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Chemo Regimen Shows No Benefit in Advanced Ovarian Cancer

Adding the chemotherapy drug topotecan to a standard first-line chemotherapy regimen in women with advanced ovarian cancer offers no benefit, according to the final results of an international phase III clinical trial published in the August 2 *Journal of the National Cancer Institute*. Patients who received topotecan also had higher grade hematological side effects such as low platelet and red blood cell levels.

Combined with similarly disappointing findings in other phase III trials assessing different chemotherapy regimens, these results suggest that standard cytotoxic chemotherapy drugs have run their course in ovarian cancer.

"Certainly we have pushed the available agents very far," said Dr. Edward Trimble of NCI's Division of Cancer Treatment and Diagnosis. "It's unclear where we go next with chemotherapy."

Dr. Trimble did stress that, in the appropriate patients, intraperitoneal delivery of chemotherapy has now proven to have a substantial benefit.

Ovarian cancer continues to be a highly fatal disease. Even patients who

(continued on page 2)

Director's Update

Focusing on Cancer Stem Cells

Many solid tumors appear to have a small population of stem cells that are partially resistant to chemotherapy and can perpetuate themselves indefinitely. These cancer stem cells thus far have been isolated from breast and brain tumors as well as blood. The exact origin of these cancer stem cells remains to be defined.

With mounting evidence to support the hypothesis that genetic alterations in tissue stem cells may represent the origins of some cancers, the time is right to more vigorously explore the properties, mechanisms, and vulnerabilities of this subset of cells. The presence of such cells, first demonstrated in acute myeloid leukemia patients, provides a different and exciting model with which to further explore cancer biology.

As a result, NCI is establishing a trans-NIH group of scientists interested in embryogenesis and cancer stem cell biology to advance the study of the underlying mechanisms in these processes. Establishing this group will facilitate the sharing of data, reagents, and animal models, and also provide a meaningful scientific interface with similar groups of extramural scientists.

Isolating and studying cancer stem cells should give us new insights into cancer and therapies. A defining characteristic of cancer stem cells is their ability to self-renew while giving rise to a diverse

(continued on page 2)

(Chemo Regimen continued from page 1)
respond to initial treatments often have disease recurrence and die. In response, several large phase III trials have tested adding different chemotherapy drugs—including doxorubicin, gemcitabine, and epirubicin—to the currently recommended first-line therapy of paclitaxel and carboplatin. But, explained this most recent study's lead author, Dr. Jacobus Pfisterer of the Universtitatsklinikum Schleswig-Holstein in Kiel, Germany, none have demonstrated improvements in overall or progression-free survival compared with the standard regimen alone.

The current trial, led by French and German clinical trial groups, involved more than 1,300 women with previously untreated advanced ovarian cancer. Participants were randomized to the standard first-line therapy of six cycles of paclitaxel and carboplatin with or without four cycles of topotecan. The overall and progression-free survival rates were effectively the same.

In an accompanying editorial, Dr. William P. McGuire from the Weinberg Cancer Institute in Baltimore, argued that it was time to abandon testing new chemotherapy regimens in clinical trials and, instead, "use all our valuable patient resources to evaluate whether ovarian cancer responds to the targeted therapies as other solid tumors have."

A number of phase II clinical trials, and at least one phase III trial, are testing different targeted therapies in patients with ovarian cancer. Most of these trials involve anti-angiogenic agents.

There also is a randomized phase III trial pitting the trio of carboplatin, paclitaxel, and the anti-angiogenic agent bevacizumab (Avastin) against carboplatin and paclitaxel alone in women with advanced ovarian cancer. According to Dr. Robert F. Ozols, senior vice president of Fox Chase Cancer Center in Philadelphia, bevacizumab has promise in this setting.

"What's striking is that bevacizumab has had activity as a single agent in ovarian cancer, whereas in other tumor types it has had very little activity [when used alone]," he said.

Although targeted therapies should be aggressively pursued, Dr. Ozols added, some investigational cytotoxic agents may yet have value against ovarian cancer.

"We still don't know whether some of the newer agents may have a benefit," he said. "I wouldn't abandon cytotoxic drugs just yet." ◆

By Carmen Phillips

(Director's Update continued from page 1)
population of cells. In this respect, cancer stem cells are like embryonic stem cells, and the lessons of embryology, in which the role of stem cells are well defined, are crucial to understanding their role in carcinogenesis.

The mechanisms that allow controlled growth and migration of cells during the development of complex organisms from a single cell may be the same genetically programmed signal pathways that, when left unregulated in the adult organism, allow the development of tumors. Tumors are, in essence, complex "organs" complete with neovasculature and phenotypically altered supporting tissues.

Relatively little is known about the mechanisms of self-renewal, but researchers are beginning to identify potential genes and pathways involved. This could eventually lead to targets for intervening in the process, but without disrupting the behavior of normal tissue stem cells.

Some good news in this regard was reported last month. Researchers at the Dana-Farber Cancer Institute found differences between genetic signatures associated with self-renewal in cancer stem cells and in normal blood stem cells in mice. This suggests that it may be possible to target cancer stem cells in humans.

So where do cancer stem cells come from? One theory says they start out as normal stem cells until they become altered and start producing cancer cells. Another says that some more mature, differentiated cells may regain the ability to self-renew through genetic changes—a process of de-differentiation as they become malignant.

There may be evidence for both theories. It's important to remember that these rare cells have only recently been discovered. To answer fundamental questions about them, we need to develop more efficient techniques for isolating the cells and maintaining them in culture, and we need to draw on our knowledge of embryogenesis. Single-cell analyses will likely be needed to distinguish events present in cancer stem cells from the more differentiated cells that make up the majority of the tumor.

I am excited about the formation of this group. We have seen the success of another trans-NIH group in which NCI plays an integral role. The Trans-NIH Angiogenesis Research Program has improved the exchange of information and resources for angiogenesis researchers focused on diverse topics such as macular degeneration, cancer, and heart disease. Likewise, the new group has the potential to advance the science around stem cell biology and bring us closer to new and potentially highly effective therapies in cancer and other diseases. ◆

Dr. John E. Niederhuber
Acting Director
National Cancer Institute

Spotlight

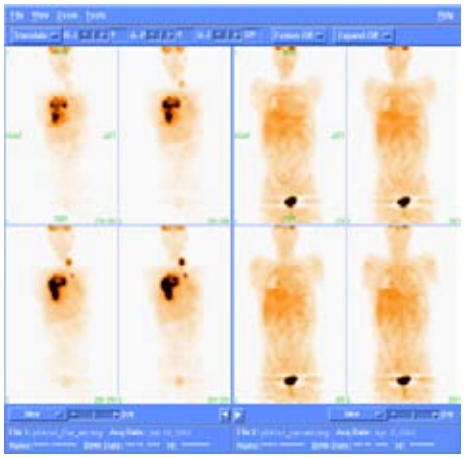
Recommendations Focus on Imaging to Predict Treatment Response

NCI recently published new clinical recommendations on the use of the imaging technique known as FDG-PET in NCI-sponsored clinical trials. The recommendations, developed in collaboration with some of the nation's top researchers and clinicians in nuclear medicine and radiology following a NCI-sponsored workshop in 2005, apply to clinical trials where FDG-PET results are being studied as early indicators, or biomarkers, of response to treatment.

The premise behind the use of FDG-PET relies on the inner workings of tumor cells, which need a lot of energy to survive and proliferate. This need is so great that tumor cells will simultaneously use two different methods of consuming glucose to provide enough energy to fuel their activity.

FDG is a glucose analog with a radioactive tracer (F^{18}) attached to it. Tumor cells, particularly those from especially aggressive tumors, will consume significantly larger amounts of it than normal surrounding tissue. The result is that FDG's presence can be detected by PET imaging in tumors as small as 1 cm.

Currently, FDG-PET is used in everyday clinical practice to help detect the presence of a variety of tumor types and to stage them (at initial diagnosis as well as for restaging after treatment), explained Dr. Lalitha K. Shankar, of the NCI Cancer Imaging Program and the lead author of the clinical recommendations.



Coronal images of FDG-PET before (four left panels) and after 3 months of treatment (four right panels) in a lymphoma patient. The left panels show increased FDG uptake in the right chest and in the left cervical and mediastinal lymph nodes. The right panels show a normal distribution of FDG, indicating response to therapy.

More recently, though, researchers have been investigating whether FDG-PET results can predict treatment response early (in the first 2 to 6 weeks) after treatment. In these studies, the levels of "tumor uptake" of FDG are measured before treatment and then again a short time later to see if that uptake has decreased, signaling a decline in the tumor cell population.

For instance, a small clinical trial published last year, of patients with advanced ovarian cancer undergoing presurgical chemotherapy, showed that changes in FDG-PET, even after the first chemotherapy cycle, accurately predicted outcomes and had superior accuracy compared with standard response criteria.

Similar trials involving other tumor types—lymphoma, esophageal and lung cancer—also have had good results, said Dr. Anthony Shields, a medical oncologist at the Karmanos Cancer Institute at Wayne State University, who also develops radiopharmaceuticals for use with PET imaging.

"Now we need to know in detail the sensitivity and specificity of that measurement," Dr. Shields said. "We need to figure out how good it is at predicting response and whether you can change treatment based on the PET results."

What's been missing from the studies and small clinical trials done to date, Dr. Shankar said, is consistency in the technical aspects of how the imaging procedures are performed. This includes measures such as preparing patients for the imaging procedures (varying blood glucose levels, for example, can skew the results); the timing of when the procedures are performed after treatment; and analyzing the resulting images, which can be done in different ways according to a number of different variables.

Ensuring consistency in the clinical trials testing FDG-PET in this fashion will be critical to moving the field ahead, says Dr. Steven M. Larson, of Memorial Sloan-Kettering Cancer Center, who directs the Laurent and Alberta Gerschel Positron Emission Tomography Center there.

"FDG-PET is likely to be the best candidate for a qualified biomarker," Dr. Larson argues. "But it will need to be assessed in large, multicenter trials. That's why standardization of

(continued on page 7)

Cancer Research Highlights

Taxol, Immunotoxin Combo Boosts Antitumor Effect in Mice

In mice injected with mesothelin-bearing tumors, researchers observed a synergistic antitumor effect by combining the drug paclitaxel (Taxol) and an immunotoxin—a bacterial toxin genetically engineered to target cancer cells. The combination was more effective than either the immunotoxin, SS1P, or the drug alone, and caused long-lasting complete remission in these mice.

"Either treatment alone had a small effect, but together they had an effect that was clearly more than additive," says lead researcher Dr. Ira Pastan of the Laboratory of Molecular Biology in NCI's Center for Cancer Research (CCR). His team previously reported an additive antitumor effect from combining the antibody bevacizumab (Avastin) with SS1P. The new study, in the August 1 *Clinical Cancer Research*, is the first description of a synergistic effect between a drug and an immunotoxin.

SS1P targets the protein mesothelin. This drug is active against both mouse tumors and tumor cells from patients with mesothelioma and ovarian cancer, all of which express mesothelin. Dr. Pastan's team showed that paclitaxel, at a dose that by itself has minimal antitumor effect, greatly increased the antitumor activity of SS1P against the injected tumors. They did not see a synergistic effect when the same tumors were treated in culture.

The researchers are still investigating the mechanism responsible for the different results. "The effect is what is important," says Dr. Pastan. "Even if we don't understand the mechanism, we should be able to design better treatment for patients with mesothelin-bearing tumors."

His team recently completed phase I trials with SS1P for mesothelioma and ovarian cancer, and a phase II trial is being planned. The researchers believe a paclitaxel/SS1P combination would be a good treatment plan for ovarian cancer because paclitaxel alone is effective for ovarian cancer and SS1P showed minor responses to ovarian cancer in the completed phase I trial.

Loss of Cellular Motor Protein Contributes to Tumor Formation

Investigators in NCI's CCR have shown that loss of the cellular motor protein KIF4, which plays a role in mitosis, may contribute to tumor formation, according to a study in the August 8 *Current Biology*.

The investigators isolated mouse embryonic stem cells lacking KIF4 (KIF4 KO cells), and observed defects in mitosis leading to aneuploidy (abnormal chromosome number) in more than 70 percent of KIF4 KO cells. When KIF4 KO cells were injected into nude mice, they formed significantly more and larger tumors than control cells, likely due to an increase in cellular proliferation.

In further *in vitro* experiments, the investigators showed that cell-cycle checkpoints were overridden in KIF4 KO cells, and these cells were significantly more likely than control cells to contain aberrant centrosomes, organelles that organize the cellular microtubules during cell division. Loss of KIF4 caused activation of cellular DNA damage-response pathways, which is a sign of cells with potential to form tumor cells.

In a probe of human tumor cell lines, including ovarian, lung, breast, and central nervous system cancers, KIF4 was absent or underexpressed in 35 percent of samples, strongly suggesting a link between loss of function of this protein and human tumor formation. "These results are important for two reasons," says Dr. Tom Misteli, one of the paper's authors. "First, the demonstration of a link between a molecular motor and tumor formation represents a new paradigm in the fields of molecule motors and cancer biology. Second, although the hypothesis that mitotic defects and aneuploidy can be causative in tumor formation has been around for a long time, it has been very difficult to prove experimentally. Our experiments support this idea."

Prenatal DES Exposure Linked to Breast Cancer Risk

Daughters of women who took diethylstilbestrol (DES) during pregnancy have an increased risk of breast cancer after age 40, according to a study in the August *Cancer Epidemiology Biomarkers & Prevention.*

DES is a synthetic estrogen prescribed to many pregnant women between 1938 and 1971 to prevent spontaneous abortion. It's estimated

(continued on page 5)

(Highlights continued from page 4)
that one to two million women had prenatal exposure to DES.

The study followed four cohorts of DES-exposed and -unexposed women identified from the National Cooperative Diethylstilbestrol Adenosis Project, a University of Chicago clinical trial, a Massachusetts private infertility clinic, and a study of health effects in mothers who took DES. The women completed questionnaires in 1994, 1997, 2001, and 2003 that gathered information on lifestyle, reproductive and hormonal factors, occurrence of cancer, and frequency of mammographic screening.

Researchers found that DES-exposed women aged 40 and older had 1.9 times the risk of breast cancer of unexposed women of the same ages. Women with the highest cumulative dose of DES also had the highest relative risk of breast cancer.

"These findings support the hypothesis that prenatal hormone levels affect breast cancer risk," said senior author Dr. Robert Hoover of NCI's Division of Cancer Epidemiology and Genetics.

"The study also highlights two important clinical implications: DES-exposed women should rigorously follow breast cancer screening guidelines and should carefully consider whether to take female hormone supplements," added study author Dr. Julie Palmer of Boston University.

CHEK2 Gene Mutation Increases Risk of Breast Cancer

A prospective study of more than 9,000 Danish women found that those who had a specific mutation in the tumor-suppressor gene *CHEK2* had a threefold increase in the lifetime risk for breast cancer compared with non-carriers of the mutation, according to a study published online July 31 in the *Journal of Clinical Oncology*.

Previously, smaller case-control studies suggested an association between the CHEK2*1100delC mutation and cancers of the breast, prostate, and colorectum. Researchers, led by Dr. Borge G. Nordestgaard at Herlev University Hospital in Denmark, decided to study the prevalence of the mutation and its impact on cancer risk in the general population. They randomly selected 9,231 participants from the Copenhagen City Heart Study who had been monitored for an average of 34 years for cancer development.

They found that 0.5 percent carried the *CHEK2* mutation. Among the women carriers, 12.5 percent developed breast cancer compared with 5 percent of noncarriers. Adjusting for other risk factors, the scientists found that carriers were 3.2 times more likely to develop breast cancer. However, they found no statistically significant association among *CHEK2* mutation carriers for prostate, colorectal, or general cancer risk.

Dr. Nordestgaard commented: "The identification of *CHEK2* as a biomarker gives us a better picture of the genetic risk factors, and may help to identify a significant subset of women who would benefit from more vigilant screening for the disease." Additional research is needed to identify if the study's findings apply to other ethnic groups, including blacks and Hispanics.

Synthetic Scorpion Venom Targets Brain Tumor Cells

The giant yellow Israeli scorpion kills its prey with venom that blocks chloride channels, but its bite is not fatal to people. The first human trial testing a synthetic version of the active protein in this venom, known as TM-601, shows that it may be a safe way to improve results in recurrent glioblastoma multiforme (GBM), a deadly brain cancer.

The drug is "simple to deliver, well tolerated, remains highly localized to the treatment site, and preliminarily seems safe for repeated injections," writes Dr. Adam N. Mamelak, of Cedars-Sinai Medical Center in Los Angeles, and colleagues in the August 1 *Journal of Clinical Oncology*.

The 18 adult patients in this phase I trial underwent surgery for GBM that had relapsed after first-line treatment. After removing all visible tumor tissue, surgeons implanted a small device under the patients' scalps with a tube leading to the surgical site. Two to 4 weeks later, when the patients had recovered from surgery, TM-601 tagged with iodine-131 was injected directly into the tumor cavity, with six patients each getting 0.25, 0.50, and 1.0 mg of the drug.

Patients had very few and only minor adverse effects 3 weeks after receiving the drug. Imaging showed that TM-601 attached almost exclusively to tumor cells, with very little residue elsewhere in the body. Two-thirds of patients achieved stable disease, and two women receiving the 0.50 mg dose had complete responses, no recurrent disease, and were still alive 37 and 39 months, respectively, after surgery. ◆

Featured Meetings and Events

A calendar of scientific meetings and events sponsored by the National Institutes of Health is available at http://calendar.nih.gov ◆

Funding Opportunities

Following are newly released NCI research funding opportunities:

Exfoliated Cells and Circulating DNA in Cancer Detection and Diagnosis

Announcement Number: RFA-CA-07-027
Letter of Intent Receipt Dates: Aug. 26 and Dec. 29, 2006; April 23, 2007.
Application Receipt Dates: Sept. 26, 2006; Jan. 29 and May 23, 2007.

This is a renewal of RFA-CA-06-001 and will use the R43/R44 award mechanism. For more information, see http://cri.nci.nih.gov/4abst.cfm?initiativeparfa_id=3517. Inquiries: Dr. Padma Maruvada—maruvadp@mail.nih.gov

Exfoliated Cells and Circulating DNA in Cancer Detection and Diagnosis

Announcement Number: RFA-CA-07-028
Letter of Intent Receipt Dates: Aug. 26 and Dec. 29, 2006; April 23, 2007.
Application Receipt Dates: Sept. 26, 2006; Jan. 29 and May 23, 2007.

This is a renewal of RFA-CA-06-001 and will use the R41/R42 award mechanism. For more information, see http://cri.nci.nih.gov/4abst.cfm?initiativeparfa_id=3518. Inquiries: Dr. Padma Maruvada—maruvadp@mail.nih.gov

For comprehensive information about NCI funding priorities and opportunities, go to http://www.cancer.gov/researchandfunding. ◆

The NIH Roadmap for Medical Research Funding *provides a framework of the priorities NIH must address to optimize its research portfolio. It identifies the most compelling opportunities in three main areas: new pathways to discovery, research teams of the future, and re-engineering the clinical research enterprise. For information on additional Roadmap funding opportunities, go to http://nihroadmap.nih.gov.*

Featured Clinical Trial

Extending Immunotherapy for Metastatic Melanoma

Name of the Trial
Phase I Study of Lymphodepleting Chemotherapy Comprising Cyclophosphamide and Fludarabine Followed by MART-1 Antigen Vaccination, Transduced Autologous Tumor-Infiltrating Lymphocytes or Peripheral Blood Lymphocytes, and High-Dose Interleukin-2 in Patients with HLA-A*0201-Positive Metastatic Melanoma. See the protocol summary at http://cancer.gov/clinicaltrials/NCI-04-C-0251.

Dr. Steven Rosenberg

Principal Investigator
Dr. Steven Rosenberg, NCI Center for Cancer Research

Why This Trial Is Important
Clinical trials involving an immunotherapy method known as adoptive cell transfer have shown promising results in some patients with melanoma that has metastasized (spread) to other parts of the body.

In adoptive cell transfer, tumor-infiltrating T lymphocytes, or TILs, are harvested from a patient's tumor(s), and the cancer-fighting properties of these cells are enhanced in the laboratory. The TILs are subsequently expanded (grown) to increase their numbers and then injected back into the patient. Adoptive cell transfer for melanoma focuses on TILs that target an antigen called MART-1, which is found on melanoma cells.

Tumor-reactive TILs cannot be obtained, however, from many patients. Thus, researchers have developed techniques to genetically engineer a patient's T lymphocytes to express the receptor protein that recognizes and binds to MART-1. The modified cells are then grown and infused into the patient.

This study will involve two groups of patients. One group will receive TILs containing transferred genes for the MART-1 receptor; the second group will receive T lymphocytes isolated from blood that also contain added MART-1 receptor genes.

"If these genetically engineered cells prove safe and show antitumor activity," said Dr. Rosenberg, "we plan to create lymphocytes that can target more common malignancies, including breast and colorectal cancers. There is tremendous potential here."

Who Can Join This Trial
Researchers will enroll 80 patients aged 18 and over who have been diagnosed with metastatic melanoma. See the complete list of eligibility criteria at http://www.cancer.gov/clinicaltrials/NCI-04-C-0251#EntryCriteria_CDR0000383246.

Study Site and Contact Information
The trial is taking place at the NIH Clinical Center in Bethesda, Md. For more information, call the NCI Clinical Studies Support Center at 1-888-NCI-1937. The toll-free call is confidential. ◆

An archive of "Featured Clinical Trial" columns is available at http://cancer.gov/clinicaltrials/ft-all-featured-trials.

Notes

Two NCI Nurses Selected as AAN Fellows

Two NCI nurses, Kathleen Calzone and Dr. Ann O'Mara, were among 55 nurse leaders who will be inducted as Fellows of the American Academy of Nursing at the Academy's annual meeting in November. Ms. Calzone is with the Clinical Cancer Genetics Branch of CCR and Dr. O'Mara is with the Community Oncology and Prevention Trials Research Group in the Division of Cancer Prevention.

Criteria for selection to the Academy include evidence of significant contributions to nursing and health care, and selection is based, in part, on the extent to which nominees' nursing careers influence health policies for the benefit of all Americans.

President's Cancer Panel Examines Lifestyles

During 2006 and 2007, the President's Cancer Panel will hold a series of meetings on "Promoting Healthy Lifestyles to Reduce the Risk of Cancer." The series will begin on September 11 in Minneapolis, where the Panel will hear testimony from invited participants and the public on how obesity, physical activity, and nutrition affect cancer risk. The Panel will explore both current research and existing knowledge gaps in these areas, as well as programs relevant to healthy lifestyles and cancer risk reduction.

Meetings of the President's Cancer Panel are free, open to the public, and require no registration. For more information on these meetings or the Panel itself, go to http://pcp.cancer.gov or contact Karen Parker at 301-452-9462 or klparker@mail.nih.gov.

NIH to Host Conference on Health Disparities

The NIH Office of Behavioral and Social Research will hold a conference, "Understanding and Reducing Disparities in Health: Behavioral and Social Sciences Research Contributions," on October 23–24 on the NIH campus.

The conference will focus on three broad areas influencing health disparities: policy, prevention, and health care. It will emphasize basic research on the behavioral, social, and biomedical pathways giving rise to disparities in health, as well as applied research on the development, testing, and delivery of interventions to reduce disparities in these three areas.

The agenda and registration information are available at http://obssr.od.nih.gov/HealthDisparities/index.html.

Surgeon General's Term Ends

Last week, Surgeon General Dr. Richard H. Carmona left his post upon completion of his 4-year term. In late June, Dr. Carmona issued a comprehensive scientific report that concluded there is no risk-free level of exposure to secondhand smoke. This finding is a major public health concern since nearly half of all nonsmoking Americans are still regularly exposed to secondhand smoke.

The report, *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*, found that even brief secondhand smoke exposure can cause immediate harm to people's health. The report noted that the only way to fully protect nonsmokers from the dangerous chemicals in secondhand smoke is to eliminate smoking indoors. ◆

(Spotlight continued from page 3)

the procedures from site to site is so important—to improve the reproducibility of the test."

Implementing the clinical recommendations, published in the June 2006 issue of *The Journal of Nuclear Medicine*, in NCI-sponsored trials "gives us a good place to start the next series of evaluations of FDG-PET as a marker of therapeutic response," Dr. Shankar explains. "This way, we can better evaluate, in a more uniform fashion, whether FDG-PET can help as a biomarker for assessing treatment response in a variety of tumors, doing it as a correlative study within the context of a larger therapeutic trial."

Approximately 10 clinical trials approved by the NCI Cancer Therapy Evaluation Program (CTEP) are already working under the auspices of these recommendations, and Dr. Shankar is working with CTEP to ensure that other trials follow suit.

"The imaging and oncology communities have really welcomed this activity," Dr. Shankar says. "And our colleagues in the pharmaceutical industry have as well. They participated in the workshop last year, and they are also using these recommendations in their trials."

Because of the rapid changes in imaging technologies, including PET, the recommendations will be revisited every few years, Dr. Shankar notes. NCI is also interested in consulting with cancer centers and other institutions who wish to work the recommendations into their own single- or multi-institution trials. ◆

By Carmen Phillips

Community Update

Video Game Educates and Entertains Young Cancer Patients

Swiftly maneuvering through the blood stream, Roxxi, an RX5-E Class nanobot, spots a medulloblastoma cell. Roxxi pulls out a chemoblaster and lets loose with several rounds of green projectiles that seek and destroy the malignant cell before it can multiply.

Although it's a shoot-em-up video game—complete with a "Teen" rating—*Re-Mission*, the game that features Roxxi, is geared toward a very specific audience: teenagers and young adults being treated for cancer. Roxxi relies on an unconventional combat arsenal to battle bacterial infections, constipation, anxiety, and other treatment-related side effects.

Re-Mission, explained Dr. Steve W. Cole, vice president of research for HopeLab, the nonprofit organization behind the game, was designed to help young cancer patients better understand their cancer "and to do it in a way that helps them understand how their behavior impacts the biology of their disease."

In addition to offering a welcome distraction from treatment and side effects, the game reinforces the importance of things like sticking to a home chemotherapy regimen or taking a stool softener in the event of constipation—something that, left untreated, can be extremely dangerous, even fatal.

And it appears to work.

In Re-Mission*, young players guide Roxxi through the complex environments of the human body.*

HopeLab—at the direction of its founder, Pam Omidyar, who worked as a research assistant in an immunology lab while pursuing a master's degree in molecular biology—put the game through the rigors of a randomized, controlled intervention trial. Involving 375 male and female patients aged 13 to 29, the trial demonstrated that, compared with patients who regularly played another popular video game, patients who played *Re-Mission* had better scores on psychosocial assessments such as quality of life. More important, though, patients who played *Re-Mission* had significantly higher chemotherapy blood metabolite levels and rates of antibiotic utilization.

"The upshot is that this game works," Dr. Cole said. "It shows that video games can be a powerful tool for behavior change in the real lives of patients."

Re-Mission was carefully developed to ensure that its presentation of different cancers was biologically precise, while at the same time ensuring that it had the elements of fun and challenge of popular video games. HopeLab recruited cancer researchers, doctors, nurses, and psychologists to work with experienced video game developers to craft *Re-Mission*'s 20 stages, and HopeLab solicited feedback from and regularly tested the game with young cancer patients to make sure that it was fun, and above all, spoke to their situations.

"We have heard over and over from kids who played this game that 'This is about me and the issues I'm confronting,'" Dr. Cole says. "It's gratifying to hear them say that we hit the mark."

Re-Mission even has its own Internet community, http://www.re-mission.net, where young cancer patients, clinicians, and caregivers can order the game, free of charge. The Web site also has information about cancer and message boards and blogs. ◆

The *NCI Cancer Bulletin* is produced by the National Cancer Institute (NCI). NCI, which was established in 1937, leads the national effort to eliminate the suffering and death due to cancer. Through basic, clinical, and population-based biomedical research and training, NCI conducts and supports research that will lead to a future in which we can identify the environmental and genetic causes of cancer, prevent cancer before it starts, identify cancers that do develop at the earliest stage, eliminate cancers through innovative treatment interventions, and biologically control those cancers that we cannot eliminate so they become manageable, chronic diseases.

For more information on cancer, call 1-800-4-CANCER or visit http://www.cancer.gov. Contact the *NCI Cancer Bulletin* staff at ncicancerbulletin@mail.nih.gov.