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Biospecimens: Challenges and Solutions in Clinical Cancer Research

This article contains excerpts of the talks given at the Plenary Session of the Fall Group Meeting 2005 in Amelia Island. The plenary session was planned and organized by Deborah Collyar, Chair of the Committee on Advocacy, Research Communications and Ethics and Sandra Batte, Co-Chair, Patient Advocacy Subcommittee.

A panel of experts presented information on biospecimens including: regulatory issues, ethical implications of consent, collection, storage and use, as well as a patient's perspective.

Carolyn Compton: Director, Office of Biorepositories and Biospecimen Research, National Cancer Institutes

Biospecimen quality has been identified as the number one road block to curing cancer. Cancer overtook heart disease this year as the number one cause of mortality in America. The availability of human biospecimens is the key to translational research and the future of cancer medicine.

The overarching goal of the NCI as iterated by its current director, Dr. Andrew von Eschenbach is that the NCI will strive to eliminate the suffering and death due to cancer by 2015. This doesn't mean we're going to cure cancer in the conventional sense. It means we're striving to eliminate the death due to this disease, to turn it into a chronic illness people can live with or prevent altogether.

The number one roadblock to our progress, as defined at the think tank *Dialogues on Cancer (2002)*, is the lack of availability of high quality, highly characterized human specimens for translational research.

Molecular data are available on an unprecedented scale, along with clinical data from groups such as the CALGB.

High quality biospecimens and data appended to them are needed in order



to apply the huge amounts of molecular and clinical data we now generate. They are needed to identify and validate new molecular targets. They are needed to support the development of targeted drugs; to rapidly identify new uses for existing target drugs; and to accelerate the era of personal medicine wherein we will treat patients' individual tumors by their molecular signatures.

Reproducibility is the mantra of good science. The enemy of reproducibility is variation. Human analytes are as variable as human beings themselves. Varying methods of collection, processing, storage and analyses that specimens undergo may alter the physical/biologic state of the specimens. The amount of variability can be staggering. However, the analytic platforms we use to analyze them are becoming more sensitive and specific. This has raised the bar for biospecimen quality.

Biospecimen quality is defined not only by the physical quality of the specimen and the physical integrity of the biomolecules within it, but is also defined by the quality of the associated data that gives us the power to translate this into something clinically meaningful. Quality also depends on the rigor of quality control exercised in the entire process of gathering the materials and distributing them to investigators. Ethical,

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MESSAGE FROM THE GROUP CHAIR



Richard L. Schilsky, MD

The First CALGB Protocol

Dick Silver, a founding member of CALGB, former Group vice chairman and former principal investigator for Weill Medical College-New York Hospital, recently sent me a copy of the first CALGB protocol. As a fellow at the National Cancer Institute in the mid-1950s, Dick claims to have personally typed the protocol (CALGB 5601), as neither Tom Frei nor Jim Holland knew how to type! We will have this historic document on display at the June 2006 CALGB Group meeting when we celebrate the 50th anniversary of CALGB. The protocol is remarkable both for what is included as well as for what is lacking. The entire protocol document is 8 pages and described a collaborative effort among 3 institutions: the National Cancer Institute (Frei and Silver), Roswell Park Memorial Institute (Holland) and the Children's Hospital in Buffalo, NY (Selkirk). The study was a comparative trial of continuous versus intermittent methotrexate and 6-mercaptopurine for treatment of acute leukemia. Remarkably, this first multi-center cancer clinical trial included clearly stated eligibility and exclusion criteria, required pre-study tests, a description of the treatment plan, and a plan for randomization, as well as provisions for central morphology review, a description of anticipated toxicities, recommended supportive care measures (steroids, transfusions and antibiotics) and, importantly, detailed criteria for response evaluation. The protocol was intended for all patients with all forms of acute leukemia, both newly diagnosed and relapsed, so the eligibility criteria were essentially limited to the following requirement, "An unequivocal diagnosis of acute leukemia...". Patients were stratified by type of acute leukemia, age, history of prior therapy, and duration of prior therapy resulting in 28 possible strata and, within each stratum, new patients were randomized, "using a sealed envelope technique", to continuous or intermittent therapy with methotrexate (the variable) and 6-mercaptopurine (given at a fixed dose daily). Patients received therapy for 35 days followed by the same drugs given at twice the dose for another 35 days unless toxicity prevented dosage escalation. The protocol schema¹ is shown at left. Complete remission was prospectively defined as <10% leukemic blasts in the bone marrow, hemoglobin > 11g/dL with normal WBC and platelet counts, no evidence or

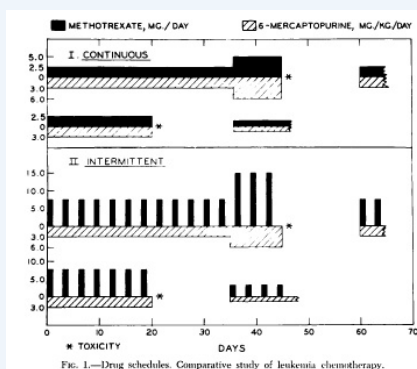


FIG. 1.—Drug schedules. Comparative study of leukemia chemotherapy.

organ infiltration by leukemia on physical examination and no symptoms that could be ascribed to leukemia. Notably, the protocol contained no background section to justify the research plan, no formal statistical section, no section on adverse event reporting and no model informed consent document. Eighty-four patients were enrolled in the study and 65 received the protocol-specified treatment. The study results, published in the December 1, 1958 issue of *Blood*, demonstrated no difference in the frequency of remission for the two treatment programs but significantly longer survival for the continuous treatment (see Figure 2 right). Principal causes of treatment-related death were hemorrhage and infection. The study provided much

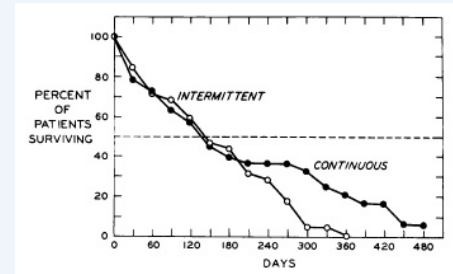


FIG. 2.—Duration of survival from start of combined therapy.

additional information of value including an analysis of the impact of age, type of leukemia and prior therapy on treatment outcomes. The Discussion section of the paper began, "This work is one of the first comparative studies in the chemotherapy of malignant neoplastic disease." In addition to comments on the study results, the Discussion also described the complex logistics of "...a cooperative study conducted in different places by several individuals..." and noted that "these factors should not be overlooked in the budgetary planning of cooperative clinical trials."

In his letter to me, Dick Silver noted that this protocol launched his career. Indeed, I think it is fair to say that this protocol launched the careers of thousands of investigators who have participated in CALGB studies since 1956. CALGB 5601 provided the foundation of multi-center clinical trials that remains in place today. Eligibility criteria, toxicity grading, response criteria, uniform data collection tools, and quality assurance measures can all trace their origins to this 8-page document. To a great extent, the early history of CALGB is the history of cancer chemotherapy and is wonderfully recounted in a lecture given by Jim Holland in the mid-1990s that has been preserved as a digital recording and will be shown at our next Group meeting. The founders of our Group were the pioneers who forged the discipline of medical oncology, demonstrated that drugs could be used to cure advanced cancer, developed the principles of contemporary multidisciplinary cancer treatment and recognized that successful cancer treatment must focus on the patient as well as on the disease. For more information about the history of CALGB please refer to my column in the Winter 2005 edition of the *CALGaB*. I look forward to seeing all CALGB members in June for our gala celebration.

1. A Comparative Study of Two Regimens of Combination Chemotherapy in Acute Leukemia

Frei EF, Holland JF, Schneiderman MA, Pinkel D, Selkirk G, Freireich EJ, Silver RT, Gold L, Regelson W *Blood* 13:1126-1148, 1958

CALGB Tag Line Contest

Many successful ventures like the CALGB have tag lines that accompany their logo to further illustrate the purpose or mission of the organization. We would like to pair such a tag line with the CALGB logo to commemorate CALGB's 50th Anniversary. The tag line for CALGB will ideally incorporate aspects of excellence in both research and patient care, as well as show what sets us apart. All this and yet a good tag line needs to be short and snappy. For example, *Making Cancer History* is the tag line for MD Anderson Cancer Center.

Ethics in Clinical Research - Getting it Right!

The Ethics Subcommittee of the Committee on Advocacy, Research Communications and Ethics (CARE) has developed a PowerPoint Presentation for use by CALGB members at their institutions. The presentation is now available to download from the CALGB web site at http://www.calgb.org/Private/COOP_Groups/CALGB/resources/care/care_resources.php. The presentation is intended to increase awareness about the safeguards in place to protect participants in clinical trials; the presentation includes some history of the development of these protections. Ethics in Clinical Research - Getting it Right is appropriate for physicians, nurses, clinical research associates, and other clinical staff. The presentation has been used for grand rounds and as in-service training in hospital departments and private practices. There are notes with the slides to assist presenters. Several slides can be customized with information specific to the presenting location. An evaluation form is also available on the web site. The presentation is based on material from a training module sponsored by the Coalition of Cancer Cooperative Groups. These slides offer material for CALGB members to promote clinical trial accrual as well as food-for-thought on ethical considerations.

A sample slide from the presentation



Please think about words that will best represent CALGB and our accomplishments. Brain storm with your colleagues and share your suggestions with the 50th Anniversary Program Committee. Tag line submissions will be reviewed by the committee and Dr. Schilsky. The best three will be posted on the web site for voting by our membership to determine the winner.

Send tag lines for consideration to taglinecontest@calgb.org by January 13th, 2005.

New Central Office Employee

Aaron Pinsley has been hired as the Network Administrator for the Central Office. Aaron came to us from Sytel Inc., an NIH contractor where he was a MacIntosh Lead Programmer. He earned his Bachelor of Arts degree in Political Science at the University of Michigan. A native of New Jersey, Aaron now lives in the Wicker Park neighborhood of Chicago. He enjoys skiing, foreign films, and jazz.

New Statistical Center Employees

Rob McAllister has joined the Information Systems team at the Statistical Center as an IT Analyst. Rob studied at the University of Illinois at Urbana-Champaign and received a Bachelor of Science degree in Mathematics and Computer Science. Prior to joining the CALGB he worked for Railinc as a software engineer. Rob is married, and has two sons. He volunteers as a Cub Scout den leader, likes to juggle, see movies and solve mechanical puzzles.

Amish Shah has also joined the Information Systems team at the Statistical Center as Manager of Software Development. His role will be to manage applications and software development. Amish holds a Bachelor's degree in Business Information Systems from Shippensburg University. His expertise is in the areas of software architecture, database design, and visual data analysis. Amish lives in North Carolina with his wife and daughter. He enjoys hockey, skiing, national parks, and motor sports.

New Institutional PIs

Joanne Mortimer has been named as the Principal Investigator for the University of California at San Diego.

William Walsh has been named as the Principal Investigator for the University of Massachusetts. Medical Center

The CAL•GaB is published by the Cancer and Leukemia Group B and is distributed to the CALGB active membership via the web site. Contributions for the Winter 2006 issue are due January 25, 2006. Suggestions for articles are encouraged.

Articles and correspondence should be directed to: Anne Battershell, CALGB Publications Coordinator at: abatters@uchicago.edu

BIOSPECIMENS CHALLENGES AND SOLUTIONS CONT

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legal and policy issues that govern specimen use must also be considered. Even with the world's best platinum-grade biospecimens at hand, the lack of proper consent would preclude using them in research.

Research is our road to personalized medicine and research is dependent on biospecimens. Despite this, there are as yet no uniformly applied standards for the elements needed to define quality in these specimens. We're all striving to find out what the real biologic differences in tumors are. If we don't standardize the analytes, we will never know for sure if we are studying the biology of tumors or an artifact.

We must develop standards that define the best way to preserve biospecimens, but we currently lack the necessary data to make these standards evidence-based. Most standard operating procedures now are based on empirical evidence from the the expertise of people who have been doing this for a long time.

CALGB has taken a leadership position in standardization within our PCO. Within the Group Banking Committee, we are starting out with empirical, but at least uniform, standard operating procedures.

We are working to achieve the goal of purely data-driven standard operating procedures so we may make the leap from basic research to differences in health care outcomes. To reach this goal, we need solid reproducible high quality data at every level. Better science with trustworthy analytes, greater reproducibility, efficacy, speed and applicability will lead to better cancer medicine.

**Steve Joffe: Hospital Ethicist/Pediatric Oncologist,
Dana Farber Cancer Institute**

With biospecimen/stored tissue research comes information, either from querying the tissue itself or from the clinical chart. In theory, such information has the potential to affect aspects of the participant's life, including insurability or employability, or the information may simply cause embarrassment to research participants.

Although this theory has been claimed, there is very little evidence that this is a real and serious problem in the United States today. That said, investigators do have an obligation to minimize these information risks so they don't become an issue for the study participant in the future. Risks should be "minimal" as defined in the federal regulations and are equated to ordinary risks of every day life.

The regulations charge researchers to do everything that is reasonably in our power to make the risks as low as they can be.

When we explicitly set out to collect additional tissue for research purposes alone, how much physical risk can we justify? A consideration is the degree of risk that comes from the particular procedure required. One more aspirate from the same bone marrow needle might be looked at very differently than an additional liver biopsy not clinically indicated. Another is the strength of the scientific

rationale for collecting additional tissue. The stronger the scientific rationale for collecting the tissue, the stronger the hypothesis, the better the planned analysis, the more justified we are in seeking additional tissue.

How relevant to the primary or secondary objectives of the parent study are the questions being asked of the tissue? Ethically it is important to take this into account when deciding whether participation in this extra biopsy or this extra specimen collection will be an optional or required part of the protocol.

Issues of privacy and confidentiality often come up. Many people are unclear on the distinction between privacy and confidentiality. Privacy is: don't look for information that you're not entitled to have, and confidentiality is: when you are entrusted with information, don't share it inappropriately or beyond your initial authorization.

Research participants have the right to expect that medical information and personal information acquired in the course of research will remain private and confidential. Ordinarily, participant consent is needed to access private medical information used for non-care purposes. But, both HIPAA and the common rule, the two regulations that govern research in this country, have exceptions that allow you to waive confidentiality in certain circumstances.

There are different pieces of consent for different protocols. The elements may include consent to the collection, storage and use of tissue for research; access to the medical record to query the clinical correlates that you need; and consent to future recontact after the immediate procedure or study is over. There are controversial issues such as how broadly you can use the waiver of consent permissions the regulations give you. How many options do you give people in deciding what sorts of uses can be made of their tissue? One extreme is allowing people to specify 8 to 10 different levels of use of their issue. The other extreme is in the study or out depending on consent to tissue collection. For the number of people you might lose to adopt the strict in or out perspective, is it worth the administrative burdens of collecting and tracking the permissions and then enacting all participant-chosen restrictions for how you use the tissue?

Federal bodies have looked at and made recommendations about how open-ended versus limited a consent should be. For example, can you say when collecting tissue that's related to breast cancer that this tissue might also be used for all kinds of other purposes, both other cancers and then other diseases?

HIPAA doesn't explicitly permit the use of open-ended consent. Most institutions have interpreted this to mean that under HIPAA regulations they can't ask for open-ended unlimited consent.

It's been said that individual results shouldn't be given unless there are clear clinical implications. A paper in JAMA earlier this year by Frank Miller and colleagues questions whether this view is appropriate. Should we be more open to giving individual results to participants?

BIOSPECIMENS CHALLENGES AND SOLUTIONS CONT

William Carson, Chair Cancer IRB, The Ohio State University:

Guidance for Institutional Review Boards (IRB) and some of the consent issues that come up with biospecimens come from the Code of Federal Regulation Title 45, Part 46, for protection of human participants. Conducting a systematic investigation of samples from living human participants requires IRB oversight.

Another area of guidance comes from a release from the Office of Human Research Protections (OHRP) last year regarding specimens being used for other than the original purpose. In these cases the identifiers to those specimens must not be known to the investigator. The identifiers have either been destroyed or the identifying code is withheld from the investigator until such time as all the participants have passed away.

The repository that collects the tissues is responsible for maintaining confidentiality. It will provide the collectors with sample collection forms and also with a sample consent. The basic requirements for a tissue repository are IRB oversight, procedures for protecting participant privacy, and written informed consent. The tissue bank should also have a certificate of confidentiality.

The recipient investigators who will use the biospecimens in their research are not under the same IRB umbrella as the repository. They should not receive any identifying information on the specimens or know the patient's identity.

The written informed consent needs to be very specific. The guidelines from HHS are that there should be no exculpatory language; the participant can't be seen to waive any rights or appear to waive any rights they might have. They should also be made aware of consequences of DNA typing such as learning of a genetic susceptibility to a disease.

In some consents there is a provision for recontact of the individual prior to future research. A study at the NCI published this year looked at 1,200 completed consent forms, the results are very interesting. When you give patients the right to refuse all further research, only about 6% check the box saying "I don't want my specimen used for any other research". Over 90% of participants allow their specimens to be used for further research on the same disease. Even when the request is broadened to include any disease, 87% agree. As far as the recontact provision, only about 26% will ask to be recontacted when their specimens are going to be used.

Who owns the tissue? Not the patient. There have been two legal precedents set. One was in California in the 1980s. The patient had leukemia and his spleen was used by the investigator to make a T-cell line that was then patented. The ruling by the Supreme Court in California was that individuals do not retain property rights or any rights

of ownership for excised tissue. This ruling was reinforced by *Greenberg v. Miami's Children's Hospital*. This case was about the development of a prenatal test to screen for Canavan's Disease, a rare, fatal, recessive childhood brain-wasting disease. It affects 25% of children if both parents are carriers. Prior to 1993 there was no means to identify carriers. In the 1980s Greenberg and other parents of children with Canavan's disease organized, located affected families, funded research, and created an invaluable database/tissue registry. It was done with full consent and voluntary donation of tissues. Dr. Reuben Matalon used their database to isolate the Canavan gene and develop a screening test. Greenberg and the other parents sued Miami's Children's Hospital's (MCH) claiming Dr. Matalon secretly applied for the patent and restrictive licensing. Federal district court agreed to the merit of plaintiffs claim that Dr. Matalon/MCH received "unjust enrichment". The parties settled in 2003. MCH may continue to license the Canavan test and perform fee-based testing; however, MCH must permit license-free use of the gene for any Canavan-related research.

Laura Cleveland, Research Participant/Patient Advocate

Patients are very inclined to participate and to donate tissue to research. We feel positive about making donations for the overall good and helping others. We do ask that our tissue be used responsibly. This leads to the issue of privacy. We want the assurance of anonymity. We want to know where the tissue is going, who's going to be handling it. Is it going to be just the principal investigator? Is it going for a gene study?

We also want to know who is going to use our tissue. Only researchers, or is it going to a large pharmaceutical company? Who will profit? Ultimately, we know patients profit from research. We're very grateful for that. We also know there are other players in the game and we're not sure how we feel about it.

We ask that you handle our biospecimens with care. Assure us our contribution is worth the risk of insurance and employability implications should our information be compromised. That our specimens be used for the common good. Don't take more than you need—but use it in as many ways as you can. Make the tissue you take stretch as far as you can.

We wish to be partners and part of the process. We would like for you to share results once they are validated so we know how the future of treatment may be affected. Keep us informed, not only about the results but about the conclusions and treatment implication in layman's terms that we can understand.

Ultimately, we trust you. We trust you to make good decisions on our behalf, we trust you with our tissue samples. We count on you to honor that trust.

BIOSPECIMENS CHALLENGES AND SOLUTIONS CONT

Lyndsay Harris: CALGB Investigator Breast Cancer Correlative Science, Dana Farber Cancer Institute

Correlative endpoints are just as important as clinical endpoints of a trial. In the past, stand-alone correlative studies and companions to clinical trials have not been well designed. Many clinical correlative studies have been designed with small sample sizes, poor attention to detail of the methodologies used to evaluate the specimens, and ultimately, little information was gained.

Sample size and statistical issues are vitally important when looking at an endpoint involving a specific biomarker. When designing correlative trials, statistical design should be of utmost prevalence.

Dan Hayes and colleagues developed levels of evidence that state the need to demand as much rigor from correlative studies as from clinical trials, this way we can believe the data coming forward and make decisions about patient care on a solid footing. A level 1 correlative study is one with a prospective design where the marker is the primary objective in the study, and it is adequately powered to reach a reasonable conclusion.

Do such studies exist? Almost none. There are perhaps a handful of studies that have been designed where the marker was really the question being asked and the clinical design was randomized around the marker. There are initiatives now looking at some of these newer tests, such as the onco type DXSA and then randomizing patients to receive chemotherapy or not depending on that assay. These are some of the first studies being conducted where we will get level 1 evidence about the value of a marker.

Sample collection is not a trivial issue – how do we optimally collect these samples in the community? Our experience has been that collection of samples in a prospective fashion is much more likely to yield optimal sample numbers. In CALGB trials where we conducted correlative studies in the context of breast cancer patients treated with paclitaxel, we performed both a prospective and a retrospective study.

In the retrospective study, we were only able to collect 42% of the blocks for a number of reasons. But, in the prospective study, with a similar patient population and similar numbers of patients, we were able to collect 82%. There are many barriers to retrospective collection which are solved by prospective collection embedded within the clinical trial.

Incentives to support sample collection at the individual institutions is fundamental and need to be considered. Most importantly, this is a team effort. Many people are involved in the conduct of these correlative studies; they need to be involved at every step of the way during collection of data, analysis of the data, and writing up the results.

This is the era of molecular therapeutics. We need to understand the heterogeneity of these diseases. Which patients are optimally treated with what therapies? To find out, some form of correlative study needs to be involved in every treatment study going forward.

Carolyn Compton for Scott Jewell, Director of the CALGB Pathology Coordinating Office

From the perspective of the NCI, the focus is on quality because we're interested in getting across the goal line faster. From the point of view of the CALGB Pathology Coordinating Office (PCO), quality is likewise our focus. The PCO is where most of CALGB's pathology and tissue banking efforts occur. They're centralized there as is the Leukemia Tissue Bank(LTB). The Lung Cancer Tissue Bank(LCTB) is at Harvard because of the tremendous infrastructure that already existed and made available to us through David Sugarbaker.

As much as possible we want to consolidate, centralize, coordinate, and standardize everything we do within CALGB. Through the Group Banking Committee we will work to standardize what we're doing across the cooperative groups so we can do intergroup correlative studies, assured we are all handling the specimens in the same way.

The PCO collects solid tumors, mostly in the form of paraffin blocks, but frozen tissue, serum, plasma and urine are also collected as are normal white cells for germ line DNA. Live leukemia cells are in the LTB and frozen lung cancer tissue is at the LCTB. There are also a couple of special collections such as lymphoma tissue and serum from prostate cancer patients for certain studies within CALGB.

The PCO web site can be accessed through The Ohio State University web site and there is also a link to the PCO from the CALGB web site. CALGB investigators and CRAs can view active and closed protocols organized by disease site and consult the quick reference guide for PCO submissions. By clicking on a specific study, the patient eligibility criteria, what tissue samples are being collected for the correlative science, and the cutting schema can be consulted.

The complexity and the amount of labor that goes into the processing of a sample to go out to an investigator is not to be underestimated. Blocks and slides are received which must then be validated to make sure the right sample came in from the submitting institution. The blocks stored typically aren't cut until there is sufficient supply to send investigators. However, an institution may demand to have their block sent back to them right away, so the correct sample(s) must be cut immediately, and their block returned. Everything goes through a quality control process before it leaves the PCO. It's a highly ordered, highly regulated process. The PCO is a high throughput operation and the facilities are very modern. Specimens are carefully annotated and stored in vacuum containers.

The number of specimens processed by the CALGB PCO is ever increasing. The workload has skyrocketed over the last five years. An even greater workflow through the PCO is anticipated, given the hope that virtually every new trial that's opened within CALGB will have a correlative science study appended to it. The dependency on the efficiency and quality of our PCO will be ever more important to our enterprise.

Carolyn Compton: from the perspective of a hospital pathologist

“Why is it so hard for us to get specimens out of our participating institutions? Why can’t we have 100% specimen collection on every single CALGB trial?”

The pathologist in the hospital sits at the interface between science and medicine. The pathologist’s number one priority is to work up the specimen for patient care. The specimen was taken out of the patient for a reason other than CALGB correlative science. The first goal is to make the right diagnosis, determine the stage of disease, analyze the margins, and to do this within the confines of cost containment. Fewer and smaller samples are being taken, just enough to get clinical information to care for the patient.

Investigators are lining up requesting tissue samples. Who has priority? There is the necessity for the pathologist to know the protocol and the status of the IRB approval. Are they allowed to give this tissue away? Precisely what tissue is being asked for? They may not have read the protocol or know what the banking requirements are for the specific study or even whether the patient has agreed to participate because they aren’t always provided this information. The process would work better if pathologists were included in the process as a full participant.

The pathologist is also unsure of the relative value to the patient of relinquishing the block for research versus keeping the block for a future clinical need of the patient.

The medical-legal system in our country has pathologists thinking about their ability to defend their medical evaluation in court should they give away the only evidence. They are understandably reluctant to give up something they may need to protect their professional reputation.

There is the uncertainty about who’s tissue it is. Does the patient own the tissue? Does the researcher own the tissue? Does the pathologist own the tissue? Pathologists are unsure because there are very few guidelines from hospital administration and federal agencies.

The actual physical process of getting tissue to a tissue bank requires considerable effort. The pathology staff have to get the tissue and related documents, then match them with the request. They have to review the entire case to pick out the right block. They have to document they’re sending it out of their department, package it up, send it to the PCO according to protocol, then record it for reimbursement from their institutional PI. There’s inadequate staffing to fulfill all these requirements. These are impediments to tissue banking.

Jennifer Shoemaker: Director, CALGB Bioinformatics

At CALGB, we see bioinformatics as an extension of correlative sciences. At the Statistical Center, we maintain a central resource for the storage of the data for stewardship, quality control, and standardization. The Bioinformatics Unit was formed a few years ago after the last competing renewal in order to handle the increasing number of studies coming through with genomic and proteomic data. Our mission statement is to collaborate in the design and analysis of studies with a bioinformatics component.

The difference between a typical clinical study and a typical gene expression study is that in a typical clinical study there are dozens, hundreds, thousands of cases and just a few variables; whereas in a gene expression study that matrix is flipped, there are only a few cases relative to the number of variables, thousands or tens of thousands of variables. This creates some issues with the data analysis because there are many more variables than specimens. Examples of variables include microarray data, proteomic data, single nucleotide polymorphism data, or serial analysis of gene expression (SAGE) data.

If a study concept includes a bioinformatics component, it must be reviewed by the Bioinformatics Unit before being submitted to the Executive Committee. There is typically a conference call to discuss the collaborative model, the roles and responsibilities of the external statistician and the CALGB faculty statistician as well as the logistics of sending data to and from the Statistical Center. All the correlative science data that will need to be stored at the Statistical Center is also outlined. File server needs and data file sizes are also reviewed. Often Kim Johnson, Director of Information Systems, will join the call to address overlapping IS issues.

Data sharing applies to all data, not just bioinformatics. More and more people outside the Statistical Center, or outside CALGB altogether, want to analyze CALGB data. The first thing to consider is whether there’s informed consent and HIPAA authorization for the particular person who would like to analyze the data. If yes, then it’s a matter of sending the data securely, and sending what’s called the minimum necessary data. If there isn’t consent, then the data have to go through a de-identification process, which is a bit more involved. These policies are outlined in more detail on the CALGB web site.

Highlights from the question and answer portion of the biospecimen plenary session follow on the next page



BIOSPECIMENS CHALLENGES AND SOLUTIONS CONT

Richard Schilsky: I have a question about the appropriate use of specimens from patients who are deceased. My understanding is that at least for the NIH, a research participant is defined as a living human being. We have many specimens in CALGB now that have been collected over decades. Many of those individuals unfortunately have died over time. We have specimens obtained for a particular purpose, the patient consented that the specimens could be used for a particular purpose. Now, it's 10 years later, the patient has died, there are new research questions, there are new technologies that could be applied to those specimens. Can we in fact use those specimens for new research purposes that may not have been included in the original informed consent?

Steve Joffe: That was the topic of the guidance that came out last year in August. If you follow that guidance, yes, you can do the research. The investigator cannot know the identity of the individuals either with an agreement that the co-holder will not release it, or because it's actually been destroyed.

So long as that barrier of not having information regarding where the specimen came from is in place, you're allowed to do the new research. It's not specifically addressing older samples where the patient has since died. The regulations both in that guidance and the common rule – the federal code – are very broad just because of these sorts of issues. There are always special cases. So, the regulations are kept a bit loose on purpose.

Carolyn Compton: It's clear that OHRP does not define you as a human participant if you're dead. This is in conflict with the definition of a human participant at the FDA level. It's a problem because the FDA never waives consent. It doesn't matter if the participant is dead. They're going to hold you responsible for having consent. If any of the discoveries we make in CALGB get to the formulation of drugs that go through the FDA process, it will be a problematic issue. The NIH is addressing this at the federal level with agencies outside of the NIH to try to harmonize these definitions.

William Carson: I would add that although human participant regulations under OHRP do not include deceased persons, HIPAA does include deceased persons. To get private identifiable information from individuals in the absence of prior consent, a waiver is needed. All these regulations have pathways for obtaining waivers of consent or in HIPAA language, authorization. With research participants who are deceased, the waiver process is used, otherwise permission must be requested of the next-of-kin.

Ross McIntyre: This whole discussion of getting waivers and so on bothers me. The legalistic document-driven aspect is arrogant with respect to our ability today to predict what we might need 50 years from now. We would have had no idea what happened with the flu virus from

1916-17 relative to the flu virus today were it not for the fact that prior to the imposition of conditions for conducting research on human participants, we had collected samples of it. Somebody took care of them long after our regulations today would have us discard them. There's a lesson in that. In probably half a dozen very substantial events in my lifetime, having old samples has paid off. We ought to think about that and do something about it.

Carolyn Compton: It's developing into an interesting ethical dilemma because most patients as you saw from the statistics presented earlier want open-ended use of specimens, they want to get as much mileage out of their specimens as possible. They trust you to do ethical and scientifically sound things with their specimens. They want them used. It becomes unethical to keep that from happening.

The use of specimens down the road came up recently in a summit convened to decide what to do with the AFIP collection of tissue blocks – 50 million tissue blocks of different diseases, most of which are cancers in the United States going back 150 years. How long should we keep them? People thought at least 100 years. We were able to sequence the genome of that flu virus by going back to Civil War specimens.

So although we can't anticipate precisely what specimens are going to be useful for in the future, they have been shown to be very useful. Then there is the economic issue. How are we going to be able to do this? We need some smart technologies to help us store very long-term specimens in a more cost-effective way.

Richard Schilsky: We recently looked at some data on what our sample submission rates are in the group as required by our protocols. We actually do quite well. Across the board, if you look at all of our protocols that have required specimen submission over the last 3 years, about 75% of the expected specimens have actually been submitted. In breast cancer, it's greater than 90%. I think in the lowest rated area, we were still at about 65%. So, generally speaking we do very well.

What we don't really know is when we don't get specimens why we're not getting them. I'm sure there are a variety of reasons. The group in general should be commended, because despite all of the barriers mentioned, all of which I agree with and acknowledge, the group does a terrific job of getting specimens.

The PowerPoint presentations of the session are available on the CALGB member web site at http://www.calgb.org/Private/COOP_Groups/CALGB/meetings/meetings.php.

Thank you to the panel members, Deborah Collyar, Sandra Batte, and all the members of CARE who helped plan and implement this plenary session.

Instructions for Secure Mail

With the advent of HIPAA came more stringent requirements for safeguarding protected health information (PHI). Regular email is not considered to adequately safeguard PHI. Therefore, CALGB has instituted Secure Mail, a messaging system with the high degree of security necessary to communicate information that includes PHI. Staff at the CALGB Statistical Center and Central Office will utilize Secure Mail to send correspondence containing PHI to CALGB members and other relevant parties. Recipients can forward or reply to Secure Mail messages but cannot initiate new messages. Instructions for the use of the Secure Mail system follow.

1. When a Secure Mail message is sent, the receiving party will get an email message informing them there is a secure email waiting for them. A link to the CALGB Secure Mail web site is included with the notification message.
2. At the CALGB Secure Mail web site - If the receiver is already a registered user, they will see the login screen for secure mail.

If the receiver is not registered user, they will see a screen asking them to fill out their name and create a password. Upon completion they will be a registered user.

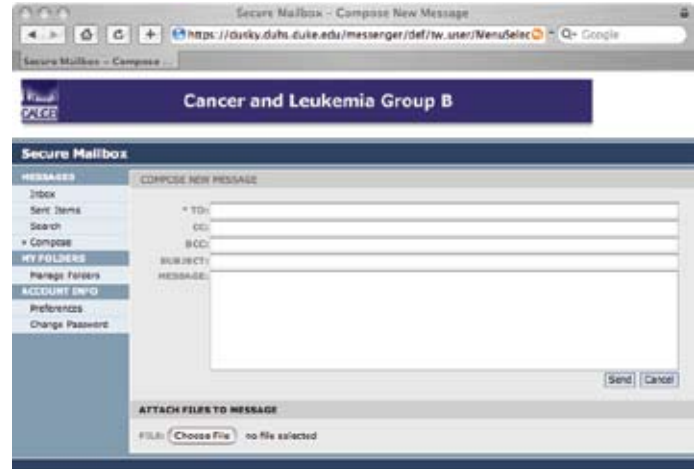


3. When logged in, the recipient will see their inbox where they can view the Secure Mail message sent to them. They can generate a reply to the email that will also be sent through Secure Mail.



4. Each time Secure Mail is accessed, the user is required to log in with their email address and password.

5. To compose a new Secure Mail message, click on the “compose” link located on the left-hand side under the “messages” section. Fill in the To, CC, and/or BCC with the appropriate email addresses and complete the subject line. Draft the body of the message. Note: recipients outside of the CALGB Central Office and Statistical Center may not create a new message.



To attach a file to the message, click the “browse” button located at the bottom of the screen, and choose the correct file from the list. After you have chosen the document, press the “Attach File” button to attach the file to the message. (NOTE: if you do not press the “attach file” button after you have chosen the document, the file will not be attached to the message.) When finished composing the message, click on the “send” button.

6. Recipients can forward a message and the secondary recipient can forward the message again, but a message cannot be forwarded a third time

To check your secure mail use the following link:

<https://www.calgbapps.org/securemail>

If you have any questions or problems with using secure mail, please call the CALGB Helpdesk at 1-877-442-4542 or email calgb-support@calgb.duhs.duke.edu

Important!

- Secure Mail is ONLY to be used for sending PHI and is not intended for personal use.
- Any mail sent or received will only be retained for 90 days. All messages 90 days and older will be deleted automatically.
- Secure mail does not contain address lists and does not have the option of creating address lists.
- Messages over 1 gb in size will not be sent. (the maximum size secure mail will allow)
- Secure mail sessions will timeout after 30 minutes of inactivity.

William Humphrey, Manager, Network Operations
Jennifer Zelazny, Web Operations Manager

ONCOLOGY NURSING PERSPECTIVE

Advances in Myelodysplastic Syndromes – Nursing Implications of Azacitidine (Vidaza®)

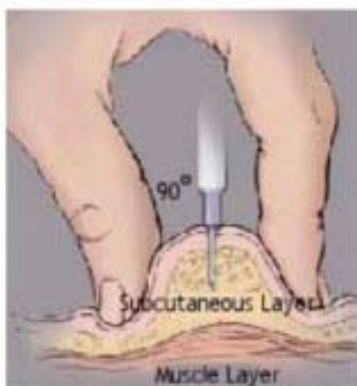
Myelodysplastic syndrome (MDS) is a group of clonal hematopoietic stem cell disorders associated with abnormalities of cellular differentiation and maturation leading to varying degrees of bone marrow failure and peripheral blood cytopenias (Perry, Maghfoor, & Dorr, 1999). In conjunction with the National Cancer Institute, CALGB investigators tested the safety and efficacy of azacitidine in patients with MDS in two phase II studies and one phase III study: CALGB 8421, 8921, 9221 (Silverman et al., 2002). In 2004, the Food and Drug Administration (FDA) approved azacitidine (Vidaza®) for the treatment of MDS; azacitidine is the first drug to be approved for this complex disease. A publication outlining the nursing implications of azacitidine for the treatment of MDS was recently published in the *Clinical Journal of Oncology Nursing*. An overview of the article follows.

Dosage and Administration

The recommended starting dose of azacitidine is 75 mg/m² subcutaneously, daily for 7 days, every 4 weeks. To ensure adequate exposure to demonstrate a beneficial hematological response, a minimum of four cycles of azacitidine is recommended; however, complete or partial hematological response may require additional cycles. Nurses should help increase patient awareness that they should not expect to see an immediate clinical response. Because azacitidine is approved for daily administration for 7 days, arrangements must be made for patients to go to an outpatient center that is open on weekends. Recommendations for injection site techniques and locations are summarized below:

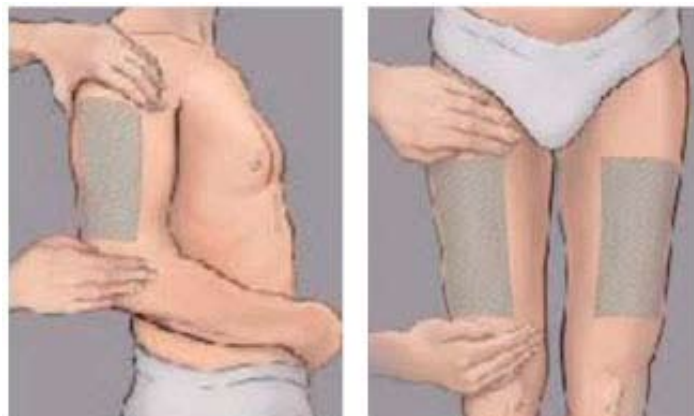
Injection Site Technique Recommendations and Locations for Subcutaneous Azacitidine

- Doses greater than 4 ml should be divided equally into two syringes and injected into separate sites.
- Once the reconstituted suspension is drawn into the syringe, the needle should be changed prior to injection. This avoids residual drug on the needle, which may cause irritation as it enters the superficial layers of the skin.



- Injections should be given in a 25G needle between the skin and muscle by pinching the skin and injecting at a 90-degree angle (or 45-degree angle for people with little subcutaneous fat).

- Rotate sites for each injection (thigh, abdomen, and upper arm).
- New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red, or hard.
- Patients with low platelet counts should be instructed to apply gentle pressure to the injection site for about 10–15 minutes after the injection.



Graphic from National Institutes of Health, 2005

Laboratory Tests

Complete blood counts (CBC) should be performed as needed to monitor response and toxicity, but at a minimum prior to each cycle. As a guide to subsequent dose modification, a bone marrow biopsy and aspirate should be considered in patients with low baseline WBC ($<3.0 \times 10^9/L$), ANC ($<1.5 \times 10^9/L$) or platelets ($<75.0 \times 10^9/L$) that remain low. Patients should be made aware that it may take up to 3–4 cycles of azacitidine before a clinical effect is apparent. Furthermore, occasional transfusions may still be required.

Liver chemistries and serum creatinine should be obtained prior to initiation of therapy. Azacitidine is potentially hepatotoxic in patients with severe preexisting hepatic impairment; therefore, caution is warranted in patients with liver disease.

Knowing dosage and administration of azacitidine, monitoring and managing possible side effects and laboratory tests, and ensuring that patients and their families are aware of treatment requirements are essential to patient care.

Adverse Events

In clinical studies using subcutaneous azacitidine, adverse events were characteristic of this class of compounds and most commonly involved hematologic (e.g., anemia, thrombocytopenia, and leukopenia) and gastrointestinal events (e.g., nausea, vomiting, diarrhea, and constipation). Given the route of administration, injection site reactions are also among the most frequent adverse events. Suggested supportive-care measures for managing these common adverse events are provided in the following table:

Supportive Care for Common Adverse Events Associated With Azacitidine

Toxicity	Supportive Care
Nausea and vomiting	<ul style="list-style-type: none"> • Premedicate patients (approximately 30 minutes before injection) with antiemetics (e.g., 5-HT₃ antagonist). Patients should take antiemetics every day of injection, regardless of presence of nausea. Azacitidine is considered to be a moderate emetogenic agent. • The occurrence of nausea seems to decrease after the first 2 cycles of treatment. • Saltines may help with mild nausea. • Patients should increase fluid intake.
Diarrhea	<ul style="list-style-type: none"> • Monitor vital signs and nutritional status; administer antidiarrheals (e.g., loperamide). • Azacitidine and anti-nausea medication often balance each other; therefore some patients have little diarrhea. • Patients should increase fluid intake.
Constipation	<ul style="list-style-type: none"> • Constipation may be the result of concurrent treatment with antiemetics. • Patients should increase fluid intake and foods high in fiber, such as fruits, grains, and vegetables. • Patients may consider a stool softener. • If patients continue to have constipation, they may want to consider a laxative.

Injection site reaction

- Local warm soaks, cool soaks, or ice packs to injection site may decrease irritation.
- Corticosteroid cream or antihistamines may be used to treat allergic response; consider analgesics if the rash is painful.
- Instruct patient to contact the physician if injection-site reaction worsens or the patient develops a fever.

Quality of Life

The impact of azacitidine on quality of life (QOL) has been evaluated (Kornblith et al., 2002). Over time, patients treated with azacitidine experienced significantly greater improvement in fatigue, dyspnea, physical functioning, positive affect, and psychological distress compared with patients receiving supportive care only. The authors concluded that improved QOL for patients treated with azacitidine, combined with significantly greater treatment response and delayed time to transformation to AML or death, compared with patients on supportive care establishes azacitidine as an important treatment option for MDS.

Summary

The FDA approval of azacitidine for the treatment of MDS represents an important advancement in the treatment of this complex disease. Although azacitidine is a safe and effective treatment for MDS, patients should have realistic expectations of their treatment. Nursing staff should explain to patients and their families that patience with their treatment expectations is necessary because responses to treatment may take several months.

Erin P. Demakos, RN, CCRC and Jeanette Linebaugh, RN, BSN, OCN, CCRP

The full publication is available in *Clinical Journal of Oncology Nursing*, 9(4):417-423, 2005.

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SPOTLIGHT ON CALGB TRIALS

40101 Cyclophosphamide and doxorubicin (CA) (4 vs 6 cycles) versus paclitaxel (4 vs 6 cycles) as adjuvant therapy for breast cancer in women with 0-3 positive axillary lymph nodes: a 2x2 factorial phase III randomized study

The trial is a 2x2 factorial trial comparing single agent paclitaxel with standard chemotherapy (cyclophosphamide and doxorubicin) and, at the same time, testing standard duration treatment (4 cycles of each agent delivered in dose-dense fashion) with extended therapy, 6 cycles of each regimen. Currently, there are more than 2,000 patients enrolled on 40101; the target accrual is 4,600 patients.

For the last several years, 40101 has been the Breast Intergroup node-negative adjuvant trial. The eligibility criteria have now been expanded and the trial is open for women with primary breast cancer with 0-3 involved axillary lymph nodes. The Intergroup and NCI made this change in the belief that women with relatively low risk, node-positive breast cancer, would be good candidates for the chemotherapy regimens in 40101.

In addition, trastuzumab is now permitted for patients whose tumors overexpress HER2. For patients who are randomized to receive CA, trastuzumab should be initiated after the conclusion of chemotherapy. For patients randomized to receive paclitaxel, trastuzumab can be initiated either concurrently with paclitaxel or after paclitaxel. Cardiac monitoring is recommended prior to initiation of trastuzumab and every 3 months during trastuzumab therapy.

The questions in this study are chemotherapy questions and not hormonal therapy questions. The protocol specifically permits, and encourages, enrollment of participants to this study who are concurrently enrolled in adjuvant hormonal therapy studies. This includes SOFT and TEXT, as well as other adjuvant hormonal trials.

Two important companion studies are available with 40101. Embedded within the protocol is the pharmacogenomics companion 60202, it will look at metabolic phenotypes that might affect chemotherapy metabolism and, therefore, influence both efficacy and toxicity of these regimens. This would be one of the largest pharmacogenomic studies ever performed, examining two common regimens used in breast cancer treatment. This companion study could supply valuable information for patients in the future.

A separate companion protocol, 70301, will be assaying quality of life, employment, and care costs for patients participating in 40101. This information could be helpful in determining the optimal chemotherapy regimen.

The questions asked by 40101 and the companion studies are critical ones. We encourage you to enroll appropriate patients on the parent and companion studies whenever possible.

We are grateful for the efforts of investigators from CALGB and CTSU and the other cooperative groups in

enrolling the first 2,000 patients. We also hope that with the inclusion of patients with 0-3 positive axillary nodes, that accrual will increase allowing us to reach our accrual goal of 4,600 patients, so as to answer the questions posed by this study as soon as possible. In particular, if paclitaxel is shown to be equivalent to cyclophosphamide and doxorubicin, this could be a potentially less toxic non-anthracycline alternative regimen for patients with early stage primary breast cancer, particularly those patients who might also be receiving adjuvant trastuzumab. The addition of the pharmacogenomic and quality of life data will greatly aid in our interpretation of the results of 40101, as well as provide important data for use of these regimens in any circumstance.

Your support of this study in the past and in the future is greatly appreciated.

The study chair is Lawrence Shulman, MD, Dana Farber Cancer Institute.

Email: Lawrence_Shulman@dfci.harvard.edu

80405 A phase III trial of irinotecan/5-FU/leucovorin or oxaliplatin/5-FU/leucovorin with bevacizumab, or cetuximab (C225), with the combination of bevacizumab and cetuximab for patients with untreated metastatic adenocarcinoma of the colon or rectum

Rationale

Combination chemotherapy with oxaliplatin or irinotecan has improved outcomes for patients with advanced colorectal cancer. The addition of the antibodies bevacizumab, cetuximab or both agents to chemotherapy may increase response rates, create more complete remissions, and thereby improve survival or perhaps even identify a subset of patients with advanced disease who may be cured by multimodality therapy. Preliminary data suggest that even in heavily pre-treated patients who had not been exposed to either antibody, response rates approach 40% when bevacizumab and cetuximab are used together or in combination with irinotecan. Neither antibody is without toxicities; however, in combination, these appear manageable.

This study is also designed to ask questions regarding predictive markers for response and/or toxicity to chemotherapy and biologic agents. Accordingly, blood and tumor samples will be collected and analyzed for molecular and other markers.

Trial design

This is a randomized, phase III trial. Patients will be assigned by their physician to receive either modified FOLFOX6 or FOLFIRI, which will be a stratification parameter. The randomization will be 1:1:1 for chemotherapy with 1) bevacizumab; 2) cetuximab; 3) the combination of bevacizumab and cetuximab.

The primary endpoint is overall survival, although protocol treatment will be mandated only until the time of tumor progression or until the time patients come off their front-line treatment for other reasons. Data on curative hepatic or lung resection will be collected. The protocol allows for patients to interrupt their treatment

for clinical reasons, such as oxaliplatin neuropathy or an elective surgery.

Patient characteristics

Patients untreated for advanced or metastatic adenocarcinoma of the colon or rectum are the subject of this study. Patients may have had prior adjuvant therapy completed more than 12 months prior to enrollment and may have had prior pelvic radiotherapy as part of primary treatment.

Inclusion and exclusion criteria

Patients with the above diagnosis 18 years of age or older are eligible. Because the choice of chemotherapies is the treating physician's, any patient deemed a candidate for combination treatment with chemotherapy and a biologic agent could be appropriate. Absolute contraindications to such treatment, such as a recent myocardial infarction or cerebrovascular accident, need to be considered. Prior exposure to bevacizumab or cetuximab is also an exclusion criterion.

Anticipated toxicities

As with any study including these treatments, the toxicity profile of the chosen chemotherapy can be expected. With oxaliplatin, cold sensitivity and a cumulative peripheral neuropathy can be anticipated. With irinotecan, diarrheal syndromes and hair loss would be expected. With either chemotherapy treatment, neutropenia, mucositis, mild diarrhea, nausea, vomiting and many other lesser toxicities may be anticipated.

The major concerns for patients receiving bevacizumab are hypertension and proteinuria. The risk of arterial thrombotic events or other vascular events may also be greater than one expects in patients who are receiving chemotherapy alone. Cetuximab can be expected to cause an acneiform skin rash in most patients. Either biologic may occasionally lead to infusion reactions.

Proposed statistical analysis

The accrual goal for this study is 2289 patients, with equal allocation to the three arms. The choice of chemotherapy – FOLFOX or FOLFIRI – will be a stratification parameter. The sample size is based on the assumption that overall survival in the control arm (chemotherapy plus bevacizumab) will be 22 months and that it would improve to 27.5 months in the other arms. A secondary endpoint is time to progression, with an anticipated 12 months in the control arm and 15.6 months in the experimental arms.

There are plans for multiple interim analyses and real-time data safety monitoring.

The two study chairs for this trial are: for CALGB, Alan Venook, MD at the University of California, San Francisco, Email: Venook@cc.ucsf.edu and for SWOG, Charles Blanke, MD, at the Oregon Health and Sciences University. This trial is also available through the CTSU.

100104 A phase III randomized, double-blind study of maintenance therapy with NSC#703813, IND#70116/CC-5013 or placebo following autologous stem cell transplantation for multiple myeloma

Autologous stem cell transplantation (ASCT) is part of the standard of care for selected patients with multiple myeloma. Despite improvements in the outcome of myeloma with the use of ASCT, the treatment is not curative, and most patients will have progression of disease within 2-3 years. One approach to maintaining response after autotransplant is the use of maintenance therapy. Several agents such as bisphosphonates, interferon and more recently thalidomide and glucocorticoids have been used post-autotransplant to maintain response with variable results. Thalidomide may have beneficial effects as maintenance therapy but it has a toxic side effect profile. Lenalidomide (Revlimid), a thalidomide derivative, has a superior side effect profile when compared to thalidomide, which can cause peripheral neuropathy, somnolence, bradycardia, skin rash and edema even in doses as low as 50 to 100 mg per day. This trial has the potential to define a new approach to remission extension following initial ASCT for multiple myeloma.

The primary objective of this placebo controlled phase III study is to determine the efficacy of CC-5013 in prolonging time to disease progression in patients with multiple myeloma after ASCT. The secondary objectives are: 1) to determine if lenalidomide will increase the CR rate in patients with multiple myeloma following ASCT; 2) to compare the progression-free survival (PFS) and overall survival (OS) in patients with multiple myeloma who have undergone ASCT and who then are randomized to either lenalidomide or placebo; and 3) to determine the feasibility of long-term administration of lenalidomide to multiple myeloma patients who have undergone ASCT.

Eligible patients must have active multiple myeloma requiring treatment (Durie-Salmon stage \geq 1) and have stable disease or be responsive to at least 4 cycles of any induction therapy. Patients should be within 12 months of induction therapy which may include lenalidomide and thalidomide.

Patients will undergo stem cell mobilization with cyclophosphamide, 2 to 4.5 g/m² IV over 2-3 hours on Day 1 or 1.5 g/m² IV over 1 to 3 hours daily for three days (Days +1 through +3) followed by stem cell collection and then transplant with melphalan 200 mg/m² IV over 30 to 60 minutes on Day -2 and stem cell infusion on Day 0. Patients undergo restaging between Day 90-100 post autotransplant; those with stable response or better undergo randomization to either placebo or study drug in a blinded fashion. Maintenance therapy is escalated according to platelet and neutrophils counts as tolerated. Therapy is oral and given daily as one, two or three pills depending on toxicity, if any. Patients are staged every 3 months for 4 years then every 6 months for year five and yearly for 10 years. Disease response and progression are defined according to Blade criteria. Patients remain on maintenance therapy until signs of disease progression.

The study chair is Philip McCarthy MD, Roswell Park Cancer Institute. Email : Philip.McCarthy@roswellpark.org

What CRAs Really Do

Spending eight and a half hours a day somewhere other than home is routine with most of the population. We have bills, we need money, and therefore, we must work.

I have held multiple jobs and titles in my lifetime. From waiter to registered nurse, I have helped many people and felt that my contributions to society were acceptable.

Three years ago I accepted the job as a research nurse /CRA for a large CCOP (Community Clinical Oncology Program) on the east coast working with CALGB. I had an idea of what the position entailed but soon realized it would take months, no, years, to really appreciate what I was doing. Clinical Research Associate is the job title. The job consists of collecting data, determining patient eligibility, submission of patients' specimens and completion of detailed paperwork from the initiation of treatment through follow-up care. The role requires skills from many professions. A CRA supports the process involved with entering a patient into a clinical trial in a variety of ways. The first step in the process is determining patient eligibility. A person must first present with a diagnosis of cancer. Once the disease is determined and staged by the physician, eligibility to a clinical trial must be determined by the physician and research nurse, coordinator, or CRA. Keep in mind that not all patients with cancer are appropriate candidates for a trial. Those who do fit the bill must be determined eligible according to the criteria of the specific CALGB study. This process involves reviewing the patient's chart and records. Laboratory reports, pathology records, diagnostic tests and exams need to be assessed in a rather short time frame. Initiation of treatment as soon as possible is sometimes a matter of life and death with these individuals. A basic knowledge and understanding of a variety of different diseases, lab parameters and tests are imperative to determine eligibility. If the CRA is assisting with or conducting the eligibility evaluation for the trial, time is obviously of the essence. Data that is important but not acquired from the patient's records may need to be obtained from a patient interview. At times it is also necessary to interview the patient's family. Sensitive and strong communication skills are necessary when talking with people during this difficult time. Gaps from the individual's past medical and surgical history may need to be filled-in as well.

CALGB has requirements regarding consents for clinical trials. These forms must be signed and completed correctly and entirely. A CRA may be asked to witness the signing or even explain some details of the trial. Awareness of studies that have mandatory companion consents/studies is also needed. Once eligibility is determined pre-treatment exams and labs are obtained. The patient is then registered to the study, and perhaps randomized. The CRA's work has only just begun.

Assisting the nurse, coordinator and or physician's office with the treatment schedule is the next step. The CRA may have to compile a plan or schedule for the patient who is receiving treatment. Contact with the treating office or

center may also be necessary. Where the treating agents will be acquired must be determined. Investigational drugs may be supplied directly from a drug company, obtained commercially or need to be ordered from the National Cancer Institute.

A variety of special specimens are usually required at various intervals during the treatment on CALGB studies. The study may require collection of blood, bone marrow, buccal cells, urine, or serum. Pathology blocks and slides may also be required.

Paperwork is next on the agenda. On-study forms are required within a week or two. Accurate and timely data submission is probably the most important aspect of our job. The information we submit will be used to determine the best treatment for current and future cancer patients. The results of the data may enforce or change how the doctor treats their patients. Flow sheets may be required for the phase I and II leukemic or Hodgkins trials. Although lengthy and time consuming, once again they are very important for the way these complex diseases are treated. At intervals of treatment multiple forms may be required at any given time. Patients receiving chemotherapeutic agents and investigational drugs will experience side effects at times. This is unfortunate, yet expected. Adverse event forms may need to be submitted when problems arise. Sometimes data are required to be submitted within twenty-four hours. These events should take priority over all else and should be submitted immediately. Follow-up data for CALGB patients are required anywhere from five years post treatment until death. Monthly to annual paperwork is required following treatment completion. As patients accrue to trials continuously, the volume of required follow-up data will also grow.

Today, when I meet people and they ask what I do, I can give them a number of answers: private investigator, mathematician, laboratory professional, inspector, data expert, and oncology disease specialist are all appropriate descriptions for the job I do. As a CRA with CALGB we are not fixing automobiles, selling credit cards, or making profits. We are fixing people, selling hope, and creating the possibility of a healthier and longer life for people living with cancer.

And what is more important than that?

*Edward Okonowicz R.N.
CRA Christiana Care Health Services, Newark, DE*



CANCER TRIALS SUPPORT UNIT (CTSU)

Resources Available through the CTSU

The CTSU Education and Promotion panel spends part of its time developing protocol-specific materials that can assist site staff in utilizing the CTSU and its protocols in the most efficient manner possible. While these documents can be helpful supplements for individuals who are already familiar with the CTSU and how it works, research staff who are new to cancer research in general, or the CTSU in particular, may require more basic information. According to a July 2004 Thompson CenterWatch Monthly article, more than half of all Clinical Research Coordinators (CRCs) are leaving their positions within three years. That translates to a lot of new, potentially inexperienced CRCs on the job, and the CTSU is pleased to provide a number of valuable resources for this population.

Resources on Clinical Trials

The CTSU has recently updated its listings of on-line clinical trial resources for both healthcare professionals and the public/patients. By accessing these new pages, titled "On-line Training/Education for Healthcare Professionals," and "On-line Training for the Public and Patients," users can gain easy access to a number of resources developed by the NCI including parts of the Clinical Trial Education Series, a guide to clinical trials developed by the Coalition of National Cancer Cooperative Groups, and the CTSU eCourse. Among other things, research team members can learn how to incorporate clinical trials into their practice, and can also fulfill their NIH human subjects training requirement by accessing and completing a free, Web-based tutorial. Patients and families can find step-by-step information on how to find an appropriate cancer treatment trial.

The new-and-improved educational listings can be found in the following locations:

Public Page <http://www.ctsu.org>

- Home page (left navigation bar, Guides/Training)
- Patients tab (left navigation bar)
- Physicians tab (main section, Researcher Resources)

Members' Page <http://members.ctsu.org>

- Education and Promotion tab
- Researcher Resources
- Patient Resources

CTSU Resources

Regardless of how much experience one may have in clinical trials, new and even seasoned users of the CTSU can benefit from a number of CTSU-specific resources.

Perhaps the best introduction to the CTSU and its procedures is the eCourse, an on-line educational program that introduces and explains the CTSU. It can be accessed from both the Public and Members' Web sites by clicking on the eCourse tab along the top of either home page.

CTSU members can find content that is similar to the eCourse but in a different format (plain document with

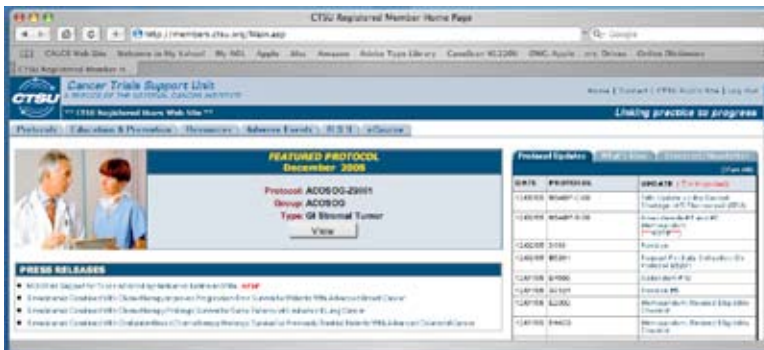
chapters) by reviewing the CTSU Operations Manual. This manual can be downloaded in its entirety or by chapter, and contains information on everything from joining the CTSU to enrolling patients to data submission and everything in between. If you do decide to print out all or part of the manual, please keep in mind that it is revised/updated every six (6) months, with the new version posted every March and September. The CTSU Operations Manual is located on the Members' Web site under the Education and Promotion tab in the section on **CTSU Operations Information**.

For a very practical resource that you can easily post in your work space, we recommend the **CTSU Process Checklist**. This one-page document provides a step-by-step guide to the CTSU processes, including how to obtain a user name and password, how to select a protocol and get IRB approval, how to register your site to conduct a particular protocol, and how to enroll patients. In some ways, it is the contents of the CTSU Operations Manual boiled down to one page of vital information. The Checklist can be found on the Public Web site on the left navigation bar under "Guides/Training" and on the Members' site under Education and Promotion and CTSU Operations Information.

Help Desk

If the above resources, a close look at the protocol, and further exploration of the CTSU Web site do not answer your questions, don't forget about the CTSU Help Desk! This living resource is available Monday through Friday, 9am-7pm (ET) at 1-888-823-5923 or CTSUContact@westat.com. If the Help Desk staff is not able to immediately answer your question, they will forward it to somebody who can and track it until it gets resolved.

The CTSU has worked hard to provide not only increased access to cancer clinical trials, but resources and tools to enhance its members' abilities to utilize them. If you have any thoughts on what other types of educational materials we can offer, please let us know!



Reference:

Deborah Borfitz, "CRC Loss Tied to Heavy Workload," The CenterWatch Monthly 11:7 (2004), 1.

Congratulations to the Northern Indiana Cancer Research Consortium; they enrolled the most patients (131) via the CTSU of all CALGB institutions!

ACKNOWLEDGMENT OF TRAINING SUPPORT FOR CRA PROGRAMS

The CALGB Clinical Research Associates Committee would like to thank the following people for contributing to the success of our training programs during 2005. We appreciate your efforts and your commitment to providing the CRAs with information critical to performing their jobs.

Alan Lyss, M.D. – Principal Investigator, Missouri Baptist Medical Center

Amy Schwarzhoff, B.S., CIP – CTIS Chesapeake Team for the NCI CIRB

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Vincent L. Schuler – CALGB Pathology Coordinating Office, The Ohio State University

William Blackstock, M.D. – Investigator, Wake Forest University School of Medicine

William Richards, Ph.D. – Investigator, Brigham and Women's Hospital

PROTOCOL NEWS**SUPPORT ACKNOWLEDGMENT****CCHO COMMITTEE****OPENED**

70301—QOL, employment & informal care costs: (comp to 40101)
Study Chair: B. Hillner, MD

GI COMMITTEE**OPENED**

80405—FOLFOX/FOLFIRI + bv, + C225, or + bv/C225 for mets colon ca
Study Chair: A. Venook, MD

CLOSED

CTSU E3201—St II-III rectal ca: pre/post RT/5-FU & post op chemo
Study Chair: R. Mayer, MD

GU COMMITTEE**CLOSED**

99809—External RT w/brachytherapy for unfav localized PCa
Study Chair: M. Hurwitz, MD

LEUKEMIA COMMITTEE**CLOSED**

10301—Bortezomib + PEG-liposomal dox in multiple myeloma
Study Chair: R. Orłowski, MD

RESPIRATORY COMMITTEE**OPENED**

30407—XRT, pemetrexed & carbo w/ or w/out cetuximab in stg 3 NSCLC
Study Chair: R. Govindan, MD

CLOSED

30206—Induction/consolidation chemo/XRT in LSCLC
Study Chair: M. Kelley, MD

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The Cancer and Leukemia Group B Foundation is a nonprofit, tax-exempt foundation formed for the primary purpose of aiding the Cancer and Leukemia Group B, a group of 29 of the most prestigious medical centers in the U.S. and more than 250 affiliated institutions collaborating in large-scale clinical trials. The CALGB Foundation supports the clinical trials and laboratory research of the CALGB, as well as efforts to educate the medical community on methods of cancer diagnosis, treatment, and prevention.

Examples of recent initiatives supported by the CALGB Foundation:

- New chemotherapy treatments for breast, prostate, lung, and colorectal cancer.
- New surgical techniques for breast and colon cancer.
- Genetic studies of breast cancer risk.
- Molecular determinants of response to therapy for breast, colorectal and lung cancer as well as leukemia.
- Improving the quality of life of cancer patients and their caregivers.

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