Chapter 1

Conventional Cancer Treatment

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1. Introduction

The era of cancer chemotherapy began in the 1940s with the first use of nitrogen mustards and antifolate drugs. The practice of cancer medicine has changed dramatically allowing treatments for many previously fatal cancers. Furthermore, the adjuvant chemotherapy and hormonal therapy can extend life and prevent disease recurrence following surgical resection of diferent types of malignancies.

Concurrently with the new discoveries of chemotherapeutic agents, the remarkable scientific and technological development allowed understanding of cell biology of human cancer cells and thereby the emergence of targeted therapy. Although the targeted therapy drugs have had outstanding successes in selected types of cancer, new therapies are not likely to replace cytotoxic agents in the foreseeable future. Rather, clinical trials have demonstrated potent synergy between targeted molecules and traditional cytotoxic agents.

The compounds used in cancer therapy are quite varied in structure and mechanism of action, including: alkylating agents, antimetabolite analogs, natural products, hormones and hormone antagonists and a variety of agents directed at specific molecular targets.

In this chapter we will discuss the history, applications and toxicity, among other aspects, of these agents that, in spite of systemic toxicity and severe side effects, became a mainstay of cancer treatment. As molecularly targeted agents have been used on a quite widespread way among different cancers, it can already be considered a conventional cancer therapy. Even more, as a full chapter of this book will be dedicated to these agents this subject will not be discussed in the present chapter.

2. Alkylating agents

Alkylating agents are genotoxic drugs which affect the nucleic acids and their function by direct binding to the DNA, interfering with replication and transcription resulting in mutations. In this way, the goal of using these agents is to induce DNA damage in cancer cells, severe enough to provoke them to enter into apoptosis. Alkylating agents act by replacing a hydrogen atom into another molecule by an alkyl radical through the electrolytic attack by the alkylating agent; however, this compound can also react with molecules containing an atom in a lower valence state that will undergo electrolytic attack instead of hydrogen.

Alkylating agents can be divided in several subgroups which include nitrogen mustards, various alkylating agents and platinum coordination complexes. Each one of these groups will be discussed below.

2.1. Nitrogen mustards

Nitrogen mustards were the first clinically useful anticancer agents [1] and its derivatives, such as cyclophosphamide, are still among the most widely used antitumor drugs [2].

Cyclophosphamide is a derivative of nitrogen mustards with a modified chemical structure that confers it a greater specificity for cancer cells [3]. The rational on developing cyclophosphamide was that cancer cells express higher levels of phosphamidase, which is able to cleave the phosphorus-nitrogen (P-N) bond, releasing the nitrogen mustard within the cancer cell [4]; this premise was later proven inaccurate [5]. The first clinical trials with cyclophosphamide occurred in 1958, when this drug was found to be the most effective anticancer compound against 33 cancer types on a 1,000 compounds screening trial [6]. In 1959, cyclophosphamide was approved by the Food and Drug Administration (FDA) as a cytotoxic anticancer compound, and up until now, over 50 years of its approval, it is still one of the most successful anticancer drugs [5]. Cyclophosphamide is used for the treatment of lymphoma, leukemias, breast and ovary cancers [7-10].

Cyclophosphamide is administered as a prodrug which is highly stable and requires hepatic mixed function oxidase system to be metabolically activated. Hepatic cytochrome P-450 systems are responsible for generating 4-hydroxycyclophosphamide by the hydroxylation of

the oxazaphosphorine ring on cyclophosphamide. Several metabolites are generated but 4-hydroxycyclophosphamide is considered the most significant as it distributes throughout the body, including reaching the tumor where it is preferentially converted into the active nitrogen mustard as described above [11].

Afterwards, the active nitrogen mustard will form adducts in the DNA in a sequential alkylation process in which each drug molecule will react with two different nucleotides: firstly it forms a monofunctional adduct followed by a second adduct on the opposite strand of the DNA, forming an interstrand cross-link. This cross-link will prevent strands from separating during replication, inhibiting DNA synthesis [12].

Iphosphamide is chemically related to cyclophosphamide by transposition of a chloroethyl group from the exocyclic to endocyclic nitrogen. Clinical investigations have highlighted the lower toxicity of iphosphamide in comparison to that observed for cyclophosphamide [13]. Doxorubicin and iphosphamide remain the backbone of chemotherapy in patients with locally advanced or metastatic soft tissue sarcoma [14]. In the mid 1980s, iphosphamide was found to be effective in patients with refractory germ cell tumors [15].

2.2. Diverse alkylating agents

2.2.1. Nitrosoureas

Nitrosoureas were synthesized at the National Cancer Institute (NCI) following rational design based on structure-activity relation [16]. Nitrosoureas can react through alkylation with both nucleic acids and proteins or specifically through carbamylation with the latter. In order to acquire its alkylating and carbamylating properties these compounds undergo a nonenzymatic decomposition to form a 2-chloroethyl carbonium ion, which is highly electrophile and capable of alkylating guanine, cytidine, and adenine. Some compounds of this drug category are: (i) 2-chloroethylnitrosoureas (*CENUs*); (ii) 1-(2-chloroethyl)-3-cyclohexyl)-1-nitrosourea (*CCNU*, lomustine); (iii) bis(chloroethyl) nitrosourea (*BCNU*, carmustine); (iv) 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (*methyl-CCNU*, semustine); (v) chlorozotocin. The most used nitrosoureas in chemotherapy are the lipid soluble agents CCNU and BCNU. Actually, hydrophobicity is an important feature of this drug category since it allows them trespassing blood-brain barrier promoting their wide usage for brain tumor's treatment as well as non-Hodgkin's lymphoma.

2.2.2. Triazenes

Triazene compounds of clinical interest, dacarbazine and temozolomide, are a group of alkylating agents with similar chemical, physical, antitumor and mutagenic properties. Their mechanism of action is mainly related to methylation of *O*6-guanine, mediated by methyldiazonium ion, a highly reactive derivative of the two compounds. The cytotoxic/mutagenic effects of these drugs are based on the presence of DNA *O*6- methylguanine adducts that generate base/base mismatches with cytosine and with thymine. These adducts lead to cell death, or if the cell survives, provoke somatic point mutations represented by C:G→T:A

transition in DNA helix. Triazene compounds have excellent pharmacokinetic properties and limited toxicity [17].

Temozolomide is an oral alkylating agent with established antitumor activity in patients with melanoma and primary brain tumors, due to its excellent bioavailability in the central nervous system [18]. Dacarbazine is employed to treat Hodgkin disease and malignant melanoma [19,20].

2.3. Platinum complexes

Rosenberg and colleagues reported, in 1965 the discovery that platinum complexes present in nutrient medium in low concentrations can inhibit cell division of *Escherichia coli* and cause the development of long filaments [21]. In the seventies the efficacy in human cancer patients was established [22].

Since then, over 3,000 platinum derivatives have been synthesized and tested against cancer cells [23]. Because of renal, oto and neurotoxicities of cisplatin, there were intensive efforts to devise analogs with fewer of these serious side effects. Moreover, analogs of cisplatin have been developed in an attempt not only to lessen the toxicity of the parent compound, but also to try to overcome the problem of platinum resistance, which may be present either in the outset of the disease, or emerging during its course or yet be acquired as a result of the treatment [24]. This effort led to the development of carboplatin, which produces primarily hematopoietic toxicity and has antitumor effects similar to those of cisplatin. Other platinum compounds have been developed and evaluated, as described later, although they haven't showed any significant advantages over cisplatin and carboplatin [25].

Today, six platinum compounds are used clinically: cisplatin (available since 1978); carboplatin and oxaliplatin (world-wide 2nd generation analogs); nedaplatin (also a 2nd generation analog); and lobaplatin and heptaplatin (3rd generation analogs). Some platinum complexes are still under clinical investigation, including those developed for oral administration.

Cytotoxicity of platinum compounds is believed to result from the formation of platinum-DNA adducts [26]. In fact, these platinum drugs can be considered as prodrugs, yielding after aquation the active diaquo-platinum compound. The main differences between these prodrugs can be related to the different kinetics of activation. Hydrolysis of cisplatin is extremely rapid, whereas it is slower for carboplatin and nedaplatin. The diaquo-platinum species react with the amine groups of proteins, RNA and DNA. The latter reaction yields platinum-DNA adducts, which appears to be associated with antitumor activity. Aquated platinum reacts preferentially with the N-7 position of guanine and adenine and produces cross-links between bases in the same strand (intrastrand) or opposite strands (interstrand). The efficacy of platinum agents against cancer cells may be mediated with the inhibition of DNA synthesis or saturation of the cellular capacity to repair platinum adducts on DNA [22].

Cisplatin is used alone and in combination with a wide range of other drugs. In combination with bleomycin, etoposide, iphosphamide, or vinblastine, cures 90% of patients with testicular cancer. Cisplatin or carboplatin used with paclitaxel induces complete response in the majority of patients with ovary carcinoma. Cisplatin produces responses in bladder, head and neck,

cervix, and endometrium cancers; all forms of lung carcinoma; anal and rectal carcinomas; and neoplasms of childhood [27,25].

Resistance and the spectrum of clinical activity of carboplatin are similar to those of cisplatin. Carboplatin is relatively well tolerated clinically, causing less nausea, neurotoxicity, ototoxicity, and nephrotoxicity than cisplatin. Instead, the dose-limiting toxicity is myelosuppression, primarily thrombocytopenia [27].

Oxaliplatin exhibits a variety of antitumor activity such as against colorectal and gastric cancers which differs from other platinum agents [27]. A great number of phase II and III trials in solid tumors administering oxaliplatin in combination with other drugs have suggested increased activity as compared to oxaliplatin alone. Further, in comparison to cisplatin, oxaliplatin has not demonstrated nephrotoxic effects, which is due to the absence of platinum accumulation in plasma [28].

3. Antimetabolites

Antimetabolites are cytotoxic agents developed for more than 65 years and considered a mainstay in cancer chemotherapy. The antimetabolites can be divided according with their structure and function as folic acid analogs, purine analogs, pyrimidine analogs and cytidine analogs.

These agents are structurally similar to natural metabolites, which are essential for normal biochemical reactions in cells. The mechanism of action of antimetabolites include: competition for binding sites of enzymes that participate in essential biosynthetic processes and incorporation into nucleic acids, which inhibits their normal function triggering the apoptosis process.

3.1. Folic acids analogs

In 1948, aminopterin, an antifolate drug, was the first drug to induce temporary remissions in children with acute lymphoblastic leukemia (ALL) [29]. This success stimulated research into new antimetabolites less toxic than aminopterin. A few years later another antifolate drug, methotrexate (MTX) showed anticancer property. Currently, this drug category plays an important role in cancer treatment acting in several ways. Mostly they compete with folates for uptake into cells and prevent the formation of folates coenzymes primarily by inhibiting dihydrofolate reductase (DHFR) or thymidylate synthase (TS).

Mammalian cells lack the ability to synthesize their own reduced folate derivatives and therefore must obtain them from exogenous sources (i.e. food and dietary supplements). In normal and cancer cells, folic acid is reduced to dihydrofolate (FH_2) and then to active tetrahydrofolate (FH_4) by the enzyme DHFR. FH_4 is a cofactor that provides methyl groups for the synthesis of precursors of DNA (thymidylate and purines) and RNA (purines). TS catalyses transfer of the carbon from the FH_4 to the target molecules by oxidizing the folate ring of the FH_4, reverting it back into a FH_2 [30].

3.1.1. Methotrexate

Although several antifolate drugs have been developed, MTX is the antifolate with the widest spectrum of use. MTX is extensively used in lymphoma, ALL and osteosarcoma. Moreover, MTX is part of chemotherapeutic schemes for choriocarcinoma, breast, bladder and head and neck cancer [27].

MTX enters the cells via reduced folate carrier (RFC) or via the membrane folate binding protein (FBP) and is polyglutamated by folylpolyglutamate synthetase (FPGS) in MTX-polyglutamate, which is retained in cells for longer periods compared with MTX [31,32]. The main target of MTX and MTX-polyglutamate is the inhibition of DHFR enzyme, leading to partial depletion of the FH_4 cofactors required for the synthesis of new thymidylate and purines nucleotides. Consequently, there will be a decrease of DNA and RNA synthesis. In addition, MTX-polyglutamates are also inhibitors of other folate-requiring enzymes such as: TS and two enzymes related with de novo purine synthesis - glycinamide ribonucleotide transformylase (GART) and aminoimidazole carboxamide ribonucleotide transformylase (AICART) [31].

In normal cells a decreased polyglutamation is observed when compared to malignant cells, which partially explains the selectivity of MTX for malignant tissue [33]. Despite this predilection for malignant cells, MTX can kill rapidly dividing normal cells such as those of the intestinal epithelium and bone marrow [34]. Common side effects are cytopenia, serious infections, liver damage, mucocutaneous problems, alopecia and allergic interstitial pneumonitis [35].

3.1.2. Pemetrexed

Pemetrexed is a multitargeted antifolate chemotherapy agent approved by FDA in 2004 for the treatment of malignant pleural mesothelioma (MPM) and advanced or metastatic non-small cell lung cancer (NSCLC). Ongoing clinical trials are evaluating pemetrexed efficacy in other malignancies such as breast, colorectal, bladder, cervical, gastric and pancreatic cancer [36].

Likewise MTX, pemetrexed inhibits DHFR and as a polyglutamate, it inhibits even more potently GART and TS [37]. The inhibition of TS and GART predominates because pemetrexed's usage produces little changes in the pool of reduced folates.

Currently, this agent is employed as a monotherapy or in combination with cisplatin. It is generally a well-tolerated drug and the most common adverse reactions with its usage as single-agent are fatigue, nausea, and anorexia. Myelosuppression is the most common and dose-limiting toxicity, predominantly developed as neutropenia [38].

3.2. Purine analogs

Purine nucleoside analogues (PNA) were identified for the first time by Hitchings and Elion in 1942 with antileukemic and immunosuppressant properties [39]. The 6-mercaptopurine (6-MP) is the oldest PNA approved for clinical use, employed in the treatment of acute leukemias. The next generation of PNAs has been available worldwide since the 1990s, comprising

primarily the cladribine, pentostatin, and fludarabine. PNAs have an important role as chemotherapeutic agents in hematological malignancies [40].

3.2.1. 6-Mercaptopurine

The 6-mercaptopurine (6-MP) was one of the first chemotherapeutic agents to be used in acute leukemia, remaining up today as one of the most useful drugs in acute leukemia's treatment [41,42]. In 1953 FDA approved the usage of 6-MP after a short 2 years mean time period of its synthesis. At this time there were only MTX and steroids as established treatment options for ALL, the commonest childhood cancer [43].

This chemotherapeutic agent is a prodrug, analogue of hypoxanthine, a naturally occurring purine derivative. 6-MP requires intracellular conversion into 6-thioinosine-5'-monophosphate (TIMP) by the hypoxanthine guanine phosphoribosyl transferase (HGPRT). TIMP is a substrate of thiopurine S-methyltransferase (TPMT) producing methylated TIMP which is an effective inhibitor of de novo purine biosynthesis. The TIMP that is not involved in catabolism is further metabolized by inosine monophosphate dehydrogenase (IMPDH) and later metabolized by a series of kinases and reductases to produce deoxy-6-thioguanosine5'triphosphate (thio-dGTP). Incorporation of thio-dGTP has been shown to trigger cell-cycle arrest and apoptosis involving the DNA mismatch repair [44].

3.2.2. Fludarabine

Fludarabine phosphate (FAMP) has activity in various indolent B cell malignancies and it was approved in 1991 for clinical usage in the treatment of chronic lymphocytic leukemia (CLL). FAMP is a prodrug that requires metabolic conversion to exert cytotoxic activity. It is rapidly dephosphorylated to 9-β-D-arabinosyl-2-fluoroadenine (F-ara-A), transported into cells and then phosphorylated by deoxycytidine kinase to the active form 2-fluoro-ara-ATP (F-ara-ATP) [45,46]. The F-ara-ATP is the only metabolite of FAMP that have cytotoxic activity, acting through different mechanisms that affect DNA synthesis.

F-ara-ATP inhibits ribonucleotide reductase (RNR), responsible for the conversion of ribonucleotides into deoxyribonucleotides which in turn are one of the key components at the construction of DNA strands. Furthermore F-ara-ATP incorporates into DNA, at the 3'-terminus, resulting in repression of DNA polymerization as well as inhibition of DNA ligase, an enzyme involved in DNA replication [47] and DNA primase, an accessory protein that synthesizes an RNA primer required for initiation of synthesis by DNA polymerase [48].

The most frequent adverse events associated with FAMP regimens are myelosuppression lymphocytopenia and infection, typically on respiratory tract. Despite the minor occurrence, severe neurotoxicity is one of the complications associated with FAMP [49].

3.2.3. Cladribine

Likewise FAMP, cladribine (2-CdA; 2-chloro-2'-deoxyadenosine) is phosphorylated and accumulated as 2-chlorodeoxyadenosine triphosphate (2-CdA-TP) in cells [50]. This metabolite

disrupts cell metabolism by incorporating into the DNA then inhibits DNA synthesis and repair, leading to accumulation of DNA strand breaks [50]. In addiction 2-CdA-TP is a potent inhibitor of RNR.

2-CdA was shown to have potent and long-term effects in the treatment of low-grade B-cell neoplasms, approved by FDA for clinical use in hairy cell leukemia (HCL). It shares the same adverse effects of FAMP, being the bone marrow suppression its major toxic effect, associated with severe infections.

3.2.4. Pentostatin

Pentostatin (deoxycoformycin; DCF) is a natural product first isolated from the culture of *Streptomyces antibioticus* [51] in 1974. This antimetabolite was the first effective agent against HCL, but nowadays its usage has largely been superseded by cladribine.

The primary site of action is the inhibition of adenosine deaminase (ADA), an enzyme that participates in purine salvage metabolic pathways. Inhibition of ADA leads to accumulation of adenosine and deoxyadenosine nucleotides in cells, which can block DNA synthesis by inhibiting RNR. Another important action of pentostatin is the inactivation of S-adenosyl homocysteine hydrolase by deoxyadenosine, resulting in accumulation of S-adenosyl homocysteine, an intermediate in the synthesis of cysteine and adenosine particularly toxic to lymphocytes. Pentostatin also has adverse effects related with the bone marrow suppression.

3.3. Pyrimidine analogs

Pyrimidine analogs sparked the interest of scientists from the observation that rat malignant tissue used pyrimidine uracil more rapidly than normal tissues [52]. In the late 1950s Charles Heidelberger and colleagues synthesized the fluoropyrimidine 5-fluorouracil (5-FU) [53], which demonstrated specific uracil antagonism within antitumor capabilities. Others pyrimidine analogs were developed later (e.g. capecitabine, cytosine arabinoside and gemcitabine) and this class is currently extensively used in cancer therapy.

3.3.1. Fluouracil

5-FU is the mainstay of treatment for many common malignant diseases, particularly for colorectal cancer. It's also used in breast, pancreatic and head and neck cancers [52]. This antimetabolite exerts its antitumor effects through several mechanisms including inhibition of the enzyme TS, related to thymidine synthesis from uridine, and incorporation of its metabolites into RNA and DNA. 5-FU enters into cells rapidly and is converted intracellularly by metabolic enzymes into its active metabolite 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP). FdUMP inhibits TS leading to nucleotide pool imbalance, decreasing thymine concentration which leads to uracil incorporation into DNA causing DNA strand breaks [52]. Another 5-FU metabolite, fluorouridine triphosphate (FUTP) is extensively incorporated into RNA, disrupting normal RNA processing and function.

Usual side effects of 5-FU are gastrointestinal, including nausea, vomiting, diarrhea, and stomatitis. Hematologic effects are also common, like myelosuppression and thrombocytopenia. Although considered unusual, cardiotoxicity has been reported as well as adverse neurological effects [54,55].

3.3.2. Capecitabine

Capecitabine (N^4-pentyloxycarbonyl-5′-deoxy-5-fuorocytidine) is an oral prodrug of 5-FU developed with the objective of improving tolerability and intratumor drug concentrations through tumor-specific conversion to the active drug. This selectivity is due the presence at higher levels of thymidine phosphorylase (TP), the final enzyme responsible for conversion to the active drug, in cancer cells [56].

In 1998, capecitabine was approved by FDA for the treatment of women with taxane- and anthracycline-refractory advanced breast cancer. Afterwards, this antimetabolite received the approval for metastatic colorectal carcinoma.

The most common toxicities related to treatment with capecitabine are gastrointestinal effects (diarrhea, nausea and vomiting) and hand-foot syndrome [57]. Other adverse effects were also observed such as alopecia, myelosuppression and cardiotoxicity [57,55].

3.3.3. Gemcitabine

The deoxycytidine analogue gemcitabine (difluorodeoxycytidine, dFdC) received its first approval by FDA in 1996 for the treatment of patients with pancreatic cancer and NSCLC. Furthermore, gemcitabine was approved for the first-line treatment of patients with metastatic breast cancer and advanced ovarian cancer, in 2004 and 2006, respectively.

Gemcitabine is phosphorylated by deoxycytidine kinase (DCK) to its 5′-monophosphate form (dFdCMP) and additionally metabolized by several other enzymes to its 5′-diphosphate (dFdCDP) and 5′-triphosphate derivatives (dFdCTP). Then, this last metabolite dFdCTP is incorporated into DNA, inhibiting DNA replication and inducing apoptosis [58].

The major dose-limiting toxicity of gemcitabine is myelosuppression, but other adverse effects are related with the therapy such as flu-like symptoms, nausea, vomiting and rash [59].

3.3.4. Cytarabine

Cytarabine (1-β-D-arabinofuranosylcytosine; ara-C) had its first approval by FDA in 1969 as a chemotherapeutic agent to be used with other drugs for the treatment of adult and pediatric acute myelogenous leukemia (AML). According to the NCI, cytarabine is also approved to treat ALL, chronic myelogenous leukemia (CML) and as a single agent to prevent and treat meningeal leukemia.

Since its approval by FDA in 1969, the clinical effectiveness of this drug has increased with knowledge of its pharmacologic and biologic properties. Ara-C is a prodrug and needs to be converted to its active form, ara-C 5′-triphosphate (Ara-CTP), by a series of intracellular enzyme-dependent phosphorylation steps [60].

Its mechanism of action is similar to that of the deoxycytidine analogue Gemcitabine: Ara-C is transported into the cell and once it is inside, it is phosphorylated into ara-C monophosphate (ara-CMP) by DCK and eventually to ara-C triphosphate (ara-CTP) which then competes with deoxycytidine triphosphate (dCTP) for incorporation into DNA and subsequently blocking DNA synthesis causing cell death [60].

Treatment with ara-C is associated with several adverse side effects, including myelosuppression (mostly leukopenia, thrombocytopenia and severe anemia), infections, mucositis, neurotoxicity, and acute pulmonary syndrome [61,27]

4. Microtubule-target agents

Microtubules are dynamic structures composed of α–β-tubulin heterodimers and microtubule-associated proteins representing one of the major components of the cytoskeleton. Microtubules are involved in many cellular processes including maintenance of cell structure, protein transportation and mitosis. Because of the central role of microtubules in mitosis, drugs that affect microtubule are useful in cancer chemotherapy. In this context, Microtubule-Targeted Agents (MTAs) constitute a class of anticancer drugs largely used in the clinics to treat solid tumors and hematological malignancies, either alone or as part of different combination regimens. MTA are potent mitotic poisons that are broadly classified into microtubule-stabilizing (e.g. taxanes and epothilones) and microtubule-destabilizing (e.g. vinca alkaloids) drugs.

4.1. Vinca alkaloids

The first natural anticancer agents approved to clinical use were the vinca alkaloids vincristine and vinblastine, introduced in the late 1960s. Vinca alkaloids were originally isolated from the Madagascar periwinkle *Catharanthus roseus* and over thirty alkaloids have been obtained of which a few are known definitely to be active [62]. Actually, there are three major vinca alkaloids in clinical use: vinblastine, vincristine and vinorelbine.

Vincas are classified as destabilizing agents due to their ability to cause microtubule depolymerization, suppress treadmilling and dynamic instability, blocking mitotic progression, and ultimately result in cell death by apoptosis. Vinca akaloids bind in one of three sites on tubulin, called the "vinca" domain, located near the exchangeable GTP binding site [63-65].

Vinca alkaloids differ in their chemotherapeutic effectiveness being part of therapeutic schemes in different types of malignancies. Vincristine is used in combination chemotherapy for treating pediatric leukemias, Hodgkin and non-Hodgkin lymphoma, as well as solid tumors such as Wilms tumor and neuroblastoma [66-68]. Vincristine can occasionally be used in the treatment of small cell lung cancer (SCLC). Currently, vinblastine is a standard component of regimens for treating lymphomas including Hodgkin's disease. It´s also used for the treatment of bladder cancer, testicular carcinomas, germ cell malignancies and breast cancer [66,69]. Moreover the semisynthetic derivate of vinblastine, vinorelbine, has activity against NSCLC and breast cancer [70,71].

Furthermore these compounds diverge in their toxicities. While severe neurotoxicity is observed less frequently with vinorelbine and vinblastine, this side effect is frequently noticed with vincristine [72,73]. Myelosuppression, in turn, predominates with vinblastine and vinorelbine [74] and is the main dose-limiting toxicity of those drugs.

Vinca alkaloids and the others MTAs can present resistance in cancer cells due to: (i) cellular efflux of the anticancer agents, especially by the overexpression of drug efflux pumps, such as P-glycoprotein and multidrug resistance-associated protein 1 (MRP1) [75]; (ii) mutations in tubulin at the drug binding sites [76,77]; (iii) changes in the tubulin isotype composition of microtubules [78] and; (iv) changes in micro-tubule-regulatory proteins [79].

4.2. Taxanes

Taxanes are natural cytotoxic diterpenes classified as microtubule-stabilizing anticancer agents. Paclitaxel and the semisynthetic analog docetaxel are considered to be among the most important anticancer drugs in cancer chemotherapy.

Paclitaxel was identified in 1971 as part of a NCI program that screened medicinal plants for potential anticancer activity, whereof the researchers found cytotoxic effects on solid tumors and leukemic cells [80]. Paclitaxel was initially derived from the bark of the Pacific yew (*Taxus brevifolia*) in a process that a centenary tree provides only a gram of the compound. This lead to a semi-synthetic method that use the 10-deacetylbaccatin-III, which is extracted from more abundant yew species such as the European yew *Taxus baccata* [81].

Docetaxel, in turn, is an esterified derivative of 10-deacetylbaccatin-III, produced by Potier and his colleagues in 1986 [82]. The structures of paclitaxel and docetaxel differ on the ester side chain attached at C-13 and in substitutions at the C-10 taxane ring position, which confers docetaxel slightly more water solubility than paclitaxel [83,25]

These drugs interact with β-tubulin promoting tubulin polymerization and formation of stable microtubules, even in the absence of GTP- and microtubule-associated proteins, which are usually essential for these processes. This inhibition of microtubule depolymerization results in mitotic arrest leading to apoptosis of the cancer cells [84]. Furthermore, taxanes have been demonstrated to induce many other cellular effects that may or may not relate to their disruptive effects on microtubule dynamics, including the directly phosphorylation, hence inactivation, of proteins that blocks apoptosis in cancer cells (such as bcl-2) [85].

Paclitaxel was approved by the FDA in 1992 for the treatment of refractory breast cancer and refractory ovarian cancer. Currently this agent has a central role in the treatment of breast, ovarian, NSCLC and AIDS-related Kaposi's sarcoma. In turn, docetaxel received the approval in 1995 for the treatment of metastatic breast cancer. Furthermore was approved for use in hormone refractory prostate cancer (HRPC), advanced squamous cell carcinoma of the head and neck, breast cancer, gastric adenocarcinoma and NSCLC.

Treatment with these drugs often results in a number of undesirable side effects, as well as resistance in cancer cells, as mentioned previously. In order to overcome those problems, novel taxanes are in development as well as novel formulations. In 2005 Abraxane® (paclitaxel

albumin-bound nanoparticles, solvent-free) was approved for advanced breast cancer. Abraxane® prevent the hypersensitivity reactions typically associated with paclitaxel, which are generally related to the solvent suspension of polyoxyethylated castor oil (Cremophor EL) [86-88].

Taxanes exerts its primary toxic effects on the bone marrow, mainly neutropenia, and may cause neuropathy [89]. Docetaxel causes greater degrees of neutropenia than paclitaxel. Furthermore, docetaxel can cause fluid retention leading to peripheral edema and pulmonary edema, in extreme cases. Despite the high incidence of major hypersensitivity reactions due to the Cremophor EL vehicle, these reactions are no longer a serious problem due to the advent of effective premedication regimens [90] and new formulations [88].

4.3. Epothilones

Epothilones are a new class of natural cytotoxic antineoplastic microtubule-stabilizing agents. Ixabepilone, a semisynthetic analog of the natural product epothilone B, is the only epothilone approved for cancer therapy, indicated for metastatic breast cancer.

The epothilones competitively inhibit the binding of paclitaxel to polymerized tubulin, indicating that the two compounds share a common binding site despite significant structural differences [90,91]. It has been reported that ixabepilone is less susceptible to drug-resistance mechanisms that limit the efficacy of taxanes, like P-glycoprotein mediated efflux and the overexpression of class III β-tubulin, due to its reduction in polymerization rate of microtubules [91,92].

Likewise taxanes, ixabepilone is also formulated in Cremophor EL yielding hypersensitivity reactions. Other side effects related to its use are neuropathy, neutropenia, severe diarrhea and fatigue [93,94].

5. Camptothecin analogs

Likewise paclitaxel, camptothecin was discovered as part of a NCI program in 1966 by Wall and Wani [95]. Camptothecin is a pentacyclic quinoline alkaloid present in wood, bark, and fruit of the Asian tree *Camptotheca acuminate*, that specifically target the topoisomerase I (Top-I), a nuclear enzyme that plays a critical role in DNA replication and transcription [96].

Top-I promote relaxation of the supercoiled DNA, prior to transcription, through the formation of a single strand break and religation. The camptothecins bind the covalent Top-I-DNA complex, known as the "cleavable complex", stabilizing it and inhibiting reannealing of the parent DNA. Consequently, camptothecins lead to reversible accumulation of double-stranded DNA breaks and tumor cell death [97-99].

Several derivatives of camptothecin have been synthesized, but only irinotecan and topotecan have been approved for clinical use. Irinotecan and topotecan, which are more soluble and less toxic analogs, are currently used in a wide spectrum of cancers. Topotecan is part of regimens

to treat ovarian, lung and cervical cancer. Irinotecan is a prodrug, currently used for metastatic colorectal cancer.

Irinotecan and topotecan produces dose-limiting side effects restricting safety administration and then their anti-tumor efficacy. Diarrhea is the principal side effect related to irinotecan. Moreover the use of this drug can cause nausea, vomiting, anorexia, fatigue, abdominal pain, alopecia and neutropenia. The principal toxicity of topotecan when administered at standard doses is neutropenia, while the nonhematological toxicities are usually mild [100,101].

6. Epipodophyllotoxins

Podophyllotoxin was first isolated in 1880, but its structure was determined later by Hartwell and Schrecker [102]. Despite the antineoplastic activity, podophyllotoxin was not used in clinical practice due to its toxicity. Several less toxic analogs of podophyllotoxin were produced and two analogs were approved for clinical use (etoposide and teniposide).

While etoposide is most widely used to treat lung cancer and testicular cancer, it is also effective for Hodgkin and non-Hodgkin lymphomas, acute nonlymphocytic leukemia, gastric cancer, and soft-tissue sarcomas. Teniposide has significant activity in SCLC and in the treatment of childhood lymphomas and leukemias [103-105].

The cellular target for etoposide and teniposide is topoisomerase II (Top-II) [106,107]. Top-II enzymes regulate essential cellular processes, including DNA replication and chromosome segregation, by altering the topology of chromosomal DNA. These enzymes induce transient double-stranded breaks in the DNA allowing DNA strands to pass through each other and unwind or unknot tangled DNA. Etoposide and teniposide inhibit Top-II to religate cleaved DNA molecules [108]. This phenomenon leads to accumulation of covalent complexes Top-II-DNA resulting in permanent DNA strand breaks, which trigger mutagenic and cell death pathways [109].

In addition to causing cell death, these agents may, under certain circumstances, lead to neoplastic transformation. Epipodophyllotoxin therapy can cause AML characterized by chromosomal translocations, especially in chromosome 11q23 [110,111]. Other common side effects related to antineoplastic drugs might arise, such as bone marrow suppression, nausea, vomiting and alopecia.

7. Antibiotics

7.1. Anthracyclines and anthracenediones

The anthracyclines, which include doxorubicin, daunorubicin, epirubicin and idarubicin, are a class of antibiotic chemotherapeutic agents routinely used in the treatment of several cancers. While daunorubicin and idarubicin are more effective in acute leukemias, doxorubicin and

epirubicin display broader activity against human solid tumors. Doxorubicin has a central role in the therapy of breast, lung, gastric, ovarian, thyroid, non-Hodgkin's and Hodgkin's lymphoma, sarcoma and pediatric cancers. Epirubicin is an epimer of doxorubicin indicated as component of therapy for breast cancer [112,113].

These chemotherapeutic agents attack cancer cells by multiple mechanisms (i) intercalation with DNA and disruption of Top-II, directly affecting DNA replication and repair, (ii) generation of quinone-type free radicals and their damage to cellular membranes, DNA and proteins and (iii) triggering of apoptotic cell death through complex signaling pathways [27,113].

Despite the large use, the most serious toxicity associated with anthracyclins is cardiotoxicity which can be cumulative and irreversible [114]. However, liposomal formulation of doxorubicin was shown to be less cardiotoxic than traditional doxorubicin without compromising efficacy in adults with solid tumors [115].

Another important antibiotic chemotherapeutic agent is the anthracenediones, which also inhibit Top-II. Mitoxantrone is the most active compound in the anthracenediones class and has been approved for use in AML and prostate cancer [116,117]. It is relevant to point that mitoxantrone has limited ability to produce quinone-type free radicals and causes less cardiac toxicity than does doxorubicin.

7.2. Bleomycin

Bleomycins are a group of glycopeptides antibiotics, isolated in the early 1960s from *Streptomyces verticillis* [118]. Its cytotoxic properties result from generation of free radicals leading to single- and double-stranded breaks in DNA.

Bleomycins are attractive components of chemotherapy regimens due to minimal myelotoxicity and immunosuppression whilst the pulmonary toxicity related to its use limits the applicability of this drug [119]. Currently bleomycins have antitumor activity against certain types of lymphoma, testicular tumors, head and neck cancers, Kaposi sarcoma, cervical cancer and germ-cell tumors.

8. Enzymes

8.1. L-Asparaginase (L-ASNase)

L-Asparaginases (L-ASNase) are effective antineoplastic agents used in first-line treatment of a variety of lymphoproliferative disorders, especially in ALL. It has been used in combination with other agents, including methotrexate, doxorubicin, vincristine, and prednisone [120]. Currently, there are three preparations of L-ASNase available for clinical use: native enzyme from *Escherichia coli* (Elspar®); a pegylated *E. coli* L-ASNase (Oncospar®), and native erwinia enzyme from *Erwinia chrysanthemi* (Erwinase®).

The mechanism of action of L-ASNase is based on the assumption that tumor cells, especially leukemic cells, require a huge amount of amino acid asparagine (Asn) to maintain their rapid malignant growth. Those cells lack adequate amounts of asparagine synthetase and are dependent on an exogenous source of Asn for survival. L-ASNase catalyzes the hydrolysis of L-ASN to L-aspartic acid and ammonia, significantly depleting the circulating asparagines from plasma [27,121].

The most common side effect is related to inhibition of protein synthesis and allergic reactions. Hypersensitivity reactions can be solved by use of modified versions of L-ASNase such as polyethylene glycol (PEG)-conjugated asparaginase (pegasparaginase). Pegasparaginase reduce immunogenic reactions and posses a considerably longer half-life, reducing the number of injections for the patient. In recent years, clinical trials have established the importance of pegasparaginase in frontline pediatric and adult ALL therapy [120,122]

Resistance arises through induction of asparagine synthetase in tumor cells [123] and administrations of ASNase may induce the development of antibodies that neutralize the enzyme [120, 121,124].

9. Diverse agents

9.1. Hydroxyurea

The synthesis of Hydroxyurea (HU) occurred for the first time in 1869 by Dresler and Stein [125], meanwhile its biological activities as a myelossupressive drug were only demonstrated 60 years later [126]. Further studies regarding its mechanism of action were able to demonstrate its activity at impairing DNA synthesis through blocking its deoxyribonucleotides subunits formation by acting at the ribonucleotide reductase (RNR) enzyme [127]. The RNR enzyme inhibited by HU is responsible for the conversion of ribonucleotides into deoxyribonucleotides which in turn are one of the key components at the construction of DNA strands. Once HU is mainly effective at the S phase of the cell cycle, when its target, e.g. the catalytic subunit of RNR, is highly activated in cells, it also provides synergistic effect with radiotherapy [128]. Additionally, regardless of the origin of the HU-induced release of nitric oxide [129,130], its contribution to the antineoplastic effect of HU remains relatively unexplored.

HU is currently used in combination therapies along with other chemotherapeutic agents and radiation regimens to treat resistant chronic myelocytic leukemia (CML), cervical carcinomas, malignant melanomas, head and neck cancers and brain tumors (e.g., glioma, meningioma) [127,128].

HU is well-known by its dose-limiting myelosuppressive effect which appears within a few days after the beginning of its use and is mostly reversed through the discontinuation of the drug. Skin and nail hyperpigmentation, malleolar ulcerations and solar hypersensitivity are some of the most observed cutaneous side effects in long-term exposed patients [131,132]. Multiple skin tumors as well as its precursor lesions may also develop after sun exposure [133,134].

9.2. Thalidomide

In the late 1950s thalidomide was introduced by Chemie Grunenthal company into the market as a sedative drug and within a few years later the disseminated teratogenic consequences of its use during pregnancy practically banned its worldwide commercialization [135]. Further studies demonstrated the antiangiogenic activity of thalidomide *in vivo* through inhibition of bFGF/VEGF as well as its immunomodularory effects by suppression of the pro-inflamatory TNF-alfa synthesis and T-cell co-stimulatory activity [136]. Those properties encouraged further studies regarding its advantages of usage in a series of cancers, such as multiple myeloma (MM), renal cell carcinoma, prostate cancer, among others [135]. Thalidomide has currently been used in combination with dexamethasone in the treatment of MM [137]. Thalidomide has at least a partial benefit in response to cancer-related cachexia, mitigating the total weight and lean body mass reduction [138,139].

The most common adverse effects associated with thalidomide's employment include constipation and sedation. Meanwhile cardiovascular effects like hypotension and bradycardia, somnolence, thromboembolism and peripheral neuropathy are the most severe toxic events related to this drug and may require the withdrawal of it, which is generally sufficient to achieve clinical improvement [140,141].

9.3. Estramustine

Estramustine is a nitrogen mustard derivative formed by the union of normustine (nitrogen mustard) and estradiol-17beta-phosphate with antineoplastic effects that rely on its properties as an anti-mitotic drug through disruption of the microtubule organization in HRPC cells as well as by pro-apoptotic events [142]. Recently concluded trials also assigned an additional benefit in treating prostate cancer with the addition of other chemotherapeutics, e.g. docetaxel, in comparison to the administration of estramustine alone [143].

The most common side effects observable within the use of estramustine are vomiting and nausea, affecting nearly 50% of the patients. Meanwhile the pro-estrogenic consequences (gynecomastia, impotence) and thromboembolic events are some of the most severe adverse effects. The latter, specifically is also due to the contribution of the disease itself [143].

9.4. Bortezomib

Bortezomib was the first proteasome inhibitor approved by the FDA in 2003 as an alternative treatment for refractory MM. Its approval was extended in 2008 for the treatment of newly diagnosed MM. Bortezomib's usage as an anticancer agent was also approved by the FDA in 2006 for the treatment of relapsed or refractory mantle cell lymphoma (MCL) [144].

This drug acts through inhibition of the 26S proteasome by blocking its 20S core subunit's chymotrypsin-like activity, which affects several intracellular signaling pathways, as the NF-kB anti-apoptotic pathway. The NF-kB molecule is found directly attached to its inhibitor (IkB) which in turn becomes ubiquitinated and degraded at the proteasome in response to specific stressful situations, releasing NF-kB to enter the nucleus and exert its pro-survival effects. By

this means, targeting the proteasome structure would lead to inhibition of NF-kB activation. Additionally, bortezomib may also promotes cancer cells to sensitization towards cytotoxic drugs [145].

The commonest toxic effects related to the use of bortezomib are fatigue, gastrointestinal disturbances, thrombocytopenia, paresthesia and peripheral neuropathy. Besides the adverse events aforementioned, intrinsic/acquired resistance and unsatisfactory response toward solid tumors represent some of the disadvantages associated with the utilization of bortezomib [145].

9.5. Zoledronic acid

Zoledronic acid is a heterocyclic nitrogen-containing bisphosphonate [146]. Bisphosphonates, such as zoledronic acid, are anti-resorptive agents approved for treatment of skeletal complication associated with metastatic breast cancer and prostate cancer. These agents act on osteoclasts, key cells in the bone microenvironment, inhibiting bone resorption [147, 148].

Moreover, zoledronic acid is used extensively in diseases with high bone turnover such as MM. Nephrotoxicity can be observed with use of this drug, and is related to dose, infusion time and plasma concentration. Furthemore, zoledronic acid has a long renal half-life, contributing to renal damage. Osteonecrosis of the jaw is also associated with zoledronic acid [149,150].

10. Hormones and related agents

10.1. Glucocorticoids

Glucocorticoids are primary stress hormones that function to maintain homeostasis regulating many biological processes, including immune function, skeletal growth, reproduction, cognition, behavior, and cell proliferation and survival [151]. Glucocorticoids act through their binding to a specific physiological receptor that translocates to the nucleus and induces antiproliferative and apoptotic responses in sensitive cells [27]. These actions are important in their usage as therapeutic agents in cancer treatment.

Glucocorticoids, dexamethasone and prednisone, are widely used for the treatment of leukemias and lymphomas because of their effects on cell cycle progression and apoptosis. They are also adopted as a co-medication in the therapy of solid tumors, either because of their effectiveness in treating the malignancy or for decreasing edema, pain, electrolyte imbalance, nausea and emesis or yet to reduce cytotoxic reactions caused by other treatment regimens [152].

10.2. Progestins

Progesterone is an essential regulator of normal human female reproductive function in the uterus, ovary, mammary gland and brain, and also plays an important role in non-reproductive tissues such as the cardiovascular system, bone and the central nervous system. This highlights the widespread role of this hormone in normal physiology. The effects of progester-

one are mediated through the nuclear progesterone receptor (PR), which interacts with transcriptional coregulators, moves into nuclear aggregates and regulates gene expression [153].

Progestational agents, such as the agonists of the PR megestrol and megestrol acetate, have been used as second-line hormonal therapy for metastatic hormone-dependent breast cancer and in the management of endometrial carcinoma previously treated by surgery and radiotherapy [27].

10.3. Antiestrogens and antiandrogens

Antiestrogens and antiandrogens inhibit the binding of the natural endogenous ligands with the estrogen and androgen receptors (ER; AR) respectively. Thus they act preventing exacerbation of these receptors signaling pathways frequently observable in cancer cells. This fact lead to inhibition of cancer cells division [154, 155].

Fulvestrant is an antiestrogen approved by the FDA in 2002 for the treatment of hormone receptor positive metastatic breast cancer in post-menopausal women refractory to previous tamoxifen regimen [156]. Fulvestrant is a complete antagonist of the ER-alfa/ER-beta and inhibits estrogen signaling by promoting mainly the degradation of ER-alfa and PRs after binding to the ER [157]. The most observable side effects due to the usage of fulvestrant include hot flashes, thrombosis, joint disorders, pain and gastrointestinal events [158].

Flutamide, Bicalutamide and Nilutamide are non-steroidal antiandrogens introduced in the 1970s in order to preclude the unwanted effects caused by the nonselective profile of steroidal agents. These non-steroidal agents are only used in combination with other drugs, mostly with GnRH agonists, for the treatment of prostate cancer in order to counterbalance the effect of the released testosterone following GnRH administration. Bicalutamide has been recently approved in the European Union for the treatment of locally advanced prostate cancer and present the best schedule and adverse effects profiles. Toxic effects include hot flashes, hepatotoxicity, diarrhea, decreased libido and gynecomastia. Patients in treatment with nilulatamide may experience ocular alterations [155].

10.4. Selective Estrogen Receptor Modulators (SERMs)

Selective estrogen receptor modulators (SERMs) are tissue-selective compounds and depending on the site of action, exhibit agonistic (bone, liver, brain, cardiovascular system), antagonistic (brain, breast) and mixed agonist/antagonist (uterus) effects. This phenomenon occurs due to different ER subtypes expression throughout the body among other factors [159,160].

The currently SERMs approved by the FDA are tamoxifen, toremifene and raloxifen. Raloxifen is used in osteoporosis's treatment and prevention for postmenopausal women and reduction of invasive breast cancer's risk for women with osteoporosis or at increased risk of invasive breast cancer.

Tamoxifen is used in the treatment of metastatic breast cancer as well as in the adjuvant treatment of node-positive breast cancer. Additionally, tamoxifen demonstrates preventive effects in women at high-risk of developing breast cancer [161]. Toremifene is used in the

treatment of metastatic breast cancer in postmenopausal women with ER+ or tumors with unknown ER status [162].

Due to its agonistic properties, tamoxifen significantly increases the risk of endometrial cancer, pulmonary embolism and stroke, rendering the treatment based on aromatase inhibitors an interesting alternative, which demonstrate reduced frequency of the aforementioned adverse effects, though not without a high risk of loss in bone mineral density (BMD) and, consequently, fractures [160]. Raloxifen and toremifene demonstrates similar effectiveness in comparison to tamoxifene regarding reduction of risks in developing advanced and invasive breast cancer respectively. They also show evidence of lower incidence of venous thromboembolic events and endometrial cancer [163,164].

10.5. Aromatase inhibitors

The aromatase enzyme is responsible for the conversion of androgens to estrogens and represent the primary source of estrogens in post-menopausal women. Accordingly, the aromatase inhibitors (AI) provide reduction of estrogen concentration within ER+ breast cancer cells. There are three generations of AI, which may also be classified as belonging to the type 1 (steroidal) and type 2 (non-steroidal) [27]. Aminoglutethimide is a 1st generation nonsteroidal AI which was utilized in association to glucocorticoid in the treatment of breast cancer and is currently replaced by the following generations of AI. Formestane, a 2nd generation steroidal AI, administrated via intramuscular-injection, led to localized reactions. It also presents clinical benefits within the group of patients that experienced progressive disease after treatment with tamoxifen and nonsteroidal AI [25,165]. Exemestane is an irreversible 3rd generation orally administrated steroidal AI, which exhibits higher estrogen deprivation effect in comparison to formestane in the treatment of ER+ breast cancer progressive cases previously treated with tamoxifen. Anastrozole and letrozole are 3rd generation nonsteroidal AI which have demonstrated improved results with respect to disease free survival, recurrence rate and time to recurrence when compared to tamoxifen. This observation regards early, advanced and metastatic ER+ breast cancer treatment, irrespective of functioning as a first line adjuvant or post-tamoxifen drug. Despite the aforementioned improved clinical outcome provided by 3rd generation AIs, further long-term studies should be conducted in order to assess whether its safety profiles are superior when compared to that of tamoxifen [164,166-170).

11. Conclusion

Despite the increased number of therapeutic options, the cancer therapy remains a challenge for physicians and researchers, especially with regards to the tumor resistance. In this scenario, a better understanding about the molecular basis of cancer will enable the improvement and development of therapeutic strategies that allow an effective combat against this malignancy and better quality of life for patients.

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