

Activities and Accomplishments of the Cancer and Leukemia Group B Genitourinary Committee

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Abstract The Cancer and Leukemia Group B Genitourinary (GU) Committee has developed a multidisciplinary approach to treatment of GU cancer and has integrated correlative science research into the major research themes of the GU Committee. In localized prostate cancer, trials have evaluated novel approaches in radiation therapy. For patients with recurrence after local therapy, a trial evaluating local recurrence with salvage prostatectomy and a study of systemic therapy with "peripheral androgen blockade" were undertaken. Major contributions have been made in developing and testing therapeutics for advanced, androgen-independent prostate cancer (ketoconazole, suramin, estramustine/docetaxel, and docetaxel/bevacizumab), and in developing predictive markers and algorithms to assess prognosis in these patients. Contributions in kidney cancer have included the development of novel trial methodology, such as the randomized discontinuation trial design, and the testing of antiangiogenics. In addition to these areas, future work of the committee will include further development of therapy for earlier-stage prostate cancer patients and bladder cancer patients.

The Cancer and Leukemia Group B (CALGB) Genitourinary (GU) Committee is the successor to the CALGB Prostate Committee that was established in November 1993 under the leadership of Nicholas Vogelzang, and in late 1999 was charged with broadening its scope to include all urologic malignancies. The principle goals of the GU Committee have been to expand the strengths of the CALGB in advanced prostate cancer (and primarily in hormone-resistant prostate cancer) to include research themes in localized prostate cancer, urothelial carcinoma, renal cell carcinoma, and germ cell tumors. Implicit in this goal is a commitment to a multidisciplinary approach, and an increased involvement, representation, and participation of urologists and radiation oncologists. Through collaboration with the GU Correlative Sciences Working Group, the integration of correlative science research into the major research themes of the GU Committee is also a primary goal of the Committee.

Localized Prostate Cancer

Protocols have recently been developed to evaluate new treatment approaches to early-stage prostate cancer. There have been three prospective phase II radiation oncology studies

recently completed by the CALGB GU Committee. The first examined whether the change in the radiographic size and stage of prostate cancer as assessed using a 1.5 T endorectal MRI following 2 months of neoadjuvant androgen suppression therapy was associated with prostate-specific antigen (PSA) failure-free survival following combined 70 Gy external beam radiation therapy and 6 months of hormonal therapy for men with high risk or locally advanced prostate cancer. This study accrued 180 men and is currently in follow-up. Two additional phase II studies were done to investigate toxicity and feasibility of two novel approaches in the management of newly diagnosed prostate cancer. The first focused on men with high-risk or locally advanced disease where the combination of dose-escalated (75.6 Gy) radiation therapy, hormonal, and taxane-based chemotherapy was piloted and the second focused on men with intermediate-risk disease where combined radiation therapy, brachytherapy, and 6 months of hormonal therapy was done. The toxicity of these approaches was deemed acceptable. Similar approaches combining dose-escalated radiation therapy (using intensity-modulated radiation therapy or brachytherapy) and adding taxane-based chemotherapy are now being further evaluated in nationwide randomized phase III studies led by other cooperative groups, where conventional dose radiation therapy (70 Gy) and hormonal therapy comprise the standard arm for men with intermediate- and high-risk disease.

Surgical trials are also in development for early-stage prostate cancer. To test the hypothesis that neoadjuvant chemotherapy in combination with androgen deprivation will result in better disease control, the CALGB GU Committee has developed an ambitious intergroup preprostatectomy study for patients with high-risk localized prostate cancer. Short-term preprostatectomy (neoadjuvant) androgen deprivation seems to reduce the positive margin rate, but has failed to result in an improvement in PSA progression-free survival. Thus, a phase III trial of

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neoadjuvant chemotherapy plus androgen deprivation therapy is in development. Because there is as yet no proven role for neoadjuvant therapy in this setting, the control arm will consist of radical prostatectomy alone (1). Patients will be randomized to immediate prostatectomy or short-term combined chemohormonal therapy followed by prostatectomy. Clinical end points will include time to PSA failure as well as overall survival. Prostatectomy specimens will be collected to identify biological predictors of failure.

Prostate Cancer Recurrence after Local Therapy

Predictive algorithms have been used to assist clinical decision-making as to whether local or systemic therapy should be used in patients with a climbing PSA after local therapy. The CALGB GU Committee has undertaken several important trials addressing both local and systemic treatment approaches to this group of patients. CALGB 9687 was the first prospective multicenter study to evaluate the feasibility and morbidity of salvage radical prostatectomy in patients with a local recurrence after radiation therapy. Although this approach is not widely embraced, at many centers this study has shown that salvage radical prostatectomy is reasonably well tolerated and feasible (2). Long-term progression and survival outcomes continue to mature.

The use of androgen-deprivation therapy in patients with a climbing PSA after definitive local therapy has not been established and there are concerns with the morbidity associated with long-term androgen deprivation. Yet, given the survival advantages observed with long-term adjuvant hormone therapy after either radiation therapy in high-risk patients, or after prostatectomy in lymph node-positive patients, such therapy warrants further study, perhaps with an emphasis on reducing morbidity. It is in this context that the CALGB GU Committee undertook CALGB 9782, a study of finasteride plus flutamide (so called "peripheral androgen blockade") for patients with serologic progression after definitive local therapy. One hundred and one patients were accrued. Ninety-seven percent of patients had a >80% drop in PSA, and the vast majority have had durable responses, with the median progression-free survival exceeding 5 years. This study continues to mature, but provides evidence that this approach, which is extremely well tolerated, may provide an alternative to gonadal androgen ablation (3).

Androgen-Independent Prostate Cancer

Whether hormonal therapy is used for patients with serologic progression or more advanced disease, androgen-independent disease will eventually develop. It was in this group of androgen-independent prostate cancer (AIPC) patients that CALGB 9583, a randomized phase III trial of antiandrogen withdrawal alone versus antiandrogen withdrawal plus ketoconazole, was developed (4).

This study represents the first prospective multicenter trial evaluating the effect of antiandrogen withdrawal and also has yielded important information about the efficacy of ketoconazole. Adrenal androgen levels have been measured throughout the course of therapy. Baseline DHEA levels were an independent predictor of survival (hazard ratio, 1.27; $P = 0.001$). Furthermore, adrenal androgen levels clearly decline with the

use of ketoconazole, and the development of resistance to ketoconazole correlates with a subsequent increase in adrenal androgen levels. In addition, 194 bone marrow biopsies and aspirates were obtained from these patients, representing, to our knowledge, the largest such tissue repository. These specimens have been assayed for mutations in the hormone-binding domain of the androgen receptor. Preliminary data suggest that <10% of patients harbor such mutations, and importantly suggest that there is no correlation between the presence of an androgen receptor mutation and an antiandrogen withdrawal response (*vide infra*; ref. 5).

The CALGB GU Committee lead an intergroup randomized phase III trial (CALGB 9480) that evaluated three different doses of suramin for the treatment of patients with metastatic AIPC, based on phase I trials suggesting a dose-response relationship. This study failed to show an advantage to higher suramin dosing (6), but prospective collection of serum and plasma provided the opportunity to identify several biomarkers found to be independent prognostic markers in AIPC (*vide infra*).

Sequential pilot phase II trials based on a common chemotherapy backbone were developed to allow rapid progression from one trial to the next. It has become clear that taxane-based combinations are among the most active regimens in AIPC. The CALGB GU Committee was the first cooperative group to develop group-wide experience with an estramustine plus taxane regimen, CALGB 9780, using estramustine and docetaxel (7). Novel agents have subsequently been added to this backbone. The resulting triplets have been used to screen for activity of the novel agent. Thus, CALGB 99813 was added the cytotoxic agent carboplatin (8), and CALGB 90004 was added the proapoptotic agent exisulind to an estramustine/docetaxel backbone (9). It was felt that this approach offered a rational strategy to examine new regimens and agents, and provided the potential to identify a comparator arm for a follow-up study to the intergroup phase III trial that compared estramustine/docetaxel with mitoxantrone plus prednisone. Indeed, the observation that vascular endothelial growth factor (VEGF) levels were inversely correlated with survival was the basis for the subsequent development of bevacizumab for the treatment of AIPC. CALGB 90006 added the anti-VEGF antibody bevacizumab to the estramustine/docetaxel doublet (10). Response and progression data from this phase II trial were encouraging, and are the basis of an ongoing intergroup trial led by the CALGB of docetaxel/prednisone (which has replaced docetaxel/estramustine) with and without bevacizumab. This aim of this study is to test the hypothesis that the addition of bevacizumab will prolong survival in patients with AIPC treated with docetaxel/prednisone.

Risk Assessment in AIPC

In AIPC patients treated on sequential phase II "triplets," the potential of conducting a series of uninformative phase II trials exists, particularly if PSA response proportion is used as an end point. Failure to show a benefit may be due to the use of inactive agents to the fact that there is a very high response proportion in the historical control group, or to stage migration and patient selection. This concern has been addressed by the construction of a risk nomogram based on over 1,000 AIPC

patients treated on CALGB trials (11). The "Halabi Nomogram" has been validated on a test data set, and has become widely accepted as a tool for predicting outcome for individual patients, as well as for calculating the predicted median survival for a given regimen based on the pretreatment characteristics of the treated patients. Further refinement of the model will include biological markers [VEGF urine and plasma levels, and reverse transcription-PCR (RT-PCR) for PSA] as variables in this model.

Correlative Studies in Prostate Cancer

Thus far, the main focus of the correlative studies that have been undertaken by the committee has been the assessment of prognostic and predictive factors in men with advanced prostate cancer. Single gene/protein analyses have been conducted and have led to some progress in risk stratification of patients. In addition, studies of minimal residual disease and androgen receptor mutations have been completed. The biomarkers evaluated have included interleukin 6, chromogranin A, VEGF, and circulating cells positive for PSA by RT-PCR. The polypeptide cytokine interleukin 6 has been shown in preliminary studies to be associated with relapse after radical prostatectomy and to be higher in men with advanced prostate cancer compared with those with early stage disease. We studied interleukin 6 levels in 191 men with metastatic AiPCa treated on CALGB 9480 (Suramin) and found it to be a significant predictor of survival in univariate and multivariate models (12). Similarly, in preliminary data using expression profiling (13), the neuroendocrine gene *chromogranin A* (CgA) was found, along with four other genes, to be a predictor of relapse after radical prostatectomy. Other studies have suggested that the neuroendocrine phenotype in prostate cancer is associated with a poorer prognosis. We studied 321 men from protocol 9480 and determined that CgA was a significant predictor of survival by univariate and multivariate models (14). As noted above, VEGF levels in the plasma and urine of patients with AiPCa were evaluated. In both studies, VEGF levels were found to be inversely related to survival and were predictive of survival, independent of other prognostic factors (15, 16).

Finally, in two successive studies, we analyzed the prognostic significance of circulating cells that were positive for PSA by RT-PCR in men with AiPCa. In the first study, peripheral blood was obtained from 193 men enrolled on CALGB 9480, a prospective randomized comparison of three doses of suramin. RNA was isolated from the samples and assayed for the presence of PSA transcripts by RT-PCR. RNA could be isolated in 156 (83%) of samples. PSA transcripts were detectable in 75 (48%) of the 156 patients. The median survival for those patients in whom no transcripts were detectable was 18 months (95% confidence interval, 14-22 months) compared with 13 months (95% confidence interval, 11-15 months; $P = 0.004$) for those in whom transcripts were detectable. In a multivariate analysis in which other factors predictive of survival were used, RT-PCR for PSA provided independent prognostic information (17). In the second study, 162 patients were analyzed from CALGB 9583, a study of antiandrogen withdrawal with or without simultaneous ketoconazole. Ninety-one (56%) patients were negative for RT-PCR for PSA and 71 (44%) patients were positive. The

median survival time was 21 months (95% confidence interval, 18-27 months) for RT-PCR-negative patients compared with 11 months (95% confidence interval, 8-15 months) for RT-PCR-positive patients ($P \leq 0.001$). In multivariable analysis, the hazard ratio for death was 1.7 (95% confidence interval, 1.2-2.4; $P = 0.006$) for positive RT-PCR patients compared with negative RT-PCR patients. A fitted model that incorporated RT-PCR for PSA and other factors was used to classify patients from CALGB 9480 into one of two risk groups: low or high. We observed good agreement between the observed and predicted survival probabilities for the two risk groups.

RT-PCR to detect PSA-positive circulating cells is confirmed to be a significant prognostic factor of survival in patients with hormone refractory prostate cancer (18). This model could be used to stratify patients in randomized phase III trials.

A large tissue repository of bone marrow biopsies and aspirates in patients with AiPCa has been developed. From this repository, the prevalence of prostate cancer involvement of bone marrow (30%) in patients with advanced prostate cancer has been determined. In an important study, assessment of these specimens for mutations in the hormone-binding domain of the androgen receptor, has shown that, contrary to early reports, the frequency of androgen receptor mutations in the hormone-binding domain is <10% of patients with hormone refractory prostate cancer. Interestingly, the presence of these mutations did not correlate with the likelihood of an antiandrogen withdrawal response. These observations have resulted in a completely new understanding of the mechanisms of androgen independent prostate cancer growth.

Renal Cell Carcinoma

The CALGB renal cell cancer activities began before expansion of the Prostate Committee to a full GU Cancer Committee. Initially under the auspices of the Pharmacology and Experimental Therapeutics Committee, and then with support of the newly expanded GU Committee, a 368 patient randomized discontinuation trial of the putative antiangiogenic agent carboxyaminoimidazole was conducted between 12/00 and 7/02 (CALGB 69901). Evaluating the efficacy of a potentially cytostatic agent in a disease like renal cell cancer, in which many patients can have indolent, seemingly stable disease, is difficult. The intent of the randomized discontinuation trial design is to help identify disease nonprogression (stable disease) that can be attributed to the therapeutic intervention. In the randomized discontinuation trial design, all patients received carboxyaminoimidazole for an initial 16 weeks and those with stable disease were then randomized to continuing or discontinuing therapy in a double blind, placebo-controlled manner. The primary end point was the fraction of patients in each randomized group who maintained stable disease 16 weeks later. This design thus specifically assessed the potential growth inhibitory activity of carboxyaminoimidazole and CALGB 69901 was the first application of this trial design in oncology (19). Although carboxyaminoimidazole was shown not to have any significant activity, we were able to show the use of the trial design and that CALGB was able to accrue rapidly to renal cancer studies.

The Committee continued its efforts in evaluating antiangiogenic agents in renal cancer by conducting and completing one of the largest phase III trials conducted in this disease to date. In CALGB 90206, the combination of IFN/bevacizumab was compared with IFN alone in 738 patients accrued between 10/03 and 5/05. The final results are pending at this time, but are expected to provide definitive data on the role of bevacizumab in the treatment of patients with metastatic renal cell cancer (20). Importantly, tissue specimens have been banked from most patients, and an assessment of mutations in the *VHL* gene, and correlation with outcome after antiangiogenic therapy, will be evaluated.

The Committee was also able to complete in a record 19 weeks a single-arm 60-patient phase II study confirming low-level activity of gemcitabine and capecitabine in metastatic renal cancer (CALGB 90008).⁹ Previous single-institution observations were confirmed, but the study also revealed that toxicities in the multi-institutional setting were greater than previously reported. In fact, the study strongly suggested that the risk/benefit ratio of gemcitabine/capecitabine was not worthy of further phase III evaluation.

Another important confirmatory study was a collaborative effort with the Transplant Committee to follow-up reported efficacy of nonmyeloablative allogeneic marrow transplant as a novel immunotherapeutic approach in this disease (CALGB 90003). The trial showed the feasibility of conducting a multi-institutional transplant trial. Although successful donor chimerism was observed in 17 of 19 patients, no evidence of a graft versus tumor effect was observed (21). This is a critical contribution in that the need for better understanding of the graft versus tumor effect will be necessary before this treatment can be more widely adopted.

Because of increased recognition that renal cell carcinoma is composed of multiple defined subtypes, each of which will likely require specific therapies, a formal renal cell cancer tissue

bank is also being initiated (CALGB 150406). This tissue bank will collect renal cancer specimens in a carefully defined prospective manner such that various macromolecular profiling studies can be done and then correlated with patient outcome. Presumably many of the patients contributing tissue will also participate in CALGB renal cell cancer treatment trials, thus allowing future studies evaluating predictive markers of drug benefit to be conducted.

Bladder Cancer

The CALGB GU Committee was not involved in urothelial carcinoma protocol development until 2000. Since then, the Committee has evaluated the use of adding gefitinib to standard gemcitabine/cisplatin chemotherapy for metastatic disease (22) and tested arsenic trioxide as second-line therapy. For patients with superficial bladder cancer, few options short of cystectomy exist for *Bacillus Calmette-Guerin*-resistant patients. Based on work conducted at a CALGB institution, a phase III trial of retreatment with *Bacillus Calmette-Guerin* compared with the combination of *Bacillus Calmette-Guerin* and IFN- α will be undertaken.

Conclusions

The CALGB GU Committee has contributed with distinction to the growing field of urologic oncology. We have developed a multidisciplinary approach, with the integration of correlative science research into the major research themes of the Committee. Major contributions have been made in developing therapeutics for advanced prostate cancer and in developing predictive markers and algorithms for these patients. Additional contributions in kidney cancer have included the development of novel trial methodology and the testing of antiangiogenics. In addition to these areas, future work of the Committee will include further development of therapy for earlier-stage prostate cancer patients and bladder cancer patients.

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