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Experts Share Tips for Advocating for Biomedical Research Federal Funding

BY ERIC T. ROSENTHAL

SAN DIEGO, Calif.—Continuing its clarion call to motivate scientists and clinicians to advocate on behalf of cancer research funding one year after convening the 2013 Rally for Medical Research (*OT 5/25/13 issue*) at last year's Annual Meeting in Washington, DC, the American Association for Cancer Research this year held a science policy session titled "NIH and NCI Funding: How the AACR and Our Partners are Taking a Stand Against the Decades-Long Decline in Federal Funding for Research and Development."

The perspectives of an AACR government affairs and science policy expert, former member of Congress, patient advocate, and cancer center director were expressed during a panel discussion.

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Tumor Lysis Syndrome: Making Headway Toward Better Prevention & Management

BY KURT SAMSON

Researchers are making headway in developing strategies to better categorize, prevent, and treat tumor lysis syndrome, a potentially fatal overload of potassium, phosphate, and uric acid that can occur in as many as one in five patients with certain blood or lymph tumors as a consequence of chemotherapy or spontaneous cell death.

Tumor lysis syndrome, or TLS, is triggered by the sudden and massive release of components of dead tumor cells entering the bloodstream, which cause severe disruption in blood metabolism leading to serious and sometimes fatal clinical events related to the buildup of potassium, phosphate, and/or uric acid—most notably acute renal failure.

In an interview, Mitchell Cairo, MD, Chief of Pediatric Hematology, Oncology, and Stem Cell Transplantation and Director of the Children and Adolescent Cancer and Blood Diseases Center at Maria Fareri Children's Hospital at Westchester Medical Center New York Medical College, in Valhalla, NY, gave an overview about the current status of the condition.

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In APL, Warning about Differentiation Syndrome

BY ROBERT H. CARLSON

NEW YORK—ATRA/ATO is the new standard of care for non-high risk patients with acute promyelocytic leukemia (APL), and overall survival rates with the regimen are over 90 percent, even without chemotherapy. But the incidence of early death during induction therapy is still high, and the development of APL differentiation syndrome, although rare, can be fatal if not treated immediately upon suspicion.

"APL is clearly one of our success stories," said Charles Schiffer, MD, Professor of Medicine and Oncology, and Interim Chair of the Department of Oncology at Karmanos Cancer Institute in Detroit, moderator of a session on leukemia here at the International Congress on Hematologic Malignancies.

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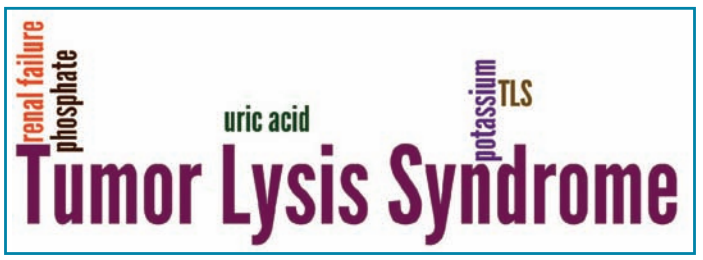
He noted that TLS is the most common emergency faced by physicians treating patients with malignancies of the blood, bone marrow, or lymph nodes, including leukemias, lymphomas, and myelomas, and is seen most often in those with acute lymphoblastic leukemia (ALL) and Burkitt's lymphoma.

TLS, however, can also occur with other hematologic malignancies and solid tumors and those with a high proliferation rate or a large tumor burden, or who are highly sensitive to cytotoxic treatment, he added.

In 2004, he was part of an international TLS expert consensus panel that proposed a set of guidelines for managing and treating the disorder, and categorized blood malignancies and solid tumors as being of low, intermediate, or high risk. A more refined version was published in 2010, and although the system is in wide use, it has yet to be formally adopted by professional cancer societies.

> "The potential severity of complications due to TLS requires measures for prevention in high-risk patients and prompt treatment in the event that symptoms arise."



Laboratory or Clinical TLS

Their research built off of the Hande-Garrow classification system, published in 1993 by Vanderbilt University oncologists, which proposed classifying TLS into two types—laboratory or clinical (LTLS or CTLS)—based on patients who do not require therapeutic intervention and those with life-threatening clinical abnormalities (***Am J Med 1993;94:133-139***).

The earlier model required an increase in laboratory values of 25 percent above baseline, which did not take into account patients having pre-existing abnormal values, Cairo noted. That model also required that changes occur within four days of the initiation of therapy, which did not account for patients who present with TLS or develop it before therapy or after four days.

Under the 2010 guidelines (*see box*), TLS is defined as the above plus any of several clinical manifestations occurring within five days of meeting these criteria, including new-onset renal insufficiency, cardiac arrhythmias, seizures, or death. Renal insufficiency is defined as a creatinine level of at least 1.5 times the upper limit of normal.

Risk factors included biological evidence of LTLS, proliferation, the bulk and stage of the malignant tumor (and renal impairment and/or involvement at the time of TLS diagnosis). The guidelines also divided patients into low, intermediate, or high risk of TLS, and offered prophylaxis recommendations.

In general, most solid tumors are classified at low or very-low risk, but bulky solid tumors sensitive to chemotherapy, such as neuroblastomas, germ-cell tumors, and small-cell lung cancers, were classified as intermediate risk.

Cairo said that the consensus panel concluded that prevention is the best management strategy for at-risk patients, with hydration and prophylactic rasburicase for high-risk patients, hydration plus allopurinol or rasburicase for intermediate-risk patients, and close monitoring of patients at low risk. Similar recommendations were made for the primary management of patients with established TLS, with the addition of aggressive hydration and diuresis. The guides do not recommend alkalinization.

"The potential severity of complications due to TLS requires measures for prevention in high-risk patients and prompt treatment in the event that symptoms arise," he said. "Recognition of risk factors, monitoring of at-risk patients, and appropriate interventions are key to preventing or managing TLS."

Diagnostic Thresholds

The international consensus panel has defined tumor lysis syndrome based on the thresholds for serum uric acid, phosphate, potassium, and calcium, with at least two of the following required for diagnosis:

- Uric acid ≥ 8 mg/dL
- Potassium ≥ 6 mEq/L
- Phosphorus ≥ 2.10 mmol/L for children or ≥ 1.45 mmol/L for adults
- Calcium ≤ 1.75 mmol/L

Laboratory TLS is defined in the criteria as serum uric acid levels within normal limits, but serum phosphate and potassium levels exceeding the upper limit of normal. LTLS was also diagnosed when uric acid levels are above the upper limit of normal and either phosphate or potassium levels are above the upper limit of normal. An elevated uric acid, potassium and phosphate has previously been determined to be ≥476 µmol/l or ≥25% increase from baseline, ≥6.0 mmol/l or ≥25% increase from baseline and ≥2.1 mmol/l or ≥25% increase from baseline, respectively.

During the time period when patients are at risk of developing LTLS, electrolyte and chemistry monitoring should be conducted at least every six hours or sooner, according to the panel's recommendations.

In addition, calcium levels are not included as a criterion for establishing LTLS because hypocalcaemia may not be considered a direct consequence of TLS and is associated with high phosphate levels in most cases. This model should not however be used in patients with preexisting high uric acid levels due to gout prior to the diagnosis of their malignancy.

Incidence Rates

In 2012 at the American Society of Hematology Annual Meeting, Cairo and colleagues presented findings from a retrospective study of TLS among 951 cancer patients treated in the Henry Ford Health System in Detroit, the largest cohort to be studied to date (***Abstract 238***). The rate of TLS was 9.3 percent overall within one week of diagnosis, but among patients with certain hematologic malignancies—including leukemias, multiple myeloma, and esophageal and liver cancers—the rate was as high as 20 percent. In other major categories of malignancies, the prevalence ranged from about four to eight percent.

About two-thirds of patients with TLS had at least one clinical manifestation and, among subtypes of hematologic malignancies, the highest rates were seen in patients with leukemias (26% in LTLS patients and 16.4% in CTLS patients), followed by multiple myeloma, but the syndrome was not reported in any patients with Hodgkin lymphoma. For solid tumors, esophageal malignancies showed the highest rate (23.5%), but CTLS was much less common and occurred in only six percent of patients. In contrast, 14 percent of liver cancer patients had the syndrome, all of whom had clinical manifestations.

Nearly 85 percent of cases of laboratory tumor lysis syndrome occurred followed chemotherapy, but the remainder appeared to develop as a result of spontaneous tumor cell death.

Cairo said that elevated phosphorus was the most common component of the laboratory diagnoses, while high levels of creatinine was the most common clinical sign, and was observed in more than 50 percent of patients, followed by arrhythmias, which were seen in about 40 percent of patients.

"The incidence of LTLS and CTLS appears to be more prevalent among newly diagnosed cancer patients undergoing induction chemotherapy than previously recognized," he said.

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Stand Up To Cancer: New Research in HPV-Related and Pancreatic Cancers, and 'Innovation in Collaboration' Awards

BY ERIC T. ROSENTHAL

SAN DIEGO, Calif.—Stand Up To Cancer (SU2C) announced new areas of cancer research and additional research award recipients at the American Association for Cancer Research's Annual Meeting here.

An HPV Translational Research Team Grant investigating new approaches to developing novel immune therapies for HPV-related cancers, and a second Dream Team dedicated to pancreatic cancer focusing on novel immunotherapies highlighted the research award announcements, which also included naming the SU2C-Phillip A. Sharp Innovation in Collaboration Awards recipients.

Ellis L. Reinherz, MD, Chief of the Laboratory of Immunobiology and Co-director of the Cancer Vaccine Center at Dana-Farber Cancer Institute, and **Robert I. Haddad, MD**, Chief of the Head and Neck Oncology Program, also at Dana-Farber were named Leader and Co-leader, respectively, of the SU2C-Farrah Fawcett Foundation HPV Translational Research Team, receiving $1.2 million over a three-year period.

Their research project, "Therapeutic CD8 Vaccines Against Conserved E7 HPV Epitopes Identified by MS," will focus on treatments for patients with HPV-associated cancers—including anal, cervical, and head and neck cancers—who have disease relapse after initial therapy.

"Stand Up's collaboration with the Farrah Fawcett Foundation [with additional support from the HPV and Anal Cancer Foundation] is another example of our breaking down the 'silos of science and foundations,'" said Sherry Lansing, a SU2C Co-founder and Chair of the Entertainment Industry Foundation's (EIF) Board of Directors.

It's also another example of how longtime Hollywood connections can lead to future ventures in medical research. Lansing, Founder of her namesake foundation and former CEO of Paramount Pictures, recalled during an interview that she had first met Fawcett more than 40 years ago when they were both models in an Alberto Culver television commercial: "I was the brunette and she was the blonde and Tom Selleck was my boyfriend in the commercial," she said. Although she and Fawcett were just acquaintances then, they spent more time together over the years, through mutual friends and at various events.

Lansing said she always respected the deep, loving friendship between Fawcett and Alana Stewart, the actor and talk show host who produced the 2009 NBC-TV documentary *Farrah's Story*, and who is Founder and President of the Farrah Fawcett Foundation.

Lansing said that she considered that all of Fawcett's accomplishments as an actor paled in comparison to what happened after her anal cancer had been diagnosed in 2006: "She was extraordinarily brave and did not hide her cancer or complain, and went public and wanted to help others," Lansing said.

After Fawcett died in 2009, Lansing said that Stewart asked her advice about setting up a foundation, and their friendship grew from there. Several years later, they entered the formal collaboration that resulted in the translational research team.

Lansing also credited actor Michael Douglas with increasing awareness about HPV-associated cancers, adding: "No stigma should be attached to anyone with any type of cancer. It is not their fault."

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"Perhaps the most significant development in TLS over the past decade has been in creating risk-assessment parameters. Today TLS is much better defined than in the past. Overall, significant progress has been made in averting delays in therapy and preventing acute renal failure."

"Perhaps the most significant development in TLS over the past decade has been in creating risk-assessment parameters."

Many clinicians, however, remain unaware of this progress, he noted. "In the last five years or so, more papers are using the grading system and more researchers are aware of it, but it is still difficult to get enough cases for randomized trials. Once the syndrome takes off, treatment is not as effective, so we do not want to let the horses out of the barn. Early recognition and prophylaxis are very important."

Outcomes Data Sparse

Also asked for his opinion, Jeffrey S. Berns, MD, Associate Chief of the Renal, Electrolyte, and Hypertension Division at the Hospital of the University of Pennsylvania, said that the most significant recent change in treatment of TLS is the widespread use of rasburicase.

"Today it's being used pretty early on, with an increasing trend toward using a lower fixed dose regimen—between 3 and 7.5 mg—primarily because it is less expensive, with similar reductions in uric acid levels," he said. "But we still see hyperphosphatemia and TLS—these have not gone away completely."

Recent systematic literature reviews have concluded that rasburicase improves uric acid levels, but it remains to be proven whether or not treatment alters outcomes, he added.

"One small paper recently indicated that treatment did not change renal outcomes, so the issue is still out there. We may never know. Randomized clinical trials are difficult due to the emergency nature of TLS, and these are really needed to prove whether or not treatment really helps."

He noted that one meta-analysis, published in 2013 and based on a search of electronic databases, regulatory documents, and websites through August 2012, found that rasburicase effectively reduces uric acid levels in adults (***Am J Kidney Dis 2013;62:481-492***). This comes at a significant cost, however, and evidence is lacking in adult patients on whether rasburicase improves clinical outcomes compared with other alternatives.

Those researchers concluded that until new evidence is available, use of rasburicase may be limited to adult patients with a high risk of TLS.

"Today TLS is much better defined than in the past. Overall, significant progress has been made in averting delays in therapy and preventing acute renal failure."