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Sarcomas With Complex Genetic Changes

BY JONATHAN GILL, MD, & RICHARD GORLICK, MD

Sarcomas comprise a heterogeneous group of tumors consisting of greater than 30 subtypes. The subtypes can be grouped by their histologic appearance or in more recent nomenclature the believed cell of origin: adipocytic, cartilage, Ewing sarcoma/primitive neuroectodermal, fibroblastic, fibrohistiocytic, gastrointestinal stromal, giant cell, nerve sheath, osteogenic, skeletal muscle, smooth muscle, pericytic/perivascular, vascular, and undifferentiated sarcomas.

Within these subtypes, there are varying degrees of malignant potential with low-grade tumors having low metastatic potential (<10%) and high-grade tumors having a high-risk of metastasis (>50% of patients).

Sarcomas can be divided in terms of their genetic alterations into two groups: characterized by the presence of a chromosomal translocation (**Table**). The translocations in

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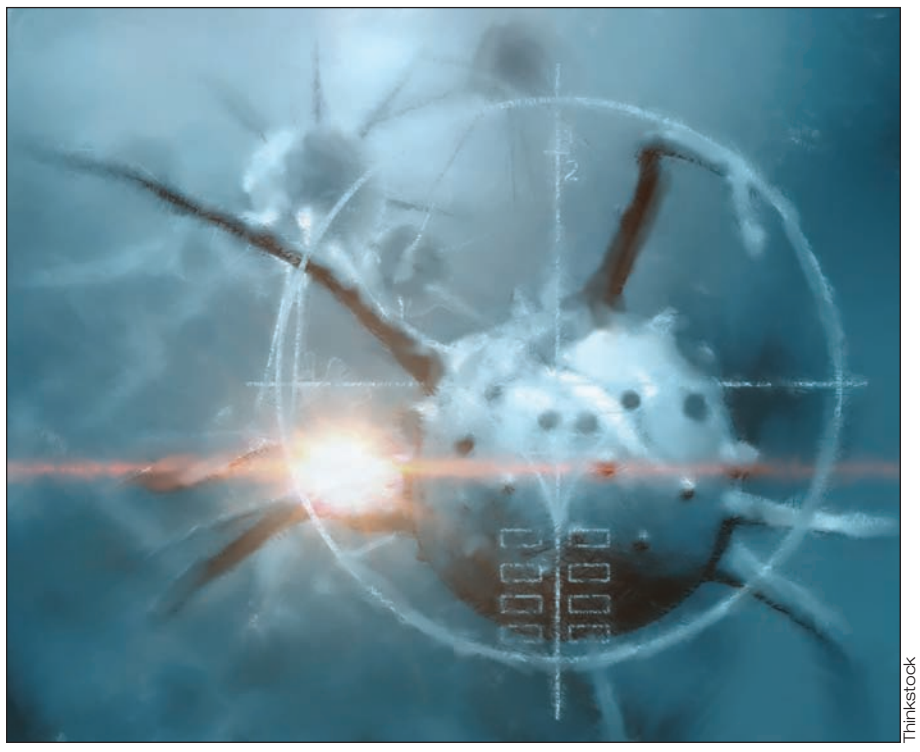

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Helping Young Cancer Survivors Make the Most of Life

BY MARY POWERS

Just weeks after undergoing surgery to remove a large mass at the base of his skull and days after beginning radiation therapy for treatment of medulloblastoma, Ricky Terry started aerobic training.

Three days a week throughout radiation therapy, Terry reported to Rehabilitation Services at St. Jude Children's Research Hospital in Memphis, Tenn., and climbed onto an exercise bike or stepped onto a treadmill. For 30 minutes, he worked to raise his heart rate into a target range and keep it there.

Terry's regimen reflects growing efforts to enhance the physical function and quality of life for the nation's increasing population of young cancer survivors. The work is underway in clinics and research laboratories as well as classrooms, fitness centers, and through Web-based interventions delivered at home. Researchers are exploring the impact of starting interventions earlier

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Brentuximab Vedotin May Cure Some Hodgkin Lymphoma

BY MARK L. FUERST

The targeted therapy brentuximab vedotin may have cured some Hodgkin lymphoma patients whose disease has persisted despite receiving previous therapies, according to a new study.

"This is the first study in relapsed or refractory Hodgkin lymphoma that shows 5-year survival results from a single drug. This study can also change the paradigm of practice and that some patients with relapsed or refractory Hodgkin lymphoma can be cured with brentuximab vedotin," noted, lead author Robert Chen, MD, of the City of Hope National Medical Center, Duarte, Calif. The authors published the final data from brentuximab vedotin monotherapy pivotal phase II clinical trial in relapsed or refractory classical Hodgkin lymphoma (*doi:10.1182/blood-2016-02-699850*).

Brentuximab Vedotin Results

The single-arm trial, which supported the FDA approval in 2011 of brentuximab vedotin for this indication, was conducted in 102 relapsed or refractory classical Hodgkin lymphoma patients who had previously received an autologous stem cell transplant to assess the efficacy and safety of single-agent brentuximab vedotin. Enrolled patients had received a median of more than three prior chemotherapy regimens.

At 5 years, the 102 patients had an estimated overall survival (OS) rate of 41 percent and progression-free survival (PFS) rate of 22 percent. The 34 patients who achieved a complete

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these sarcomas are disease defining and the rest of the genome is relatively normal. The second and larger group of sarcomas are those with complex genetic changes.

Even within one histiotype examples of both genetic bases may exist. For example, rhabdomyosarcoma can be divided by histology into embryonal and alveolar subtypes. Alveolar rhabdomyosarcoma is defined most commonly by the PAX-FKHR t(2;13) translocation, whereas embryonal rhabdomyosarcoma is a genetically complex sarcoma.

In embryonal rhabdomyosarcomas, which as a group do not have the characteristic translocation, the rate of somatic nonsynonymous mutations is nearly three times the level of translocation-positive alveolar rhabdomyosarcomas. Interestingly, the number of somatic single nucleotide variants in these patients increase linearly with age. This is suggestive that, for the youngest patients with the least mutations, sufficient time had not lapsed to acquire further bystander mutations, or that the pathogenic disease causing mutations had occurred early, leading them to develop the disease at a younger age.

Osteosarcoma

Osteosarcoma represents one of the sarcoma with the greatest genetic heterogeneity. Most osteosarcomas harbor aberrations in TP53. Alterations in TP53 include mutations, deletions, and translocations leading to breakpoints in 80-95 percent of tumors examined.

In those not harboring mutations in TP53, most tumors have amplification of MDM2, a known repressor of p53. In addition, 20-33 percent of osteosarcomas harbor alterations in RB1 (***Oncotarget 2016;7:5273-88***). As such, osteosarcomas have tremendous genomic instability. Circos plots demonstrate genome wide chromosomal translocations, with complete disarray of the normal karyotype.

Osteosarcoma was one of the cancers described as an example in the initial description of chromothripsis, chromosome shattering. Though, others have argued that the process more closely resembles kataegis, a pattern of localized hypermutation leading to chromosomal fragility and translocations. Ostesoarcomas harbor approximately 1.2 mutations per megabase, placing it in the middle of the pack of somatic mutations in human cancer. The genomic instability in osteosarcoma leads to significant intertumor as well as intratumor genomic heterogeneity.

Chondrosarcomas

Chondrosarcomas serve as another model of acquired genetic instability leading to malignant transformation. Chondrosarcomas are rare malignant cartilage forming bone tumors. In rare cases, chondrosarcomas can arise from benign tumors and can be divided into two groups: central chondrosarcomas and secondary peripheral chondrosarcomas.

Central chondrosarcomas, localized to the medullary cavity of long bones, make up the majority of cases and may rarely derive from enchondromas. Since most enchondromas are benign asymptomatic lesions, the rate of malignant transformation is uncertain but estimated to approach 4 percent. However, in patients with syndromes leading to multiple enchondromas, Ollier and Maffucci, chondrosarcomas occur in 40 percent of patients, which may have a variable latency between 6 months to 30 years.

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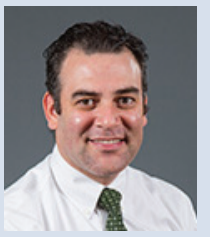

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TABLE: Chromosomal Translocations

Alveolar rhabdomyosarcoma	t(1;13) t(2;13) t(2;2) t(2;8)	PAX7-FKHR PAX3-FKHR PAX3-NCOA1 PAX3-NCOA2
Alveolar soft part sarcoma	t(x;17)	TFE3-ASPL
Angiomatoid fibrous histiocytoma	t(12;16)	FUS-ATF1
Clear cell sarcoma	t(12;22) t(2;22)	EWSR1-ATF1 EWSR1-CREB1
Congential fibrosarcoma	t(12;15)	ETV6-NTRK3
Dermatofibrosarcoma protuberans	t(17;22)	COL1A1-PDGFB
Desmoplastic round cell tumor	t(11;22)	EWSR1-WT1
Endometrial stromal sarcoma	t(7;17) t(6;7) t(6;10)	JAZF1-SUZ12 JAZF1-PHF1 EPC1-PHF1
Ewing sarcoma/ Peripheral primitive neurectodermal tumor	t(11;22) t(21:22) t(7;22) t(17;22) t(2;22) t(16;21)	EWS-FLI1 EWS-ERG EWS-ETV1 EWS-FEV EWS-E1AF FUS-ERG
Inflammatory myofibroblastic tumor	t(1;2) t(2;19) t(2;17)	TPM3-ALK TPM4-ALK CLTC-ALK
Low grade fibromyxoid sarcoma	t(7;16)	FUS-CREB312
Myxoid chondrosarcoma	t(9;22) t(9;15) t(9;17)	EWS-CHN TFC12-CHN TAF2N-CHN
Myxoid liposarcoma	t(12;16) t(12;22)	TLS-CHOP EWS-CHOP
Pericytoma	t(7;12)	ACTB-GLI
Synovial sarcoma	t(X;18)	SSX1-SYT SSX2-SYT SSX4-SYT

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Learning Objective for This Month's CME Activity: After participating in this CME activity, readers should be better able to discern the varying degrees of malignant potential within the histologic subtypes of sarcomas.

Brentuximab Vedotin May Cure Some Hodgkin Lymphoma Patients

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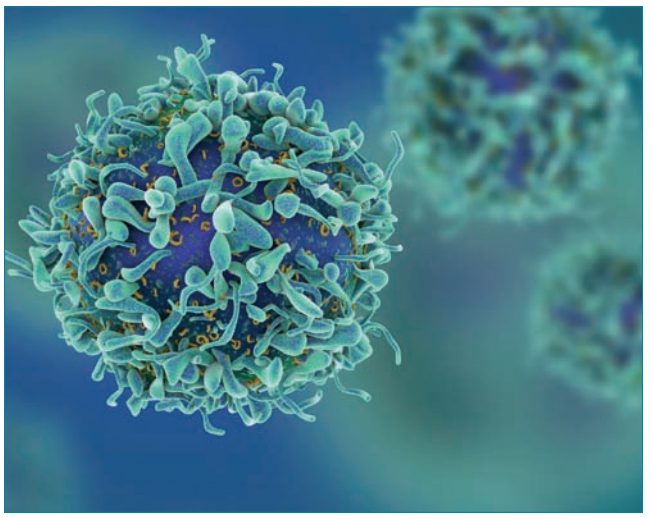
response (CR) to brentuximab vedotin had estimated OS and PFS rates of 64 percent and 52 percent, respectively. The median OS and PFS were not reached in CR patients.

Of the 34 (38%) patients who achieved CR, 13 patients have remained disease-free for more than 5 years and may be cured. Of these 13 patients, four patients received consolidative hematopoietic allogeneic-SCT and nine patients (9% of all enrolled patients) remain in sustained CR without receiving any further anti-cancer therapy after treatment with brentuximab vedotin.



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The most common adverse events of any grade were peripheral sensory neuropathy, fatigue, nausea, neutropenia, and diarrhea. Treatment emergent peripheral neuropathy was experienced by 56 patients (55%). Eighty-eight percent of these patients experienced improvement of their peripheral neuropathy symptoms, including 73 percent with complete resolution.

"After 5 years of follow-up, 41 percent of the patients are alive. Also, 15 patients are currently alive without any evidence of lymphoma from the initial 102 patients, and for the 33 percent of patients that achieved CR, 52 percent of them are alive 5 years out without any evidence of lymphoma," said Chen.

He noted that "prior to this drug, historical outcomes for Hodgkin lymphoma patients who relapsed after an autologous stem cell transplant were poor, with median post-progression survival of 1.3 years, and the only long-term disease control option for these patients was considered to be an allogeneic stem cell transplant. The median survival of the patients on brentuximab vedotin monotherapy in this pivotal phase II trial exceeds these historic figures."

Chen added that "brentuximab vedotin is now the standard of care for patients who relapse after stem cell transplantation or two lines of therapy. For the patients who are able to achieve CR on brentuximab vedotin, this drug can cure some Hodgkin lymphoma patients."

Hodgkin Lymphoma Studies

Brentuximab vedotin is an antibody-drug conjugate directed to CD30, a key driver of classical Hodgkin lymphoma tumor pathogenesis. The drug is being evaluated broadly in more than 70 ongoing clinical trials, including the phase III ALCANZA trial and two additional phase III studies, ECHELON-1 in frontline classical Hodgkin lymphoma, and ECHELON-2 in frontline mature T-cell lymphomas, as well as trials in many additional types of CD30-expressing malignancies, including B-cell lymphomas.

The drug via IV injection has received approval from the FDA for three indications:

- Regular approval for the treatment of patients with classical Hodgkin lymphoma after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates.
- Regular approval for the treatment of classical Hodgkin lymphoma patients at high risk of relapse or progression as post-auto-HSCT consolidation.
- Accelerated approval for the treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen. The sALCL indication is approved under accelerated approval based on overall response rate. Continued approval for the sALCL indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Chen said the message for practicing oncologists is that "this study shows that there are durable responses to brentuximab vedotin even 5 years out from treatment, and that the drug is very tolerable with largely reversible peripheral neuropathy side effects. The fact that we can report such durable results after 5 years is incredible. Each day that these individuals continue to spend with their loved ones is a testament to the strides our community is making in understanding and beating treatment-resistant lymphomas." OT

Mark L. Fuerst is a contributing writer.

SARCOMAS

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This suggests a potential mechanism of a stepwise process of malignant transformation in which an initiating mutation leads to altered growth of the multiple benign lesions, but which requires further mutations for malignant transformations. Mutations in isocitrate dehydrogenase genes (IDH1 and IDH2) have been described in both enchondromas and chondrosaromas, and the introduction of a mutant IDH gene in a conditional transgenic mouse was sufficient to cause multiple enchondromas, which may then be an initiating event in the process of malignant transformation (***Proc Natl Acad Sci USA 2015;112:2829-34***). There are currently three clinical trials of IDH inhibitors in chondrosarcomas as well as other malignancies that harbor mutations in IDH.

Secondary peripheral chondrosarcomas comprise a minority of cases and derive from pre-exisiting osteochondromas. Similarily, peripheral chondrosarcomas occur rarely in less than 1 percent of patients with sporadic osteochondromas, but have been described in about 1-5 percent of patients with hereditary multiple exostoses, known to harbor germline mutations in EXT1 and EXT2, and glycotransferases that elongate heparan and may have tumor suppressor activity.

A comparable mechanism of stepwise malignant transformation can be inferred in the development of malignant peripheral nerve sheath tumors (MPNST) in neurofibromatosis. However, even in this population, malignant transformation is a rare event: estimated that MPNSTs occur in approximately 10 percent of patients of with neurofibromatosis, type 1.

In MPNST, as in chondrosarcomas, the majority of the patients who develop the malignancy do not have an underlying predisposition (genetic or precursor benign lesions). From this we can conclude, that although an underlying genetic alteration may be an initiating event, it is neither required nor sufficient for malignant transformation. For example, patients with MPNST and NF-1 are more likely to have activation of EGFR, Raf, and PI3K/AKT pathways, whereas those with sporadic MPNSTs are more likely to carry mutations in *TP53* (***Am J Surg Pathol 2016;40:896-908***).

Personalized Sarcoma Treatment

The genetic complexity in sarcomas is then not only defined by the mutational load of the individual tumor, but also by the fact that different patients with the "same disease" may have different underlying biochemical alterations leading to malignant transformation.

The histologic grouping of sarcomas by their presumed cell of origin belies a common pathophysiology. The histologic classification of genetically complex sarcomas is thus primarily descriptive of the tissue milieu in which the malignant transformation occurred.

Unlike sarcomas associated with translocations, genetically complex translocations present a significant challenge in defining a driver mutation leading to the malignant transformation. This is further confounded by the fact that each histology is rare, requiring they are often grouped together in clinical trials to test a common treatment protocol. The results usually demonstrate variable response between and within histologies.

As we improve our understanding of the different potential driver mutations and improve our ability to detect actionable targets, these entities may derive benefit of personalized approaches in treating our patients. Given the rarity of these tumors and the heterogeneity within the histologic subtypes, designing clinical trials testing these approaches presents additional challenges.

Likewise, while immunotherapy with checkpoint inhibitors presents a potential option for some patients, there is a need to describe biomarkers for those patients most likely to benefit as our current definition of histologic subtypes may not provide sufficient precision. OT