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Patient Care

Chemotherapy Dosing in Overweight and Obese Patients

Excess body weight (overweight and obesity) is becoming more common and is a risk factor for many diseases and conditions. It increases the risk for such disorders as hypertension, diabetes, hyperlipidemia, stroke, and even some cancers (e.g., breast, colon, esophagus, and kidney). It is therefore not uncommon for oncologists to encounter obese patients in their practice settings. However, there is much debate on how to properly dose chemotherapeutic agents in this population, and this decision is not without some very sobering concerns and consequences. Too much exposure to chemotherapy runs the risk of excessive toxicity. Not enough may compromise response and survival.

Defining Overweight and Obesity

While overweight and obesity can both be defined as a body weight greater than what is typically considered healthy, obesity further implies a significant degree of excess adipose tissue. The most widely accepted method for determining the two is body mass index (BMI), which is calculated as:

$$BMI = \frac{\text{weight}}{\text{height}^2}$$

where weight is measured in kilograms and height in meters². This formula is the same for adults and children;

cont., p. 2



Dr. Shane Cross
Department
of Pharmaceutical
Sciences

Translational Research

St. Jude Investigators Find the Signaling System That Halts Medulloblastoma Growth

Medulloblastoma, a rare and often fatal childhood tumor that occurs in the cerebellum, strikes about 350 young children in the United States annually. Although patients who undergo treatment have an overall 5-year survival rate of 70%, conventional therapies combining surgery, irradiation, and chemotherapy frequently cause permanent neurocognitive impairment. A recent discovery by St. Jude scientists may lead to safer treatments for medulloblastoma.

Signaling in the developing cerebellum

A team led by Martine Roussel, PhD, Genetics and Tumor Cell Biology, found that one of the brain's signaling pathways inhibits the growth of the highly aggressive cancer cells. Three proteins critical to limb development, BMP2, BMP4, and BMP7, halted the growth of medulloblastoma tumors and induced the malignant cells to develop into normal neurons. "We think we have identified a pathway that can be used to prevent tumor formation and [as] a potential target for therapy," said Roussel.

Granule neuron progenitor cells (GNPs) normally develop into neurons in the cerebellum during

cont., p. 5



Dr. Martine Roussel
Department of Genetics
and Tumor Cell Biology

Obese cont. from p. 1

however, there are some differences in how the results are interpreted. For instance, adult BMI results are separated into clusters to determine weight categories. These categories are the same for all adults and do not make distinctions with regard to age or sex (Table 1).

Table 1. Adult weight categories based on BMI

BMI	Weight Status Category
< 18.5	Underweight
18.5 – 24.9	Normal
25.0 – 29.9	Overweight
≥ 30.0	Obese

In children and adolescents, BMI results are plotted onto growth charts from the Centers for Disease Control and Prevention (CDC) and used to determine a corresponding BMI-for-age percentile; a method analogous to what is currently done for height, length, and head circumference. These charts are sex-specific and include ages ranging from 2 to 20 years. The terminology is also slightly different between children and adults, because children are not labeled “obese” (Table 2).

Table 2. Pediatric weight categories based on BMI

BMI Percentile Range	Weight Status Category
< 5th percentile	Underweight
5th – 85th percentile	Healthy Weight
85th – 95th percentile	At Risk for Overweight
> 95th percentile	Overweight

There are some limitations to using BMI, most notably that BMI is not a direct measure of body fat. Nevertheless, it does correlate well with more direct measures and is inexpensive and easy to calculate, making BMI a useful screening tool for clinicians.

Overweight and Obesity in the United States

U.S. population data from the National Health and Nutrition Examination Survey (NHANES), which is conducted by the CDC, show that roughly two thirds of adults in the United States are considered overweight or obese, with this number being divided equally between the two categories. Furthermore, the percentage of obese adults has more than doubled since the beginning of NHANES in the early 1970s.

The data concerning children and adolescents are also quite striking. Roughly one third of children in the United States are either overweight or at risk for overweight, with that number also being about equally divided between the two categories. These percentages have tripled since NHANES began.

Chemotherapy Dosing in Overweight and Obesity

As mentioned previously, one of the major concerns for clinicians dosing obese patients is the potential danger of che-

motherapy overexposure and the subsequent risk of toxicity. Currently, there is no consensus or guideline in place to help steer practitioners, and a lack of sound data in this arena only complicates matters. In the clinical setting, various empirical methods are utilized to calculate doses for obese patients. These include the capping of body surface area (BSA) to an arbitrary value and other alternative dosing strategies based on estimates of body size, such as ideal body weight, adjusted ideal body weight, and lean body mass.

Former St. Jude investigator Nobuko Hijiya, MD, Oncology, and colleagues¹ retrospectively studied the influence of BMI on toxicity, outcome, and pharmacokinetics of several chemotherapeutic agents used in the treatment of pediatric acute lymphoblastic leukemia over a 12-year period. Chemotherapy doses were calculated on the basis of actual body weight or BSA, and there were no recommendations for overweight or obesity adjustments. Patients were sorted into weight categories according to Table 2 above. Of 621 patients, 102 (16.4%) were underweight, 64 (10.3%) were at risk for overweight, and 55 (8.3%) were overweight. They found no significant differences in the rates of complete remission, overall survival, event-free survival, or cumulative incidence of relapse between groups (Table 3). From a pharmacokinetic perspective, they also found no significant differences in the systemic clearance of four chemotherapy agents among the BMI groups (Table 4).

Table 3. Clinical outcomes of patients according to BMI category

	Underweight	Normal Weight	At Risk of Overweight	Overweight	p value
CR	99%	97%	98.4%	98.2%	0.626
5-yr OS	86.1%	86%	85.9%	78.2%	0.533
5-yr EFS	76.2%	78.7%	73.4%	72.7%	0.722
CIR	16%	14.4%	20.6%	16.7%	0.862

CR, complete remission; OS, overall survival; EFS, event-free survival; CIR, cumulative incidence of relapse.

Table 4. Clearance (based upon actual body weight) of chemotherapeutic agents according to BMI category

	Population average systemic clearance (ml/min/m ²)				p value
	Underweight	Normal Weight	At Risk of Overweight	Overweight	
High-dose methotrexate	111.1	114.1	115.3	114.9	0.47
Etoposide	43.6	48.7	48.4	50.2	0.41
Cytarabine	852.2	773.8	645.1	782.9	0.56
Teniposide	14.2	14	12.1	14.2	0.35

Another St. Jude team analyzed and compared the pharmacokinetics of eight chemotherapeutic agents in lean (BMI

cont., p. 3

St. Jude Clinical Trial Protocols

Below is a subset of clinical research protocols currently conducted at St. Jude. To find out more about the objectives of the studies below and their complete eligibility criteria, visit www.stjude.org/protocols, send an e-mail message to protocolinfo@stjude.org, or call the toll-free Physician Referral Line, 1-888-226-4343.

NKEXP: Pilot study of expanded, activated haploidentical natural killer cell infusions for non-B lineage hematologic malignancies.

- Eligibility: Patients diagnosed with relapsed or refractory AML, T-cell ALL, CML, JMML, or MDS who are not eligible for SCT and have persistent disease after remission induction(s) therapy
- Principal Investigators: Dario Campana, MD, PhD and Wing Leung, MD, PhD

SJGD2: A Phase I trial of the humanized anti-GD2 antibody (Hu14.18K322A) in children and adolescents with neuroblastoma or melanoma

- Eligibility: Patients less than or equal to 21 years of age with refractory or recurrent neuroblastoma or melanoma.
- Principal Investigator: Fariba Navid, MD

NKAML: Pilot study of haplo-identical natural killer cell transplantation for acute myeloid leukemia.

- Eligibility: Patients diagnosed with AML who are in complete remission, have relapsed or refractory AML, or with AML and increasing minimal residual disease (MRD).
- Principal Investigator: Jeffrey Rubnitz, MD, PhD

HUSTLE: Long term effects of hydroxyurea therapy in children with sickle cell disease.

- Eligibility: Patients with a diagnosis of Sickle Cell Disease who are receiving hydroxyurea therapy (or plan to begin therapy within 3 months)
- Principal Investigator: Russell Ware, MD

SJYC07: Risk-adapted therapy for children less than 3 with embryonal brain tumors, choroid plexus carcinoma or ependymoma.

- Eligibility: Patients under 3 with newly diagnosed medulloblastoma, supratentorial primitive neuroectodermal tumor (PNET), atypical teratoid/rhabdoid tumor (ATRT), choroid plexus carcinoma (CPC) or ependymoma.
- Principal Investigator: Amar Gajjar, MD

Obese, cont. from p. 2

≤ 25 kg/m²) and obese (BMI ≥ 30 kg/m²) adult cancer patients. Alex Sparreboom, PhD, Pharmaceutical Sciences, and colleagues² studied 1206 subjects, of whom 162 (13.4%) were classified as obese. Their results also indicated no significant difference for any of the eight drugs studied in systemic clearance when normalized to BSA based on actual body weight (Table 5). They did not explore toxicity or other outcome measures.

Table 5. Systemic clearance (CL) of chemotherapy agents in lean and obese subjects

	Lean Subjects		Obese Subjects		p value
	No. of subjects	CL (L/hr/m ²)	No. of subjects	CL (L/hr/m ²)	
Carboplatin	64	3.49	14	3.2	0.39
Cisplatin	165	30.2	23	28.3	0.10
Docetaxel	92	21.2	21	19.4	0.29
Paclitaxel	38	191	14	200	0.56
Irinotecan	102	16.6	25	15.1	0.27
Topotecan	108	12.4	21	11.3	0.55
Doxorubicin	41	34.1	23	29.5	0.18
Troxacitabine	50	5	21	4.7	0.16

There are a number of other studies addressing toxicity and outcomes in cancer patients, with a majority of the data supporting an approach in which anticancer drugs are dosed based on BSA using actual body weight.

Conclusions

Currently available data indicate that clearance of selected chemotherapeutic agents is not affected by overweight or obesity and that there is no reason to arbitrarily adjust chemotherapy doses in this population. Moreover, there appears to be no evidence that dosing patients based on BSA using actual body weight will adversely affect overall outcomes. St. Jude pharmacists are available to provide consults on dosing for individual patients or for novel treatment regimens.

References

1. Hijjiya N, Panetta JC, Zhou Y, Kyzer EP, Howard SC, Jeha S, Razzouk BI, Ribeiro RC, Rubnitz JE, Hudson MM, Sandlund JT, Pui CH, Relling MV. Body mass index does not influence pharmacokinetics or outcome of treatment in children with acute lymphoblastic leukemia. *Blood*. 2007;109(10):4151–7.
2. Sparreboom A, Wolff AC, Mathijssen RH, Chatelut E, Rowinsky EK, Verweij J, Baker SD. Evaluation of alternate size descriptors for dose calculation of anticancer drugs in the obese. *J Clin Oncol*. 2007;25(30):4707–13. ■

CME credits are available for selected educational seminars on Cure4Kids.org. For more information contact lindap.taylor@stjude.org.

St. Jude Receives NCI Cancer Center Designation

St. Jude Children's Research Hospital recently received the prestigious recognition of being designated as a National Cancer Institute (NCI) Comprehensive Cancer Center. The designation makes St. Jude the first and only NCI-designated Comprehensive Cancer Center solely focused on pediatric cancer to receive this distinction.

"It is always gratifying to see one of the NCI-designated cancer centers achieve comprehensive status: recognition of excellence, not only in state-of-the-art care and cancer research, but also in patient education, community outreach, and the dissemination of vital information to professionals and the public," NCI Director John Niederhuber said. "These extra efforts to establish programs that reach out to surrounding communities and patients are the hallmarks of our comprehensive centers, which now number 41. This enhanced designation is a timely recognition of important contributions and advances made by the dedicated staff of St. Jude." (May 16, 2008 *Cancer Letter*)

In addition to a proven track record and impact in laboratory, clinical and population-based cancer research, NCI-designated Comprehensive Cancer Centers must have significant efforts in professional and lay cancer education and provide notable community service and outreach. Of the many hundreds of institutions in the country that treat cancer patients, only 63 of them are NCI-designated Cancer Centers and receive funds from the NCI to support their infrastructure. Of these centers, only 41 have the Comprehensive designation.

"Being designated a Comprehensive Cancer Center is a prestigious accomplishment and to be the only pediatric center is an incomparable distinction for St. Jude," says Dr. William E. Evans, St. Jude CEO. "St. Jude is well known for having innovative programs led by the best and the brightest faculty and staff; now being awarded 'Comprehensive' stature places an additional

NCI imprimatur on St. Jude and further validates our position among the country's leading cancer centers. This also speaks volumes about Dr. Kastan's strong leadership as our Cancer Center Director."

St. Jude has been an NCI-designated Cancer Center since 1977 and has been a worldwide leader in both basic and clinical cancer research. The St. Jude After Completion of Therapy (ACT) program, initiated in the mid 1980s, was the first step in adding population science to the St. Jude portfolio of research. In 2006, St. Jude broadened its population science research with the addition of a new epidemiology and population research program headed by Les Robison, PhD and the establishment of a formal Cancer Prevention and Control Program.

"It's rewarding to see a designation of comprehensive to an institution that is exclusively focused on children," said Greg Reaman, chairman of the Children's Oncology Group and professor of Pediatrics at George Washington University and Children's Hospital in Washington, D.C. "They have a huge population of survivors that they alone have the resources and capability to bring back for follow-up studies, so they are to be congratulated—and envied, in that they are the only uniquely pediatric cancer center in the country," Reaman said. (May 16, 2008 issue of *The Cancer Letter*)

The non-scientific requirements for Comprehensive status are education and community outreach, and St. Jude has a long history of significant efforts in both of these areas. St. Jude has a world-renowned International Outreach Program which has served as the center for many of these efforts, ranging from local to statewide to regional to international outreach.

Among the outreach and educational initiatives developed by St. Jude are two highly accessed Web-based programs, Cure4Kids (www.cure4kids.org) and Oncopedia (www.onclopedia.org),

which provide educational resources for both lay and medical communities and are used by individuals, nationally and worldwide. These sites are of particular importance to underprivileged regions. "Our International Outreach program, directed by Dr. Raul Ribeiro, is a wonderful example of how a medical institution can provide important services to local, national, and worldwide communities," said Michael Kastan, MD, PhD, St. Jude Comprehensive Cancer Center Director. "In addition to the effective Web-based efforts, St. Jude has a long and successful track record of bringing modern medicine to less-advantaged countries through education of local health care providers and establishment of pediatric cancer clinics."



Dr. Michael Kastan
Cancer Center Director

Locally, St. Jude's outreach efforts include programs in schools and hospitals. St. Jude also provides cancer education and community outreach throughout the region via its domestic affiliate hospitals located in Huntsville, AL; Johnson City, TN; Baton Rouge, LA; Shreveport, LA and Peoria, Ill.

"While maintaining significant activities in education and community service, St. Jude will continue its major efforts in both basic laboratory research and clinical investigation to better understand the biology of cancer and develop novel treatment approaches," said Kastan. "These insights can impact both pediatric and adult cancers."

The St. Jude Comprehensive Cancer Center will continue to enhance its efforts in epidemiology and population research, with particular interests in understanding the late medical and psychosocial effects of successfully treating childhood cancer, according to Kastan. ■

Translational Research

Medulloblastoma cont. from p. 1

the first year of life, but the disruption of this differentiation process can trigger medulloblastoma. Therefore, several research teams are seeking to elucidate the signaling mechanisms that govern the proliferation and differentiation of GNPs. Previous research has shown that for GNPs to differentiate into neurons BMPs must bind to a set of receptors on their cell surface to block the activity of a signaling pathway. “What was not known and what we now find is that the effect of BMPs on normal GNPs is almost exactly mimicked in GNP-like tumor cells,” Roussel said.

In cell culture experiments, BMPs rapidly caused the degradation of Math1 protein, which is expressed by dividing GNPs but not by nonproliferating neurons. Twelve hours after BMP treatment, Math1 was no longer detected in the GNPs, and cell growth soon stopped. Exactly how Math1 works remains unknown; however, in mice the protein is vital to the normal formation of the brain. Mice carrying a deletion of the gene that encodes Math1 fail to develop cerebellums. The St. Jude team also performed gene transfer experiments in mice to determine whether BMPs are a potential treatment for medulloblastoma. Using a genetically altered virus, they inserted the gene that encodes BMPs into the cancer cells. The transfer not only halted tumor growth but also induced the cancer cells to change into neurons.

Potential treatment for medulloblastoma

One obstacle to using BMPs to treat medulloblastoma is that their purification is an extremely expensive process. Currently, St. Jude researchers are searching for less expensive biological molecules that mimic the action of BMPs

on medulloblastoma cells. Roussel also suggested that the ability of BMPs to transform medulloblastoma cells into normal neurons, coupled with an earlier discovery made at St. Jude, could offer a combination treatment for the cancer.

In 2004, a St. Jude team reported that the experimental drug HhAntag, which inhibits Sonic hedgehog signaling, killed medulloblastoma cells and eliminated the tumors in mice. However, HhAntag treatment also interfered with bone development in the animals, suggesting an unwelcome side effect in young children. Roussel’s group reported that although both the Sonic hedgehog and BMP pathways regulate cell division, they do so in distinctly different ways. This finding led to her group testing a lower dose of HhAntag in combination with BMPs. They found that the combination treatment provided the same therapeutic effect as high doses of the hedgehog inhibitor. “We hope that by reducing the levels of both compounds, we might prevent the secondary effects on bone of this potential therapy,” said Roussel.

Reference

1. Zhao H, Ayrault O, Zindy F, Kim, JH, Roussel MF. Post-transcriptional down-regulation of Atoh1/Math1 by bone morphogenic proteins suppresses medulloblastoma development. *Genes Dev.* 2008;22:722–7. ■

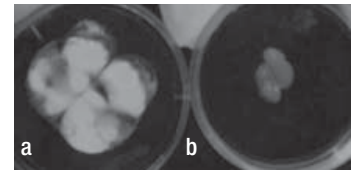


Fig. 1. Allografts of murine medulloblastoma cells infected with either control virus expressing GFP (a) or virus expressing BMP4 and GFP (b) demonstrate the antitumor effects of transferring BMP genes.

Translational Research

New Clue to Machinery of Autoimmune Disease

St. Jude researchers have discovered an intriguing insight into how T cells, the immune system’s master regulatory cells, wage war on the body’s own tissues in such autoimmune disorders as multiple sclerosis (MS), type 1 diabetes, and rheumatoid arthritis. Their findings about T cells add another piece to the puzzle of understanding such diseases. While the findings are quite basic, they could contribute to designing therapies to suppress the immune responses that are misdirected against a person’s own tissues in autoimmune disorders.

T cells sense antigens from invading viruses or bacteria through receptors

on the T cells’ surface. These receptors recognize and attach to specific antigens like a key fitting a lock. Many autoimmune diseases arise when T cell receptors that recognize the body’s own proteins spur T cells to mistakenly launch an immune system to attack body tissues.

“T cells have potentially millions of different possible receptors,” said Terrence Geiger, MD, PhD, Pathology.¹ “Some T cell receptors are adept at promoting autoimmunity, some are poor, and some are protective. It is not clear why one T cell receptor can promote autoimmunity, whereas another T cell receptor specific for the same an-

tigen on a similar kind of T cell either doesn’t do anything or even protects against the autoimmune reaction.”

Geiger and his colleagues began their study with the hypothesis that T cell receptors that trigger autoimmunity might be those that have a greater affinity for a self antigen. To test this possibility, they engineered mice to express one of five slightly different T cell receptors, all of which recognize a piece of myelin oligodendrocyte glycoprotein (MOG), a central nervous system protein. T-cells are directed against MOG in patients with MS or mice with an MS-like disease. To insert the recep-

cont., p. 7

Therapeutic Trends

Study Shows How Pneumonia Bacteria Use Stolen Genetic Material

A few bacteria are especially adept at stealing genetic material from other bacterial species and incorporating those foreign genes into their own machinery. In a new study, St. Jude researchers have gained insight into how pneumococcus, the primary cause of pneumonia, uses a particular piece of stolen genetic material to render it more virulent.

The research is part of the hospital's ongoing effort to develop affordable and effective pneumonia vaccines for children in developing countries. This is an especially critical effort, given that pneumonia causes more than 2 million deaths a year in children worldwide—more than AIDS, malaria, and measles combined.

The St. Jude researchers sought to understand how pneumococcus regulates a stolen piece of genetic material that enables the bacterium to construct a pilus, a long, hair-like appendage that it uses to reach out to human cells that it infects.

“Even though pneumococcus is very common, until recently no one had realized that it could develop this pilus to reach out and touch a human cell,” said Elaine Tuomanen, MD, Infectious Diseases chair and senior author of a report on this work.¹ “Oral streptococci, which are normally in the mouth and throat, have the pilus genetic package, and we believe pneumococcus picked it up in the back of the throat. We decided to look at how the bacterium figures out how to use that package.”

The scientists hypothesized that the imported pilus genetic package had adapted to a preexisting set of molecular controls in its new host environment. In their experiments, the researchers genetically altered strains of pneumococci to shut down those controls to see whether pilus development was affected.

Those experiments established that pneumococci do use those controls to regulate the pilus locus. Furthermore, the experiments with mice revealed how pneumococci use the pilus locus to improve their ability to infect lung cells.

“When bacteria attack the lung, there are two steps they need to do to establish pneumonia,” Tuomanen said. “They need to stick to lung cells, and they also need to invade the lung cells. Our experiments were designed to separately test

those two steps, and we established that the pili are not used for adhesion but for invasion, which was not understood before.”

While the findings help scientists understand the basic machinery of pneumococcal infection, Tuomanen said, the results also indicate that pilus is not a good candidate for a new vaccine against pneumonia. Such vaccines consist of a mix of bacterial proteins that can be administered to children to trigger their immune systems to battle a broad array of pneumococci strains.

“So far, only 20 percent or so of the clinically important strains of pneumococci have developed this trick of producing the proteins for making pili,” Tuomanen said. “In creating vaccines, we want to use proteins that occur in a wide variety of bacterial strains. These pili-related proteins are not prime candidates. So, we can now concentrate on other proteins that we know are expressed almost universally by pneumococci and that we can put into a vaccine.”

The ultimate goal, Tuomanen added, is for St. Jude and its collaborators to produce pneumococcal vaccines that will have a profound impact on the disease worldwide.

“Current vaccines used in the developed world cost more than \$100 a dose and are limited to protecting against perhaps 10 to 15 types of pneumococci,” she said. “But that price is far too high for developing countries, and there are 90 types of pneumococci out there.” However, St. Jude and its collaborators have already identified bacterial proteins that occur almost universally in pneumococci and that could be the basis for a vaccine inexpensive enough to be used in developing countries, Tuomanen said.

Vaccines based on these proteins will be produced in the Children's GMP, LLC, a sophisticated biomedical workshop for making high-quality vaccines, drugs, and other biological products. The GMP's capabilities enable researchers' discoveries to be quickly brought to clinical trial.

Reference

1. Rosch JW, Mann B, Thornton J, Sublett J, Tuomanen E. Convergence of regulatory networks on the pilus locus of *Streptococcus pneumoniae*. *Infect Immun*. 2008;76(7):3187–96. ■

The Fourth Annual St. Jude Biomedical Research Symposium will be held Wednesday, December 3, 2008, in the St. Jude Auditorium

The theme for this year Symposium will be “It's ALL about Genetics.” The field of genetics has seen amazing advances over the last decade in topics that span genome structure and evolution, development, regulation of gene expression, and protein structure and function. Research in this field has greatly enhanced our understanding of the molecular and genetic bases of human diseases including the childhood cancers treated at St. Jude. Basic scientists, medical researchers, and clinicians should make plans to attend. If you would like to register, please go to www.cure4kids.org/cme/30 or www.stjude.org/seminars. This symposium has been approved for 6.75 CME credit hours.

Referrals, Consultations, and Treatment Policy

Referrals

St. Jude Children's Research Hospital welcomes referrals of children and adolescents with newly diagnosed, untreated or suspected cancer; HIV infections; or certain hematologic, immunologic, or genetic diseases. Patients are accepted based on the eligibility to enroll in an open St. Jude clinical research protocol. Patients with certain genetic disorders, hematologic, immunologic diseases or HIV infection may be accepted anytime in their disease history based on protocol eligibility or potential to contribute to research projects. Other patients who have received treatment elsewhere may be considered on an individual basis, if they are eligible for a St. Jude clinical trial. Patients are enrolled on clinical trials designed to provide the best available care while answering important research questions.

All children accepted for treatment at St. Jude are treated without regard to the

family's ability to pay. The American Lebanese Syrian Associated Charities (ALSAC, the fund-raising organization that supports St. Jude) cover all costs of treatment beyond those reimbursed by third-party insurers and cover total costs when no insurance is available. ALSAC also provides assistance with transportation costs and local living expenses during treatment.

After the initial therapy has been completed, patients are typically managed in close collaboration with their private physicians. St. Jude experts in hematology, oncology, bone marrow transplantation, immunology, genetic diseases, infectious diseases, and pharmacotherapeutics are available for consultation regarding possible side effects of therapy, signs of recurring disease, or other questions related to the care of patients on St. Jude clinical trials and survivors.

Consultations

St. Jude provides free formal consultations to treating physicians about difficult diagnostic or medical management questions. For a formal consultation, the physician should send complete medical information, such as detailed medical history, copies of relevant diagnostic imaging evaluations, and pathology/histological material. The hospital's multidisciplinary groups will discuss the case and offer recommendations. St. Jude does not bring patients to Memphis for consultations unless they are likely to be eligible for a St. Jude protocol.

Physician Referral Line

Phone: 1-866-2ST-JUDE,
(1-866-278-5833),

fax: 901-495-4011,

e-mail: referralinfo@stjude.org,

Web: www.stjude.org/referringmds

Autoimmune cont. from p. 5

tors into the mouse T cells, the researchers used a technique called retrogenic modeling that was perfected by the laboratory of Dario Vignali, PhD, Immunology. In this technique, a harmless virus is used as a carrier to insert specific T cell receptors into bone marrow cells that then mature into T cells.

The researchers' measurements established that each T cell receptor had a different affinity for the MOG protein. They then tested whether the mice with receptors that grabbed more tightly onto MOG developed more severe autoimmune disease than those that bound less tightly.

Young mice expressing each of the different receptors on their T cells did not differ in their development of the MS-like disease when they were immunized with the MOG protein. However, as the mice aged, they did spontaneously develop disease. The mice expressing the different receptors differed significantly in their susceptibility to this spontaneous autoimmunity.

Curiously, receptor affinity did not appear to affect disease susceptibility or severity. Instead, the researchers found that mice that were more likely to spontaneously develop autoimmune disease were those that, for some reason, had produced a greater number of T cells with the MOG receptor—that is, they had a higher level of engraftment. Indeed, the researchers were able to associate the number of T cells measured in a mouse's blood with the likelihood of that mouse developing disease months later.

"This finding of an association between T cell engraftment and spontaneous disease suggested to us that there is some barrier to the development of disease," Geiger said. "Why are cells that engraft better more likely to cause disease? We really don't know the answer. Once the mice start to get disease, they get very sick, but there is sort of a triggering point. Our findings may suggest that disease triggering in these models involves a mass effect that requires some quantity of specific T cells to ignite disease. But we really want to find out whether it is the cell number itself or whether receptor recognition properties that lead to increased engraftment also lead to increased susceptibility to disease. These are things we can test."

"These findings don't have a direct clinical implication right now, but if we understand which T cells induce pathology and why, and which cells are protective or passive, we will gain a better sense of where to target what are called antigen-specific therapies," Geiger said. "Those therapies try to selectively target the T cells that cause disease, sparing the rest of the immune system."

Reference

1. Alli R, Nguyen P, Geiger TL. Retrogenic modeling of experimental allergic encephalomyelitis associates T cell frequency but not TCR functional affinity with pathogenicity. *J Immunol.* 2008;181:136-45. ■

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The Rounds Quiz

Question: A 2 y/o WM has been referred to you because he has not been thriving despite a good caloric intake. Recently he has had prolonged nosebleeds and excessive bruising.

His past medical history is significant for 3 bouts of pneumonia (with 2 hospitalizations).

On physical examination, his height and weight are in the 3rd percentile. His abdomen is protuberant but non-tender (Figure). There is dried blood present in both nares and several bruises (with hematomas) are present on the anterior aspect of his legs.

Lab: CBC WNL; PT 22 sec (11-14); aPTT 30 sec (22-33); fibrinogen 400 mg /dl (200-400).



Answer: The x-ray shows evidence of significant constipation and the history and physical exam are suggestive of chronic malabsorption. This patient has cystic fibrosis (CF) and the prolonged PT shows evidence of a coagulopathy. Children with CF classically malabsorb the fat soluble vitamins (A,D,E,K) and the PT is prolonged because of an acquired vitamin K deficiency.



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