Cancer Association of South Africa (CANSA)

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Fact Sheet on Gliosarcoma

Introduction

Cancerous (malignant) tumours of connective tissues are called 'sarcomas'. The term sarcoma comes from a Greek word meaning 'fleshy growth'. Sarcoma arises in the connective tissue of the body. Normal connective tissue includes, fat, blood vessels, nerves, bones, muscles, deep skin tissues, and cartilage.

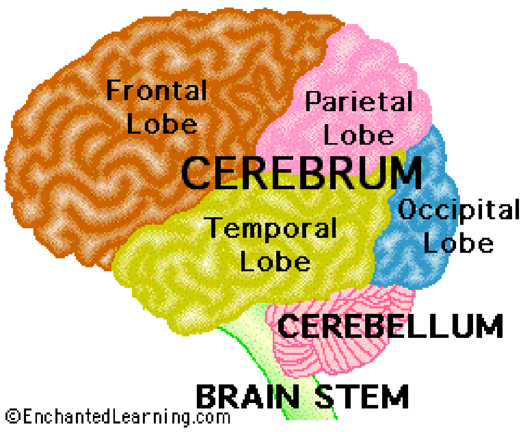
[Picture Credit: Gliosarcoma]

Sarcomas are divided into two main groups, bone sarcomas and soft tissue sarcomas. They are further sub-classified based on the type of presumed cell of origin found in the tumour. They all share certain microscopic characteristics and have similar symptoms.

Sarcomas can develop in children and adults. For children under 20 approximately 15 percent of cancer diagnoses are sarcomas.
(Sarcoma Alliance).

Gliosarcoma

Gliosarcoma is a rare type of glioma, a cancer of the brain that comes from glial, or supportive, brain cells, as opposed to the neural brain cells. Glial cells, sometimes called neuroglia or simply glia (Greek γλία and γλοία 'glue'), are non-neuronal cells that maintain homeostasis, form myelin (a mixture of proteins and phospholipids forming a whitish insulating sheath around many nerve fibres, which increases the speed at which impulses are conducted), and provide support and protection for neurons in the central and peripheral nervous systems.



[Picture Credit: Parts of the Human Brain]

Gliosarcoma is a malignant cancer found mostly in the temporal lobe of the brain, and is defined as a glioblastoma consisting of gliomatous and sarcomatous components. It is estimated that approximately 2% of all glioblastomas are gliosarcomas. Although most gliomas rarely show metastases outside the cerebrum, gliosarcomas have a propensity to do so, most commonly spreading through the blood to the lungs, and also to the liver and lymph nodes.

Gliosarcomas have an epidemiology (study and analysis of the patterns, causes, and effects of health and disease conditions) similar to that of glioblastomas, with the average age of onset being 54 years, and males being affected twice as often as females.
(Wikipedia).

Incidence of Gliosarcoma in South Africa
The National Cancer Registry (2011) does not provide information regarding the incidence of either Glioblastoma nor Gliosarcoma in South Africa.

The Cause of Gliosarcoma
Gliosarcoma seems to be a hereditary disorder. The genetic structure of sufferers is often believed to be mainly responsible for this clinical condition. Missing or mutated genes are suggested as leading to this abnormality in brain cells. The abnormal cells eventually form a tumour because of uncontrolled cell multiplication. Genetic structure is often the cause of the clinical condition. It is usually caused by mutated or missing genes that result in abnormal cells. These abnormal cells eventually will form a tumour when they multiply. It is usually hereditary.
(Hx Benefit Health Information; SignsSymptoms.Org).

Signs and Symptoms of Gliosarcoma
The most common signs include the following:

- Recurring headaches
- Vomiting
- Unsteadiness
- Vision loss
- Cognitive problems
- Seizures
- Personality changes

(hxBenefit Heaklth Information).

Diagnosis of Gliosarcoma
According to the new World Health Organization (WHO) classification gliosarcoma is defined as a glioblastoma variant characterised by a biphasic tissue pattern with alternating areas displaying glial and mesenchymal differentiation. Invariably the clinical history of the patient is short and the presenting symptoms depend upon the location of the tumour. The aetiology of gliosarcoma remains speculative although it is recognised that gliomas can induce sarcomatous transformation in the supporting mesenchymal elements and irradiation of the central nervous system can induce malignant transformation of the brain parenchyma and the meninges predominantly to fibrosarcoma.
(Final Diagnosis).

Treatment of Gliosarcoma
There are important first steps a patient must take in order to maximize the chances of survival and a successful therapy.

First one needs to clarify and confirm the pathologic diagnosis. This pathologic diagnosis is made based on the tissue obtained from the initial surgery. Going forward, the treatment plan will be created based on this diagnosis. This formal diagnosis is made by the neuro-pathologists and is the most important piece of information of any treatment plan.

It is important to note that it is critical to save all tumour tissue collected at the initial surgery. Not only for pathologic diagnosis but also many clinical trials down the road will require frozen tissue from the initial surgery.

Next one wants to make sure the pathology diagnosis matches what one sees on the MRI scan and what is going on with the patient. Taking all of these data points into consideration helps one get a better picture of what is going on with the patient, and can help to better determine how to move forward.

Once one is sure about the diagnosis one can move forward with Treatment Options. Sometimes the treatment will include a more extensive surgery in order to maximise the total resection of the tumour. In higher grade tumours, treatment options can include Radiation Therapy alone, combination therapy of Radiation and Chemotherapy, or combination therapy of Radiation and Chemotherapy followed by additional Chemotherapy.

The decision of what therapy to administer is provided by the Neuro-Oncologists.

If traditional therapy fails in the newly diagnosed setting, additional therapy can be administered in the recurrent setting.

The treatment approaches in the recurrent setting mirror some of the options in the newly diagnosed setting. For example, one will need to identify if the patient needs additional surgery for de-bulking or further tumour resection. The neuro-oncologist will also need to identify if further radiation is needed. Most of the time in these recurrent settings additional systemic treatment will need to occur. These forms of treatment can be either standard chemotherapy agents or experimental therapies as part of an ongoing clinical trial.

Because each patient's treatment plan is unique, therapy normally is dictated by several factors including a person’s age, Karnofsky Score and any previous therapy they have received. Advances in molecular diagnostics laboratory is enabling one to better predict what agents will benefit a particular patient group. In general, the following is an overview of agents used to treat Gliosarcoma patients. This list includes all patients treated at UCLA Neuro-Oncology between 1/16/2015 and 1/16/2017.

Chemotherapy Agents:
- Accutane
- Avastin (Bevacizumab)
- BiCNU Carmustine
- Carboplatin
- CCNU Lomustine
- CPT -11 (CAMPTOSAR, Irinotecan)
- Etoposide (Eposin, Etopophos, Vepesid)
- TEMODAR

(UCLA Neuro-Oncology).

Prognosis (Outlook) of Gliosarcoma

Gliosarcoma is a rare primary malignant tumour of the central nervous system with poor prognosis. The median survival time of this disease ranges from 6 months to 14.8 months. However, a computer literature search indicated few long-term survivors. There is a case of a survivor of Gliosarcoma with radiation-induced meningeal sarcomas, who showed no indication of recurrence for more than 9 years.
(CancerJournal.net).

About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

<u>Types of Clinical Trials</u>

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (<u>recurrence</u>) of the original cancer or reduce the chance of developing a new type of cancer

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.
Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or “control” interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as ‘biospecimens’) obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care. (National Cancer Institute).

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