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Review Article

General Principles of Medical Cancer Treatment

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Abstract

Cancer is a global health problem responsible for one in six deaths worldwide. Treating cancer has been a highly complex process. Conventional treatment approaches, such as surgery, chemotherapy, and radiotherapy, have been in use, while significant advances are being made in recent times, including stem cell therapy, targeted therapy, ablation therapy, nanoparticles, natural antioxidants, radionics, chemo dynamic therapy, sonodynamic therapy, and ferroptosis-based therapy. Current methods in oncology focus on the development of safe and efficient cancer nanomedicines. Stem cell therapy has brought promising efficacy in regenerating and repairing diseased or damaged tissues by targeting both primary and metastatic cancer foci, and nanoparticles brought new diagnostic and therapeutic options. Targeted therapy possessed breakthrough potential inhibiting the growth and spread of specific cancer cells, causing less damage to healthy cells. Ablation therapy has emerged as a minimally invasive procedure that burns or freezes cancers without the need for open surgery. Natural antioxidants demonstrated potential tracking down free radicals and neutralizing their harmful effects thereby treating or preventing cancer. Several new technologies are currently under research in clinical trials, and some of them have already been approved. This review presented an update on recent advances and breakthroughs in cancer therapies [1,2].

Keywords: Cancer prevention; Medical treatment; Surgery; Chemotherapy; Radiotherapy; Nanomedicines; Stem cell therapy; Ablation therapy; Natural antioxidants; Clinical trials; Surgery.

Introduction

Although deaths from cardiovascular disease outnumber deaths from cancer (36% vs. 22.5% of all deaths), cancer is one of the most feared diseases threatening mankind. Recent data from our country, Argentina, refer that in people under 30 years of age it is the second cause of death:

1. 21.7%: accidents, suicides, and urban violence.
2. 14.2%: tumors (smoking, 32% and aging)
3. 12.9%: cardiovascular diseases
4. 8.9%: infectious diseases
5. 42.3%: non typeable factors

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Objectives

- Describe the history of chemotherapeutic agents currently on the market.
- Review the mechanism of action of common chemotherapeutic classes and agents.
- Outline the most frequent adverse effects of the basic drug types, as well as some specific drug side effects.
- Identify interprofessional team strategies for improving care coordination and communication to advance cancer chemotherapy and improve outcomes [3,4]. In the United States, and already in the COVID 19 pandemic, these are the data for the year 2020.

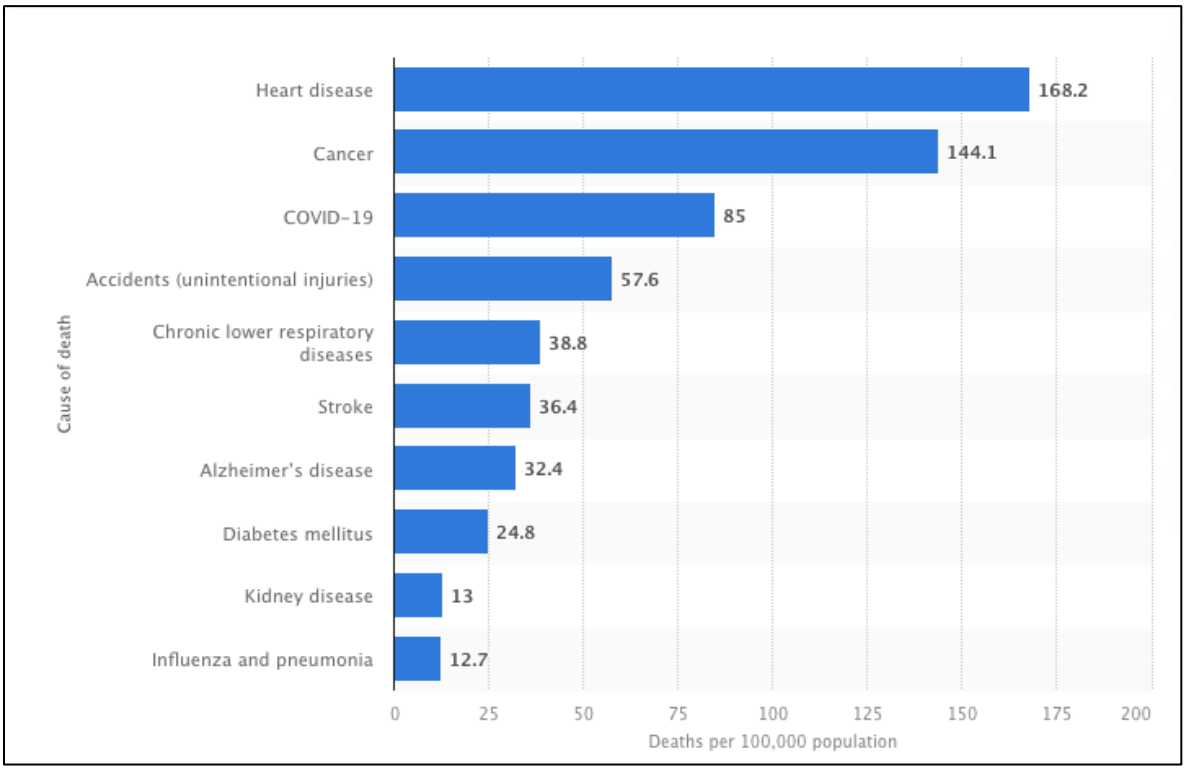

Figure 1: Rates of the 10 leading causes of death in the United States in 2020 (per 100,000 population)

The impact of this disease on the economy of the countries is extremely important and the concept of the industrialized states is to invest money in research to later save many millions. It is very likely that, thanks to molecular biology, more progress will be made in the understanding of cancer in the coming decade than in the rest of the history of medicine. Surely, we will no longer approach malignant tumors according to their location (head and neck, breast, stomach, etc.) but according to the damaged genetic pattern.

Something similar occurs in Infectious Diseases, where we not only speak of "Pneumonia", but of "Strep pneumonia" and it is based on the germ responsible for the infection that we choose the most appropriate antibiotic treatment [5,6].

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The future of cancer treatment will be based on four main pillars:

Molecular diagnosis, Functional classification of tumors (according to genetic alterations), Early treatment and more effective and less toxic therapies. Until a few years ago, neoplastic transformation was a poorly understood process, and this lack of knowledge limited the availability of solutions to the problem. The better knowledge of epidemiology and the contributions of ecology resulted in the possibility of currently stating that cancer is a predictable disease. This is so in almost 80% of the tumors that affect humans. Cancer is a disorder of genetic origin, and thus chemical, physical and/or biological changes in the genome can lead to the development of tumors. Some people can be born with abnormal DNA, inherited from the father or mother or both, and others can acquire it when their cells are exposed to carcinogenic agents, such as tobacco. Therefore, in cancer there is an interaction between genetics and the environment. Methods are already available that help us to know why these alterations in DNA occur. Some environmental chemicals are carcinogenic, and their potential has been known since Dickens's classic description of scrotal skin cancer in English chimney sweeps (chimney sweeps, at the time of the Industrial Revolution). Modification of environmental factors that are well established as causes of cancer, especially harmful habits, and dietary habits, can effectively contribute to lower cancer mortality. These are: tobacco, alcohol, ultraviolet radiation, ionizing radiation, environmental pollution, drugs, viruses, genetic factors, and diet [7,8].

Disease development

Malignant tumors are the presence of an abnormal mass of tissue within an organ, which grows independently of physiological regulatory controls and does not stop growing even when the initial stimulus that caused it disappears. Thus, at the cellular level, a tumor is the result of a stepwise process of genotypic mutations that lead to the appearance of a population of cells with "different" phenotypic characteristics within a tissue. This process, of undetermined time, is called carcinogenesis. It is noteworthy that it can have a physical, chemical, or biological origin or a mixture of them and can be divided into 4 stages: initiation: in which the cell in a heritable and constitutive manner, undergoes alterations that modify its biology; promotion, in which cell proliferation and selection occurs, tumor growth and, finally, progression, where the primary neoplasm is installed with all its characteristics of malignancy. Knowing it is important, since all prevention maneuvers are aimed at this carcinogenic process, and it has different boxes according to the tissue where the tumor will be produced. Due to the "different" characteristics mentioned above, this abnormal cell group can divide independently of tissue controls, and cause space occupation and/or metabolic phenomena within the organ that is found, thus forming the primary tumor. According to the natural history of each tumor, it is that from the primary tumor, a group of cells with characteristics of selective advantage, detach from it, travel through the blood and lymphatic stream, and develop in other organs, thus constituting the metastases or secondary growth of the tumor (Figure 2).

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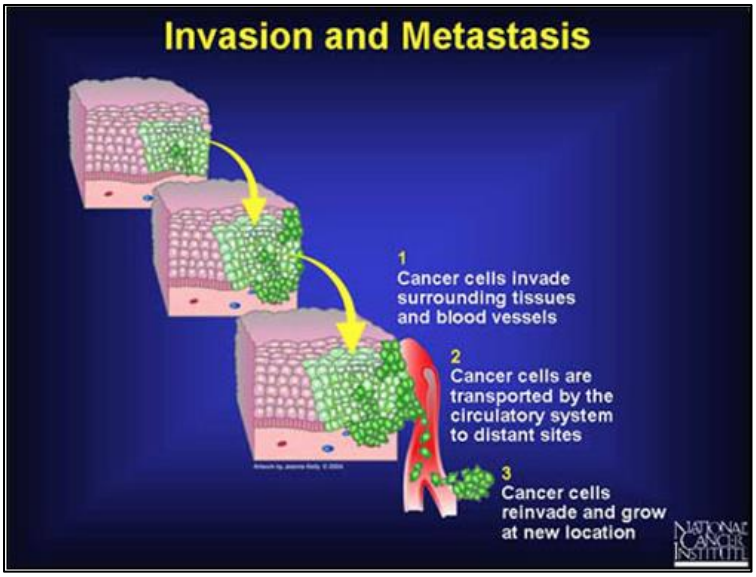

Figure 2: Invasion and Metastasis.

Metastases follow the seed-soil principle, enunciated by Paget in the 19th century, by means of which metastatic cells do not develop in any organ but in the one that has the biological soil to receive them. This has clinical relevance in the sense that it is known that certain tumors have a predilection for metastatically colonizing specific organs and not others [9]. For example: prostate cancer has a metastatic affinity for bone, generating predominantly osteoblastic metastases, soft tissue sarcomas with an affinity for metastasizing to the lungs, and breast cancer producing both bone and lung metastases. Although a voluminous primary tumor causes local and regional effects, metastases are the true paradigm of this pathology, which, if they are resistant and progress to the instituted medical treatment, are the cause of medical complications that lead the cancer patient to death.

Traditional cancer treatments

Historically, the first known and applied treatment for this disease was surgery. At that time, it was held that, with the surgical removal of the primary tumor and adjacent anatomical structures, not only local and regional control was achieved, but also systemic. Remember the historical relevance of Halsted radical mastectomy in the primary treatment of breast cancer. The rationale for this type of surgery, in which both the tumor, adjacent local structures and regional structures were removed, was based on epithelial removal tumors, since the first metastatic site is the regional lymph nodes and that from these cells with metastatic potential are shed. A few years ago, it was considered that cells traveling through the bloodstream had no further implication in the development of metastasis, moreover, of the compression of a primary tumor, there is always an outflow of cells into the bloodstream without generating the metastatic process (only 1% of a tumor population has the selective advantage of metastatic potential). But, more recently and applied to the tumor model of metastatic breast cancer, it was observed that the detection of circulating neoplastic cells before treatment has direct implications for disease-

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free survival and overall survival in these patients. Thus, surgery continues to be a first-line treatment today, less mutilating than before but generally complemented by radiotherapy and medical treatments [10,11]. A posteriori and with the advent of modern radiotherapy, this physical treatment, also local and regional like surgery, began to have its precise indications. Radiotherapy is initially used as a treatment for the disease in low-volume tumors and in those in which surgery is contraindicated due to causes inherent to the patient or in locations not accessible to the surgeon, with radical criteria, such as cavum tumors. It is also used as a complement and after surgery with the aim of increasing local and regional control of the disease, or in association with chemotherapy for both local and systemic control of the disease (chemoradiotherapy), e.g.: epidermoid tumors of the head and neck. Finally, the third therapeutic modality is medical treatment, which we will develop in this chapter, and of which chemotherapy is the best known and most widely used. Chemotherapy reduces inoperable primary tumors, a clinical situation called induction or neoadjuvant treatment, but its primary role is systemic disease control, either treating established metastases or preventing them from appearing clinically (micrometastases), the latter treatment called adjuvant, prophylactic or precautionary.

The scientific bases of medical treatment

Cancer cell biology

The appearance of tumors is directly related to the evolution of the species in question. Only animal and complex multicellular organisms can develop tumors within them. Vegetables do too. Thus, it is highlighted that, although in the etiology, tumorigenesis is a phenomenon that occurs from a single cell, in its pathogenesis, it is considered a tissue disease. Human tumors vary greatly in their properties. They originate in different tissues and may vary with respect to retention of phenotypic characteristics of the tissue of origin (this corresponds to the degree of differentiation) and in their ability to invade adjacent normal tissue and metastasize to distant sites (this corresponds to clinically with stage) [12,13].

Tumors

They originate from a single cell transformed into neoplastic, which would be the stem or stem cell, which would generate cells with identical characteristics to it and would be responsible for maintaining the tumor population. Thus, it is said that tumors are monoclonal, that is, they derive from a single clone of cells, which remains as such at least at the beginning of the natural history of a tumor. Studies of cell proliferation in animals and humans have revealed that there are 3 types of tissues:

1. Those that constantly proliferate and renew themselves: E.g.: skin and intestine.
2. Those that renew themselves slowly but do so quickly in the face of an injury. E.g., lung, kidney, and liver.
3. Those that are static such as the nervous system and the muscle.

As in normal tissues, in tumors there would be a stem or precursor cell, which would cause the expansion of the altered cell clone, leaving then in the tumor population stem cells, responsible for cell growth and non-clonal malignant cells, which would fulfill regulatory functions. The best biological

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evidence of tumor clonality derives from the knowledge of a bone marrow pathology that we know as chronic myeloid leukemia. This disease has a chromosomal marker called the Philadelphia chromosome (Ph 1) (Figure 3).

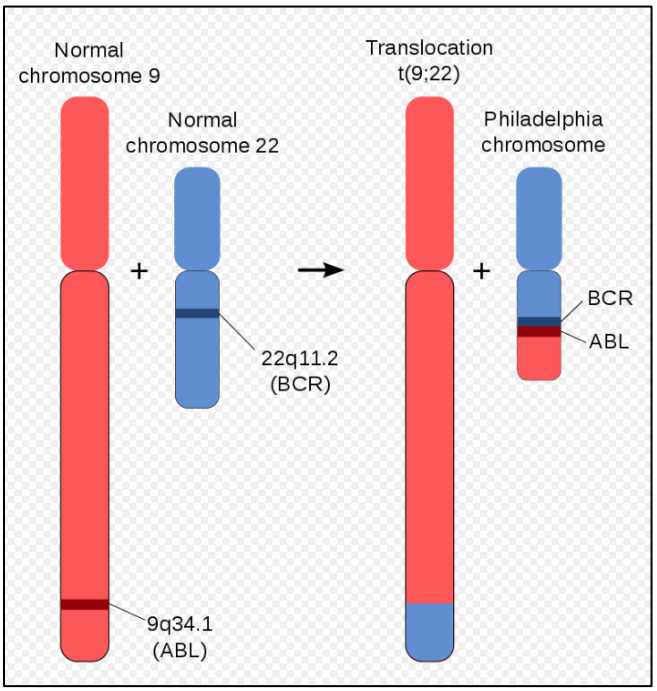

Figure 3: Chronic myeloid leukemia marker: Philadelphia chromosome (Ph 1).

This aberrant chromosome arises from abnormal reciprocal translocation between the long arm of chromosome 9 and the long arm of chromosome 22, t(9;22). At the subcellular level, this gene-chromosomal translocation produces the juxtaposition of two genes. The c-abl proto-oncogene (normal cellular homolog of Abelson murine leukemia virus: ABL) is located on chromosome 9. The other gene involved on chromosome 22 is a region called BCR (break point cluster region) [14,15]. The BCR-ABL fusion results in the activation of the c-abl proto-oncogene to its active oncogenic conformation to initiate tumorigenesis. This Ph 1 chromosome marker is also present in identical form in the precursors of erythrocytes and in those of megakaryocytes, leading to the relevant conclusion that the one affected by the pathology is the pluripotent marrow stem or staminal cell. Finally, it should be noted that stem cells have 2 critical functions: the first is that they generate a large family of descendants that develop the function of the tissue in which they are found. The second is that they must have the property of self-perpetuation, preventing their number from decreasing due to the differentiation process. The application of the stem cell model to tumor biology has important clinical implications for treatment. With curative intent, the treatment used must eradicate all stem cells of the tumor.

Phenotypic characteristics of the tumor cell

One of the biggest current problems in the medical treatment of cancer is that the tumor cell is very similar in its phenotypic characteristics to the normal one, in fact

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under the electron microscope they are almost identical. Differences in appearance (phenotype) can be seen under the light microscope and include the presence of giant nuclei, prominent nucleoli, large numbers of atypical mitotic figures (Figure 4).

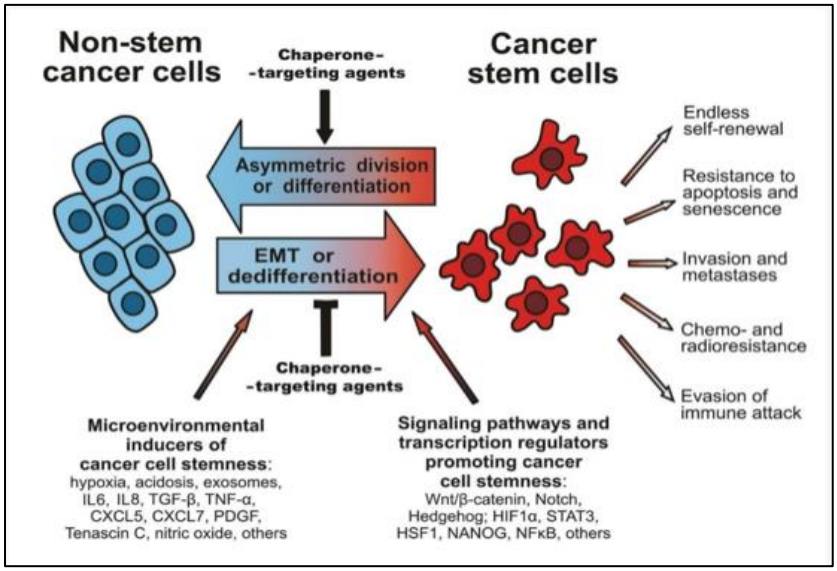

Figure 4: Department of Pathology, Erasmus MC Cancer Institute, Erasmus University Medical Center, 3015 GD Rotterdam, The Netherlands.

Due to the similarity between the two, it follows that the cell targets to be explored are very similar in both, thus there is a lack of "treatment-oriented" selectivity. If we analyze at a higher organizational level, the problem is generated in that there are no "cancer-specific" processes e.g., of it: inflammation and cancer share similar biochemistries; metastases and macrophage migration. Biochemically, the tumor cell has less oxygen requirement than the normal one, speaking this phenomenon of an increase in the anaerobic glycolytic pathway (Warburg). Thus, the enzyme LDH (lactic dehydrogenase) that catalyzes this pathway (passage from pyruvate to lactate) is found to have increased activity in certain tumors, with the then therapeutic implication of plasmatic LDH, as a marker of tumor load, e.g.: tumor of Ewing, lymphomas, etc. Also, protein synthesis is increased since structural proteins are required for cell division. At the level of tissue cultures, the tumor cell has interesting edges for its study. In them, it generates continuous or established cell lines in relation to loss of contact inhibition unlike normal cell cultures in which when a cell comes into contact with another cell movement and division ceases. Also, the tumor cell can grow in cultures without solid substrates and thus generate several polyp layers in the cultures [16]. Another characteristic of malignancy is the production of plasminogen activator in culture, which, by transforming it into plasmin, can break down fibrin and therefore act in the processes of invasion and metastasis. In neoplastic cells there are the denomined oncogenes (genes that, activated from proto-oncogenes, can produce cell transformation in culture) and tumor suppressor genes or antioncogenes. These genes have been conserved during

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evolution and are generally different according to tumor types. They code for the formation of cellular proteins called growth factors. Examples of oncogenes: K-ras in lung adenocarcinoma, N-myc in neuroblastoma, etc., and the prognosis of the neoplasm often depends on their expression. Ex: tumor suppressor genes: P 53 (called the guardian of the genome) whose absence or mutation in several tumor types is related to prognosis and evolution. The cells have a control regarding their growth that can be autocrine or paracrine, that is, protein factors are released that can stimulate their own growth or to stimulate neighboring cells (Figure 5).

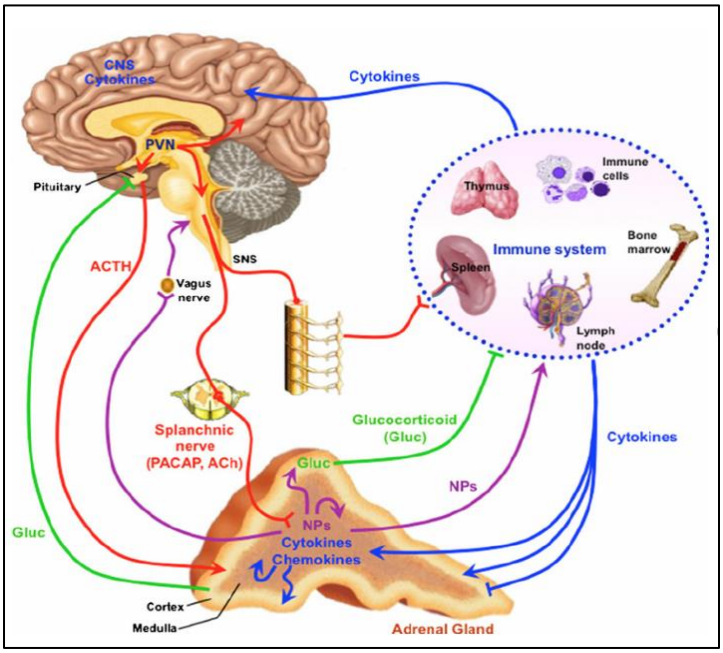

Figure 5: These factors were isolated for the first time in the nervous system, and it was called NGF (nerve growth factor).

Subsequently, they were found in other cell types and were called growth factors (GF). They present a receptor at the membrane level, to which they bind and from this union the factor-receptor complex is internalized in the cell and at the cytosol level it is split into its 2 components, of which the CF will produce its effects through its interaction indirectly with the cellular genome. This receptor has clinical-therapeutic implications since it is a target of action of monoclonal antibodies [17,18]. Both normal and tumor cells secrete FC, but the latter would secrete somewhat modified factors, or else the difference would be quantitative, the tumor cells would secrete a greater quantity. Another postulated mechanism would be that in tumor cells, due to receptor mutation, the binding of FC to the receptor would be more stable, with the consequent greater stimulation of cell growth. The CFs can then be encoded by oncogenes, or on the other hand, in their protein structure bear similarities with certain regions of other proteins encoded by them.

Several of them are known

- EGF: epidermal growth factor, responsible for the growth of

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ectodermal and endodermal epithelial tissues.

- Alpha TGF (Transforming Growth Factor) also stimulator at epithelial level, fundamentally of glandular type structure.
- Beta TGF which is a growth inhibitor.
- PDGF (platelet derived growth factor).
- VEGF (vascular endothelial growth factor) associated with normal and tumor neoangiogenic.
- FGF (fibroblast growth factor), important in stroma-epithelium interactions, e.g., in the genesis of prostate cancer.
- IGF 1 and 2 (insulin-like growth factor) present in breast cancer and osteosarcomas.

Cellular cycle

Knowledge of it is important not only because of its relationship with the kinetics of cell populations, but also because it is the target of classical chemotherapy treatments. Cancer is a disease of the cell cycle; tumor cells proliferate under conditions in which normal cells do not. In other words, the cancer cell's replication has become uncoupled from the signals that normally prevent it from dividing. We know from biology that a stem cell originates 2 daughter cells equal and to the stem cell that originated them. Also, that the progression in cell division is geometric (2,4,8,16,32,64, etc.). The is relevant when applied to the life of a single cell, thus the cell cycle of a cell represents all the phenomena that occur to a cell from its birth until it divides into two daughter cells. This cycle is finely regulated by proteins that manage cell proliferation. To study the events in this cycle, Howard and Pelc in 1951 divided it into periods and phases (Figure 6).

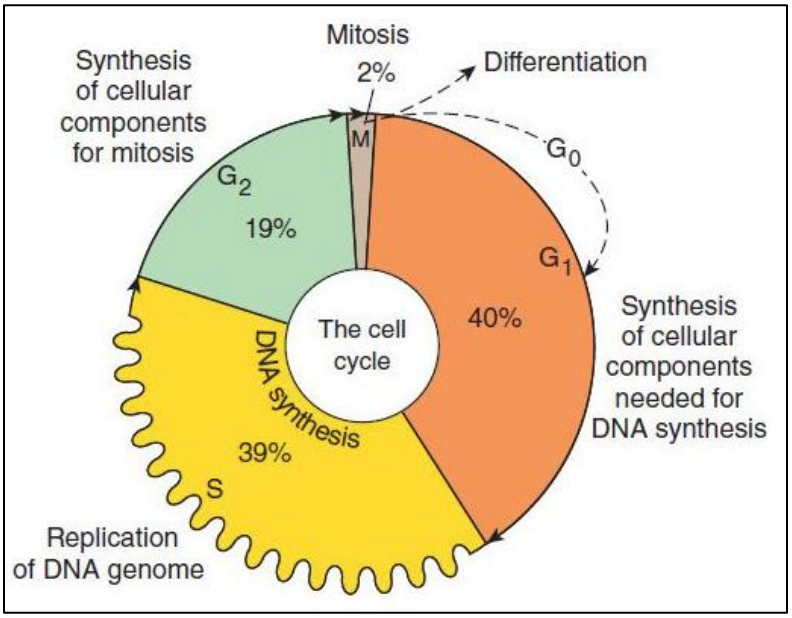

Figure 6: Cell Division.

After cell division, the cell enters a period called G1 (G of Gap) which is the most variable of the cell cycle. In some cells such as neurons, muscle, and adult cartilage, it lasts a

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lifetime, and this period is called Go (this also refers to cells that are quiescent or in a latency period). In G1 the cell synthesizes proteins and normally carries out its metabolic pathways. Then by protein stimulation, the cell passes from G1 to S (S phase of synthesis), in this phase the duplication of DNA and other structures such as histones (basic proteins bound to DNA) and RNA occurs.

This phase was initially studied using thymidine bound to tritium (3H), a radioactive isotope of H, and easily identified by radioautography. It is important that the duplication is carried out correctly because use the duplicated structures, they must be distributed equally in both daughter cells [19-21]. The duration of S varies according to the tissue and clinicopathological situation: in normal skin it is 16 hours, in psoriasis it is 8 hours, in squamous cell carcinoma it is 11 to 12 hours and in basal cell carcinoma it is 20 hours. The S phase is followed by the G2 period, which is characterized by synthesizing RNA and Proteins; in the gametes by rearranging the DNA altered by the exchange of chromatids, and it lasts between 1 and 7 hours. It is the premycotic period. G2 is followed by the M or mitotic period, with its 4 phases and from which two daughter cells are generated from telophase, which will re-enter a new cycle, or go to maturation which, if total, leads to the cell to programmed death (apoptosis), or they can remain in Go, which corresponds to a period of apparent rest, without DNA duplication, but from which the cell can exit and rejoin the cell cycle. The duration of M varies according to the different fabrics, from 30 minutes to 2 and a half hours. During this phase, protein synthesis is minimal, while RNA is synthesized at the beginning of prophase and at the end of telophase. The sum of the times of the different phases is called cell time, and through this we can determine the duration of G1 that corresponds to the most variable phase of the cycle. Biochemical regulation of the cell cycle is mediated by proteins called cyclins, or CDKS (cyclin kinase). These proteins are made up of a cyclin regulatory subunit and a kinase catalytic subunit (enzymes that work with ATP). During G1, the CDKS are activated by the mitogenic stimulus and thus phosphorylate other proteins responsible for cycle progression.

This occurs in a similar way in each of the phases of the cycle. In turn, this activation reaction is regulated by proteins that inhibit the CDKS, which are the CKIs (cyclin inhibitor proteins). CDKS are currently being studied as therapeutic targets. Tumors retain many characteristics of growing and renewing cell populations. There are cells within the tumor that have less proliferative capacity and show a differentiation phenotype. However, tumor stem cells are the main target of antitumor treatments and in tissue culture they express all the characteristics of their malignant potential. Tumor cells have a high mutation rate, and selection of mutant subclones with a selective growth advantage leads to tumor progression to a more malignant phenotype (metastatic disease). As the population grows, spontaneous mutations occur that lead to cellular heterogeneity. The latter has therapeutic implications in the sense that one of the failures of antineoplastic treatment may arise from cellular heterogeneity. Ex: in a population there are cells A,B,C,D,E,F,G. If cytostatic kill population A, B, C, D, leaving E, F and G, these will mark resistance to treatment and tumor progression.

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Cell Kinetics Concepts

Tumors grow because they contain a population of cells that expands because of cell division. This abnormal growth occurs because the homeostatic control mechanisms that maintain an appropriate cell number in a normal population are defective. The development of tritiated thymidine with autoradiography and the more recent development of flow cytometry have allowed a detailed analysis of tumor growth in terms of cell proliferation kinetics.

The rate of proliferation varies among tumors; cells in the no proliferative compartment are common, and there is often a high rate of cell death. The proliferation rate in tumors is a relevant prognostic factor and will also indicate the response to radiotherapy and chemotherapy treatment. While the concept of drug resistance is very important, the concept of drug resistance by normal tissues does not exist and that makes toxicities the limiting treatment at times [22].

In a tumor population there are 3 compartments: Proliferative, No proliferative and of differentiation. When, due to treatments, the cell number decreases in the proliferative compartment, the non-proliferative cells must repopulate the first one.

Skipper's Laws

Several decades ago, Skipper developed a series of experiments in the L 1210 murine leukemia model, which had an important extrapolation to the concepts of antitumor chemotherapy. These laws still in force today (although modified by Gompertzian growth), reveal that in the L1210, the cells are in exponential growth, all cells divide and are in cycle, without resting cells or Go, and the cell number doubles depending on the tumor. Thus, in tumors with cells in Go, this is applicable for cells in the proliferative compartment only.

The first of Skipper's laws states that the cell doubling time of proliferating cells is constant, forming a straight line on a semilogarithmic scale. In this model, it was shown that a single surviving cell implies treatment failure. The second law states that cell death by drugs follows first order kinetics, the percentage of cells killed by a dose in a tumor is a constant, regardless of tumor mass.

The latter has clinical relevance in the sense that since cytostatic kill tumor cells in a percentage and constant manner, if 99.9% of a tumor cell population dies due to treatment, the remaining percentage would be responsible for relapse. of the tumor (or cellular persistence at the molecular level).

Growth fraction

Presumably, the model developed by Skipper applies to a tumor curable by chemotherapy, such as a testicular tumor or Burkitt's lymphoma. But, in the situation of other tumors these principles cannot be applied. In solid tumors, Skipper's laws apply to the proliferative compartment of a tumor. Thus, in 1960 J. Mendelsohn proposed the concept of growth fraction for the population of stem cells responsible for growth within a tumor (proliferative compartment). Contrary to popular belief, numerous studies reveal that the growth fraction is greater in normal tissues (another item related to toxicity) than in tumor tissues. The growth fraction becomes clinically relevant in the early treatment of micro metastatic disease, which are treated in a precautionary manner with

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adjuvant chemotherapy, e.g.: breast cancer, osteosarcoma, soft tissue sarcoma, colorectal carcinoma [23,24].

Gompertzian growth

Most human tumors show growth other than Skipper's curve at L 1210. They follow a curve called Gompertzian, which describes an increasing cell population due to birth and a decreasing cell population due to cell death. Gompertzian growth is presented as a sigmoid curve, first exponential and then logarithmic growth (Figure 7).

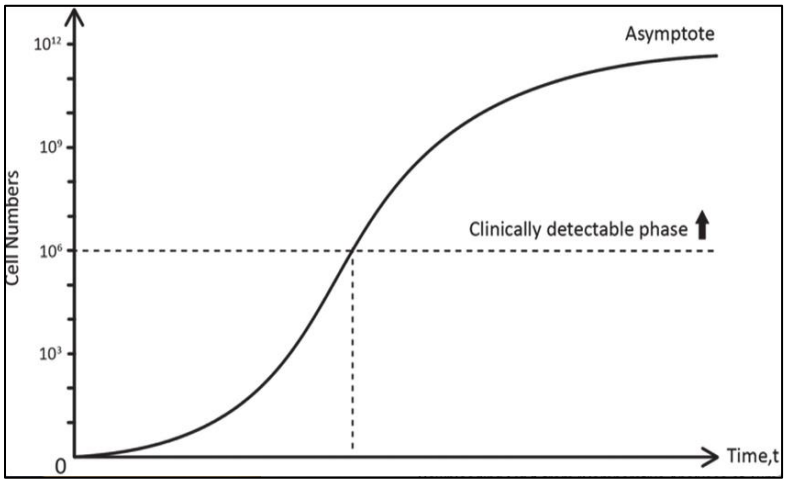

Figure 7: Gompertzian growth is presented as a sigmoid curve, first exponential and then logarithmic growth.

At first, the number of cells accumulate slowly, because the number of dividing cells is small, then there is a rapid accumulation of cells that reach maximum growth in about one third of the maximum tumor volume. This is followed by a gradual slowing in growth rate to a plateau as the tumor reaches a volume that is incompatible with life. In the exponential growth phase of the present model, we witness a subclinical stage with approximately 106 cells. When the tumor reaches 109 cells, it weighs 1 gram and is clinically detectable (equivalent to 1cm3). Then, in the plateau phase, the tumor grows by accumulation (lack of cell death) until it reaches 109 cells and weighs 1 kg, which is incurable by any treatment. It is known that a solid tumor must go through about 30 to 33 doublings in volume from a single cell before it reaches a detectable size of 1 to 10 g. Metastases appear to have been established before detection of the primary tumor. Then with a few doublings in volume, the tumor reaches a size that is incompatible with life (1 kg, 1012 cells). Cell kinetics studies suggest that cell cycle-dependent resistance to chemotherapy increases with tumor size and loss of exponential growth characteristics. Resistance is a general term that describes the insensitivity of tumors to treatment [25,26]. An important mechanism that can be analyzed mathematically is the acquisition of spontaneous resistance to chemotherapy. This process is believed to stem specifically from alterations in the genome, which are then preserved during mitosis, and may confer either specific or general resistance to chemotherapeutic agents. Goldie and Colman (1979 and 1983) have studied this process mathematically and have obtained

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conclusions applicable to the treatment of human and animal cancer (Figure 8).

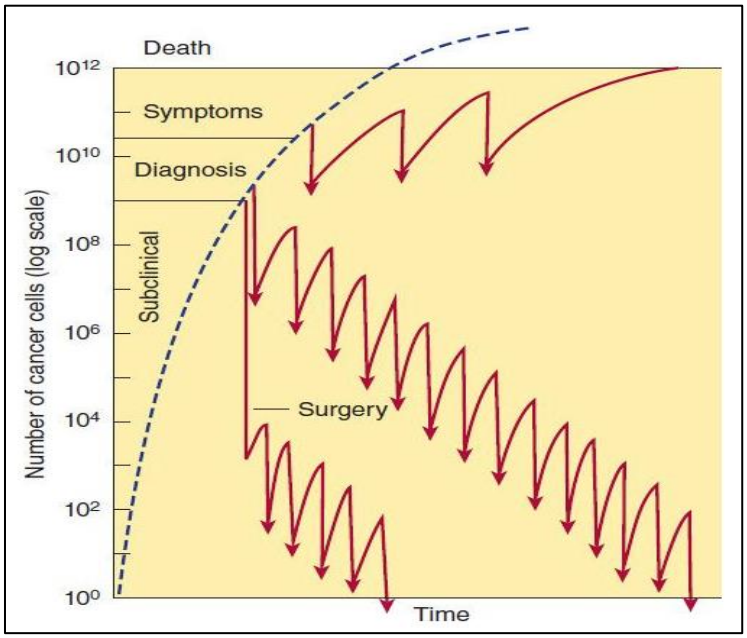

Figure 8: Mathematically conclusions applicable to the treatment of human and animal cancer.

The models made suggest

- Sensitive stem cells spontaneously mutate to a state of permanent drug resistance with a given probability per division, which is a function of drug dose and tumor aggressiveness, often referred to as the mutation rate.
- Resistant stem cells and sensitive cells divide and grow at the same rate.
- Each cell can have unlimited proliferation.

Using these assumptions, it is possible to calculate the number of chemo resistant cells, as a function of mutation rate and tumor size. According to this model, the presence of any resistant cell is sufficient to cause therapeutic failure. However, not every cell is capable of unlimited proliferation, and tumors are considered in part, as we saw earlier, stem cell systems like many normal tissue systems. Stem cells can divide to form either two new stem cells or two transitional cells. Also, it is not clear that all stem cell systems behave in this way. In some of them, it has been postulated that the stem cells divide to form two new staminal cells (birth) or one transitional and one staminal cell (renewal). Goldie and Colman, based on their model to consider resistance, suggest that it can be demonstrated mathematically, by analyzing 3 rates: Birth rate, Renewal fee and Rate of cell death.

Tumor staging

Staging a tumor is evaluating its extension. Between 1943 and 1952, Pierre Denoix developed a system for the classification of malignant tumors, called TNM. The T (tumor) describes the extent and size of the primary tumor; the N (node) the absence or presence and extension of the metastases in the regional lymph nodes; and the M (metastasis) the absence or presence of

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metastasis. Since 1950, when the UICC (International Union Against Cancer) appointed a committee on tumor nomenclature and statistics, the TNM system has been constantly updated. The TNM is primarily clinical, but there is a pathological TNM, putting the letter p before each component (Figure 9). There is a TNM for each site within an anatomical region and the association of each T, with the N and with the M gives rise to the stage of the tumor [27].

TNM 8th - Primary tumor characteristics	
T_x	Tumor in sputum/bronchial washings but not be assessed in imaging or bronchoscopy
T_0	No evidence of tumor
T_{is}	Carcinoma in situ
T_1	≤ 3 cm surrounded by lung/visceral pleura, not involving main bronchus
$T_{1a(mi)}$	Minimally invasive carcinoma
T_{1a}	≤ 1 cm
T_{1b}	> 1 to ≤ 2 cm
T_{1c}	> 2 to ≤ 3 cm
T_2	> 3 to ≤ 5 cm *or* involvement of main bronchus without carina, regardless of distance from carina or invasion visceral pleural *or* atelectasis or post obstructive pneumonitis extending to hilum
T_{2a}	>3 to ≤4cm
T_{2b}	>4 to ≤5cm
T_3	>5 to ≤7cm in greatest dimension *or* tumor of any size that involves chest wall, pericardium, phrenic nerve *or* satellite nodules in the same lobe
T_4	> 7cm in greatest dimension *or* any tumor with invasion of mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, oesophagus, spine *or* separate tumor in different lobe of ipsilateral lung
N_1	Ipsilateral peribronchial and/or hilar nodes and intrapulmonary nodes
2	Ipsilateral mediastinal and/or subcarinal nodes
3	Contralateral mediastinal or hilar; ipsilateral/contralateral scalene/ supraclavicular
M_1	Distant metastasis
M_{1a}	Tumor in contralateral lung or pleural/pericardial nodule/malignant effusion
M_{1b}	Single extrathoracic metastasis, including single non-regional lymphnode
M_{1c}	Multiple extrathoracic metastases in one or more organs

Figure 9: TNM 8th-Primary tumor characteristics.

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Measurement of antineoplastic treatment responses

To evaluate the therapeutic efficacy of medical treatments, we measure in Clinical Oncology what are called antitumor responses.mAlthough in hematological tumors the measurement of the same is different from that of solid tumors, we will develop here the responses in solid tumors. Complete response (CR): total disappearance of the pre-existing measurable mass for a minimum period of one month.

- Partial response (PR) > 50%: reduction of the largest diameters of the tumor in a percentage greater than 50% for a minimum period of one month.
- Partial response < 50%: reduction of the largest diameters of the tumor in a percentage < 50% for a minimum period of one month.
- Stable disease: no change in tumor measurements or no greater than 25% increase in pre-existing lesions.
- Disease progression: increase in the diameter of the pre-existing mass or increase of more than 25% of the pre-existing lesions.

The sum of CR + PR is called objective response (OR) although there are authors who call it global response (GR) and it is relevant in the evaluation of medical treatments. Although the response to treatment is clinical and iconographic, it is also evaluated anatomopathological. The decrease in plasma levels of certain molecules called biological markers can also be considered as responses, e.g., prostate-specific antigen (PSA) in prostate cancer. In leukemias, the molecular concept of minimal residual disease after treatment is very important.

Chemotherapy: biological properties of antineoplastic Agents

Cytostatic are drugs that slow down the growth of tumor cells in the sense that they are programmed to die (apoptosis or programmed cell death) or destroy them directly, causing death after their administration (necrosis). The first historical precedent for the use of antineoplastic chemotherapy dates to 1942, when nitrogen mustard was used to improve symptoms in a patient with lymphoma (Gilman, 1963). This is a unique event, as an experimental concept, lymphatic aplasia in rabbits receiving nitrogen mustard, was transferred to the patient's clinic. There are currently more than 60 cytostatic agents on the market (excluding antihormonal compounds) and others are in Clinical Trials. They can be classified according to their origin or their mechanism of action. From the pharmacological point of view, they are specific but not selective drugs. Specific in the sense that they have a target that is the tumor cell and non-selective, given that they can act on all tissues and cellular systems, hence the toxicity of chemotherapy. Thus, cytostatic have their limiting toxicity in rapidly growing tissues such as the bone marrow (myelosuppression, thrombocytopenia, and anemia) and the intestine. In high-dose chemotherapy schemes (bone marrow transplant), with the aim of overcoming tumor resistance, the organ that is the focus of toxicity is the bone marrow, and for this, growth factors are now available to produce the regeneration of the medullar precursors after the mentioned chemotherapy (G-CSF; GM-CSF; erythropoietin; interleukin-6) [28].

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Routes of administration of cytostatic

The main routes of administration are intravenous and oral. But other routes can be used in special clinical situations such as intraarterial, intrapleural, intraperitoneal, intraspinal (S.N.C.). The route and technique of administration of a drug are important determinants of its concentration and the time of exposure to cytotoxic levels, both at the site of therapeutic action and at the systemic level. In local administration, the drug is placed at the site of action, from where it is absorbed. Ideally, the area under the concentration-time curve (AUC) at the site of application is greater than the systemic AUC, that is, the total amount of drug that passes through the site of action is greater than the total amount of drug that passes through the site of action. reaches the systemic circulation. In the case of intraperitoneal administration, since the veins that drain the peritoneum are tributaries of the portal vein, if drugs with high hepatic extraction are applied intraperitoneally, they are absorbed and, passing through the liver, are eliminated at least partially before to reach the systemic circulation. In this way, the AUC in the peritoneal fluid is greater than the systemic AUC. The intra-arterial administration of drugs generally only achieves the minor objective: higher local peak than systemic Ex: hepatic intra-arterial route in the treatment of liver metastases resistant to systemic chemotherapy. Local administration is almost always used in cases of advanced tumors without a curative objective. But, in some cases, the objective to obtain is more than palliative, as is the case of Mitomycin-C with activated carbon particles at the peritoneal level, to avoid peritoneal carcinomatosis after total gastrectomy. The intravenous route is the most widely used clinically. Administration can be done as a bolus or push, in which case the drug fluctuates between a peak and a valley, or as a continuous infusion where levels are maintained approximately constant. Peaks are necessary for an optimal therapeutic effect: bolus administration is irreplaceable, continuous intravenous infusion at a rate sufficient to obtain peak-like levels implies a large increase in AUC, generally accompanied by unacceptable toxicity. The values are sufficient to obtain the desired therapeutic effect: intravenous infusion will allow these levels to be maintained with a smaller amount of drug (lower AUC), if toxicity depends, at least partially, on serum peaks, continuous infusion can achieve a lower toxicity. The therapeutic effect depends on the ABC: the infusion must be carried out at such a rate that the ABC obtained is equal to the sum of the ABC corresponding to the successive boluses, thus continuous infusion is useful whenever it can Beak-related toxicity can be avoided. Serum peaks are higher the higher the bolus injection rate. Very high peaks are generally associated with increased toxicity without increased therapeutic efficacy. For this reason, slow boluses are preferred, often in the form of a short-term infusion, they are administered intermittently, they behave from the pharmacokinetic point of view, as intravenous boluses, and not as continuous infusions [29]. As for another chapter such as chrono pharmacology, the treatment schedule has been shown to have less toxicity with certain drugs in certain types of tumors. There are circadian variations in pharmacokinetics. Fluorouracil, for example, reveals greater efficacy when administered as a continuous infusion between 10 am. at 4 p.m. But this has been observed in a single

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tumor model and refractory to other lines of treatment (colorectal carcinoma). Cisplatin is less emetogenic if administered in the evening than in the morning.

Chemotherapy with a single drug (mono chemotherapy) or with combinations of drugs (polychemotherapy)

In the early days of chemotherapy, it was used with a single cytostatic agent. Even so, significant responses were obtained in certain tumors, reaching complete responses in some of them, such as female chorionic carcinoma. The important thing about it was that the tumor is simply sensitive. But, from the possibility of using a single cell target, the concept of a greater possibility of collateral resistance arises. Thus, although initially empirical, combined chemotherapy emerged (E. Frei III). It presents different drugs with different mechanisms of action, different cellular chemical targets with additive and probably synergistic effects. Even though the latter (synergy) is very difficult to demonstrate experimentally. The combination schemes cured advanced tumors, such as testicular germ cell tumors, female chorionic carcinoma, Burkitt's lymphoma, acute lymphoblastic leukemia, among others. To reach a cure, they present 100% complete lasting responses, which becomes a cure if the patient is disease-free at 5 years. Another concept of this chemotherapy modality is that drugs with different limiting toxicities are used, which, although the most frequent limitation is myelosuppression, the doses of the drugs used can be reduced, reducing the toxicities and without therefore presenting a detriment in the antitumor response. Drugs with different resistance patterns must be associated, but it is also interesting to know that with the combination of agent's metabolic pathways can be blocked sequentially, e.g.: Hydroxyurea and Cytosine Arabinoside; the antitumor action can be modulated, as in the case of folinic acid or leucovorin, which increases the activity of fluorouracil and that the treatment of advanced and adjuvant disease of colorectal carcinoma emerged from this combination. An important milestone in Oncology was the administration of high doses of Methotrexate (MTX) with leucovorin rescue in osteosarcoma. In relation to high doses of MTX, a resistance is overcome directly due to a relative decrease in the target (dihydrofolic reductase enzyme) that cannot be overcome at conventional doses of MTX. It is important to emphasize that the ideal is to administer maximum doses of drugs with the shortest interval possible, to avoid resistance due to increased cell repopulation of the proliferative compartment.

Currently, conventional chemotherapy is combined with cell target therapy (targeted), to enhance the effects of both, taking advantage of the fact that the toxicities of targeted therapies are manageable. Essential requirements to start a cycle of chemotherapy are residual or metastatic disease proven by biopsy, indicator lesion (except in the case of adjuvant chemotherapy), good performance status score and nutritional status, good marrow reserve, and renal and hepatic functions within of physiological ranges [30]. Finally, the principles of combination chemotherapy are:

1. Only those agents that have been shown to be effective individually are to be used.
2. Each drug used must have a different mechanism of action.

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3. Each drug must have a different pattern of toxicity.
4. Each drug must be used in its maximum dose.
5. Drugs with a similar type of limiting toxicity can be combined only by reducing the doses of both, resulting in a decrease in toxic effects.
6. Combined drugs should be administered in the shortest time interval between cycles to maintain their efficacy and allow normal tissue repair.

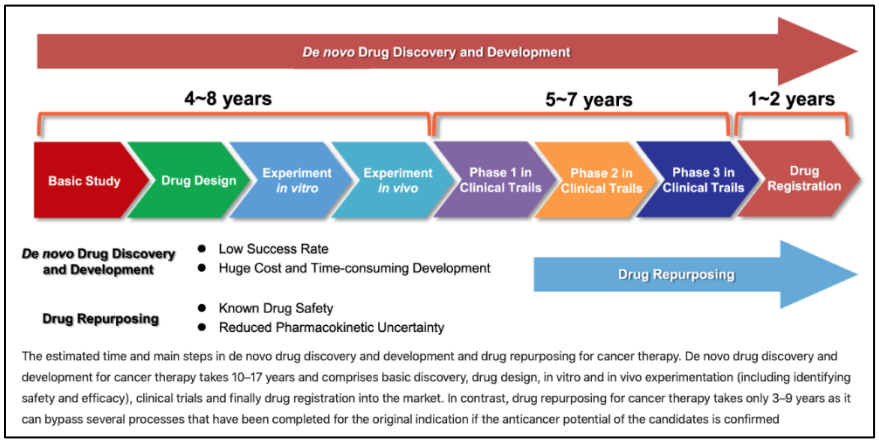

Figure 10: Evaluation of chemotherapeutic agents.

Compounds to be tested with probable antineoplastic activity arise from various sources. Some are synthetic, some are semi-synthetic, and some are natural products isolated from plants or microorganisms. They are frequently sent for initial evaluation by universities and companies to laboratories. The largest program is at the NCI (National Cancer Institute, USA). The first evaluation system is critical because it represents the key for the future testing or discarding of the drug. The evaluation can be divided into three stages:

- In vitro stage, known as pre-evaluation.
- In vivo stage, in which the first model used is known as the primary evaluation.
- Secondary evaluation, which includes the spectrum of antitumor activity using various in vivo tumor models, activity in advanced disease, administration route and schedule studies, evaluation of cross-resistance and combination chemotherapy studies [31].

The production and formulation steps must be completed before the toxicological evaluation, since the toxicological phase must be carried out with the formulation used for clinical studies. The last preclinical step is the toxicological evaluation. It is extremely structured and codified and its purpose is to determine a safe starting clinical dose and the nature, degree, and reversibility of toxicities. Other studies that are carried out in the same phase include: pharmacology, pharmacokinetics, and mechanism of action. These studies will be able to determine the basic mechanism of action of the drug and whether it or a metabolite is the active agent. The information obtained from the scheme

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used in animal pharmacology, the disposition of the drug and/or metabolite, the main routes of excretion, and the toxicology, will be used to determine the appropriate scheme for Phase I studies, and patient selection. Finally, and if the compound has passed all the previously mentioned stages, it will enter clinical evaluation (Phases I-IV), and if approved, the drug will enter general medical practice. The time it takes from obtaining a compound to its use in clinical practice is around 10 years. In the early 20th century, most drug evaluation was done in vivo using murine tumors such as sarcoma 37, sarcoma 180, carcinoma 755, and leukemia 1210. Between 1955 and 1985, the NCI, with its new drug research program, focused on the use of two models of murine leukemia, L1210 (before 1975) and P388 after 1975. In 1975, the NCI introduced new murine solid tumors to its evaluation panel, as well as human tumors that grow in nude mice. (Mice with a complete absence of the T lymphocyte system which then allows the growth of tumors within it). Then in 1983 the renal capsule model was used for tumor growth. About 40 clinically useful compounds were obtained by chance, rational synthesis, or astute observations, using the animal tumor models.

In vivo evaluation models (NCI)

- 1935: Sarcoma 37
- 1955: Sarcoma 180.Leukemia L1210.Carcinoma 755.
- 1960: L1210 + 2 models from a pool of 21.
- 1965: L1210 + Carcinosarcoma of Walter 256.
- 1968: L1210 for synthetic products; L1210 and P388 for natural products.
- 1972: L1210 for synthetic products; P388 for natural products; B16 melanoma and Lewis lung carcinoma.
- 1975: Pre-evaluation: P388.
- 2nd stage: murine tumors (CD8F1, C38, B16, LL, L1210).
- Xenotransplant human tumors: MX-1, LX-1, CX-1
- 1983: Pre-evaluation: P388.
- 2nd stage: L1210, B16, M5076, MX-1
- 3rd stage: L1210, B16, M5076, CD8F1, C38, MX-1.

The excessive cost of in vivo evaluation has led to in vitro assays, since they were used to reduce the number of agents to be tested in vivo. A wide variety have been used, generally measuring a single response parameter as the target. The most widely used are microbial inhibition tests, such as highly sensitive gram+ germs, DNA repair-deficient mutant, phage tests for DNA, RNA, protein synthesis inhibition, tubulin binding, and circular DNA interaction [32]. Enzymatic assays are also widely used, with the aim of interfering with or inhibiting the following enzymes: aminopeptidase, esterase, phosphodiesterase, beta galactosidase, S-adenosylmethionine decarboxylase, phospholipase, dihydrofolate reductase, DNA gyrase, reverse transcriptase, ornithine decarboxylase, adenosine deaminase, tyrosine hydroxylase, topoisomerases. At the tissue culture level, the screening group includes cytotoxicity assays using continuous or established cell lines KB, L1210, phase-specific stage using synchronized cell populations, malignant transformation assays using normal fibroblasts transformed by carcinogenic or oncogenic viruses, and clonogenic with human tumors. Due to advances in molecular biology in the last decade, other targets and

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agents were created. These include cell membrane and signaling at its level, inhibitors of growth factors, products of oncogenes, protein kinases, and other proteins involved in malignant transformation and maintenance of the transformed phenotype. In vivo studies require pre-established models such as tumor implantation in the renal capsule, the use of nude mice, when new drugs are tested. At the tissue culture level, the screening group includes cytotoxicity assays using continuous or established cell lines KB, L1210, phase-specific stage using synchronized cell populations, malignant transformation assays using normal fibroblasts transformed by carcinogenic or oncogenic viruses, and clonogenic with human tumors. Due to advances in molecular biology in the last decade, other targets and agents were created. These include cell membrane and signaling at its level, inhibitors of growth factors, products of oncogenes, protein kinases, and other proteins involved in malignant transformation and maintenance of the transformed phenotype. In vivo studies require pre-established models such as implantation of the tumor in the renal capsule, the use of nude mice, when new drugs are evaluated. Drug susceptibility information from in vitro testing is used to use different protocols and combinations. Its efficacy is evaluated as a decrease in tumor diameters after treatment, or an increase in the survival of the animal that harbors the tumor. Parallel to the in vivo evaluation, the corresponding toxicological and pharmacological studies are carried out in a certain species. Lethality is a good toxicity parameter and thus the concept of lethal dose (LD) is used, LD10, as the dose that kills 10% of the animals and LD50, which kills 50% of the animals. The NCI also uses a different study design, which administers increasing doses of a drug to groups of mice. Instead of lethality, they determine the dose that produces severe but reversible toxicity (maximum tolerable dose: MTD). Then these doses are evaluated in other species such as rats and dogs to assess the variability of toxicity between species. If no toxicities are observed or they are different between species, then the maximum tolerable dose is defined from the second species (Figure 10).

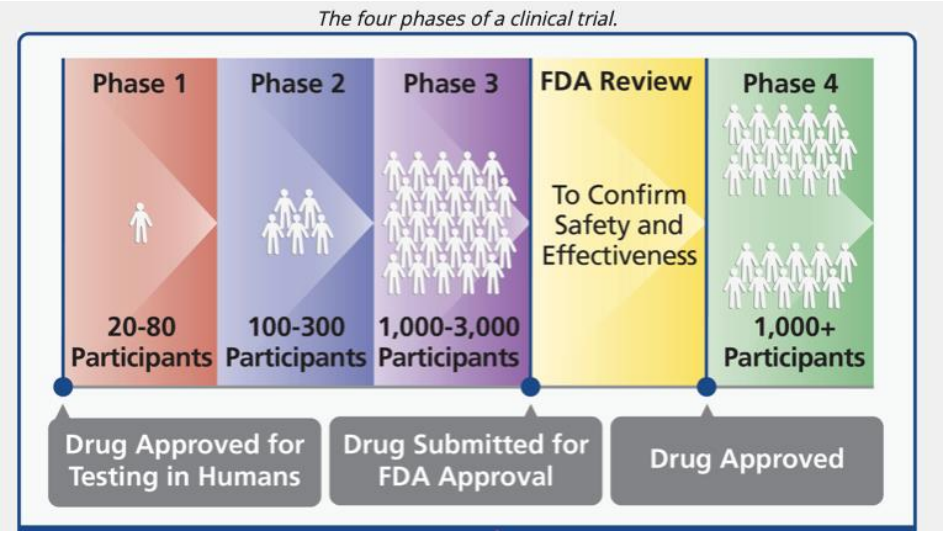

Figure 11: The phases of a clinical trial.

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Phase I studies

These are trials that evaluate a drug for the first time in cancer patients. Although its objectives are to determine the maximum tolerable dose and to evaluate the pharmacokinetics of the drug, the response in the tumor model evaluated is of greater importance. The starting dose uses a fraction of the MTD of the most sensitive animal species or is determined by animal pharmacokinetic and toxicity studies. The patient must present a correct performance status (ECOG up to 2), biochemical functions within physiological parameters, and primarily be refractory to the standard therapies received. Dose escalation is planned in steps and usually three patients are treated at each dose level until significant toxicity is obtained. If this occurs, three new patients are admitted at the same dose level for the purpose of evaluating subsequent toxicity [33,34]. When a predetermined proportion of patients at a given dose experience unacceptable toxicity, that dose is defined as the MTD for that regimen. Generally, BAT with classic cytostatic was evaluated at the level of myelosuppression, but with the development of drugs with new mechanisms of action, other toxicities turned out to be BAT, eg diarrhea due to Irinotecan. A dose approximately 10 to 25% less than the MTD is recommended for Phase II studies. It is noteworthy that antineoplastic drugs are always evaluated in sick volunteers, while new drugs for other pathologies are evaluated in healthy volunteers.

Phase II studies

After different Phase I schemes used in different institutions, the decision is made to begin Phase II studies. The absence of response to the drug in Phase I was not an impediment to its use in Phase II in the past, but today a relative is sought. or tumor target profile already in Phase I. The objective in Phase II is to obtain types of tumors sensitive to the drug. The choice of tumor types is empirical, and the aim is to obtain information on the maximum therapeutic efficacy of the drug. Enough patients are required in each Study to accept or reject the null hypothesis (the drug has no activity). This requires a confidence interval (90 to 95%) that the drug is not more effective than stipulated. For example, if one wishes to know with 95% confidence that a drug is not more than 20% effective in a certain type of tumor, 14 patients need to be enrolled in the Study. If a response is observed in these 14 patients, then more patients should be admitted evaluating response in a greater number of them. You must also stipulate what percentage of response you want to obtain for each tumor.

Phase III studies

Once this is obtained, it is passed to the Phase III Trials, which are randomized and compare the standard treatment for that pathology, with the scheme and dose that was obtained in Phase II with the new drug. Randomization allows the groups to be treated to be comparable. It is important that these studies are sufficiently powered to detect a difference between the two if one exists. Therefore, the sample size is essential in the design of this type of study. Since the differences are generally minimal, many patients are needed to detect them, which is why these studies are generally cooperative between institutions. Parameters such as quality of life and pharmacoeconomic items are also evaluated.

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Historical development of cytostatic

- 1945-1950: Nitrogen mustard (war gas).
- 1950-1955: Busulfan, 6-Mercaptopurine, Methotrexate.
- 1955-1960: Cyclophosphamide, Chlorambucil
- 1960-1965: Vincristine, Vinblastine, Actinomycin-D, 5-Fluorouracil, Melphalan.
- 1965-1970: 6-Thioguanine, Cytosine Arabinoside, CMFVP (Cooper): combined treatment for breast cancer; MOPP: combined treatment for Hodgkin's disease.
- 1970-1975: Doxorubicin, Bleomycin, Mitomycin-C
- 1975-1980: DTIC, CCNU, BCNU, Cisplatin.
- 1980-1985: VP-16, Mitoxantrone.
- 1985-1990: Interferon, Carboplatin, Ifosfamide/Mesna.
- 1990-2000: Irinotecan, Topotecan, Capecitabine, Imatinib
- 2000-2004: small molecules: Tyrosine kinase inhibitors, Monoclonal antibodies: Rituximab, Cetuximab, Tratuzumab, Bevacizumab

Topological, pharmacological classification and development of cytostatic

Agents that act throughout the cell cycle (predominantly in G1)

non-specific cycle: ALKYLATING AGENTS, Bischloroethylamines: Mechlorethamine, Chlorambucil, Cyclophosphamide, Ifosfamide, Melphalan, Aziridines: Thiotepa, Alkylsulfonates: Busulfan, Nitrosoureas: Carmustine (BiCNU), Lomustine (CCNU), Methyl CCNU, Streptozotocin. Non-classical alkylating agents: Dacarbazine (DTIC), Hexamethylmelamine, Procarbazine. Platinum compounds: Cisplatin, Carboplatin, Oxaliplatin.

Alkylating agents are chemically diverse drugs that can be activated to produce intermediate reagents that are deficient in electrons. These so-called alkyl groups can form covalent bonds with other groups at the DNA level, such as amino, phosphate, sulfhydryl, hydroxyl groups. This covalent bonding process is called alkylation. Alkylating agents can have one or two reactive groups and are called monofunctional and bifunctional. The first (nitrosoureas) can produce point mutations in DNA and be responsible for alterations in the genome that lead to second tumors. Bifunctional alkylating agents can generate cross-links at the DNA level (cross-linking), and both the formation of single-stranded and double-stranded bonds present significant lethality, leading to cell death. Mechlorethamine was the first drug used in Hodgkin's disease, in association with Vincristine, Procarbazine and Prednisone. This MOPP scheme was curative for this disease and is still used today. Compared to the other scheme used (ABVD), MOPP presents greater myelosuppression. Chlorambucil has its precise indications in oncohematology (chronic lymphocytic leukemia). Cyclophosphamide is the alkylating agent with the widest spectrum of use in oncology. It is a prodrug that at the level of the hepatic microsomal system is transformed into 4-hydroxycyclophosphamide and its aldophosphamide isomer, both with alkylating capacity. A toxic metabolite is acrolein, which is excreted in the urine and

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can be the cause of bladder irritation and the appearance of bladder tumors since it is toxic and carcinogenic. Used in high doses in bone marrow transplantation, it can cause fatal pericarditis. The main use of cyclophosphamide is in combination with anthracyclines and 5-Fluorouracil in the treatment of breast cancer; in the COPP and CHOP schemes in the treatment of Hodgkin's Disease and non-Hodgkin's lymphomas, respectively, and also in the induction phase and in high doses in bone marrow transplantation. Alopecia caused by cyclophosphamide is very common, as is caused by most cytostatics. Ifosfamide is an analog of cyclophosphamide and could not be used until the appearance of the bladder uroprotectant MESNA (sodium mercaptoethanol sulfonate). Both are used together in tumors such as soft tissue sarcomas, pediatric tumors, lung cancer, and testicular germ cell tumors. The other bischloroethylamine is the drug Melphalan, which is used orally, with erratic bioavailability. Its indications are in multiple myeloma and relapsed ovarian cancer. In multiple myeloma, if it is feasible to treat it with a bone marrow transplant, melphalan is used in high doses and intravenously. Thiotepa was initially used in breast carcinoma, but today its use is limited in transitional carcinoma of the superficial bladder, where it is used by local instillation. Busulfan and Hydroxyurea have indications in oncohematology in chronic myeloid leukemia, where it presents 90% of remissions with greater activity in those with positive Ph1 chromosome. Because they are fat-soluble alkylating agents, nitrosoureas have the ability to cross the blood-brain barrier and are therefore used in the treatment of brain tumors in adults and children. Streptozotocin is the one with the lowest lipid solubility and has a precise indication in the treatment of metastatic endocrine tumors of the pancreas and carcinoid tumors. Dacarbazine is active in malignant melanoma and is a first-line drug in this pathology. It is also associated with Doxorubicin, Bleomycin and Vinblastine to form part of the ABVD curative scheme in Hodgkin's disease. Soft tissue sarcomas are also a group of tumors in which Dacarbazine is useful in association with other drugs. Procarbazine is used in Hodgkin's disease (MOPP scheme) and is formulated to be used orally, and Hexamethylmelamine is active in refractory ovarian cancer. Platinum compounds represent today the most used agents in solid tumors. Cisplatin (fig. 9), which could only definitively enter the clinic in 1975, the year from which a protocol with hyperhydration before, during and after its use was designed. Its main indications are testicular germ cell tumors, lung cancer, ovarian cancer, and squamous cell tumors of the head and neck. Carboplatin, a derivative with less nephrotoxicity, has almost the same indications as Cisplatin. Finally, Oxaliplatin has activity in metastatic colon cancer in association with Leucovorin and Fluorouracil. Classical alkylating agents have myelosuppression as limiting toxicity. It begins between days 7 to 10 after chemotherapy, presenting its nadir on day 15 and beginning bone marrow recovery between days 18-20. Toxicities are the urotoxicity with hemorrhagic cystitis that Ifosfamide can present if it is not used correctly together with MESNA, the nephrotoxicity and otoxicity of Cisplatin if it is not used correctly prehydrated and hydrated. Cisplatin nephrotoxicity can be acute or chronic. The first courses with

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elevated urea and creatinine, hypokalaemia, hypomagnesaemia and hypocalcaemia, and due to the interaction of cisplatin with the sulfhydryl groups, proximal tubular damage is produced. This toxicity is greater if the treatment is associated with furosemide and aminoglycosides. Peripheral neurotoxicity can be seen with Platinum compounds, and central neurotoxicity (hallucinations, seizures, coma) with Ifosfamide.

Agents that act in Phase S

Antitumor antibiotics and plants products

Doxorubicin, Epidoxorubicin, Daunorubicin, Idarubicin, Mitoxantrone, Dactinomycin, Mitomycin-C, Vincristine, Vinblastine, Vindesine, Paclitaxel, Docetaxel, VP-16(Etoposide), VM-26(Teniposide), Irinotecan, Topotecan. Antitumor antibiotics and other plant products currently represent the most widely used group of agents. Anthracyclines (Doxorubicin, Epidoxorubicin, Daunorubicin and Idarubicin) have precise indications in both solid and hematological tumors. Doxorubicin is a major drug in the treatment of breast cancer, Epidoxorubicin too, being less cardiotoxic. Anthracycline cardiotoxicity can be acute, which is manifested by changes in the electrocardiogram compatible with arrhythmias, which are asymptomatic or chronic, which presents as refractory digitalis heart failure. It occurs with cumulative doses greater than 550 mg/m2 or with doses of 450 mg/m2 added to a history of mediastinal irradiation. It occurs from days after the administration of anthracyclines to years later. Its diagnosis is clinical and is complemented by measuring the left ventricular ejection fraction using radioisotopes or echocardiography. For confirmation of certainty, a myocardial biopsy can be performed through the jugular route. Anthracyclines are associated with alkylating agents, antimetabolites, and taxanes. The anthracenedione Mitoxantrone, although it is useful in mammary carcinoma, and is less cardiotoxic than anthracyclines, has an indication associated with prednisone in the treatment of hormone-refractory prostate cancer. This association not only produces responses at the PSA level, but compared to Prednisone alone, it improves the patient's quality of life. Mitomycin-C has indications in advanced gastric cancer, squamous cell cancer of the anus, and pancreatic cancer, but its use today is almost limited to superficial transitional carcinoma of the bladder. Like nitrosoureas, it can present delayed myelotoxicity. Reports of pulmonary toxicity are known. The agents derived from podophyllum, Etoposide (VP-16) and Teniposide (VM-26) are indicated in solid and hematological tumors, respectively. As for VP-16, it has activity in lung carcinoma and in pediatric tumors. Its pharmacological activity is greater when it is administered in divided doses for several days (oral etoposide). By the classic intravenous route, it should be administered in a period of no less than one hour, since otherwise arterial hypotension occurs. Its limiting toxicity is myelosuppression and mucositis. Vinca alkaloids: Vincristine, Vinblastine, Vindesine, Vinorelbine, are widely used in combination with other drugs. Myelosuppression is limiting for Vinblastine and Vinorelbine and all agents in this group have peripheral neurotoxicity, in some cases irreversible. Taxanes are active drugs in ovarian, breast, lung, and prostate cancer, and represent one of the most important developments of the

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last decade. They present a predictable and manageable pattern of toxicity, with myelosuppression and neurotoxicity being the most cautious. Weekly or fortnightly schedules of these have recently revealed their therapeutic efficacy. Topotecan is active in lung carcinoma and Irinotecan is the drug that, due to its indication in advanced colorectal cancer and associated with Leucovorin and Fluorouracil, represents a very original development also in the last decade. This drug with a new mechanism of action (TOPO I inhibition), has affinity for colon cancer cells and normal colon cells. Its limiting toxicity, diarrhea, is manageable with high doses of loperamide. During the infusion, patients may have side effects of a cholinergic syndrome, which subsides with subcutaneous atropine [34].

Drugs acting in G2

Bleomycin

Of the Bleomycins, the A2 subtype is the clinically active one, and is active in testicular germ cell tumors, squamous cell carcinoma of the head and neck, esophagus, Hodgkin's disease, and non-Hodgkin's lymphoma. This drug presents little myelotoxicity, but it presents in cumulative doses greater than 150 I.U. dermatological toxicity, manifested by "coffee with milk" skin spots (Photo 3)

At 300 I.U. a peculiar and serious toxicity is pulmonary. It can be subacute or chronic. Subacute presents as interstitial pneumonitis, appearing 1 to 3 months after treatment. 10% of patients progress to fibrosis. They are risk factors for it: advanced age, COPD, and patients who received Bleomycin must be thoroughly monitored during anesthesia, taking care not to pass abundant fluids or high concentrations of oxygen. These two factors can trigger pulmonary toxicity. The cell affected by bleomycin is the pneumonocyte II. In the chronic form, the onset is directly insidious, with predominant fibrosis, a progressive course that does not respond to glucocorticoids. Other cytostatics that produce pulmonary toxicity are: Procarbazine (reversible), Methotrexate (acute reversible and chronic fibrotic), Mitomycin-C, Busulfan (fibrosis with calcifications on chest X-ray: "Busulfan lung"), Chlorambucil, Cyclophosphamide, and Mitomycin -C. Nail changes, such as minor toxicity, are classic and due to bleomycin.

Antimetabolites

6-Mercaptopurine, 6-Thioguanine, Cytosine, binoside, Gemcitabine, Pentostatin, Fludarabine, Cladribine, Hydroxyurea, L-Asparaginase, 5-Fluorouracil, Capecitabine, Methotrexate, Floxuridine and Leucovorin (rescue of Methotrexate and modulator of Fluorouracil). Antimetabolites are used, some of them in solid tumors and others exclusively in oncohematology. Thus, indications in the latter have 6-Mercaptopurine, 6-Thioguanine, Cytosinarabinoside, Pentostatin, Fludarabine, Cladribine, L-Asparaginase, Hydroxyurea. Hydroxyurea, apart from its mechanism of inhibiting ribonucleotide reductase, has radiosensitizing capacity and that is why it is used in association with Fluorouracil and Radiotherapy in epidermoid tumors of the head and neck that have relapsed locoregionally and are inoperable. Fluorouracil was the first drug in solid tumors, and its indications in association with other agents are multiple. Its inhibition of the enzyme thymidylate synthetase allows it to cut an important metabolic pathway of tumor

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cells and this inhibitory activity is increased by the addition of Leucovorin. In metastatic colorectal cancer, a combination used is the IFL scheme (Irinotecan, Fluorouracil, Leucovorin). Capecitabine is a relatively new development, formulated orally as a prodrug of Fluorouracil. It is indicated in breast and colorectal carcinoma. Methotrexate, also with multiple indications, represents in association with Cyclophosphamide and Fluorouracil (CMF-1973), the paradigm of adjuvant treatment in breast cancer, with almost 49 years of experience with it (G. Bonadonna). It is also indicated in patients with relapsed head and neck tumors, and in this indication its tolerance is optimized by weekly administration, and in high doses associated with leucovorin rescue, it is indicated in osteosarcoma. Antimetabolite toxicities are primarily myelosuppression and mucositis. Fluorouracil in patients with head and neck tumors preferably and who receive this drug in continuous infusion and associated with Cisplatin may present cardiotoxicity, with angina pectoris and patterns of ischemia in the electrocardiographic tracing. The mechanism involved is believed to be due to intramitochondrial formation of fluoroacetate, which would slow down the intramitochondrial Krebs cycle of myocytes. Cerebellar ataxia has also been observed with 5-Fluorouracil, and a pharmacogenetic phenomenon has been known with this drug, which is an unexpected toxicity related to the deficiency of the enzyme Dihydropyridine dehydrogenase (DPD). The cytostatic mentioned above can be considered as the classic type and are mostly dosed in mg/m2 of body surface. For this, the Clinical Oncologist uses the body surface rule, which relates weight to height through a central axis that corresponds to the body surface (old Dubois table, 1916).

Hormonal Agents

They are not classic cytostatics in the strict sense, but because of their wide clinical use, they are included here.

Used in breast cancer: Tamoxifen, Toremifene, Raloxifene, Letrozole, Anastrozole, Aminoglutethimide, Megestrol acetate, Medroxyprogesterone acetate and Examestane.

Used in prostate cancer: Flutamide, Bicalutamide, Nilutamide, Buserilin, Cyproterone, Triptorelin, Leuprolide acetate, Goserelin, Diethylstilbestrol, Ketoconazole, Estramustine, Dexamethasone and Prednisone

Targeted cancer therapies

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer. Targeted cancer therapies are sometimes called "molecularly targeted drugs," "molecularly targeted therapies," "precision medicines," or similar names.

- Hormone therapies slow or stop the growth of hormone-sensitive tumors, which require certain hormones to grow. Hormone therapies act by preventing the body from producing the hormones or by interfering with the action of the hormones. Hormone therapies have been approved for both breast cancer and prostate cancer.

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- Signal transduction inhibitors block the activities of molecules that participate in signal transduction, the process by which a cell responds to signals from its environment. During this process, once a cell has received a specific signal, the signal is relayed within the cell through a series of biochemical reactions that ultimately produce the appropriate response(s). In some cancers, the malignant cells are stimulated to divide continuously without being prompted to do so by external growth factors. Signal transduction inhibitors interfere with this inappropriate signaling.
- Gene expression modulators modify the function of proteins that play a role in controlling gene expression.
- Apoptosis inducers cause cancer cells to undergo a process of controlled cell death called apoptosis. Apoptosis is one method the body uses to get rid of unneeded or abnormal cells, but cancer cells have strategies to avoid apoptosis. Apoptosis inducers can get around these strategies to cause the death of cancer cells.
- Angiogenesis inhibitors block the growth of new blood vessels to tumors (a process called tumor angiogenesis). A blood supply is necessary for tumors to grow beyond a certain size because blood provides the oxygen and nutrients that tumors need for continued growth. Treatments that interfere with angiogenesis may block tumor growth. Some targeted therapies that inhibit angiogenesis interfere with the action of vascular endothelial growth factor (VEGF), a substance that stimulates new blood vessel formation. Other angiogenesis inhibitors target other molecules that stimulate new blood vessel growth.
- Immunotherapies trigger the immune system to destroy cancer cells. Some immunotherapies are monoclonal antibodies that recognize specific molecules on the surface of cancer cells. Binding of the monoclonal antibody to the target molecule results in the immune destruction of cells that express that target molecule. Other monoclonal antibodies bind to certain immune cells to help these cells better kill cancer cells.
- Monoclonal antibodies that deliver toxic molecules can cause the death of cancer cells specifically. Once the antibody has bound to its target cell, the toxic molecule that is linked to the antibody—such as a radioactive substance or a poisonous chemical—is taken up by the cell, ultimately killing that cell. The toxin will not affect cells that lack the target for the antibody—i.e., most cells in the body.

Cancer vaccines and gene therapy are sometimes considered targeted therapies because they interfere with the growth of specific cancer cells. Information about cancer vaccines.

Membrane anti receptor agents (Target Therapy)

Rituximab, Cetuximab, Trastuzumab and Bevacizumab.

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Signal transduction inhibitor

Imatinib, Erlotinib and Gefitinib.

Action mechanisms of target topology for Cytostatics

Nuclear targets

DNA sequence specificity

Many of the classic cytostatic have DNA as their main locus of action. Highly reactive compounds such as Nitrogen Mustards and Cisplatin form covalent bonds with DNA and thus interfere with the processes of replication and genetic transcription. Many of these covalent bonds produce intra- and interstream crosslinks and/or adduct breaks that directly disrupt DNA structure and function.

Although this interaction of alkylating agents with DNA has been considered random, drugs with a certain sequence specificity have been discovered in recent years. These drugs seem to act in the areas rich in AT (adenine-thymine) within the minor groove of the double helix, thus altering its conformation and preventing the binding of regulatory proteins at their level.

DNA bio reductive activation

The example here is Mitomycin-C which is an antineoplastic antibiotic that is act ivated by an intracellular reductase and that has increased activity in hypoxic areas, a situation which is common in various tumors.

DNA analogs with better tissue toxicity profile

Although there is some controversy about its mechanism of action, doxorubicin is thought to intercalate at the level of the DNA double helix. Its use in Oncology is wide, but its chronic cardiotoxicity continues to be a negative aspect of it. Thus, drugs were developed that, even though they are cardiotoxic but at cumulative doses greater than those of Doxorubicin, present less toxicity. Examples of these are 4-Epidoxorubicin and Mitoxantrone. Cisplatin is another major drug in the therapeutic arsenal for many tumors, but its toxicity pattern is peculiar (nephro- and ototoxicity).

Without replacing Cisplatin, Carboplatin was developed, its limiting toxicity is myelosuppression and not nephrotoxicity, presenting activity in those tumors where Cisplatin is active. The third platinum compound is Oxaliplatin, which, apart from not being nephrotoxic, is active in tumors such as colon cancer, where neither Cisplatin nor Carboplatin are.

DNA associated enzymes

DNA topoisomerases (TOPO) are enzymes that change the topological shape of DNA. They are responsible for the cleavage of one or both of its chains, for the passage of a DNA segment through its break (Topo II). TOPO I cleaves a single strand and TOPO II cleaves both strands. Both enzymes form a complex with DNA as an intermediate step in the reaction they catalyze.

At this level we have Etoposide (VP-16) and Teniposide (VM-26) that stabilize the DNA-TOPO II complex, thus preventing the division of the chains and allowing endogenous nucleases to degrade DNA, causing cell death. Anthracyclines and Mitoxantrone act in a similar way. At the TOPO I level, Camptothecin-11 (Irinotecan) derived from the Chinese plant camptotheca

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accuminata, and Topotecan produce the same effect on the TOPO I –DNA complex.

DNA reversal of multiple drug resistance

It is known that the MDR (Multiple Drug Resistance) phenotype is due to the presence in certain tumors of a membrane glycoprotein, GP-170, which is responsible for the efflux of cellular toxins [35]. Once the cytostatic agent (derived from plant alkaloids and anthracyclines) enters the cell by passive diffusion, it is expelled from the cell by GP-170 (a mechanism that requires ATP).

Many drugs (Cyclosporine, Verapamil) and substances demonstrated in vitro capacity for affinity and blockade of GP-170, but they did not have clinical repercussions in part because their levels in the clinic would be toxic and in part because in tumor, not all resistant cells express GP-170.

Antisense Oligonucleotides

They are interested in their development if they complement the nucleotide sequences of oncogenes, thus inhibiting their information. Although in vitro data were encouraging, in vivo the problem arises from their metabolic instability as well as their poor penetration into target cells due to decreased uptake.

Cytosol targets (micro filamentous microtubular system)

Formation inhibition

The microtubule system is formed from dimers of the protein tubulin, which polymerize during mitosis and form the mitotic microtubule spindle. Drugs that interfere with its polymerization are therefore cytotoxic. Vincristine, Vinblastine, Vindesine, Vinorelbine, are examples of the plant alkaloids.

Spindle stabilization

Paclitaxel and Docetaxel are relatively new drugs which polymerize and stabilize the microtubular spindle leading to cell death. Both are important for their activity in lung, breast, and ovarian cancer.

Antimetabolites

The pathways responsible for the de novo synthesis of purine and pyrimidine nucleosides have been important targets of antineoplastic therapy. Methotrexate, an inhibitor of the enzyme dihydrofolic reductase (DHFR) is known to favor the depletion of reduced folates, which are cofactors required in nucleoside biosynthesis reactions. It is also suggested that methotrexate-polyglutamate complexes contribute to the cytotoxic action of methotrexate by directly inhibiting other enzymes of the purine and pyrimidine synthesis pathway such as thymidylate synthetase and glycinamide ribotide transformylases (GAR). 5-Fluorouracil was and continues to be in wide clinical use. Its primary site of action is inhibition of thymidylate synthetase. This inhibition can be modulated by increasing the inhibitory effect by means of folinic acid or Leucovorin. This association not only increases the cytotoxic effects but also the toxic ones. The association is of wide clinical utility in the treatment of colorectal carcinoma.

Membrane Targets

Various efforts have been directed towards this target. Although with great rationale for preclinical development, its transfer to the

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clinic was less. The antiparasitic agent Suramin is an agent that is active in vitro against various tumors. Phase II studies in adrenal cortex carcinoma, hormone-refractory prostate, and low-grade lymphomas demonstrated its activity, but due to its excessive toxicity (especially neurotoxicity), which was unmanageable and predictable, its development had to be discontinued. Drugs that act at the level of specific lipids at the membrane level have also been developed. Miltefosine (Hexadecylphosphocholine) is an agent of this class, and it shows activity in skin permeation nodules in mammary carcinoma. At the level of the transduction of intracytoplasmic signals and growth factor receptors, there are today several drugs for clinical use.

Target Topology for Hormonal Agents

The effects of hormonal manipulation on neoplasms were known in the eighteenth century, when surgical castration revealed its efficacy in the treatment of advanced prostate cancer (Huggins) [36]. With this treatment, the surgical ablation of androgens is produced, with which the symptoms present in the patient disappear in a spectacular way. It is known that prostate cancer, at least in part of its natural history, requires the male hormone for its growth (beginning of tumorigenesis). In its final stages, there is a transformation of the phenotype to one of relative independence from androgens (hormone-resistance). Over time, medical treatments evolved, and then surgical castration became medical. In principle, radiotherapy was used as an ablative method, to later reach the pharmacological methods that we currently have. Leuprolide acetate, Goserelin (LH-RH analogs) and others are drugs that, injected subcutaneously and monthly or three-monthly, produce chemical castration. The mechanism involved is initially to release pituitary gonadotrophic hormones which will peripherally stimulate the release of testosterone from the testis. The latter, through a negative feed-back mechanism, will inhibit the hypothalamic-pituitary axis from releasing new gonadotropins (axis blocking mechanism). At the peripheral level, testosterone activity can be inhibited either by inhibiting its synthesis at the testicular level (inhibition of the 5-alpha reductase enzyme that catalyzes the passage of testosterone to dihydrotestosterone, which is the active form of androgen), or by occupying the peripheral receptors to testosterone (drugs such as Flutamide and Bicalutamide). There is also a source of androgen secretion at the level of the adrenal gland. It secretes androstenedione and its synthesis involves enzymes called aromatases, which can be inhibited by compounds such as aminoglutethimide and ketoconazole. At a clinical level, it is common practice in the treatment of advanced prostate cancer to carry out what is called complete androgen blockade, using both drugs that act at a central level and drugs that act at a peripheral level. In patients with hormone-refractory tumors, Estramustine associated with Docetaxel is used. Estramustine fulfills its function as an alkylating agent and hormonal antagonist, both functions related to its chemical structure. Prednisone and dexamethasone are corticosteroids widely used in treatment protocols for solid and hematological tumors, as well as in palliative and supportive treatments. In gynecological tumors, the basic model is breast cancer. Breast tumor cells have estrogen receptors at

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the nuclear and cytosolic levels. They can be detected in tumor tissues by radioimmunoassay and have prognostic value and response to treatment. Postmenopausal women have 60% receptor-positive tumors, perimenopausal women 40%, and premenopausal women 20% expression. Associated with this estrogen receptor is the progesterone receptor, which is induced in its synthesis by the estrogen receptor. At the level of the estrogen receptor, Tamoxifen is a partial agonist drug of the same and widely used clinically, both in the treatment of advanced disease, as a precaution, in postmenopausal patients, or as a chemoprevention agent. Toremifene is a drug related to Tamoxifen. Drugs that inhibit adrenal aromatases, such as Aminoglutethimide, Letrozole, Examestane and Anastrozole, are also used in this entity. Another hormonal target to block is the Progesterone receptor and according to its expression in the primary tumor can be used in advanced breast cancer and as a third therapeutic line Medroxyprogesterone acetate and Megestrol acetate. LH-RH analogs such as Goserelin can also be associated with hormonal treatment.

White or target therapy

The notion of therapeutic target or target implies that in the past it lacked unique targets. Most of the chemotherapeutic agents, as we saw earlier, are directed at DNA synthesis or repair as a general principle. Also, other types of drugs such as plant-derived alkaloids and other agents that affect the microtubular-microfilament system of the cytoplasm do so to the same extent in both tumor cells and normal cells. With the development of new concepts in cancer cell biology, this type of therapy was developed. The presence of oncogenes code for growth factors and their somewhat modified receptors, and it is then towards the latter or towards the intracellular signal transduction system that this new therapeutic modality is directed. But the above depends on the dynamics of the target, that is, a target therapy is useful if the tumor depends on that target for its functioning and the host does not. The paradigm of a target therapy that we know is hormone therapy in breast cancer, where the target for Tamoxifen and related (antiestrogenic compounds) is the estrogen receptor. It has recently been discovered that there are several receptors for them. Another target therapy with which we are familiar is the treatment of promyelocytic leukemia with ATRA: all-trans retinoic acid. In this pathology there is a translocation between chromosome 15 and 17 that generates a PML-RAR alpha fusion protein. Thus, ATRA causes the degradation of the complex, leading to the induction of differentiation. This ATRA therapy obtains remissions in 87% of which 81% are complete and last an average of 12 months. Exactly 100 years ago, Paul Ehrlich, the pioneer of chemotherapy, used the term "magic bullets" for those antibodies (AC) that attacked only the pathogenic element. In 1975, César Milstein published his seminal work on monoclonal CAs in Nature (which subsequently earned him the Nobel Prize in Medicine). Initially, monoclonal ACs were widely used in the diagnosis of pathologies and today, as we will see, in treatment as a target therapy [37].

Target therapy with monoclonal ACs

Rituximab was the first monoclonal antibody successfully introduced in Oncohematology. It is an anti-CD20 and shows 48% remissions (6% are complete) in patients with relapsed

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or refractory low-grade lymphomas. Currently and to improve the responses obtained with conventional chemotherapy, it is combined with Rituximab. Ex: CHOP associated with Rituximab in elderly patients with aggressive non-Hodgkin's lymphomas. Trastuzumab: This is the first humanized monoclonal antibody used in solid tumors. It targets the extracellular domain of the transmembrane glycoprotein HER-2. With it, a 15% objective response is obtained in patients with breast cancer who overexpress HER-2 and progressed after chemotherapy. Cetuximab: this monoclonal antibody blocks the EGF (epidermal growth factor) receptor, thus preventing the binding of EGF and alpha TGF to it. This prevents the internalization of the Factor-Receptor complex, also inhibiting receptor phosphorylation and therefore cell proliferation. Colon cancer cells overexpress EGF, so cetuximab was used in patients with Irinotecan-resistant colorectal carcinoma. 11% of responses were obtained. A posteriori, the efficacy of the same was compared with the association of the same plus Irinotecan in patients with colorectal carcinoma resistant to Irinotecan. The associated therapy group obtained 17% of responses and the one with Cetuximab alone, 8% of responses. Bevacizumab: Humanized monoclonal antibody directed against VEGF (vascular and endothelial growth factor). This is the first antiangiogenic therapy developed in the clinic. Promising results were observed in colorectal carcinoma.

Target therapy with small molecules

Imatinib: This is a tyrosine kinase inhibitor that has been used effectively in chronic myeloid leukemia and GISTs (gastrointestinal stromal tumors). In the latter, it yields partial answers between 59 and 69%.

Gefitinib: inhibits EGF tyrosine kinase activity. It shows promising activity in non-small cell lung carcinoma. It has been approved in this pathology in relapsed patients after treatment with Cisplatin and taxanes.

Erlotinib: Has activity in advanced stage non-small lung cancer.

Biological response modifiers

This modality, considered as the fourth therapeutic modality, began to have a boom in the 1980s. The presence of a tumor in the body has important aspects such as the host's response to it. Tumors have unique properties and not only that of being foreign to the body. For example: they have the characteristic of releasing membrane neoantigens into the circulation with which they can escape from the controls of the immune system.

These antigens (AG) generate a humoral immune response and then the antibodies (AC) are directed at them, forming the circulating AG-AC complex which will fix the complement and be eliminated from the body. In relation to the effective antitumor immunity is cellular (T, NK lymphocytes) and not humoral. In tumors, if their cells are surrounded by antibodies, this causes the T system not to recognize them, thus being a negative factor or an escape factor for tumor cells.

In other words, tumors have mechanisms to produce an immunological pseudo-tolerance in the body. Molecules that can be released in the body in response to certain chemical or biological stimuli were studied. The first of these were the Interferons. This group of proteins are released in the body by leukocyte or fibroblast-type cells in response to

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biological stimuli such as viruses. Three families of interferons are known: alpha, beta and gamma. Of these, alpha is the most studied and effective in Oncology, and 3 subfamilies are known: alpha 2a, alpha 2b and n. It is noteworthy that they are recombinant and that there are currently clinical studies with interferon alpha PEG (polyethylene glycol), which has a greater intracellular diffusion. Its mechanism of action, not entirely known, is to act on the intracellular levels of an enzyme, oligoadenylate synthetase, which is responsible for signal transduction at the intracellular level and is related to the antiproliferative effects of interferon.

At a clinical level, the therapeutic efficacy of alpha interferons is primarily in immunogenic tumors such as melanoma and clear cell carcinoma of the kidney. In these cases, therapy (especially in melanoma) was used alone or associated with chemotherapy, but positive studies reveal responses when interferon alpha is used in high doses (melanoma). An increase in disease-free survival and overall survival was observed when interferon is used as an adjuvant in patients with high-risk stage I-II melanoma.

Another type of biological response modifier is interleukin-2, which, as a T-lymphocyte growth factor, also has a positive impact on immunogenic tumors. The FDA has approved the use of interleukin-2 in the treatment of advanced kidney cancer. Other drugs that fall within this therapeutic modality are: tumor necrosis factor (Alpha TNF), BCG (for the treatment of superficial carcinomas of the bladder) Following the line of tumors such as melanoma, today there are some promising results with vaccines.

Support treatment

Chemotherapy presents emesis among its most frequent adverse effects. Cytostatic have different emetogenic power, but Cisplatin and Dacarbazine are the ones that produce the greatest emesis [38]. The latter is triggered because chemotherapy either directly stimulates both the Borison and Wang chemoreceptor trigger zone and the vomiting center or induces the release of the neurotransmitter serotonin from gastrointestinal enterochromaffin cells. The patients in turn are classified as pre-vomiters (they are medicated with Lorazepam) those who present emesis before chemotherapy; those who present emesis within 24 hours of chemotherapy: patients who present acute vomiting and, those who present vomiting after 24 hours of chemotherapy administration: patients who present delayed emesis. Regarding acute emesis, it can be successfully treated with central serotonin receptor blocking agents (5-HT3): ondansetron; granisetron; tropisetron, or by high doses of Metoclopramide (1mg/Kg.) which pharmacologically blocks serotonergic receptors. Delayed emesis responds to corticosteroids, since the mechanism involved in its genesis is different (Enkephalins). In this area, compounds are developed that present other targets for the avoidance of emesis and/or its treatment, such as Substance P; the neurokinin receptor. The other branch of supportive therapy arises from the adverse effects of chemotherapy such as myelosuppression, thrombocytopenia, and anemia. Recombinant compounds have been developed such as GM-CSF (Sargramostim), G-CSF (Filgrastim) to improve myelosuppression, interleukin-6 to increase

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platelet count, and erythropoietin to treat anemia due to chemotherapy. Specific antibiotics, antifungals, opioid and nonopioid analgesic compounds are also part of the therapeutic arsenal of cancer patients.

Performance Status or activity status

Cancer patients prior to their treatment and during their disease present a certain state of health that is called "performance status". It has clinical utility since if it is very altered, the patient can only receive palliative care and not specific cancer treatment.

The Karnofsky index indicates the "Perfomance Status" in percentages. Another way to classify performance status is the ECOG (Eastern Cooperative Oncology Group) scale.

Antineoplastic toxicity scales

Its measurement is based on the NCI or ECOG scales. They range from 0 to 4 and allow knowing the toxicity of a drug in a certain organ.

They are considered as topographies for the same: Neurotoxicity (Sensorineural, visual changes, auditory changes, neuromotor, constipation, neurocortical, neurocerebellar, headache, pain); cardiac (cardiac status, edema); pulmonary; gastrointestinal (emesis, diarrhea, mucositis, changes in taste); genitourinary (hematuria, proteinuria); skin (skin condition); alopecia; bleeding; infection; fever; flu-like syndrome; fatigue; sleep.

The doses between cycles must be adjusted according to the drug and its toxicity in the presence of persistent myelosuppression, hepatic, or renal alteration.

Mechanisms of resistance to cytostatic

The mechanisms of resistance to cytostatic drugs are an exciting field in constant evolution. The concept arises from the clinic where situations can be observed in which, after medical treatment, the patient relapses, and must be treated with different drugs than in the initial scheme. Drug resistance factors are divided into pharmacokinetic factors and pharmacodynamic factors.

Pharmacokinetic resistance

Pharmacokinetics describes all the steps from when a drug enters the body until it is eliminated from it. It is what the body does to the drug. The pharmacological factors involved in relative drug resistance, ineffective concentrations of the drug in the tumor, are: Goes variations in the bioavailability of the drug, Variations in drug metabolism, Variations in drug elimination, Location of the tumor in inaccessible sanctuary sites, Excessive toxicity in the host, Limited diffusion of the drug and Differences in cell kinetics of the cell target.

Absorption

There is an apparent resistance phenomenon with Melphalan. This drug has an erratic absorption between 40 to 60% at the gastrointestinal level, so when adequate amounts of the drug do not reach the target site, an apparent resistance mechanism is generated. The same happens with hexamethyl melamine and 6-Mercapto-purine. With the latter, it has been observed in patients with acute lymphoblastic leukemia, that there are variations from patient to patient of more than 6 times in the maximum plasma level and 5 times in the area under the curve (AUC).

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Distribution

Some drugs may compete at the level of plasma proteins with other non-antineoplastic drugs.

Metabolism

At this level and biotransformation, there is a whole pharmacogenetics, by means of which it is known that at the level of the microsomal cytochrome system, drugs are activated or deactivated differently and can also compete at the level of microsomes with other drugs of the same class or of a different gender.

Excretion

Also here, mechanisms of competition for it have been described, especially at the renal level.

Sanctuary organs

They are those in which chemotherapy spreads less easily, generating an apparent resistance. Ex: testicle, S.N.C. (Central Nervous System). Relapses e.g., of lymphomas can be in the S.N.C. or at the testicular level.

Tumor neoangiogenic

Tumors from a certain volume generate their own blood vessels to receive oxygen and nutrients and eliminate toxic substances for them. Oxygen can diffuse from capillaries only 150 to 200 microns away, and when cells are further than this distance, they die. Tumor blood vessels are weaker and anfractuous, which is why they become necrotic, leading to a lower supply of metabolites, especially in the central part of the tumor where there are greater necrosis phenomena, and the diffusion of oxygen and nutrients is less. Due to this last phenomenon, a resistance mechanism could be produced, thus the drugs would reach the tumor target in less quantity. This process of neoangiogenic has the intervention of substances that regulate it by stimulating or inhibiting it (angiostatin, angiogenin, etc.). Target therapy also has drugs that act at its level: Bevacizumab at VEGF level: vascular and endothelial factor.

Tumor interstitial pressure

According to it, if it increases, less drug will be absorbed by tumor cells. Important experimental studies have been carried out in this regard.

Pharmacodynamic resistance

Although numerous factors influence the determination of response to treatment, the lack of effective second-line treatment for patients who relapse indicates that the selection of drug-resistant cells is an important clinical problem [39]. As we saw earlier, Goldie and Colman have developed a mathematical model to describe the appearance of drug resistance in tumor cells, which is mainly based on classical studies of the development of resistance in bacteria. The model assumes that the main reason for treatment failure is the selection of drug-resistant tumor cells with stable genetic alterations. The frequency with which these gene mutations produce resistance to cytostatic appears to be a function of both the total number of tumor cells and the rate of spontaneous mutation. The model then favors the use of multiple agents in combination, since the selection of cells that are resistant to two agents at the same time without cross-resistance would be less frequent. This is an important principle used to reduce the frequency of antibiotic

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resistance in mycobacterial infections and may also be one of the main reasons for the increased effectiveness of combination chemotherapy, when compared to single agent treatment in the treatment of many tumors. In addition, the model favors the concept of adjuvance since the probability of cells with spontaneous resistance to cytostatic would be lower in early stages of the tumor (low overall volume). The model also predicts that treatment with alternating regimens without cross-resistance would be superior to their sequential use. Finally, because many of the fa Cytotoxic drugs used in the treatment of tumors are themselves mutagenic and may increase the frequency of spontaneous mutations that result in a drug-resistant phenotype, removal of such agents from treatment protocols should be considered when their individual efficacy be in doubt.

At the level of the tumor target we have the following resistance mechanisms:

1. Alterations in the incorporation of the drug into the cell (transporter-mediated incorporation): Methotrexate, Melphalan, Mechlorethamine.
2. Alterations in the intracellular accumulation of the drug: Methotrexate, Doxorubicin, Vinca alkaloids and D-Actinomycin. In the case of Methotrexate, when it enters the cell, glutamic acid residues are added to stabilize the molecule and remain inside the cell. The failure in this polyglutamation process of Methotrexate causes it to leave the cell.
3. Decreased drug activation: Cytarabine, 5-Fluorouracil, 6-Thioguanine, 6-Mercaptopurine, Methotrexate.
4. Increased metabolic inactivation: Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Cisplatin, classical alkylating agents.
5. Alterations in target proteins: Methotrexate, Steroid Hormones, Vinca alkaloids, FUDR.
6. Alterations in cell metabolism: Cytarabine, 5-Fluorouracil, Methotrexate, 6-Mercaptopurine.
7. Alterations in cofactor levels: 6-Tioguanine, FUDR.
8. Alterations in cell repair mechanisms: Alkylating agents.
9. Increased levels of target proteins or enzymes: Methotrexate, Hydroxyurea, FUDR, Deoxycoformycin.

The MDR Phenotype

A resistance mechanism through which the entry of a cytostatic into the cell can be affected is the presence of the MDR (Multiple Drug Resistance) genotype-phenotype in the tumor, encoded by the MDR1 gene [39]. Mainly, in the cells of all the emunctories of the body, at the adrenal level, in the CNS, and in some tumor cells, there is a glycoprotein in the cell membrane that weighs 170 Daltons, which is why it is called GP 170. It is conserved throughout evolution and is found in both bacteria and protozoa, fulfilling detoxification phenomena in both species. It works in a circular way having a domain so that once the drug enters the cell by passive transport, it is expelled from the cell by GP 170. The latter works energetically and therefore requires ATP. When the tumor cell performs this mechanism of extracellular drug extrusion, it can do so not only to one,

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but to several related drugs. In general, it is the plant alkaloids that have this resistance mechanism. This last concept is linked to the teleonomic fact that the function of GP 170 in emunctories such as the intestine, originally prevented man from becoming intoxicated by ingesting the alkaloids present in plants. Numerous non-cancer drugs have been used experimentally to reverse this resistance, but none have clinical relevance. The reason for the latter is probably that in a tumor population, not all resistant cells function with this target dynamic, and the MDR phenotype would only be present in some cells but not in all. This further enhances the concept of tumor heterogeneity as a concept of resistance. On the other hand, the doses required at the clinical level for reversal agents are incompatible due to their toxicity.

DHFR enzyme (dihydrofolic reductase)

Methotrexate enters the cell by active transport. When, for example, osteosarcoma cells become resistant, it is due to an intracellular increase in copies of DHFR, thus the Methotrexate target is not inhibited since there is a greater amount of target at its level (DHFR) to inhibit. This resistance is overcome with high doses of Methotrexate (and leucovorin rescue) which will enter the cell by passive diffusion and inhibit increased levels of DHFR. This mechanism is called the phenomenon of gene amplification and its phenotype is the appearance of chromosomes called double minutes if the amplification phenomenon is reversible, or the appearance of homogeneously stained regions in the chromatin if the phenomenon is constitutive or permanent. Other mechanisms of resistance to MTX are a lower entry by active transport into the cell, a lower binding of MTX to the target enzyme, the existence of variant constitutive forms of DHFR, a decrease in the mechanism of intracytoplasmic polyglutamation of MTX.

Intracellular glutathione levels

Increases in the levels of this tripeptide with -SH groups would correspond to an increase in DNA repair after the use of certain cytostatic. At the experimental level, the drug BSO (butionine sulfoximine) was used to antagonize the increased levels of Cytotoxic drugs used in the treatment of tumors are themselves mutagenic and may increase the frequency of spontaneous mutations that result in a drug-resistant phenotype, removal of such agents from treatment protocols should be considered when their individual efficacy be in doubt.

Intracellular glutathione levels

Increases in the levels of this tripeptide with -SH groups would correspond to an increase in DNA repair after the use of certain cytostatics. At the experimental level, the drug BSO (butionine sulfoximine) was used to antagonize the increased levels of glutathione. Pilot studies in relation to Cisplatin-based chemotherapy in patients with head and neck tumors have not revealed the validity of glutathione and its enzymes as a prognostic factor for response to regimens containing Cisplatin.

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