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IMMUNOTHERAPY OF HEMATOLOGICAL MALIGNANCIES

(About 69 cases of NHL)

THESIS

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LIST OF ABBREVIATIONS

APCs : antigen-presenting cells

ADCC : Antibody-dependent cellular cytotoxicity

Ab : antibody

Ag : antigen

BiTEs : Bispecific T cell engagers

BTG : B Cell Translocation Gene-1

BCR : B cell receptor

BRCA gene : BReast CAncer gene

CIN : chromosome instability

CDKs : Cyclin-dependent kinases

CD40L : CD40 ligand

CTLs : cytotoxic T lymphocytes

(COX)-2 : Cyclooxygenase-2

(CTLA-4) : Cytotoxic T lymphocyte associated antigen

CSF : colony-stimulating factor

DNA : deoxyribonucleic acid

DNAM- 1 : DNAX accessory molecule-1

E-box: enhancer box

EGFR : epidermal growth factor receptor

ECOG : Eastern Cooperative Oncology Group

EBV : Epstein-Barr virus

Fab : Ag-binding fragment

FcR : Fc receptors (e.g., FcgRI)

FLIPI : Follicular Lymphoma International Prognostic Index

GALT : gut-associated lymphoid tissue

G-CSF : granulocyte CSF

HIV : human immunodeficiency virus

HLA : human histocompatibility leukocyte Ag

HSV : herpes simplex virus

ICAM : intercellular adhesion molecule

IFN : interferon (e.g., IFN-γ)

IL : interleukin (e.g., IL-2)

JAK or Jak : Janus kinase

MSI : microsatellite instability

MSH2 Gene : mismatch repair protein

MLH1 promoter: MutL Homolog 1

MHC : major histocompatibility complex

miRNAs : microRNA

MALT : mucosa-associated lymphoid tissue

mAb : monoclonal Ab

MEK : mitogen-activated protein kinase kinase

MDSCs : myeloid derived suppressor cells

NK cell : natural killer cell

NKG2A : Natural Killer Cell Inhibitory Receptor

NKp30 : natural cytotoxicity receptors

NKp46 : natural cytotoxicity activation receptors

NHL : Non-Hodgkin Lymphoma

pRB : The retinoblastoma protein

p53 : Tumor protein p53

PD-1 : Programmed cell death protein 1

PD-L1 : Programmed death-ligand 1

PGE2 : Prostaglandin E2

PGD2 : Prostaglandin D2

RTKs : Receptor tyrosine kinases

ROS : reactive oxygen species

STAT : signal transducer and activator of transcription

TNF-α : Tumor necrosis factor alpha

TGFβ : Transforming growth factor β

TSGs : Tumor suppressor genes

TNF : Tumor necrosis factor

TLR : Toll-like receptor

TCR : T cell receptor for Ag

TILs : Tumor-infiltrating lymphocytes

TIM-3 : T cell immunoglobulin and mucin domain 3

Treg cells : Regulatory T Cells

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INTRODUCTION

Cancer is a major burden of disease worldwide today. Affecting all categories of the world's population regardless of age, gender or socioeconomic status, each and every year, tens of millions of people are diagnosed with cancer around the world, and more than half of patients die from it, during 2018 the mortality rate was more than 9.6 million deaths and about 1 in 6 deaths are due to cancer.

The global burden of cancer is expected to increase from 14.1 million newly diagnosed cases and 8.2 million cancer deaths in 2012 to 22 million cases and 13 million deaths in 2030 [1].

In Morocco, cancer is a major health problem. It is the second leading cause of death after cardiovascular disease, According to data from the Cancer Registry of the Greater Casablanca Region (CRCR), the annual national incidence of cancer is estimated at 101.7 new cases per 100 000 inhabitants, corresponding to 30 500 new cases of cancer each year [2].

The future cancer burden is likely to be even higher than predicted from demographic changes alone, because of the ongoing adoption of Westernized patterns of diet, physical inactivity, delayed reproduction, and smoking.

In high-income countries, the incidence rates of the most common cancers are higher compared to less developed countries, depending on the underlying risk factors and the extent to which early detection and screening approaches are utilized. The over-diagnosis of certain tumors adds to the cancer burden in affluent countries, yet mortality rates are decreasing for many sides due to a combination of prevention and improved treatment.

Despite the progress made in improving the care of patients with cancer, the treatment for most cancers is still a long way from reality. Particularly, the toxicity of treatment and lack of efficiency in certain tumor diseases beside serious side effects and resistance to chemotherapy.

However, outstanding discoveries in the mechanisms of cancer allowed the development of new treatments in addition Our insight into antitumor immune responses along with major advances in cancer immunotherapy has increased considerably, which shift the management of certain hematological diseases previously incurable (eg tyrosine kinase inhibitors in chronic myeloid leukemia) [3].

These extraordinary advances are expected to overcome and resolve many of previous treatments challenges.

MOLECULAR CANCER PATHOLOGY

A. Oncogenesis

The development of cancer is a multistage process characterized by alterations in at least two distinct classes of genes. Functionally, these genetic alterations result in either the aberrant activation of an oncogene, whose protein product now promotes carcinogenesis or inactivation of tumor suppressor genes. When active, tumor suppressor genes control neoplastic growth in a negative manner.

Genetic alterations can take the form of mutations (changes in the sequence of the DNA code), balanced translocations, deletions (loss of sections of DNA), amplifications (multiple copies of the same DNA section), or epigenetic changes (altering the methylation status of DNA, resulting in activation or repression of genes in the region) [4][5].

However, No genetic mutation on its own is sufficient to overcome all barriers for the full transformation of a normal cell into a cancer cell, there is a variety of linkages between environmental exposures (chemicals), diet, lifestyle factors, and cancer.

A growing body of knowledge dramatically supports the concept that cancer is generally a polygenic multifactorial disease, which makes environment an important modifier in the risk of cancer, stated Kari Hemminki, Karolinska Institute [6].

Cancer is nowadays recognized as a multistep process involving the activation of proto-oncogenes and the inactivation of tumor suppressor genes through genetic and epigenetic disease mechanisms.

B. Molecular alterations in cancer

1. Oncogenes

Although the regular use of the term and recent advances in our understanding of the genetic causes of cancer, there are many different definitions of an oncogene, some of which are less accurate. For Example, an oncogene mainly defined as a mutated gene that turns cell division on, which excludes genes that are over expressed such as the HER2 gene in breast cancer. Some definitions advertently include TSGs, while others do not make it clear that an oncogene may be a mutated form of a normal gene.

Due to lack of clarity concerning the definition of an oncogene, the NCI defined oncogene as: a gene that codes for a protein that is activated above normal levels by mutation or overexpression, which consequently drives or sustains tumor growth or progression (Figure 1). The term drive refers to the initiation of cell division, while sustain refers to processes that support cell growth and cell division. Progression refers to the advancement of a tumor from one state to the next, such as invasive to malignant. Without the contribution of an oncogene, a tumor would increase to grow or progress to the next state, and then be benign, malignant, or metastatic.

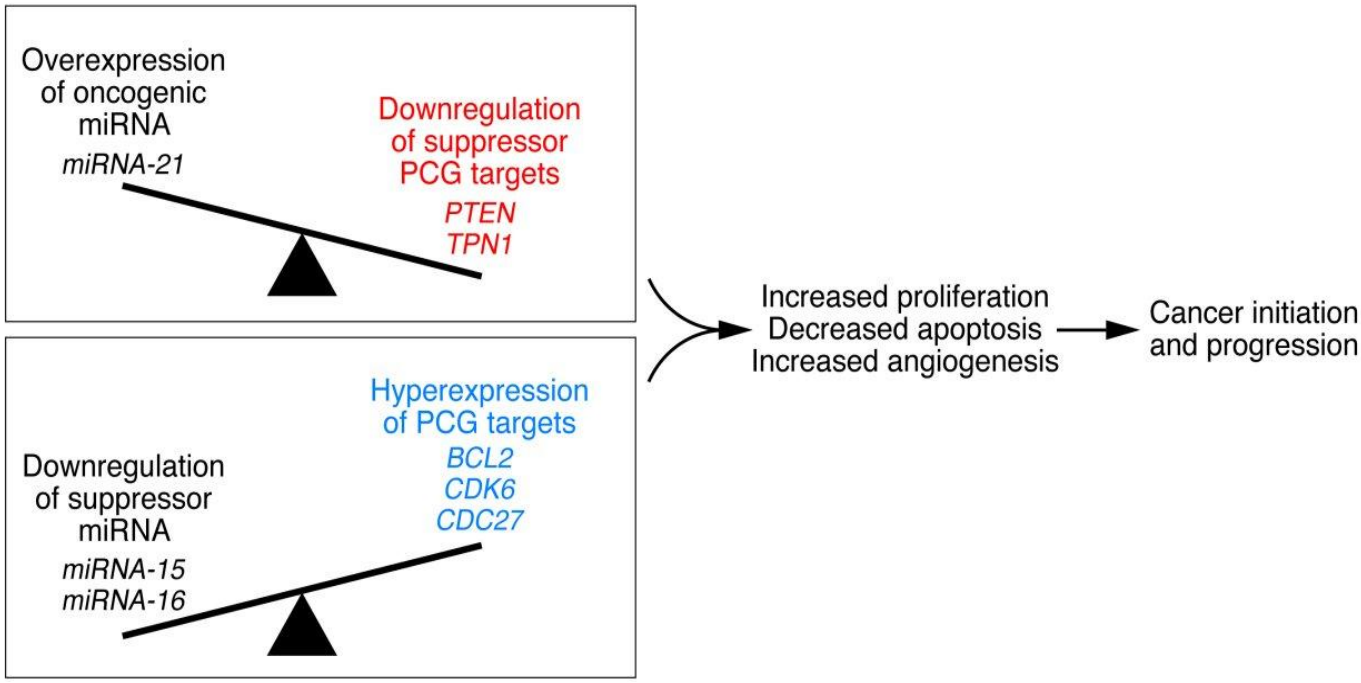


Figure 1: miRNA involvement in cancer initiation and progression. Alterations in miRNA genes play acritical role in the pathophysiology of many, perhaps all, human cancers [7].

Since the discovery that human tumors contain activated oncogenes in 1980 by A.P. Czernilofsky, many efforts have been made to understand the mechanisms of oncogene-directed cancer cell metabolism regulation and its role in cancer [8].

Functionally, Oncogenes are genes that cause cancer. Their counterparts in normal cells, proto-oncogenes, are involved in normal growth and development. If oncogenes enter cells as a consequence of viral infection or if the normal proto-oncogenes are altered or expressed abnormally, cancer can result.

Many oncogenes encode proteins that are related to growth factors, to receptors for growth factors, to transcription factors, or to proteins whose synthesis is induced by growth factors. Some oncogene products enter the nucleus and activate genes.

According to the oncogene theory, viruses cause cancer by inserting additional or abnormal copies of proto-oncogenes into cells or by inserting strong promoters into regions that regulate the expression of these genes. Proto-oncogenes can be amplified (Figure 2).

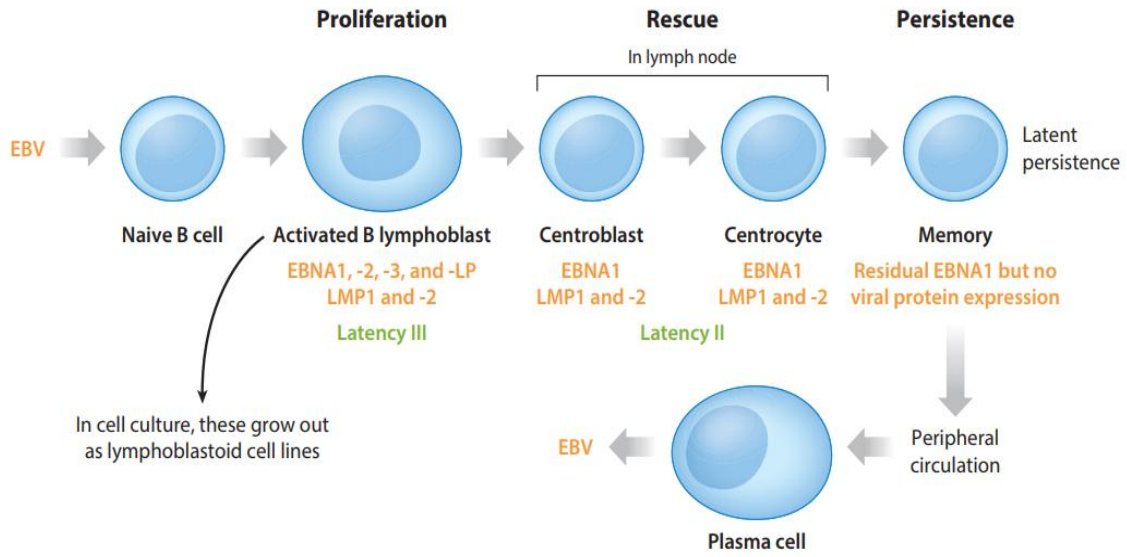


Figure 2: Schematic of the EBV life cycle in B cells (9). Latency pattern associated with lymphoma and Carcinoma (green) and EBV protein expression (orange) are shown [9].

The gene for the proto-oncogene or its control region may undergo mutations owing to radiation or chemicals exposure. Alteration of the product or of the level of expression of a proto-oncogene produces changes in the growth characteristics of cells that can result in cancer.

Cancer can also result from alterations in genes that produce proteins that act as suppressors of cell growth. Decreased expression of these suppressor genes (e.g., p53, the retinoblastoma gene) results in increased cell growth. MicroRNAs (miRNAs) can be classified as either oncogenes or tumor suppressors, depending on the function of the genes they regulate.

2. Nature and sequence of the oncogenic events

In almost all solid and hematological malignancies, Oncogenes are key drivers of tumor growth. Although several cancer-driving mechanisms have been identified, the role of oncogenes in modelling metabolic patterns in cancer cells is only beginning to be appreciated [10].

Recent studies show that oncogenes directly regulate critical metabolic enzymes and metabolic signaling pathways, as a common example; deregulation of the MYC oncogene in human cancers.

The MYC proteins (c-MYC, N-MYC, and L-MYC) are transcription factors that bind to enhancer box (E-box) sequences in gene promoters and can activate or repress transcription, hence controlling various aspects of cellular transformation and tumor growth.

In tumor, cells expressing high levels of c-Myc the transcription factor accumulates in the promoter (E-box) regions of active genes and causes transcriptional amplification (Figure 3), producing increased levels of transcripts within the cell's gene expression program. Thus, rather than binding and regulating a new set of genes, c-Myc amplifies the output of the existing gene expression program [10].

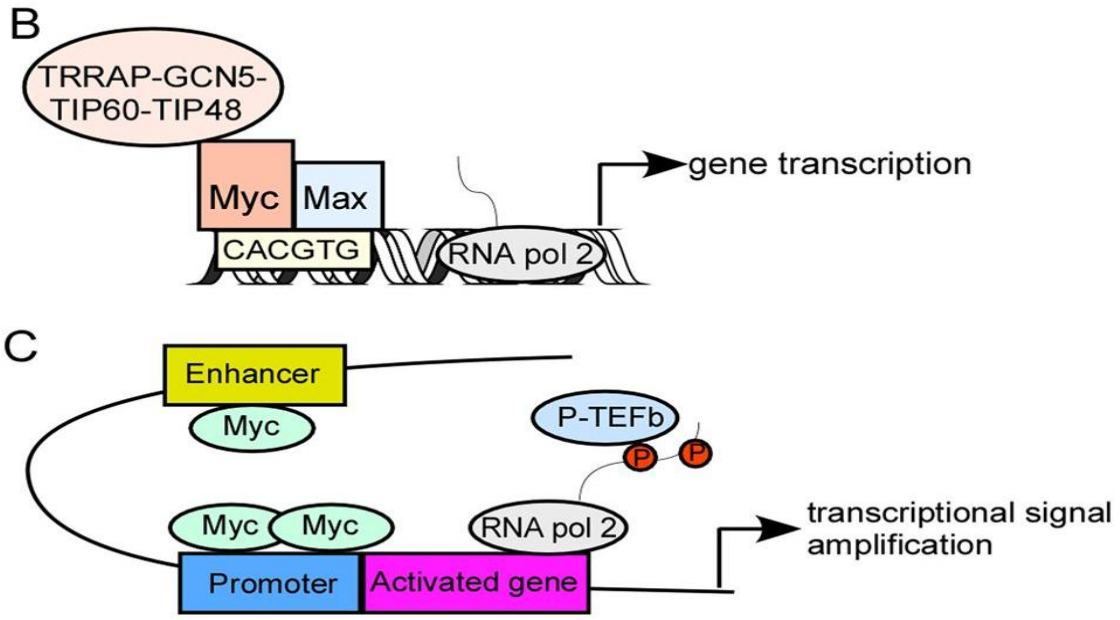


Figure 3: Transcriptional activation of target genes by Myc family members. **b** Myc functions as a transcription factor. **c** Myc functions as a transcriptional signal amplifier. In this model, Myc binding is not E-box dependent. Myc accumulates in the promoter and enhancer region of all active genes and causes transcriptional signal amplification [11].

Amplification of this gene is frequently observed in numerous human cancers such as Burkitt, lymphoma and multiple myeloma under a translocations process. Again, chromosomal aberration involving MYC may be a cause of a form of B-cell chronic lymphocytic leukemia. Translocation t(8;12)(q24;q22) with BTG1 [12].

3. Genomic Instability and Tumor Progression

It is well known that genomic integrity is closely monitored by several surveillance mechanisms, DNA-damage sensing repair, cell-cycle checkpoints, and DNA replication. A defect in the regulation of any of these mechanisms often results in genomic instability, which might be a potential driving force in the transformation of normal stem cells into cancer cells.

Genomic instability refers to alterations in copy of genetic sequence, such as increased frequencies of base pair mutation, microsatellite instability (MSI), as well as significant structure variation such as chromosome number or structure changes, also called chromosome instability (CIN) [13].

Microsatellites are repeated sequences of DNA with tandem nucleotide; these sequences can be made of repeating units of one to six base pairs nucleotides, most often seen as GT/CA. Which occurs in tens of thousands locations in our genome.

The presence of microsatellite instability is a sign of DNA mismatch repair deficiency that can be inherited (e.g., caused by a germline mutation in the MSH2 gene in hereditary nonpolyposis colon cancer syndrome) or sporadic (e.g., due to hypermethylation of the MLH1 promoter in sporadic colorectal cancer). It is generally approved that MSI is largely attributable to the failure of repairing insertion-deletion loops arising from replication slippage, yielding non-functioning proteins.

On the other hand, Chromosome instability provides important clues to the genetic changes in cancer, the chromosomal basis for these aberrations is either translocations, which change the integrity of genes, or abnormal numbers of chromosomes, a condition referred to as aneuploidy, which results in abnormal gene expression levels.

Such structural or numerical chromosomal aberrations are specific for distinct tumor entities. As an example, chromosome alterations in myeloid and lymphoid tumors are often simple translocations, i.e., reciprocal transfers of chromosome arms from one chromosome to another. In contrast, the chromosomal alteration in human solid tumors such as carcinomas are heterogeneous and complex and occur as a result of the frequent chromosomal instability (CIN) [14].

An interesting example is Burkitt's lymphoma, in which a reciprocal translocation between chromosomes 8 and 14 puts expression of myc under a constitutive promoter such that myc is inappropriately expressed in the cell cycle, leading to inappropriate lymphoid cells growth (Figure 4). (myc is normally found on chromosome 8, and it is moved to chromosome 14 under the control of immunoglobulin regulatory elements) [15].

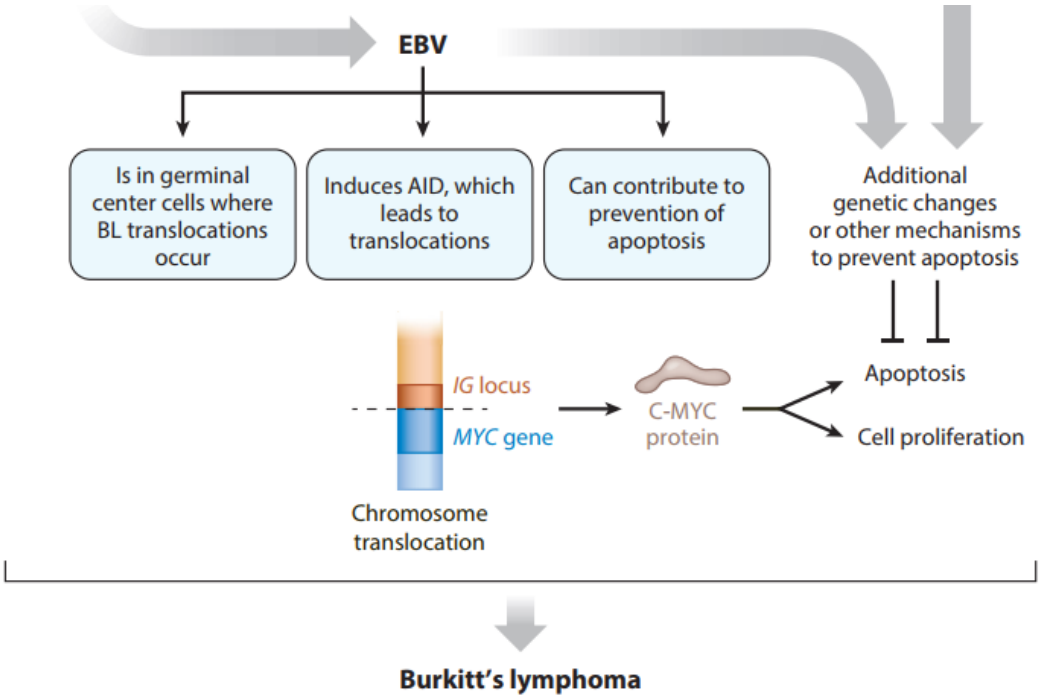


Figure 4: Summary of the mechanisms of Burkitt's lymphoma Abbreviations: AID, activation-induced cytidine deaminase; BL, Burkitt's lymphoma; EBV, Epstein-Barr virus.

4. Cell cycle Deregulation and oncogenesis

The process by which a cell divides is very similar in both cancer and normal cells. However, in many cases, cancers exhibit loss of control of the cell cycle, and they behave differently than normal cells in the body. Many of these differences are related to cell division behavior.

Cells with the ability to divide remain in an inactive quit state until they receive signals to proliferate. This inactive state is also referred to as G0. The various messages brought by the various growth factors and growth inhibitors from other cells are weighed up by each cell, from which it reaches a decision whether to:

- Remain in a quiescent state
- Proliferate
- Differentiate

- Undergo apoptosis

The normal somatic cell cycle consists of 4 phases; the G , or gap phase , in which the cell grows and prepares to synthesize DNA, the S or synthesis phase during which the cell synthesizes DNA, the G2 or second gap during this phase the cell prepares to divides and the M or mitosis phase in which cell division occurs [16].

As a cell draw near the end of the G1 phase, it is controlled at a vital checkpoint, called G1/S restriction point, where the cell determines whether or not to replicate its DNA. A number of growth factors and a number of critical genes, including p53 and pRB, regulate passage through this checkpoint.

This also applies for the second checkpoint at the G2 following the synthesis of DNA in S phase but before cell division in M phase, using another group of regulatory proteins called cyclin dependent kinases, or CDKs.

Functionally, p53 plays a key role in maintaining genomic stability between G1 and S phase, cells with intact DNA continue to S phase; cells with damaged DNA that cannot be repaired undergo programmed cell death apoptosis [17].

p53 is the most commonly mutated gene in human cancer along with suppress tumor formation (ie Breast cancer gene “BRCA”), which is not surprising since loss of control of genomic stability is a central feature of cancers. Once these crucial cell cycle genes start behaving abnormally, cancer cells start to proliferate widely by repeated, uncontrolled mitosis [18].

Cancer cells often ignore the usual-density-dependent inhibition growth, unlike normal cell, cancer cells ignore signals that should cause them to stop dividing and may make their own growth factors, either through self-production or by deceiving adjacent cells into producing growth factors to sustain them. As a common example activation of an RTK or downstream signaling member of an RTK pathway.

Another hallmark of cancer cells is their “replicative immortality”, an impressive term defined as an unlimited capacity of cellular proliferation. In general, human cells can go through only about 50 rounds of division before they loose the capacity to divide, “grow old”, and eventually die.

In contrast Cancer cells can divide many more times than this, largely because they express an enzyme called telomerase, which reverses the wearing down of chromosome ends that normally happens during each cell division [19].

In addition, emerging research shows that cancer cells may undergo metabolic changes that support increased cell growth and division [20].

C. Therapeutic Perspective in cancer

We have a much better perception of how cancer is caused now than we did only in 30 years ago. It is raised up by the accumulation of genetic aberrations that confer growth advantages to a cell over surrounding cells. This build up spontaneously and slowly over time, which may extend into decades, but their rate of accumulation is accelerated by many factors.

Some genetic alteration that drive tumor development are inherited, which is a key promoter to the development of cancer at a young age. The cells of those who carry such traits are already a step forward on the road to malignancy. The risk of developing cancer is amplified because driver mutations present at birth exist in nearly every single cell of the body, making the chance of one of them acquiring other mutations and becoming malignant very likely. The inheritance of mutations that impair the function of genes that regulate the cell cycle or repair DNA are particularly detrimental, because in the absence of their active contributions, mutations accumulate at a faster rate.

Due to genetic modifications, oncogenes are swapped on or over expressed, tumor suppressor genes are switched off or under-expressed and signaling pathways are rewired. The combination of genetic defects is unique for each tumor due to the stochastic way they accumulate, the large number of target driver genes, and the variety of ways in which genetic material can be modified. Mutations of gene-coding regions may give the proteins they code greater or lesser activity, while alterations of non-coding regions may raise or lower the amount of proteins expressed.

We know enough about cancers now to appreciate why it is so challenging to cure them. We also have an appreciation of what we need to do to find cures for cancer. There isn't ever likely to be a specific cure, because there isn't a unique common cause.

Although chemotherapy and radiotherapy treatment are currently being used with varying degrees of success, they cannot be the way forward. The use of chemotherapeutic drug combinations is an enhancement of a theme that should be petered out in favor of more effective treatment options, such as "targeted therapy", or mixtures of targeted therapeutic drugs. There is a persuasive need for alternate drugs that do not work purely by damaging dividing cells to the point where they commit suicide [21].

ANTI-TUMOR IMMUNITY

The idea that the immune system overwhelms the development of cancer has circulated for many years. Since 1909, the German scientist Paul Ehrlich suggested that were if it not for the action of our immune system, the incidence of cancer would be much higher.

It seems reasonable that the immune system protects against cancer since Patients with severely suppressed immune systems, similar to those with AIDS and organ transplants, have higher rates of some cancers compared to immunocompetent subjects [22].

A. Anti-tumor responses

1. Innate or non-specific immunity

The innate immune system contains a range of non-specific defense mechanisms that, first, protect against the invasion of pathogens, and second, fight against those that manage to breach frontline obstacles. These mechanisms include physical barriers such as skin, tears, saliva, mucus, and stomach acid, as well as an inflammatory response that uses killer cells to eliminate microorganisms and mop up foreign molecules, such as toxins.

Mucus contains substances that kill pathogens or inhibit their growth, which includes a group of antimicrobial molecules referred to as defensins. Tears, mucus, and saliva contain lysozyme, an enzyme that breaks down the cell wall of many bacteria [23].

As a first call of defense, innate immune cells fight foreign beasts at points of entry, and call upon other circulating immune cells in the blood, such as natural killer cells and neutrophils, to reach the area of infection towards help.

As a second call of duty, cells of the innate immune system gather intelligence on pathogens and present it to the adaptive immune system so that a delayed, more specific response can be initiated. Dendritic cells and macrophages carry out this function [23].

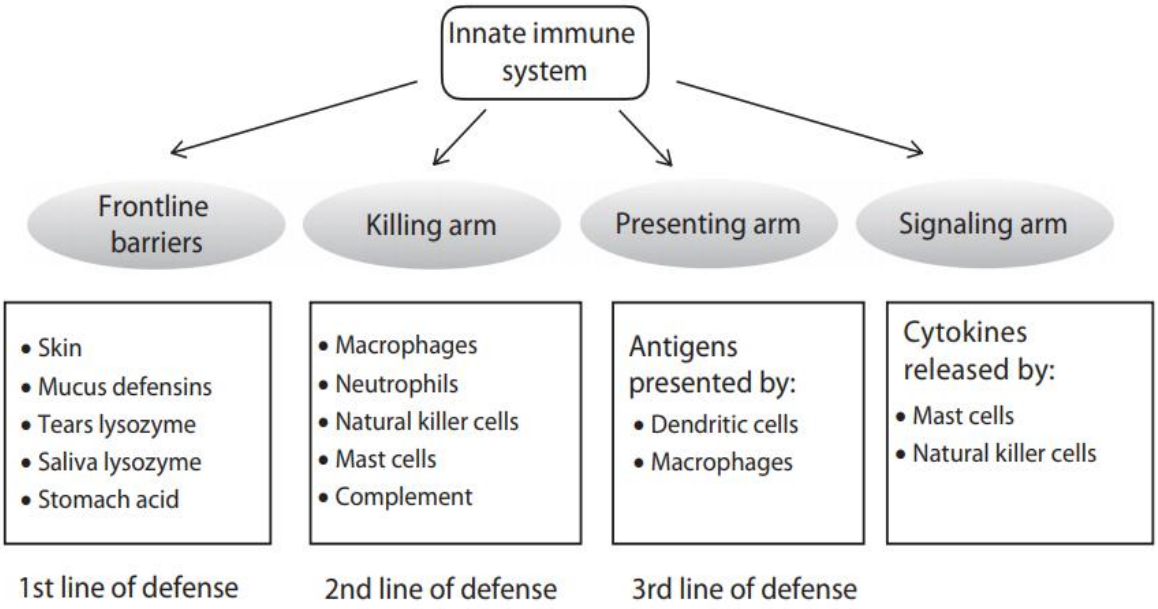


Figure 5 : The innate immune system, different arms.

2. Acquired immunity

In contrast to innate immunity, which attacks based on the identification of general threats, the adaptive immune system, also called acquired immunity, uses specific antigens to strategically rise an immune response. Three unique features characterize the adaptive immune system; specificity, diversity and memory.

Despite its delayed response, the adaptive immune system uses an immunological memory to learn about the threat and enhance the immune response then.

On the other hand, adaptive immunity refers to host defense proteins encoded by genes that undergo process called rearrangement to generate great binding diversity. This rearrangement process is not driven by the infection agent but occurs by genetic programming recombination.

Among the components of the adaptive system are specialized white blood cells knows as lymphocytes of which there are two main types, B and T cells. B cells secrete antibodies; these antibodies bind specific parts of pathogens known as antigens – either presented extracellularly on infected cells or free-floating in the body.

Some of these B cells become memory cells following infection, which help the body to reacts more rapidly and builds up a memory of the disease and prevent reinfection. T-cells can either be helper T cells or cytotoxic T cells, and bind pathogens via the T-cell receptor (TCR), which senses specific protein sequences [24].

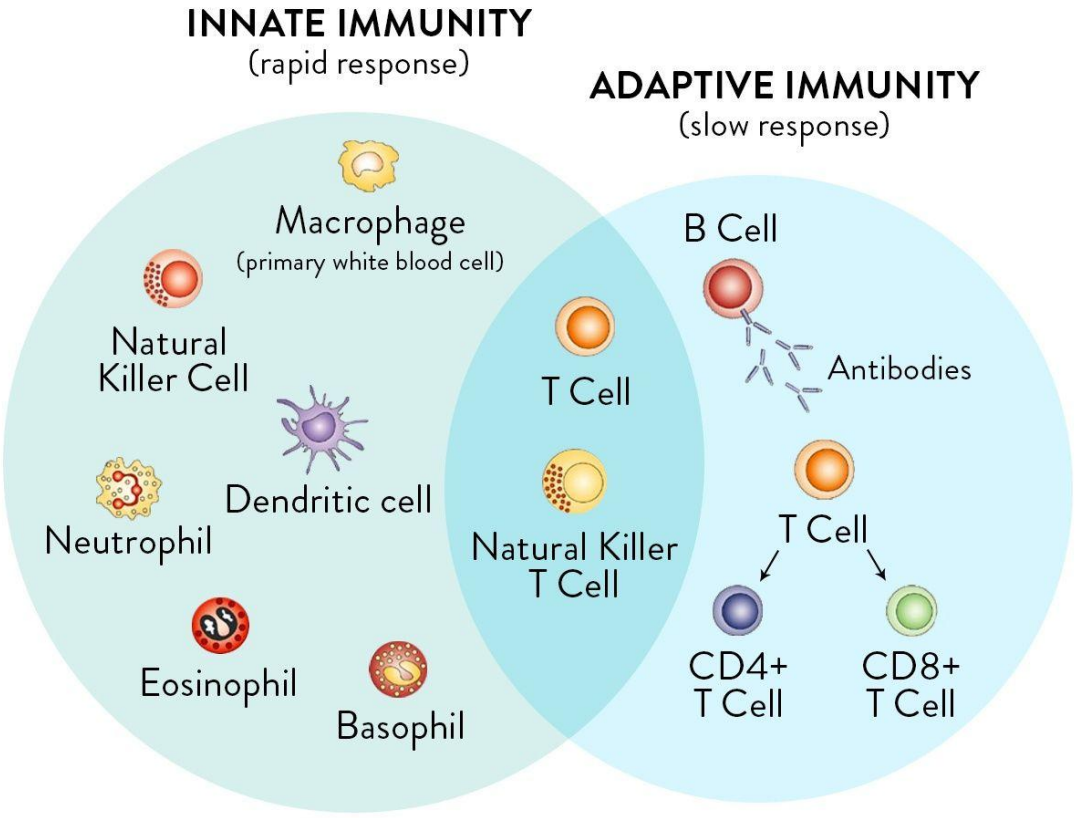


Figure 6: Innate vs Adaptive Immune Players [25].

B. The cancer immunosurveillance theory

The idea that the immune system could overwhelm the development of cancer was made around the turn of the 20th century by the German scientist Paul Ehrlich who predicted that cancer would occur at "incredible frequency" if host defenses did not prevent the outgrowth of continuously arising cancer cells, at that time so little was known about the immune system and nothing could be done to test this prediction.

It takes about fifty years before this idea would resurfaced with two great immunologist "Burnet" and "Thomas" using for the first time the concept of cancer "immune-surveillance". Predicting that the adaptive immune system would be able of detecting transformed cells and destroy them before they became clinically obvious.

Ten years after, Building on Burnet's immunosurveillance theory, Schreiber realized that cancer immunosurveillance was the words were the problem more than the concept, because it really implied that the immune system was only protective while large data suggest that it not only protected against cancer development but also shaped or sculpted the immunogenicity of any tumors that would form and so, Schreiber renamed the concept of cancer immunosurveillance by "immunoediting" theory to describe how the immune system works to prevent cancer growth and development in the human body. There are three phases of immunoediting, which have been described as the "3 Es": elimination, equilibrium, and escape.[26]

1. Elimination

Elimination is initiated when cells of the innate immune system are alerted to the presence of a growing tumor.

Elimination involves the recruitment of interferon-gamma natural Killer cells or NK cells perforin TNF related apoptosis and type 1 interferon which contribute to T

cell-mediated tumor destruction, once activated by the DC-MHC-antigen complex, effector T cells are trafficked to the tumor and cause the destruction of antigen-bearing tumour cells anywhere in the body [27].

2. Immune Selection (Equilibrium)

Equilibrium or a balance phase is a temporary state in which tumor cells are hypothesized to Remain dormant or continuously evolve by accumulating further changes in their DNA simultaneously, and this is why, for example, prostate cancer could take 20 years before it becomes full-blown cancer.

The immune system continues to eliminate tumor cells recognized as foreigners which essentially creates the Selective pressure on the tumor cells leading them to evade the immune system then survive and proliferate.

Equilibrium is a function of adaptive immunity only. Which is characterized by a lymphocyte-mediated response, it is possible that the cancer immunoediting process may prevent clinical progression for the lifetime of the host and is the deadly process [27].

3. Immune subversion (Escape)

Tumor cells that survive the equilibrium phase enter the escape phase, in which the tumor begins to develop beyond the control of the immune system and subsequently reaches metastasis.

There are several mechanisms used to achieve this escape from the immune system for example through the alteration of the expression of the HLA and the loss of co-stimulatory molecules, which are essential for an immune response.

Secondly, the tumour cells can through cell surface antigens or immune complexes induces the production of T regulatory cells, which suppress the immune response; third mechanism is the induction of lymphocyte Apoptosis.

Recently, targeted immunotherapy based on immune escape mechanisms has been developed and confirmed to work synergistically to target cancer cells [27].

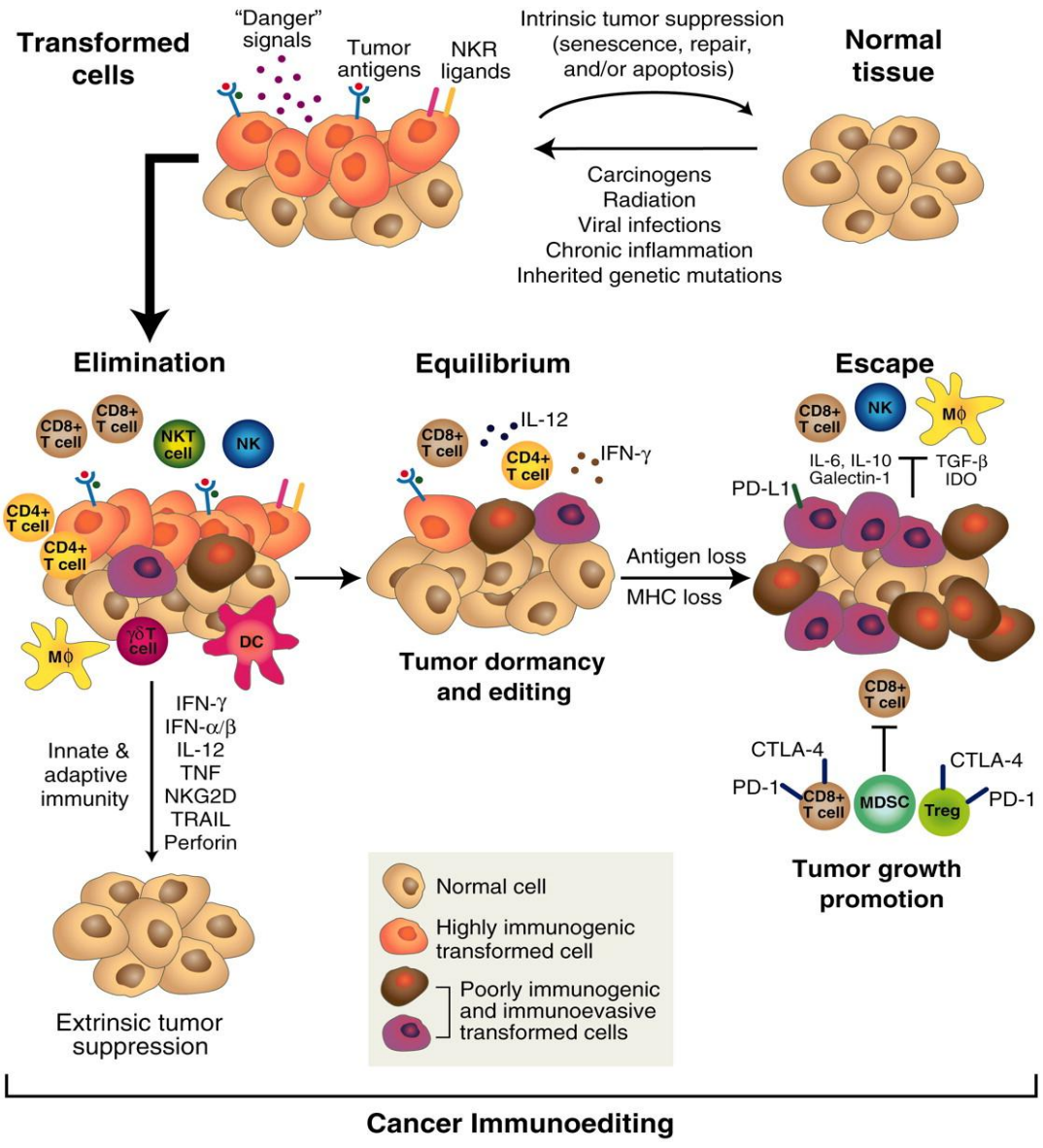


Figure 7 : Cancer immunoediting concept.CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DC, dendritic cell; IDO, Indole amine 2,3-dioxygenase; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; NK, natural killer; NKT, natural killer T cell [66].

Tumor Immune Escape Mechanisms as a Guide for Cancer Immunotherapy

Like pathogens, cancer cells developed ways of evading or suppressing the immune system. Even the immune system is quite effective at suppressing most abnormal cell growth. Cancers cells by definition consists of that tiny fraction of abnormal cells that have managed to evade or suppress the immune system.

There are several mechanisms for escaping the immune surveillance such as :

- Loss or alteration of specific antigens or antigenic machinery. Tumors can loose major MHC class 1 expression or the intracellular machinery required to present tumor antigens to T cell (Figure 8).
- Tumors can promote an immune-tolerant microenvironment by manipulation of cytokines (increased secretion of IL-6, IL-10, and TGF-beta; consumption of IL-2) that encourage infiltration of Treg cells, myeloid derived suppressor cells (MDSCs), and other cell types that inhibit cytotoxic T cell function. These cells can then actively suppress proliferation of CD4+ and CD8+ T lymphocytes that would otherwise recognize tumor antigens.
- Tumors can upregulate the expression of immune checkpoint molecules such as PD-1 and PD ligand 1 (PD-L1) that promote peripheral T cell exhaustion.
- Many oncogenic cell signalling pathways that were originally viewed as pure accelerators of cell division and growth are now understood to be mediators of immunologic escape. For example, constitutive KIT signalling in gastrointestinal stromal tumors leads to overexpression of indoleamine-2,3-dioxygenase (IDO), which enhances Treg infiltration that promotes tumor growth; this can be reversed in a CD8 T cell-dependent fashion with the KIT inhibitor, imatinib.

Melanomas with beta-catenin/Wnt signalling inhibit dendritic-cell mediated antigen presentation and exclude CD8+ T cell infiltration.

Understanding these mechanisms of immunologic escape can suggest mechanisms for immune-based therapies that may be broadly applicable across cancer types.

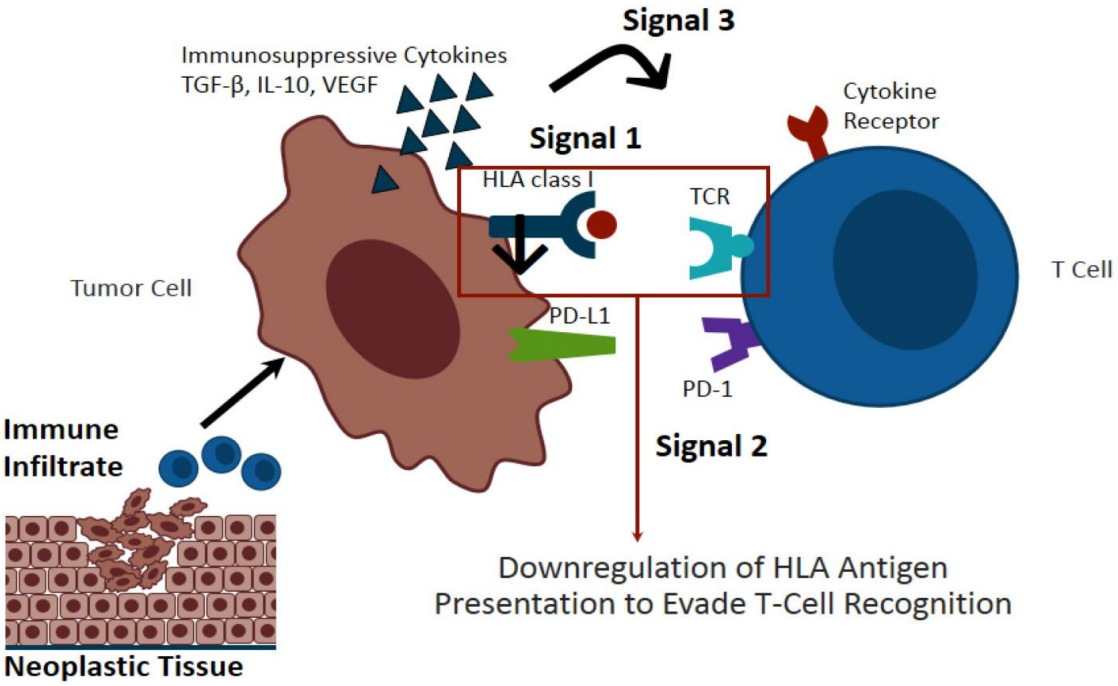


Figure 8: Tumor cell mediated immune escape, aberrant signal 1,2, or 3 in the tumor microenvironment [28].

A. TUMOR MICROENVIRONMENT

In the way to suppress cytotoxic and antigen presenting cells, cancer cells change their metabolism and they becomes a very promising target for anticancer treatment by lowering O2 level and pH in the tumor microenvironment, this could facilitate tumor growth, angiogenesis, and metastasis over abnormal blood vessels and vulnerable matrix.

For example the most deadly human tumors ; pancreatic adenocarcinoma where the rate of five year survival have not really budged in over 30 years around five to six percent besides what's remarkable about this tumor is only 5% of the cells squeeze

over 95% of microenvironment telling us that's the most deadly tumor is lethal because of microenvironment [20].

Recent studies showed that inside the tumor microenvironment, there are several mechanisms for suppressing or defeating antitumor immune responses. For example, T cells in tumors often have amplified expression of inhibitory molecules such as CTLA-4 and PD-1 on T cells, and some of these T cells fall into the category of T regulatory cells (Tregs). In either case, such T cells are likely to have low or absent antitumor reactivity. In addition, there is frequently a substantial growth of myeloid-derived suppressor cells and tumor-associated macrophages and also high levels of suppressive cytokines such as IL-10 and transforming growth factor-β [29].

B. ESCAPING IMMUNODETECTION

With the purpose to escape successfully both arms of the immune system, cancer cells have acquired a joint strategy of both stealth and camouflage.

In order to hide the tumor antigens they express and disguise themselves as

Something that the body will not reject. The CTLs of the adaptive immune system recognize antigens bound on MHC class I molecules expressed by nearly all nucleated cells of the body. If the MHC class I molecule on the tumor cells presents a viral or unusual peptide, then the antigen-specific CTLs eliminate the tumor cell. Unlike The foetus as an allograft that survives within the maternal host despite its low expression of allogenic MHC molecules that would regularly result in immune destruction by the natural killer (NK) cells of the innate immune system.

The same immune evasion strategies used by the foetus cover up the cancer cells and allow them to escape the NK cells. Together, this stealth and "camouflage" strategy described in the following two subheadings enables the cancer cells to evade detection [30].

1. Evading the CTLs

Production of immunosuppressive molecules that downregulate the expression of MHC class I on nucleated cells and defects in the antigen processing machinery along with poor expression or loss of class I peptide presentation have been clearly demonstrated as mechanisms used by a large tumor to escape CTLs killing.

Recently, Profound defects via altered glycosylation of O-glycosylation in HLA class I were found to be a mechanism of escape in bladder and colon carcinoma. In addition, downregulation of the proteasome multi-catalytic complex subunits LMP-2 and LMP-7 in prostate and renal carcinoma also show as mechanism for evasion of CTLs.

All these examples indicate that class I down-regulation is an important mechanism of tumor escape [31][30].

2. Tricking the NK cells

The importance of NK cells in cancer control is supported among others by the findings that tumors use a multitude of mechanisms to subvert and evade the NK cell system.

It is well known that Lack of recognition of leukemia by the immune system can be achieved through several mechanisms. Different reports discovered that the patient autologous PB NK cells often show phenotypic and functional defects at diagnosis. Activating receptors, such as DNAM- 1, NKp30, andNKp46, display low expression levels on patient NK cell surfaces paralleled by an increased expression of CD94 / NKG2A inhibitory receptors. Along with the phenotypic defects, cytolytic activity and TNFα and/ or IFNγ production are also impaired.

These defects are associated with poor clinical outcomes. Interestingly, the NK cell phenotype and function can be restored ex vivo in patients undergoing successful

therapy, thus achieving complete remission. This observation underlies the role for acute myeloid leukemia (AML) blasts in inhibition NK cell function. Such perturbation in PB NK cell physiology can also be observed in myelodysplastic syndromes (MDS), in which PB NK cells show severe defects including downregulation of activating receptors, reduced cytotoxic potential, and reduced cytokine- induced proliferation in vitro.

Several mechanisms are involved in the suppression of NK - cell function in hematologic malignancies including alterations in the expression of some activating receptors through cell- to- cell contacts, production of immunosuppressive soluble factors by leukemic cells, and defects in the normal lymphopoiesis.

Other receptors, such as CD96 and CD200, expressed by the NK cells and by some AML, respectively, have been recently identified as suppressors of a patient's NK cell cytotoxic and cytokine production during the antitumor response.

In addition to cell- to- cell contact- based inhibition, various soluble molecules, including soluble ligands of activating NK receptors; soluble factors, such as TGFβ or IL- 10; reactive oxygen species (ROS); and tryptophan catabolites, can inhibit NK cell functions.

C. IMMUNOMODULATORY MECHANISMS

The immunomodulatory mechanisms found in tumors are based on normal homeostatic control processes of the immune response set in place to prevent uninhibited proliferation of the immune cells, or to sustain tolerance towards self-tissues.

Besides the immune evasion strategies listed overhead, modulation of the immune response to incapacitate the antitumor response is a powerful evolutionary adaptation of the cancer cells.

Three most common mechanisms are described in cancer cells as an approach to modulate immune systems:

- Disrupting cell-cell interaction: disrupting the interaction between the ICAM-1(The intercellular adhesion molecule) on NK cell and malignant cell by producing the matrix metalloproteinase 9.
- Opposite costimulatory signal: by inhibitory molecule of the B7 family, Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. Promoting the apoptosis of activated B-cells and T-cells. That express the ligand PD-1. B7-H1 has been detected in human lung carcinomas, ovary carcinomas, colon carcinomas, and melanomas.
- CD40 over-expression

D. ACQUIRING RESISTANCE TO DEATH EFFECTOR MECHANISMS

The immune eradication of tumor cells is mediated by apoptosis that can be persuaded by the release of cytotoxic granules or death receptors. Tumors have evolved ways to become resistant to the death effector mechanisms, thereby becoming truly resistant to immune attack. The perforin/granzyme and Fas/FasL pathways are the two main effector mechanisms by which CTLs and NK cells mediate antitumor immunity. The downstream effects of both pathways are similar, as they both lead to activation of the caspase cascade and mitochondrial-dependent cell death. The caspases and cytochrome c released from the mitochondria further synergize by enhancing each other's activation [32][33].

E. TUMOR IMMUNE EVASION

The most common pathway for neo-vessel growth in malignancy is angiogenesis known as tumor angiogenesis. Multiple lines evidence indicated that vascular endothelium growth factor (VEGF) is a key player in the progression of angiogenesis because of their immunosuppressive effects. VEGF is a key mediator in both vasculogenesis and angiogenesis.

VEGF expression is associated with poor prognosis and increased metastatic spreading in many cancers as example ovarian cancer.

Moreover, VEGF also inhibits T-cell development and contributes to tumor-mediated immune suppression.

Beyond VEGF activity, Cyclooxygenase (COX)-2 is also implicated in the angiogenic process. COX-2 contributes to the production of prostaglandins by catalyzing the oxygenation of arachidonic acid to the common precursor of all prostanoids. The various prostaglandins are synthesized by distinct synthases in different tissues. The local production of prostaglandin PGE2 leads to immunosuppression in the tumor microenvironment through inhibition of T-cell and B-cell proliferation and diminished cytotoxicity of NK cells PGE2 is a powerful inhibitor of TNF-α and type 1 cytokine production and causes the downregulation of the cellular antitumor immune response.

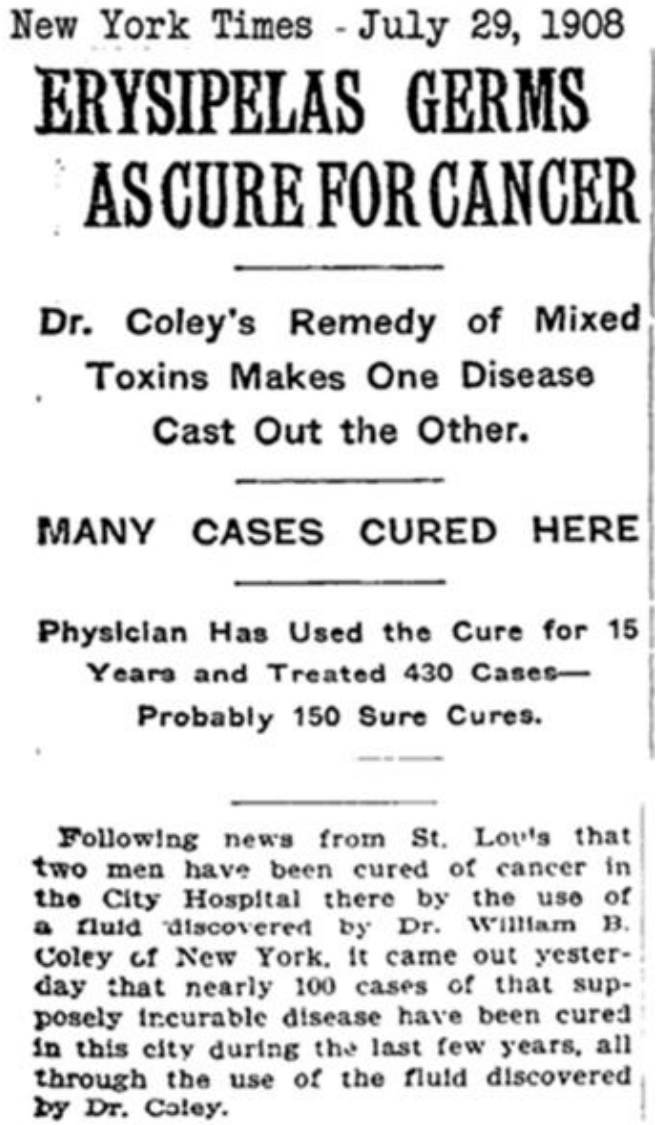
Another prostaglandin that can negatively affect antitumor immunity is PGD2. PGD2 is the ligand for the PGD2 receptor expressed on effector memory Th2 cells. An increased COX-2 activity and subsequent PGD2 production could promote the trafficking and activation of Th2 cells into tumor, suppressing the production of type 1 cytokines as a form of tumor immune evasion [30].

ANTI-TUMOR IMMUNOTHERAPY

A. Introduction

The concept of cancer immunotherapy can be traced back to the late nineteenth century, once William B. Coley noticed tumor shrinkage and even disappearance following the injection of bacterial products into patients with inoperable cancers.

Within that time, many observations — such as the unusual but well documented occurrence of spontaneous remissions, the higher incidence of cancer in patients who are immunosuppressed, and the identification of tumor-specific antigens and lymphocytes — have moved research on strategies that aim to induce specific anti-tumor responses. Currently, allogeneic bone marrow transplantation and monoclonal antibodies that target tumor cells are two examples of broadly used and effective immunotherapies. Cancer immunotherapy can now be considered the “fourth pillar” of cancer therapy, joining the ranks of surgery, cytotoxic chemotherapy, and radiation therapy [34].



New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yesterday that nearly 100 cases of that supposely incurable disease have been cured in this city during the last few years, all through the use of the fluid discovered by Dr. Coley.

Figure 9 : An article in a major U.S. newspaper printed in 1908 reflects the widespread attention given to Coley's toxins [34].

B. History of Cancer Immunotherapy

Since histologic confirmation of a malignancy became possible, further attempts at modulating the immune system to treat cancer find its modern roots merely in the second half of the 18th century.

Tumor antigens, expressed by tumor cells, are key targets for immunotherapies and have fueled the hope of developing therapeutic vaccines against tumors expressing these antigens.

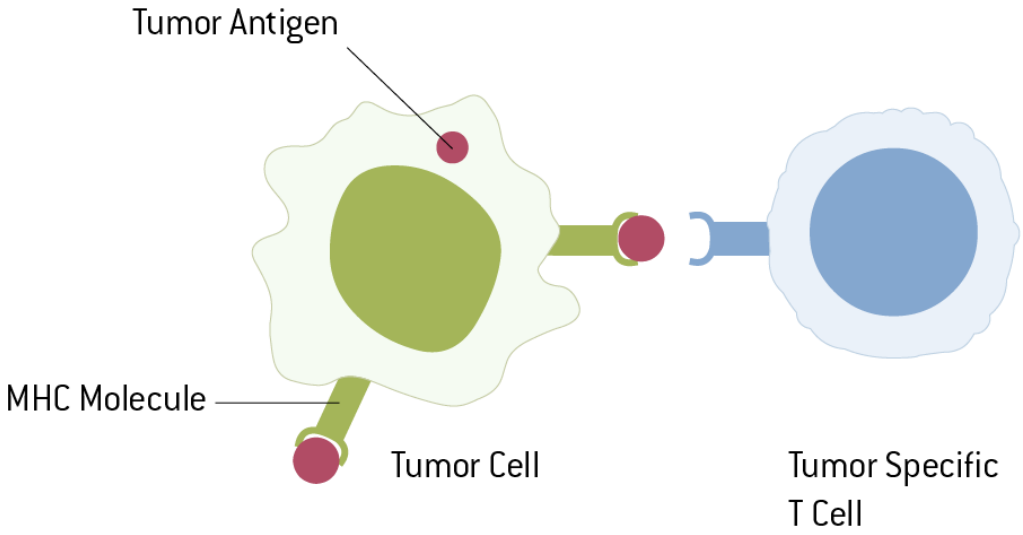


Figure 10: T cells recognize tumor antigen on tumor cell major histocompatibility complex (MHC) and are activated.

Indeed, several mouse models have shown the effectiveness of antitumor vaccines, often able to prevent the development of tumors (preventive vaccines) and, more rarely, to treat them (therapeutic vaccines).

However, the request of these works in humans has been a source of several failures that could have stopped the adventure of anti-tumor immunotherapy as many targeted therapies emerged. Until a series of recent discoveries essential to the success of these approaches: the understanding that endogenous tumors acquire numerous escape mechanisms over time.

Therefore, the development of effective immunotherapies involves not only transferring or inducing the development of anti-tumor effectors in order to stimulate anti-tumor immune responses, but also to neutralize escape mechanisms, which oppose their action.

Since that time, cancer immunotherapy has been evaluated as the "medical breakthrough of the year 2013" by the prestigious journal Science, and acclaimed at the 50th edition of the ASCO Congress (American Society of Clinical Oncology), in 2014, in part because it can induce a rapid, durable, adaptive and self-propagating immune response.

This adventure illustrated in the provided timeline below [35][36].

Table 1 : Timeline of selected key events in modern cancer immunotherapy [34].

YEAR	EVENT
1863	Description of immune infiltrates in tumours by Virchow Treatment of cancer with bacterial products by Coley
1893	Hypothesis of cancer 'immunosurveillance' by Burnet
1957	First report of allogeneic bone marrow transplantation
1976	First study with BCG in bladder cancer
1983	First study with IL-2 by Rosenberg
1984	First report of interferon response in patients with hairy cell Leukaemia
1985	First study with adoptive cell transfer in cancer First study with IFNα in melanoma
1991	(1991,1994) Characterization of human tumour-associated antigens by Rosenberg and Boon
1992	First study of isolated limb perfusion with TNF in melanoma and sarcoma
1996	(1996, 1997, 2000) Discovery of the immunological function of Toll-like Receptor
1998	Discoveries regarding the activation of innate immunity, by R.Medzhitov, Preston-Hurlburt, C. Janeway; & B. Beutler, awarded Nobel Prize in 2011
2002	Non-myeloablative chemotherapies and adoptive T cell transfer in melanoma
2005	Memory T-cells in colorectal tumors shown to predict clinical outcome.
2010	First successful use of gene-edited T-cells for the treatment of CD19+ hematologic malignancies in humans.
2011	Anti-CTLA-4 (ipilimumab), is the first inhibitory checkpoint inhibitor (ICI) approved by the FDA for treatment of stage IV melanoma
2016	A second class of ICIs, anti-PD-1 (pembrolizumab), is approved for the treatment of melanoma
2018	Awarded Noble Prize Tasuku Honjo, James Allison for their discovery of cancer therapy by inhibition of negative immune regulation Anti-CTLA-4 and, anti-PD-1.

C. Cancer Immunotherapy targets and classes

1. Cytokines and nonspecific immune activators

Early approaches to immunotherapy trained the numerous downstream effects of cytokines and other substances that influence immune cell activity. Examples include:

- Interleukin (IL)-2 was initially discovered as T cell growth factor. IL-2 has pleiotropic effects on both cytotoxic T cell function as well as T regulatory (Treg) cell maintenance. The effects partially depend upon the dose and timing of IL-2 administration.[37] At higher doses, IL-2 promotes CD8+ effector T cell and natural killer (NK) cytolytic activity and promotes differentiation of CD4+ cells into T helper (Th)1 and Th2 subclasses. At lower doses, IL-2 appears to preferentially expand Treg populations, probably due to the higher affinity of the trimeric IL-2 receptor (IL-2R, also known as CD25) on those cells, and inhibits the formation of Th17 cells implicated in autoimmunity.[38] Although IL-2 use has been largely supplanted by the use of checkpoint inhibitors, bolus, high-dose IL-2 achieved durable objective responses in a minority of patients with melanoma and renal cell carcinoma (RCC), serving as proof of principle that the immune system could eliminate cancer cells.
- Lenalidomide and pomalidomide are immunomodulatory agents that have prolonged survival in multiple myeloma. These agents mediate their antitumor effects largely via the cereblon-mediated destruction of Ikaros family proteins that inhibit IL-2 secretion [38].
- Interferon (IFN) alfa-2b promotes Th1-mediated effector cell responses such as IL-12 secretion via STAT-1 and STAT-2-mediated downstream signaling events. IFN alfa has been used as adjuvant treatment of high-risk melanoma, although its long-term impact on overall survival is controversial; more recent

data have demonstrated the role of immune checkpoint blockade as an adjuvant treatment with a likely better therapeutic index [39].

- Bacillus Calmette-Guerin (BCG), derived from attenuated mycobacterium bovis, induces a robust inflammatory response when injected in the bladder and is used for the treatment and secondary prevention of superficial bladder cancer [40].

2. Adoptive cell transfer (Manipulating T cells)

Adoptive T cell transfer broadly refers to the practice of manipulating patient-specific T cells ex vivo to make them more reactive to specific antigens.

Chimeric antigen receptors — Chimeric antigen receptor (CAR) T cells are genetically modified T cells, where a patient's own (autologous) T cells are manipulated ex vivo to express the antigen-binding domain from a B cell receptor that is fused to the intracellular domain of a CD3 TCR (CD3-zeta). As a result, recognition of a specific cell surface antigen activates T cell response independently of MHC recognition. Various modifications can enhance CAR effector function, such as co-expression of intracellular costimulatory domains such as CD28 or 4-1BB (CD137) or pro-effector cytokines such as IL-12.

CAR T cells have been studied most extensively in hematologic malignancies. Clinical trials targeting CD19, the pan-B cell antigen, have shown remarkable success in B cell acute lymphoblastic leukemia (B-ALL) and pre-B-cell ALL. Side effects are substantial in certain patients and include signs of the cytokine release syndrome such as fever, hypotension, altered mental status, and seizures, with some patients requiring intensive care. Trials in patients with chronic lymphocytic leukemia (CLL) have also shown promising results.

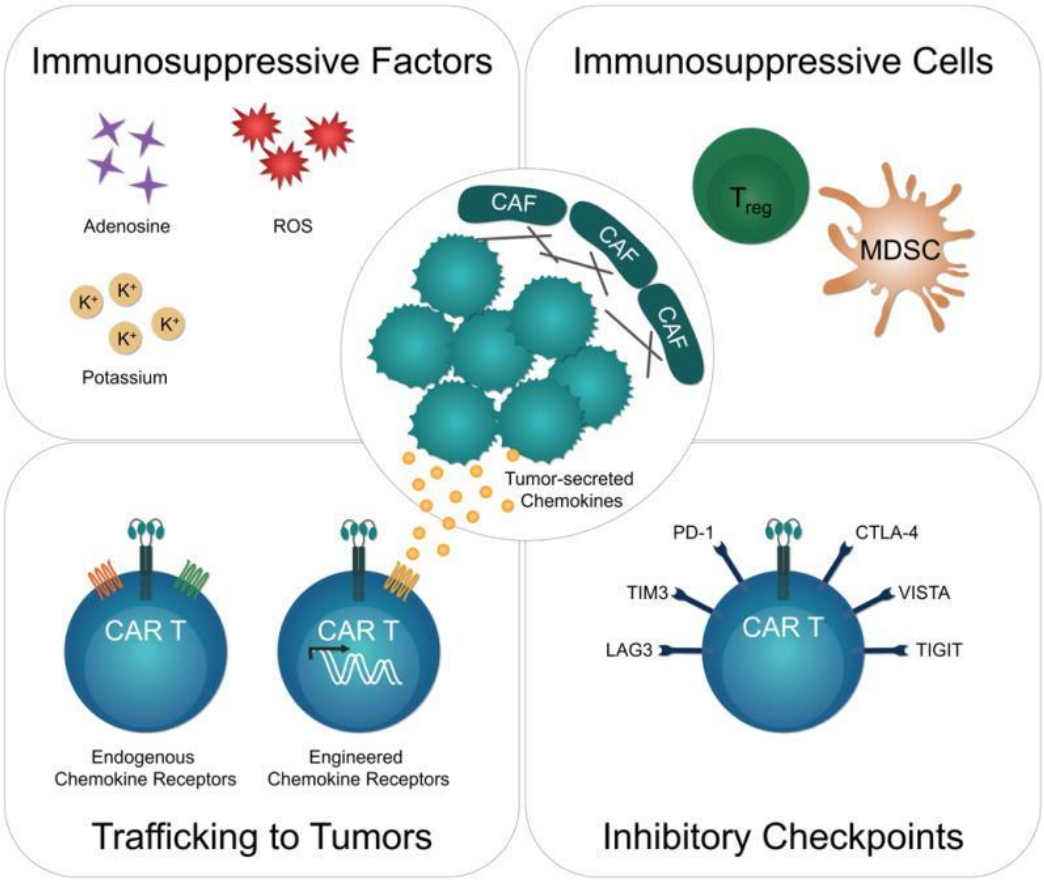


Figure 11: Barriers to CAR T cell therapy for solid tumors [41].

Numerous trials in hematologic malignancies are ongoing, with early development in some solid tumors targeting shared antigens such as CEA, mesothelin, and HER2.

Ex-vivo expansion of tumor-infiltrating lymphocytes — Tumor-infiltrating lymphocytes (TILs) represent an immune cell population that recognizes tumor antigen but may have developed an exhausted phenotype due to the tumor microenvironment.

Ex-vivo expansion of TILs utilizes freshly resected tumor tissue to extract TILs and co-culture with IL-2 to stimulate in vitro TIL expansion. Prior to reinfusion of expanded TILs, the patient receives nonmyeloablative chemotherapy regimens such as cyclophosphamide or total body irradiation, which functions to deplete inhibitory Treg cells and other lymphocytes in the patient to improve the rate of in vivo

expansion of the stimulated TILs [108]. The in-vitro-stimulated TILs, largely comprised of CD8+ and to a lesser extent CD4+ T lymphocytes, are then reintroduced into patients at high doses, together with HD IL-2, where they can recognize specific tumor antigens in a microenvironment that is now less prone to induce tolerance.

In a series of highly selected patients with advanced melanoma, 56 percent of those who received the T cell infusion had an objective response. The major limitations of this approach are that it cannot be performed in many patients (not all tumor tissues have extractable TILs and not all TILs expand in vitro) and that the process takes weeks from initial TIL extraction to reinfusion. Nonetheless, this approach was effective therapy for a group of patients with melanoma and has demonstrated objective responses in other malignancies (eg, cervical squamous cell carcinoma, cholangiocarcinoma).

CD3-directed therapies

Bispecific T cell engagers — Conceptually, bispecific T cell engager antibodies (BiTEs) function as linkers between T cells and specific target antigens in an MHC-subtype independent manner. They consist of a protein fragment containing two separate single-chain variable regions. One end recognizes CD3, which is expressed on all T cells, and one end recognizes the target antigen. BiTEs thus aim to induce cytotoxic T cell-mediated tumor eradication. Because BiTEs are not MHC-specific, they can be administered to all patients regardless of human leukocyte antigen (HLA) type and do not require patient-specific processing. One consequence of this more broadly applicable approach is its relative lack of specificity in T cell recruitment when compared with the more labor-intensive method of adoptive T cell transfer. Because many different T cell subtypes express CD3, BiTEs recruit polyclonal cytotoxic T cells, Th1 and Th2 CD4+ cells, and Tregs.

The most well developed BiTE is blinatumomab, which has specificity for CD19 antigen found on many B cell malignancies and the Fc region of the CD3 receptor found on T lymphocytes. Blinatumomab was given accelerated approval by the US Food and Drug Administration (FDA) for Philadelphia-chromosome negative B-ALL. (See "Treatment of relapsed or refractory acute lymphoblastic leukemia in adults", section on 'Blinatumomab'.)

Monoclonal TCRs — Another approach to increasing effector T cell function against a particular antigen is engineering a soluble TCR (CD8) to recognize a particular antigen target and fusing this to the variable fragment that recognizes an effector target, such as CD3. The ability to engineer a TCR rather than an antibody fragment can lead to higher affinity for a given peptide chain and allow for targeting of intracellular peptide fragments. This approach must be engineered using a specific MHC class 1 molecule, and complications have occurred through TCR cross-recognition of other antigens. MHC A*02-restricted TCRs are furthest along in clinical development because these are the most common alleles (50 percent) in people of Western European descent. See the figure for a simplified schematic representation of the key differences in the above four T cell-directed therapies.

3. CHECKPOINT INHIBITORS

Immune checkpoints are accessory molecules that regulate the control and eradication of infections, malignancies, and resistance against a host of autoantigens. Initiation point of the immune response is T cells, which have a critical role in this pathway.

As several immune checkpoints are initiated by ligand-receptor interactions, they can be freely blocked by antibodies or modulated by recombinant forms of ligands or receptors [42].

The primary targets for checkpoint inhibition include:

- Programmed cell death receptor 1 (PD-1) and programmed cell death ligand 1 (PD-L1) – Multiple antibodies against PD-1 and PD-L1 are in development and have shown great promise in multiple malignancies. Nivolumab and pembrolizumab, both of which target PD-1, and atezolizumab, avelumab, and durvalumab, all of which target PD-L1, have been approved in various indications (e.g, melanoma, renal cell carcinoma, non-small cell lung cancer, head and neck cancer, urothelial carcinoma, Hodgkin lymphoma, Merkel cell carcinoma, as well as microsatellite instability-high or mismatch repair deficient [dMMR] solid tumors).
- Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) – Ipilimumab, an anti-CTLA-4 antibody, is approved for use in patients with advanced melanoma, based upon a significant improvement in overall survival. Inhibition of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1)was first studied in and approved for patients with metastatic solid cancers as they provide significant survival rate [43].

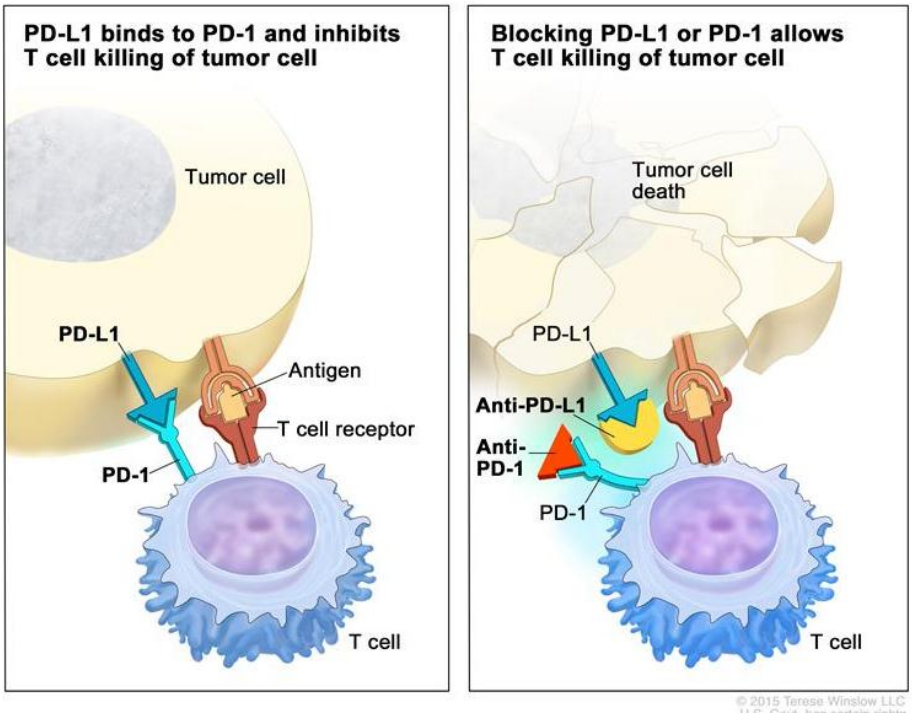


Figure 12 : Mechanism of action of PD-1 and PD-L1 inhibitors. Tumor cells develop PD-L1 to bind with PD-1 on T cells, which prevents T cells from destroying the tumor cells (left). By blocking the ability of PD-L1 to bind to PD-1 with a PD-1 or PD-L1 inhibitor, T cells are then able to kill the tumor cells (right). PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1. (For the National Cancer Institute © 2015 Terese Winslow LLC, U.S. Govt. has certain rights) [67].

Despite important clinical benefits, checkpoint inhibition is associated with a unique spectrum of side effects termed immune-related adverse events (irAEs) or, occasionally, adverse events of special interest. IrAEs include dermatologic, gastrointestinal, hepatic, endocrine, and other less common inflammatory events. IrAEs are believed to arise from general immunologic enhancement, and temporary immunosuppression with corticosteroids, tumor necrosis factor-alpha antagonists, mycophenolate mofetil, or other agents can be an effective treatment in most cases.

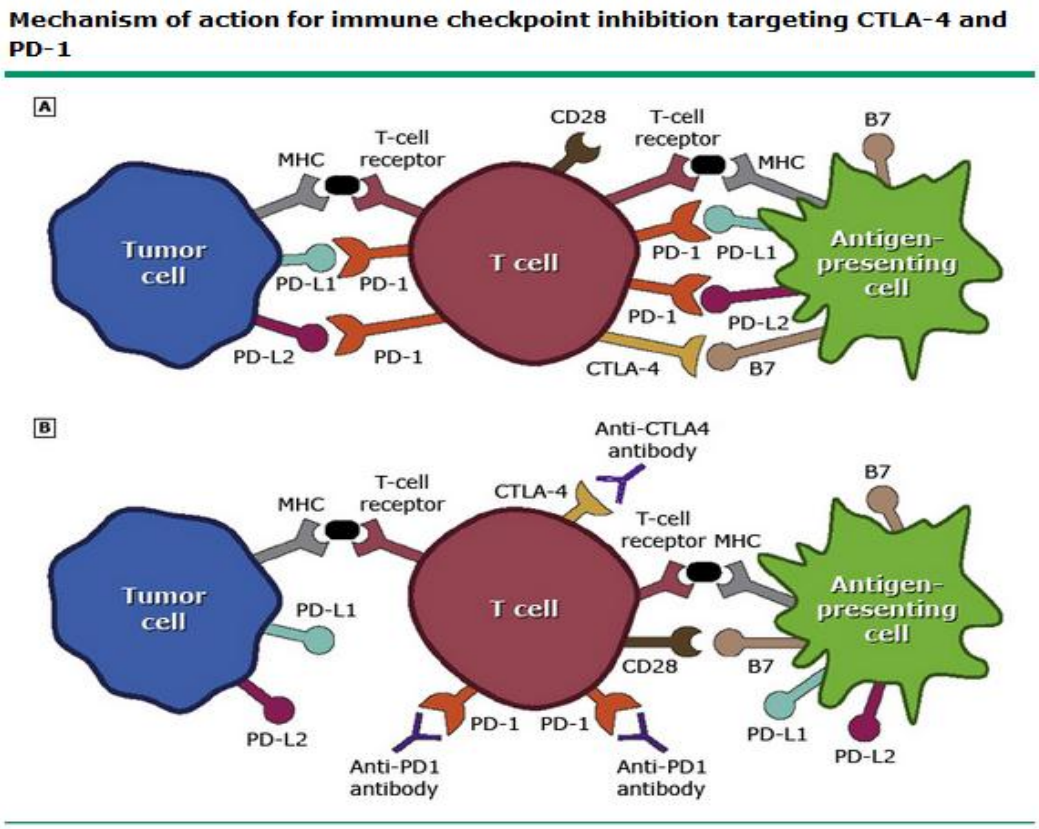


Figure 13: (A) Inhibition of T-cell activation by interactions with tumor cells and APCs. PD-L1 and PD-L2 on tumor cells and APCs bind to PD-1 on the T cell, and B7 on APCs binds to CTLA-4 on the T cell.

(B) Antibodies to PD-1 or CTLA-4 block inhibitory interactions, allowing for positive co-stimulation (B7 binds CD28).CTLA-4: cytotoxic lymphocyte antigen protein 4; PD-1: programmed cell death receptor 1; MHC: major histocompatibility complex; CD28: cluster of differentiation 28; PD-L1: programmed cell death ligand 1; PD-L2: programmed cell death ligand 2; APCs: antigen-presenting cells [44].

Increased understanding of the underlying immunologic mechanisms is leading to the identification of several additional potential targets for checkpoint inhibition. Examples of these include the following, although all are currently only in early stage clinical development:

- BTLA – B and T cell lymphocyte attenuator (BTLA) is a ligand of herpes virus entry mediator (HVEM) whose interaction leads to decreased production of cytokines and cell proliferation by CD4+ T cells [45].
- VISTA – V-domain Ig suppressor of T cell activation (VISTA), as connoted by its name, shares homology with PD-L1 and is a negative checkpoint ligand. It is found in hematopoietic tissues and T cell-infiltrated structures, including tumors. VISTA blockade has been shown to increase T cell infiltration and function in tumors, thereby reducing tumor growth [46][47].
- TIM-3 – T cell immunoglobulin and mucin domain 3 (TIM-3) is expressed by dendritic cells, monocytes, CD8 T cells, and T-helper-1 (Th1) cells. When TIM-3 binds galectin-9, its ligand that is often found on tumors, this causes TH1 cell death; conversely, TIM-3 blockade causes TH1 cell hyperproliferation and cytokine release. In combination with anti-CTLA4 or anti-PD-1, TIM-3 blockade led to tumor shrinkage in a mouse model [48][49].

4. Therapeutic antibodies

Over recent years, the negative perception of immunotherapy was first reduced as a result of the success of monoclonal antibodies, which was a major breakthrough.

Thus, antibodies against HER2 (trastuzumab: Herceptine®), CD20 (rituximab: Mabthéra®), EGFR (cetuximab: Erbitux®) or VEGF (bevacizumab: Avastin®) have been shown to be effective and are prescribed in a growing number of tumors (breast cancer, lymphomas, colon tumors, kidney cancers, lung cancer). Certainly, these antibodies can block the activation and / or proliferation of tumor cells (by targeting

growth factor receptors such as EGFR or HER2), induce apoptosis, even if discrete (anti-CD20), inhibit pro-angiogenic molecules (anti-VEGF), or interfere with abilities adhesion of tumor cells (anti-EpCAM, epithelial cell adhesion molecule).

Currently, it is accepted that immunotherapy is also based on activation of the effector mechanisms of immunity, such as antibody dependent cellular cytotoxicity ADC, phagocytosis via the immune cells binding the antibody by its Fc fragment, or via activation of the classical complement pathway resulting to the formation of a membrane attack complex responsible for cell death [50].

More recently, using mice, the clinical efficacy of certain antibodies therapeutics has also been linked to their ability to induce antitumor T lymphocytes by promoting the presentation of tumor antigen to T cells.

In humans, CD4 + T cells and an endogenous antibody response have been detected after administration of trastuzumab. The endogenous cellular and humoral immune responses induced by the administration of antibodies are most often directed against the same target as that of the therapeutic antibody. Thus, the lymphocyte T memory response generated could be a key element of the durability of the antibody response monoclonal.

Antibodies can also be used as vehicles, so many engineering efforts have been undertaken over the last decade, mainly by manipulating the constant region of these antibodies to couple them to drugs or making them bispecific, which allows the recruitment of immunity cells such as T cells.

- **Antibody–drug conjugates (ADCs)** : Antibody drug conjugates (ADCs)in which a monoclonal antibody (mAb) is conjugated to biologically active drugs through chemical linkers, were initially designed as a hopeful class of anticancer treatment agents, being one of the fastest growing fields in cancer therapy, with the intention of improving the therapeutic index.

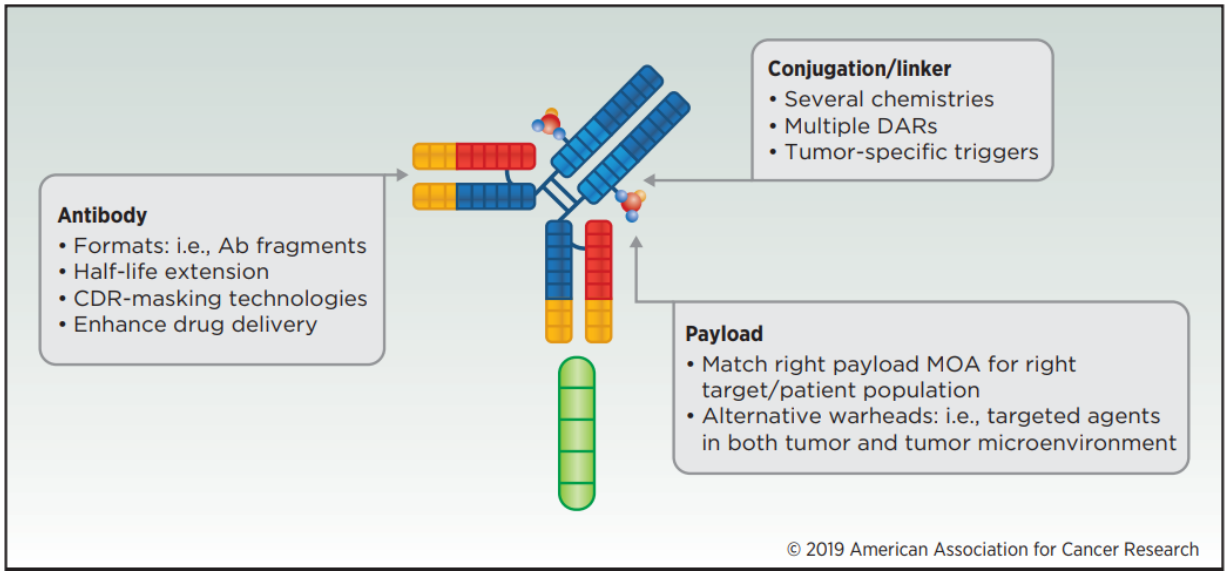


Figure 14: ADC structure and therapeutic index optimization strategies. ADCs comprised a tumor-specific antibody, a linker, and a cytotoxic payload. Advances in chemistry of all 3 components are underway to potentially increase the therapeutic index. CDR, complement determining region; DAR, drug-antibody ratio; MOA, mechanism of action. [50][44].

Four ADCs have been approved over the last 20 years. The first ADC Approved for clinical use was gemtuzumab ozogamicin (Mylotarg; CD33 targeted) for relapsed acute myeloid leukemia in 2000. Other ADCs that have been approved are brentuximab vedotin (Adcetris;CD30 targeted) and inotuzumab ozogamicin (Besponsa; CD22 targeted) which were approved for hematologic malignancies, and trastuzumab emtansine (Kadcyla; HER2 targeted), which was approved for breast cancer.

Combining ADCs with immune checkpoint inhibitors, T-cell agonists, and other agents that affect immune response has the potential to reverse many of the elusive strategies that tumors use to evade Immunosurveillance.

At this time, approximately 36 trials with 20 Individual ADCs in combination with immuno-oncology (IO) therapies are ongoing, most of which are checkpoint inhibitors [50].

- **Bispecific antibodies**: BiTE or bispecific T cell engager (BiTE) immunotherapies are now emerging as a growing class of immunotherapies with potential to further mend clinical efficacy and safety. BiTE can recognize two different antigens by using two different variable region [51].

By targeting markers on tumors as well as CD3, an important component of the T cell receptor, BiTEs can activate T cells, guide them to cancer cells, and stimulate their cancer-killing capabilities. today, a BiTE targeting the CD19 marker associated with B cell cancers has been approved by the FDA for leukemia [51].

5. Combined Immunotherapy

Multiple clinical trials investigating combinations of various checkpoint inhibitors based upon the results with checkpoint inhibitors as monotherapy.

Concurrent CTLA-4 and PD-1 blockade is furthest along in clinical development. The combination of ipilimumab plus nivolumab has demonstrated a significantly higher response rate, progression-free survival, and overall survival than ipilimumab monotherapy in metastatic melanoma. Similarly, the combination of nivolumab plus ipilimumab has demonstrated an improved response rate, overall survival, and tolerability compared with sunitinib in patients with naïve advanced RCC.

At present, The tumor microenvironment (TME), macrophage- associated

Colony- stimulating factor 1 receptor (CSF - 1R), myeloidderived stem cells, and T- cell suppressive indoleamine 2,3-dioxygenase (IDO) and vascular endothelial growth factor (VEGF) are novel targets for combination immunotherapy [52].

6. Update Therapy (Noble prize 2018)

Last year's Nobel Prize in physiology went jointly to "James P. Allison" and "Tasuku Honjo" for their discovery of cancer therapy by inhibition of negative immune regulation".

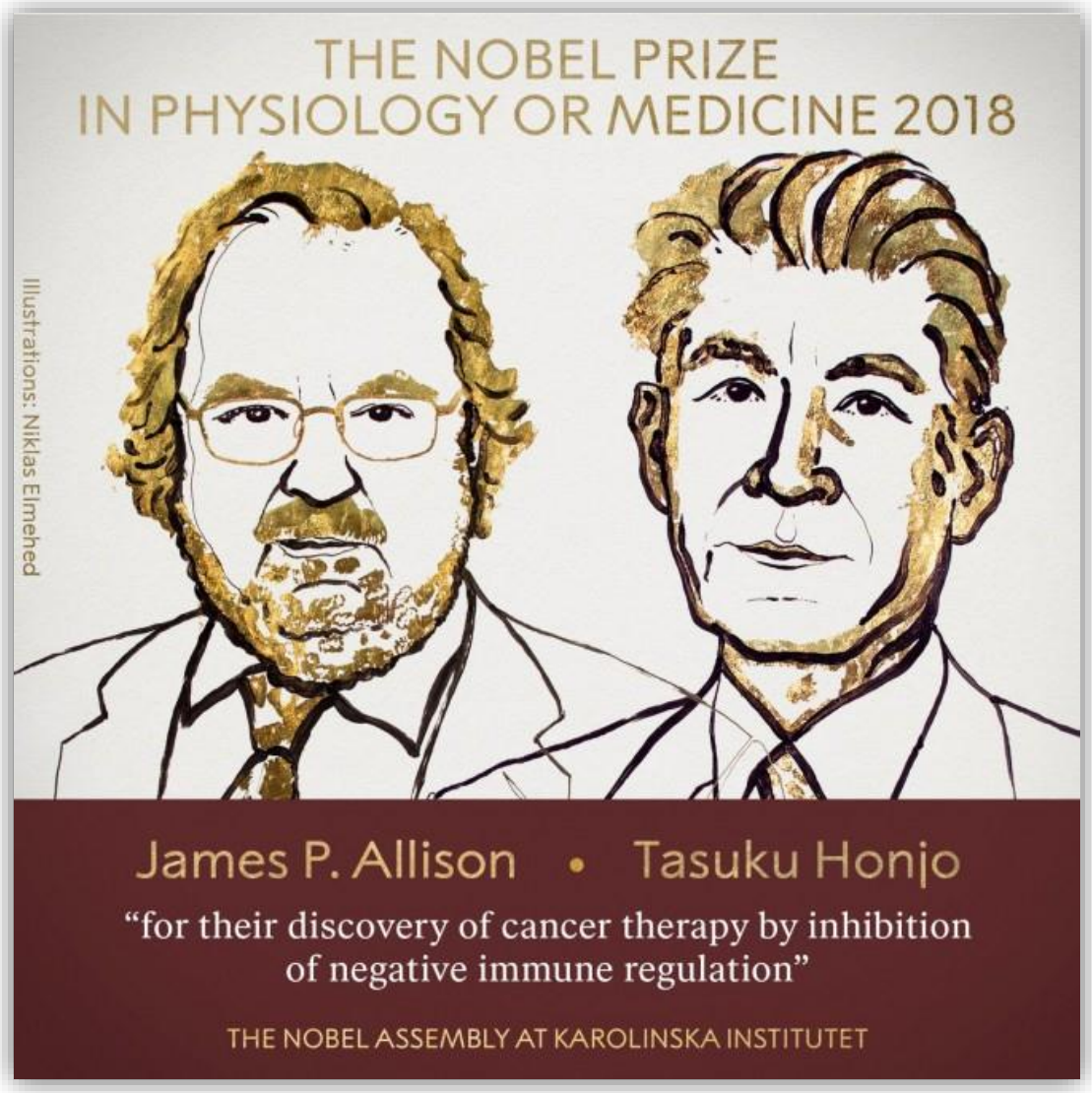


Figure 15: American James Allison (University of Texas MD Anderson Cancer Center) and Japan's Tasuku Honjo (Kyoto University School of Medicine) share the 2018 Nobel Prize in Physiology or Medicine [53].

The award-winning work is based on James Allison studying a protein called Cytotoxic T lymphocyte associated antigen 4 (CTLA-4) that works as a break on the immune system and unleashes immune cells to attack tumors if the break could be released. Similarly, the joint winner Tasuku Honjo worked on another protein called Programmed cell death protein 1 (PD-1) that worked as a break, but with a different mechanism.

In the preview of Allison's work, the PD-1 protein acts by keeping T cells from attacking other cells in the body. Some normal cells and tumor cells carry a protein called programmed death ligand 1 (PD-L1), which exploits the checkpoint mechanism, helping the cells to hide from immune attack. When PD-1 attaches to PD-L1 it protects the cell from attack by T cells (fig 1). Therapies targeting either PD-1 or PD-L1 prevent this attachment so that the cell remains vulnerable to attack from the immune system [54].

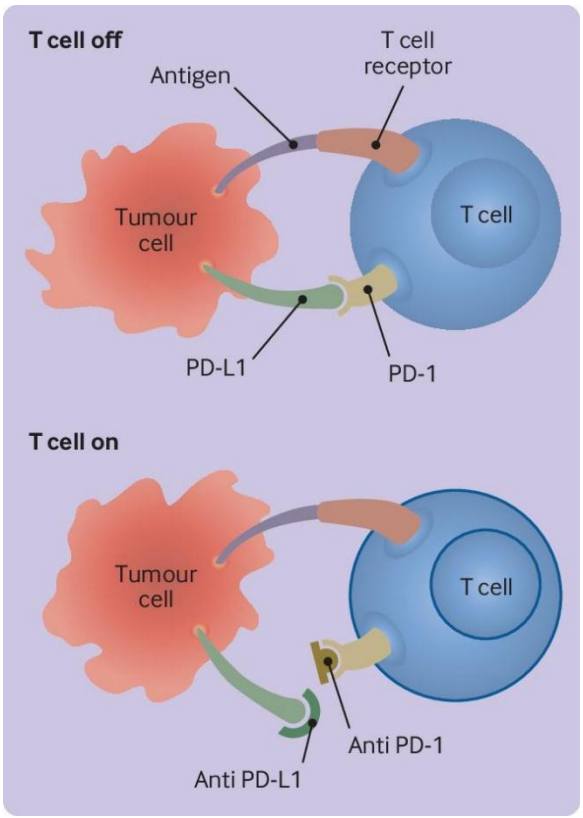


Figure 16: How checkpoint inhibitors target PD-1 and PD-L1, enabling T cells to attack tumor cells [54].

HEMATOLOGICAL MALIGNANCIES

A. Overview

Malignancies of the hematopoietic and lymphoid tissues coverall cancers of the blood and lymphoid organs could be lymphomas, leukemia, myeloproliferative neoplasms, mast cell neoplasms, plasma cell neoplasms, histiocytic tumors, and dendritic cell neoplasms. Multiple classification patterns have been employed for these diseases over the years.

The 2016 World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues uses morphologic, immunophenotypic, genetic, and clinical features to define distinct diagnoses. In addition, there are borderline categories for cases that do not fit into a defined entity. This approach has been adapted to improve the accurate assessment of patient outcomes in "typical" disease and to enable the study of borderline cases.

Indeed, the main varieties of hematopoietic neoplasia, as proposed by the 2016 WHO classification, are mature lymphoid, histiocytic, and dendritic neoplasms along with myeloid neoplasms and acute leukemia [55].

B. Non-Hodgkin's lymphoma

NHLs are a mixed group of malignancies with more than 30 entities. Therefore, the clinical presentation can be very diverse, varying from acute presentation in aggressive lymphomas to being asymptomatic in ones that are more indolent [56][57].

C. History and exam

The evaluation of the patient with suspected NHL starts with a complete history and physical examination. A personal or family history of lymphoma or other prior hematopoietic malignancy along with past radiation or chemotherapy treatment allows us to guide or modify the therapeutic deeds. NHLs present polymorphic clinical pictures according to the affected site, ganglionic or extra-ganglionic, and the histological type of NHL, whether it is indolent or aggressive [58].

The diagnosis of NHL should be considered in the case of:

- Unexplained general signs: Weight loss over 10 %, fever over 38 ° C or profuse nocturnal sweats; they constitute signs of NHL scalability. The general state can be evaluated by the index of "The Eastern Cooperative Oncology Group (ECOG) score ", also called the WHO or Zubrod score, index of 0 to 1, good general state, 2 to 3altered intermediate state, 4 a very altered state [59][58].
- Unexplained inflammatory syndrome or sometimes an abnormality of the blood count (cytopenia, hyper-lymphocytosis).
- Lymphadenopathy: present in 56 % case, expressed by Persistent superficial ADP, with a malignant character, often not painful and non-inflammatory, whatever the location. Sometimes Deep lymph nodes discovered incidentally, with a compressive nature.
- Uncommon extra-ganglionic or visceral involvement: present in 44 % cases. They vary considerably depending on the location of the NHL at a specific site :
    - ENT
    - Digestive tract: in order of frequency, stomach, ileum and colon.
    - Bone
    - Mammary, testicular, ovarian
    - SNC
    - Others
- Hepatomegaly or splenomegaly.

D. Diagnostic approach and Investigations

The diagnosis of NHL is based on the histological analysis of an affected site.

Preferably excisional or core biopsy to provide information on lymph node architecture.

The quality of the sampling is essential for the analysis, it allows:

- First sample for the cytologist (affixing the ganglion on a slide).
- Second sample meant for the histologist.
- Third sample intended for phenotyping.

According to WHO classification, NHL phenotype B make up 85% of NHL in the world while NHL phenotype T represents only 15% of cases.

Some NHLs behave indolently with waxing and waning lymphadenopathy for years. Others are highly aggressive, resulting in death within weeks if left untreated. In typical cases:

- ✓ Aggressive lymphomas :commonly present acutely or sub-acutely with a rapidly growing mass, consist of:
  - Diffuse large B cell lymphoma: the most common aggressive NHL, diagnosed easily based on B phenotype markers: CD20+, CD79a+. Represent 33% of cases.
  - Burkitt lymphoma: is a rare form of NHL, initially described in Africa (linked to EBV), and common among HIV +.
  - Anaplastic large-cell lymphoma type T: mostly represented by the peripheral T lymphomas along with NK phenotype, post-thymic phenotype CD1-, tdt- ; representing 7% of cases.
  - Other peripheral T cell lymphomas.

- Indolent lymphomas: are often insidious, presenting only with slow growing lymphadenopathy, splenomegaly, or cytopenias. Examples of lymphomas that typically have indolent presentations include:
  - Follicular lymphoma: including the proliferation of CD10 + phenotype, CD5, CD23, responsible for BCL2 overexpression; representing 22% of cases.
  - Mantle Cell Lymphoma the indolent type: include phenotype, IgM+ / IgD-, CD5 +, CD10-, CD23-, 6 % cases; with the steady incidence of translocation type t (11; 14) (q13; q32).
  - Marginal zone lymphoma:
    - NHL extra nodal MALT type of the marginal zone: most common, IgM + / IgD + CD5-CD10 -CD23-; represents 8% of cases; Cytogenetic abnormalities found in 1/3 of cases.
    - Splenic NHL
    - NHL of the lymph nodes
    - Disseminated forms.
  - Diffuse small lymphocyte lymphoma (CLL): 7% of cases only.

E. Assessment of extension:

NHL extension assessment is the key component to decide which types of therapeutic strategy must be trailed, as well as to assess the prognostic. It begins with clinical examination and continues with biology and medical imaging.

In addition, CT scan remains the gold standard and the preferred imaging modality for staging a patient with NHL.

Despite its great value, integrated positron emission tomography or PET SCAN remains an expensive examination used for staging a patient with NHL [60].

Other radiological examinations might be prescribed according to the different clinical cases, such as chest x-rays and abdominal ultrasounds as alternatives in some cases or MRI Scan (Magnetic Resonance Imaging) specifically used in certain locations of NHL, including spinal bone and CNS.

The 1st biological investigations to order in NHL:

- complete blood count with PTL before lymph node biopsy to exclude an LLC
- Blood Ionogram, serum uricemia, serum calcium, phosphoremia, in case of aggressive lymphoma, (especially looking for a lysis syndrome spontaneous) and creatinine.
- Serology HIV, Hepatitis B and C
- HTLV on demand or if T lymphoma.
- EPP and immunofixation
- Liver function
- Lumbar puncture if aggressive lymphoma with intrathecal prophylaxis.
- Myelogram and BOM: allows evaluation of the bone morrow infiltration.
- Karyotype on marrow if possible.
- LDH and beta-2-microglobulin: LDH is a prognostic factor for NHL. NHLs often have high levels of LDH that influence negatively the duration of survival therefore a factor of poor prognosis. The high level of beta-2-microglobulin is also a factor of poor prognosis.
- Pregnancy test in women of childbearing age.
- Fertility preservation — An overall discussion of fertility issues should be undertaken in patients of childbearing age prior to the initiation of treatment, including the possibility of sperm or fertilized ovum banking.

Medical Imaging exams

- Chest x-ray
- CT scan neck-chest-abdomen-pelvis: remains the reference examination to evaluate the extension of NHL.
- Gastric fibroscopy and endoscopy in case of gastric MALT NHL.
- PET-Scan: Despite its high value in aggressive NHLs, it remains a costly test.
- Pretherapeutic Investigations: EKG and echo-heart to assess cardiac function and ejection fraction especially when considering the use of cardio toxic products.

F. NHL Classification

a. Modified Ann Arbor Staging System for NHL

After clinical and Para clinical analysis, the stadification of Ann Arbor allows us to differentiate NHL according to 4 stages: I, II, II, IV, A and B according to the existence of signs of evolution or not and E according to the existence of extra -nodal extension or single isolated site of extra-nodal disease.

b. Prognosis

In general, prognosis depends on the type of lymphoma, stage of disease, treatment, and comorbidities.

Worse prognosis is indicated by the following:

- B symptoms (weight loss, night sweats, and pyrexia)
- Lymphadenopathy
- Organomegaly
- Skin changes
- Poor Eastern Cooperative Oncology Group (ECOG) performance status.

The determination of prognosis for each of the NHL variants is known to be related to the multiple differences in tumor cell biology (eg, cytogenetics, immunophenotype, growth fraction, cytokine production) found within each of the specific disease variants. It is therefore likely that prognostic indicators in the NHLs will take three semi-independent formats:

- For diffuse large B cell lymphoma, International Prognostic Index (IPI) and age-adjusted index for DLBCL have been validated and provide an estimate for prognosis. For follicular lymphoma, Follicular Lymphoma International Prognostic Index (FLIPI) has been validated for prognosis.[61][62]

The IPI model incorporates clinical features that reflect the growth and invasive potential of the tumour (tumour stage, serum lactate dehydrogenase [LDH] level, and number of extranodal disease sites), the patient's response to the tumour (performance status), and the patient's ability to tolerate intensive therapy (age and performance status) [61].

- FLIPI model incorporates 5 adverse prognostic factors: age (>60 years), Ann Arbor stage (III to IV), haemoglobin level (<120 g/L), number of nodal areas (>4), and serum LDH level (above normal). Three risk groups were defined: low-risk (0–1 adverse factors), intermediate-risk (2 factors), and poor-risk (3 or more adverse factors) [62].

ECOG performance status is an important parameter of prognostic models for aggressive lymphomas. IPI greatly predicts prognosis and may influence the treatment strategy; for example, aggressive treatment and/or bone marrow transplantation is more likely to be employed in patients with good performance status, versus palliative care in patients with poor performance status. In addition, most clinical research protocols exclude patients with an ECOG performance status of 3 or above [63].

Table 2 : International Pronostics Index NHL [61]

Risk group	Score	Complete response (CR) rates (%)	Five-year overall survival (%)
Low risk	0 to 1	87	73
Low-intermediate risk	2	67	51
High-intermediate risk	3	55	43
High risk	4 to 5	44	26

Table 3 : Age adjusted International Prognostic Index [62]

Score	Risk Group	Five-year overall survival (%)	Complete response (CR) rates (%)
0	Low risk	56	91
1	Low-intermediate risk	44	71
2	High-intermediate risk	37	56
3	High risk	21	36

Patients with FL generally have an excellent prognosis; however, there are groups of patients who have more as well as less favorable survival. The Follicular Lymphoma International Prognostic Index (FLIPI) (table 3) was developed specifically for patients with FL, since the International Prognostic Index, which was developed in patients with DLBCL, resulted in conflicting outcomes, due in large part to a low number of patients with clinically indolent lymphoma (approximately 10 percent) belonging to the higher risk groups.

Table 4: Follicular lymphoma international prognostic index (FLIPI)

Score	Two-year overall survival, (%)	Two-year progression-free survival, (%)	Median progression-free survival, months
0 to 1	98	84	84
2	94	72	70
3 or more	87	65	42

G. Treatment management

a. Therapeutic strategies

Treatment protocols for NHL are complex. They are mainly based on poly

Chemotherapy along with immunotherapy; the type and intensity are based on the histological type and age.

Further complementary treatments might be used, including:

- Loco-regional radiotherapy at the initial sites, especially in stages II and I after chemotherapy.
- Surgical resection prior to chemotherapy, notably in localized digestive case.
- CNS prophylaxis: Treatment recommended for some patients in selected patient group, include being HIV-positive; stages III and IV and/or testicular, paranasal sinus, epidural, adrenal, kidney, or bone marrow involvement; and high lactate dehydrogenase.
- Autologous cell transplant (if the patient can tolerate it based on age, general fitness, and comorbidity)
- Growth factor; prophylactic granulocyte colony-stimulating factor.

- Antimicrobial prophylaxis: may be considered if severe neutropenia (absolute neutrophil count <0.0005 x 10^9/L [500 cells/mL, 0.5 cells/microlitre]).[58]

b. Therapeutic Modalities

i. Polychemotherapy

Polychemotherapy (CHOP) combined with rituximab represents the standard Gold for B cell lymphoma.

R-CHOP-21 (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisolone given for 21 days) is given for 6 to 8 cycles. It is relatively well tolerated, with the main toxicities being hematological.

Other associations may be used to treat specific types of NHLs such as:

- FND
  - Fludarabine
  - Mitoxantrone (Novantrone)
  - Dexamethasone (Decadron, Dexasone)
- Hyper-CVAD: Treatment recommended for some patients with aggressive lymphomas, such as Burkitt's lymphoma or in pre-transplant.
  - Cyclophosphamide
  - Vincristine
  - Doxorubicin
  - Dexamethasone
  - In combination with methotrexate and cytarabine (Cytosar, Ara-C)
- MACOP-B
  - Methotrexate

(Folinic acid rescue therapy is needed for patients receiving high-dose methotrexate, to avoid toxicities from methotrexate)

- Doxorubicin
- Cyclophosphamide
- Vincristine
- Prednisone
- Bleomycin (Blenoxane)

- GRAALL for lymphoblastic lymphomas
- Methotrexate-based chemotherapy with or without whole-brain radiotherapy (WBRT)

Salvage chemotherapy:

A significant proportion of NHL patients experience either relapse or failure of treatment to first-line therapy, in this case second line option are offered.

- DHAP
  - Dexamethasone
  - Cytarabine
  - Cisplatin (Platinol AQ)
- EPOCH
  - Etoposide (Vepesid, VP-16)
  - Prednisone
  - vincristine
  - cyclophosphamide
  - doxorubicin
- ESHAP
  - Etoposide
  - Methylprednisolone (Medrol, Solu-medrol)
  - Cytarabine

- Cisplatin

- GDP
  - gemcitabine (Gemzar)
  - Dexamethasone
  - Cisplatin
- ICE
  - Ifosfamide (IFEX) (Mesna (Uromitexan)to prevent haemorrhagic cystitis)
  - Carboplatine (Paraplatin, Paraplatin AQ) or Cisplatine
  - Etoposide
- Mini-BEAM
  - Carmustine (BiCNU, BCNU)
  - Etoposide
  - Cytarabine
  - Melphalan (Alkeran, L-PAM)

Intrathecal chemotherapy:

The risk factors for central nervous system (CNS) relapse include being HIV-positive; stages III and IV and/or testicular, paranasal sinus, epidural, adrenal, kidney, or bone marrow involvement; and high lactate dehydrogenase.

For these patients, CNS prophylaxis should be given with intrathecal methotrexate or intrathecal cytarabine or intravenous methotrexate concurrently with systemic chemotherapy.

ii.Immunotherapy

Rituximab used in the majority of cases in combination or alone in some cases of indolent NHL who have responded to the initial chemotherapy or treatment with Rituximab. The results can be maintained with this treatment every 2 months for 2 years, especially for follicular lymphomas.

iii.Radiotherapy

Limited to the initial sites. In the case of stage I follicular NHLs, the "involved-node radiotherapy (INRT) which cover only the initially involved lymph node(s).

iv.Autologous stem-cell transplantation

Stem-cell transplantation used in some cases to treat a recurrent/refractory or occasional aggressive NHL if the risk of re-offending is high (high PII).

H. Complications

It is crucial to highlight that treatment of NHL may present early or late complications. Close monitoring of the patients makes it possible to detect these complications as well as to treat them.

Early complications are often related to drug toxicity (chemotherapy products or Rituximab). More frequently, we distinguish:

- Digestive toxicity (nausea, vomiting, abdominal pain, constipation, diarrhea)
- Hematological toxicity (varies according to the affected lines)
- Mucosal toxicity (mucositis)(high-dose methotrexate)
- Cutaneous toxicity and alopecia (pruritus, rush)
- Neurological toxicity (sensory and motor neuropathies; vinca alkaloids: e.g., vincristine)
- Febrile access and asthenia
- Bacterial and viral infection
- Complications related to infusion, angioedema
- Congestive heart failure (high-dose cyclophosphamide; anthracycline-induced cardiotoxicity: e.g., from doxorubicin)

In addition, potential late effects of lymphoma treatment may include:

- Second cancers.
- Heart disease.
- Lung complications.
- Hormone problems.
- HVB reactivation.
- Other late effects (multifocal leukoenchiopathy)[58].

I. Follow up and Response Assessment

In general, patients should be examined and monitored prior to each cycle of chemotherapy, with full blood count (FBC), basic metabolic profile, liver function tests, and lactate dehydrogenase (LDH).

Laboratory parameters including FBC with differential are routinely monitored for severe neutropenia.

Restaging with CT Scan/PET Scan are recommended either during therapy or after therapy completion.

Conventional response criteria for NHL define response categories (eg, complete or partial response; stable, and progressive disease) that are based on history, physical examination, laboratory studies, CT scan, bone marrow evaluation, and PET/CT (table 4), which are incorporated into the Lugano Classification.

Some research studies utilize the International Working Group RECIL 2017 criteria, but this approach is not currently applied to clinical practice.

NHL response include:

- Complete remission (CR) with disappearance of all clinical and preclinical signs

- Partial remission (RP) with regression of 50% of symptoms or persistence of a residual mass, in this case patients might need restaging with or without biopsy.
- Relapse or refractory state.
- Recurrence.

If a complete response is achieved, some patients might require at least 2 more cycles of chemotherapy, and all should be followed up once every 3 months for the first year, then every 3 to 6 months for the next 2 years, and 6 to 12 months thereafter [64][65].

PATIENTS AND METHODS

1. Type of study:

This study aims to describe retrospectively the clinical characteristics of patients with NHL, in a tertiary care hospital "Hassan 2" fez at the department of internal medicine and onco-hematology Fez.

2. Patients:

We retrospectively reviewed the case records of all patients diagnosed with NHL((n= 69) were eligible), from January 1st 2017 to December 31st 2018. Information obtained included patient demographics, characteristics of NHL and treatment responses.

3. Population studied:

3.1 Inclusion criteria:

Cases of NHL hospitalized in the department of Internal Medicine, for whose rituximab were indicated.

3.2 Exclusion criteria:

Patients diagnosed with NHL and whose files were lost or incomplete.

4. Data Extraction:

Patients were identified using hospital information system (HOSIX) via ID identification.

5. Statistical analysis:

All patient's Clinical and laboratory data were collected using "Google forms" and imported into MS Excel® worksheets then analyzed using software: Kaplan Meier survival curve analysis (IBM SPSS 25) (was employed to compare probability of survival for the two groups (CHOP/salvage therapy), Power BI, NVIVO, and Supervised by the epidemiology team of the Faculty of Medicine and Pharmacy of Fez.

STATISTICAL RESULTS

A. EPIDEMIOLOGIC DATA:

1. Distribution by age:

In our series, we identified four age groups whose NHL frequency arrival is mutable.

The occurrence was higher in subjects aged 65 years and above with an incidence of 39%. However, the size of patients aged less than 29 represent only 11% of the cases (Figure 16).

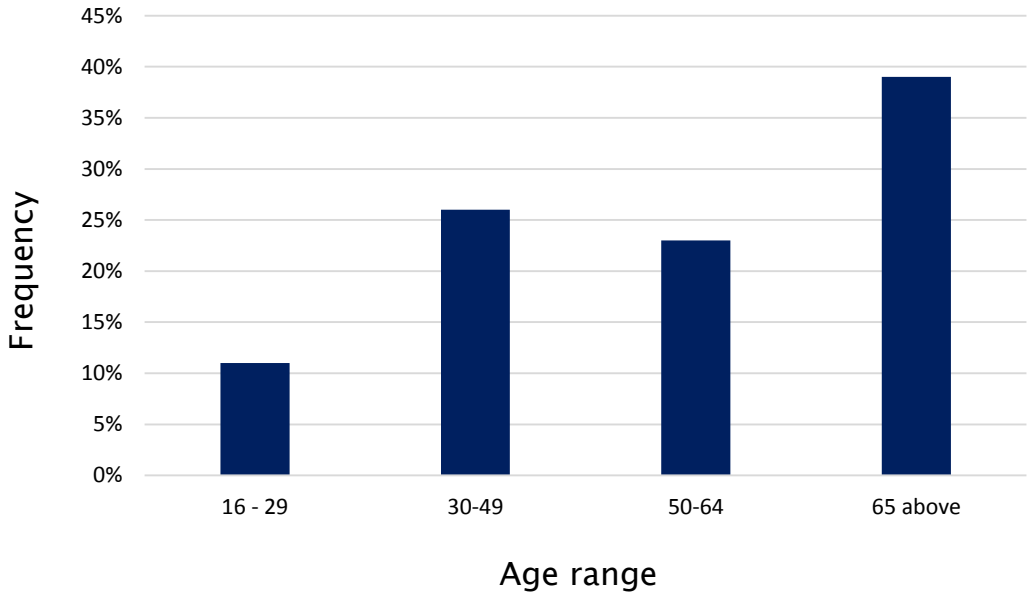


Figure 17 : Distribution by age

2. Gender distribution:

Hematological malignancies specifically NHL are more common in males. within each gender groups, we identified a rate of 59% of males with a sex-ratio of M/F= 1.46 (Figure 17).

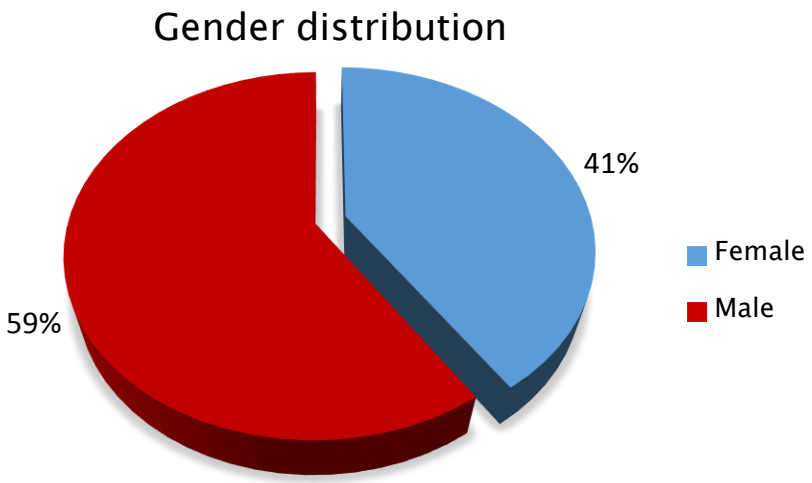


Figure 18: Gender distribution

3.Distribution by profession:

Thirty percent of our patients are without a job and twenty nine percent are housewives, nine percent are retired. In addition, more than 80% of patients had a low socioeconomic level along with 10% an average level, estimated from the existence or not of a fixed source of income (Figure 18).

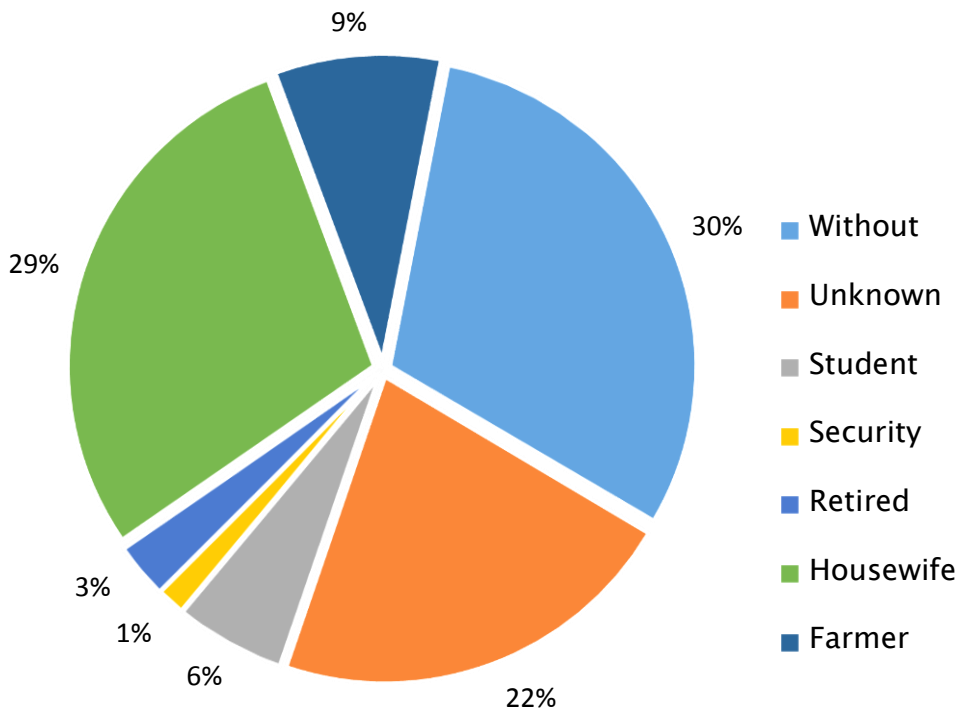


Figure 19 : Distribution by profession

4. Distribution by area of origin:

Around half of our patients live in fez-Meknes region (48%), and the rest spread among the different regions of the north Morocco; Al Hoceïma 8%, followed by Taounate with a frequency of 6% and Errachidia with 6% (Figure 19,20)

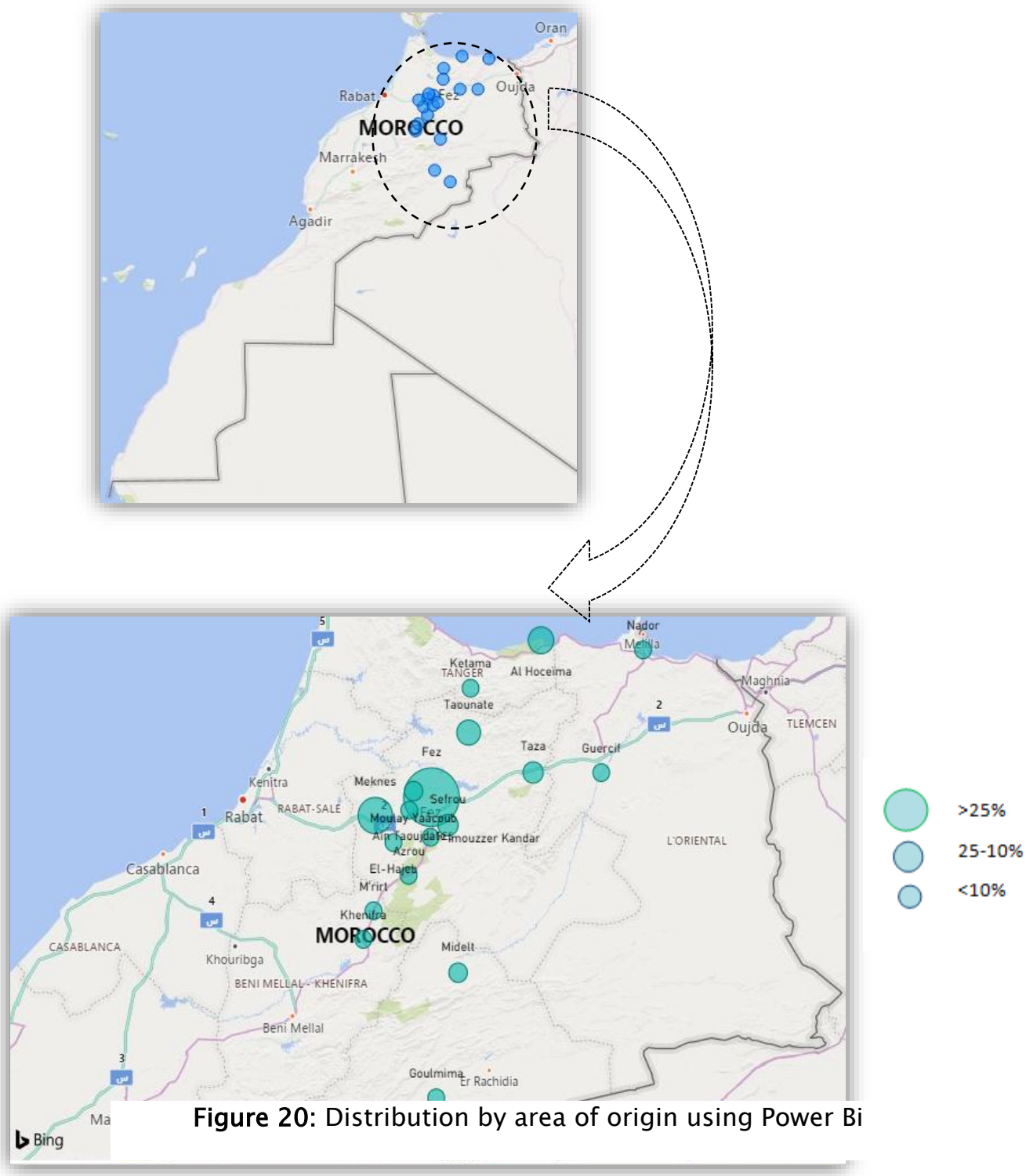


Figure 20: Distribution by area of origin using Power Bi

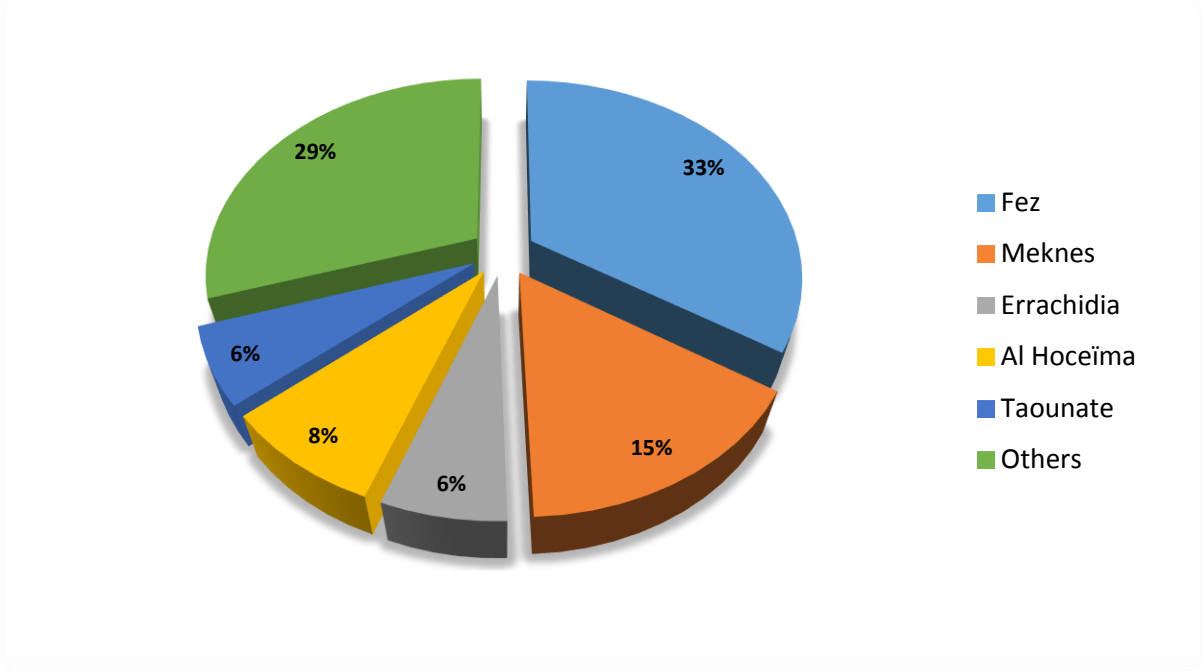


Figure 21: Distribution by region

5. Health insurance:

We identified about 86 % of hospitalized and followed patients belong to the RAMED system, and less than 7% are either CNOPS or CNSS (Figure 21).

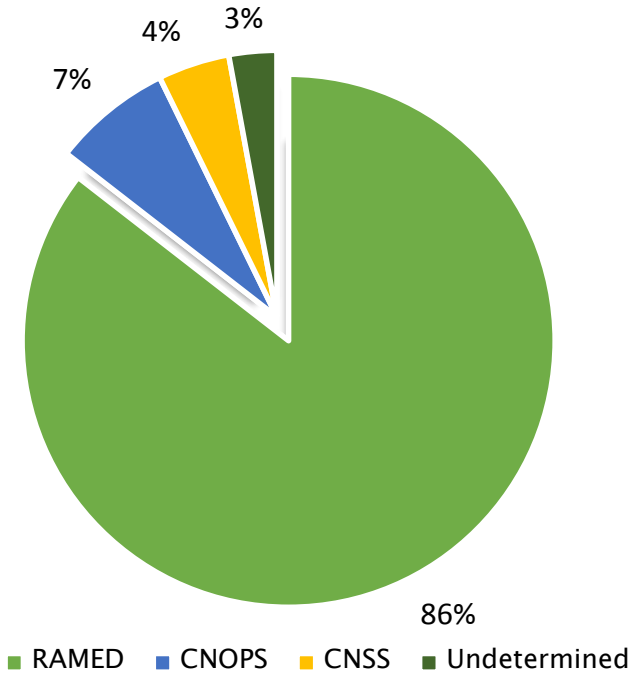


Figure 22: Count of health insurance

II. CLINICAL STUDY:

1. Backgrounds:

1.1 Personal history:

Among the forty-four patients' clinical records, we identified the presence of:

- 20 cases(29%) had diabetes type 2 ;
- 14 cases(20%) of active smokers;
- 11 cases(15%) of High blood pressure ;
- 7 cases(10%) had a history of Chemotherapy as treatment ;
- 5 cases(7%) had history of treated lymphoma ;

Table 4: Personal medical history incidence

Chemotherapy	Diabetes	Hepatitis	HTA	Lymphoma	TB	Tobacco
7	20	1	11	5	1	14
10%	30%	1%	15%	7%	1%	20%

1.2. Evolution time prior to consultation:

Evolution time or wasted time before medical consultation, defined as the time interval between the onset of symptoms and the specialized consultation.

It has been clarified in all patients. The average duration was 6 months with extremes of 1 and 48 months (Figure 22).

About 33% of our patients consulted between 5 months and 1 year.

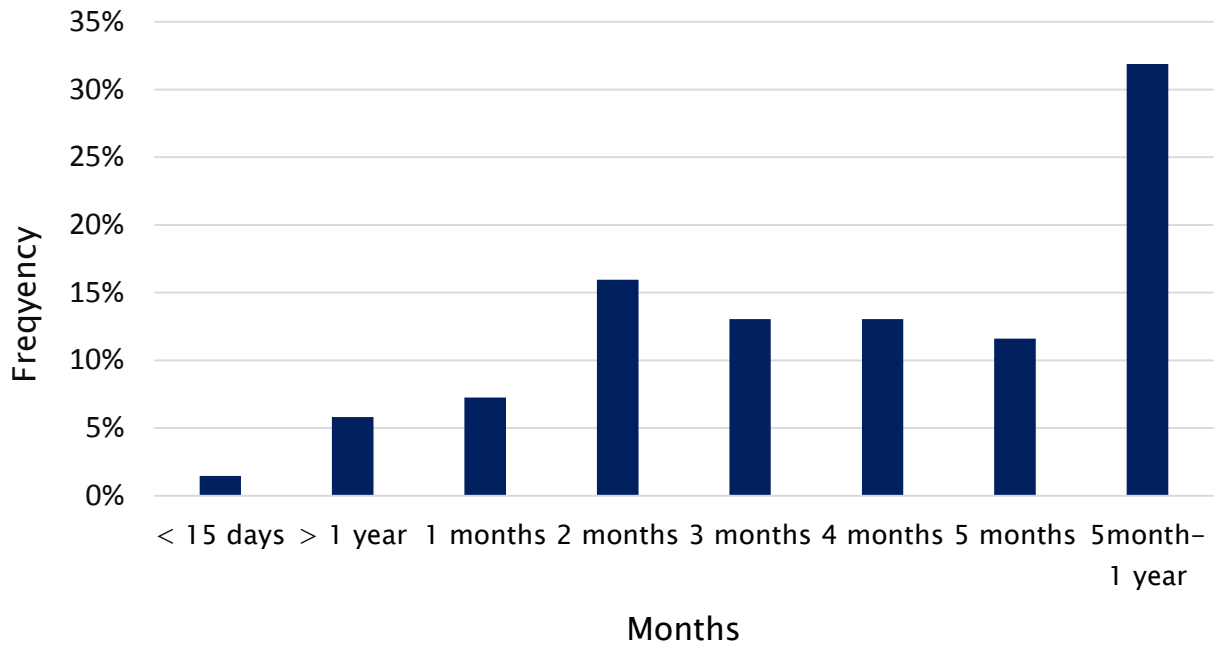


Figure 23: Wasted time before consultation

1.3. Mode of revelation and chief complaints:

The clinical manifestations of non-Hodgkin lymphoma (NHL) vary with such factors as the location of the lymphomatous process, and the function of the organ being compromised or displaced by the malignant process along with the subtypes.

In our series, Peripheral lymphadenopathies remained the main symptom, were found in thirty patients i.e. 43% of cases. In 57% of cases, patients had signs related to extra lymph nodes involvement, 24% had digestive signs, and 34% had weight loss and general alteration. Followed by signs of ear, nose and throat involvement in 10%, Dysphagia in 7% of cases, Shortness of breath in 5% of cases. Uncommon signs like neurological and bone pain represent 1%-3% respectively, testicular hypertrophy found in 4% (Table 5).

Table 5: Chief complaint

Chief complaint	Number of cases	Percentage
Lymphadenopathy	30	43%
SMG	2	3%
Bone pain	2	3%
Infectious syndrome	3	4%
Abdominal pain	17	24%
Vomiting	2	3%
Rectal hemorrhage	1	1%
Melena	3	4%
Pulmonary pain	2	3%
Shortness of breath	4	5%
Cough	3	4%
weight loss and general alteration	24	34%
Dysphagia	5	7%
Skin nodules	1	1%
Confusion syndrome	1	1%
Vertigo	1	1%
Orl hemorrhage –epistaxis	7	10%
Testicular hypertrophy	3	4%
Tumefaction	3	4%
Others	2	3%

2. NHL Localization and confirmatory diagnosis with subtype

2.1. Lymph-nodes localization

Peripheral lymph-nodes areas revealed the existence of ADP in 49% of the cases (i.e. 34 patients). Cervical involvement was the most common parts (Table 6).

Table 6: Lymph-nodes localization

Non-Hodgkin lymphomas localization	Incidence	Number of cases
Gastric	20%	14
Intestinal	1%	1
Lymph-nodes	49%	34
Palpebral	1%	1
Pulmonary	6%	4
Cavum	3%	2
Rectal	1%	1
Splenic	3%	2
Inguinal	1%	1
Nasal	3%	2
Medullary	1%	1
Cutaneous	1%	1
Sacral bone	1%	1
Mediastinal	1%	1
Maxillary bone	1%	1
Testicular	3%	2
Oral tongue	1%	1

2.2. Extra lymph-nodes involvement

Splenomegaly (SPM) was present in two patients (3%) and cavum localization in 3% of cases along with testicular parts.

Apart from these abnormalities, we objectified:

- Digestive involvement in 15 patients (21%);
- involvement of the ENT sphere in 5 patients;
- Cutaneous enhancement in 1 patients;
- Bone localization in 2 patients;

2.3. General symptoms

The presence of vague Clinical symptoms or signs, commonly referred to as B symptoms such as unexplained fever above 38 ° C, nocturnal sweating or weight loss (10% of the initial weight in six months) explain the evolution of the disease and influences the prognosis and therapeutic strategy. These general signs were present in 24 patients, i.e.34% of cases.

2.4. Histology

The biopsy was performed in all our patients, all locations. We note in our study, that in 53% cases, it is a lymph node biopsy and in 20% of cases, was gastric. ENT biopsy site constituted 6% of the cases (Table 7).

Table 7: Biopsy localisation

Biopsy localization	Number of cases	Percentage
Gastric	14	20%
Lymph-nodes	37	53%
Bronchial and Pulmonary	4	6%
Cavum	2	3%
Nasopharynx and oral	2	3%
Cutaneous	1	1%
Testicular	2	3%
Rectal and intestinal	2	3%
Bone	1	1%
Others	4	6%

In addition, the immunohistochemical study made it possible to draw up the histopathological profile of the various cases of NHL.

In our case, B lymphomas present in 98% of cases, while T lymphomas are found in only 1% of cases.

Aggressive B cells Lymphoma are the common type of NHL upon 66 (i.e. 95%) cases with a predominance of lymphomas large B cells through 72% of cases, Burkitt and lymphoblastic stand for 6% of cases, NK and T cell lymphoma represent 2-1% respectively (Figure 23).

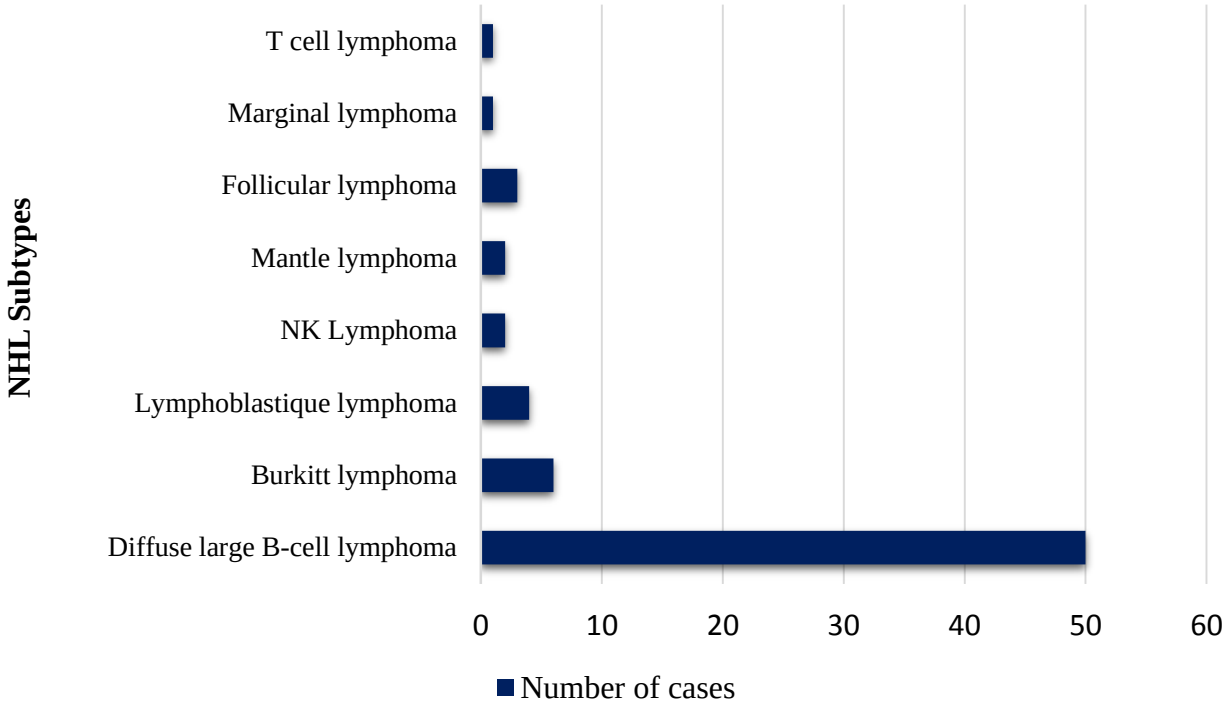


Figure 24: NHL subtypes

3. Para-clinical parameters:

3.3. Biology:

3.3.1. Complete blood count

Regularly, most of all our patients had a complete blood count as first investigations to order. The results of our population were as follow:

- Anemia was objectified in 40% of cases; the range of hemoglobin variation was between 5 and 12.8 g / dl, with a mean of 9,89g / dl.
- Unexpected neutrocytosis in 24% of cases, besides 7% of lymphocytosis while neutropenia was found in 3% of cases (Table 8).

Table 8: CBC abnormalities

CBC abnormalities	Number of Patients	Percentage
Anemia	29	42%
Leukocytosis	20	29%
Neutrocytosis	17	24%
Thrombocytosis	7	10%
Lymphocytosis	5	7%
Leukopenia	1	1%
Neutropenia	2	3%
Normal blood count	23	33%

3.3.2. Erythrocyte sedimentation rate ESR

It was performed in 32 patients, an accelerated ESR seen in 23 patients otherwise 72% of cases.

3.3.3. Serum lactate dehydrogenase (LDH)

Accordingly, serum LDH can be considered a useful predictor of response to therapy and survival in non-Hodgkin's lymphoma, also imitate the proliferative rate of the tumor; it is high in about 38 of our patients otherwise 55% of cases.

3.3.4. Renal function tests

Kidney assessment test was performed in 65 patients, 20% had an increase in creatinine and urea.

3.3.5. Hepatitis serology

Intended for prevention, 67 patients screened for HBV (HBsAg and anti-HBc IgG) along with HCV infection, only 21% had HBV (i.e. 15 cases)

3.3.6. Syphilis and HIV screening

After the patient's consent for HIV and syphilis screening, we have noted only one patient with (VDRL) test positive.

Other biological tests for prognosis is illustrated in the provided table below:

Table 9: Biological test for prognosis.

Biological abnormalities	Number of cases	Percentage
Accelerated ESR	25	36%
SPE hypergammaglobulinemia	2	3%
Abnormal Renal Function Tests	13	18%
High LDH levels	38	55%
Hypo-Calcemia	6	8%
Hyper-Calcemia	2	3%
Hypoalbuminemia	25	36%
B2 microglobuline >3	44	63%
Lymphocytosis	6	8%
Markers of infection		
C-reactive protein	56	81%
Procalctonin	4	5%
Sputum TB test Positive	0	0%
Serology		
HBV	15	21%
HCV	1	1%
HIV	0	0%
Syphilis	1	1%

4. Radiology imaging:

4.1. Chest X-ray

Abnormal chest x-ray detected nearly in 6% cases, commonly shows mediastinal widening (i.e. *« Bulky »)* due to grossly enlarged right paratracheal and left paratracheal nodes. Pleural participation isolated in one case.

4.2. Transthoracic echocardiogram (ETT)

In order to decrease the chance of anthracycline-induced cardiotoxicity. Echocardiography established for 67 patients. In 10 (i.e. 14%) cases the ejection fraction was compromised.

4.3. Abdominal ultrasound

The incidence of pathological findings identified by abdominal ultrasound in our patients was about 11% of cases; splenomegaly and bulky lymph nodes are the common abnormalities (Table 10).

Table 10: Radiology imaging

	Abnormal imaging Results	Percentage
Chest X-ray	4	6%
Transthoracic echocardiogram (ETT)	10	14%
abdominal and pelvic ultrasound	8	11%
CT Scan of Neck/Chest/Abdomen/Pelvis	66	95%
Endoscopy	14	20%
Colonoscopy	8	11%

4.4. CT Scan

CT scan is a part of standard work-up for lymphoma staging.Around69 patients, 66(i.e.95%) had abnormal CT scan (Chest/Abdomen/Pelvic)We objectified mediastinal lymph nodes in 10 patients, pulmonary involvement in 4 patients and pleural involvement in 3 patients.

Profound lymph nodes in 25 cases, including 13 cases of isolated ADPs, 2 cases associated with splenic involvement.

4.5. Endoscopy – colonoscopy investigation

Sixteen of the 69 patients underwent endoscopy; among them, GI involvement was found in 14 patients. Only 12 out of 69 patients were available for colonoscopy, eight cases had abnormal colonoscopy features.

5. Treatment

5.1. Immunotherapy

Rituximab, the anti CD20 monoclonal antibody has been delivered among 78% of our patients (i.e. 54) compare to 22% cases (Among 22%, 10% had NK nasal lymphoma and T-cell lymphoma and 12% treated during shortage period) (figure 24).

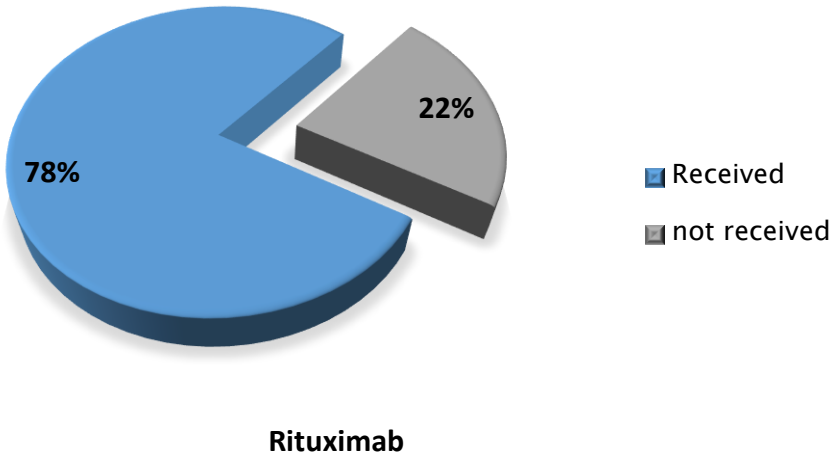


Figure 25: Rituximab implication

5.2. Protocols

As a standard therapy for diffuse large cell lymphoma (either bulky or not) R-CHOP-21 (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisolone given for 21 days, up to 6-8 cycles) has been given to 44 of our patients (i.e. 62%) as a first line therapy. Cop of desinfiltration has been given to 14 cases otherwise 20% as an Initial Cytoreduction Phase (table 11).

Table 11: Percentage of different protocols in our study

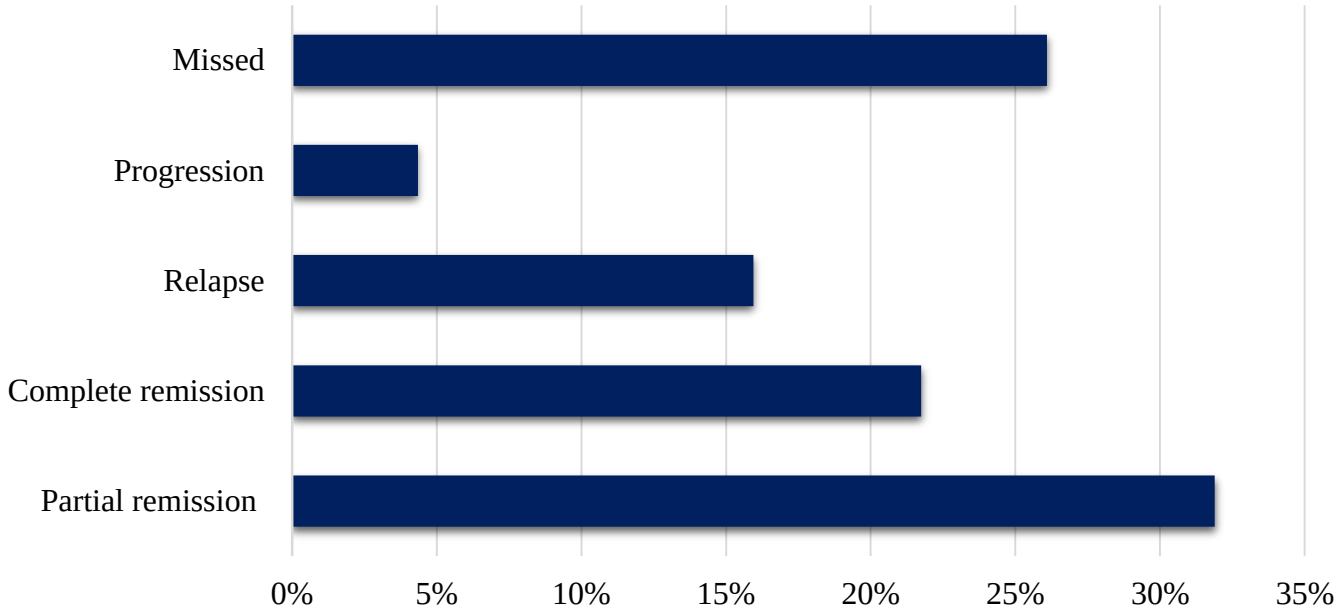
	Number of patients	Percentage
R-CHOP	43	62%
R-DHAOX	8	11%
R-Copadm	7	10%
R-MINICHOP	8	11%
R-REGMOX	1	1%
R-bendamustine	2	3%
GRAALL	1	1%
R-ICE	1	1%
R-DaEPOCH	1	1%

5.3. Type of response after 4 cure of treatment

Patients who have a positive PET scan after 4 cycle of R-CHOP have a very poor prognosis (~10% chance of cure) and may have an improved outcome if switched to a non-cross resistant chemotherapy combination.

Among 14 patients for whom R-CHOP (or MINICHOP) mid-therapy fails, three cases suffer from primary refractory disease (progress during or right after treatment) whereas seven cases had a relapse, R-DHAOX, R-bendamustine and R-REGMOX, typically represent the standard salvage regimens after relapse/refractory response to standard therapy (figure 25).

The provided bar chart below represents the different kind of response after 4 cycle of treatment for all 69 patients within different protocols, predicted by PET scan.



	Partial remission	Complete remission	Relapse	Progression	Missed
Percentage	32%	22%	16%	4%	26%

Figure 26:First response assessement C4

5.4. Common Protocols used in second line

R-CHOP is found to be inadequate in 17% to 26% of patients. For these patients, different processes may account for their lack of response to R-CHOP. R-DHAOX represent the first common used regimen after unwell response with 10% along with R-bendamustine in 3% and R-ICE (table 13).

Table 13: Second line therapy incidence

Second Course therapy	Number of cases	Percentage
R-bendamustine	2	3%
R-DHAOX	7	10%
R-ICE	1	1%

5.5. Final response statement Predicated by PET - CT -Scan

The overall response rate was 48%, with a complete response in 43% at the end of consolidation and a partial response in 5%. 27% had discontinued therapy. In the entire population, death occurred in 17% (i.e. 12 cases)(figure 26).

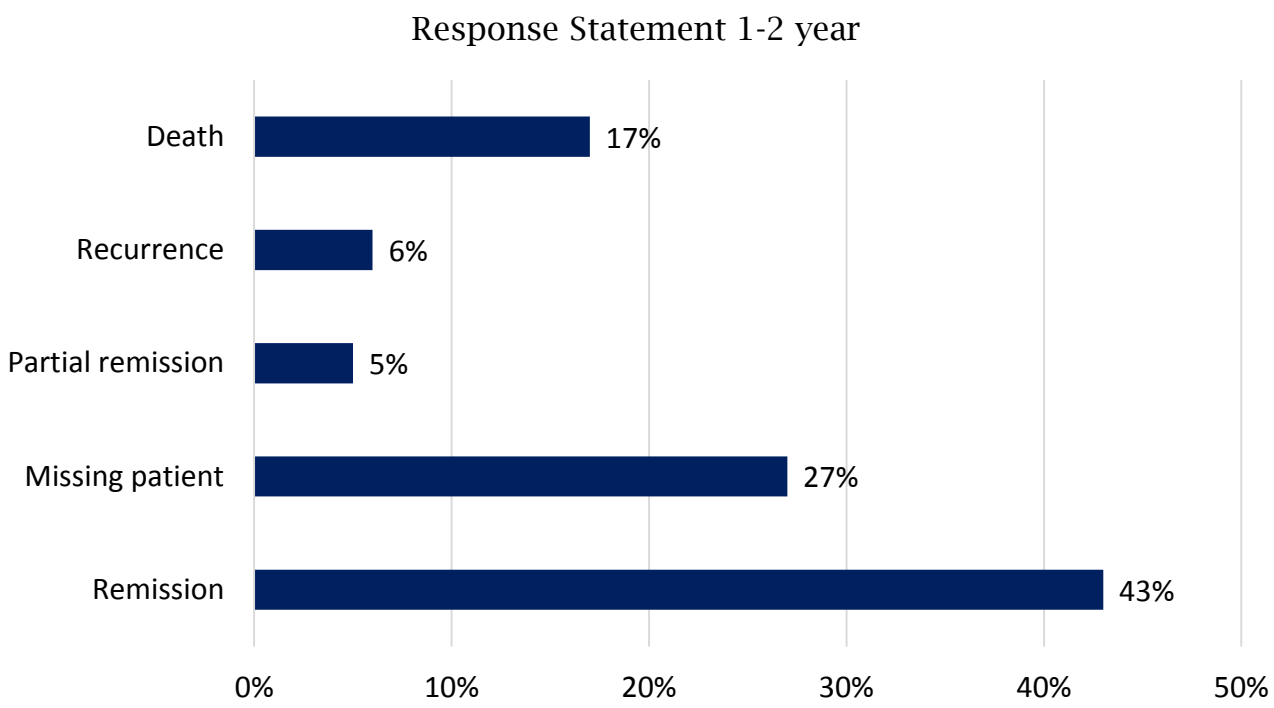


Figure 27: Final response statement

5.6. PET SCAN and CT-SCAN Response test assessment

PET scanning using 18F-fluorodeoxyglucose (18F-FDG) can be performed as an independent study or can be fused with a near-simultaneous CT scan into a single image (i.e. integrated PET/CT imaging).

The Deauville score (also known as the 5-point scale) determine a positive PET scan.

Using this method, 20% among our patients had a Deauville score of 1 to 3, consistent with a complete metabolic response. Compare to 7% patients with a positive PET/CT (defined by Deauville score = 4 or 5) corresponding to incomplete metabolic response.

Close to 33% of response justified via CT-SCAN and 6% of cases had positive CT-scan results, which in turn stated on remission after PET scan. (Table 14)

Table 14: Response test assessment

	Number of cases	Percentage
complete metabolic response (PET Scan)	14	20%
Incomplete metabolic response (PET Scan)	5	7%
CT-SCAN response assessment	23	33%
CT-SCAN And PET SCAN assessment	4	6%

6. Adverse Effect

In our study, admitted bacterial infection was10%, in 2 cases was linked to death, 20% to 24% experienced leucopenia – neutropenia with one episode of neutropenic fever associated with death.

Mild to moderate Anemia was reported in 30% along with 10% of lymphopenia, most cases are not life threatening.

Renal insufficiency has been reported in 3%, complicated in 1% with deathful severe hypercalcemia. Hepatitis below grade 3 developed in 1% (figure 27).

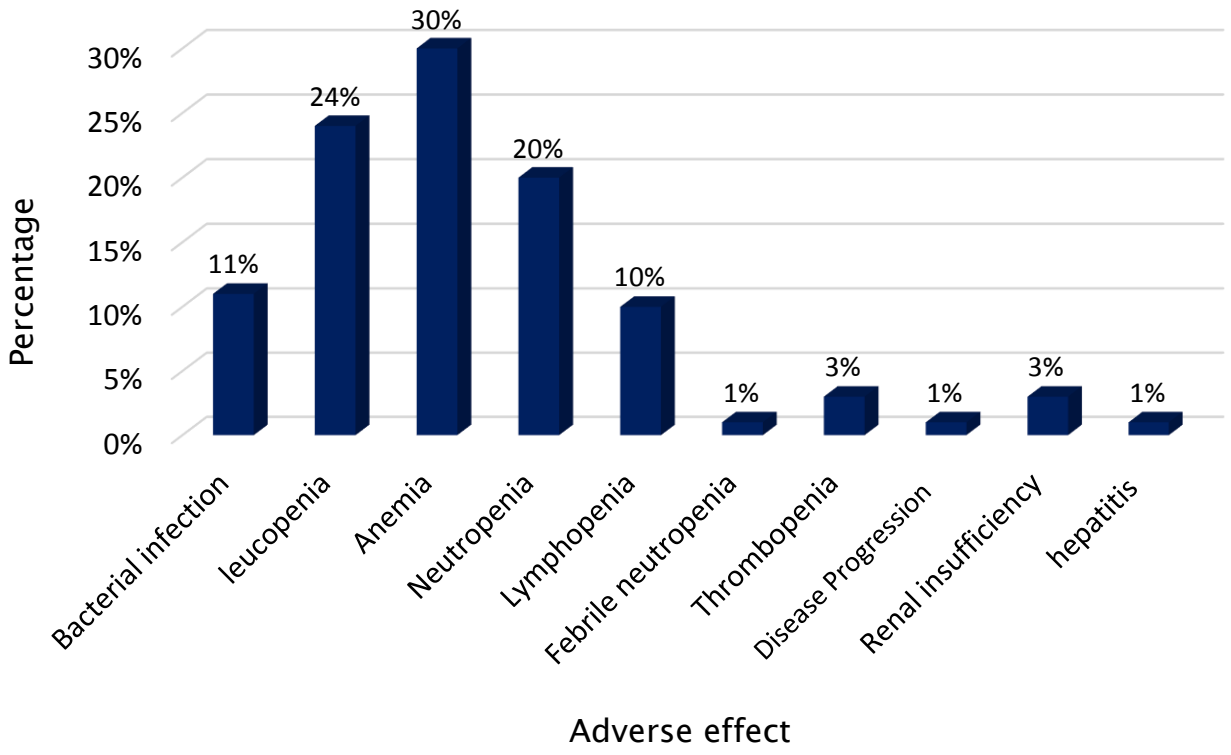


Figure 28: Adverse effect chart

DISCUSSION

Many studies attempted to examine clinical response to R-CHOP vs. Other protocols in Adult Patients with NHL.

The aim of this study was to address the question of "Benefit" of R-CHOP versus other regimens", with addition of Rituximab (Immunotherapy) to CHOP as first line therapy, regarding survival of patients suffering of NHL focusing particularly on DLBCL subtype.

A. NHL Frequencies

1.Age

The incidence of lymphomas particularly DLBCL increases with age. They are uncommon before age 50 years, the most concerned age group are above 60 years old with the mean age 57yrs in our study compare to 55yrs during 2003-2012 series (CHU FEZ study) and this meets the data of certain international studies, as submitted by " the Groupe d'Etude des Lymphomes de l'Adulte".

2.Gender

NHL incidence among males is significantly higher than in females; the overall incidence was about 59% and 60% in our population and between 2003-2012 within the project of CHU fez.

In the aggregate, men have a slightly greater chance of developing NHL than women.

3.Personal History

Researchers have found several factors that can affect a person's chance of getting non-Hodgkin lymphoma (NHL), in our population,10% had a history of chemotherapy and 1% of HBV along with 20% of active smokers and 7% of treated

lymphoma while in 2003-2012 series 70% had no significant background and only 4% had hepatitis B and C along with HIV and 6% of active smokers.

B. Chief compliant

The clinical presentation of NHL varies tremendously depending on the type of lymphoma and the areas of involvement and are often vague.

Peripheral lymphadenopathy and B symptoms represent the most common presentation with 43% -34% in our population, compare to 54% -85% cases during 2003-2012 series (Study by Pr.Bono in CHU Fez).

C. Time before consultation

Wasted time before consulting stretched between 5 months to 1year in 33%, and in 67% above 6 month during 2003-2012 series. Moreover, this negatively affects the response to therapy and survival rate.

D. Biopsy and subtypes of NHL

The diagnosis of NHL has been established over a half of cases through biopsy lymph node, and about a fifth (1/5) by gastric biopsy, relative to 2003-2012 series the results remained static with insignificant change.

Our study also found a significantly higher relative frequency of immunophenotype B, affected by diffuse large B-cell lymphoma as a common subtype, representing 72% of the total number of cases, behind that the incidence was approximately 2% higher than that reported between 2003-2012 and 10% higher compared to western countries. The reason underlying the higher incidence of this subtype is unknown. We hypothesize that it may be partly due to the lower incidence of the follicular lymphoma subtype in this part of the world.

Our population had a lower frequency of follicular lymphoma (4%) than that found in other geographical sites, as its stands the second most common subtype in the developing world (15.3%) (table 15).

Table 15: Comparative table of our patient and the other series

	Our study (DLBCL) N: 50	2003-2012 CHU fez Series	Study by « Centre Hospitalier Universitaire (CHU) de Brabois »
Mean Age (years) DLBCL	57 years	55years	69 years
Sexe -Male	44% (DLBCL) 59.42% overall	60% (overall)	46% R-CHOP 54% CHOP
Chief complaint	34% General signs (B symptoms) 43% Lymphnodes	85% General signs (B symptoms) 54% Lymphnodes	39% B symptoms R-CHOP 36% B symptoms CHOP
Wasted Time before diagnosis	5 month-1yrs 33%	6 months 67%	-
Biopsy	53% Lymphnodes 20% Gastric	67% Lymphnodes 18% Gastric	-
Elevated LDH	55%	30%	65% (R-CHOP) 67% (CHOP)

E. Therapeutic Management and Evolution

The Kaplan Meier survival curve analysis (log rank, Breslow and Tarone ware tests) was employed to compare the means and probability of overall survival for the two groups (R-CHOP/ Other regimen) to find any difference in response due to treatment protocols.

Significant result were obtained in all three tests with the p value is less than 0.05 (P=0.01) which showed that patients treated with the combination of rituximab and CHOP had higher survival time. In addition, this can be explained by the lower rate of toxicity and disease progression during therapy and fewer relapses among patients who had a complete response among CHOP-plus-rituximab group.

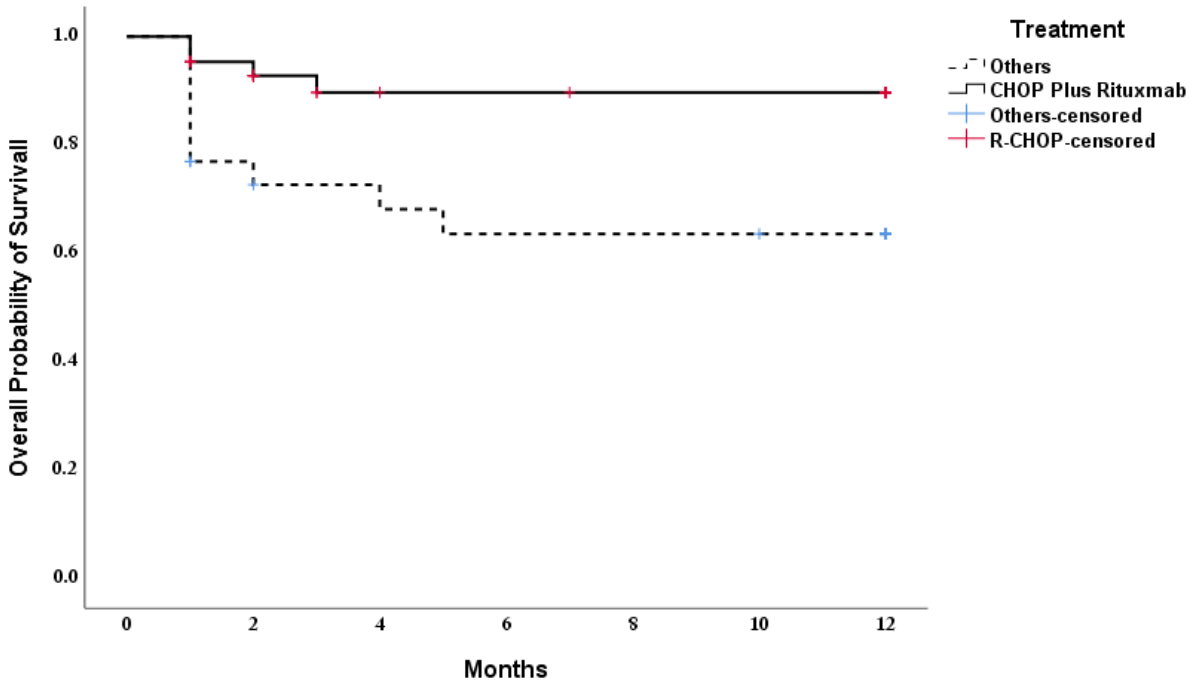


Figure 29: Probability of survival during 12 months

Subgroup analysis within patients diagnosed with diffuse large-B-cell lymphoma (DLBCL), showed superior complete response and partial response

In patients treated with the combination of rituximab and CHOP compare to other groups (CHOP or other salvage therapy) with 38% of CR and 10% of PR and this is less significant than the provided data by the study groups of adult lymphoma (CHU Barbois).

As a logical consequence, lower rate of relapse and death, the rate of relapse was 8% lower than non R-CHOP group; also, the rate of death was significantly lower by 7.5% versus 10%.These results seem to be acceptable given our context.

On the other hand, Loss to follow-up rate remain serious problem in 27% among the total number of participant (table 16).

Table 16: Comparative table of different types of responses

Event (DLBCL)	Our study (N=50 of DLBCL)		2003-2012 CHU FEZ series		Groups of study (CHU) of Brabois	
	R-CHOP	Salvage therapy	R-CHOP	CHOP	R-CHOP	CHOP
Percentage of treated cases	80%	20%	61%	28%	80%	72%
complete response	38%	6%	33%	17%	75%	63%
Partial response	10%	6%	28%	-	6%	8%
Progressive disease	2%	2%	-	-	9%	22%
Relapse	10%	4%	17%	-	20%	34%
death during treatment	6%	2%	22%	-	6%	6%

Patients treated with R-CHOP seemed to do better than those treated with other regimens. These results might be interpreted as consistent with our findings, but a longer follow-up is certainly necessary to draw any conclusion.

CONCLUSION

Based on previous results, it seems that the incidence of NHL is growing significantly in recent years, with a higher frequency of diffuse large B-cell lymphoma and a lower frequency of follicular lymphoma compared to those reported in Western countries.

Although it was not a randomized study, we depicted that the results of three clinical outcomes like complete response, partial response and overall survival were in favor of the addition of rituximab to the CHOP regimen as first line therapy in elderly patients with diffuse large-B-cell lymphoma, without a clinically significant increase in toxicity.

ABSTRACT

Non-Hodgkin lymphoma (NHL) consists of a diverse group of malignant neoplasms variously derived from B cells or T cells line, or (rarely) natural killer cells.

NHL is the fifth most common malignancy and the sixth most common cause of cancer death. There are a growing number of long-term survivors of NHL. This is predominantly due to an increasing incidence and improved survival after initial treatment.

Our retrospective series study, which was conducted over a 2-year period from 2017 to 2018, aimed to develop an epidemiological profile, along with different elements of diagnosis and management of NHL, besides the weight of immunotherapy.

Sixty-nine patients of non-Hodgkin lymphoma were selected from hospital information system and managed by the Internal Medicine Department at Hassan II University Hospital in Fez, and then analyzed based on the SPSS version 25.

Patients in our study ranged in age from 16 to 80 years (median, 57) with 39% greater than or equal to 60 years of age. Male to female ratio are about 1.5 times higher. Around half of our patients live in fez-Meknes territory and over 86% are covered by RAMED system.

Among these patients, The average duration before consultation was 6 months with extremes of 1 and 48 months and the most common reason for consultation was the finding of lymphadenopathy in 43%, followed by gastrointestinal symptoms in 24% of cases. As logical consequence, lymph-nodes biopsy remained predominated with 53%, followed by gastrointestinal biopsy in 20%.

The relative frequencies of non-Hodgkin lymphoma subtypes in our population were in favor of DLBCL (diffuse large B-cell lymphoma (DLBCL)) in 72%

cases followed by Burkitt lymphoma. Among 69 cases 62% had treated with R-CHOP initially (80% of DLBCL received R-CHOP).

The evolution was marked by 43% of total remission, 5% of partial remission and 6% of relapse, a death rate of 17% and a rate of loss of follow-up about 27%.

Late complications are mainly hematological, the infectious causes detected in 10% of cases.

Although it was not a randomized study, our results of three clinical outcomes like complete response, partial response and overall survival were in favor of the addition of rituximab to the CHOP regimen, without a clinically significant increase in toxicity.

Résumé

Le lymphome non hodgkinien (LNH) comprend un groupe divers de néoplasmes malins dérivés de cellules B ou de lignées de cellules T, ou (rarement) de cellules tueuses naturelles dites NK.

Les LNH constituent le 5ème cancer et la sixième cause de décès par cancer. Il y a un nombre croissant de survivants à long terme de la LNH. Ceci est principalement dû à une incidence croissante et à une amélioration de la survie après le traitement initial.

Notre étude de série de type rétrospectif, qui s'étalait sur une période de 2 ans

De 2017 à 2018, visait à dresser un profil épidémiologique et à énumérer les

Différents éléments de diagnostic et de prise en charge des LNH, en plus du bénéfice de l'immunothérapie.

Soixante-neuf patients atteints de lymphome non hodgkinien ont été sélectionnés dans le système d'information de l'hôpital et gérés par le département de médecine interne et onco-hématologies de l'hôpital universitaire Hassan II de Fès, puis analysés à l'aide de la version 25 de SPSS.

Les patients de notre étude avaient entre 16 et 80 ans (âge médian : 57 ans) et 39% étaient âgés de 60 ans ou plus. Le ratio hommes / femmes est environ 1,5. Environ la moitié de nos patients vivent sur la région de Fès-Meknès et plus de 86% ont une couverture sanitaire type RAMED.

Parmi ces patients, La durée moyenne avant consultation était de 6 mois avec des extrêmes de 1 et 48 mois et le motif de consultation le plus fréquent était la découverte d'une adénopathie dans 43% des cas, suivie de symptômes gastro-intestinaux dans 24% des cas. Cela ayant comme Conséquence logique la biopsie ganglionnaire lymphatiques initialement puis la biopsie gastro-intestinale dans 20% des cas.

Les fréquences relatives des sous-types de lymphomes non hodgkiniens dans notre population étaient en faveur du DLBCL (lymphome diffus à grandes cellules B (DLBCL)) dans 72% des cas, suivi du lymphome de burkitt. Parmi les 69 cas, 62% avaient été traités avec R-CHOP en 1er lignée (80% des DLBCL avaient reçu du R-CHOP).

L'évolution a été marquée par 43% de rémission totale, 5% de rémission partielle et 6% de rechute, un taux de mortalité de 17% et un taux de perte de suivi d'environ 27%. De plus, la survie globale était en faveur du rituximab plus CHOP (R-CHOP).

Les complications tardives sont principalement hématologiques, les causes infectieuses étant détectées dans 10% des cas.

Bien qu'il n'ait pas été une étude randomisée, notre suivi a montré que les résultats des réponses cliniques et la survie globale étaient en faveur de l'ajout de rituximab au régime CHOP, sans augmentation significative de la toxicité.

ملخص

الأورام اللمفاوية الغير"هودجكينية" هي مجموعة متنوعة من الأورام الخبيثة المستمدة بشكل مختلف من الخلايا نوع "ب ‘‘أو نوع "ت"، آو نادرا من الخلايا القاتلة الطبيعية .

تعتبر الأورام اللمفاوية الغير"هودجكينية" خامس أكثر الأورام الخبيثة شيوعًا والسادسة المسببة للوفايات من السرطان. مؤخرا لاحظنا تزايد الناجين على المدى الطويل من الأورام اللمفاوية. هذا في الغالب بسبب زيادة الإصابة وتحسين جودة العيش بعد العلاج الأولي.

تهدف هده الدراسة الاستعاضية، التي أجريت على مدى عامين من 2017 إلى 2018، إلى تكوين تصور وبائي، مع إدراج عناصر مختلفة من التشخيص وإدارة الأورام اللمفاوية الغير"هودجكينية"، إلى جانب تطوير العلاج المناعي.

تم اختيار 69 مريضا من ليمفوما اللاهودجكين من نظام معلومات قسم الطب الباطني في مستشفى الحسن الثاني الجامعي في فاس، ثم تم تحليلها بواسطة نظام SPSS.

تراوحت أعمار المرضى في دراستنا بين 16 و 80 عامًا (متوسط 57) بنسبة 39٪ من المرضى البالغين أكثر من 60 عامًا. نسبة الذكور أعلى بنحو 1.5 مرة من نسبة الإناث. يعيش حوالي نصف مرضانا في منطقة فاس-مكناس وأكثر من 86٪ منهم مستفيدون من نظام الراميد للتغطية الصحية.

من بين هؤلاء المرضى، كانت مدة تطور المرض قبل الاستشارة في المتوسط 6 أشهرمع النقيض من عام الى 48 شهرا، اما السبب الأكثر شيوعا للاستشارة الطبية هو اكتشاف اعتلال عقد لمفية في 43% تليها أعراض المعدة في 24% من الحالات ,كنتيجة منطقية ،حدد موقع الأورام اللمفاوية الغير"هودجكينية" داخل العقد اللمفاوية في 53% من الحالات يتبعها الجهاز الهضمي في 20% من الحالات .

كما كانت الترددات النسبية للأنواع الفرعية من ليمفوما اللاهودجكينا لصالح الخلايا الكبيرة الحجم من نوع "ب في 72% من الحالات تليها سرطان الغدد الليمفاوية ببركت.

من بين 69 حالة 62% تلقوا العلاج ببروتوكول العلاج الكيمائي RCHOP (80 ٪ من DLBCL تلقى R-CHOP) .

تميز التطور بنسبة 43 ٪ من إجمالي الاستيجابة الكاملة، 5 ٪ من الاستيجابة جزئية و 6 ٪ من الانتكاسة ، و17 ٪ من الوفايات و فقدان المتابعة بحوالي 27 ٪.

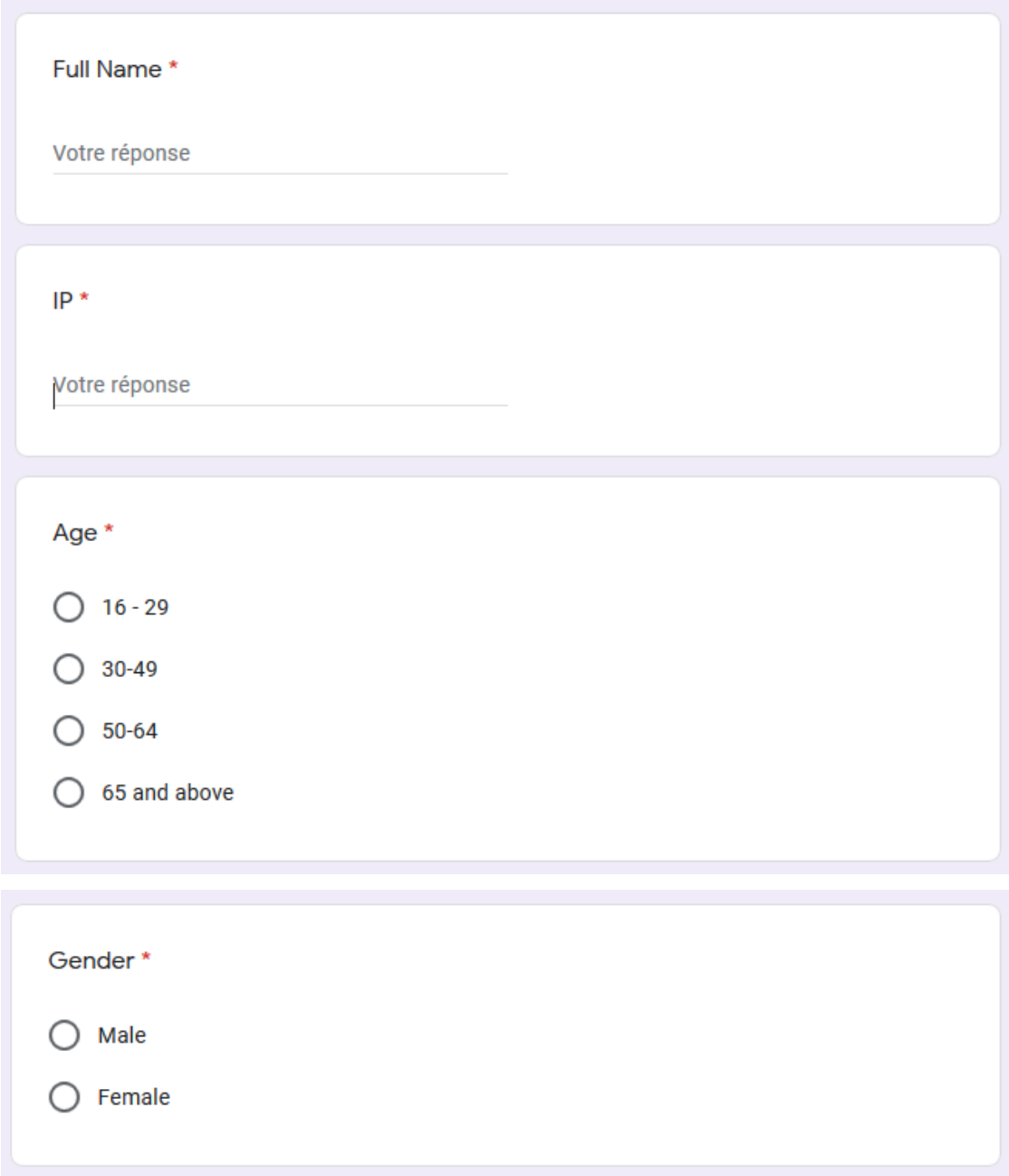
أما المضاعفات المتأخرة فكانت أمراض في الغالب دموية بشكل رئيسي ، حيث تم اكتشاف الأسباب المعدية في 10٪ من الحالات.

على الرغم من أنها لم تكن دراسة منضبطة المعشّاة، إلا أن المتابعة التي أجريناها أظهرت أن نتائج الاستجابات السريرية والبقاء الكلي كانت في صالح إضافة ريتوكسيماب إلى نظام العلاجي شوب ، دون أي زيادة ملحوظة في المضعافات الناتجة عن العلاج.

ANNEX I: OPERATING FORM

The medical operating form made via google Forms sheet.

Links:https://docs.google.com/forms/d/e/1FAIpQLSdYSxVKJ_6Re_8S07v51zJ5M_ADuSzuKAgAZ8Q4apolz6wn8A/viewform



Origin *

- ○ Fez
- ○ Out Fez
- ○ Autre : _____

health insurance

- ○ RAMD
- ○ CNSS
- ○ CNOPS
- ○ PAYABLE

PROFESSION *

Votre réponse

Personal history *

- ☐ Tobacco
- ☐ Alcoholism
- ☐ HTA
- ☐ Diabetes T1
- ☐ Diabetes T2
- ☐ TB
- ☐ HBV
- ☐ HVC
- ☐ VIH
- ☐ Radiotherapy
- ☐ Chimiotherapy
- ☐ nothing
- ☐ Autre : _____

Family History *

- [ ] TABAC
- [ ] ALCOOLISME
- [ ] HTA
- [ ] DIABETE T1
- [ ] DIABETE T2
- [ ] TB
- [ ] HBV
- [ ] HVC
- [ ] VIH
- [ ] RADIOTHERPY
- [ ] CHIMIOTHERPY
- [ ] others
- [ ] nothing
- [ ] Autre : _____

DIAGNOSIS *

- [ ] Acute leukemia
- [ ] Chronic Myeloproliferative disorders
- [ ] Chronic lymphoproliferative disorders
- [ ] Lymphomas

- ○ Primary myelofibrosis
- ○ Chronic lymphoid leukemias
- ○ Waldenstrom macroglobulinemia
- ○ Hairy cell leukemia (tricholeucocytes)
- ○ Non-Hodgkin lymphomas
- ○ Hodgkin lymphoma
- ○ NK Lymphoma
- ○ Multiple myeloma (Kahler's disease)
- ○ Others

- [ ] Splenic lymphoma
- [ ] Pulmonary lymphoma
- [ ] Others

Confirmatory test

- [ ] FBC+ BLOOD SMEAR
- [ ] BONE MARROW ASPIRATION
- [ ] BONE MARROW BIOPSY
- [ ] IMMUNOPHENOTYPE
- [ ] CARYOTYPE
- [ ] FISH
- [ ] Gasteric or intestinal Biopsy
- [ ] local biopsy

The chief complaint *

- [ ] lymphadenopathy
- [ ] SMG
- [ ] Bone pain
- [ ] Pathological fractures
- [ ] Infectious syndrome
- [ ] Abdominal pain
- [ ] Vomiting
- [ ] Rectal hemorrhage
- [ ] Melena
- [ ] Pulmonary pain
- [ ] Shortness of breath
- [ ] Caugh
- [ ] weight loss and general alteration
- [ ] Dysphagia
- [ ] Skin nodules

- [ ] Confusion syndrom
- [ ] Vertigo
- [ ] Headach
- [ ] Orl hemorrhage -epistaxia and other..-
- [ ] Testicular hypertrophie
- [ ] tumefaction
- [ ] Others

Non-Hodgkin lymphomas localisation and type

- [ ] Burkitt lymphoma
- [ ] MALT Lymphoma
- [ ] Cutaneous lymphoma
- [ ] Lymphocytique lymphoma
- [ ] Lymphoblastique lymphoma
- [ ] Anaplastique lymphoma
- [ ] Peripheral T lymphoma
- [ ] NHL
- [ ] Mantle lymphoma
- [ ] Marginal Lymphoma
- [ ] Gastric lymphoma
- [ ] Brain lymphoma
- [ ] Diffuse large B-cell lymphoma
- [ ] Follicular lymphoma
- [ ] Lymphoplasmocytic

Time prior to consultation *

- ◯ < 15 days
- ◯ 1 months
- ◯ 2 months
- ◯ 3 months
- ◯ 4 months
- ◯ 5 months
- ◯ 5month- 1 year
- ◯ > 1 year
- ◯ unknown

BLOOD COUNT

- ☐ Anemia
- ☐ Thrombocytopenia
- ☐ Thrombocytosis
- ☐ polycythemia
- ☐ Leukopenia
- ☐ Lymphocytopenia
- ☐ Lymphocytosis
- ☐ Neutropenia
- ☐ Neutrocytosis
- ☐ leukocytosis
- ☐ normal blood count

Inflammatory Markers

	HIGH	LOW	UNKNOWN
ESR(VS)	☐	☐	☐
Protein Electrophoresis (EPP)	☐	☐	☐

Blood film(smear)

	Present	Absent	unknown
BLAST	☐	☐	☐
myelemia	☐	☐	☐
Lymphocytosis	☐	☐	☐

Renal function

	Normal	High	Unknown
creatinine	☐	☐	☐
urea	☐	☐	☐
Proteinuria 24h	☐	☐	☐

Other biology test for prognosis

	Normal	High	Low	Unknown
LDH	☐	☐	☐	☐
Calcemia	☐	☐	☐	☐
Serum albumin	☐	☐	☐	☐
B2 microglobuline (>3 or not)	☐	☐	☐	☐
Bence Jones Proteinuria (+/-)	☐	☐	☐	☐
Lymphocytosis>30G/l	☐	☐	☐	☐

Markers of infection

	High	low	unknown
CRP	○	○	○

Markers of infection

	Postive	Negative	Unknown
Procalctonin	○	○	○
BK test	○	○	○

Serology

	Postive	Negative	Unknown
HBV	○	○	○
HCV	○	○	○
HIV	○	○	○
Syphilis	○	○	○

Radiology imaging

	Normal	Abnormal	Unrealized
X-ray of chest	☐	☐	☐
Transthoracic echocardiogram (ETT)	☐	☐	☐
abdominal and pelvic ultrasound	☐	☐	☐
CT Scan of Neck/Chest /Abdomen/Pelvis	☐	☐	☐
PET Scan	☐	☐	☐
Endoscopy	☐	☐	☐
Coloscopy	☐	☐	☐

Treatment of Pain

- [ ] First-tier (Palier1)
- [ ] Second-tier
- [ ] third-tier
- [ ] Association1+2
- [ ] Association 1+3

Name of the Painkiller and indication

Votre réponse

Immunotherapy (Molecules)

- [ ] Rituximab
- [ ] Imatinib
- [ ] Lenalidomide
- [ ] Bortezomib
- [ ] Dasatinib
- [ ] Nilotinib
- [ ] Trastuzumab
- [ ] Others
- [ ] not received
- [ ] Autre :

Immunotherapy (Dosage/Number of the cure)

Votre réponse

Immunotherapy duration

- ◯ <1 month
- ◯ 1-2month
- ◯ >2month
- ◯ Unknown

Immunosuppressive Drug Therapy

- ☐ Cyclophosphamide
- ☐ Vincristine
- ☐ Doxorubicin
- ☐ MTX
- ☐ Cytarabine
- ☐ Etoposide
- ☐ Others

Immunosuppressive (protocol/number of cure/dosage/duration)

Votre réponse

Corticotherapy

- ◯ bolus
- ◯ Per os (orally)

Corticotherapy dosage

Votre réponse

Response

- ○ Complete remission
- ○ Partial remission
- ○ Remain constant
- ○ Progression
- ○ Relapse

Protocols

- ☐ R-MINICHOP
- ☐ R-CHOP
- ☐ R-DHAOX
- ☐ Cop of inflitration
- ☐ R-Copadm
- ☐ R-bendamustine
- ☐ R-REGMOX
- ☐ RCD
- ☐ R-DaEPOCH
- ☐ R-FC
- ☐ R-ICE
- ☐ GRALL
- ☐ SMILE
- ☐ CHOEP
- ☐ Others

Relapse interval and evolution

Votre réponse

Complication

- [ ] Allergic skin reaction
- [ ] Autre skin problem
- [ ] Viral infection
- [ ] Bacterial infection
- [ ] fungal infection
- [ ] leuopenia
- [ ] lymphopenia
- [ ] Anemia
- [ ] Neutropenia
- [ ] Thrombopenia
- [ ] Acute leukemia
- [ ] others

Evolution >1-2 years

- ○ Death
- ○ Remission
- ○ Recurrence
- ○ Missing patient

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FACULTÉ DE MÉDECINE ET DE PHARMACIE

سنـــة 2019

أطروحة رقم 19/233

العلاج المنـــــاعـي للأورام الدمويـــــة

(بصدد 69 حالة من اللمفويات الغير الهودجكينية)

الأطروحة

قدمت و نوقشت علانية يوم 2019/12/23

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