The Cancer and Leukemia Group B Respiratory Committee

Everett E. Vokes,1 Michael C. Perry,2 Hedy L. Kindler,1 and Mark R. Green3,4

Abstract

The Cancer and Leukemia Group B Respiratory Committee has a 30-year track record of clinical investigation in patients with small-cell lung cancer and non–small-cell lung cancer (NSCLC) and mesothelioma. The most widely recognized contributions of the Committee include the early confirmation of the role of concurrent chemoradiotherapy in LD-SCLC, the effect of combination chemotherapy followed by radiation in stage III NSCLC, the introduction of third-generation agents into concurrent chemoradiation for stage III disease, the prospective demonstration of the benefit of treating older (70 years old) and poorer performance status (performance status = 2) patients with first-line combinations for stage IV disease, and the development of the “Herndon prognostic index” to normalize patient characteristics and outcomes in sequential phase II trials of new agents in patients with mesothelioma. Many other contributions have also emerged from the Committee’s clinical trials and correlative science programs. We look forward to making additional critical contributions during future decades of Cancer and Leukemia Group B Respiratory Committee research.

The Respiratory Committee of the Cancer and Leukemia Group B (CALGB) was formed in 1978 and was led by Robert Comis until 1985. Mark Green chaired the committee from 1985 to 2004, followed by Everett E. Vokes. Drs. Michael Perry (1978-1996) and Everett E. Vokes (1996-2004) served as Vice Chairs. Andrew Terris and David Sugarbaker also served on the Respiratory Committee as radiotherapy and surgical modality Vice Chairs. Drs. Jeffrey Crawford and Robert Kratzke are the current Vice Chairs. The Committee has conducted clinical and translational studies in all stages and treatment modalities of small-cell lung cancer (SCLC) and non–small-cell lung cancer (NSCLC). In addition, it has been highly active in mesothelioma research. The following is a brief summary of the Committee’s activities focusing on advanced and intermediate stage NSCLC, small-cell lung cancer, and mesothelioma.

Advanced NSCLC. CALGB trials in advanced NSCLC began in 1978. At that time, no standard systemic therapy had been defined. The first study, CALGB 7802, evaluated an empirically constructed four-drug regimen using a single-arm phase II design (1). The agents were of the “preplatinum” era, the primary outcome measure was tumor response, and plans for follow-up of the findings were poorly defined. The study was characteristic of the time: a “kitchen sink” approach used available agents of very modest efficacy and substantial toxicity. Many of the guidelines that we now follow in clinical trial design were violated. For example, the single-arm phase II study accrued 125 patients, an unnecessarily large number. In addition, registered patients were called “inevaluable” and removed from the study denominator for major protocol violations or inadequate records. The overall response rate, even with the inappropriate reduction in the denominator size, was low at 15%. The regimen did not deserve further exploration. However, the study data did highlight the significance of performance status (PS) as a predictive factor. Among 62 “evaluable” patients with PS 0 to 1, the objective response rate was 24% and the median survival was 37 weeks. For 36 patients with PS ≥ 2, only 1 (3%) responded and the median survival was 7 weeks.

Including C7802, the CALGB Respiratory Committee has activated 30 unique studies in patients with advanced NSCLC over the years. These have included single agent studies of traditional cytotoxic or newer targeted agents in first-line or salvage therapy, randomized phase II trials of single agents or combinations, and large-scale randomized phase III studies. New concepts have been evaluated, complementary cancer therapies have been studied, special populations have been identified, and critical phase III questions have been addressed and answered. Rather than reviewing each study, five trials (see Table 1) representing important examples of these initiatives will be described in some detail.

Table 1. Five trials representative of 30 studies in patients with advanced NSCLC

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Phase</th>
<th>Brief title</th>
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<tr>
<td>8243</td>
<td>Random II</td>
<td>Ara-C plus cisplatin or vinblastine plus cisplatin</td>
</tr>
<tr>
<td>8931</td>
<td>Phase III</td>
<td>Vinblastine/cisplatin + Hydrazine sulfate</td>
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<tr>
<td>9730</td>
<td>Phase III</td>
<td>Paclitaxel + carboplatin; first line.</td>
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<tr>
<td>30203</td>
<td>Random II</td>
<td>Gemcitabine/carboplatin + celecoxib, zileuton, or celecoxib + zileuton</td>
</tr>
<tr>
<td>30406</td>
<td>Phase II</td>
<td>Erlotinib + chemotherapy in phenotypically selected patients</td>
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The first CALGB trial using cisplatin in advanced NSCLC was study 8243 (2). It was also the first time the Respiratory Committee had done a two-arm trial in NSCLC patients. The design was two arms using regimens that differed by a single agent testing cisplatin/vinblastine and cisplatin/1-p-D-arabinofuranosylcytosine (ara-C), the latter chosen because of preclinical evidence of a synergistic interaction between these two agents. This trial was an early example of the "randomized phase II" or "pick the winner" approach. Approximately 80 patients per arm were accrued over less than 1 year. Both response rate and survival were numerically superior in the vinblastine-cisplatin arm (3). Overall response rates were 9% and 22%, respectively, and 6-month survival figures were 47% and 63%. Neither regimen was felt to define an acceptable "standard" therapy for stage IV disease; however, the vinblastine/cisplatin regimen was used in subsequent CALGB and Intergroup studies testing the efficacy of chemotherapy in the stage III setting.

In the late 1980s, second-generation cisplatin-based regimens were shown to improve survival compared with best supportive care in patients with advanced NSCLC (4). This period was also a prologue to the emergence of a number of new "third-generation" cytotoxic agents for NSCLC (5). In this interval, some of the most provocative assertions in the lay medical press surrounded claims that a component of rocket fuel, hydrazine sulfate, could positively affect the survival of lung cancer patients without the toxicity tradeoffs that cancer patients and physicians had come to expect and accept. In this environment, the Respiratory Committee decided to undertake a bold pivotal phase III assessment (CALGB 8931) of the effect of hydrazine sulfate when added to chemotherapy as first-line management of patients with advanced NSCLC (6).

The 8931 study protocol was reviewed by hydrazine sulfate therapy advocates and the hydrazine sulfate was provided by National Cancer Institute. Two hundred sixty-six patients were randomized to the vinblastine/cisplatin regimen from 8243 plus either hydrazine sulfate or placebo. The primary end point was survival. Toxicity profiles and changes in nutritional status, PS, and quality of life were also addressed. No significant differences were seen in response rates or survival [Objective Response Rate: hydrazine sulfate 24%, placebo 26%; mean survival time: hydrazine sulfate 7.78, placebo 7.70 months]. In the hydrazine sulfate patients, sensory and motor neuropathy were significantly increased whereas the quality of life worsened significantly. The unambiguous findings from this work did not go unchallenged by hydrazine sulfate supporters. Their political clout led to a formal U.S. Government General Accounting Office audit of the study records and intense scrutiny of the published CALGB 8931 manuscript (7). The results of 8931 were validated by this review. This work represented critical evidence that clinical trial methods could be used to successfully address unfounded assertions of components of the complementary and alternative therapy advocacy community and, at a minimum, this case could offer evidence-based protection from toxicity associated with therapies of no proven efficacy.

In the 1980s and 1990s, CALGB lung cancer investigators, as well as most other lung cancer specialists worldwide, embraced two-drug platinum-based regimens as the standard of care. Eventually, some phase III trials emerged that supported or suggested that third-generation platinum regimens (with vinorelbine or taxanes or gemcitabine) were superior to second-generation (etoposide or vindesine) platinum-based doublets. In view of the apparently greater activity of the third-generation agents, a more frequently asked question was whether two-drug programs really were "better" in terms of survival than were third-generation single agents. In a literature-based meta-analysis, Roelof Lilenbaum, a member of the CALGB Respiratory Committee, had shown that response rates with doublets were clearly greater than with single agents. However, there was a single exception: a transient, early survival advantage for first-line doublet therapy compared with single agent treatment (8). The tension between what had become the de facto standard and the work of Lilenbaum, suggesting that "standard" doublet therapy might not really be better than a single agent, led to the development of CALGB 9730, a seminal trial of single agent paclitaxel alone or in combination with carboplatin as initial therapy for patients with advanced NSCLC (9).

CALGB 9730, chaired by Lilenbaum, was a critical trial for reasons beyond its primary comparison of one versus two drugs. It was also designed to prospectively address two other uncertainties within the treatment algorithm for patients with advanced NSCLC: Could two-drug regimens be given safely and effectively to older patients (≥70 years) and/or to patients with a PS of 2?

The trial results included the following:

- Response rates were significantly higher in the two-drug arm [30% versus 17% (P < 0.0001)].
- Median failure-free survival was significantly prolonged with doublet therapy [4.6 versus 2.5 months (P < 0.0005)].
- Median survival was extended by >2 months (8.7 versus 6.6 months) but neither overall survival (P = 0.25) nor 1-year survival (37% versus 32%) was significantly improved by the paclitaxel/carboplatin two-drug regimen.
- The two-drug regimen was clearly feasible in patients over the age of 70 years.
- In PS 2 patients, there was a significant improvement (P = 0.019) in overall survival (median, 8.8 versus 3.0 months; 1-year survival, 38% versus 14%) in the doublet therapy arm.

These results have been widely embraced as one basis for doublet therapy as standard off-protocol treatment and as the necessary comparison for further investigations in advanced NSCLC. In addition, the findings about PS 2 patients have changed the thinking of clinicians and clinical investigators about the appropriateness of treating PS 2 patients with NSCLC in the clinic and on clinical trials.

Since the late 1990s, there has been little progress in first-line chemotherapy for patients with advanced NSCLC. Instead, targeted therapy has emerged as the new strategy under intense evaluation. At American Society of Clinical Oncology (ASCO) 2004 National Cancer Institute Canada, investigators reported that single agent erlotinib improved survival compared with the best supportive care as second-line or third-line therapy for NSCLC patients (10). At ASCO 2005, the results of Eastern Cooperative Oncology Group 4599 (11) revealed that addition of bevacizumab to paclitaxel plus carboplatin improved response rate and survival in first-line therapy. To move beyond these seminal initial observations, two approaches require
testing. One is to determine whether rational combinations of targeted therapies can further improve outcome and a second is to begin to investigate targeted therapy in more selected populations enriched for patients with an increased likelihood of benefit.

CALGB 30203 was the first large U.S. cooperative group trial of double targeted therapy combined with chemotherapy in NSCLC. In this randomized phase II study, chaired by Dr. Martin Edelman, all patients were treated with the chemotherapy regimen of gemcitabine and carboplatin (12). Patients were also randomized to receive additional concurrent targeted therapy with inhibitors of two critical eicosanoid pathways: the cyclooxygenase-2 inhibitor celecoxib (arm A), the 5-lipoxygenase inhibitor zileuton (arm B), or both (arm C). Each agent inhibits critical components of the eicosanoid pathways (e.g., prostaglandins and lipoxins) and has shown enhancement of cytotoxic agents in preclinical experiments. Therefore, the use of two agents that block separate but related eicosanoid pathways may synergize in the induction of apoptosis. The objective of this randomized phase II trial was to show a failure-free survival of 50% at 9 months. Overall response rates were 27%, 32%, and 36%, respectively, and the percentage of patients with failure-free survival at 9 months was 13%, 16%, and 20%. Whereas the trend towards improved failure-free survival in arm C is intriguing, no arm achieved the primary end point. Correlative studies which may be able to identify patients likely to benefit from this approach are in progress.

In the four large phase III trials of chemotherapy with or without oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors as first-line therapy in unselected patients with advanced NSCLC, there was neither a response nor a survival benefit associated with the addition of the targeted agents (13). However, in one subset of the “Tribute” trial of paclitaxel/carboplatin with or without erlotinib, patients considered as “never smokers” (defined as <100 cigarettes in a lifetime) that were treated with chemotherapy plus the targeted agent had a median survival of 22.5 months, compared with ~10 months for those treated with chemotherapy alone (14). This finding and other retrospective subgroup analyses from phase II trials (15) suggested that combinations of chemotherapy and an oral receptor tyrosine kinase inhibitor should be reevaluated as first-line therapy in these clinically selected groups of patients. Similarly, phase II data of single agent oral receptor tyrosine kinase inhibitor therapy in NSCLC patients showed impressive response rates and progression-free survival in clinically identified groups of patients (16). Based on these observations, the Respiratory Committee has activated study 30406, chaired by Dr. Pasi Janne. In this trial, patients with previously untreated, advanced adenocarcinoma of the lung who are either never (<100 cigarettes in a lifetime) or light smokers (<10 total pack years and stopped >1 year ago) are randomized to either erlotinib alone or erlotinib and paclitaxel plus carboplatin. The primary end point of interest is progression-free survival. Tumor tissue and blood are obtained from all patients in an effort to evaluate molecular variables of the EGFR receptor and its signaling pathway. The study was activated in August of 2005.

Despite several decades of clinical investigations, patients with advanced NSCLC remain in critical need of improved therapies. Even with the recent evidence that bevacizumab can improve overall survival when combined with chemotherapy, the gains from most therapeutic advances in stage IV disease have been small and incremental rather than paradigm shifting from palliation to long-term disease control. The promise of future targeted therapies is the potential to create such a paradigm shift, either in clinically selected patients or in those whose tumors are molecularly defined. This will require the integration of tissue-based experiments with clinical trial data to identify tumors for which a given therapeutic target is relevant and to establish that a target is indeed affected by administration of the agent. In addition, the duration of targeted therapy and the value (if any) of intermittent versus continuous “maintenance” must be assessed. Strategies combining narrowly focused targeted agents and the development of single agents with multi-targeted activity will be the work of the next several years. These efforts will occur in partnership among translational scientists, clinician investigators, and the many thousands of unfortunate but brave and generous patients with advanced NSCLC who share in the development of new treatment options. CALGB investigators look forward to this partnership and in meeting these challenges.

Stage III Disease

In locoregionally advanced NSCLC, the Committee focused on combined modality therapy early on. By the early 1980s, it had become clear that chemotherapy could lead to tumor shrinkage in a good percentage of patients with stage IV disease. Furthermore, induction chemotherapy had been successfully explored in other tumor types, particularly head and neck cancer (17). Standard therapy for locoregionally advanced, unresectable disease at the time consisted of single modality radiotherapy administered at 60 Gy. Thus, the Committee designed a randomized phase III trial investigating the administration of two cycles of induction chemotherapy before standard radiotherapy versus standard radiotherapy alone (18, 19). This landmark study was closed early to accrual after review by the study team and the Respiratory Committee. (This was in the era before formal DSMB monitoring when a survival advantage for the chemotherapy-treated patients became apparent.) Therefore, the study closed with a total of only 155 eligible patients entered. Nevertheless, median survival was statistically significantly increased from 10 to 14 months for the combined modality treatment. Furthermore, long-term follow-up suggested an approximate doubling of the 5-year survival rate from 7% to 19%. CALGB 8433 and a similar trial conducted in France were the first to show a survival advantage from the sequential administration of combined modality therapy. The findings were also confirmed by a subsequent large Radiation Therapy Oncology Group study (20).

CALGB subsequently investigated the addition of a radiation sensitizer during the radiotherapy treatment. In CALGB 9130, Clamon et al. (21) compared the administration of two cycles of induction chemotherapy followed by standard radiotherapy (now to 63 Gy) with or without sensitizing doses of carboplatin administered at 100 mg/m²/wk during radiotherapy. The study confirmed the median survival of 13 months in the control arm but failed to show any added benefit from the administration of sensitizing chemotherapy during radiation. Of interest, a
similar recent trial by French investigators was reported at the ASCO meeting in 2005 and also failed to show any benefit from the addition of radiation sensitizing chemotherapy after induction chemotherapy (22).

With the identification of several new cytotoxic agents with single agent activity against NSCLC in the early 1990s, the Committee became interested in investigating these agents in the stage III curative intent treatment setting. Vinorelbine, paclitaxel, and gemcitabine all had been shown to be active both as single agents and in combination with cisplatin. Furthermore, preclinical and early clinical data suggested that each might have a role as a radiation sensitizer. In CALGB 9431, therefore, the Committee conducted a randomized phase II trial in which patients were randomized to receive two cycles of induction chemotherapy, followed by two additional cycles of chemotherapy administered with concurrent radiotherapy (Figs. 1 and 2; ref. 23).

In all three arms, patients received four cycles of cisplatin at 80 mg/m² every 3 weeks with paclitaxel, vinorelbine, or gemcitabine. This was the first large cooperative group trial to investigate these agents both during induction as well as concomitantly with radiotherapy. Results of this trial showed encouraging activity for each of the three arms. In particular, the vinorelbine arm had a favorable therapeutic ratio. Median survival in this arm was 17 months with grade 3/4 esophagitis occurring in 25% of patients. The gemcitabine arm was also highly active with median survival of 18 months. However, the incidence of severe esophagitis (grade 3/4, 52%) or/and thrombocytopenia were higher than on the two other study arms. In parallel with this study, the Committee investigated a similar approach for the carboplatin and paclitaxel combination (24). Following two cycles of induction chemotherapy, weekly doses of chemotherapy were administered with standard radiotherapy. Median survival from this phase II study was 15 months; however, the regimen was found to be well tolerated.

By the mid-1990s, other investigators had established concomitant chemoradiotherapy using doublet chemotherapy to be feasible and, in randomized trials, superior to administration of the same agents as induction chemotherapy. Therefore, concomitant combined modality therapy was widely adopted as standard and replaced the sequential (induction) combined modality therapy approach. However, many patients develop recurrent disease following concomitant chemoradiotherapy, frequently in the form of systemic metastases. Induction chemotherapy allows for administration of systematically active doses and may be the approach to target micrometastatic disease. Therefore, in protocol 39801, the Committee designed a study comparing concomitant chemoradiotherapy alone to two cycles of induction chemotherapy followed by the same concomitant chemoradiotherapy. Given the feasibility and good tolerance of the carboplatin/paclitaxel combination, we chose to use this doublet regimen as the chemotherapy and chemoradiotherapy platform. When reported at ASCO in 2004, this study showed no statistically significant difference between the two study arms. Furthermore, median survival times for both arms were disappointing at 11 and 13 months. Patients with pretreatment weight loss exceeding 5% were noted to have a particularly poor prognosis (25).

Following this trial, the Committee felt that investigations of new platform chemoradiotherapy regimens might be warranted. The combination of carboplatin and pemetrexed has been shown a phase I evaluation at the University of Chicago to be feasible (26). In particular, these agents could be given at full or near full systemic doses during radiotherapy. Therefore, the Committee is now conducting a randomized phase II study consisting of concurrent chemoradiotherapy with carboplatin and pemetrexed, followed by maintenance pemetrexed for an additional 4 cycles. In arm II, identical chemoradiotherapy is given with the addition of weekly doses of cetuximab during the concurrent chemoradiotherapy phase of treatment.

**Adjuvant Chemotherapy**

Investigations of adjuvant chemotherapy have largely been done on a national intergroup level. CALGB participated in the North American Intergroup trial of vinorelbine/cisplatin versus...
observation among patients with completely resected stage IB-II NSCLC. Similarly, CALGB led another Intergroup trial in patients with stage IB disease. In this study, CALGB 9633, patients with stage IB disease ($T_N_{1-2}M_0$) were randomized to receive four cycles of adjuvant carboplatin and paclitaxel versus observation. This trial accrued slowly reflecting the prevailing skepticism about adjuvant chemotherapy of lung cancer at the time. Nevertheless, a scheduled interim review by the Data and Safety Monitoring Board, at a time when 340 of a planned total of 380 patients had been entered, revealed a survival outcome favoring adjuvant chemotherapy. This finding led to the early closure of this trial and report of this preliminary analysis at the ASCO meeting 2004. Currently, additional follow-up data are being collected and a more mature analysis of this study is planned for later this year. Together with the results of the International Adjuvant Lung Trial North American Intergroup trial, this study led to widespread acceptance of the use of adjuvant chemotherapy in resected NSCLC (27, 28).

Small-Cell Lung Cancer

Since the late 1970s, CALGB has been a leading contributor to the development of better therapy for small-cell lung cancer, especially in the areas of the importance of thoracic radiation therapy, dosing of thoracic radiation therapy, the selection of chemotherapeutic agents, and psychological distress and quality of life.

CALGB ventured into small-cell lung cancer in 1977 with protocols 7781 and 7782, phase III trials of chemotherapy with the methanol-extractable residue of bacillus Calmette-Guerin and radiation therapy in limited and extensive disease, respectively (29). There followed several phase II studies of new agents (CALGB 8046 and 8074).

The first CALGB success in small-cell lung cancer was CALGB 8083, a phase III trial of chemotherapy with and without thoracic radiation therapy in limited-stage disease. The results were reported in 1987 and updated in 1998 (30, 31). A total of 399 patients were evaluable. Arm I, immediate concurrent chemotherapy and radiation therapy, had a complete response rate of 49% and a partial response rate of 30%, for a total response rate of 79%. For regimen II, delayed concurrent chemotherapy and radiation therapy, the corresponding rates were 58%, 25%, and 83%, and for arm III, chemotherapy alone, 36%, 28%, and 64%. Arm III produced a lower percentage of responses than either of the two radiation containing regimens. Complete response rates were higher in women than men, but age, prior surgery, PS, weight loss, and small cell subtype had no significant effect on outcome. Overall, 2-year survival was 27%. Median survival was 13.1, 14.6, and 13.6 months in arms I, II, and III, respectively ($P = 0.0099$). There was a trend toward improved survival in arm II compared with arm I, which was not significant ($P = 0.078$). Better PS and absence of weight loss were correlated with improved survival.

At the 10-year update of this study, arm I patients had a median survival of 13.04 months, arm II patients 14.54 months, and arm III patients 13.58 months (log-rank test, $P = 0.0072$). Median time to clinical failure was 11 months in arm I, 12.21 months in arm II, and 8.7 months in arm III. It was concluded that the addition of thoracic radiation therapy to combination chemotherapy improved both complete response rates and survival with increased, but acceptable, toxicity. This effect has been confirmed by two separate meta-analyses (32, 33).

CALGB 8083 had several limitations. By contemporary standards, the staging was inadequate, the chemotherapy was not cisplatin based, and it was much too long in duration. However, with this trial, the central observation of the critical importance of administering radiation concurrently with chemotherapy to improve survival for patients with limited-stage small-cell lung cancer became an evidence-based paradigm.

Other studies followed: a phase III trial, CALGB 8177, MACC (methotrexate, Adriamycin, cyclophosphamide, and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) chemotherapy with hyperfractionated radiation therapy (34); a phase II trial of etoposide (then known as VP-16) and cisplatin and a pilot; CALGB 8332, PACE (cisplatin, Adriamycin, cyclophosphamide, and etoposide) chemotherapy, and radiation therapy (35); last, CALGB 8432, a pilot study using five cycles of cyclophosphamide, etoposide, and cisplatin with radiation therapy to the chest and brain during cycles 4 and 5, followed by three cycles of cyclophosphamide, etoposide, and doxorubicin (36). In this study, the overall response rate was 88%, with 57% complete responders and a median survival of 14 months.

Based on preclinical and pilot data suggesting that the addition of anticoagulants to standard chemotherapy for patients with small-cell lung cancer might be beneficial, the next strategy of CALGB was to test the addition of the anticoagulant warfarin to chemotherapy and thoracic radiation therapy in a pilot study (CALGB 8532; ref. 37). The chemotherapy was changed to induction ACE (doxorubicin, cyclophosphamide, and etoposide) chemotherapy for cycles 1 to 3; then cisplatin, cyclophosphamide, and etoposide (courses 4 and 5) during radiation therapy; followed by three additional courses of ACE given after the completion of radiation therapy. Warfarin was given throughout the treatment period in a dose sufficient to prolong the prothrombin time to 1.5 to 2 times the control. Thoracic radiation therapy and prophylactic whole-brain radiation were also given. The response rate was 89% with 57% complete responses, and a median survival of 18 months with 33% alive at 3 years. Unfortunately, toxicity was significant with 90% severe or life-threatening myelosuppression, 6% pulmonary toxicity, and 6% severe or life-threatening hemorrhage (38).

A randomized phase III study, CALGB 8534 was built on the early efficacy observations from 8432 and 8532 but initiated before the reporting of toxicity from the pilot study. All patients received chemotherapy and radiation therapy as above and were randomized to receive warfarin or to receive no anticoagulation. When an unacceptable rate of pulmonary toxicity was again encountered among the randomized patients, independent of assignment to warfarin or no warfarin, the protocol was modified and the last three cycles of chemotherapy were dropped for the remaining patients.

Overall, no significant differences in response rates, survival, failure-free survival, disease-free survival, or patterns of relapse were found between the treatment groups. The analysis was complicated by the change in therapy. In patients who were treated according to the original design, an increase in
failure-free survival for the warfarin-treated patients approached significance \( (P = 0.07) \). Nevertheless, the group decided not to pursue the study of anticoagulant therapy in subsequent trials.

CALGB 8837 was a phase I study designed to determine the maximum-tolerated dose of radiation in both standard once-daily and hyperfractionated-accelerated twice-daily schedules concurrent with chemotherapy (39). The maximum-tolerated dose of hyperfractionated-accelerated twice-daily radiation therapy was determined to be 45 Gy in 30 fractions over 3 weeks, whereas it was judged to be in excess of 70 Gy in 35 fractions over 7 weeks for once-daily radiation therapy. The optimal dose of thoracic radiation therapy for small-cell lung cancer remains unresolved and a phase III trial has yet to be done.

The next CALGB study, 9235, addressed the question of drug resistance by adding tamoxifen to etoposide-cisplatin chemotherapy and thoracic radiation therapy. Unfortunately, no benefit was shown from this approach (40).

Early on, a CALGB review of previously completed studies confirmed the importance of prognostic factors of female sex, limited-stage disease, and good PS score (41). There were some blind alleys along the way: Anticoagulation did not add to chemotherapy in spite of promising preclinical data and pilot studies. Tamoxifen did not reduce acquired drug resistance. The use of neurophysins as tumor markers was disappointing (42) and, at the cost of increased toxicity, higher doses of etoposide and carboplatin did not improve results (43, 44). Interleukin-2 and IFN-\( \gamma \) did not, as hoped, eliminate minimal residual disease (45, 46). High-dose chemotherapy with stem cell support proved not to be feasible.

Most recently, CALGB 9732 showed in a large, randomized, controlled phase III trial that paclitaxel, although an effective agent in small-cell lung cancer, improved response rates, but not survival, when added to standard chemotherapy (47).

In conjunction with the CALGB Psycho-oncology Committee, the Respiratory Committee was among the first to evaluate the effect of psychological stress, quality of life, and neurocognitive function in small-cell lung cancer patients (48–50).

More recent CALGB trials have evaluated new doublets in the induction therapy and concurrent chemoradiation of limited-stage disease. Although several cooperative groups have proposed phase III trials of radiation dosing in limited-stage disease, no protocol has been developed to address this question. The latest advance in the treatment of small-cell lung cancer has been the introduction of the campothecins, irinotecan and topotecan, into chemotherapy regimens.

Because so little progress has been made in the therapy of small-cell lung cancer, new insights into the biology of this tumor are desperately needed and will, perhaps, lead to the development of novel therapies directed against critical targets.

**Mesothelioma**

For the past two decades, the CALGB has taken a national leadership role in the evaluation of new chemotherapy agents for mesothelioma. Nicholas Vogelzang chaired the Mesothelioma Subcommittee from its inception in 1984; Hedy Kindler assumed this responsibility in 1998. Since 1984, CALGB has conducted 14 mesothelioma trials involving more than 560 patients, including sequential phase II studies of cytotoxic drugs and novel targeted agents, a randomized phase II trial of cytotoxic doublets, and a seminal analysis of prognostic factors. Although mesothelioma affects only about 2,500 Americans annually, CALGB has successfully accrued to clinical trials, in part because several CALGB institutions are in proximity to World War II shipyards and manufacturing centers that used asbestos. CALGB has a network of medical oncologists, thoracic surgeons, and pathologists with significant expertise in mesothelioma.

Philippe Chahinian chaired the first CALGB mesothelioma study, CALGB 8435, a randomized phase II trial of cisplatin with mitomycin or doxorubicin (51). This was actually a confirmatory evaluation of two regimens that were reported to have activity in two single-center trials, of 12 and 6 patients, respectively. The tiny size of those earlier studies highlights the need for cooperative group trials in this uncommon tumor. Seventy-nine patients were enrolled between June 1984 and October 1986. Time to treatment failure or overall survival between the two regimens was similar and, as expected, the high response rates of the earlier, smaller trials were not confirmed. Because chest computed tomography scans were obtained only at baseline and at the time of best response or progression, it is difficult to assess the accuracy of the response and time to treatment failure data.

CALGB 8435 required central review of pathology slides and submission of paraffin blocks. This was fortunate as there was considerable disagreement about the diagnosis in a substantial proportion of cases. CALGB pathologists Joseph Corson and Yasunosuke Suzuki determined that 7 of the 79 patients did not, in fact, have mesothelioma and they reclassified the pathologic subtype in 21 other cases. Central pathologic review is no longer required in CALGB mesothelioma studies, as diagnostic accuracy has improved with routine use of immunohistochemical panels.

Subsequent trials produced some disappointing results: Single-agent carboplatin (CALGB 8638) had only modest activity (52). Dihydroazacytidine achieved a promising response rate of 17% in CALGB 8833 (53). When cisplatin was added (CALGB 9031), toxicity increased but the response rate remained unchanged (54). The authors concluded, perhaps erroneously, that it is more appropriate to evaluate single agents than platinum combinations in this disease. We now know that the addition of platinum enhances the activity of drugs such as gemcitabine, although in CALGB 9530, single agent gemcitabine was ineffective (55). Paclitaxel (CALGB 9234), irinotecan (CALGB 9733), and capecitabine (CALGB 39807) were also inactive (56–58). High-dose doxorubicin administered with the cardioprotectant dexrazoxane and granulocyte macrophage colony-stimulating factor (CALGB 9631) was excessively toxic (59).

Vitamin supplementation decreases toxicity and improves the activity of pemetrexed, the only drug currently approved for mesothelioma. Could administration of folic acid and B12 have altered the results of earlier CALGB antifolate trials? Trimetrexate (CALGB 8933) produced identical, modest response rates of 12% for two different dose levels; patients who received the higher dose had a better rate of survival (60). Edatrexate (CALGB 9131) achieved a promising response rate...
of 25% and a median survival of 9.6 months. Toxicity, however, was intolerable. Of interest, the addition of leucovorin rescue produced a less toxic regimen that was also less active (61).

CALGB statistician James Herndon’s 1998 analysis of prognostic factors in 337 patients from the first seven CALGB mesothelioma trials was a major contribution to the field (62). He found multivariate analysis, pleural involvement, high lactate dehydrogenase, poor PS, chest pain, thrombocytosis, nonepithelial histology, and age >75 jointly predicted poor survival rates. Exponential survival trees defined six patient subgroups; survival ranged from 13.9 months for prognostic group 1 to 1.4 months for prognostic group 5. These “Herndon criteria” are now widely used to assess prognostic characteristics in mesothelioma trials.

In 2001, CALGB became the first cooperative group to test a novel targeted agent in this disease and the first to incorporate correlative laboratory studies. Because mesothelioma commonly overexpresses EGFR, and EGFR inhibitors have activity in vitro, it seemed reasonable to evaluate the EGFR tyrosine kinase inhibitor gefitinib (CALGB 30101; ref. 63). Although 96% of patient tumors overexpressed EGFR, failure-free survival did not correlate with EGFR expression, nor was it affected by gefitinib. More recent trials of other novel targeted agents, including vatalanib (CALGB 30107; ref. 64) and sorafenib (CALGB 30307), also integrate correlative laboratory end points.

Studies currently in development add targeted agents to standard chemotherapy, evaluate novel agents in the second-line setting, and incorporate systemic therapy into multimodality treatment.

References


Clinical Cancer Research

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