addition of levamisole to 5-FU/leucovorin did not improve the efficacy of adjuvant therapy.⁵⁰ In addition, the trial included tests of the five-day Mayo clinic 5FU/leucovorin regimen and the weekly Roswell Park approach. While there were no meaningful efficacy differences between these two approaches, the different toxicity profiles of the two approaches (more neutropenia and stomatitis with the Mayo approach; increased severe diarrhea with the weekly Roswell Park regimen) were clarified. Following the completion of CALGB 8896, the Committee began a definitive phase III test of weekly bolus 5 FU-leucovorin alone or with the addition of irinotecan (IFL) as surgical adjuvant therapy for patients with completely resected stage III colon cancer. While the pre-study assumption was that there would be an advantage for the three-drug regimen (and in fact many clinicians had already moved to using IFL as their standard adjuvant regimen), the results demonstrated something quite different: no improvement in either recurrence free or overall survival for the IFL adjuvant regimen and a three-fold increase in treatment related deaths with IFL.⁵¹ These findings led to an evidence-based reversal of the trend to incorporate IFL into adjuvant therapy, protecting thousands of patients from unnecessary treatment related toxicity.

Defining the role of hepatic artery infusion (HAI) of chemotherapy in management of patients with metastatic colorectal cancer has been challenging. The GI Committee completed a small phase III study of systemic 5-FU/LV or FUDR by HAI in patients with unresectable metastatic disease involving the liver alone. Findings included a significant increase in response rate, delayed time to hepatic tumor progression and an overall survival benefit among the HAI treated patients.⁵² The current NSABP led intergroup trial of systemic capecitabine-oxaliplatin ± additional chemotherapy by HAI following resection of colorectal cancer metastases in the liver is built on the findings of the CALGB HAI trial.

In a collaboration between the GI and Surgery Committees, CALGB investigators led a phase III intergroup trial (CALGB 9781) of definitive surgery alone versus induction chemoradiotherapy followed by surgery for primary management of patients with esophageal cancer. Because of an emerging lack of equipoise about the role of induction therapy, accrual was slow and the study was closed after only 59 patients were enrolled. Nevertheless, CALGB investigators observed a 4.5 year median survival time and 39% five-year survival for those patients randomized to trimodality therapy whereas the median and five-year survivals were 1.8 years and 16% for patients randomized to surgery alone.⁵³ Given these data and the general movement in the field, it is unlikely that a more robust test of the surgery alone versus trimodality therapy question will ever again be undertaken by US investigators.

The GI Committee correlative science investigators have contributed important clinically-relevant insights in several disease areas. For example, Committee investigators showed that groups of patients whose colon cancers had a high frequency of microsatellite instability had greater probability of disease-free survival at five years than those individuals whose tumors did not express this characteristic of altered mismatch repair.⁵⁴ They subsequently showed that approximately 70% of tumors with high levels of microsatellite instability had methylation of the hMLH1 promoter, indicating that an epigenetic event in sporadic colon cancer can lead to the MSI phenotype.⁵⁵ More recent investigations suggest that patients whose tumors have high frequency MSI might benefit from inclusion of irinotecan as part of

their adjuvant chemotherapy. In molecular studies of GIST tumors coordinated by CALGB GI committee investigators, the very high frequency of KIT oncogene mutations was confirmed and the presence of an exon 11 mutation in KIT correlated with both a high likelihood of response to imatinib and a favorable time to progression.⁵⁶ These studies also highlighted the need for new therapeutic approaches to patients whose GIST did not express an exon 11 mutant KIT isoform.

Genitourinary Committee

CALGB activities in the GU cancer area began in 1993 when the CALGB Prostate Committee was organized. At that time the Committee's membership was predominantly medical oncologists and its clinical research portfolio was focused on androgen independent prostate cancer (AIPC). The focus expanded to several additional GU sites in 1999 and since then the Committee has included committed cadres of both radiation oncologists and urologists. Participation of translational scientists has steadily increased over the past decade.²⁰

In 1994, GU Committee investigators collaborated with members of the CALGB Pharmacology and Experimental Therapeutics [PET] Committee to evaluate three doses of suramin as treatment for patients with AIPC.⁵⁷ The study design was based on pilot work suggesting a dose- response relationship for suramin in this setting. However, there was no evident advantage for higher dose suramin in the phase III trial. This trial provided an opportunity for acquisition of plasma and urine specimens that were used by CALGB investigators to identify several prognostic biomarkers in patients with AIPC. Among these, plasma and urine VEGF levels were found to be inversely related to survival and were independent prognostic factors.⁵⁸ These findings provided a rationale for the pivotal CALGB trial of bevacizumab in combination with docetaxel chemotherapy in patients with AIPC. This trial is now nearing completion of accrual.

The initial phase III trial developed by the GU Committee, CALGB 9583, involved patients with advanced prostate cancer who progressed during initial therapy with total androgen blockade.⁵⁹ The standard sequential management of such individuals was cessation of the anti-androgen component of the treatment program. In 9583, GU Committee investigators evaluated the addition of ketoconazole to the residual castration therapy compared to simply discontinuing anti-androgen treatment. Eleven percent of patients undergoing anti-androgen withdrawal alone had a prostate specific antigen (PSA) response, compared to 27% of patients who underwent concurrent anti-androgen discontinuation and ketoconazole ($p=.0002$). Objective responses were observed in 2% of patients treated with withdrawal alone, compared to 20% in patients treated with the addition of ketoconazole ($p=.02$). There was no difference in survival. Correlative science studies performed on metastatic prostate cancer recovered from bone marrow biopsies failed to demonstrate a high frequency of androgen receptor mutations as an explanation for the hormone refractory state.⁶⁰

Chemotherapy is standard treatment for patients with advanced prostate cancer whose tumors are no longer responsive to hormonal manipulation. The combination of mitoxantrone and prednisone and single agent docetaxel are both approved approaches in this setting. Beginning in the mid 1990s, the GU Committee investigators developed a group-wide experience with the regimen of docetaxel and estramustine.⁶¹ In a series of phase II trials they then tested a sequence of three-drug regimens built upon this backbone. The regimens included docetaxel-estramustine-carboplatin,⁶² docetaxel-estramustine-exisulind,⁶³ and docetaxel-estramustine-bevacizumab.⁶⁴ Favorable findings from the bevacizumab phase II trial, the demonstration that VEGF levels correlated inversely with survival in AIPC, and data generated by investigators outside CALGB led to a pivotal phase

III trial of docetaxel – prednisone (equally efficacious and less toxic than the docetaxel estamustine doublet) with or without bevacizumab in patients with no prior chemotherapy for metastatic, androgen-independent disease. As with the previous test of anti-androgen withdrawal and ketoconazole, the primary endpoint in this study is overall survival. Accrual to this trial has been very rapid and should be completed by the end of 2007.

An important practical tool emerging from more than a decade of phase II studies in androgen independent prostate cancer (AIPC) is a risk prediction nomogram for the survival of individual patients with AIPC as well as for prediction of expected median survival for a novel treatment regimen based on the pretreatment characteristics of the study patients. This tool, known as the “Halabi nomogram”⁶⁵ because of its development by the GU Committee’s lead statistician Susan Halabi, is widely used by clinical investigators to benchmark outcomes of phase II studies in this disease area as well as by clinicians to allow data driven assessments of prognosis in individual patients with AIPC.

In addition to the current phase III test of the impact of adding bevacizumab to chemotherapy in the patients with metastatic prostate cancer, the GU committee has completed a definitive trial of the impact of adding bevacizumab to alpha interferon for patients with metastatic renal cell carcinoma, CALGB 90206. The primary endpoint of 90206 is survival with a secondary endpoint of time to disease progression. This trial was initiated in 2002, before the explosion of new targeted therapies for clear cell kidney cancer dramatically altered the landscape of therapy options and survival expectations for these patients. Notably, the randomized discontinuation trial that was used in the clinical development of sorafenib was first applied by CALGB investigators in a study of carboxyaminoimidazole in renal cell carcinoma in a collaboration between the CALGB GU and PET Committees.⁶⁶ At ASCO 2007, the findings from a trial similar to 90206 done by European investigators were reported.⁶⁷ Since the European study was placebo controlled (Interferon alpha + bevacizumab or placebo), the primary endpoint was progression free survival and the results strongly favored the combination of interferon-bevacizumab. The data from the CALGB trial were subsequently released to the GU Committee by the CALGB DSMB because the PFS data also show an advantage for adding bevacizumab to interferon. The overall survival data remain immature and have not yet been reported.

CALGB Modality Committee Milestones

One of the hallmarks of CALGB research has been the integration of input from many scientific disciplines in the design of innovative treatment trials. As such, all the disease committees include representation from the scientific modalities (e.g., medical oncology, surgical oncology, radiation oncology, oncology nursing, quality of life, imaging, pathology, health outcomes) as well as translational scientists from a myriad of scientific disciplines. Much of CALGB modality research is embedded within treatment studies, however, there are numerous signal accomplishments of CALGB modality committees that represent critical stand-alone contributions to the totality of CALGB science. Several of those accomplishments will be described in the subsequent sections of this review.

Surgery Committee

There has been an organized surgical activity within the CALGB since the early 1970s. However, the development of a distinct surgery modality committee with major input into multimodality clinical investigation and a specific surgery research agenda began approximately 20 years ago. Since then, the Surgery Committee has made major contributions to Group science in numerous areas.⁶⁸ In lung cancer, thoracic surgeons led the development and accrual to CALGB 9761, an evaluation of light microscopic, immunohistochemical (IHC), and molecular evaluations of lymph node involvement with

metastatic tumor among patients with clinical stage I NSCLC. Among 502 patients with resection of both the primary tumor and hilar and mediastinal nodes, immunostaining using antibodies to cytokeratin (AE1/3) was twice as likely as traditional light microscopy to identify nodal involvement with tumor. Overall, pre-operative staging of patients with clinical stage I disease (largely accrued in the pre-PET scan era) was predictive of pathologic stage only 62% of the time.⁶⁹⁻⁷¹ The study population is currently in long term follow up to determine whether the demonstration of nodal involvement solely by IHC has prognostic significance and can be a determinant of the need for adjuvant chemotherapy

CALGB thoracic surgeons also performed the definitive evaluation of talc slurry pleural cavity sclerosis versus thoracoscopic evaluation and talc insufflation for management of malignant pleural effusions. The hypothesis was that thoracoscopic inspection and lysis of adhesions could enhance the control of symptomatic malignant pleural effusions. More than 500 patients were randomized. Respiratory complications were equal in both groups, with a low but measurable rate of treatment related deaths with both approaches. Interestingly, both methods of talc administration were equally efficacious, leading to the persistence of talc slurry by bedside chest tube administration as the standard local management for patients with symptomatic malignant effusions.⁷²

Surgery Committee investigators were successful in securing NCI funding for a minimally invasive surgery program led by CALGB surgeons. Research initiatives completed under the auspices of this program included the evaluation of thoracoscopic staging for esophageal cancer⁷³ and video-assisted thoracoscopic surgery (VATS) restaging following induction therapy for patients with stage IIIA NSCLC,⁷⁴ the demonstration of the feasibility of VATS lobectomy in the multi-institutional setting,⁷⁵ as well as the previously described phase III test of talc slurry versus thoracoscopic talc poudrage for treatment of malignant pleural effusions.

CALGB thoracic surgeons have also spear-headed development of a CALGB Lung Cancer Tissue Bank that contains frozen lung cancer, associated normal lung and plasma, and germ line DNA from hundreds of patients with newly diagnosed non small lung cancer. This repository will be an invaluable source of specimens for study of the molecular underpinnings of NSCLC.

Radiation Oncology

The Radiation Oncology Committee of CALGB was organized in 1972. Its initial focus was on regional therapy designed to augment cure rates offered by systemic treatment in patients with hematologic malignancies. Early studies of cranial irradiation in children with ALL and extended field radiation for patients with selected stages of Hodgkin's disease demonstrated differences in patterns of failure without overall survival benefits when radiation was used in combination with definitive chemotherapy. Long term follow-up from these studies provided some of the earliest evidence of the risk of late radiation complications such as decreased full scale IQ scores, and increased psychological distress among children with acute leukemia given cranial irradiation,⁷⁶ and an increased risk for non-leukemia second malignancies after radiation in patients with an initial diagnosis of Hodgkin's disease.⁷⁷

Radiation oncology investigators have been core participants in the research programs of the Respiratory Committee. Seminal CALGB trials demonstrating the ability of chest radiation given concurrent with chemotherapy to significantly improve survival compared to chemotherapy alone for patients with limited stage small cell lung cancer³² and the survival advantage conferred upon patients with stage IIIA NSCLC by the sequence of induction chemotherapy followed by definitive radiation³⁵ compared to standard radiation alone were both developed as an equal partnership between medical and radiation oncologists in

CALGB. In subsequent studies of radiation dose escalation for patients with either small cell or non-small cell lung cancer, Radiation Oncology committee members have shown the feasibility of dose escalation to at least 70 Gy in standard once per day fractions given concurrent with chemotherapy.³⁴ The findings of these phase I/II studies serve as the basis for two ongoing intergroup phase III studies testing the impact of radiation dose escalation on survival of patients with both types of lung cancer. In a phase II trial of radiation alone for patients with medically inoperable early stage NSCLC, committee investigators demonstrated the ability to shorten the standard treatment course of definitive radiation from 5.5 weeks to 3.5 weeks while maintaining a nominal total dose of 70 Gy. No dose limiting toxicities were observed with this short course.

CALGB radiation oncologists have also been active investigators in other disease committees. In breast cancer, CALGB conducted a phase III trial of lumpectomy followed by tamoxifen with or without breast irradiation for elderly (70 years and older) women with hormone receptor positive early stage disease.⁷⁸ The in-breast recurrence rates were 1% and 4%, respectively. There were no survival differences in the two treatment groups. This trial provides important data to guide treatment decision-making in older women with early stage, hormone receptor positive breast cancer. In collaboration with GI Committee investigators, CALGB radiation oncologists performed a critical phase I/II evaluation of the maximum radiation dose that could be safely administered concurrently with 5FU and oxaliplatin in patients with locally advanced rectal cancer.⁷⁹ Based on a 25% pathologic complete response rate for patients treated at the 60 Gy dose, this regimen has been taken forward as one of the arms of an ongoing randomized trial in rectal cancer patients sponsored by the GI Intergroup.

Cancer Control and Health Outcomes

This modality committee is an umbrella structure for 4 distinct but related subcommittees, Symptom Intervention, Quality of life, Prevention, and Health Services Research.⁸⁰

Quality of Life

The Quality of Life (formerly Psycho-oncology) initiatives of the CALGB have included ground-breaking studies of the effects of cancer diagnosis and treatment on the lives of adult, long-term survivors. In studies of patients treated for Hodgkin's disease, 22% of long-term survivors were found to have distress sufficient to qualify as a psychiatric disorder. Their post-therapy adaptation was found to be less effective than for adult leukemia patients at a similar stage of follow up. Nearly 40% reported experiencing a conditioned response of nausea and emesis triggered by ambient sensations reminiscent of their treatment.⁸¹⁻⁸³

CALGB studies have often incorporated quality of life endpoints in randomized phase III treatment trials. These studies often provide crucial information that helps to reveal the overall value of a therapeutic intervention in specific groups of cancer patients. For example, in the pivotal test of 5-azacytidine chemotherapy (led by the CALGB Leukemia Committee, *vide supra*) for patients with myelodysplastic syndrome, the improved survival produced by the chemotherapy was accompanied by significant improvements in fatigue, physical functioning, and psychological distress.⁸⁴ The demonstration of these improvements in quality of life parameters was an important element in the FDA approval of 5-azacytidine for this indication. In an opposite but equally powerful way, CALGB investigators demonstrated that there was a significant decrease in quality of life among patients with advanced non-small cell lung cancer treated on CALGB 8931 with chemotherapy plus hydrazine sulfate compared to chemotherapy alone.⁴⁶ This finding was pivotal in debunking the alleged therapeutic benefits of hydrazine therapy for cancer patients widely reported by advocates for this approach within the alternative therapy community.

Clinical Economics/Health Services Research

Health services researchers within CALGB have contributed important novel observations in both methodologic and empiric research domains. In a study of direct treatment costs associated with participation in approved clinical trials versus non-protocol care in similar settings, there was a minimal 6.5% increase in costs generated by study participation.⁸⁵ These data were of substantial use to policy makers considering ongoing support for clinical trials costs as part of the larger national agenda for improving cancer care. In a study of two surgical approaches to definitive colon cancer resection, CALGB outcomes investigators found only modest short-term quality of life benefits for patients undergoing a laparoscopy assisted procedure compared to open colectomy.⁸⁶ More recently, CALGB investigators have demonstrated that Medicare claims data provide an accurate assessment of treatment outcomes for older patients with breast and non small cell lung cancer treated on clinical trials.⁸⁷ This observation paves the way for studies that link SEER and Medicare data to examine patterns of care and treatment outcomes for older individuals with cancer.

Prevention

In 1992, CALGB began a seminal study (CALGB 9270) of aspirin as an intervention to prevent colon adenoma development in patients with a completely resected colon cancer.⁸⁸ Using a randomized, placebo-controlled, phase III design, patients were assigned to daily dosing with 325 mg of aspirin or a placebo and monitored for polyp formation as part of standard post surgical surveillance. At a median of 12.8 months after initiating study therapy, 27% of the control patients had at least one colonic adenoma documented by colonoscopic biopsy compared to 17% of the patients randomized to the aspirin regimen. These data expanded the evidence base supporting the benefit of aspirin therapy as an effective chemoprevention strategy and provide an effective alternative to other NSAIDs that carry potential cardiovascular risks.

Pharmacology and Experimental Therapeutics (PET)

The focus of this committee has evolved over its near 30 years from one that was largely advisory on chemotherapy administration to one with a robust scientific agenda. In recent years PET investigators have pursued three inter-related programs in clinical pharmacology including studies in special populations, drug development using novel study designs, and pharmacogenetics. The last of these areas, pharmacogenetics, is the unifying theme of the Committee's current research, developed around the hypothesis that "germ line polymorphisms are a significant determinant of the toxicity and efficacy of anti-cancer therapy".⁸⁹

An early contribution of the PET Committee was the demonstration that an evidence based approach to patients with specific types of organ dysfunction was critical to safe and effective dosing of anticancer agents. The initial study in this area, which served as a paradigm for the development of an entire NCI sponsored organ dysfunction working group, evaluated the impact of hepatic dysfunction on paclitaxel toxicity⁹⁰ and led to current guidelines for taxane dose adjustments in patients with hepatic dysfunction and/or metastatic disease in the liver. Follow-up studies investigated the impact of organ dysfunction on the disposition and toxicity of gemcitabine,⁹¹ erlotinib,⁹² sorafenib⁹³ and irinotecan.⁹⁴ Detailed evaluations of this last agent served as a transitional link to pharmacogenetic studies by the Committee, through studies of UGT1A1 polymorphisms and appropriate dosing of irinotecan therapy.

PET Committee investigators also developed a core CALGB program of multi-institutional phase I trials of novel agents and combinations. In nearly all cases, these successful phase I studies, developed jointly by PET and disease committee investigators, have led to phase II

efficacy trials within selected disease committees. Collaborations of the PET and Respiratory Committees have been particularly robust in this regard, with a number of studies involving topotecan/platinum/taxane combinations.

PET Committee investigators were the first to evaluate the efficacy of a putatively non-cytotoxic targeted therapy agent, anticipated to be more likely to cause “tumor dormancy” [stable disease] than disease regression, by using a randomized placebo-controlled discontinuation design. This work was done in patients with metastatic renal cell carcinoma well prior to the availability of the current array of targeted agents for this disease. In this trial design all patients were treated with the novel agent and monitored carefully over a 16-week interval.⁶⁶ Those with immediate progression were removed from study and offered other therapy options. Those demonstrating disease regression were kept on open label therapy. The remaining patients, with stable disease at 16 weeks were then randomized to either continued therapy with the test agent or an identical placebo. Patients were then followed to progression. At progression patients who had been assigned to the placebo arm could receive the test agent while those continued on active treatment were managed post progression at the discretion of the patient and her/his physician. A total of 368 patients entered this trial and nearly 20% of them were randomized at the 16-week re-evaluation point. The feasibility and power of this study design for evaluating targeted agents were clearly demonstrated by the rapid patient accrual, ease of the fixed time reassessment and acceptance of the delayed randomization seen with this study. The design paradigm has now been embraced by others in the drug development arena and figured prominently in the clinical development of sorafenib.

Pathology

The primary mission of the CALGB Pathology Committee is to ensure the highest possibly quality of all tissue-based correlative science in CALGB. This has led to a remarkably functional Pathology Coordinating Office which acquires and manages most patient-related specimens generated within CALGB. Prospective scientific input during protocol development and the initiation and expansion of innovative pathology-driven research are also missions of the Committee.⁹⁵ Select examples of the output of Pathology Committee activities include the demonstration that Her-2 positive breast cancers are less responsive to paclitaxel than are Her-2 negative tumors;⁹⁶ serum hepatocyte growth factor levels are prognostic for patients with androgen independent prostate cancer;⁹⁷ immunohistochemistry detects lymph node metastases twice as often as evaluation by routine light microscopy in patients with clinical stage I NSCLC;⁶⁹ epigenetic alterations in DNA repair genes are common in colon cancer specimens with microsatellite instability;⁵⁵ morphology predicts the presence of cytogenetic abnormalities [inv (16) and t(8;21)] in AML.⁹⁸ Each of these results has direct applications both for CALGB research and care of patients with these and other malignancies.

Imaging

Careful objective assessment of the baseline status of disease and documentation of changes from baseline during therapy are a *sine qua non* of modern clinical research. In oncology, especially as the field moves away from a survival endpoint toward surrogates based on disease status, the documentation is most often radiologic. Definitions of suitable baseline imaging techniques and protocols, the timing and detail of re-evaluation, and the consistent and accurate application of response evaluation criteria are critical components of effective oncology clinical investigation. Furthermore, the introduction of new imaging techniques into the multi-institutional setting requires CALGB imaging scientists to connect with radiology faculty and practitioners working within the CALGB institutions. Within the past

five years, the CALGB Imaging Committee had been formed and begun to contribute in each of these areas. In addition, Committee members have integrated imaging science in a number of CALGB disease areas, particularly lymphoma, esophageal cancer, and early stage NSCLC.

Cancer in the Elderly

Since 1995, CALGB has had a program focused on the broad issues raised by the fact that cancers are largely diseases of aging and that cancer therapy can be particularly challenging in older individuals. Designated as a full CALGB modality committee in 2002, its members have collaborated with several disease committees to study age related issues in the context of CALGB trials. They have also developed a Committee driven research agenda, including assessment of barriers to clinical trials participation by older individuals, treatment tolerance and pharmacology in older patients with cancer, and strategies for improving quality of life for elderly individuals undergoing cancer treatment. Accomplishments of the Committee include defining age as a “provider-specific bias” barrier limiting accrual of older individuals to clinical studies. The Committee demonstrated that when offered participation in a clinical trial, older and younger patients each agreed to accept study participation at approximately a 50% rate.⁹⁹ In follow up the Committee studied the utility of a formal educational intervention to increase participation of older patients in clinical trials. Disappointingly, the educational intervention did not result in a significant increase in accrual of elderly patients.

CALGB 9762 (“Clinical Pharmacology of Paclitaxel in Relation to Patient Age”) was the first CALGB study to assess the impact of age on pharmacologic variables and the tolerability of standard dose paclitaxel. This work confirmed that advancing age correlates with a significant decline in total body paclitaxel clearance and deeper WBC and neutrophil count nadirs. However, this was not accompanied by an increase in clinically significant complications such as febrile neutropenia or hospitalization.¹⁰⁰ More recently Committee investigators have implemented a phase III trial evaluating the efficacy (non-inferiority) and tolerability of a single agent, capecitabine, compared to CMF or AC as adjuvant therapy in older women (≥ 65 years) with early stage breast cancer. Embedded companion studies are evaluating quality of life, adherence to the oral agent schedule, and an assessment of functional status and co-morbidities. The trial has completed enrollment of more than 600 women and represents one of the largest trials ever conducted in this age group.

Other Modality Activities

Oncology nurses, clinical research associates, and oncology pharmacists have all contributed to the research productivity of the CALGB. Oncology nurse investigators¹⁰¹ have focused on developing educational tools to better inform patients about their disease, the available treatment options, and critical features of participation in clinical trials. In addition, a CALGB oncology nurse is included among the study leadership for each CALGB trial, contributing to the study design, to the vetting of required data forms, and as a resource for drug administration issues. Recently, CALGB has designated three positions within the Oncology Nursing Committee specifically for doctoral level oncology nurse investigators and the Oncology Nursing Committee has activated its first phase III trial, a study of duloxetine versus placebo for treatment of chemotherapy-related neuropathic pain.

The Clinical Research Associates Committee¹⁰² has taken on the critical tasks of ongoing CRA education in all aspects of data collection and the clinical trials research process and audit preparation training for all CALGB institutions. Committee members are specifically involved in the careful development of study protocol documents, facilitating the availability of a completely functional, internally consistent, protocol document at the time of study

activation. These activities have contributed substantially to the consistently high quality of CALGB research data. At the level of individual institutions, Committee members are integral to processes that include grant and budget preparation and development of institutionally appropriate informed consent documents.

Summary

CALGB has recently celebrated its 50th anniversary as an NCI funded cooperative group. From its beginnings as a small, intensely academic consortium focused on new approaches to treatment of acute leukemia, the Group has grown into a multi-disciplinary consortium of clinical and translational scientists, focusing on the broad interface of cancer biology and cancer treatment. The work of the Group would not be possible without the devotion of thousands of physicians nurses, and clinical research associates at CALGB institutions to improving the lives of cancer patients and, of course, without the courageous participation of cancer patients and their families in CALGB studies. We keenly feel a commitment to improve the lives of the larger universe of patients with cancer through the findings of our research. This commitment will remain the guiding principle of the CALGB.

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