Syrian Arab Republic

Ministry of Education

National Center for Distinguished

2016-2017

Seminar in biology Entitled:

Lymphoma..

Preparation of student: Laura Deeb….

The twelfth grade ….

Supervisor teacher: teacher Fadia Ali ….

2016/2017

Table of Contents

Index of figures

Introduction

In each country there is a ministry of defense, which is responsible for protecting the country and defending it against enemies and their attacks. And so, any small defect or problem in it may affect (threaten) the whole country, especially if that mistake occurred between soldiers (the first defense line).

In a like manner ,our bodies which are complicated structures need a system that protect the body an defense it against any foreign body and monitor the other tissues while doing their functions .And this system is called the lymph system .But sometimes ,a problem may occur in a part of this system like lymphocytes (the first defense line).And thing get more complicated to cause bigger problems like lymphoma ,a cancer that infects lymphocytes and spreads to other parts of the lymph system and maybe other tissues .And that does not affect the lymph system only ,but also threaten the whole body (because of this system's role in protecting our bodies). So, this this disease has to be cured because of its riskiness on our bodies.

And then we may ask ourselves:

- Are there any new discovered treatments of this disease rather than traditional (standard) treatments for cancer??? and what is special about them??
- What is the most appropriate 'optimal' treatment for lymphoma??

1.The lymphatic system

1.1 What is the lymphatic system??

The lymphatic system is a very important part of the immune system (which defenses the body against infections and other diseases), it consists of:

- Lymph vessels: the lymph system has a spidery network of thin tubes that branches out into all tissues of the body called lymph vessels. They connect the other parts of the lymph system with each other (especially lymph nodes).
- lymph fluid: it is a clear fluid that flows through the lymph vessels. It contains white blood cells especially lymphocytes such as B and T cells, protein molecules and other immune components.
- lymph nodes :they are bean-shaped organs that can be found in various places in the body like the neck ,shoulders ,chest groin ,underarms ,abdomen and elbows ,the number of the lymph vessels that enters that lymph nodes is bigger than the number of those which carry the lymph outside them (the lymph nodes) ,which enables lymph nodes to filter the lymph fluid from bacteria ,viruses and other foreign substances, lymphocytes(a kind of white blood cells that will be explained later) can mostly be found in lymph nodes where they can monitor the lymph for any signs of infections in the body ,lymph nodes also can change in size , in other words ,they can get bigger or smaller depending on the number of lymphocytes inside them.
- Bone marrow: it is the medium where blood stem cells are made.
- spleen: it forms immune cells in the fetus body.
- lymphocytes: they are a type of white blood cells that originate from hematopoietic stem cells, they travel in the blood stream and lymph vessels.[1, 2]

1.2 Lymphocytes

Healthy bone marrow produces hematopoietic stem cells that can take various roles, then they mature to produce specialized white and red blood cells as well as lymphocytes. Once lymphoid stem cells detect any foreign- body (antigen), they get bigger (increase in size) and become lymphoblast's, then lymphoblast's specialize and divide. Lymphocytes (lymphoblast's) include:

T-cells: they originate in the bone marrow and mature in the thymus gland, they include:

- Cytotoxic T cells: They abolish viruses, bacteria, parasites and funguses, they secrete proteins that make holes in the foreign cells' ectoplasms, then they secrete toxic substance, they also attack cancer cells.
- Helper T cells: they regulate(organize) and control the immune system functions by making (producing) lymphocytes, they help B-cells to divide and make antibodies.
- Regulatory T cells: they control the way that B and T cells fight infections, they stop them after their task is done, they also regulate and control the number of antibodies in the blood.
- Memory T cells: they recognize (remember) antigens when they enter the body again.

B-cells: They originate and mature in the bone marrow. They are instigated by the antigens and lymphocytes that are produced by (helper cells) to divide and give memory cells that live for a long time, and plasma cells, that make antibodies when a foreign cell enters the body and they live for a short time.

Natural killer cells: they attack and kill cancer cells and virus-infected cells. They also make chemicals that can attack viruses and tumor cells called cytokines. Other parts include: the tonsils, thymus

gland…etc. Lymphatic tissues can also be found in stomach, skin, small intestine and other parts of the body.[3]

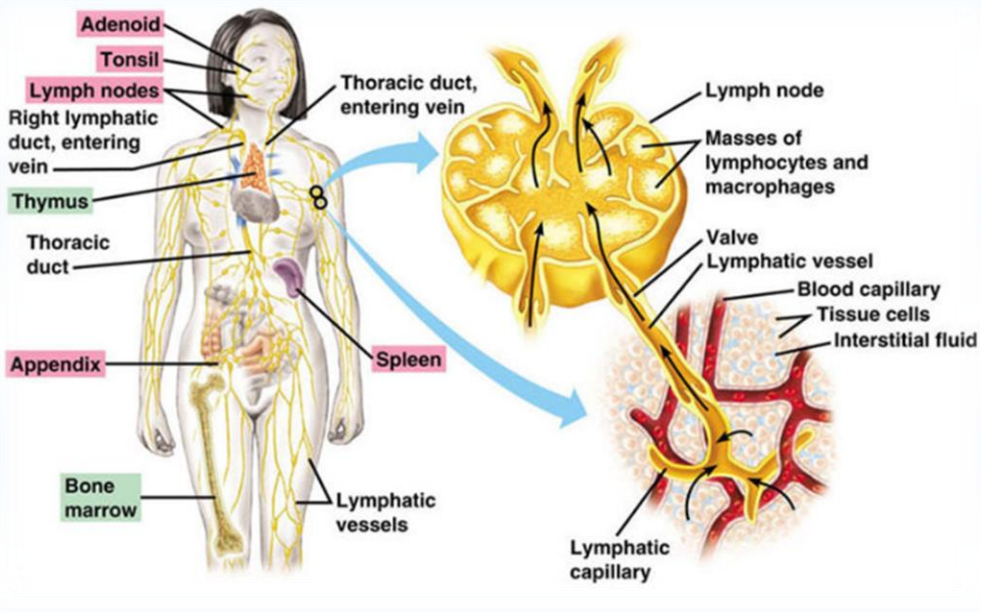

Figure 1:The lymphatic system

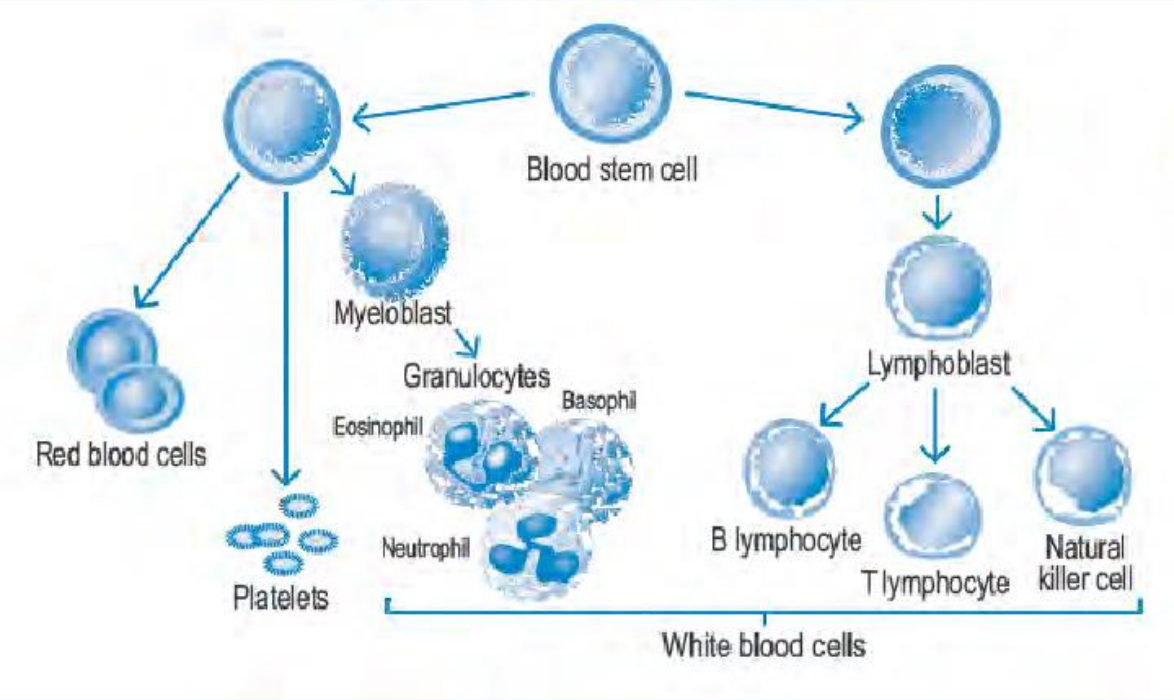

Figure 2 :Blood cell lineage

2.Lymphoma

2.1 What is lymphoma??

Lymphoma is a type of cancer that originates from lymphocytes in a lymphoid organ (the lymph nodes, spleen or even bone marrow).

As we said previously, lymphocytes are very important part of the immune system, they work together with other cells in the immune system to defend the body against invaders like bacteria, parasites and viruses by making antibodies and other mechanisms. And like the other cells of the body, they have a limited life span ,which means that when one of these cells becomes senescent (too old) or when it gets damaged ,a self –destruct mechanism called programmed cell death is triggered for it .But, sometimes a damage to the genetic material (DNA) of the cell, makes it able to override this self-destruct mechanism and continue to live and grow ,making the cell" immortal " in many ways ,which means that the cell that wouldn't normally be able to divide and grow continue to grow and divide uncontrollably without stopping .These abnormal cells don't protect or defend the body against infections or other diseases anymore and accumulate to form a mass called tumor that interfere with the organ function ,and that is how lymphoma develops .And these abnormal lymphoma cells travel through lymph and blood vessels to infiltrate not only the other lymphoid organs but also other tissues.[4, 5]

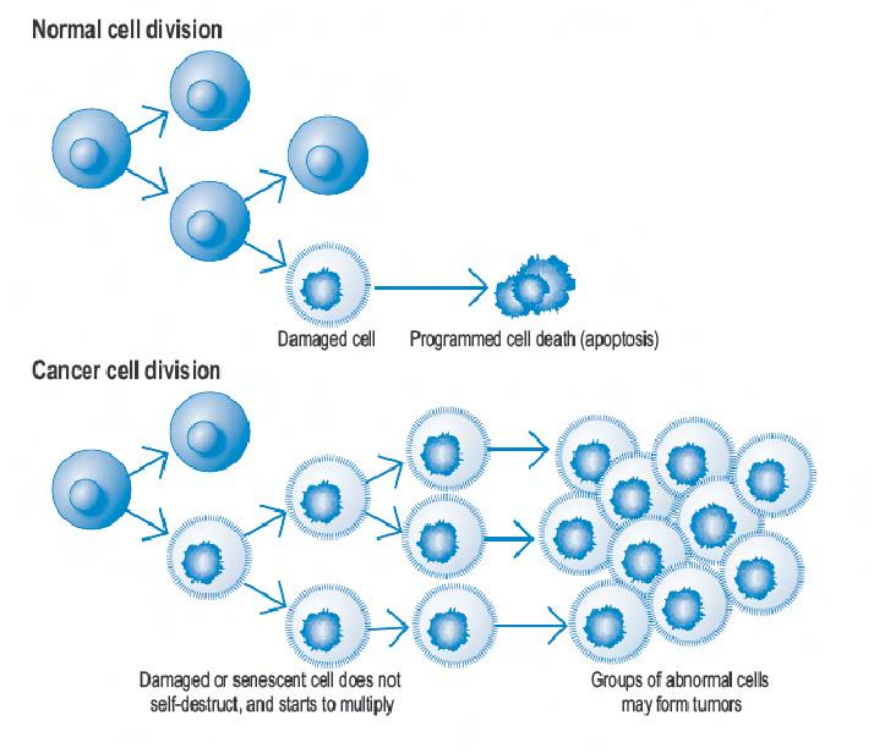

Figure 3: How cancer forms inside the body

2.2 Lymphoma types

There are two main categories of lymphomas: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). And each one of these categories has numerous subtypes that are different in the way they develop and spread.

2.2.1Hodgkin lymphoma

2.2.1.1 What is Hodgkin lymphoma??

It originates from a mature B-lymphocyte at the germinal center of differentiation, it becomes usually larger and carry more than one nucleus, then we call it stern-berg cell. This disease is usually limited to a single axial lymph node region ((including the neck, underarms and chest). It spreads in contiguous manner (that means that the Hodgkin lymphoma that starts in lymph nodes in the neck for example spreads first to the lymph nodes above the collar bones and then to the lymph nodes under the arms and within the chest. And bone marrow involvement is rare.

It is unknown what causes most cases of Hodgkin's lymphoma, and there is no way to prevent lymphoma but it is rare and not contagious. It is commonly diagnosed when a person is in his or her 20s ,30s or after age 60. And it is often diagnosed before it reaches an advanced stage.[6]

2.2.1.2 Signs and symptoms

The most common signs of HL are one or more swollen painless lymph nodes that maybe in the neck, upper chest, armpit, abdomen or groin.

Other signs and symptoms include:

- Cough and shortness of breath.
- Fever.
- Night sweats.
- Tiredness.
- Weight loss.
- Itchy skin.[7]

2.2.2 Non-Hodgkin lymphoma

2.2.2.1 What is Non-Hodgkin lymphoma??

It arises from B or T cell and usually involves multiple peripheral lymph nodes with noncontiguous dissemination to distant organs, and bone marrow involvement is more common. This disease is more common than HL and it has at least 60 different types but it is not contagious. It is diagnosed at more advanced stage than HL.

The reason why someone develops NHL while another doesn't is unknown. But there are certain risk factors that increase the chance that a person will develop NHL they include:

- Weakened immune system: such as from an inherited condition or certain drugs that is used after an organ transplant.

- Certain infections: such as Hepatitis C virus, Human T-cell leukemia /lymphoma virus, Human immunodeficiency virus (the virus that causes AIDs), Helicobacter pylori (bacteria that can cause stomach ulcers and Epstein –Barr virus.
- Age: Although NHL can occur at any age, the risk of having it increases with age, it more common with people over age 60.
- Male gender: for unknown reason NHL is slightly more common in men than in women.
- Treatment with radiation therapy for some other cancers including NHL.
- Being exposed to certain chemicals, such as certain herbicides and pesticides or some chemotherapy drugs used to treat other cancers or autoimmune diseases.
- Previous treatment for lymphoma.

Having one or more risk factors for NHL doesn't mean that a person will develop the disease. Most people with these risk factors never develop NHL. At the same time, many people diagnosed with NHL don't have any of these risk factors, but there is maybe a correlation between the risk factors and the development of NHL. Children and siblings of patients with NHL have also slightly increased risk to have this disease compared with ordinary people. However, there is no clear genetic or hereditary factors to predict this slightly increased risk.[7]

2.2.2.2 NHL symptoms and signs

- Lumps under the skin on the sides of the neck, above the collar bone, underarms, elbows, or in the groin.
- Swollen tender abdomen either "belly" or "stomach".
- Abdominal or stomach pain.
- Nausea or vomiting.
- Decreased appetite and unexplained weight loss.
- Coughing, trouble breathing, chest pain or pressure.
- Rash, itchy, red or purple lumps or nodules under the skin.
- Headache, trouble thinking, personality changes or trouble speaking.
- Double or blurred vision.
- Facial numbness, weakness in extremity (leg or arm) and sometimes seizures.
- Severe or frequent infections.
- Fever, chills for no reason and/or drenching night sweats.[7]

Parameter	Hodgkin's lymphoma	Non-Hodgkin's lymphoma
1. Incidence	Stable	Steadily increasing
2. Age	Usually in young adults	Incidence increases with age
3. Cell of origin	Usually B lymphocyte	B or T lymphocyte
4. Lymphadenopathy	Axial, especially cervical or mediastinal	Multiple, peripheral
5. Extranodal disease	Rare	More common
6. Defining morphological feature	Reed-Sternberg cell in a characteristic cellular milieu	—
7. Prognosis	Curable in majority of cases	Variable

Figure 4: comparison between Hodgkin and Non-Hodgkin lymphoma

2.3 Lymphoma types according to their growth speed

Lymphoma maybe grouped according to how quickly they grow in two groups.

- Indolent lymphomas (low-grade lymphoma): They grow slowly and usually tend to cause few symptoms, while indolent lymphomas are generally not curable, patients can potentially live for a long time with these types of lymphomas because they tend to respond well to treatment and can remain in remission for many years. And although they grow slowly, they tend to be more widespread at diagnosis than aggressive lymphomas. Over time, many indolent lymphomas become aggressive lymphomas.
- Aggressive lymphomas (intermediate-grade and high-grade lymphoma): they grow and spread more quickly, they tend to cause severe symptoms. Although aggressive lymphomas are threating, they can be cured with chemotherapy drugs that can kill tumor cells that divide rapidly.[8]

2.4 Stages of lymphoma

The stage of lymphoma depends on some main factors including:

- The number and location of lymph nodes that have HL cells.
- Whether the disease has spread to the spleen, liver, bone marrow, lung or bone.

And depending on these factors, the disease is classified into many stages:

Stage I

Lymphoma cells are in one lymph node group (such as the lymph nodes in the neck or armpit). Very rarely, Hodgkin lymphoma may start somewhere in the body other than a lymph node and lymphoma cells are found in only that one part.[9]

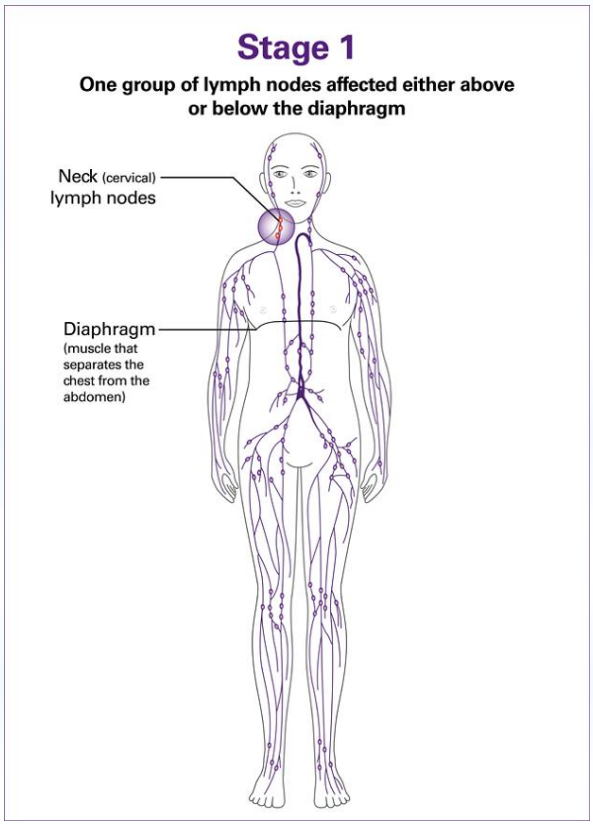

Figure 5:Stage 1

Stage II

Lymphoma cells are in at least two lymph node groups, but both groups are on the same side of the diaphragm. Or lymphoma cells are in one part of a tissue or an organ and the lymph nodes near that organ on the same side of the diaphragm. Lymphoma cells may be in other lymph node groups on the same side of the diaphragm.[9]

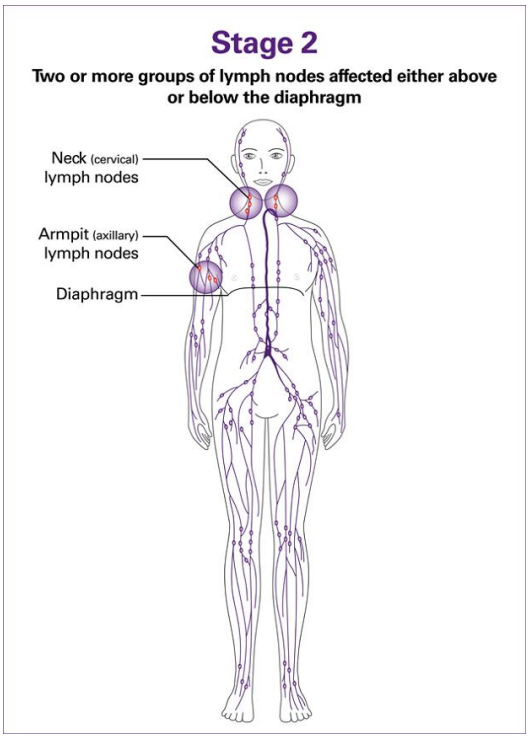

Figure 6:Stage 2

Stage III

Lymphoma cells are in lymph nodes on both sides Of the diaphragm. Lymphoma cells may also be found in one part of a tissue or an organ near these lymph node groups or in the spleen.[9]

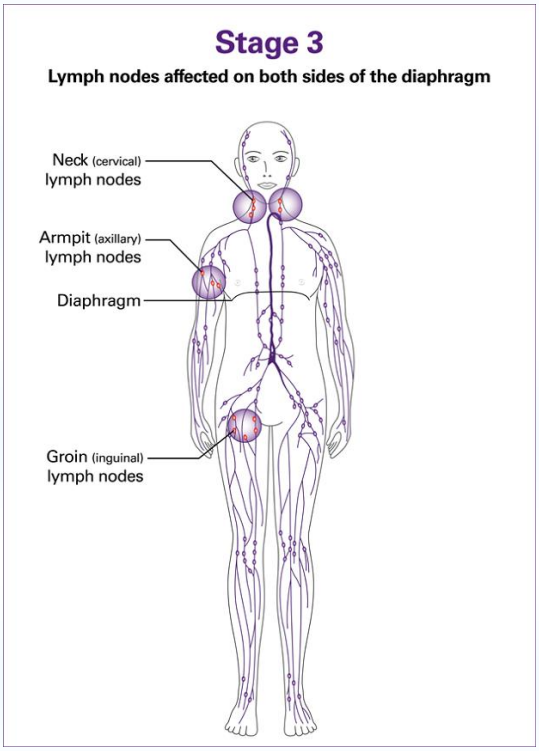

Figure 7:Stage 3

Stage IV

Lymphoma cells are found in several parts of at least one organ or tissue. Or, lymphoma cells are in an organ (such as the liver, lung, or bone) and in lymph nodes on the other side of the diaphragm.[9]

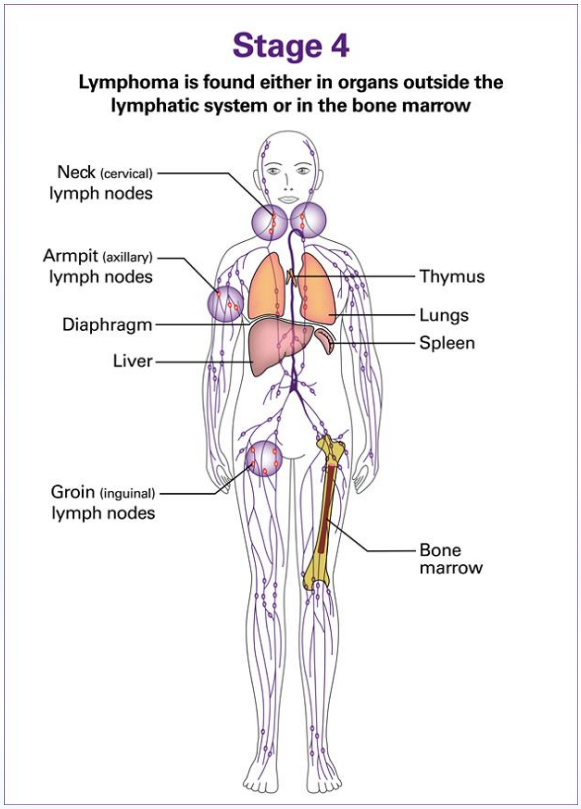

Figure 8:Stage 4

3.LymphomaTreatment

Choosing the right (appropriate) treatment for the person who has lymphoma is very important because the treatment that may work well with one patient may not have the same positive effect in another. So, choosing the right treatment depends on many factors:

- The type of lymphoma you have: there may be small but important differences between different types of lymphoma.
- Its stage and where it is found.
- Its growth speed: whether it is indolent or aggressive lymphoma.
- The patient's age.
- Whether the patient have another health problem.[4]

3.1 Types of treatments used in patients with Lymphoma

- Watchful waiting :In this kind of treatments patients aren't given any treatments ,but their health and disease are monitored carefully .These patients continue to remain untreated as long as they don't show any signs or symptoms ,and there is no evidence that the lymphoma is growing or spreading .So ,it is a good choice for patients with indolent lymphoma or patients with no symptoms from their disease ,while is not a treatment option for patients with aggressive lymphoma who should be treated as soon as possible after diagnosis .
- Chemotherapy: this types affects general cell growth and proliferation.
- Monoclonal antibodies: which can specifically attack lymphoma cells.
- Targeted or biological therapies: they affect special characteristics or internal working of lymphoma cells.
- Immunomodulatory drugs: they interact with the immune system to encourage the destruction of lymphoma cells.
- Radiation therapy: which uses high energy radiation to kill lymphoma cells.
- Stem cell transplantation.[10]

3.2 Chemotherapy

3.2.1 What is chemotherapy??

Chemotherapy for lymphoma uses drugs that work against general characteristics of cancer cells, such as their tendency to grow and divide very quickly or they work even on killing them. They work by poising the cancerous cells and so, they are known as "cytotoxic drugs". It is usually used to treat advanced Hodgkin lymphoma (some stage 2, most stage 3, all stage 4, and B symptoms at any stage).[11]

3.2.2 How does it work??

As mentioned previously ,every cell in our body have a limited lifespan ,and so, they need to be replaced by new cells and these new cells form when a cells divides into two new cells ,which divide into four cells (then eight ,then sixteen ….etc.),and through (during) this division ,the cell goes on several steps called (phases) which make up a process called the cell cycle .And chemotherapy drugs work by either stopping cancer cells dividing or triggering the cancer cells to die ,or by these two methods (mechanisms) together .

Some drugs work only on cells in one phase of the cell cycle (so they stop any cell in the affected phase from dividing), while other drugs work on any cell that is dividing in spite of the phase it is in. So, these drugs have little or even no effect on cells that are not dividing.[11]

3.2.3 How is chemotherapy given??

It is given in cycles with rest periods between them. It can be given as a pill by mouth, a liquid infused directly to a vein or it can be injected just under the skin, or into the cerebrospinal fluid that surround the brain and spine. Then they travel through the blood stream and reach almost all areas of the body.[12, 13]

3.2.4 What is bad about chemotherapy??

Chemotherapy is not very accurate, many cytotoxic drugs don't stop only cancer cells dividing but they can also stop normal healthy cells and that what causes many of the side effects to occur. They can harm normal cells that divide naturally including:

Blood cells: chemotherapy may lower your levels of healthy blood cells and that makes you more likely to get infections, bruise or bleed easily and feel very weak and tired.

Cells in hair roots: and that what causes hair loss. IF you lose your hair it grows back, but it may be different in color and texture (but then it will return to its normal hair and texture).

Cells that line the digestive track: chemotherapy can cause poor appétit, nausea and vomiting, diarrhea, trouble swallowing or mouth and lip sores.

Chemotherapy also may cause skin rashes or blisters, headaches or other aches and the skin may become darker. The nails may develop ridges or dark bands.

Chemotherapy cannot attack all the dividing lymphoma cells in our bodies. And so, these survival cells will travel through the blood and the lymph vessels to infiltrate other areas of the body and start growing and accumulating again and again.[10]

3.3 Radiotherapy

It uses high energy radiation (like X-rays, gamma rays and charged particles) to kill cancer cells and shrink tumors. It also can help control pain. It is usually used when large lymph nodes are pressing on an organ and chemotherapy cannot control the problem.[11]

3.3.1 Types of radiation therapy

It has two types:

- **External radiation**: which is delivered by a large machine that aims the rays at the part of the body where lymphoma cells have assembled. So, it affects the cells in the treated area only and that why it is called (local therapy). People can receive this treatment 5 day a week for several weeks.
- **Systemic radiation**: it uses radioactive materials such as radioactive iodine that travels through the blood all around the body. And this radioactive material is bound to monoclonal antibodies that seek out the lymphoma cells then the radiation destroys these lymphoma cells.[14]

3.3.2 How does radiation therapy work??

Radiation therapy works on killing cancer cells either by damaging their DNA directly or creating charged particles within the cells that can in turn damage the DNA, that what leads the cell to stop dividing or even die (because of the DNA's importance in carrying genetic information and passing it from one generation to another. After the damaged cells die, they are broken down and abolished by the body's natural processes.[14]

3.3.3 What is bad about radiation therapy??

Radiation therapy (external radiation therapy) affects lymphoma cells in the area that is exposed to radiation only, so it cannot be the only treatment (which means that it isn't enough) when lymphoma cells are spread into many areas of the body.

It doesn't kill only cancer cells, but it can also damage normal cells (in the area that is exposed to radiation) leading to many side effects which can be either acute side effects that occur during treatment and disappear after treatment ends, or chronic side effects that occur months or even years after treatment ends.

Acute radiation side effects: they are caused by damage to rapidly dividing normal cells in the area that is being treated, they include:

- Skin irritation.
- Fatigue.
- Nausea with or without vomiting when the abdomen is treated and sometimes when the brain is treated.

Chronic side effects: they do not necessarily occur. They include:

- Damage to the bowels causing diarrhea and bleeding.
- Memory loss.
- Infertility which means inability to have children.

- A second cancer caused by radiation exposure, depending on the part of the body that was treated (for example girls treated with radiation to the chest have an increased risk of developing breast cancer later. But developing a second cancer acer happens rarely and the risk of developing it is higher in people treated as children or adolescents.[11]

3.4 Radio chemotherapy

Radiation therapy can be given alone or with chemotherapy and this combination is called radio chemotherapy or chemo radiation when there are very large masses of lymphoma cells in a small area of the body in order to kill more cancer cells but it can cause more side effects.

3.5 H225 the new hope for patients

As mentioned previously, after originating in a lymph node, lymphoma cells travel through the blood vessels. And since they can't survive in the blood for a long time, they are compelled to find a more accommodating environment, where they can proliferate. So, they leave the blood vessels and multiply in the lymphatic system, and then they become really dangerous.

So, a group of researchers at the university of Geneva and the Geneva university hospitals in Switzerland, worked hard and found a new approach to stop the disease from developing. This approach depends on using an antibody called 'H225 ' able to neutralize a specific protein to prevent lymphoma cells from migrating outside the blood vessels.[15]

3.5.1 How does the 'H225' prevent malignant cell circulation??

The inner wall of blood vessels is formed by a layer of endothelial cells that acts as a barrier which prevents the blood cells from leaving the circulation. But when some lymphocytes become cancerous, they are equipped with a specific surface marker, the JAM-C protein, also present on the surface of endothelial cells. Like a free pass, its presence on the surface of lymphoma cells facilitates their migration through the vessel walls between adjacent endothelial cells. So, in order to block the effect of this protein, the scientists developed the antibody called 'H225' to bind solely to JAM-C by masking JAM-C,'H225' was able to prevent the cells from migrating out of the blood vessels.[15]

3.5.2 What is special about 'H225’

Decreasing the transit cancerous cells into the organs of the lymphatic system by over 50% wasn't the only effect of 'H225’. But it also limited cell proliferation, even when tumor cells had already settled in the lymphatic system. Thomas Matthews, a professor at UNIGE, faculty of medicine and Doctor at UUG, who supervised the study, says: “In our mice, we observed the nearly complete disappearance of already present tumor cells in the organs".[15]

Conclusion

As a conclusion, it can be found that there is no 'optimal' treatment that can be relied on for all cases of lymphoma, because lymphoma has many types, and even the same type can be different from a patient to another. And so, choosing the right treatment depends on the patient's overall conditions and factors that were discussed in the research. But using the 'H225' antibody, this still experimental immunotherapy strategy seems to be more accurate (precise) and less or even unarming for the normal cells comparing to other standard treatments, and may not cause any side effects or weakness for the body. And so, it can pave the way for more efficient and less harming treatments.

So, I hope that scientists pay attention for this really important discovery, and try to develop it to get a really reliable strategy against lymphoma and efficient treatment that could in the near future, be offered to patients.

References

1. Cecie Starr, B.M., *Human Biology*. 11 ed. 2015: Cengage Learning 158,159.
2. Alexander Fridman, G.F., *Plasma Medicine*. 2012: John Wiley & Sons. 3.
3. D.Bambard, N., *Signaling in Natural Killer Cells:NK Cell Activation by LLT1 Receptor* 2008: ProQuest. 2,3,4,5.
4. Tammy Schacher, T.S., Judith Mckay, *The Chemotherapy Survival Guide :Every thing you need to know to Get through Treatment*. Third edition ed. 2009: New Harbinger Publications 10,11,19.
5. Peter Holman, G.B., *100 Questions & Answers About Lymphoma*. Third edition ed. 2014: Jones & Bartlett Publishers 18.
6. Kawthalkar, S.M., *Essentials of Haematology*. second edition ed. 2012: JP Medical Ltd. 335.
7. Wilkins, L.W., *Portable signs and symptoms*. First editiion ed, ed. L.s. Julie Munden 2008, United states of America: Judith A.Schilling McCann,RN,MSN. 353.
8. Al-Tubaikh, J., *Internal Medicine :An illustrated Radiological Guide* second edition ed. 2016, Switzerland: Springer. 362.
9. Perry, M.C., ed. *The Chemotherapy Source Book*. Fourth edition ed. 2008, Lippincott Williams & Wilkins: philadelphia. 521.
10. M.Adler, E., *Living with lymphoma*. second edition ed. 2016: JHU Press. 62,69,73-86.
11. Hoppe, R., ed. *Hodgkin lymphoma*. second ed. 2007, Lippincott Williams & Wilkins: philadelphia. 105,189.
12. Dolinger, M., *Everyone's Guide to Cncer Therapy*. 4th edition ed. 2002: Andrews McCMeel Publishing. 626.
13. Dreyer, Z., *Living with Cancer*. 2007: Infobase Publishing 54.
14. D.Tamparo, C., *Diseases Of The human Body* 2016: F.A.Davis. 90.
15. Do±ate, C., et al., *Frontline Science: Anti-JAM-C therapy eliminates tumor engraftment in a xenograft model of mantle cell lymphoma.* Journal of leukocyte biology, 2016: p. jlb. 1HI1114-549RR.