Cancer Association of South Africa (CANSA)

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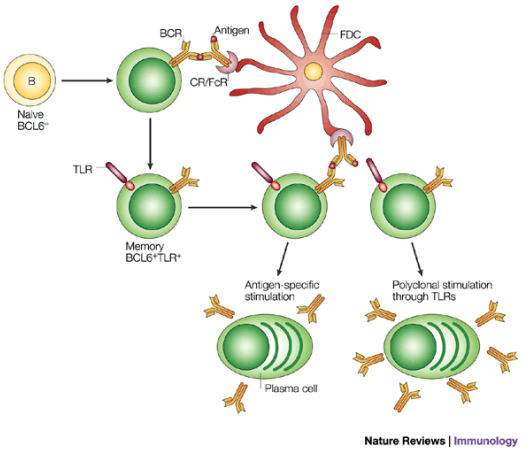
Fact Sheet on Follicular Dendritic Cell Sarcoma

Introduction

Follicular dendritic cells (FDC) are a different type of cell in the lymph nodes. FDCs are found in the part of the lymph node called the lymphoid follicle where a type of white blood cell (lymphocyte) is made. Lymphocytes help to fight infection.



[Picture Credit: Follicular Dendritic Cells]

Follicular dendritic cells (FDCs) are cells of the immune system found in primary and secondary lymph follicles of the B cell areas of the lymphoid tissue. These cells were first described in 1965 and, although they have a very dendritic morphology, are not dendritic cells (DCs). Unlike DCs, FDCs are not derived from the bone-marrow haematopoietic stem cell, but are of mesenchymal origin. Mesenchymal stem cells, or MSCs, are multipotent stromal cells that can differentiate into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells) and adipocytes (fat cells).

Haematopoietic stem cells (HSCs) or haemocytoblasts are the stem cells that give rise to all the other blood cells through the process of haematopoiesis (blood cell formation). They are derived from mesoderm and located in the red bone marrow, which is contained in the core of most bones. The mesoderm is one of the three primary germ layers in the very early embryo. The other two layers are the ectoderm (outside layer) and endoderm (inside layer), with the mesoderm as the middle layer between them.

Follicular dendritic cells support lymphocytes by recognising cells that are foreign or unwanted in the body. They pick them out by looking at the proteins (antigens) on the cell surface, which are different from proteins on normal cells. The FD cells then capture the foreign cells and take them to lymphocytes. The lymph nodes can then make lymphocytes that recognise the particular cells that the FDC cells have found. The foreign cells can then be picked up quickly and destroyed by the immune system.
(Cancer Research UK; Wikipedia).

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Follicular Dendritic Cell Sarcoma
Follicular dendritic cell sarcoma (FDC sarcoma) is a very rare type of blood cancer. Fewer than 100 cases have been reported in medical literature worldwide.

Follicular dendritic cell sarcoma develops from specialised cells in the lymph nodes. Most develop in the lymph nodes and are called nodal cancers. But about 3 out of 10 (30%) develop elsewhere in the body in the:

- Head and neck
- Digestive system (bowel, stomach)
- Spleen
- Liver

These FDC sarcomas are known as extranodal tumours, because they grow outside the lymph nodes and bone marrow.
(Modern Pathology; Cancer Research UK).

Incidence of Follicular Dendritic Cell Sarcoma in South Africa
The National Cancer Registry (2012) does not provide information regarding the incidence of Follicular Dendritic Cell Sarcoma.

Signs and Symptoms of Follicular Dendritic Cell Sarcoma
Systemic symptoms are rare. Patients most often present with a slow growing painless mass. Castleman disease is one clinical setting where hyperplasia and dysplasia of follicular dendritic cells has been implicated as precursor lesions to this neoplasm. Nearly 10-20% of cases are associated with Castleman disease (of hyaline vascular type). EBV genome has been identified in several putative FDC sarcomas that show morphologic resemblance to inflammatory pseudotumour.

Gross appearance is similar to that of other sarcomas with a well-circumscribed tan grey cut surface. Necrosis and cystic change may be seen in larger tumours. Histologic appearance is that of a spindled and ovoid cell proliferation forming fascicles and a storiform pattern with whirling, reminiscent of a meningioma. Tumour cells have plump eosinophilic cytoplasm and indistinct cell borders. Nuclei are elongated with vesicular or finely granular chromatin and distinct nucleoli. Although most cases are cytologically bland with a low mitotic rate (0-10/10 HPF), cases with greater cytologic atypia and higher mitotic rates may be seen. Often there is a sparse infiltrate of mature lymphocytes and plasma cells, predominantly in a perivascular distribution. In cases involving the liver and spleen, the tumour cells often do not demonstrate a cohesive proliferation of spindled cells, and have a greater degree of inflammatory infiltrate causing diagnostic confusion with inflammatory pseudotumour.
(Final Diagnosis).

Diagnosis of Follicular Dendritic Cell Sarcoma
The homeostatic chemokine CXCL13 is preferentially produced in B-follicles and is crucial in the lymphoid organ development by attracting B-lymphocytes that express its selective receptor CXCR5. Follicular dendritic cells (FDCs) have been identified as the main cellular source of this chemokine in lymphoid organs.

CXCL13 is produced by dysplastic and neoplastic FDCs and can be instrumental in recruiting intratumoural CXCR5+ lymphocytes. In addition to the potential biological relevance of this expression, the use of reagents directed against CXCL13 can be useful to properly identify the origin of spindle cell and epithelioid neoplasms.
(Vermi, *et al*., 2008).

Treatment of Follicular Dendritic Cell Sarcoma
Dendritic cell tumours are extremely rare and current knowledge of these tumours is limited. The characteristics of three dendritic cell sarcoma subtypes and their optimal treatment approaches are not fully clarified.

Pooled analysis of 462 reported cases revealed that the tumour had no age, gender or racial predilection. Analysis suggests that the young age, advanced stage, intra-abdominal involvement and unfavourable histological features (i.e. large tumour size, absence of lymphoplasmacytic infiltration, coagulative necrosis, high mitotic count) may predict poor prognosis.

Subtypes of this tumour have different clinical behaviours with interdigitating dendritic cell sarcoma being the most aggressive form. In general, surgery is the most effective treatment modality and adjuvant radiotherapy has no significant effect on overall survival of patients. The role of chemotherapy for the management of advanced disease is controversial.

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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