Cancer Association of South Africa (CANSA)

Fact Sheet on Synovial Sarcoma of Childhood and Adolescence

Introduction
Soft-tissue sarcomas that are not rhabdomyosarcomas are classified as non-rhabdomyosarcoma soft tissue sarcomas (NRSTS). Examples of the many types of NRSTS cancers include fibrosarcoma, leiomyosarcoma, liposarcoma, neurofibrosarcoma, peripheral nerve sheath tumours and synovial sarcoma. These cancerous tumours arise in the soft tissues of the body including tendons, muscles, nerves, fatty tissue and fibrous tissue. NRSTS can essentially occur at any site in the body containing these normal types of tissues, such as in the arms and legs, the head and neck region, the chest, abdomen and pelvis. NRSTS accounts for ~ 5 percent of all paediatric cancers.

Certain types of NRSTS are most likely to affect infants (under 1 year of age), while other types are more common in adolescents and young adults. Because soft tissue is expandable, these tumours can sometimes grow rather large before they are felt or cause problems for the patient. Like all cancers, they can invade surrounding tissues and metastasise (spread) to other organs of the body.

Synovial Sarcoma of Childhood and Adolescence
Synovial sarcoma (also referred to as ‘SS’) is the most common non-rhabdomyosarcomatous childhood soft-tissue sarcoma. The median age of patients at diagnosis is in the third decade of life, with 31% of the cases being in adolescents younger than 20 years of age.

Despite its name, synovial sarcoma is not related to the synovial tissues that are a part of the joints. The disease starts most commonly in the legs or arms, but it can appear in any part of the body. On a pathology report, synovial sarcoma may be classified in different subtypes depending on what it looks like under the microscope or what specific gene mutation is involved. Synovial sarcoma is a high grade tumour. It spreads to distant sites in up to 50% of cases. (Okcu, et al, 2003).
“Synovial Sarcomas (SS) are a type of Soft Tissue Sarcoma (STS) and represent 8-10% of all STS cases. Although SS can arise at any age, it typically affects younger individuals aged 15-35 and is therefore part of both pediatric and adult clinical practices. SS occurs primarily in the limbs, often near joints, but can present anywhere. It is characterized by the recurrent pathognomonic chromosomal translocation t(X;18)(p11.2;q11.2) that most frequently fuses SSX1 or SSX2 genes with SS18. This leads to the expression of the SS18-SSX fusion protein, which causes disturbances in several interacting multiprotein complexes such as the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex, also known as the BAF complex and the Polycomb Repressive Complex 1 and 2 (PRC1 and PRC2). Furthermore, this promotes widespread epigenetic rewiring, leading to aberrant gene expression that drives the pathogenesis of SS. Good prognoses are characterized predominantly by small tumor size and young patient age. Whereas, high tumor grade and an increased genomic complexity of the tumor constitute poor prognostic factors. The current therapeutic strategy relies on chemotherapy and radiotherapy, the latter of which can lead to chronic side effects for pediatric patients. We will focus on the known roles of SWI/SNF, PRC1, and PRC2 as the main effectors of the SS18-SSX-mediated genome modifications and we present existing biological rationale for potential therapeutic targets and treatment strategies.”

Causes of Synovial Sarcoma of Childhood and Adolescence

There are no well-established risk factors for synovial sarcoma, but the disease is associated with the chromosomal translocation t(X;18) (p11;q11). This means that parts of chromosome 18 and chromosome X have switched places in synovial sarcoma tumour cells. It is not known whether this mutation occurs randomly or follows a specific chain of events.

Because of this translocation, synovial sarcoma cells contain a mutant gene. This mutant gene is thought to contribute to the development of the disease. (The Liddy Shriver Sarcoma Initiative).

The exact cause of synovial sarcoma is not entirely understood, however, studies have indicated that genetic alterations may play a role in the formation of soft tissue sarcomas. Researchers have studied a small number of families that contain several members of one generation who have developed soft tissue sarcomas. In addition, limited studies have shown a possible link between soft tissue sarcomas and the development of other types of cancer.

Certain inherited diseases are also associated with an increased risk of developing soft tissue sarcomas. These include people with Li-Fraumeni syndrome (which involves alterations in the p53 gene) or neurofibromatosis (which involves alterations in the NF1 gene). For some soft tissue tumours, there seems to be an association with an Epstein-Barr virus infection. (Dana-Farber Cancer Institute).
Epidemiology

Synovial sarcomas typically present in adolescents and young adults (15-40 years of age). There may be a mild (M:F - 1.2:1) male predilection.

Presentation is most often with a slowly enlarging soft tissue mass which may have been noted for a number of years and gives a false impression of a benign (non-cancerous) process.

The most common location for these tumours is within the soft tissues adjacent to large joints, e.g. the knee and popliteal fossa. While these tumours arise near joints, it is rare for them to arise from the joint itself and despite their name, they do not arise from synovial structures, e.g. joints, tendon sheaths and bursae.

Incidence of Synovial Sarcoma of Childhood and Adolescence in South Africa

The National Cancer Registry (2014) does not provide any statistics regarding the incidence of synovial sarcoma of childhood and adolescence.

Signs and Symptoms of Synovial Sarcoma of Childhood and Adolescence

The following are the most common symptoms of synovial sarcoma. However, each child may experience symptoms differently. Symptoms can depend on the size and location of the tumour. Sometimes the symptoms of synovial sarcoma can resemble those of arthritis, bursitis or synovitis.

Symptoms may include:

- Swelling or mass (usually deep-seated)
- Mass that may or may not be accompanied by pain – it may be painful, in particular if nerves are involved
- Limping or difficulty using legs, arms, hands or feet
- The mass may hinder a bodily function. For example, in the head and neck region, it may cause difficulties swallowing and breathing or it may alter the voice.

The symptoms of synovial sarcoma may resemble other conditions. Always consult a child’s physician for a diagnosis.

Diagnosis of Synovial Sarcoma of Childhood and Adolescence

The diagnosis usually starts with imaging studies. X-ray, sonogram, CT scan, and MRI scan may be used in the course of evaluating a suspicious mass.

After imaging studies, a next step in diagnosis may include a biopsy to remove a sample of the tumour for further analysis. Among the different types of biopsies, open biopsy (a surgical incision is made to remove the sample) or core needle biopsy (a large needle is used to take the sample) are preferred. The use of a fine needle to remove cells can establish the presence of cancer, but often those cells do not provide enough tissue to best characterise synovial sarcoma.
Once a tumour has been deemed malignant, further imaging studies such as a PET scan of the whole body and/or CT scan of the chest, abdomen or pelvis may be used to look for possible metastases (areas where the cancer has spread to).

Doctors use the material gathered during diagnosis to develop a patient’s treatment plan. During this process, they consider many factors that are specific to the patient, including:

- the tumour’s size and how invasive it is
- whether or not there is metastasis at the time of diagnosis
- whether or not the lymph nodes are involved.

### Treatment of Synovial Sarcoma of Childhood and Adolescence

For tumour size of 5 cm or less, limb-saving surgical resection with generous margin with or without radiation therapy may be recommended. For tumour greater than 5 cm, multi-disciplinary approach using pre-operative (neoadjuvant) chemotherapy, plus pre-operative radiation treatment, followed by surgery is sometimes recommended, although the role of chemotherapy continues to be debated.

“Soft-tissue sarcoma (sts) is rare and represents approximately 7% of cancers in children and in adolescents less than 20 years of age. Rhabdomyosarcoma (rms) is most prevalent in children less than 10 years of age and peaks again during adolescence (16-19 years of age). Multi-agent chemotherapy constitutes the mainstay of treatment for rms. In other non-rhabdomyosarcoma soft-tissue tumours, such as synovial sarcoma, evidence for routine use of chemotherapy is less robust, and alternative treatment options, including targeted agents and immunotherapy, are being explored. In this review, we focus on chemotherapy for pediatric-type rms and discuss the advances and challenges in systemic treatment for select non-rhabdomyosarcoma soft-tissue tumours in children and adolescents. We support an increasingly cooperative approach for treating pediatric and adult sts.”

“Vascular endothelial growth factor receptor 2 (VEGFR2) is an attractive therapeutic target in solid malignancies due to its central role in tumor angiogenesis. Ramucirumab (Cyramza™, LY3009806) is a human monoclonal antibody specific for VEGFR2 approved for several adult indications and currently in a phase 1 clinical trial for pediatric patients with solid tumors (NCT02564198). Here, we evaluated ramucirumab *in vitro* and the anti-murine VEGFR2 antibody DC101 *in vivo* with or without chemotherapy across a range of pediatric cancer models. Ramucirumab abrogated *in vitro* endothelial cord formation driven by cancer cell lines representing multiple pediatric histologies; this response was independent of the origin of the tumor cell-line. Several pediatric cancer mouse models responded to single agent DC101-mediated VEGFR2 inhibition with tumor growth delay. Preclinical stable disease and partial xenograft regressions were observed in mouse models of Ewing’s sarcoma, synovial sarcoma, neuroblastoma, and desmoplastic small round cell tumor treated with DC101 and cytotoxic chemotherapy. In contrast, DC101 treatment in osteosarcoma models had limited efficacy alone or in combination with chemotherapeutics. Our data indicate differential efficacy of targeting the VEGFR2 pathway in pediatric models and support
the continued evaluation of VEGFR2 inhibition in combination with cytotoxic chemotherapy in multiple pediatric indications.”

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:
- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Sources and References Consulted or Utilised
Dana-Farber Cancer Institute

Genetics
https://www.google.co.za/search?q=t(X%3B18)+(p11%3Bq11)&source=lnms&tbm=isch&sa=X&ei=U3fkU6vzG6fH7Aac74DoCQ&ved=0CAcQ_AUoAg&biw=1517&bih=714&dpr=0.9#facrc=1&imgdii=_&imgref=82rsF0LjMIE%253A%253Bw4vhjTF7eUOM%3Bhttp%253A%252F%252Fatlasegene%253A%253Bfala%253A%253Bt%253A%253Bfatlas%253A%253Bt%253A%253Bfala%253A%253BAtl%253A%253Bg%253A%253Bt%253A%253Bfatlas%253A%253Bt%253A%253Bfala%253A%253Bt%253A%253Bfala%253A%253Bfatlas%253A%253Bt%253A%253Bfala%253A%253Bt

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National Cancer Institute
http://www.cancer.gov/about-cancer/treatment/clinical-trials


Radiopaedia.org
http://radiopaedia.org/articles/synovial-sarcoma

Sarcoma Foundation of America

Synovial Sarcoma

The Liddy Shriver Sarcoma Initiative
http://sarcomahelp.org/synovial-sarcoma.html

University of Chicago Medicine
http://www.uchicagokidshospital.org/specialties/cancer/sarcoma/non-rhabdomyosarcoma/