American College of Radiology

Annual Progress Report: 2006 Formula Grant

Reporting Period

July 1, 2010 – December 31, 2010

Formula Grant Overview

The American College of Radiology received $2,511,654 in formula funds for the grant award period January 1, 2007 through December 31, 2010. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Factors Associated with Attrition in RTOG Clinical Trials - To date, many studies have examined barriers to clinical trial recruitment; however, we know substantially less about retention of subjects enrolled in randomized controlled trials (RCT). Indeed, only one out of four subjects remains in RCT until study completion. Therefore, there is a compelling need to study retention in order to design strategies to enhance retention in Radiation Therapy Oncology Trials (RTOG). The purpose of the proposed project is to assess individual (e.g., socio-demographics of age, gender, race/ethnicity), organizational (e.g., community versus academic setting), and protocol-related factors (e.g., phase of trial, group assignment, adverse events) associated with attrition in all RTOG treatment studies that were opened to accrual as of January 1, 1985 and have completed accrual and had the primary endpoint published by January 1, 2005.

Duration of Project

7/1/2007 – 6/30/2009

Summary of Research Completed

This project ended during a prior state fiscal year. For additional information, please refer to the Commonwealth Universal Research Enhancement C.U.R.E. Annual Reports on the Department's Tobacco Settlement/Act 77 web page at http://www.health.state.pa.us/cure."

Research Project 2: Project Title and Purpose

Identifying Interventions for Cancer Patients at High Risk for Poor Outcomes - In this two phase project, the first goal is to document the combined influence of gender, marital/partner status, and race in identifying patients with cancer at risk for poor outcomes in a pooled analysis of patients with cancers treated with radiotherapy on large, national clinical trials. This analysis will facilitate understanding how the interaction of these factors influences intermediate indicators [e.g., treatment breaks, weight loss, etc.] of primary outcomes [e.g., survival, quality

of life]. The second goal is to use these results in designing a second phase of focus group discussions aimed at developing targeted interventions to improve both the intermediate indicators and, ultimately, survival and quality of life.

Duration of Project

7/1/2007 - 12/31/2010

Project Overview

Objective: The classic prognostic factors in clinical oncology trials remain clinical stage and performance status. Recently, a striking disadvantage in cancer outcomes has been observed for single males. This work leads to the hypothesis that the interaction among gender, partner status, and race delineates a group at particular risk for poor outcomes, namely unpartnered African American males. The broad objective is to identify targeted interventions to ameliorate the effects of factors that place this population at risk.

Specific aims: To investigate disparities in health outcomes among specific populations prevalent in the Commonwealth by assessing differential primary outcomes [e.g., survival and quality of life] and secondary intermediate outcomes [e.g., treatment breaks, weight loss, etc] by key sociodemographic factors [gender, marital/partner status, race] in a meta-analysis of patients treated for cancer on national clinical trials. This information will be used to guide focus group discussions identifying factors amenable to targeted interventions to improve intermediate outcomes. The project thus progresses from clinical epidemiological findings to interventions development, addressing health disparities concentrated among African American males, particularly those without partners.

Design and methods: A two phase, quantitative-qualitative design: Phase 1: A pooled analysis of prospective data for colorectal, head & neck, lung and prostate cancer clinical trials will be conducted using statistical methods to identify interactions among key sociodemographic factors [gender, martial/partner status, race] that, when combined, may lead to poorer outcomes than would be expected based upon standard prognosticators alone. After the populations at highest risk are identified, the next step will be to explore how the interaction of these factors influences intermediate indicators [e.g. treatment breaks, weight loss, etc] of primary outcomes [e.g., survival, quality of life]. In Phase 2, results of Phase 1 will determine purposive sampling and interview guides for focus groups. The objective of these focus group discussions will be to determine how disparities emerge in the process of care and how timely and targeted interventions could improve outcomes in the high-risk population.
Candidates for intervention include deficits in self-care, such as nutrition and receipt of prompt medical care for treatment side effects and symptom distress that otherwise interfere with treatment adherence.

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Expected Research Outcomes and Benefits

The outcomes of this project will be a clearer understanding of specific populations at high risk for poor outcomes after state of the art cancer therapies and the concrete means by which disparities in outcomes can be remedied. The identification of African American single males as a particularly high risk could have important clinical and policy implications. Moreover, the two phase strategy provides a means of using qualitative focus group discussions to translate recognition of quantitative factors directly into cost-effective interventions to facilitate intermediate factors [such as scheduled doctor visits, treatment breaks, weight loss, or medication compliance] that impact on primary outcomes [such as survival, toxicity, and quality of life] among those patients at highest risk. Such intermediate factors present opportunities for prompt intervention forestalling negative outcomes, including failure to derive the full potential benefit of treatment.

The proposed project is novel in specifying a way in which more precise delineation of health disparities can be translated directly into appropriate interventions and improved outcomes. The benefits of this study are that the findings will lead to targeted interventions to improve these intermediate factors that have a cascade effect on primary outcomes, such as quality of life and survival. Specifically, once the cancer patient populations are identified [by gender, marital/partner status, race, or specific combinations of these factors] at highest risk for poor outcomes, this will facilitate testing of methods of early identification and social support interventions to directly improve cancer outcomes. These interventions will be based upon the focus group recommendations composed of the high-risk cancer patient populations. This project will thereby address disparities in health status that affect many Commonwealth populations.

Summary of Research Completed

<u>Focus Groups</u>
Data analyses. Transcripts were subjected to systematic content analysis. First, a line-by-line analysis of the transcripts was independently conducted by two authors to identify data variables.

Identified variables were discussed by three authors to resolve differences and to define categories and subcategories for creation of a coding scheme. The coding scheme was entered into an Excel workbook and transcripts were coded accordingly to identify points of agreement and difference among groups. Coding was accomplished independently by two trained research personnel by selecting and assigning statements to the scheme. Text was assigned multiple times in cases where more than one category was involved. The two coding workbooks were combined by one author. Last, theoretical implications of the categories and their relationships were identified by authors to develop a conceptual model of therapeutic targets to reduce the survival discrepancy between partnered and unpartnered head and neck cancer patients.

Results

Participants

The groups consisted of 13 men with partners and 5 men without partners. The mean age of the men with partners was 59.4 years (*R* = 33–78), and for those without partners, 60.4 years (*R* = 45–70). All but one man in each group identified as Caucasian. Of the respective groups, 100% compared to 60.0% lived with an adult, and a person in need of care resided with 38.5% and 40.0% of the men. A post-secondary educational degree was obtained by 53.9% and 40.0%. The mean time since treatment for men with partners was 21.4 months (*R* = 2–48), and for those without partners, 29.2 months (*R* = 2–48). Cancer stage was unknown by 53.8% and 40.0%, respectively.

Challenges

There were no differences in the challenges reported by participants with and without partners. The challenges encountered by participants occurred across a broad spectrum of issues. See Table 1 for a list of the challenges. Nine of the 18 men discussed having difficulties receiving a correct cancer diagnosis. Other common challenges included having difficulty accepting the diagnosis or treatment (n = 7) as well as experiencing specific adverse events of cancer treatments (n = 10). Two men considered not initiating treatment and another two considered stopping treatment prematurely. *"I was seriously thinking about quitting and I talked to my mom and she said, 'You've never quit anything in your life. You're not going to quit now.'"*

Treatment adherence

Despite the hardships of treatment, 14 participants did not encounter insurmountable barriers to attending their treatment or follow-up appointments. For the 4 men who rescheduled an appointment, the reasons given were being too sick from treatment, having a prior work obligation, or the physician cancelled. Multiple facilitators of treatment adherence were identified in the transcripts, such as, ease of rescheduling appointments, grouping appointments together, automated reminder telephone calls, physician persuasion, fear of reoccurrence, and assistance from others.

Support during cancer care

Participants received support from a variety of sources as shown in Figure 1. The number of sources reported by men with partners averaged at 2.8 (*R* = 1–4), and for men without partners, 4.4 (*R* = 4–5). Among family and friends, multiple individuals were listed as providing support. Including romantic companions, the mean number of family and friends for men with partners

was 2.3 (*R* = 1–7), and for men without partners, 2.6 (*R* = 2–3). Cancer care providers were also a source of support identified by 9 participants.

The types of support received by men with and without partners were similar. Cancer care providers were described by 11 participants as emotionally supportive: "*There was always someone, a cheerleader pushing you on, and that's been a very big help to me knowing that I can come here and relax."* "*The [health providers] are probably the biggest supporters I had in the process."* In addition to emotional support, 4 participants stated that their providers provided them with information, such as prognosis and treatment effects, and another 4 participants stated they were referred to support staff, such as a cancer navigator or social worker. Six participants mentioned that the cancer center assisted them with scheduling appointments or sending appointment reminders.

Emotional support was also commonly received by participants from people within their social network (n = 9). People sent participants encouraging letters and prayed and talked with them: *"I just threw up for 15, every 15 minutes for three days straight. I just couldn't stop. And my wife just was there then and she kept saying, 'Look, just hang in there, you know, you're at the end. It's going to get better.'"* Another common means of support was assistance with medical appointments. Fourteen participants stated that someone drove and/or accompanied them to their appointment. Reasons for treatment escorts included that an escort enabled patient to "*deny*" diagnosis, the escort enjoyed meeting with treatment providers, and functional limitations of the participants, such as poor memory and inability to drive. Other support included receiving cancer-related information, provision of food, babysitting, house cleaning, and medication management.

Patient perspective of support

Similar perspectives of support during treatment were found for patients with and without partners. See Table 2 for participants' perspective on social support. Nearly all the participants stated that the support they received was helpful (n = 16). On the other hand, participants also made comments reflecting that they did not always want or need support. Two men stated that they would have completed treatment whether they had support or not. Another two men stated that they did not need assistance for certain medical appointments. Privacy was more important than receiving more support for 4 men, and 4 men were uncomfortable receiving support because they felt like a burden to others.

Patient role in cancer experience

In the group discussions, another common theme was the role participants played in their own experience with cancer. See Table 2. Most participants who had difficulty with receiving a correct diagnosis (n = 6) described persistently searching for the correct medical professional or procedures to determine the cause of their symptoms. Eleven men talked about how they made a concerted effort to make their cancer treatment appointments. In reaction to questions about support, participants clarified that their motivation was key to completing treatment: *"[My wife] has always said that if it wasn't for my motivation and my desire to get better, I wouldn't've gotten there."* Participants also pursued finding solutions to problems related to their cancer treatment, maintained their way of life, and perceived positive outcomes of their cancer experience.

Publications

The manuscript for the prostate cancer study presented in the previous report, *Impact of Marital Status and Race on Outcomes of Patients Enrolled in Radiation Therapy Oncology Group Prostate Cancer Trials*, was submitted to the International Journal of Radiation Oncology, Biology, Physics (IJROBP), rejected, revised, and resubmitted in June, 2010, to the Journal of Supportive Care in Cancer. It is still under review.

The manuscript detailing the procedures and conclusions of the above referenced focus groups is under preparation.

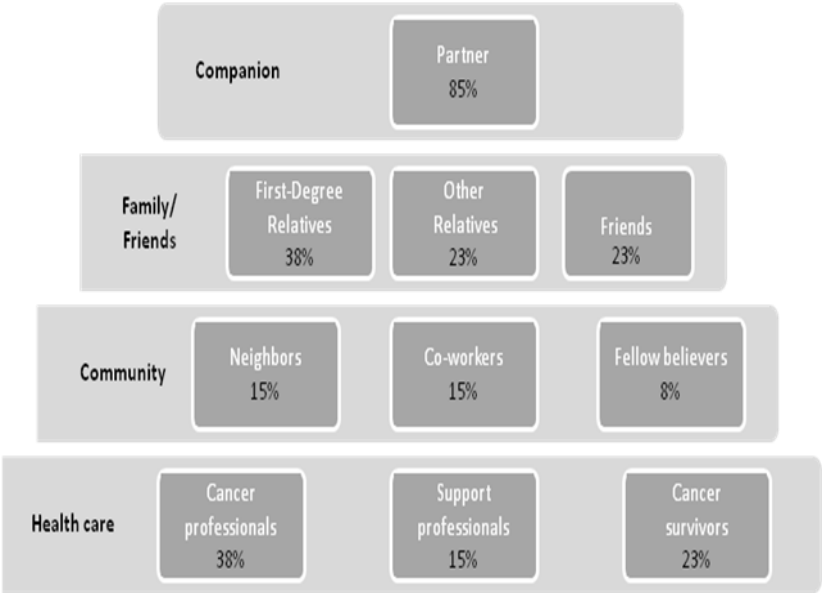
Table 1: Challenges for patients during treatment for head and neck cancers

Patient challenges
Receiving correct diagnosis *"I had a swelling on my neck, went to my local family doctor, who thought it was everything but cancer." "I had a problem with an ENT, too, that I had been going to for years. And I went to him with a huge lump, and to my surprise, he treated it nonchalantly like, 'Go home and come back in a month.' After a month he still acted like, 'It is nothing. Do not worry about it.'"*
Accepting diagnosis/treatment *"My biggest challenge was admitting that I had cancer." "I couldn't get rid of the idea of 'Why me?'"*
Making decisions related to treatment *"Is it worth it to go through this [treatment] and have it be a waste of time?" "There's no clear process for sitting down and having a discussion and coming up with a treatment plan."*
Insufficient Information *"[Providers] have the results within hours after the scan's done. And most of them, they do not give you the results for a week or two." "But after [treatment] there was no communication it seemed. There was no kind of followup after that. Even though there was, it was just…it was too, too far apart. You didn't really know what to do."*
Obstacles of medical appointments *"I was so sick that I missed [an appointment]." "I asked them, could you all please put them all in one day, but nope."*
Undergoing radiotherapy *"The first day they put the mask on me, when they put me down, I had a panic attack." "There's trouble breathing because phlegm accumulates."*
Percutaneous endoscopic gastrostomy (PEG) tube *"The PEG tube is the most emotionally debilitating part of the whole thing. It makes you feel like an invalid." "It should be disclosed that when they pull your friggin Peg tube out, it hurts so bad."*
Special treatment needs *"Before they could treat my cancer they had to fix other problems in my body. So for me I went through four surgeries and nine procedures in six weeks."*
Specific adverse events *"I was just so nauseous." "Because the radiation was so intense, I got second degree burns on my neck and my mouth and all. I had a lot of pain."*
General treatment-related malaise *"The chemo just about killed me." "[Radiation] just sucks every bit of strength out of your body."*
Interpersonal difficulties *"I would have to say that the worst time through the whole experience was just that initial five minutes of having to call my wife and tell her." "I'm worried about what am I going to do with my son and my daughter and my mother. I mean, she…I still go over there and make sure they're all right because they are old."*
Employment/Financial difficulties *"I want to come back to work. I need…I got…I'm trying to get my son to go through college."*

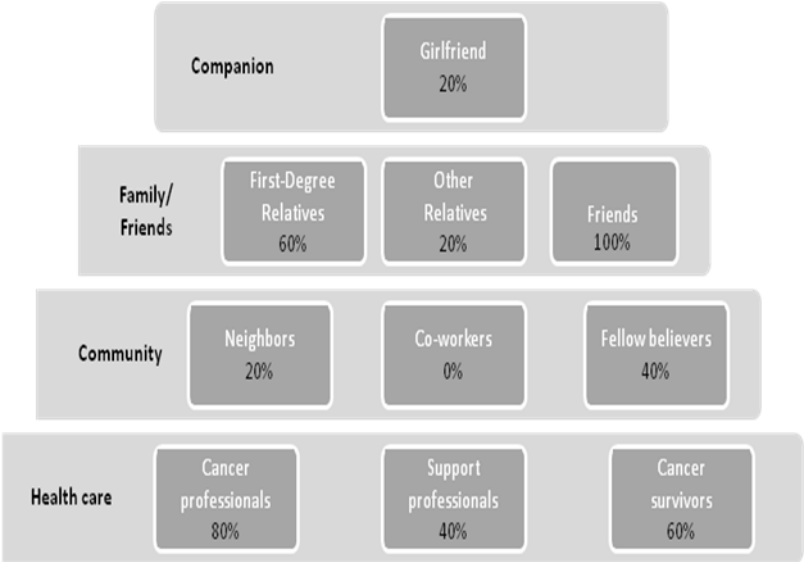
Table 2: Perspectives and reactions of head and neck cancer patients

Perspectives and reactions
Perceived support as beneficial
"It is so important when everybody is supportive and you have somebody there with you." "Having my friend stay with me was…it was nice." "[My daughter] was there making sure I made all my appointments*."*
Perceived support as not always essential
"I told my family, don't tell anybody that I had this cancer. I says I can't stand people coming up and saying, 'Oh, how do you feel?' I says I don't want to hear that. I don't want support." "I was happy for the support I have had, but had I had none, I would have done the same thing. I mean what are the choices? I mean I'm not going to die just because nobody cares to support me." "[I did not] want to burden other people as much as possible. So for me a lot of it I tried to do on my own, but I've always been that way*.'"*
Pursued diagnosis
"I kept telling [the physician] when I went there, I kept having sore throats. And I'm like, 'Look, I know something's wrong.' And you know what? It took me to go to the emergency ward for them to really sit up."
Pursued treatment
"I was in the car five hours a day to get my treatment. … I made a point out of making that drive. It was not easy. There were times I was tired. But I did it."
Solved problems
"[The end of treatment] was a little bit abrupt, but [Participant G] picked up weight lifting. I picked up something else and I'm sure everybody else tried to do something." "I perceived that I couldn't have long conversations with my doctors but I made friends with their support staff. The nurses … do take the time and explain."
Maintained lifestyle
"I worked through all 33 of my treatments."
Positive outcomes from cancer experience
"I've gotten closer and appreciate my wife a hell of a lot more after this." "Do you know what's great about cancer? It strips your veneers away." "[Cancer] just made me…it kind of made me stronger, you know. It made me like a lot stronger and mentally stronger."

Figure 1: Patient-reported sources of support during cancer treatment



a. Men with partners (N = 13)



b. Men without partners (N =5)

Research Project 3: Project Title and Purpose

Translational Studies on Eliciting Effective Immune Responses to Pancreatic Carcinoma - The development of multiple forms of cancer including pancreatic carcinoma may be prevented by maintaining effective immune surveillance mechanisms or by eliciting immune responses to tumor cells with therapeutic intent. Two molecules which are produced by pancreatic tumor cell that may induce ineffective anti-tumor immune responses have been identified; these are interleukin-10 (IL-10) and transforming growth factor-β (TGF-β). This project explores new strategies to block inappropriate production of IL-10 and TGF-β. These studies originally focused on using drugs (EGFR/ErbB2 and STAT3 antagonists), which are already either in preclinical or clinical studies in various tumor forms including pancreatic carcinoma. Due to negative results obtained in the course of this work we have refocused our efforts on the development of more effective ways to enable immunologically-mediated, antibody-directed tumor cell destruction using engineered anti-EGFR antibodies.

Duration of Project

7/1/2007 - 12/31/2010

Project Overview

Previous work has implicated aberrant activation of the epidermal growth factor receptor (EGFR) and the related ErbB2 receptor in progression of pancreatic cancer. Similarly, deregulated STAT3 signaling has previously been described in this tumor form. In addition, EGFR/ErbB2 signaling has been found to contribute to STAT3 activation in pancreatic cancer cell lines. These molecular aberrations have primarily been viewed as mechanisms by which pancreatic cancer cells achieve apoptosis resistance and acquire growth potential.

However, recent work in T cell lymphomas has highlighted a novel role of STAT3 activation in regulating the production of immunomodulatory cytokines by tumor cells, specifically, TGF-β and IL-10. In preliminary work the principal investigator (PI) of this project demonstrated aberrant production of TGF-β and IL-10 by pancreatic tumor cells *in vitro* and in patients. Furthermore, these tumor-derived cytokines appear to skew the immune response in pancreatic cancer patients to respond ineffectively to the tumor challenge. Specifically, the PI demonstrated previously that tumor-derived TGF-β and IL-10 induce a DC2/Th2 immune phenotype.

Collectively, these findings raised several important questions: (1) Does aberrant STAT3 activation in pancreatic cancer cells contribute to IL-10/TGF-β production? (2) What is the role of EGFR/ErbB2 signaling in STAT3 activation in pancreatic carcinoma? (3) Can EGFR/ErbB2/STAT3 blockade be used to reset ineffective immune responses to pancreatic tumor cells?

We determined that the EGFR/ErbB2/STAT3 signaling axis does not significantly contribute to production of IL-10 and/or TGF-β , at least not in a panel of pancreatic carcinoma cell lines cultured in vitro. Thus, having refuted the main hypothesis of our original application and as outlined in detail in the last progress report we switched our focus towards developing EGFR

antagonistic antibody derivatives with improved therapeutic efficacy. This was within the purview of translational studies to elicit effective immune mechanisms with anti-tumor properties. Specifically, we set out to test a novel concept to molecularly 'mask' clinically proven monoclonal antibodies recognizing the EGFR such that they preferentially recognize antigen at disease (tumor) sites but not in normal tissues. This would lead to a very favorable therapeutic index of these agents compared to monoclonal antibodies currently in use in tumor therapy. As outlined above the EGFR is a molecular target frequently expressed or overexpressed in pancreatic carcinoma.

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Expected Research Outcomes and Benefits

Pancreatic cancer constitutes a deadly tumor form which, at the time of diagnosis, is largely refractory to conventional treatments. As in many epithelial cancers the EGFR has been implicated in the pathogenesis of pancreatic cancer and EGFR inhibitors have been used in the clinical management of pancreatic cancer. However, the use of EGFR inhibitors in the clinic is limited by adverse side effects, primarily affecting the skin and the gastrointestinal system. This circumstance prompted us to develop a new concept to target EGFR antagonistic antibodies to disease sites while avoiding binding to normal tissues under homeostatic conditions. Proving this concept has the potential to not only design better EGFR antagonistic antibodies but to improve a host of other monoclonal antibodies currently in clinical use as well.

Summary of Research Completed

In the last funding period of this project we focused on producing full recombinant antibodies (see below) amenable to testing the reversible masking principle in mice.

To this end we embarked on production of recombinant C225/cetuximab containing a masking N-terminal extension in NSO hybridoma cells. This was necessary to establish a stable source of antibodies for in vivo studies in mice. The work entailed DNA synthesis for light and heavy IgG (C225) chains with a cleavable N-terminal extension encoding EGFRdIII, cloning into expression constructs, transfection into NSO cells and extensive screening of NSO cells expressing the transgenes effectively and in a manner that leads to assembly of a functional IgG

consisting of heavy and light chains. Approximately ten different NSO variants expressing high levels of recombinant antibody were generated and we are ready to test binding of these cetuximab variants to MDA-MB-468 target cells by FACS analysis.

In addition, we have prepared a large batch of cross-masked 425/C225 scFvs and have used them to explore the utility of crossmasked antibodies in imaging approaches using MDA-MB-468 xenografts in nude mice. This work has led to one publication in press and another publication in preparation. Although not directly relevant to tumor therapy, application of masked antibody constructs in imaging approaches demonstrates the versatility and practical value of the work supported through this grant. It further may be extended to use antibody derivatives binding specifically to tumor cells to more specifically target cytotoxic drugs to tumor sites.

In summary, at the conclusion of this project we have made significant progress in developing a novel approach to enhance antibody-mediated tumor cell recognition and, potentially, destruction. This approach can be applied to pancreatic cancer as well as to other neoplasm characterized by aberrant EGFR expression and/or regulation.

Research Project 4: Project Title and Purpose

Correlating Tumor Markers/Genes with Clinical Outcome - The vast RTOG clinical trials database offers extensive opportunities to explore associations between correlative data, such as tumor marker analysis, and patient outcome data. The purpose of this project is to perform translational research analyses that are not specified in the clinical trial protocol. The project will correlate translational data with clinical outcome and interpret the results for RTOG-run protocols for patients with brain tumors, sarcoma, pancreatic cancer, cervical cancer and head & neck cancer.

Duration of Project

71/2007 - 12/31/2010

Project Overview

The broad objectives of this research proposal are to (i) generate hypotheses that may lead to more efficient clinical trials and more patient-targeted treatments, and (ii) to add to the literature regarding correlations between tumor markers/genes and clinical outcomes. Specifically, clinical outcomes such as survival and disease progression will be correlated with the presence or absence of specific tumor markers/genes for patients treated for brain tumors, sarcoma, pancreatic cancer, cervical cancer, and head & neck cancer. Separate funding from several sources has been awarded to RTOG investigators to do tumor marker/gene biologic analyses in the aforementioned disease sites. After the tissue is analyzed, the resulting data is sent to and stored at RTOG headquarters in Philadelphia. The clinical trials have all completed patient accrual and their protocol specified primary endpoints reported. For this project, the marker/gene data will be combined with the clinical outcome data, analyzed and reported.

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Expected Research Outcomes and Benefits

The identification of specific tumor markers/genes associated with better or worse outcome for cancer patients may allow future researchers to generate new hypotheses that may potentially lead to more efficient clinical trials that assign patient treatment based on the patient's tumor marker/genetic profile. In addition to aiding in the conduct of clinical trials, this type of research may help to tailor treatments to individual patients based on their genetic make-up. The combination of tumor marker data with RTOG's clinical outcome database is an extensive source for exploring these possible associations.

Summary of Research Completed

During the final period of the grant, three analyses were completed and presented/accepted for presentation:

The first analysis focused on confirming a previously observed association between a DNA repair gene and clinical outcome of resectable pancreatic cancer patients treated with preoperative chemoradiation is reproducible using the RTOG Phase III trial 9704. RecQ1 A159C variant (rs13035) was evaluated in patients with resected pancreatic cancer who were enrolled on the RTOG 9704 trial of 5FU-based chemoradiation preceded and followed by 5-FU or gemcitabine. DNA was extracted from paraffin-embedded tissue sections and genotype was determined using the Taqman method. A multivariate Cox proportional hazards model was used to evaluate for a correlation between genotype and overall survival (OS). Models were built using the stepwise selection procedure. The following variables were included in the model: genotype, treatment arm, age, gender, race, nodal involvement, tumor diameter, and surgical margin status. The genotype distribution followed the Hardy-Weinberg Equilibrium, i.e. 37% had genotype AA, 43% AC, and 20% CC. The RecQ1 variant AC/CC genotype carriers were more likely to be node positive compared to the AA carrier (p=0.03). The median survival times (95% C.I.) for AA, AC, and CC carriers were 1.72 (1.36, 2.17), 1.57 (1.18, 1.80), and 1.18 (0.86, 1.75) years, respectively. On multivariate analysis, patients with the AC/CC genotypes were more likely to die than patients with AA genotype (HR=1.54, 95% C.I. = [1.07, 2.23], p=0.022). This effect is more definitive for patients on the 5-FU arm (n=82) (HR=1.64, 95% C.I. = [0.99,

2.70], p=0.055) than for patients on the gemcitabine arm (n=72, HR=1.46, 95% C.I. = [0.81, 2.63], p=0.21). The results of this analysis suggest that the RecQ1 A159C genotype is associated with OS for resectable pancreatic cancer patients who are treated with adjuvant chemoradiation.

Accepted for presentation at the 2011 ASCO GI Symposium.

The second analysis focused on evaluating KRAS expression in patients with endometrial adenocarcinoma enrolled in RTOG 9708 and 9905. Adjuvant treatment included pelvic radiotherapy, vaginal brachytherapy +/- cisplatin and paclitaxel. DNA was isolated from tissue blocks (DNeasy kit) and the presence of the KRAS-variant was detected using a TaqMan PCR assay to identify the wildtype (T) or variant (G) allele. Clinical and treatment characteristics were compared by allele type. Actuarial estimates of overall survival (OS) and disease-free survival (DFS) were calculated by the Kaplan-Meier method; and rates of local-regional failure (LRF) and distant failure (DF) by the cumulative incidence method. Univariate analysis was performed by Cox proportional hazards model. Estimated prevalence rates for the variant allele were used for power calculations.

KRAS-variant data was obtained in 53% of evaluable patients. The variant allele was identified in 22% of those. Median follow-up for patients with allele data was 29.3 months (min-max, 6.8-124.1). Clinical characteristics were: FIGO IB-IIB (70%) and IIIA/IIIC (30%), FIGO grade 3 (46%), >50% MMI (85%), and chemotherapy (72%), which did not differ significantly by allele type. The 3-year OS rates for the variant and wildtype allele were 100% and 77% (HR 0.3, p=0.24), and corresponding DFS rates were 61% and 60% (HR 0.58, p=0.39). Among the 10 patients with the KRAS-variant, 1 (10%) had LRF and 2 (20%) had DF, compared to 7 (19%) and 13 (36%) with the wildtype allele. The hazard ratios for LRF and DF were 0.45 (p=0.45) and 0.44 (p=0.28) for variant carriers. With a prevalence rate of 20% for the KRAS-variant, the analysis had limited power to detect a significant difference in clinical endpoints. This study represents a preliminary analysis of the prognostic value of the KRAS-variant in patients with endometrial adenocarcinoma. While the KRAS-variant was not significantly associated with disease recurrence or survival, the hazard ratio point estimates were less than 0.6 for all clinical endpoints, favoring the variant. A larger study with longer follow-up will be required to adequately power and detect an association with clinical outcome.

Presented at the 2010 ASTRO annual meeting and the manuscript is in process.

The third analysis focused on CA19-9 expression using the long-term efficacy results of RTOG 9704, which was the largest randomized trial utilizing adjuvant chemoradiation (CRT) therapy for patients with resected pancreatic cancer (PC). In this trial, all patients received 5-FU CRT with adjuvant 5-FU vs. Gemcitabine (Gem). The 5-year survival results were analyzed according to CA19-9 ≤ 90 vs. >90 and compared it to 5-year results reported for the CONKO-001 trial (adjuvant Gem alone). Cox proportional hazard models were utilized to identify the impact of CA 19-9 value on overall survival (OS). The following variables were included in the multivariate analyses: treatment, tumor stage, nodal involvement, tumor diameter, margin status, and RT quality assurance (QA) score (per protocol vs. < per protocol). Actuarial estimates of OS were calculated using the Kaplan-Meier method. Of the study patients analyzable for CA19-9, 86% had baseline CA19-9 ≤ 90, while 14% had values >90. Both univariate (HR = 3.2 (95% CI

= 2.32-4.29) $p < 0.0001$) and multivariate (HR = 3.1 (95% CI = 2.24-4.17) $p < 0.0001$) analyses demonstrated a highly statistically significant decrease in OS for CA19-9 >90. For patients treated on the Gem arm with a CA19-9 ≤ 90, the median survival was 21 months with 5-year survival of 24% (95% CI = 17%-30%). For patients with CA19-9 >90, these numbers drop dramatically to 10 months and 4% (95% CI = 0.3%-18%). In patients on the Gem arm with radiation therapy quality assurance per protocol, previously reported to be associated with better survival, median and 5-year survivals were 23 months and 32% (95% CI = 22%-43%) for those with CA19-9 ≤ 90. In comparison, the median and 5-year OS for patients in the Gem arm of CONKO were 22.8 months and 21%. This is despite 35% of patients with CA19-9 ≤ 90 in the RTOG trial having a known R1 resection which is twice that seen in the CONKO trial. Finally, for patients with pancreatic head tumors with CA 19-9 ≤ 90, and treated with Gem, the median and 5 year survivals are 22 months and 25% (95% CI = 18%-32%), respectively. This analysis demonstrates, with long-term follow-up, that patients with post-resection CA 19-9 values > 90 have a significantly worse survival. CA 19-9 is a stratification factor for the current RTOG Phase III adjuvant pancreas trial.

Presented at the 2010 ASTRO annual meeting and the manuscript is in process.

Research Project 5: Project Title and Purpose

Emerging Imaging Technology Clinical Trials in PA - This project represents the continued development of a clinical trials research network (developed under the 2004 C.U.R.E.formula funding) which will perform early stage imaging studies at selected Pennsylvania academic medical centers to advance the role of imaging in the detection and/or treatment of disease. Participants of the network will conduct a clinical trial to evaluate the role of Positron Emission Tomography (PET) and the classification ability of two novel imaging compounds to distinguish Alzheimer's disease from cognitively normal subjects. The conduct of this specific trial will extend the study design work previously funded through the 2005 C.U.R.E. formula grant.

Duration of Project

7/1/2007 - 12/31/2010

Project Overview

The broad objective is to foster the work of a network of academic medical centers in Pennsylvania to perform imaging studies of early phase technology at academic medical centers in Pennsylvania. The American College of Radiology Imaging Network – Pennsylvania (ACRIN PA) presently consists of the University of Pennsylvania, University of Pittsburgh, Hershey Medical Center, Thomas Jefferson University and Fox Chase Cancer Center. The broader initiative seeks to conduct research in three targeted areas: 1) osteoarthritis; 2) cancer; and 3) neurodegenerative disease.

This particular project will focus on a neurodegenerative disease clinical trial originally envisioned as part of the 2005 FY funding. The study design work will be completed with the

2005 FY funding while the actual conduct of a clinical trial will require support from the 2006 FY funding.

The specific aim consists of the conduct of a clinical trial to determine the ability of two novel imaging agents, which target amyloid plaques in Alzheimer's disease patients, to be used for early diagnosis of Alzheimer's disease and/or to monitor the effectiveness of drug treatments targeted at Alzheimer's disease. The proposed trial will compare the quantification of amyloid plaques in Alzheimer's patients using imaging agents developed at the University of Pennsylvania and the University of Pittsburgh in a population of approximately 60 patients to be recruited at those sites. In addition to images collected on these subjects, the study will collect EKG, vital signs, and blood chemistry values to validate that these agents do not produce a pharmacological effect on the body.

Principal Investigator

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Other Participating Researchers

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Expected Research Outcomes and Benefits

Through the funding received under the Emerging Imaging Technology Clinical Trials in PA: Part III, the ACRIN PA network will continue to foster multi-institutional clinical trials which allow Pennsylvania laboratories to have their work on new technologies quickly validated in a dedicated multicenter setting, providing them with a competitive advantage over similar work performed at other centers across the world. The network itself could then become an attractive target for pharmaceutical companies initiating additional early phase trials of drugs targeted at arthritis, cancer, and neurodegenerative disease.

The neurodegenerative disease clinical trial described in this project will use novel imaging agents to enable the imaging of proteins associated with Alzheimer's disease (amyloid plaque). If proven effective, these agents will enable early clinical diagnosis (and therefore treatment) of Alzheimer's disease as well as provide an important method for quantifying the extent of disease and, in turn, support more advanced research in determining the effectiveness of new drugs for this debilitating condition.

Summary of Research Completed

Subject Enrollment – as of December 31, 2010

The total enrollment goal for the Alzheimer's trials (ACRIN PA 4003-4004) is 30 subjects at each site; 15 controls and 15 with Alzheimer's disease (AD). The 4003 trial is conducted at the University of Pennsylvania; the 4004 study at the University of Pittsburgh. Table I details total enrollment.

The University of Pennsylvania cyclotron was inoperative for more than 10 weeks between August and November. The 4003 trial continued to accrue through December, 2010 in an effort to make up for the time in which the cyclotron was undergoing upgrades. The total accrual figure of 32 subjects reflects replacements needed when subjects withdrew from the trial. The database lock for 4003 is delayed into January pending the completion of the quantitative image analysis by an external contract research organization (CRO).

The 4004 trial enrollment closed to enrollment in September when their cyclotron was shut down. This unfortunate event prevented the site from achieving full accrual. The total accrual figure was 24. This allowed data querying and preliminary analysis to begin in October. All outstanding quantitative and *qualitative* image analyses were completed during the reporting period. Per protocol design, the quantitative image analysis was reported as standardized uptake value assessed in eight regions of the brain. The qualitative image analysis consisted of a visual interpretation of the two PET scans (per patient) by two experts blinded to the patient diagnosis. A training session was held prior to the reading sessions to ensure consistency in the approach by the two readers. The qualitative data was added to the database in December and the 4004 database lock procedure commenced. The statistical analysis was prepared and iterated among the study team.

Table I: Study enrollment

Institution	Normal Participants	Alzheimer's Participants	Total Accrual
Hospital of the University of Pennsylvania (4003)	18	14	32*
University of Pittsburgh Medical Center (4004)	15	9	24
TOTAL	27	19	56

* 4003 study: 3 subjects withdrew so total definitive enrollment equal to 29 subjects.

Results

An abstract was prepared and submitted to the Society of Nuclear Medicine for their annual meeting in June, 2011 and is included below.

ACRIN-PA 4004 Study: Comparison of [F-18] flutemetamol and [C-11] PiB in Normal Control and Alzheimer's Subjects

Mountz JM, Zhang Z, Laymon C, Price J, Boudhar S, Newberg A, Mathis CA

Introduction:
This single center study is designed to evaluate the performance characteristics of [^{18}F] flutemetamol (flute) with respect to its ability to distinguish patients with clinically-diagnosed probable Alzheimer's disease (AD) from cognitively normal elderly (NL) subjects and to independently compare its results to [^{11}C] Pittsburgh Compound B (PiB) in the same subjects.

Methods:
Twenty-three of the 24 accrued subjects (15 NL (71±8.4 years old) and 8 AD (75±10.0 years old)) underwent two PET scans using either PiB or flute with ≥120 min between scans. ROC analysis (AUC) was used to determine whether global cortical (anterior and posterior cingulate, and frontal, parietal, lateral temporal cortex) SUVR levels distinguished AD from NL subjects. Cohort flute and PiB global SUVR measures were compared using the two-sample t test. Blinded visual reads were conducted by two experienced raters interpreting global tracer uptake on scale of 1 to 5 (low to high). Averaged results from the raters were correlated with global SUVR measures by Pearson correlation coefficient (r).

Results:
Global SUVR levels produced AUC values of 0.77(95% CI: 0.54 to 1.00) for flute and 0.78(95% CI: 0.53 to 1.00) for PiB. Global SUVR levels in AD subjects trended higher than the levels found in NL subjects (P=0.042 for flute and 0.054 for PiB by t test). The average visual reads were significantly correlated with global SUVR values in all subjects (flute r=0.80, P<0.0001; PiB r=0.78, P<0.0001).

Conclusions:
The uptake of flute and PiB can be used to classify AD versus NL subjects. Both compounds performed similarly. AUC values increase to 0.90 and 0.89 for flute and PiB, respectively by excluding amyloid-positive NL subjects (6/15) in the ROC analyses, highlighting high specificity of flute and PiB for amyloid detection and not the diagnosis of AD. Visual reads of both compounds provided similar outcome measures indicating a close correspondence of the in vivo properties of flute and PiB.