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Review Article
Advantages of Drug Selective Distribution in Cancer Treatment: Brentuximab Vedotin

[1,2]Luis Mario Villela-Martinez, [1]Ana Karen Velez-Ayala, [1]Rosa del Carmen Lopez-Sanchez, [1]Jorge A Martinez-Cardona and [1]Jose A Hernandez-Hernandez

[1]Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Edificio CITES, 3er Piso. Av. Morones Prieto No. 3000 Poniente, Col. Los Doctores. C.P. 64710. Monterrey, Nuevo León, México
[2]Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado de Sonora (ISSSTESON). Centro Medico "Dr. Ignacio Chavez". Blood bank & Hematology Department. Aguascalientes S/N, Centro, 83000 Hermosillo, Sonora, Mexico

Abstract

Medical practice has different forms of treatments for cancer. Different challenges are presented in chemotherapy, limited therapeutic efficacy as single drugs, needed to increase doses or co-administration with other cytotoxic, high frequency and severity of adverse events, due low selectivity of drugs. Researchers have innovated in the treatment of cancer, either by creating selective drug delivery systems or by drugs specifically designed to a unique target site of action. This has not just improved the therapeutic efficacy but also limited the adverse events. Some innovations have been focused on exploiting the selectivity properties of the antigen-antibody reactions, which has allowed the development of therapeutic antibodies. Antibodies can destroy cancer cells by different mechanisms. Some can activate apoptosis pathways directly. Other are linked with cytotoxic drugs that are released into the tumor cells when they have been incorporated by the process of endocytosis (Trojan horse phenomenon). Lymphoproliferative syndromes have gotten benefit from these innovations. Most of the treatment regimens use “traditional” drugs on combinations (i.e., CHOP= cyclophosphamide, doxorubicin, vincristine, prednisone for Non-Hodgkin's lymphoma or ABVD = doxorubicin, bleomycin, vinblastine, dacarbacyne; for Hodgkin's lymphoma) that have good therapeutic efficacy but low selectivity. The introduction of monoclonal antibody therapy (mAb) or conjugated antibody therapy (ADCs) have increased disease-free survival and some types of lymphoma overall survival. In this review we make a great approach to mAb and ADC, from the development of these innovative drugs to the clinical use of them, showing the results obtained in different trials, as well as their adverse effects and monitoring as part of pharmacovigilance which they must have.

Key words: ADC, biodistribution, brentuximab vedotin, hematological malignancies

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Corresponding Author: Jose A Hernandez-Hernandez, Tecnológico de Monterrey. Escuela de Medicina y Ciencias de la Salud, Edificio CITES, 3er Piso. Av. Morones Prieto No. 3000 Poniente, Col. Los Doctores. C.P. 64710. Monterrey, Nuevo León, México

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INTRODUCTION

Until the second middle of the nineteenth century, concepts as potency and specificity were used to explain pharmacological effects of drugs, any of them of natural origin. These important effects could be explained vaguely by the properties that changes in their chemical structures have on affinity to certain organs and tissues[1,2].

Pharmacology as a scientific discipline was born in the mid-19th century, amid of a huge biomedical resurgence of that period. In 1860's the relationship between the chemical structure of a drug and its pharmacologic action were studied systematically[2-4]. Later, the same concepts were applied to explain how endogenous substances different could produce several effects according to the organ involved or how they participate in various biological, physiological and pathophysiological processes at the same time[5]. Physiologically, chemical signaling is the principal mechanism by which biological functions are controlled, from a single cell to the whole organism. So for pharmacological/therapeutic effects always to exert an effect, chemical recognition is always needed. In classical pharmacology proteins or receptors are used as an experimental or therapeutic target; this paradigm has to change[6].

From pharmacodynamics point view, the use of substances to generate pharmacological effects and potentially therapeutic effects depends mainly on that chemical recognition between substance (drug) and the target protein, enzyme, transporter or receptor[7-9]. However, in the therapeutic process, not only the recognition between drug and protein receptor o enzyme are important but also pharmacokinetic processes. Pharmacokinetic is the process that directs the drug to the site where it should act. Currently, Pharmacokinetics is defined as the study of the time course of a drug since administration, absorption, distribution, metabolism and elimination (ADME). This definition does not include pharmacological or therapeutic effects but those processes are imperative to reach drug concentration appropriately[10]. Clinically this process is critical although pharmacokinetic processes should guarantee sufficient concentration in the active site to enhance clinical response and reduce concentration on other sites to decreases drug toxicity[11]. The drug molecules, however, may pass through the body several times before ultimately leaving the system by metabolism or excretion or whether that arrive at target site could have the most of the times is a stochastic process[11].

In cancer treatment, pharmacokinetic is of particular importance because therapy should be focused on having selective toxicity but if cytotoxic effect depends on of tissue target concentration more than plasma concentration, how could we have selectivity distribution to maximize cytotoxic effect without o reducing its adverse effects? The idea behind targeted anticancer therapies originates from the 'magic bullet concept' which was introduced at the beginning of the 20th century by Paul Ehrlich, the father of modern immunology and chemotherapy. Ehrlich proposed that to reduce adverse effects of toxic molecules on healthy tissues drugs should be selectively delivered to disease-causing cells "magic bullets" [12]. This concept could be referred to as "selective distribution" and is useful not only for cancer treatment but also for other pathologies treatment that requires more selective effects[13,14].

Therapeutic challenges in cancer treatment: Cancer is a major public health problem worldwide and is the second-leading cause of death in the United States[15]. Radiation and chemotherapy are standards for cancer treatment; however, traditional radiation and chemotherapies have many limitations. Although radiation therapy is focused on the cancer tumor, therapy risks severe damage to nonmalignant tissues that are in the path of the radiation beam[16]. Recently, more accurate equipment has been developed to apply radiotherapy in a more secure and convenient way, reducing significantly treatment-related adverse effects[17,18]. Radiation also has reduced effectiveness to treated metastases because it would require localization of metastatic tumors for treatment. Sometimes, a comprehensive irradiation approach has been used, principally when cancer is in advanced stages (spinal metastases)[19], when is untreatable by surgical or chemotherapy (inoperable non-small-cell lung cancer)[20] or for some kinds of cancer (Ewing's sarcoma or rhabdomyosarcoma)[21].

The other therapeutic approach is drug-mediated treatment. Chemotherapy is a systemic treatment that typically targets to highly proliferative cells. Systemic delivery exposes all cells to the drug. However, the lack of specificity also results in damage to highly proliferative non-malignant cells, in bone marrow, gonads, gastrointestinal mucosa and hair follicles, resulting in acute complications and systemic toxicity[22,23]. Systemic toxicity sometimes limits treatment, reduces drug effectivity, contributes to drug resistance and facilitates recurrence. Traditional chemotherapy would also be ineffective in overcoming multidrug resistance, responsible for early or late recurrence. However, adverse effects are also increasing in frequency and severity. Thus there is an urgent need for a more targeted approach that will increase treatment efficacy and reduce treatment adverse effects[23].

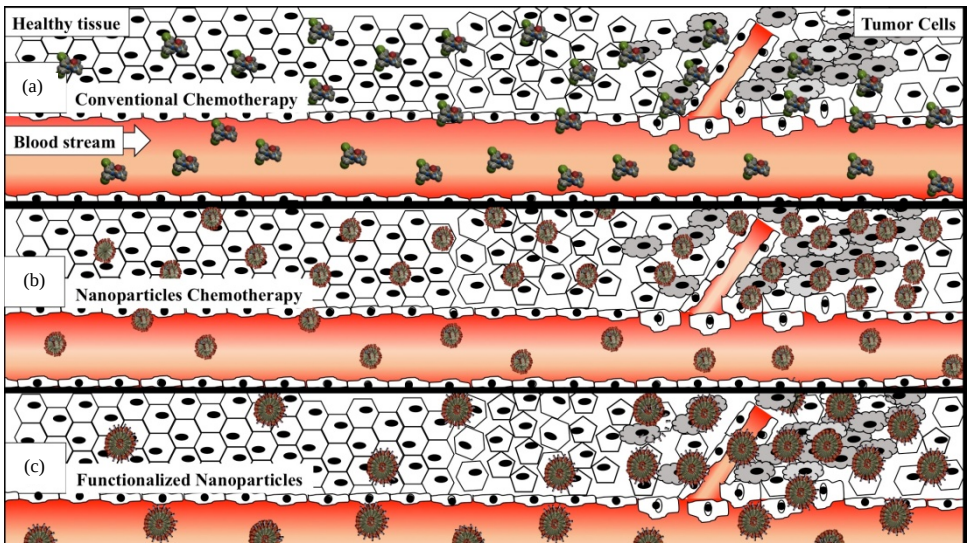

Fig. 1: Advantages selective distribution in cancer treatment. The figure depicts improvements in selective cancer distribution. Panel A: In traditional chemotherapy, the drug is widely distributed in the human body according to its physicochemical properties. This process reduces the available concentration of the drug and its therapeutic effect. Panel B: Improvements in drug delivery have made possible to obtain better distribution of antineoplastic drugs increasing drug concentration in areas next to tumor, this reduces no specific distribution to healthy tissue. Panel C: 3rd generation of system delivery (functionalization-based nanoparticles) have increased selective distribution and therapeutic efficacy against cancer cells. However, this process represents a big challenge

Improving selectivity of cytotoxic drugs: To improve selective distribution process of drugs and optimize pharmacotherapy of cancer. Researchers have begun to find strategies to improve the selective distribution of cytotoxic and thus optimize chemotherapy, maximizing the therapeutic effects and decreasing its adverse effects[24]. The goals of targeted cancer therapy design are: (1) selectively deliver a high dose of an anticancer drug directly to the site of a tumor using low systemic doses, (2) enhance drug uptake by malignant cells or its microenvironment and (3) reduce drug absorption and effects on nonmalignant cells[23]. An approach for designing targeted cancer therapies is exploited features that are unique to tumor cells and propose drug delivery systems directed to tumor tissues or its microenvironment. Targeted delivery research has been focused on unique features of the tumor microenvironment, such as leaky vasculature, overexpressed cell surface receptors and proteins and intratumoral pH differences, metabolic changes and adaptations as well as features of the cell uptake process[23,25,26]. An important issue in chemotherapy is to solve the particular distribution of anticancer drugs, according to its pharmacokinetic properties. Consequently, this lack selectively is responsible for the adverse effects of the anticancer treatment[27-30] (Fig. 1 panel A).

Nanoparticle in cancer: Recent interest has been focused on developing nanoscale delivery vehicles capable of controlling the release of chemotherapeutic agents directly inside cancer cells. To make this delivery vehicle, natural or synthetic polymers or both are combined with a drug in a way that it becomes encapsulated into the polymeric system[31,32]. Polymeric drug delivery vehicles that are designed as particles can range in size from 50 nm to over 10 μm and can release encapsulated drugs through surface or bulk erosion, diffusion, or swelling followed by diffusion, in a time-or condition-dependent manner[31] (Fig. 1 panel a).

Some of these improvements are the development of novel forms of cytotoxic administration, which not only improve and facilitate the administration process but also allow to confine and direct the compounds limiting the appearance of adverse effects. Examples of these novel forms of administration are carbon nanoparticles or nanotubes[33,34], magnetic nanoparticles[35], polymeric nanoparticles[36,37], liposomes and biocompatible lipids nanoparticles[38-40], chitosan nanoparticles[41,42], metallic nanoparticles[43-45] or silica derived nanoparticles[46] (Fig. 2). Current nanoparticles are loaded with several anticancer drugs like doxorubicin, mifepristone, paclitaxel[39,42,47,48], antiangiogenic agents as endostatin peptide[49-52], novel adjuvant for cancer treatment as

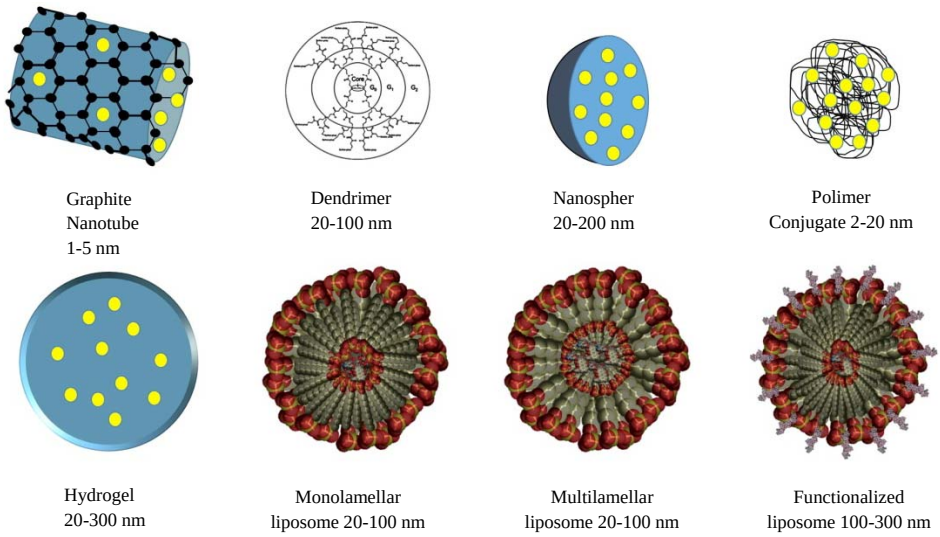

Fig. 2: Nanoparticles for cancer. Different drug delivery systems have been developed to optimize cancer treatment. New functional or multifunctional nanoparticles have been developed. The yellow dots indicate drug/gene incorporation. The approximate size of each nanoparticle is given in the figure

phenformin, ferrocifen, cathepsin B or curcumin[40,44,53], peptidomimetic-drugs as integrin peptide[41,54] and recently as systems for delivery of mRNAi Therapeutic as miR-34a, miR-143 or miR145 for hematological cancers[35,38 55-57].

As expected, these systems for the transport of drugs, not only improve the effectiveness of the treatment but also significantly reduce the development of toxicity or adverse effects in preclinical or clinical trials[24]. However, at the beginning of the development of these new carriers, the common problem was the targeting of the drug to the tumor cells or the nearby microenvironment to guarantee its cytotoxic effect[58]. In some cases, nanoparticulate systems use simple strategies to release drugs, such as low pH activation, as is present in the tumor microenvironment, or by enhancing its permeability and retention effect[59]. Both methods have a disadvantage that is non-selective and can generate the nonspecific release of drugs and toxic effects in sites with infectious or inflammatory active processes [47,60] another factor is that vascularization and angiogenesis are different according to tumor type, localization and development stage[61,62].

To reduce the selectivity difficulties, many of the nanoparticulate systems have been functionalized placing on its surface, molecules that guide it to find its specific target to improve their therapeutic target[54] (Fig. 1c, Fig. 2b). For example, nanoparticles have been developed using an integrin-target peptide. In particular, αvβ3, αvβ5, αvβ6 and α5β1, integrins involved in tumor angiogenesis and metastasis, have been the subject of studies aimed at the discovery of novel cancer therapeutics[54]. Likewise, pancreatic ductal adenocarcinoma (PDAC) that is cancer with unmet medical needs. There is an abundant expression of the anti-phagocytosis signal CD47 that has also been observed in pancreatic cancer cells, in particular, a subset of cancer stem cells (CSCs) responsible for resistance to standard therapy and metastatic potential not only for pancreatic cancer but also for others[63-65]. Nanoparticles for this cancer have been developed to carry gemcitabine or abraxane and were functionalizing using antibodies or protein fragments directed to the CD47 receptor. These particles have shown a promissory therapeutic effects in animal models of this disease[66].

Antibody-driven cancer therapies: Another approach to reduce the problem of selective toxicity for cancer therapy is based on the ability of high selectivity of the immune system. The German physician and scientist, Paul Ehrlich, is considered the pioneer of targeted therapy as more than a century ago suggested the expression "magic bullet" in the early 1900s[67]. Ehrlich proposed a concept of selectively delivering cytotoxic agents to a target and also suggested the use of an antibody conjugated to diphtheria toxin[68]. Although this theory was proposed more than 100 years ago, it was not since relatively a few years ago that the immunology era applied to cancer drug therapy began, starting until scientific and technological advances allowed it to[69].

In the beginning, the antibodies generated by the recombinant technology were murine and they were obtained from mice using hybridoma techniques[70]. The first antibody

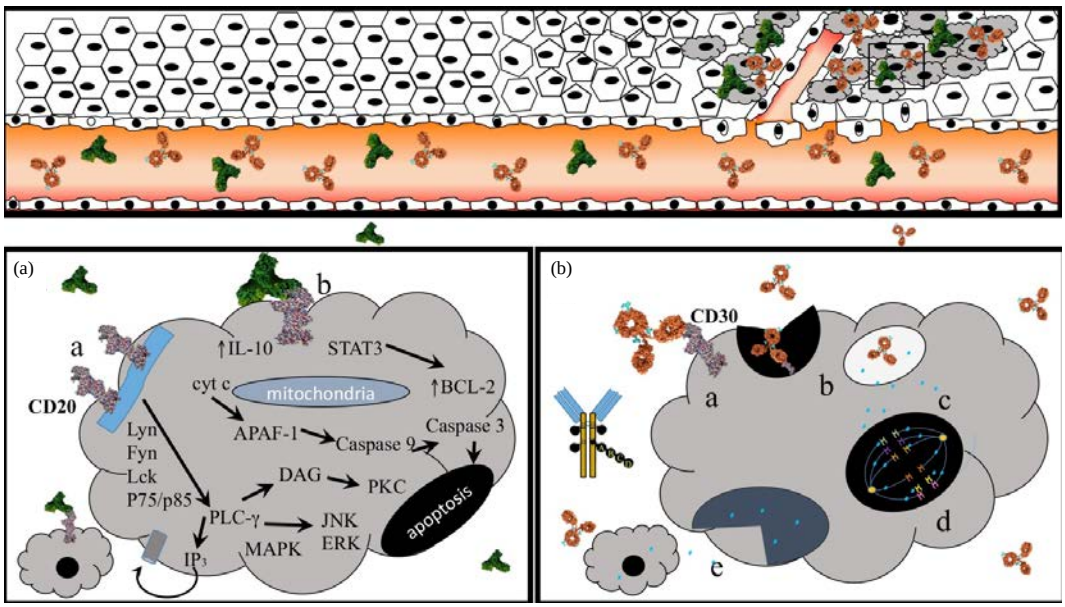

Fig. 3: Immunological-driven selective drug distribution in cancer treatment. The figure depicts a schematic representation of particular distribution and drug action of two immunologic cancer therapies. Rituximab and Brentuximab Vedotin play a therapeutic role in lymphoma cancer cells subtyped CD20+ or CD30+, respectively. After being administrated, each antibody (separately) travels through the bloodstream until they find its antigen. Panel A: Cellular processes controlled by CD20 receptor (a) and pro-apoptotic mechanism activated by rituximab (b)[72, 73] Panel B: Mechanism of action proposed to ADC Brentuximab Vedotin (BV) (a) BV binds to the CD30 receptor on the cell membrane. (b) The CD30-BV complex is internalized into the cell, it is directed to the lysosome where the enzyme cleaves the linker between the antibody and the monomethyl aurastatin E (MMAE). (c) MMAE is released into the cell and binds to the tubulin, (d) Upon binding to the tubulin, MMAE stops the cell division process and leads the cell to G2 / M arrest. This results in the promotion of apoptosis of the cancer cell and (E) MMAE is released from dead cells to the extracellular space. As a result, it can penetrate into near tumor cells

clinically available was muromonab-CD3, a murine antibody that has been effective in reversing corticosteroid-resistant acute rejection in renal, liver and cardiac transplant recipients. This antibody had the main disadvantage that it was able to develop reactive human antimurine antibodies that, over time, may lead to tachyphylaxis and neutralization of the murine antibody. Muromonab could be removed by opsonization by the reticuloendothelial system when it was bound to T lymphocytes, or by neutralization for human antimurine antibody production, which shortened its therapeutic properties[71].

As the biotechnology processes were improved, humanized chimeric antibodies were produced increasing the clinical application success to be introduced into the drug market. Advantages of this new antibodies were that they had a lower activation of immune response than before, thereby reducing the rate of elimination and improving the duration of their effects and reducing its adverse effects[23]. These biotechnological improvements made possible to produce two types of chimeric antibodies. The first that have been able to activate cell death mechanisms (Abs Non-immunotoxin type) (Fig. 3a) and a different kind that is loaded with cytotoxic compounds. This Ab is carried into the cells and cytotoxic compounds are released, finally promoting cell death (Immunotoxins or ADCs) (Fig. 3b).

Tumor-associated antigens as therapeutic targets: A fundamental challenge to develop Abs has been to identify antigens that are suitable for antibody-based therapeutics. Such therapeutics can function through mediating alterations in antigen or receptor function (such as agonist or antagonist functions) modulating the immune system (for example, changing Fc function and T cell activation) or being subjects to rapid internalization through a process called endocytosis. These processes let us have more specificity in drug action through a highly selective recognition of specific targets[74].

Therapeutic monoclonal antibodies (mAbs) recognize Tumor-associated antigens, the antigens can be divided into different categories according to its localization or function. Hematopoietic differentiation antigens are glycoproteins that are usually associated with a cluster of differentiation (CD) groupings and include CD20, CD30, CD33 and CD52[74]. CD20 is a surface antigen expressed on the surface of all B-cells which is expressed at certain stages of B-cell differentiation. It has been used as a target with mAbs. Clinically it has been an effective strategy in the treatment of hematologic malignancies such as non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL)[75]. The expression of CD20 is regulated by the chemokine signaling through the CXCR4/SDF1 axis and this can be impaired by drugs interfering with microenvironmental interactions[76].

It has been shown that inhibition of BCR signaling pathway by ibrutinib affects the expression of CD20 and the efficacy of anti-CD20 antibodies like rituximab, ibinutuzumab and recently tositumomab[76]. CD30 was originally described as a marker of Hodgkin's and Reed-Sternberg cells in Hodgkin's lymphoma. Molecular cloning and characterization of cDNAs encoding CD30 and its ligand (CD30L) established these proteins as members of the tumor necrosis factor receptor (TNFR) and tumor necrosis factor (TNF) superfamilies, respectively. The expression is mostly restricted to virus-infected T cells and resting B cells granulocytes as well as various leukemia cells[77], however, its presence helps to define a novel subgroup of Diffuse Large B-Cell Lymphoma (DLBCL) with favorable prognosis in combination with a distinct gene expression signature[78]. This receptor is a positive regulator of apoptosis by activation of NF-kappaB[79] and also has been shown to limit the proliferative potential of autoreactive CD8 effector T cells and protect the body against autoimmunity.

CD33 is a transmembrane receptor expressed on cells of myeloid lineage. It is usually considered myeloid-specific. However, it can also be found on some lymphoid cells[80]. The intracellular portion of CD33 contains immunoreceptor tyrosine-based inhibitory motifs (ITIMs) that are implicated in inhibition of cellular activity[81]. The CD52 is present on the surface of mature lymphocytes but not on the stem cells from which these lymphocytes were derived. It is also found on monocytes and dendritic cells. Furthermore, it is found in the male genital tract and is present on the surface of mature sperm cells[82]. It is a peptide of 12 amino acids anchored to glycosylphosphatidylinositol and it has been associated with certain types of lymphoma[83]. It has been demonstrated that when a humanized monoclonal antibody (mAb) recognizes CD52, it directs cell-mediated cytotoxicity and induction of apoptosis by complement-induced cell lysis[84,85].

Cell surface differentiation antigens are a diverse group of glycoproteins and carbohydrates that are found on the surface of both normal and tumor cells. Antigens that are involved in growth and differentiation signaling are often growth factors and growth factor receptors[74]. Growth factors that are targets for antibodies in cancer patients include CEA, epidermal growth factor receptor (EGFR; also known as ERBB1), ERBB2 (also known as HER2), ERBB3, MET (also known as HGFR), insulin-like growth factor 1 receptor (IGF1R), ephrin receptor A3 (EPHA3), tumor necrosis factor (TNF)-related apoptosis inducing ligand receptor 1 (TRAILR1, also known as TNFRSF10A), TRAILR2 (also known as TNFRSF10B) and receptor activator of nuclear factor-κB ligand (RANKL, also known as TNFSF11)[74,86].

Angiogenesis antigens involved in angiogenesis are usually proteins or growth factors that support the formation of new microvasculature, including Vascular Endothelial Growth Factor (VEGF), VEGF receptor (VEGFR), integrin αVβ3 and integrin α5β1[87]. Tumor stroma and the extracellular matrix are necessary to support structures for a tumor. Stromal and extracellular matrix antigens that are therapeutic targets include Fibroblast Activation Protein (FAP) and tenascin[74,86], as it was previously described. Each day, novel antigens are identified as biomarkers for different groups of cancer. Using a proteomic-based approach has made possible to identify different antigenic proteins[88] that can be utilized not only for diagnosis, classify subtypes of cancer or better understanding of cancer biology but also to be targeted in immunotherapies[89,90].

Antibodies for cancer treatment, non-immunotoxin: Since the initial description by Köhler and Milstein, mAbs have increased the clinical use for diagnosis and treatment of malignant diseases[70]. Antibody-based therapy for cancer has become to be established over the past 15 years and is now one of the most successful and influential strategies for treating patients with hematological malignancies and solid tumors[68,74,91]. There are different mechanisms through antibodies can kill neoplastic cells through antibodies. Some involve direct action of the antibody on cancer cells. Antibodies can act as an antagonist or as an agonist to activate apoptosis pathway (according to the receptor bound and its transductional mechanism). Other immune-mediated cell killing mechanism includes Complement-Driven Cytotoxicity (CDC), Antibody-Directed Cellular Cytotoxicity (ADCC) and regulation of T cell function, each one through specific effects on tumor, vasculature or stroma[74].

Rituximab: Rituximab (Rituxan®) was the first monoclonal antibody developed and approved for cancer therapy and the first single-agent approved as a treatment for lymphoma. An important target for Rituximab is the CD20 B-cell lineage antigen located on the surface of malignant and normal B lymphocytes[92]. Mechanisms of cell destruction have been demonstrated to be activated by rituximab binding to CD20 include direct signaling of apoptosis, complement activation and cell-mediated cytotoxicity (Fig. 3a)[93]. Rituximab has rapidly become the most immunotherapeutic drug used. If used in combination with CHOP, rituximab is the only drug that has been shown to improve survival of a subpopulation of patients with diffuse large cell lymphoma during the last three decades. The FDA approved it for the treatment of patients with relapsed or refractory low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma in 1997. Rituximab is also being studied in many other B-cell malignancies alone and combination with other agents. Furthermore, it is currently being evaluated in several nonmalignant diseases, such as autoimmune disorders[94,72]. Recently rituximab has been used experimentally in other various immune-related diseases such as immune thrombocytopenic purpura, systemic lupus erythematosus, myasthenia gravis and rheumatoid arthritis but controlled clinical trials are needed to support new therapeutic uses[95].

Trastuzumab: Trastuzumab (Herceptin®), a humanized monoclonal antibody specifically developed to target human epidermal growth factor receptor 2 (HER2), is regarded as standard treatment in those patients with HER2-positive tumors[96]. It was the first antibody authorized and registered for use in patients with HER2-overexpressing breast cancer[96,97]. As an antibody, one of the major mechanisms of trastuzumab is to attract immune cells to tumor sites that overexpress HER2, by a mechanism called Antibody-Dependent Cellular Cytotoxicity (ADCC). After treating patients with trastuzumab and docetaxel, tumor samples showed an increase in the number of both natural killer cells and cytotoxic proteins[98].

Cetuximab: Cetuximab Erbitux (R) is a recombinant, human-murine chimeric monoclonal antibody targeted specifically to the Epidermal Growth Factor Receptor (EGFR). This binding inhibits receptor phosphorylation and activation and it leads to receptor internalization and degradation. Cetuximab biological effects are linked to inhibition of cell cycle, tumor progression, neo-angiogenesis, invasion and metastasis, as well as increase and activation of pro-apoptotic molecules[99]. Moreover, numerous clinical trials demonstrated cetuximab efficacy in different tumor types. It has been approved by Food and Drugs Administration for the treatment of metastatic colorectal cancer as a single agent or combination with chemotherapy, in locally and regionally advanced head and neck squamous cell carcinoma in combination with radiation and as monotherapy for recurrent and metastatic head and neck squamous cell carcinoma after failing platinum-based chemotherapy[99].

Ipilimumab: Ipilimumab (Yervoy, Medarex and Bristol-Myers Squibb) is a human mAb against cytotoxic T-lymphocyte antigen 4, which enhances co-stimulation of cytotoxic T-lymphocytes, resulting in their proliferation and an anti-tumor response[100]. It was licensed for the treatment of unresectable or metastatic malignant melanoma, while multiple clinical trials using this medication in the treatment of other malignancies are ongoing. As a clinical response to ipilimumab results from immune stimulation, it predictably generates autoimmunity as well, causing immune-related adverse events in the majority of patients[101]. Phase II trials of ipilimumab in advanced melanoma showed objective responses but a greater number of patients had disease stabilization. In a phase III trial, ipilimumab was the first agent to demonstrate an improvement in overall survival in patients with previously treated, advanced melanoma. The adverse event profile associated with ipilimumab was primarily immune-related. Adverse events can be severe and life-threatening but most were reversible using treatment guidelines[100].

Antibodies-drug-conjugated (ADCs): ADCs have become a promising targeted drive therapy for cancer. This strategy combines the specificity of antigen-antibody reaction that increases pharmacokinetic properties particularly antibodies-drug biodistribution increasing destructive potential of new and more potent cytotoxic drugs that directly payload delivery on the tumor.

The first generation of monoclonal antibodies drug-conjugated (ADC) became available in the 1970s (ADCs). Researchers aimed that these strategies would allow to enhance the tumor specificity and clinical benefits of the current drug if they were combined with immunotherapy[102,103]. The first cytotoxic, used to load antibodies, were drugs with current clinical use not only with well-established mechanisms of action but also with well-known toxicity profiles. The drugs used were: antimetabolites (methotrexate MTX and 5-fluorouracil), DNA cross-linkers (mitomycin C) or anti-microtubule agents (vinblastine)[102,103]. Today, the main advantages of antibody–drug conjugates are that they have the highest tumor selectivity and cytotoxic potency that is not achievable with conventional drugs[104] (Fig. 3b).

Challenges in ADC design: The first generation of ADCs encountered some problems[105] such as an insufficient potency of the effector molecule, limited expression of the antigen, internalization mechanisms of antibodies that were inefficient, the localization rate of the antibodies at the tumor in patients was too low and problematic linker stability[106].

Antibody type: The first challenge to be solved was the immune response resulting from the use of a murine origin or chimeric monoclonal antibodies when it was used in human beings and the generation of human anti-murine antibodies (HAMA) which levels arose with repeated cycles of therapy[104]. This problem was partially solved replacing murine antibodies with humanized chimeric or fully human antibodies to prevent immunogenicity[106]. However, it was despite change production of antibodies. Also, antigen-binding affinity can be improved by using phage display libraries to isolate antibodies with strong affinities for specific antigens. In some cases, when antibodies with a lower affinity for the antigen are required to allow better penetration of a tumor, changes in the Abs structure quaternary can be designed by genetically engineering to improve the Fc region recognition through point mutations or glycan modifications[107].

Development of defucosylated antibodies have increased affinities for the FcγRIIIa receptor and enhanced Antibody-dependent cell-mediated cytotoxicity (ADCC). This change not only has an effect on therapeutic efficacy but also it provides changes in pharmacokinetic properties into the human body[108]. Cytotoxic Compound Conjugated: Other lessons learned from these early efforts led to improvements in technology and renewed interest in antibody-drug conjugates. The cytotoxic potency of the drug was improved by using other cytotoxic compounds that are 100-1000 times more potent than those currently used in chemotherapy. Thereby methotrexate, 5-fluorouracil, mitomycin C and vinblastine, were substituted by more powerful drugs (Some them without therapeutic use at the time) that were too toxic to use in an untargeted manner and have now been more promising than ADCs[109]. Most drugs used in ADC production are highly cytotoxic agents with IC50 values in subpicomolar to subnanomolar range in cell culture[110]. These include aurastatins and calicheamicins. Auristatins (natural products originally isolated from the Indian Ocean sea hare Dolabella auricularia) and maytansines both exert their cytotoxic effects by binding to tubulin, causing G2/M cell cycle arrest and subsequently leading to apoptosis[111].

Duocarmycins, pyrrolobenzodiazepines and calicheamicins. Duocarmycin is a sequence-selective alkylator of adenine-N3 in the minorgroove of DNA thereby inducing apoptotic cell death[112,113]. Calicheamicins alquilant agents that target the minor groove of DNA causing DNA double-strand break by irreversible alkylation leading to cell death likely cyclophosphamide but at too low doses[110]. Pyrrolobenzodiazepines (PBDs), currently in phase II clinical trials[114], which as dimers binds sequence-selectively in the minor groove of DNA forming a covalent bond with the N2 of guanine on opposing DNA strands thus cross-linking the strands and producing highly malignant lesions[115,116]. Antigen Target Selection: For a better selection of a target, researchers must understand cell biology and how different cell tumor biology is. It can help to have a better selection using the most appropriate target.

For some ADCs internalization process is crucial for its therapeutic effect, while for others unconjugated mAb, CDC or ADCCs do not have relevance. It has been observed that internalization rate differs between antibodies. Some are internalized faster than others. For some antigens, ADC has been observed to internalize much more efficiently than unconjugated mAb[109]. Careful target and antibody selection must be made to improve selectivity and efficiency of internalization and the project success.

Antibody-drug linkers: Other challenges in the development of ADCs has been the generation of suitable linkers for conjugating the antibody and the cytotoxic agent. The linker connects the cytotoxic drug covalently to the mAb and it is a determinant of ADC activity. The linker must have enough stability because it prevents the premature spontaneous release of the drug which will cause damage to normal tissues and enable the ADC to circulate in the bloodstream for a while before reaching the target tumor site[104]. However, upon reaching the target cells, the linker must also be able to efficiently release the drug in its active form to allow the drug to effect cell killing. Several strategies have been employed to produce linkers that satisfy both of these criteria[117].

Currently, different types of linkers are released by diverse mechanisms.

Acid sensitive linkers: This class takes advantage of intracellular conditions such as the low-pH environment in lysosomes and endosomes, which can trigger hydrolysis of an acid-labile group such as a hydrazone, resulting in drug release. However, this linker is unstable up to 48-72 h in plasma[118].

β-glucuronide linker: The β-glucuronide linker provided for facile drug release and was highly stable in rat plasma. This linker is easily breakdown by the proteolytic activity of cathepsin B, once the antibody-drug has entered into the cancer cells[112]. Importantly, the resulting ADCs that uses this

linker were non-aggregated and monomeric even when heavily loaded (8 drugs/mAb) with hydrophobic anticancer drugs. This linker also helps to solubilize ADC.

Lysosomal protease sensitive linkers: Cathepsin B (CatB), recognizes and cleaves a dipeptide bond. Valine-citrulline is a dipeptide linker, imparting greater stability in plasma and increased exposure to the conjugated drug after intravenous delivery. This is the linker used in Brentuximab vedotin. This linker is more resistant in plasma because it is released by an enzyme pathway[118,119].

Glutathione sensitive linkers: Disulfide bonds within the linker are relatively stable in circulation but into the cancer cell, this could be reduced by the higher levels of intracellular glutathione allowing the release of the loaded drug. This linker has been tested in clinical trials to be used with several drug candidates for hematological cancer treatment. One example has been tested as part of SAR3419, a maytansine glutation sensitive linker anti-CD19 conjugate, recently in phase II clinical trial[120]. Also, it has been tested in IMGN901, an anti-CD56 maytansine conjugate, recently in phase, I clinical trials[121] or AVE9633, an anti-CD33 maytansine conjugate in 2012 was in phase I clinical trials. This pair of studies were early discontinued because of the drug did not show important anticancer activity even at high doses[122]. All projects were developed by ImmunoGen and its partners.

Peptide linkers: This kind of linker has been recently developed. One example is triglycyl peptide linker (CX). This was designed to be used in antibody-Drug Conjugates (ADC). The purpose of this linker was to provide an efficient release and lysosomal efflux of cytotoxic catabolites within targeted cancer cells[123]. The ADC-CX was more active that non-cleavable linker or another tested. Possibly it was due that its chemical structure is less affected even in the acid tumoral microenvironment. This linker is even in preclinical evaluation.

Metallic linkers: Another kind of linker is a bifunctional platinum (II). The ethylenediamine platinum (II) moiety, herein called Lx, was coordinated to Desferal (DFO) or Auristatin F (AF) to provide storable intermediate products, which were directly conjugated to unmodified mAbs. This procedure was able to give a mAb conjugation of approximately 85% to de Fc region, presumably to histidine residues[124]. The mAb loaded has similar cytotoxic efficiency as trastuzumab in a xenograft mouse model of gastric cancer (NCI-N87) or an ado-trastuzumab emtansine-resistant breast cancer (JIMT-1)[124].

Conjugation methods: Another critical process is how a cytotoxic drug is loaded to an antibody. This process needs to be calculated with a precise stoichiometry. Standardization of a conjugation method is required to obtain better result both in a homogeneous Abs-Drug conjugated product and reproducible therapeutic responses. After that the Abs is loaded with the drug, it must maintain its pharmacokinetic properties but most important its pharmacodynamics properties. However, conventional conjugation methods are complex and they can result in a heterogeneous mixture of ADCs, which can cause changes that can lead to significant therapeutic liabilities[125].

For example, studies of molecular characterization of ADCs production and in vitro test have been demonstrated that ADC composed by monomethyl auristatin E (MMAE) and anti CD30 Ab cytotoxic effects arises with increasing drug load[117]. However, antitumoral activity in vivo of Abs containing 4 MMAE was not different against mAbs containing 8 MMAE molecules[126]. Otherwise, with higher drug load species exhibited faster renal clearance than lower drug load[117].

The most important techniques used for drug loading are:

- Antibody engineering methods
- Reducing the number of sulfhydryl groups to control the amount of drug loaded through of fixed stoichiometry[127,128].
- Engineered cysteine mutants to reduce the number of cysteines available for loading
- The addition of unnatural amino acids[129]
- Incorporation of selenocysteine to specify the site and number for drug loading
- Enzymatic methods
- Apply glycosyltransferase to attach to site-specific[130,131]
- Transglutaminases
- Formylglycine-generating enzyme
- Chemical approaches
- Photoactive protein Z

Drug pipeline of brentuximab vedotin: Biological therapies play an increasing role in cancer treatment. Although a high number of antibodies have shown clinical efficacy, their use as single agent therapy remains limited today[23]. Once a therapeutic goal is identified to improve clinical care of cancer patients, if ADC could be a possible solution, the ACD development project should be planned to attain it. Oncology is the main focus of mAb development with approximately 50% of the total in pipeline[132]. This is because of a high number of patients, the increased growth rate and the clinical troubles that have not solved by conventional therapy[23]. For a new drug development, different stages must be carried out

to accomplish regulatory requirements to obtain FDA approval[133]. TNF receptor superfamily was recognized and involved in immune regulation processes. Natural ligands were recognized to possess cytokine-like activities[134]. Human TH1 and TH2 cells exhibit not only different functional properties but probably also distinct surface markers; TH2 but not TH1, clones express membrane CD30 and release the soluble form of CD30, a member of the TNF receptor superfamily[135].

Hodgkin Disease (HD) is characterized by the presence of a small number of the typical Hodgkin and Reed-Sternberg cells (H-RS) in a hyperplastic background of reactive lymphocytes and other cells. CD30 antigen was recognized and characterized as a marker present on H-RS cells, it has a critical pathophysiological role in malignant lymphomas, particularly Hodgkin disease, large cell anaplastic lymphomas and Burkitt lymphomas, as well as in the activation and functioning of the T cell-dependent immune system[136]. Originally, the presence of this protein appears to be an important prognostic factor and, combined with an age-adjusted International Prognostic Index, allowed researchers to design more specific clinical trials aimed at finding new, more efficacious and less toxic treatments[137]. CD30 appears to be expressed (restricted expression) on T and B Cell subpopulation on activated blasts in parafollicular areas of lymphoid tissues and thymic medulla[138]. Signaling pathway through the TNFR superfamily affects cellular proliferation, survival and differentiation are mediated by cytoplasmic domains. CD30 does not contain a death domain but can produce an apoptotic stimulus, the mechanism of this appears to be related to the degradation of TRAF2, which enhances death signaling (Fig. 3, panel b)[139]. To improve lymphoma treatment CD30+ an ADC was developed to augment the antitumor activity and selectivity using anti-CD30 based therapies[140]. This drug, identified as cAC10-vcMMAE (SGN-35), has an antiCD30 antibody conjugated with monometilaurastatin E (MMAE)[141]. The antibody was synthetically modified to include maleimide and facilitate conjugation with MMAE. SGN-35 uses a protease cleavable Val-Cit peptide as a linker to a specific release of drug from ADC128[140]. The *in vitro* and *in vivo* activity was evaluated using an H-RS lymphoma cells (L540cy cell line). After binding CD30, the antibody-drug conjugate is internalized and transported to lysosomes, where the peptide linker is specifically cleaved and selectively releases the cytotoxic agent[142]. It has been demonstrated that intracellular MMAE concentration and effects are concentration dependent and time dependent mode. The top concentration found is about 1000nM within 24-72 h after incubation[140]. MMAE released into cells the cell, binds tubulin and prompts arrest of the cell cycle between the gap 2 phase and mitosis (G2/M) and cell apoptosis[143]. Initial in vivo evaluation was done using a disease model of anaplastic large-cell lymphoma, using Karpas-299 cells that were implanted under the skin of C.B-17 SCID mice[143]. Efficacy and security were evaluated. SNG-35 showed a complete cure of 100% on tumor regression (at the beginning 50-100 mm 3 volume). Ac10 (SGN-30) did not produce equivalent results compared with SGN-35 treatment[140,143]. Nonimportant signs of toxicity were detected in this animal model[141].

Clinical experience for use an ADC (Brentuximab vedotin): Brentuximab Vedotin (BV) is a quimeric anti-CD30 monoclonal antibody (mouse variable region/constant human region). This antibody has attached a Monomethyl Aurastatin E (MMAE) molecule, which exerts the cytotoxic action[144]. It is important to recognize that despite having an abundant CD30 receptor on the surface of certain lymphomas (Hodgkin's lymphoma and anaplastic T-cell lymphoma), the first naked anti-CD30 did not have a favorable outcome[145,146]. Probably due to the existence of abundant serum soluble CD30 on patients or the generation of anti-CD30 antibodies since they were completely murine; with a significant decrease in its antineoplastic effect. An alternative way to improve its action, thus, was linked to the anti-CD30 a cytotoxic molecule like MMAE (a). In this way, the anti-CD30 antibodies are used as a Trojan horse, where it is introduced into the neoplastic cell and using the lysozyme itself releases the synthetic inhibitor of microtubules causing cell death.

Clinical finding and pivotal studies: BV has been assessed initially in a phase 1 study with a group of heterogeneous lymphomas expressing CD30 on its Surface[147]. The primary objectives of the study were to define the safety profile of BV and to determine the maximum tolerated dose (the highest dose that would not produce unacceptable toxic effects). This was characterized as being a phase 1, open-label, multicenter dose-escalation study, where BV was administered at a dose of 0.1-3.6 mg per kilogram of body weight every 3 weeks. Where the majority were Hodgkin's lymphoma (93%) and 7% cases of T-cell lymphoma (2 cases of systemic anaplastic T-cell lymphoma and 1 angioimmunoblastic lymphoma). The authors observed dosse-limiting toxic effect (grade 4 thrombocytopenia) in 1 of 6 patients who received 1.8 mg kg^{-1}, 1 of 6 patients presented acute renal failure who received 2.7 mg kg^{-1} and one patient was deceased due to sepsis who received a dose of 3.6 mg kg^{-1}. The expansion cohort was using the 1.8 and 2.7 mg kg^{-1} doses. The 2.6 mg kg^{-1} cohort, there were 3 episodes of limiting toxic effects (grade 3 hyperglycemia, prostatitis and grade 3

neutropenia fever). Thus, the researchers set the dose of 1.8 mg kg^{-1} as the most effective with less limiting toxic effects[147]. The most common adverse events, grade 1 or 2 in severity, were fatigue (36%), pyrexia (33%) and diarrhea, nausea, neutropenia and peripheral neuropathy (22% each). The objective response was noted in 38% of patients, interestingly. 88% of responders did within the first 4 weeks[147]. The following phase II studies were divided into patients with Hodgkin's lymphoma and systemic anaplastic T-cell lymphoma.

BV in systemic anaplastic T-cell lymphoma: Systemic anaplastic large T-cell lymphoma (sALCL) is an aggressive lymphoma with a surface expression of the CD30 receptor in abundant form and which in turn can be divided into positive ALK and negative ALK protein (the most common in adults); this protein gives a good prognostic if present. This kind of lymphoma corresponds 3% of all lymphomas in adults and up to 30% in children. Dr. Pro and colleagues conducted the multinational open-label, phase 2 pivotal study for the approval of BV for the Food and Drug Administration (FDA) and European Medicine Association (EMA) in this pathology[148]. BV was administered intravenously at the dose of 1.8 mg kg^{-1} every 21 days up to 16 total cycles to 56 patients. The median age was 52 years, with poor prognostic characteristics such as ALK-negative, 50% were relapsed, 62% were considered refractory to the first line of treatment, where 91% of patients had 2 or more chemotherapy regimens including autologous stem cell transplantation. The efficacy assessment was done by an independent committee where the overall response was 86%, the complete response was assessed at 57 and 29% partial response; interestingly, the overall tumor reduction was 97%, where those who achieved a complete response did so at 12 weeks of treatment. When we observed the duration of the response, in those, who had an objective response the median duration of response was 12.6 months, while in those who obtained CR, this was 13.2 months in overall. When we analyzed thirty-two patients who achieved CR, 22 continued with BV and had a median response duration of 12.6 months; in 6 patients who were undergone to an allogeneic transplant, the median was 13.2 months and in 5 patients who were undertaken to autologous stem cell transplant the median of duration has not been reached[148]. The latter is an important fact since patients with systemic anaplastic T-cell lymphoma can be rescued with BV and serve as a bridge to be consolidated with an autologous stem cell transplant. Obviously, by the number of cases, it should be explored in new trials. About the allogeneic transplantation group, an update was recently published, where a total of 8 patients were finally included in phase II pivotal study[149], [2 patients more than 6 were included in the original paper by Pro *et al.*[149]. The 87% of patients with sALCL achieved a post-BVC CR and allogeneic transplantation (median time between the last dose of BV and conditioning therapy to perform the transplant was 1.4 months). The median Progression Free Survival (PFS) has not yet been reached (95% CI: 14.6, -), the estimated PFS rate at 24 months was 66% (95% CI: 36%, 84%). The median overall survival was 33.1 months (95% CI: 21.3, -) (range, 9.4–34.2+ months)[149].

Front-line treatment phase 1 has recently been published comparing two arms in peripheral T-cell lymphomas CD30+. Where patients received subsequent treatment characterized by 2 cycles of BV at 1.8 mg kg^{-1} followed by 6 cycles of traditional CHOP or BV at doses of 1.8 mg kg^{-1} plus CHP (withdrawn vincristine) for 6 cycles, both arms every 21 days. Responders received single-agent brentuximab vedotin for 8 to 10 additional cycles (for a total of 16 cycles). The primary objective was an assessment of safety; secondary end points included objective response rate, Complete Remission (CR) rate, progression-free survival rate (PFS) and OS. Lymphomas that were included were adult T-lymphoma/leukemia (n = 2), sALCL (n = 32), angioimmunoblastic T lymphoma (n = 2), enteropathy-(N = 2)[150]. The results showed that after subsequent treatment, 11 (85%) of 13 patients achieved an objective response (CR rate, 62%, estimated 1-year PFS rate, 77%). Grade 3/4 adverse events occurred in eight (62%) of 13 patients. At the end of combination treatment, all patients (n = 26) achieved an objective response (CR rate, 88%, estimated 1-year PFS rate, 71%). All seven patients without anaplastic large-cell lymphoma achieved CR. Grade 3/4 adverse events (10%) in the combination-treatment group were febrile neutropenia (31%), neutropenia (23%), anemia (15%) and pulmonary embolism (12%). The authors concluded Brentuximab vedotin, administered sequentially with CHOP or in combination with CHP, had a manageable safety profile and exhibited substantial antitumor activity in newly diagnosed patients with CD30 PTCL. A randomized phase III trial is underway, comparing BVCHP to CHOP (clinical trial No. NCT01777152).

Hodgkin's lymphoma: Hodgkin's lymphoma, which used to be called Hodgkin's disease, is the third in frequency, just behind diffuse large B-cell lymphomas and follicular lymphoma, respectively. It is divided into classical and non-classical, being the most frequent the classic type. Its incidence is bimodal, affecting young people between 15 and 20 years, as well as those over 60 years. It is a lymphoma that expresses the CD30 protein on its surface, in addition to CD15. We talked about phase 1 and now we will talk about the pivotal study in Hodgkin lymphoma. Younes et al. published

the pivotal phase 2 study in refractory or relapsed HL152. This multinational, open-label, phase II study, the efficacy and safety of brentuximab vedotin were evaluated in patients with relapsed or refractory Hodgkin's lymphoma (HL) after autologous stem-cell transplantation (auto-SCT). Patients had histologically documented CD30-positive HL by central pathology review. A total of 102 patients were treated with brentuximab vedotin 1.8 mg kg^{-1} by intravenous infusion every 3 weeks. The overall response rate was 75% with CR in 34% of patients. The median progression-free survival time for all patients was 5.6 months and the median duration of response for those in CR was 20.5 months. The most common treatment-related adverse events were peripheral sensory neuropathy, nausea, fatigue, neutropenia and diarrhea[151], as seen in phase 1 adverse events148. The 5-year follow-up of the pivotal phase 2 study of BV was recently published153. Overall patient population (N = 102) had an estimated Overall Survival (OS) rate of 41%. Following the pivotal study, other studies have been reported within the Name Patient Program (NPP) for non-US or Canadian patients with similar outcome among patients affected by HL[152,153].

Brentuximab vedotin as monotherapy has been used in different scenarios of relapsed/refractory patients such as post-transplant consolidation treatment in high-risk patients[154], As rescue treatment before autologous stem cell transplantation[155,156]; Retreatment[157]; As a bridge for allogeneic stem cell transplantation[149] allogeneic post-transplant relapse[158]. The use of BV combined with chemotherapy in subgroups with relapse/refractories has also been reported. Different stages of research (1 and 2) have been developed using drugs such as bendamustine at standard doses of both [bendamustine 90 mg/m2 on days 1 and 2; BV 1.8 mg kg^{-1} on day 1] and in the case of response an ASCT with 16 more BV cycles after ASCT were done. The clinical response was good (ORR 93% and CR74%); the 12-months PFS was 80%. However, the data needs to more time of follow-up[159].

Because of the good results observed in relapsed/refractory patients, BV has been explored in addition to conventional first-line chemotherapy such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbacin). In a study of 51 patients with intermediate/advanced stage HL, they received escalated doses of BV (0.6.0.9 and 1.2 mg kg^{-1}) every 2 weeks for 6 cycles, in addition to ABVD initially and then only AVD, without bleomycin) by a high percentage of pulmonary adverse effects[160]. The Maximum Tolerable Dose (MTD) was not reached, CR was 95% and 96% in the arms of ABVD and ADL respectively. The 3-year failure-free survival and OS were 96 and 100% respectively, in the BV+ AVD arm[161]. Abramson *et al.*[162] reported the results of phase 2 with BV (1.2 mg kg^{-1}) + ADL for 4-6 cycles (depending on an interim PET) in HL located not bulky. Where, CR was 91% but with a high incidence of neuropathy and fever-neutropenia[162]. Currently, the same group is recruiting patients with localized non-bulky HL, for a second study, without vinblastine as a chemotherapy regimen (BV+AD) (NCT02505269). Also, Takeda/Millennium company has another Phase 3 study under way in advanced HL, where it will be compared to upfront ABVD treatment in one arm and BV+AVD in another. This study is important because it will define a paradigm shift in treatment for advanced HL (NCT01712490).

An interesting subgroup is the elderly patients (> 65 years), who practically do not have tolerance to multiple drug chemotherapy and is an unmet need issue. Therefore, BV was tested as upfront monotherapy at standard doses and although the clinical response was good, PFS was not (median 10.3 months) and there was a short duration of reaction (median 9.8 months) [163]. Therefore, BV was combined with just one drug (dacarbacin 375 mg/m2 or bendamustine at a dose of 70-90 mg/m2), obtaining ORR 100% and CR 62 and 78%, respectively. Of note, bendamustine had to be withdrawn from the treatment due to poor tolerability. The patients finished with BV as monotherapy[164].

In conclusion, BV has come to change the treatment paradigm for CD30+ hematological diseases; both T-cell lymphomas, as well as in HL and has improved results in patients with very poor prognosis such as refractory/relapsed disease. Its use as monotherapy or in combination with other drugs gives greater possibilities to patients who were previously destined to a poor outcome. Now awaiting results combined with first-line chemotherapy to know if they will produce a change in the standard care of patients with CD30+.

CONCLUSION AND FUTURE

The clinical approval of the treatment for hematological cancer or solid tumor by therapies directed by antibodies, (rituximab or brentuximab), have shown therapeutic benefits that have allowed to improve the efficiency of the antineoplastic treatment. Many clinical benefits have brought these therapies, among them a particular distribution and a very high selectivity of effects that increases the efficacy and safety of treatments. Today, these novel approaches are not only used to develop non-immunotoxin, ADC, or inclusive immuno-radiotherapy (antibodies linked to an isotope) but also for advance in chimeric proteins engineered the design to treat cancer. These advances have allowed to propose the development of new drugs or interventions those are in preclinical or clinical phases (Table 1). The most recent advances are biotech proteins as chimeric proteins. Chimeric

Table 1: Immunotherapies CD-targeted to Improve Selective Cytotoxic Effects for Hematological Cancer

Drug	Target	Type Drug	Action mechanism	Clinical use	References
SGN-CD19A	CD19	ADC	Cytotoxicity MMAF-mediated	B-cell malignancies, ALL, CLL and NHL	Maino *et al.*[165]
Coltuximab ravtansine	CD19	ADC	Cytotoxicity Maytansinoid-mediated	NHL, DLBCL	Kantarjian *et al.*[120], Ribrag *et al.*[166]
Blinatumumab	CD19	Antibody Bi-specific	Links CD3-positive T cells to CD19-positive B cells	ALL, and DLBCL	Baeuerle *et al*[166], Viardot *et al.*[168] Hoffmann *et al.*[169] NCT02013167
Adoptive cell therapy	CD19	CAR T	CAR-T cells ligate CD19 and lead to activation of the T cell to kill of the target	ALL, CLL, and ANHL	Davila *et al.*[170], Lorentzen *et al.*[171] NCT02348216
KTE C19	CD19	CAR T		ALL and ANHL	Locke *et al.*[172], Anagnostou *et al.*[173]
Rituximab	CD20	mAb, Chimeric mouse-human antibody	Binds to B cells antigen and recruits immune effector	CLL and NHL	Plosker and Figgitt[174] NCT02484053
Veltuzumab	CD20	2nd-generation humanized mAb	Antiproliferative, antiapoptotic, cytotoxicity antibody-dependent	CLL and NHL	Goldenberg *et al.*[175], Kalaycio *et al.*[176] NCT00989586
Ofatumumab	CD20	Small loop epitope anti-CD20 antibody	Like rituximab, more effective	CLL and NHL	Bologna *et al.*[177] NCT01532700
Obinutuzumab	CD20	mAb Glycoengineering modifies in Fc.	Induces direct non-apoptotic cell death, intracellular cytotoxicity and phagocytosis	CLL, NHL, LACFL	Rioufol and Salles[178], Goede *et al.*[179], Owen and Stewart[180] NCT02624986
^{90}Y-Ibritumomab	CD20	Radio immunotherapy	Cell cytotoxicity by beta-particles	DLBCL and MCL	Fietz *et al.*[181] NCT00761384
^{131}I-Tositumomab	CD20	Radio immunotherapy	Cell cytotoxicity by Beta and gamma emissions	NHL	Schlechter *et al.*[182] NCT01868035
Pinatuzumab vedotin	CD22	ADC	Cytotoxicity MMAE-mediated	CLL and NHL	Advani *et al.*[183], Li *et al.*[184], Yu *et al.*[185] NCT01691898
CD22-MCC-DM1	CD22	ADC	Cytotoxicity Maytansinoid-mediated	L and L	Polson *et al.*[186]
Inotuzumab ozogamicin (CMC-544)	CD22	ADC	Cytotoxicity Calicheamicin-mediated	ALL and NHL	Kantarjaian *et al.*[187], Betts *et al.*[188] NCT01564784
Emab–SN-38	CD22	ADC	Cytotoxicity Irinotecan-mediated	L and L	Sharkey *et al.*[189]
Epratuzumab	CD22	Humanized anti-CD22 mAb		ALL and NHL	Fleischer *et al.*[190], Leonard *et al.*[191] Raetz *et al.*[192] NCT00553501
^{90}Y-epratuzumab	CD22	Radio immunotherapy	Cell cytotoxicity by Beta-particles	NHL and DLBCL	Kraeber-Bordere *et al.*[193] Morschhauser *et al.*[194] NCT02844530
Adoptive cell therapy	CD22	CAR T	CAR-T cells ligate CD22 and lead to activation of the T cell to the kill the target	B-cell hematological malignancies, ALL	Haso *et al.*[195], NCT02935153 NCT02794961, NCT02588456
LMB-2	CD25	ADC	Cytotoxicity *Pseudomona* exotoxin-mediated.	CLL and ALL	Mazor *et al.*[196], Kreitman *et al.*[197]
Daclizumab	CD25	Humanized anti-CD25 mAb	Blocks IL-2 binding, produces cytokine deprivation and antibody-dependent cellular cytotoxicity	Leukemia and HL	Berkowitz *et al.*[198]
Y-daclizumab	CD25	Radio immunotherapy	Cell cytotoxicity by beta-particles	Leukemia and HL	Madhumathi[199], NCT01468311
Brentuximab vedotin	CD30	ADC	Cytotoxicity MMAE-mediated	ALCL, HL	Francisco *et al.*[126], Ansell *et al.*[145]
Gemtuzumab-ozogamicin	CD33	ADC	Cytotoxicity Calicheamicin-mediated	AML	Laszlo *et al.*[200], Pollard *et al.*[201], NCT01869803, NCT02473146
SGN-CD33A	CD33	ADC	Cytotoxicity Pyrrolobenzodiazepine-mediated	AML	Sutherland *et al.*[202], NCT02785900 NCT02706899
AG567E	CD37	ADC	Cytotoxicity MMAE-mediated	CLL and NHL	Pereira *et al.*[203], NCT02175433 NCT02610062

Table 1: Continue

Drug	Target	Type Drug	Action mechanism	Clinical use	References
IMGN529	CD37	ADC	Cytotoxicity Maytansinoid-mediated	CLL, BCL, and others NHL	Beckwith *et al.*[204], NCT02564744
Otlertuzumab (TRU-016)	CD37	Humanized anti-CD37 mAb	Trigger direct caspase-independent apoptosis and antibody-dependent cellular cytotoxicity	CLL and NHL	Robak *et al.*[205], Gopal *et al.*[206] NCT01644253, NCT01317901
BI836826	CD37	Anti-CD37 mAb	Proapoptotic and antibody-dependent cytotoxicity	CLL	Betrian *et al.*[207], Heider *et al.*[208] NCT02759016, NCT02538614 NCT02624492
^{177}Lu-tetulomab (betalutin™)	CD37	Radio immunotherapy	Cell cytotoxicity by Beta-particles	NHL	Repetto-Llamazares *et al.*[209]
Alemtuzumab	CD52	Anti-CD52 mAb	Activation of apoptosis pathway.	CLL	Nguyen *et al.*[210], Ishizawa *et al.*[211] NCT01982175
Polatuzumab vedotin	CD79	ADC	Cytotoxicity MMAE-mediated	CLL and NHL	Palanca *et al.*[212], Polson *et al.*[213] NCT02729896, NCT02611323 NCT02600897

ACD: Antibody conjugated drug, mAb: Monoclonal antibody, CART: Chimeric antigen receptor T-cell, NCT: Number Clinical Trial, Acute lymphoblastic leukemia: ALL, Diffuse large B-cell lymphoma: DLBCL, Chronic lymphocytic leukemia: CLL, NHL: NHL, B cells lymphoma: BCL, Acute myeloid leukemia: AML, Mantle cell lymphoma: MCL, leukemia and lymphoma: L&L, Aggressive non-Hodgkin lymphoma: ANHL, Hodgkin's lymphoma: HL, Anaplastic large cell lymphoma: ALCL, Large B-cell and follicular lymphoma: LACFL, Momomethylaurastatin E: MMAE, Monomethylaurastatin F: MMAF

proteins are biotech-designed and constructed with a mixture of fragments of antigen binding (Fab) of specific antibodies and fragments of receptors. These mixed structures allow to recognize different cells (natural killer T-cells and cancer cells for example) and optimize the activation of different immunological cell types that can improve patient's immune response against cancer. In some cases, other chimeric constructions are made directly on cells. In cancer, for example, *ex-vivo* patients circulate T-cells could be removed, modified and reintroduced to the bloodstream to increase immunological response to cancer and kill more efficiently targeted cells. However, these new therapeutic approaches present new challenges. The most important are development and strength of pharmacovigilance programs worldwide. These programs are necessary to prevent or generate timely warnings about serious adverse effects caused by these medications or interventions.

SIGNIFICANCE STATEMENTS

- Present review approaches the problem of selectivity of the current antineoplastic treatments and how advances in biological drugs have led to improve its selective toxicity
- We will provide a point of view for the complete development of Antibody Drug-Conjugated (ADC) since preclinical to clinical trials and drug approval
- Detailed analysis (as a case of study) will be done for Brentuximab vedotin an antibody-directed therapy to improve benefit-risk for lymphoma treatment
- At the end, we show a compilation of immunotherapies that are currently in clinical trials with high potential to be approved in clinical practice and increase therapeutic effects on cancer treatment

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