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Martha Askins, Ph.D., an assistant psychologist in the Department of Pediatrics and the psychosocial director of the Adolescent and Young Adult (AYA) Program, helps and with their studies in the AYA classroom. The program helps patients stay on grade level by offering a hospital school and by coordinating homebound education.

Program Addresses Medical, Psychosocial Needs of Young People with Cancer

As recently as 10 years ago, a 15-year-old facing treatment for cancer likely would find herself thrust into a state of limbo—both medically and socially. She probably would reside on a unit with patients much older or younger than herself, miss out on several years of school and related social experiences, and receive treatments designed for either children or adults.

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Program Addresses Needs of Young People with Cancer

(Continued from page 1)

Today, however, adolescence is increasingly being viewed as a distinct age group that—like pediatric, adult, and geriatric groups—has unique medical and psychosocial needs. Meeting those needs is the goal of the Adolescent and Young Adult (AYA) Program at The University of Texas M. D. Anderson Cancer Center. The program, one of the first of its kind, aims to provide more consistent treatment for adolescents with cancer in an environment that fosters educational, social, and emotional development.

“We started developing the AYA Program three years ago,” said Martha Askins, Ph.D., an assistant psychologist in the Department of Pediatrics and the psychosocial director of the program. At that time, Archie Bleyer, M.D., a professor in the Department of Pediatrics, originated the AYA Program based on his observations that teenagers and young adults with cancer, as a population group, were—in many ways—being underserved. Dr. Bleyer had published national data indicating that the rate of progress in the treatment of cancer in this age group was falling behind that being achieved in younger patients.

Age-appropriate treatments

The incidence of cancer in adolescents “is increasing at a faster rate than in children and adults,” while the mortality rate “is decreasing at a slower rate than in children and adults,” explained Sima Jeha, M.D., an assistant professor in the Department of Pediatrics and the medical director of the AYA Program.

One explanation Dr. Jeha sees for the lower cure rate is that, as adolescents have not historically been considered a separate entity, they have been treated under either pediatric or adult protocols.

For example, the decision of which department treats a teenager with osteosarcoma might be based on factors such as in which unit (pediatric or adult) the patient feels more comfortable or to which physician the patient was referred. These decisions could significantly alter the patient’s treatment if there are different protocols for pediatric and adult osteosarcoma.

The problem with dividing adolescents between protocols is that doing so makes it difficult to know which treatments are most effective for that age group. Dr. Jeha said that having treatment protocols designed specifically for adolescents would enable doctors to tailor treatment dosages and methods to the patient’s stage of development, which could lead to improvements in teen cure rates.

“There should not be one best treatment [for adolescents] on the pediatric floor and another best treatment on the adult floor for the same disease,” Dr. Jeha said.

To this end, M. D. Anderson physicians are developing protocols that ensure that adolescents with cancer who have the same disease receive the same medical treatment.

Their efforts will not necessarily result in a specific protocol for 15- to 25-year-olds. The age group on a given protocol will vary for each disease and will depend upon discoveries about the peak incidences of the disease and patients’ responses to treatment, Dr. Jeha said.

Though protocols will not be designed with the sole purpose of treating adolescents uniformly, “it would end up being that a lot of this age group would be treated under the same protocol versus split in the middle,” she said.

For example, M. D. Anderson physicians recently developed combined protocols for osteosarcoma and Ewing’s sarcoma that patients receive irrespective of whether they are being treated in the pediatric or adult service. According to Dr. Jeha, this type of consolidated care for patients of all ages would not be possible outside of a comprehensive cancer center.

Also under consideration is a modification of the treatment protocols for acute leukemia. Currently, there are two sets of protocols: one for children and one for adults. In place of this traditional division, doctors are considering instituting protocols based on the disease biology and current treatment successes. With the present protocols, cure rates are very high until patients reach the age of 10, when the rates begin dropping. Doctors intend to keep patients younger than 10 and older adults on the current protocols and design a third protocol for those in between.

Improving cure rates for teens will also require a commitment to pioneering clinical trials that focus on adolescent cancer treatment. Adolescents are not well represented in national studies, probably because they are generally considered too old for pediatric studies but too young for adult studies.

“We really need to make sure that studies are done specifically for adolescents to improve their survival rate,” Dr. Jeha said.

Psychosocial initiatives

Providing appropriate psychosocial support for patients goes hand-in-hand with improving their medical treatment. Recognizing that adolescence is a critical transitional stage when young people are developing socially, making educational and career choices, and becoming independent, the AYA Program attempts to enable teens to continue
their normal emotional, social, and educational development while receiving treatment for cancer.

According to Dr. Askins, when a teen receives a diagnosis of cancer, the family’s first reaction is often to “drop everything and focus on the cancer.” In contrast, AYA Program coordinators emphasize to teens and their families the importance of continuing education and maintaining social relationships.

“Emotionally, it’s very helpful for children to be able to continue doing many of the same things they did before they were diagnosed with cancer, so they learn that while they do have to focus a lot of energy on their cancer treatment, the other areas of their lives can still be important,” Dr. Askins said.

With the help of counselors and teachers in the AYA Program, teenagers with cancer can continue their education by attending their community schools, receiving homebound education, or enrolling in the hospital school, which works in association with the Houston Independent School District and has been successful at keeping students on grade level.

As difficult as maintaining basic educational progress in the face of cancer treatment can be, the AYA Program coordinators aim beyond minimal educational goals.

“We don’t want cancer treatment to derail those who have aspirations to go on to college and even farther,” Dr. Askins said.

Educational counselors help students prepare for college entrance exams and guide them through the college and scholarship application processes. Of the 40 current patients or long-term survivors treated at M. D. Anderson who graduated in the class of 2000, about 75% are going on to college, and at least five were in the top 10% of their class, Dr. Askins said.

At the other end of the continuum, the program also focuses on helping patients with cognitive disabilities find a rewarding educational setting.

To foster the peer interaction that teenagers often miss out on while being treated for cancer, M. D. Anderson has begun housing all teens in the same area of the hospital. “We have a unit where all the inpatient teens come together from different services, and it’s working very well,” Dr. Jeha said.

The program also provides an area for teens to regularly come together and socialize, and outings—such as ski trips, symphony concerts, or visits to the rodeo—give teens the opportunity to socialize and provide a respite from the hospital.

These activities, Dr. Askins said, provide “important opportunities for the teens to just spend time together and to share support with peers as they are going through the treatment process.”

Other services of the AYA Program include vocational and career guidance; support groups and psychotherapy; computer training; physical fitness and rehabilitation classes; counseling on sexuality, fertility, sperm banking, and body image; an annual summer camp; and life skills courses to help teens learn practical things like how to handle relationships and manage personal finances. All of the AYA Program’s psychosocial activities are funded by M. D. Anderson’s Children’s Art Project, which also supports educational programs such as the hospital classroom and scholarships for graduate and undergraduate students.

Some individual programs are particularly innovative, such as providing teens with pagers that allow them to wait for appointments in a relaxed setting with other patients of the same age, freeing them from what can be an awkward time in the waiting room prior to clinic appointments.

Another unique aspect of the AYA Program is the planned addition of Kim’s Place, which will provide a recreational area as well as vocational and psychosocial support to adolescents and young adults whose lives have been affected by cancer. Construction of the facility is made possible by a donation from the Women’s National Basketball Association Houston Comets in honor of Kim Perrot, a Comets player who died of lung and brain cancer in 1999. Kim’s Place will be located in the Albert B. and Margaret M. Alkek Hospital at M. D. Anderson and is expected to open in 2002.

The AYA Program’s focus on the non-treatment-related aspects of adolescent patients’ lives does more than make the patients’ treatment at M. D. Anderson more pleasant, according to Dr. Askins.

“It conveys our feeling of hope, that they are going to beat their illness and that they are going to have a bright future,” she said.

For more information, contact Dr. Askins at (713) 794-4466 or Dr. Jeha at (713) 792-0829.
Molecular Radiosensitizers Target Proliferation and Apoptosis Pathways in Tumor Cells

by Kerry L. Wright

A patient lies quietly on a radiation treatment table. In an instant, ionizing radiation enters the patient's tumor cells and surrounding tissue, causing single-strand and double-strand DNA breaks. But the invasion activates the cells' sophisticated repair machinery, the damage is quickly repaired, and the tumor continues to grow. To overcome the tumor cells' defense mechanisms, traditional radiosensitizers are often combined with radiation treatment to enhance the damage done to tumor cells by inducing more damage or inhibiting DNA repair. Now, scientists are moving away from these classic radiosensitizers and toward molecular ones that damage tumors in a different way—by inhibiting cell proliferation and enhancing apoptosis, the very mechanisms that determine whether a tumor cell grows or dies.

"You can do damage in so many different ways, but in fact what we are trying to achieve with radiosensitizers is a larger differential between damage to tumors and damage to normal tissues," said Luka Milas, M.D., Ph.D., professor and chairman of the Department of Experimental Radiation Oncology at The University of Texas M. D. Anderson Cancer Center.

C225 and COX-2 inhibitors

One novel way to increase damage to tumor cells while limiting damage to normal cells is to target proliferative or apoptotic proteins that are overexpressed in tumor cells. One such target is epidermal growth factor receptor (EGFR), a protein tyrosine kinase that binds ligands such as EGF to initiate pathways that lead to cell growth. EGFR exceeds normal levels in several cancers, including breast, ovarian, bladder, head and neck, and prostate cancers.

"Overexpression of epidermal growth factor receptor is associated with more aggressive tumors and tumors more resistant to chemotherapy and radiation," said Dr. Milas.

Radiation can actually increase the activity of EGFR in some tumors and may therefore increase proliferation and prevent radiation-induced apoptosis. Dr. Milas and others thought that if EGFR could be blocked, then cells would become more sensitive to apoptosis after radiation. C225, an anti-EGFR monoclonal antibody developed by M. D. Anderson President John Mendelsohn, M.D., and collaborators and originally used as a chemosensitizer, is now being examined in Dr. Milas' laboratory for its effectiveness as a radiosensitizer. C225 has been shown to be effective in vitro, but Dr. Milas and colleagues were the first to show that it is also effective in vivo.

"In preclinical models, C225 is highly effective in enhancing the radioreponse of human tumor xenografts," said Dr. Milas. Multiple intraperitoneal injections of C225 increased tumor radioreponse more than 3.5 times normal levels in nude mice bearing squamous cell carcinomas. The augmented radioreponse included decreased angiogenesis and increased necrosis, infiltration with granulocytes, and terminal differentiation of tumor cells—although the mechanisms responsible for this augmented response have not yet been established.

Other new agents target proteins that are not expressed in normal cells. The enzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) regulate the synthesis of prostaglandins, metabolites that promote tumor growth. COX-1 is ubiquitous, but COX-2 is induced by a number of different stimuli, including inflammatory stimuli and growth factors, such as those present in tumors.

"We know that tumors contain large quantities of prostaglandins,
so the logic was that if the prostaglandins are there in large quantity, then they may be another reason why tumors are radioresistant,” said Dr. Milas. He and his collaborators believed that by inhibiting COX-2, prostaglandin synthesis would be selectively inhibited in tumor cells, and tumors would become more sensitive to radiation. Dr. Milas and colleagues have shown that the COX-2 inhibitor SC-236 alone can delay growth of tumor cells in vitro and of murine tumors as well as human tumor xenografts. And it has a synergistic effect when combined with radiation. COX-2 inhibitors may indeed work by inhibiting prostaglandin synthesis, but as with C225, there may be additional mechanisms, including making cells more sensitive to radiation, shifting cells to more radiosensitive cell-cycle phases, or inhibiting angiogenesis.

**Mechanisms of classic radiosensitizers**

Classic radiosensitizers fall under two main categories: those that are used based on the assumption that tumors proliferate faster than normal cells and those that target hypoxic tumor cells.

Radiosensitizers such as halogenated pyrimidines are used to exploit the accelerated proliferation of some tumor cells, but they have not been entirely successful. Like halogenated pyrimidines, nucleoside analogues are incorporated into DNA, where they inhibit repair enzymes. However, they also alter cell-cycle sensitivity, creating an advantage over the classic pyrimidines. For example, the nucleoside analogues fludarabine and gemcitabine kill S-phase cells by apoptosis, inducing accumulation of G2/M-phase cells, which are the most sensitive to radiation.

According to James D. Cox, M.D., professor and head of the Division of Radiation Oncology at M.D. Anderson, the disadvantage of nucleoside analogues is their systemic toxicity. Even though the analogues may be more effective than classic agents in their category and as effective as new molecular agents such as C225 and COX-2 inhibitors, the new radiosensitizers may eventually prove more useful than nucleoside analogues in the clinic.

The second class of traditional radiosensitizers works by targeting hypoxic tumor cells, those that do not receive enough oxygen. Most tumors grow outward, away from the blood vessels that supply them with the oxygen they need to survive. Oxygen can diffuse about 100 to 150 μm, often leaving an area of hypoxic cells in the center of a tumor. When oxygen is absent, radiation-damaged cells can repair themselves, but when oxygen is present, damage inflicted by radiation-induced free radicals is “fixed” and becomes permanent. Thus, oxygen is essentially one of the best radiosensitizers available.

“If you irradiate the cell under well-oxygenated conditions and compare that to irradiation under complete hypoxia, then hypoxic cells are about 2.5 to 3 times more radioresistant,” said Dr. Milas. However, many classic hypoxic cell sensitizers, such as nitroimidazoles, which act as oxygen substitutes to sensitize hypoxic cells to radiation damage, are highly neurotoxic. Newer bioreductive drugs such as mitomycin C and tirapazamine, which are selectively cytotoxic to hypoxic cells, have been more successful, as they eliminate the hypoxic cells and leave behind oxygenated cells that are more sensitive to radiation. Similarly, traditional chemotherapy can be used to kill well-oxygenated cells, allowing the center of a tumor to become oxygenated and thus more susceptible to radiation.

**Molecular radiosensitizers in clinical studies**

According to Dr. Cox, the main advantage of bioreductive drugs and the new molecular agents (such as SC-236 and C225) is their lack of toxicity. In addition, most traditional radiosensitizers can be used only in the treatment of solid tumors, whereas the new molecular agents can be used for all cancers, including leukemias and lymphomas.

Other molecular radiosensitizers, including farnesyl transferase inhibitors (targeting the ras pathway of cell growth), the blocking antibody Herceptin (targeting HER-2/neu, a cell-growth receptor overexpressed in several cancers), and antiangiogenic agents, are being investigated or will be investigated in the near future, said Dr. Milas. According to Dr. Cox, however, the emphasis now is on agents such as C225 and COX-2 inhibitors that have already exhibited improvements over traditional radiosensitizers and are ready or near ready for clinical investigation.

Although COX-2 inhibitors are still in the preclinical stage of development, patients have been enrolled in pilot studies of C225 as a radiosensitizer in the treatment of squamous cell carcinoma of the head and neck.

“I think we are all enthusiastic about the molecular radiosensitizers C225 and COX-2 inhibitors,” said Dr. Cox. “We not only have the ability to show interactions of these agents with ionizing radiation in the lab and to explore their basic mechanisms, but we then have the ability to take these drugs into the patient-care environment,” he said.

For more information, contact Dr. Milas at (713) 792-3263 or Dr. Cox at (713) 792-3411.
Endostatin: Phase I Trial Yields Promising Preliminary Results

By Kris Muller and Kerry L. Wright

Early results from a much-anticipated phase I trial of recombinant human Endostatin at The University of Texas M. D. Anderson Cancer Center suggest that the drug is safe and indicate some encouraging activity.

According to James L. Abbruzzese, M.D., professor and chairman of the Department of Gastrointestinal Medical Oncology and director of the National Cancer Institute grant that funds the trial, Endostatin has been well tolerated by patients and has produced few toxic side effects. In addition, the drug’s concentration in the bloodstream has clearly reached targeted levels.

Endostatin is one of several anti-angiogenic compounds that have been shown in animal studies to shrink tumors by decreasing their blood supply.

“The beauty of these angiogenesis inhibitors is that they are probably not going to be toxic. They are working specifically against endothelial cells and not tumor cells and should produce minimal, if any, side effects on normal tissues,” said Roy Herbst, M.D., Ph.D., the principal investigator of the M. D. Anderson study and an assistant professor in the Department of Thoracic/Head and Neck Medical Oncology.

Preliminary results from 20 patients treated on the M. D. Anderson protocol were reported Nov. 9, 2000, at the annual Symposium on New Drugs in Cancer Therapies.

In the M. D. Anderson study, patients with malignant solid tumors for whom there was no available curative therapy underwent intravenous infusion of graduated doses of Endostatin (starting at 15 mg/m² and escalating in six steps to 300 mg/m²) 20 minutes a day for 28 days. Blood samples were drawn to monitor Endostatin serum concentrations, and patients underwent regular biopsies, computerized tomography (CT), and positron emission tomography (PET) to measure blood flow and metabolic activity within their tumors. CT and PET scans showed that tumor blood flow decreased with increasing doses of Endostatin. In addition, one patient had some reduction in tumor volume, and a patient with melanoma had stable disease for approximately one year. The other patients have not experienced any major clinical benefits.

“We are hoping that if we increase the dose, it might make Endostatin a more uniformly effective drug,” said Dr. Herbst. Three new patients will be added to the protocol by the end of the year, and each will receive a starting dose of 600 mg/m². Although the trial has almost completed accrual, research is still being conducted on the best way to administer the drug, and clinicians at M. D. Anderson are considering adopting a continuous infusion schedule.

“We still need to figure out what the best schedule is, how often to give it, and what dose to give it at,” said Dr. Herbst, “but we are clearly making progress in the right direction.”

Dr. Herbst and colleagues hope to see Endostatin move on to phase II studies, either as a single agent or in combination with chemotherapy. According to Dr. Herbst, Endostatin and other angiogenesis inhibitors with low toxicity also have the potential to become maintenance therapies that could be given to patients to prevent tumor growth or cancer recurrence (much like insulin is given to patients with diabetes). In addition, this type of agent might ultimately be used for chemoprevention in patients at high risk of cancer.

Other angiogenesis inhibitors being examined in clinical trials at M. D. Anderson include thalidomide, TNP-470, SU5416, squalamine, SU6668, interferon, and inhibitors of protein kinase C.

For more information, contact Dr. Abbruzzese at (713) 792-2828 or Dr. Herbst at (713) 792-6363.
Cancer Screening: Early Detection Does Make a Difference

There are many reasons to put off getting screened for cancer. You're afraid of what the results might show. You are too busy to make an appointment. You have heard that the test will be unpleasant or painful. On the other hand, there's really only one reason to have regular cancer screenings: they could save your life.

Effective screening methods are able to detect cancer before symptoms appear, allowing doctors to treat the cancer while it is still in a very early stage. But can discovering and treating a cancer early really make that much difference? In some cases, yes. Below is a look at some of the most common types of cancer and the impact of screening and early detection in each one.

(Screening recommendations are based on American Cancer Society and M. D. Anderson Cancer screening guidelines.)

■ Breast Cancer

While the incidence of breast cancer remains high, death rates have significantly declined in the past decade, most likely owing to earlier detection and improved treatment. Mammograms (x-rays of the breast) and breast exams by a health care professional have been proven in clinical trials to reduce mortality.

For women at average risk for breast cancer, M. D. Anderson encourages monthly breast self-exams beginning at age 20 and recommends a clinical breast exam every 3 years between the ages of 20 and 39 and an annual breast exam and mammogram beginning at age 40. Women at increased risk should consult their doctors for modified screening recommendations.

■ Prostate Cancer

Prostate cancer spreads slowly, and unnecessary treatment can be harmful to patients. While researchers are trying to determine how early detection and treatment affect survival, many physicians believe that current screening methods are beneficial and should be used.

M. D. Anderson recommends an annual digital rectal examination (a health professional inserts a gloved finger into the rectum and feels the prostate gland for abnormalities) and a prostate-specific antigen blood test for men ages 50 to 70 who have a life expectancy of at least 10 years and who have been counseled and understand the risks of screening.

■ Colorectal Cancer

Both the incidence of and death rates from colorectal cancer have declined significantly, possibly because of increased screening and polyp removal. Fecal occult blood tests (examination of the stool for hidden blood) and sigmoidoscopy (a flexible tube is inserted into the rectum to look for polyps, tumors, or abnormal areas in the rectum and lower colon) have been shown to improve survival in clinical trials.

M. D. Anderson recommends an annual fecal occult blood test and flexible sigmoidoscopy every 5 years beginning at age 50, a colonoscopy (similar to sigmoidoscopy but examines the entire colon) every 10 years, or a double-contrast barium enema every 5 to 10 years. A digital rectal exam is also recommended at the time of sigmoidoscopy or colonoscopy.

■ Cervical Cancer

The Pap smear, the collection of cells from the cervix for examination under a microscope, has been suggested (by observations of patients over long periods of time) to reduce mortality. Cervical cancer death rates have decreased by more than 70% in the United States since the Pap smear was developed in 1941. An annual Pap smear and pelvic examination are recommended for all women who are sexually active or over the age of 18.

According to the National Cancer Institute, if everyone in the United States followed all of the available cancer screening recommendations, the total number of cancer deaths each year could decrease by up to 35%. Make this prediction come true—ask your doctor about available screening methods and make an appointment for screening today.

For more information, contact your physician or contact the M. D. Anderson Information Line:

☐ (800) 392-1611 within the United States, or

☐ (713) 792-6161 in Houston and outside the United States.

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DiagLog

Coming of Age ... with Cancer

Sima Jheh, M.D.
Medical Director, Adolescent and Young Adult Program

Being an adolescent is difficult. Many changes take place that will ultimately shape a young person's physical, emotional, and social self. Throw in a diagnosis of cancer, and the challenge increases exponentially. How can teens learn to be independent when becoming a patient makes them rely so heavily on family support and medical interventions? How can they preserve their self-esteem in the face of disfiguring disease and treatment? How can they plan for their future when they suddenly realize they may not have one?

Several cancers have a peak incidence during adolescence and young adulthood, and yet medical services are organized such that patients in this age range are rather arbitrarily divided into either pediatric or adult medicine departments, with no service dedicated specifically to adolescents. Perhaps as a consequence, adolescents and young adults have had a lower reduction in cancer mortality than older or younger persons.

Like all patients, adolescents and young adults with cancer need more than optimal treatment for their cancer; they need care that addresses the particular needs and demands of their physical and emotional maturation. In addition to therapies that improve the cure rate of cancer in this age group while minimizing long-term negative treatment effects, successful treatment of adolescents and young adults includes a recognition of the unique developmental challenges faced by young people as they cope with their illnesses.

One of the most important challenges young people with cancer face is staying academically competitive during treatment and recovery. Patients often need encouragement and counseling to stay at grade level and plan for college, and patients who are hospitalized for long periods of time may benefit from tutors or hospital schools.

Preventing the loss of self-esteem is paramount. A successful program for the treatment of adolescents and young adults helps patients avoid weight gain or loss, continue somatic and sexual growth and development, fulfill physical and mental expectations, and improve social and intellectual skills. At M. D. Anderson, we created an age-appropriate setting where adolescents and young adults can share their experiences, support each other, and benefit from specialized emotional, educational, and vocational tutoring.

Programs such as the Adolescent and Young Adult Program at M. D. Anderson can bridge the gap between pediatric and adult cancer care. We believe that helping these patients maintain an optimal lifestyle during treatment and recovery will give them the strength to win their battles with cancer and lead successful lives.