An overview on anti-tubulin agents for the treatment of lymphoma patients

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ABSTRACT

Anti-tubulin agents constitute a large class of compounds with broad activity both in solid tumors and hematologic malignancies, due to the interference with microtubule dynamics. Since microtubules play crucial roles in the regulation of the mitotic spindles, the interference with their function usually leads to a block in cell division with arrest at the metaphase/anaphase junction of mitosis, followed to apoptosis. This explains the reason why tubulin-binding agents (TBAs) proved to be extremely active in patients with cancer.

Several anti-tubulin agents are indicated in the treatment of patients with lymphomas both alone and in combination chemotherapy regimens. The article reviews the literature on classic and more recent anti-tubulin agents, providing an insight into their mechanisms of action and their use in the treatment of lymphoma.

Keywords: vinca alkaloids, taxanes, antibody drug conjugates, dolastatins, maytansine, epothilones

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Abbreviations

ADC, antibody-drug conjugate

ALCL, anaplastic large cell lymphoma

CR, complete response

DLBCL, diffuse large B cell lymphoma

FDA, U.S. Food and Drug Administration

G-CSF, Granulocyte-colony stimulating factor

GDP, guanosine diphosphate

GTP, guanosine triphosphates

HL, Hodgkin's lymphomas

IV, intravenous

MAPs, microtubule-associated proteins

MCL, mantle cell lymphoma

MDA, microtubule-destabilizing agents

MDR, multidrug resistance

MMAE, monomethyl auristatin E

MSA, microtubule-stabilizing agent

ORR, overall response rate

OS, overall survival

PFS, progression-free survival

PR, partial response

VDA, vascular disrupting agent

VSLI, vincristine sulfate liposome injection

1. MICROTUBULES

Microtubules are highly dynamic, cytoskeletal protein filaments with a diameter of approximately 25 nm and length ranging from 200 nm to 25 μm, involved in the regulation of fundamental cell functions: cellular architecture maintenance, mitosis, cell signaling, motility and intracellular trafficking of organelles and macromolecules (Wade, 2009). Each microtubule is composed of two globular proteins, α- and β-tubulin, with a molecular weight of 50 kDa each (Krause, 2019; L. M. Miller, et al., 2010; B. R. Oakley, Paolillo, & Zheng, 2015; C. E. Oakley & Oakley, 1989).

Both α- and β-subunits are linked to form heterodimers and then arranged in a linear protein fiber known as protofilament. When 11-13 protofilaments assemble in parallel into a pipe-like structure, they generate a microtubule. The final microtubule in which α-tubulin gets exposed is negatively charged, whilst the other side, exposing β-tubulin, carries a positive charge. Both ends are involved in alternative cycling of lengthening and shortening by attaching new heterodimers, maintaining the microtubule in a state of “dynamic instability”. One end (plus) is kinetically more dynamic and grows more rapidly than the other (minus) (Cassimeris & Salmon, 1991; Dumontet & Sikic, 1999). The growth rate of microtubules is comprised between 5 and 20 μm/min and is regulated by the region of GTP-containing-tubulin at the microtubule end. Both α- and β-tubulin bind GTP in their N-terminal region but the GTP linked to α-tubulin is stable and hidden in the interior of the heterodimer and only the GTP in β-tubulin is accessible and provides the energy needed for polymerization by hydrolysis to GDP and phosphate. As long as a cap of tubulin-GTP is maintained, the lengthening is ongoing; a microtubule with a GDP molecule at his β-end is unstable and quickly depolymerize (Fig.1).

Another dynamic behavior, called "treadmilling", is the net growth in length at one microtubule end and the net shortening at the opposite end. The kinetics of these processes is controlled by microtubule-associated proteins (MAPs). MAPs mutations and altered expression of tubulin isotypes can be implicated in drug resistance.

The alteration of microtubules dynamics results in the inhibition of chromosome segregation during mitosis and into cell division block, ultimately leading to cell death. Drugs which interfere with the mitotic spindle apparatus by targeting tubulin are called anti-tubulin agents.

2. ANTI-TUBULIN AGENTS

Anti-tubulin agents constitute a large class of chemically diverse compounds, highly active in the treatment of solid and hematologic tumors and exert cytotoxic effects by altering the microtubule function.

In the last four decades much attention has been paid to microtubules as targets for anticancer drug discovery and tubulin-binding agents have been used with different purposes, including as antiparasitics and herbicides. Though, the treatment with anti-tubulin agents in humans dates back to the sixth century AD, when colchicine, an alkaloid found in *Colchicum autumnale* and various plants of the *Liliaceae* family, was used in patients with gout. Colchicine remains today a first-line treatment for this disease (Hastie, 1991).

Many anti-tubulin agents have been extracted from natural products such as plants, animals, microorganisms and marine organisms, and other classes are synthetically derived chemical compounds. All of them provide models to design and synthesize new tubulin inhibitors (Kaur, Kaur, Gill, Soni, & Bariwal, 2014; Liu, et al., 2009; Romagnoli, et al., 2017; Spanò, et al., 2019; Spano, Pennati, Parrino, Carbone, Montalbano, Cilibrasi, et al., 2016; Spano, Pennati, Parrino, Carbone, Montalbano, Lopergolo, et al., 2016; F. Yang, et al., 2019; Zhai, et al., 2017).

One the basis of the interference with dynamic equilibrium of polymerization or depolymerization of microtubules, anti-tubulin agents have been broadly classified in destabilizing agents or stabilizing agents, respectively. Tubulin inhibitors can be further distinguished depending on the domain where drugs bind to the tubulin: 1) vinca binding domain is located in the inter-dimer interface between two longitudinally aligned heterodimers; 2) colchicine binding site is situated at the intra-dimer longitudinal interface of the same heterodimer; 3) taxane binding domain is in the luminal area of the β-tubulin subunit. Vinca binding domain or colchicine binding domain are sites of action for destabilizing agents (Fig.2 and 3), while taxol binding domain for stabilizing agents (Fig.4). Additionally, laulimalide binding site on the exterior of β-tubulin is the target for many structurally unrelated compounds.

3. MICROTUBULE-DESTABILIZING AGENTS

Destabilizing agents (also called polymerization inhibitors or MDAs) impede tubulin assembly and constitute a class of structurally heterogeneous compounds including: vinca alkaloids, dolastatins, estramustine, maytansinoids, halichondrins, nocodazole, cryptophycins, colchicine and its analogues, hemiasterlins, podophyllotoxin, combretastatins, 2-methoxyoestradiol, 4-substituted methoxybenzoyl-aryl-thiazoles (SMART), phenylahistins, steganacins and curacins.

Vinca alkaloids and dolastatins especially in conjugation with monoclonal antibody are widely used in the treatment of lymphoma.

As the concentration of these agents increases, differences in the mechanism of action can be observed. At substoichiometric concentrations (less than one molecule of drug for each molecule of tubulin), destabilizing

agents bind microtubule ends preventing further tubulin addition and extending microtubule pause state with neither growth nor shrinkage. At high concentrations, these compounds stoichiometrically bind to tubulin subunits and decrease microtubule polymer mass, promoting depolymerization. Higher concentrations induce the formation of spiral aggregates of one or two protofilaments. Cells are stuck in G2/M phase, unable to proceed in anaphase and direct to apoptosis (Lobert & Correia, 2000; Moudi, Go, Yien, & Nazre, 2013).

3.1 Vinca alkaloids

Vinca alkaloids have dimeric chemical structures composed by the coupling of an indole ring (catharanthine) and a dihydroindole nucleus (vindoline). They were isolated in the 1950s from the Madagascar periwinkle plant (*Catharanthus roseus*) (Noble, 1990). Earlier, they were considered for their hypoglycemic, antimalarial and disinfectant effects; nevertheless, the cytotoxicity is their most important property and they were the first plant derivatives to be used in oncology. Five vinca alkaloids are clinically used in the treatment of several types of tumors: two natural compounds (vinblastine and vincristine) and three semi-synthetic derivatives (vinorelbine, vindesine and vinflunine). Vinca alkaloids are generally administered by IV bolus. The first two vinca alkaloids identified from plants, **vinblastine** and **vincristine**, are monoterpene indole alkaloids and have very similar structures, except for the formyl group attached to the dihydroindole nitrogen in vincristine, replaced by a methyl group in vinblastine (Ishikawa, et al., 2009). This albeit minimal structural difference markedly influences the type of tumors that the two drugs affect and the toxicity profile. Vincristine has its main toxic effects on the peripheral nervous system, in which induces axonal degeneration and decreasing of axonal transport because of the perturbation of microtubule efficacy. Vinblastine (such as vinorelbine and vindesine) is mainly toxic to the bone marrow, causing neutropenia. Because many other drugs are myelosuppressive like vinblastine, vincristine is used more often than vinblastine in combination regimens. It was the destructive effect on bone marrow that first suggested the use of vinca alkaloids in the treatment of hematologic tumors, rather than in diabetes. (Noble, 1990)

Vinblastine and vincristine are widely used in the treatment of several types of cancer such testicular cancer, breast cancer, Kaposi's sarcoma, Hodgkin's lymphomas (HL) and non-Hodgkin's lymphomas, in which they are part of frontline therapies.

In 1968, vinca alkaloids were introduced in the management of patients with malignant lymphoma. The comparative study of cyclophosphamide and vinca alkaloids demonstrated the higher proportion of remission induced by vinblastine in HL patients (Carbone, et al., 1968) and further improvements came with the introduction of combination chemotherapy. A four-drug combination of vincristine sulfate with

mechlorethamine, procarbazine hydrochloride and prednisone (MOPP) emerged in 1970 and remained the standard treatment for almost twenty years (Devita, Serpick, & Carbone, 1970).

The most revolutionary treatment of advanced HL was designed in 1981 at the National Cancer Institute in Milan, Italy, with the combination of vinblastine with doxorubicin, bleomycin and dacarbazine (ABVD), a scheme superior to MOPP in terms of cure rate (Bonadonna, Zucali, Monfardini, De Lena, & Uslenghi, 1975; Canellos, et al., 1992). In particular, ABVD has lower severe bone marrow toxicity, lower rate of infertility and less risk of second malignancies than MOPP or MOPP alternating with ABVD, although pulmonary fibrosis and cardiomyopathy can be induced by bleomycin and anthracyclines. This regimen substituted MOPP and became a standard worldwide therapy for several decades. In the last thirty years, new multi-combinatorial therapies have been developed to improve the efficacy of ABVD and vinca alkaloids continued to maintain an important role in these regimens. The German Hodgkin Study Group investigated three combinations of chemotherapy: vincristine, cyclophosphamide, procarbazine and prednisone alternating with vinblastine, doxorubicin, bleomycin and dacarbazine (COPP-ABVD); vincristine, bleomycin, etoposide, doxorubicin, cyclophosphamide, procarbazine and prednisone (BEACOPP) or increased-dose BEACOPP. The new BEACOPP regimens improved both overall survival (OS) and progression-free survival (PFS) in a three-week cycle, especially under the escalated version in which doxorubicin was increased from 25 to 35, cyclophosphamide from 650 to 1200 and etoposide from 100 mg/m^2 /die for 3 days to 200 mg/m^2 /die for 3 days. The failure-free survival rates improved from 70% for COPP-ABVD, to 79% with baseline BEACOPP and 89% with escalated BEACOPP. Unfortunately, the higher activity of BEACOPP is associated with more severe side effects such as acute hematologic and nonhematologic toxic effects, infertility and secondary tumors (Diehl, et al., 1998; Diehl, et al., 2003).

Since 1980s, vinca alkaloids are also part of the most common multidrug combination used in diffuse large B cell lymphoma (DLBCL): the CHOP regimen (T. P. Miller, et al., 1998; T. P. Miller & Jones, 1979). Numerous variations of this regimen have been tested during the past thirty years: administering some of the drugs as continuous infusion (EPOCH and hyper-CVAD regimens) (Thomas, et al., 2004), increasing the dose of some drugs (Mega-CHOP) (Dann, et al., 2005), reducing the intervals between cycles (CHOP-14) (Halaas, et al., 2005) and combining with radiotherapy or monoclonal antibodies. It was indeed the addition of rituximab, a chimeric monoclonal antibody against the CD20 antigen, that led to the definition of R-CHOP as the worldwide standard approach for lymphoma patients (Czuczman, 1999). The R-CHOP regimen is given every 3 weeks for 3-6 cycles depending on the stage of disease and consist of rituximab (375 mg/m^2, given IV on day 1), cyclophosphamide (750 mg/m^2, given IV on day 2), doxorubicin (50 mg/m^2 given IV on day 2), vincristine (1.4

mg/m^2 up to a maximal dose of 2 mg, given IV on day 2) and prednisone (60 mg/m^2, PO on day 1 to 5) delivered all at once in a bolus-type administration. Compared with CHOP alone regimen, R-CHOP significantly increases the rate of complete response (CR) and improves event-free survival and OS in DLBCL patients without a clinically significant increased toxicity (Coiffier, et al., 2002).

R-EPOCH (Jermann, et al., 2004), also known as EPOCH-R, is another chemotherapy regimen combined with rituximab commonly used for lymphoma. It includes vincristine (0.4 mg/m^2 as a continuous i.v. infusion on days 1 to 4,) with etoposide (50 mg/m^2 as a continuous i.v. infusion on days 1 to 4), prednisone (60 mg/m^2 orally on days 1 to 5), cyclophosphamide (750 mg/m^2 i.v. on day 5), doxorubicin (10 mg/m^2 as a continuous i.v. infusion on days 1 to 4) and rituximab (375 mg/m^2 i.v. on day 1), administered every 21 days for 6-8 cycles, depending on response and tolerability (Wilson, et al., 2002). Compared to R-CHOP, R-EPOCH has the addition of etoposide and the chemotherapy agents are infused over a longer period of time (four days). In a variant of this regimen, DA-R-EPOCH, the doses of the drugs are adjusted to maximize the efficacy according to the absolute neutrophil count nadir in the previous cycle (Purroy, et al., 2015). The continuous-infusion DA-R-EPOCH regimen was developed based on evidence that less tumor resistance is observed with prolonged low-dose exposure to drugs than with shorter but higher-concentration bolus regimen (Lai, Chen, Mickley, Fojo, & Bates, 1991; Wilson, et al., 1997). Additionally, the significant interpatient variations of etoposide and doxorubicin in plasma concentrations suggested the use of pharmacodynamic dose adjustments. Dose adjustments by 20% above the starting-dose level were applied to cyclophosphamide, etoposide and doxorubicin while only cyclophosphamide was adjusted below starting dose level. Vincristine dose was fixed at 0.4 mg/m^2 per day (1.6 mg/m^2 of body- surface area) to avoid sever vincristine-related neuropathy (Haim, et al., 1994). An intergroup phase III study compared patients receiving six cycles of DA-R-EPOCH or R-CHOP every 21 days as frontline therapy for DLBCL (Bartlett, et al., 2019). Among 491 eligible patients, 241 received DA-R-EPOCH and 250 received R-CHOP. The 74% of patients had stage III or IV disease. The more intensive DA-R-EPOCH regimen showed an improved toxicity without improving PFS, OS or response rate. DA-R-EPOCH arm had more frequent grade 3 to 4 hematologic (97.5% v 73.7%) and nonhematologic (72.2% v 43.25) toxicities because by design, dose escalation was used until patients experienced a dose-limiting toxicity.

Vinca alkaloids have pharmacokinetic limitations due to wide biodistribution and rapid elimination. To optimize the delivery of the drug to target tissues, minimize neurotoxicity and avoid drug resistance, a sphingomyelin and cholesterol-based nanoparticle formulation of vincristine, vincristine sulfate liposome injection (VSLI) was designed (Webb, Harasym, Masin, Bally, & Mayer, 1995) and approved in 2012 by FDA for adult patients with

Philadelphia chromosome-negative acute lymphoblastic leukemia. The liposomal formulation increases the retention of encapsulated drug, has a longer circulation time and allows a slow release of vincristine in the target tissue, exposing tumor cells to a prolonged therapeutic drug concentration (Boman, Tron, Bally, & Cullis, 1996; Zhigaltsev, et al., 2005). Comparing VSLI and standard vincristine antitumor activity in preclinical solid tumors and lymphoma models, VLSI was equivalent or more active than vincristine and had a larger maximum tolerated dose. When the efficacy of VSLI was evaluated as monotherapy in a phase 2 for relapsed or refractory aggressive lymphomas it resulted in overall response rate (ORR) of 25% and with a toxicity profile similar to standard vincristine when administrated at twice the dose (Rodriguez, et al., 2009). Due to the encouraging activity as single agent, a combination of VLSI and rituximab was tested in a phase II study for patients with advanced, relapsed and refractory DLBCL and mantle cell lymphoma (MCL) (Kaplan, Deitcher, Silverman, & Morgan, 2014). The ORR was 59% (13 of 22 patients), of which 27% achieved a complete response (CR) (6 patients) and 32% achieved a partial response (PR) (7 patients). Since VSLI induces a low clinically meaningful hematologic toxicity, it could be combined with myelosuppressive chemotherapy and is useful in patients unable to tolerate cytopenia (Kaplan, et al., 2014).

Optimization of treatments continues to evolve with the aim of getting better efficacy and reducing toxicity but the combinatory regimens including vinblastine and vincristine still remain frontline therapies for many lymphoma subtypes.

Since 1970's, remarkable efforts have been made by chemists to synthesize semi-synthetic derivatives of vinblastine and vincristine by modifying the vindoline portion of the bis-indolic structure. This region bears reactive centers accessible by simple reactions and its modifications led to the synthesis of the first semi-synthetic vinca alkaloid derivative used in clinical oncology: vindesine (Bayssas, et al., 1980; Cersosimo, Bromer, Licciardello, & Hong, 1983). **Vindesine** is a desacetyl derivative of vinblastine, registered in Europe in 1980 and available only for investigational purposes in the United States. Main indications of vindesine are in multi-drug chemotherapy protocols for lymphomas (Buzzoni, et al., 1993; Casasnovas, et al., 2017; Coiffier, et al., 1990; Coiffier, et al., 1987; Fitoussi, et al., 2011; Herbrecht, et al., 1991; Ishida, et al., 2015; Ketterer, et al., 2013; Koppler, et al., 1991; Lennard, et al., 1989; Merli, et al., 2016; Pfreundschuh, et al., 1987; Recher, et al., 2011; Riccardi, et al., 1993; Toyoda, et al., 2019). Among these, the dose intense regimen R-ACVBP (rituximab, vindesine, doxorubicin, cyclophosphamide, bleomycin and prednisone) is superior to standard R-CHOP in terms of clinical activity, but with a worse toxicity profile (Recher, et al., 2011).

After the synthesis of vindesine, the modification of vinblastine on its catharanthine nucleus led to **vinorelbine** (5'-norhydro vinblastine), first registered in France in 1989. This structural modification resulted in major

antitumor activity, increased lipophilicity and reduced side effects (Duflos, Kruczynski, & Barret, 2002). Vinorelbine has shown good efficacy in patients with Hodgkin's and non-Hodgkin's lymphoma (Balzarotti, Santoro, Tondini, Fornier, & Bonadonna, 1996; Bartlett, et al., 2007; Bonfante, et al., 1998; Cole, et al., 2009; Devizzi, et al., 1994; Ferme, et al., 1995; Gyan, et al., 2013; Horton, et al., 2015; Monfardini, et al., 2005; Santoro, et al., 2007; Santoro, et al., 2016; Zinzani, et al., 2001).

The third-generation member of the vinca alkaloids family is **vinflunine** (Kruczynski, et al., 1998), a vinorelbine derivative with two fluorine atoms in the catharanthine moiety, obtained thanks to the use of superacid chemistry. This synthetic strategy induces modifications in non-activated portions of the molecules, maintaining stable indoles and indolines. The double bond between C3' and C4' is also reduced. Vinflunine is the only fluorinated agent among the vinca alkaloids and was first described in 1998. Compared to other vinca alkaloids, vinfluinine seems to have a weaker binding affinity to tubulin than other vinca alkaloids (vincristine > vinblastine > vinorelbine > vinflunine) probably due to a higher dissociation constant (Kruczynski & Hill, 2001). Although vinflunine is not used in lymphoma, is the currently approved second-line treatment of advanced or metastasized urothelial cancer.

Vinca alkaloids are undergoing many clinical trials in patients with lymphoma as part of combinatory chemotherapies or as nanoparticle encapsulation, proving the unchanged importance of this class in oncology over the years.

The importance of vinca alkaloids in the treatment of lymphoma patients is underlined by high number of on-going clinical trials registered at clinical.trial.gov that incorporate vincristine (over 700 trials), vinblastine (over 100), vindesine (over 50) or vinorelbine (over 30).

3.2 Dolastatins

Dolastatins are marine cytotoxic pseudopeptides, originally isolated from the Indian Ocean mollusk *Dolabella auricularia* by the groups of G. R. Pettit and K. Yamada and then identified as products of the cyanobacteria *Symploca hynoides* and *Lyngbya majuscule* involved in the hare's diet. Dolastatin family includes linear and cyclic peptides, both natural and synthetic such as D-amino acids. The discovery of dolastatin 10 dates back to 1987. It is the most potent cytotoxic compound among those extracted from the sea hare with marked *in vitro* antimitotic effect due to the binding of a "peptide site" close to the vinca domain of tubulin (Bai, Pettit, & Hamel, 1990). Dolastatin 10 is a linear peptide composed of four amino acids: dolavaline, valine (Val), dolaisoleuine (Dil) and dolaproine (Dap) plus the C-terminal amine dolaphenine (Doe).

Despite the encouraging preclinical efficacy data, Dolastatin 10 failed to show appreciable therapeutic index into clinical trials because of significant toxic side effects at the maximum tolerated dose and its activity is no longer investigated (Krug, et al., 2000; Saad, et al., 2002; Vaishampayan, et al., 2000). Several synthetic analogues have been generated so far and one of them, **monomethyl auristatin E (MMAE)**, has been approved by the FDA in August 2011 as payload in the antibody-drug conjugate (ADC) **brentuximab vedotin** (SGN-35) (Francisco, et al., 2003; Okeley, et al., 2010) for the treatment of patients with relapsed HL or systemic anaplastic large cell lymphoma (ALCL) (R. Chen, et al., 2016; Forero-Torres, et al., 2015; Pro, et al., 2017; Pro, et al., 2012; Younes, et al., 2012). Brentuximab vedotin is composed of the anti-CD30 antibody cAC10. Since CD30 is highly expressed in HL and ALCL cells, the anti-CD30 antibody cAC10, on which brentuximab vedotin is based, allows the delivery of MMAE to the cells expressing CD30. MMAE maintains the same structure of Dolastatin 10 except for the C-terminal in which the dolaphenine is substituted by (1S,2R)-(+)-norephedrine (Dugal-Tessier, Barnscher, Kanai, & Mendelsohn, 2017). BV is the first ADC commercially available containing a cyanobacterial secondary metabolite. In brentuximab vedotin, each antibody is linked with an average of four molecules of MMAE via the spacer para-aminobenzylcarbamate, a cathepsin cleavable linker (valine-citrulline) and an attachment group consisting of caproic acid and maleimide. Once bound to the targeted cancer cell antigen, the conjugate is internalized into the cell, the valine-citrulline peptide linker is cleaved by lysosomal proteases and the drug is released in the specific, targeted cancer cell. The advantage of conveying the drug linked to the antibody is not only the increased selectivity towards the targets but also the higher stability in extracellular fluids and lower toxicity (Maderna, et al., 2014). Importantly, the results of a phase III trial exploring brentuximab vedotin in a combination regimen for HL patients are already available (Connors, et al., 2018). The use of brentuximab vedotin plus AVD (vinblastine, doxorubicin, dacarbazine) results in a statistically significant improvement in the 2-years PFS with a 5% increase versus the standard ABVD regimen. Because of the co-administration of two anti-tubulin agents (MMAE and vinblastine), the A+AVD regimen is associated with increased myelotoxicity (mitigated by administration of prophylactic G-CSF) and neurotoxicity (largely reversible). In contrast, pulmonary toxicity is substantially reduced by omission of bleomycin. As the concomitant use of BV and bleomycin in a phase 1 dose-escalation trial (BV plus ABVD) was associated with unacceptable incidence of pulmonary toxicity, their co-administration is contraindicated (Younes, et al., 2013). Brentuximab vedotin is a valid replacement for bleomycin in the AVD regimen and provides a more effective front-line treatment of advanced-stage classic HL.

A phase II trial of brentuximab vedotin and dose-attenuated rituximab cyclophosphamide, doxorubicin, and prednisone (R-CHP) as initial therapy for elderly patients with DLBCL is ongoing. The omission of vincristine

from standard R-CHOP prevents overlapping toxicities with brentuximab vedotin (ClinicalTrials.gov Identifier: NCT02734771).

Polatuzumab vedotin (DCDS4501A or RG7596) is another ADC based on MMAE (Pfeifer, et al., 2015; Polson, et al., 2007; Yu, et al., 2015) approved by FDA in June 2019 and by European Commission in January 2020 in combination with bendamustine and rituximab for the treatment of adults with relapsed or refractory DLBCL who have received at least two prior therapies (Deeks, 2019). Polatuzumab vedotin targets the B cell antigen receptor complex-associated protein beta chain (CD79b) with an antibody conjugated to an average of 3.5 MMAE molecules (Polson, et al., 2007). The approval of polatuzumab vedotin-BR is based on a multicenter phase Ib/II study in R/R DLBCL patients considered transplantation-ineligible and who experienced treatment failure with prior ASCT. The administration of pola-BR showed a significant improvement in CR rate (40% *v* 17.5%), PFS (median, 9.5 *v* 3.7 months) and OS (median, 12.4 *v* 4.7 months) compared to BR alone. The risk of death was reduced by 58%. Conversely, a higher rate of neutropenia, anemia and thrombocytopenia was observed in pola-Br patients (Sehn, et al., 2020). Evaluations of therapeutic regimens of pola-BR with other drugs are currently ongoing such as a phase III trial comparing R-CHOP vs polatuzumab vedotin plus R-CHP in patients with untreated DLBCL (POLARIX trial, NCT03274492).

The efficacy of polatuzumab vedotin combined with BCL2 inhibitor venetoclax in lymphoma patients has also been investigated, due to tolerable and non-overlapping toxicities. Pre-clinical data showed synergistic activity both *in vitro* and *in vivo* with a durable tumor regression in DLBCL and mantle cell lymphoma xenograft models at tolerated doses (Amin, et al., 2018). A phase 1b/II clinical trials in relapsed/refractory follicular lymphoma (FL) is currently evaluating the safety and efficacy of a treatment with polatuzumab vedotin, venetoclax, obinutuzumab and rituximab. (ClinicalTrials.gov Identifier: NCT02611323)

Another MMAE-linked ADCs used in lymphoma is **pinatuzumab vedotin** (DCDT2980S or RG-7593) (Advani, et al., 2017; Li, et al., 2013; Pfeifer, et al., 2015; Yu, et al., 2015). After showing clinical activity and tolerability in phase 1 trials, pinatuzumab vedotin (anti-CD22 antibody-drug conjugate) plus rituximab was recently compared to polatuzumab vedotin plus rituximab in a phase 2 randomized study (ROMULUS) in patients with relapsed or refractory non-Hodgkin lymphoma. Both patients with DLBCL and FL treated with R-pina achieved an objective response (OR) (60% and 62% respectively, of which 26% and 5% was CR). However, R-pola had longer durations of response than R-pina and a favorable benefit–risk (Morschhauser, et al., 2019).

Similarly to MMAE, **monomethyl auristatin F (MMAF)** is a synthetic auristatin derivative, payload in experimental ADCs such as **vorsetuzumab mafodotin** (SGN-75) (Oflazoglu, et al., 2008; Tannir, et al., 2014), **SGN-CD70A** (C.-Y. Yang, et al., 2017) and **denintuzumab mafodotin** (SGN-CD19A) (Jones, et al., 2019).

MMAF differs from MMAE for a charged phenylalanine moiety at its C-terminus that attenuates its cytotoxic activity and contributes to its membrane impermeability (Doronina, et al., 2006). The effect of SGN-75 (targeting CD70) was evaluated in a phase I study in relapsed/refractory non-Hodgkin lymphoma patients. Vorsetuzumab mafodotin was well tolerated with one CR in 12 patients treated with a Q3Wk schedule (Tannir, et al., 2014) and it was discontinued based on a strategic decision (Williams, 2015).

In an open-label, single agent, dose-escalation phase 1 study, the anti-CD70 ADC SGN-CD70A was evaluated in R/R DLBCL. The treatment showed an ORR of 20%, suggesting CD70 as a promising target for treating lymphoma, but the frequency and severity of thrombocytopenia induced by SGN-CD70A limit his applicability (Phillips, et al., 2019).

Encouraged by phase I trial in B cell lymphomas in which it proved to be well tolerated and showed encouraging activity as monotherapy in heavily pretreated (third-line or later) DLBCL, the anti-CD19 antibody-drug conjugate **denintuzumab mafodotin** was evaluated in a phase II study in combination with the second-line salvage regimen of rituximab, ifosfamide, carboplatin and etoposide in patients with DLBCL or FL. Of the 51 evaluable patients, the OR was 35%, of which 20% CR and 16% PR. Additionally, no significant myelosuppression or peripheral neuropathy were observed, suggesting that combining denintuzumab mafodotin with the 2nd-line salvage regimen of RICE could improve the outcomes (Chen, Jacobsen, Kostic, Liu, & Moskowitz, 2016).

3.3 Maytansine

Maytansine and its analogs are organic heterotetracyclic compounds and 19-membered macrocyclic lactam antibiotics that binds to tubulin at the vinca binding site (Bhattacharyya & Wolff, 1977), inducing microtubules depolymerization and cell cycle arrest in mitosis. Maytansine was originally isolated by Kupchan and coworkers from the ethiopian shrub *Maytenus serrata* and *Maytenus buchananii* and has 100 times higher cytotoxicity than vinca alkaloids (Kupchan, et al., 1972). Maytansinoids, chemical derivatives of maytansine, such as mertansine/emtansine (DM1) and Ravtansine/soravtansine (DM4) are widely used as payloads in ADCs. The conjugation strategy employs the thiol group of the maytansinoid (DM1 or DM4) and an ε-amino group of lysine residues of the antibody, with an average of 3.5 molecules of maytansinoid per antibody (Erickson & Lambert, 2012). ADCs containing maytansinoids developed for the treatment lymphoma include the anti-CD37 **naratuximab emtansine** (IMGN529/Debio1562) (Arribas, et al., 2018; Deckert, et al., 2013; Gaudio, et al., 2016; Stathis, et al., 2018), the anti-CD19 **coltuximab ravtansine** (SAR3419) (Al-Katib, Aboukameel, Mohammad, Bissery, & Zuany-Amorim, 2009; Blanc, et al., 2011; Coiffier, et al., 2016; Hicks, et al., 2019;

Ribrag, et al., 2014), the anti-CD56 **Iorvotuzumab mertansine** (hu901DM1) (Ailawadhi, et al., 2019; Whiteman, et al., 2014) and the anti-CD205 **MEN1309/OBT076** (Gaudio, et al., 2020; Merlino, et al., 2019). Table 1 summarizes the ADCs that incorporate dolastatins and maytansinoids currently used or under clinical evaluation for the treatment of lymphoma patients.

4. MICROTUBULE-STABILIZING AGENTS

Stabilizing agents (also called depolymerizing inhibitors or MSAs) prevent the depolymerization of microtubules and enhance their polymerization, leading to the formation of more stable and less functioning filaments. Likewise the destabilizing agents, the anti-microtubule activity of stabilizing agents is concentration dependent (Diaz, Strobe, Engelborghs, Souto, & Andreu, 2000). At 5-50 nmol/L the mitotic spindle is stabilized; at 1,000 times higher concentrations they increase the polymerization of microtubules and the bundle formation. The altered tubulin dynamics induces mitotic block at the G2/M phase and subsequent apoptosis. This class include: taxanes (paclitaxel and docetaxel), epothilones, taccalonolides, zampanolide, cyclostreptin, discodermolide and its analogues, dictyostatin, eleuthesides, laulimalide and peloruside A. Most of MSAs bind the taxane-binding site located in β-tubulin at the luminal side of microtubules. As above-mentioned, for laulimalide and peloruside, it has been hypothesized a novel site of binding, the laulimalide-binding site, located in the external surface of β-tubulin (Churchill, Klobukowski, & Tuszynski, 2015). Since this binding site is targeted by structurally unrelated compounds, the identification of pharmacophores interacting with the laulimalide domain is limited (Hamel, et al., 2006; Huzil, et al., 2008).

Tubulin stabilizing agents were originally obtained from plants and microorganisms. Currently, a wide number of synthetic or semi-synthetic MSAs are in different stage of preclinical and clinical development or have entered clinical use.

4.1 Taxanes

Taxanes are complex diterpene with a tetracyclic core (Parness, Kingston, Powell, Harracksingh, & Horwitz, 1982). Two cyclohexanes are linked to a central ciclooctane, creating a 15-member taxane ring bound to a four-member oxetan ring. Paclitaxel and his semi-synthetic analogue docetaxel are the main agents from this class. They have an ester side chain attached to the C-13 position of the ring but differ in the substitution at the C-10 in which docetaxel is deacetylated. Moreover, docetaxel has a trimethyl group attached to the amide portion, whereas paclitaxel has a phenyl group. This makes docetaxel more water soluble than paclitaxel, whose hydrophobicity requires the use of surfactants such as polyethylated castor oil and ethanol (Cremophor

EL) for intravenous administration, with an associated risk of hypersensitivity reactions (Pazdur, Kudelka, Kavanagh, Cohen, & Raber, 1993). The moieties at C-2' and C-3' on the C-13 chain are essential for the antimicrotubule activity (Rowinsky, 1997). Taxanes occupy the taxane-binding site with a 1:1 stoichiometry and have higher affinity to tubulins that are embedded along the length of microtubule rather than to soluble tubulin (Perez, 2009).

The latest approved taxane is the dimethoxy derivative of docetaxel, cabazitaxel (2010), used for the treatment of patients with docetaxel-refractory metastatic castration-resistant prostate cancer (Rouyer, et al., 2019). Tesetaxel and larotaxel are not approved but in clinical trials (Bissery, 2001).

Paclitaxel was the first microtubule-stabilizing agent to be described in literature in the late 1970s (Schiff, Fant, & Horwitz, 1979). It was isolated from the Pacific yew tree (*Taxus brevifolia*) but its supply, exclusively derived from the bark extract, limited the early researches. The production of one kilogram of paclitaxel required ten tons of bark. Paclitaxel is now feasibly produced semi-synthetically from 10-deacetylbaccatin III.

The efficacy of paclitaxel in treating lymphoma was investigated in several phase II trials in patients with relapsed and refractory lymphoma using different infusion schedule but, as a single agent, it seemed to have a modest clinical efficacy (response rate of 15-25%) compared with other available treatments (Casasnovas, et al., 2000; Hopfinger, et al., 1996; Lonial, et al., 2006; Press, et al., 1998; Pro, et al., 2006; Rizzieri, et al., 2004; Sinha, et al., 2013; Westin, et al., 2014; Wilson, et al., 1994; Younes, Ayoub, Sarris, Hagemeister, et al., 1997; Younes, Ayoub, Sarris, North, et al., 1997; Younes, et al., 2001; Younes, et al., 1998). In 2001, Younes conducted a phase II study to investigate the activity and tolerability of paclitaxel plus topotecan (Younes, et al., 2001). Later on the addition of rituximab to chemotherapy, a phase II study reported the efficacy of paclitaxel, topotecan and rituximab (TTR) in patients with R/R aggressive lymphomas, including those who didn't respond to second line PBC regimen (Westin, et al., 2014). Several studies have subsequently utilized paclitaxel in combinatorial chemotherapy approaches. Vinorelbine, paclitaxel, etoposide, cisplatin and cytarabine (VTEPA) regimen was designed as third-line therapy in patients with R/R DLBCL and HL, showing greater PFS and OS in HL than DLBCL (Sinha, et al., 2013).

Nanoparticle albumin-bound paclitaxel is an injectable formulation of paclitaxel bonded to albumin as a delivery vehicle (Desai, et al., 2006; Sparreboom, et al., 2005), used in the treatment of metastatic breast cancer, pancreatic cancer, non-small-cell lung cancer and adenocarcinoma of the pancreas. The albumin-bound paclitaxel was developed to avoid the association with cremophor/ethanol and to exploit the affinity of albumin for the secreted protein acidic and rich in cysteine (SPARC), a glycoprotein released by tumor cells, increasing the intra-tumoral concentration of drug. Although its efficacy in lymphoma as single agent was modest when

tested in a phase-I/phase-II study (ORR 10%) (Goyal, et al., 2018), the combination with azacytidine had a synergistic effect, inducing a durable CR (Bowen, Hahn, Butler, & Khong, 2017).

Relevant preclinical data have been obtained by the development of a Nab-paclitaxel/Rituximab-coated Nanoparticle (AR160) in which rituximab is non-covalently bound to the albumin scaffold of nab-paclitaxel (ABX). After ensuring that the drugs maintain their function when combined in vitro, the efficacy of AR160 was tested in vivo in a mouse model of human B cell lymphoma. Rituximab coated ABX (AR160) showed improved tumor targeting (biodistribution) and tumor efficacy relative to ABX and rituximab alone. All the mice treated with AR160 had a tumor response, of which 94,1% had a CR, compared to 48,2%, 25% and 0% of response in ABX 45, ABX 30 and rituximab alone treated mice. Starting from these results, the clinical development of AR160 is currently in progress. (NCT03003546) (Nevala, Butterfield, Sutor, Knauer, & Markovic, 2017)

Nowadays 29 trials at phase I and II are ongoing, valuating the efficacy of paclitaxel combined with other drugs, such as cyclosporine, gemcitabine and carboplatin, both in Hodgkin's and non-Hodgkin's lymphoma.

Docetaxel is a semisynthetic taxane derived from 10-deacetylbaccatin III (Lucatelli, Viton, Gimbert, & Greene, 2002). It has higher affinity for the tubulin binding site and induces less frequently hypersensitivity reactions and neuropathy. Since it accumulates inside the cells for longer and in a greater quantity, a lower dose of docetaxel is required to obtain the same cytotoxic effects of paclitaxel (Middleton, 2011). Limited clinical activity has been observed in patients with lymphomas (Budman, et al., 1997; Zekri, et al., 2003).

Preclinical studies have recently been carried out using docetaxel in combination with Aurora inhibitors MLN8237 (Qi, et al., 2011) and AT9283 as therapeutic strategy in aggressive lymphomas (Qi, et al., 2012). Both combinations demonstrated a statistically tumor growth inhibition and enhanced survival compared to single doses of the drugs. Other chemotherapy combinations with docetaxel for treating lymphomas are currently progressing through clinical trials: nine studies are in phase I, four in phase II and three in phase III.

4.2 Epothilones

Among the natural anti-tubulin stabilizing agents, epothilones raised high interest due to their increased efficacy compared to that observed with taxanes and their ability to overcome taxane resistance (Bollag, et al., 1995; Fumoleau, Coudert, Isambert, & Ferrant, 2007). They compete with paclitaxel for the taxane-binding site but interact in a different way with the binding pocket in β-tubulin (Nettles, et al., 2004). This could be the explanation of how epothilones have a higher activity in tumor cell lines resistant to taxanes. These compounds were first isolated in 1987 from the fermentation product of the soil myxobacterium *Sorangium cellulosum*. Their name derives from the structural features as epoxide, thiazole and ketone. Chemically, epothilones are

16-membered macrolides with a methylthiazole side chain. Based on structural differences in their C-12 and C-13, they are classified in epoxides (epothilones A, B, E and F) or olefins (epothilones C and D) (Altmann, 2005; Gerth, Bedorf, Hofle, Irschik, & Reichenbach, 1996; Gerth, Steinmetz, Hoflel, & Reichenbach, 2002). Only classes B and D have been developed to improve their anticancer activity. Six epothilones underwent preclinical and clinical valuations: **epothilone B** (patupilone or EPO-906) (Fumoleau, et al., 2007; Galmarini & Dumontet, 2003), **ixabepilone** (aza-epothilone B or BMS-247550) (Aghajanian, et al., 2007; Fumoleau, et al., 2007; Lee, et al., 2001; O'Connor, et al., 2008), **BMS-310705** (Fumoleau, et al., 2007; Kamath, Chang, Lee, Zhang, & Marathe, 2005; Kolman, 2004), **sagopilone** (ZK-EPO) (Klar, et al., 2006; Schmid, et al., 2010) (Fumoleau, et al., 2007), **epothilone D** (KOS-862) (Fumoleau, et al., 2007; Konner, et al., 2012; Monk, et al., 2012) and **KOS-1584** (Fumoleau, et al., 2007; Lam, et al., 2012). Among these, the epothilone B semisynthetic derivative ixabepilone is the one with more available clinical data and in October 2007 it had been approved by the FDA, as monotherapy or in combination with capecitabine, for the treatment of locally advanced or metastatic breast cancer. It is the first member of this class to be approved.

Preclinical and early phase II data showed activity of ixabepilone in indolent lymphomas and MCL (O'Connor, et al., 2008). One multicenter phase II trial explored ixabepilone in 51 patients with relapsed aggressive lymphomas and showed modest single-agent activity. The ORR was 27% with 12% with CR. The response varied with histology and those with either grade 3 or transformed FL had the highest response rate (63% ORR). Ixabepilone was well-tolerated, except for neuropathic toxicity. Considering that the response rate of ixabepilone is modest compared to other drugs currently in use, its use in lymphomas is very limited (Churpek, et al., 2013).

5. NON-MITOTIC EFFECTS

The antiproliferative activity of anti-tubulin agents is largely attributed to alterations of microtubule dynamics but this view has been challenged in the last years and MTAs demonstrated to act on other targets, affecting cellular process unrelated to mitosis. Non-mitotic MTAs actions are: 1) mitosis-independent induction of cell death; 2) angiogenesis; 3) vascular disruption.

The apoptotic cell death program is minutely regulated by the balance between pro- (Bim, Bad, Bid, Noxa, etc.) and antiapoptotic (Bcl-2, Bcl-x) members of the Bcl-2 family. MTAs can affect both pro-apoptotic and anti-apoptotic members. Several studies have indicated that paclitaxel, vincristine, and vinblastine induce Bcl2 inactivation (by phosphorylation) and decrease Bcl2-Bax dimerization in MCF-7, MDA-MB-231 (Srivastava, et al., 1998), acute leukemia and prostate cancer cell lines (Haldar, Basu, & Croce, 1997), thus enhancing

apoptosis. Moreover, vincristine led to phosphorylation of Bcl-2 in leukemia and lymphoma cell lines (Ehrhardt, et al., 2011); vinblastine, vincristine and colchicine in cervical carcinoma cells (Du, Lyle, & Chambers, 2005); nocodazole in a leukemia model (Han, Jun do, Lee, & Kim, 2014) and dolastatin in numerous cell lines (Haldar, Basu, & Croce, 1998).

Another mechanism by which MTAs affect Bcl-2 involves Bim (Bcl-2-interacting mediator of cell death). Under physiological conditions Bim is associated with the microtubule network by dynein light chains 1 and 8 (DLC1/8), avoiding the binding with other Bcl-2 members (BCL2, BCL2L1/BCL-XL and MCL1). The microtubule disruption by MTAs causes release of Bim from the dynein light chain and stimulates the apoptotic cascade. The importance of Bim as an apoptotic activator is demonstrated by Bim-deficient lymphocytes which developed resistance to microtubule targeting drugs (Mollinedo & Gajate, 2003).

Several MDAs (vinblastine, vincristine, colchicine and combretastatin A4) also can induce proapoptotic proteins Noxa and Puma in melanoma (Zhu, et al., 2008), leukemia and lymphoma cells (D. J. Bates, Danilov, Lowrey, & Eastman, 2013). The JNK-Noxa-apoptosis pathway activated by MDAs doesn't seem to be influenced by taxanes (D. Bates & Eastman, 2017).

A large number of studies report that MTAs (2-methoxyestradiol, taxol, vincristine, vinblastine, colchicine, nocodazole and cytochalasin D) exhibit anti-angiogenic activities, mainly decreasing endothelial cell migration and growth as well as capillary-like tube formation. Additionally, MTAs impede angiogenesis by altering microtubule-induced cell chemotaxis, spreading and cellular contacts. Vinblastine and vincristine were the most potent inhibitors of in vitro angiogenesis, inhibiting endothelial cell migration at doses of 0.011 and 0.001 μM and cell growth in a dose-dependent manner with IC50 values of 0.690 nM and 0.004 μM, respectively. Vincristine, vinblastine, colchicine, nocodazole and taxanes inhibited angiogenesis at noncytotoxic doses (Mabeta & Pepper, 2009). Moreover, docetaxel was reported to attenuate endothelial cell migration as result of the ubiquitination and subsequent proteasomal degradation of heat shock protein 90 (Hsp90) (Murtagh, Lu, & Schwartz, 2006). Docetaxel, epothilone B and vinblastine reduced angiogenesis at concentrations not affecting cell proliferation by inhibition of Rac1 and Cdc42 activity. In this case, docetaxel was slightly more efficient than epothilone B and vinblastine (Bijman, van Nieuw Amerongen, Laurens, van Hinsbergh, & Boven, 2006).

MTAs represent the largest subclass of vascular disrupting agents (VDAs), of which combretastatins are the most prominent representatives and the first to enter clinical trials for cancer. The immature, highly disorganized and more vulnerable tumor vessels are the primary cellular targets of these drugs. The vascular disruption of these vessels causes a collapse of tumor mass. The lead VDA CA4P was found to strongly impact

VE-cadherin/β-catenin/Akt signaling, Rho GTPases and actin reorganization thus altering cell-to-cell junctions and the monolayer permeability in endothelial cells.

Albeit VDAs cause profound damage to tumors, they failed to arrest tumors as single agents and their combination with other cytotoxic drugs is required to maximize antitumor efficacy (Kanthou & Tozer, 2009).

6. DRUG RESISTANCE

Development of drug resistance is a concerning issue in chemotherapy and multiple mechanisms have been described to explain the poor responsiveness of cells to antitumor drugs. Drug resistance implies that the tumor is not or no longer responding to the therapy and can originate from different mechanisms: 1) drug metabolism; 2) drug efflux; 3) target modification; 4) post-translational modifications of tubulin regulatory proteins. One type of resistance may be due to an increased metabolic capacity in patients with over-active enzymes (in particular P450 oxidizing enzymes systems) or to the co-administration of inducers of these metabolic enzymes, reducing the drug concentration in blood.

In many cases the effectiveness of drugs is reduced because of an insufficient concentration into the cancer cells. The overexpression of efflux pumps that transport the drugs out of the tumor cells is the major resistance mechanism for taxanes and vinca alkaloids but not for epothilones. Vice versa, the under expression of active transporters does not affect the intracellular concentration of anti-tubulin agents since they passively pass into the cell by diffusion. The most common overexpressed efflux pump in various multi-drug resistant cancer cells is the P-glycoprotein (P-gp), a membrane-associated ATP-binding cassette (ABC) transporter encoded by the ABCB1 gene. Various anticancer drugs are substrate of this pump (e.g. vinca alkaloids, taxanes, colchicine, anthracyclines, podophyllotoxins and newer antitumor drugs). Among the several strategies developed to overcome P-gp-mediated resistance, the co-administration of pump inhibitors (cyclosporin A, valspodar and verapamil) showed unsatisfactory activity in clinical trials. Therefore, other approaches have been introduced during the last decades, such as anti-P-gp monoclonal antibody, ABCB1 gene silencing, transcriptional modulators and new generation drugs which are not substrate for the pump. Both microtubule destabilizing and stabilizing agents have been synthesized with this purpose: cryptophycins, halicondrins, hemiasterlins, second and third generation taxanes and epothilones. Additionally, liposomal formulation and nanoparticles allow P-gp-substrate drugs to bypass resistance.

Alterations in tubulin isotypes lead to drug resistance in many types of cancer and are related to aggressive clinical outcome. Frequent modifications affect βI-, βII-, βIII-, βIVa- and βV-tubulin isotypes and were significantly expressed in taxanes and vinca alkaloids resistant cells. The overexpression of βIII-tubulin is the

most studied mutation and is associated with paclitaxel resistance. It was suggested that the bond of paclitaxel with microtubule is induced by hydrogen bond with all β-tubulin, except for βIII and βVI isotypes; overexpression of βIII consequently inhibits drug interaction with the target. Various semi-synthetic and synthetic taxanes have been developed to overcome paclitaxel resistance: cabazitaxel, larotaxel, TPI-287 and tesetaxel. On the other hand, high expression of βIII-tubulin increases sensitivity to epothilones.

Another factor inducing resistance is the alteration of microtubule-associated proteins (MAPs). Phosphorylations of these MAPs are important regulatory post-translational modifications and generally their phosphorylation results in loss of activity. MAP-4 is localized in all nonneuronal tissues and stabilizes microtubules. Therefore, low expression or phosphorylation of MAP-4 decreases microtubule stability and reduces polymerization, resulting in resistance to paclitaxel.

In contrast, stathmin destabilizes microtubules so that his overexpression shifts microtubules to a depolymerized state and induces resistance to paclitaxel. Other MAPs, including kinesins, dyneins, microtubule-based motor proteins and surviving proteins, are under investigation to explore their role in paclitaxel sensitivity.

In addition to the mentioned mechanisms, cancer cells can evade cytotoxic effects because of intracellular drug detoxification accomplished by proteins of the glutathione S-transferase family (Bohnacker, et al.), apoptosis blockade following the overexpression of anti-apoptotic protein AKT or p53 gene mutations and overexpression of oncoprotein Sorcin that shift cell life toward proliferation (Krause, 2019).

Understanding the mechanisms of drug resistance and mitigating its effects remain clinical challenges to improve future therapies.

Conclusions and future perspectives

Anti-tubulin agents constitute a large class of compounds with different applications in medicine and since the discovery of vinca alkaloids in the late 1950s, they are a milestone in the development of anticancer drugs. Even though their effects on cytoskeleton are different, both destabilizing and stabilizing agents suppress microtubule dynamics and because of the high tubulin concentrations in neuronal cells, they share neurotoxicity as common side effect.

Several drug combination strategies including TBAs are successfully used in the treatment of lymphoma (ABVD and R-CHOP) and more potent therapies have been developed in recent years with ADCs (Brentuximab vedotin and Polatuzumab vedotin). Anti-tubulin agents, attached via chemical linkers to antibodies, are specifically delivered to the targeted tumor cells, optimizing their cytotoxic effects.

The synthesis of new TBAs with improved efficacy, tolerability, specificity and that are not MDRs substrates fuels many medicinal chemistry efforts. Several anti-tubulin agents are currently in clinical trials as part of combination therapies or ADCs and they have a promising role for the treatment of lymphoma in the near future.

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Fig. 1 – Microtubule structure. α- and β-tubulin arrange in a polar head-to-tail fashion to form protofilaments. Thirteen protofilaments then assemble in parallel forming a microtubule with distinct polarity at each end: a fast-growing plus end (exposing β-tubulin) and a slow-growing minus end (exposing α-tubulin).

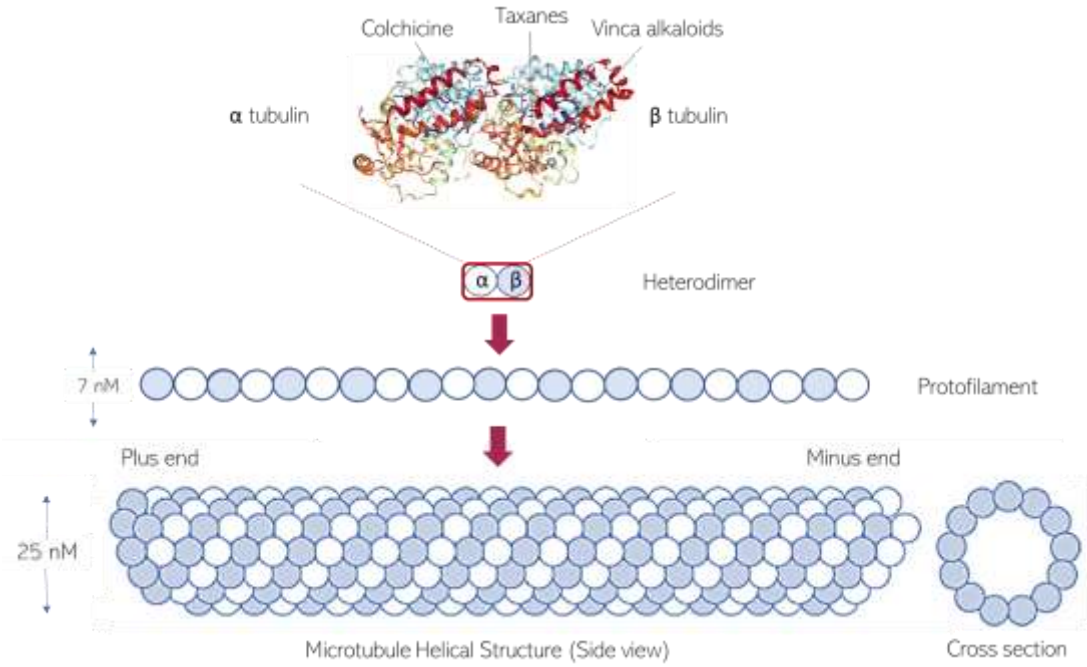

Fig. 2 – Chemical structures of MDAs targeting vinca binding site.

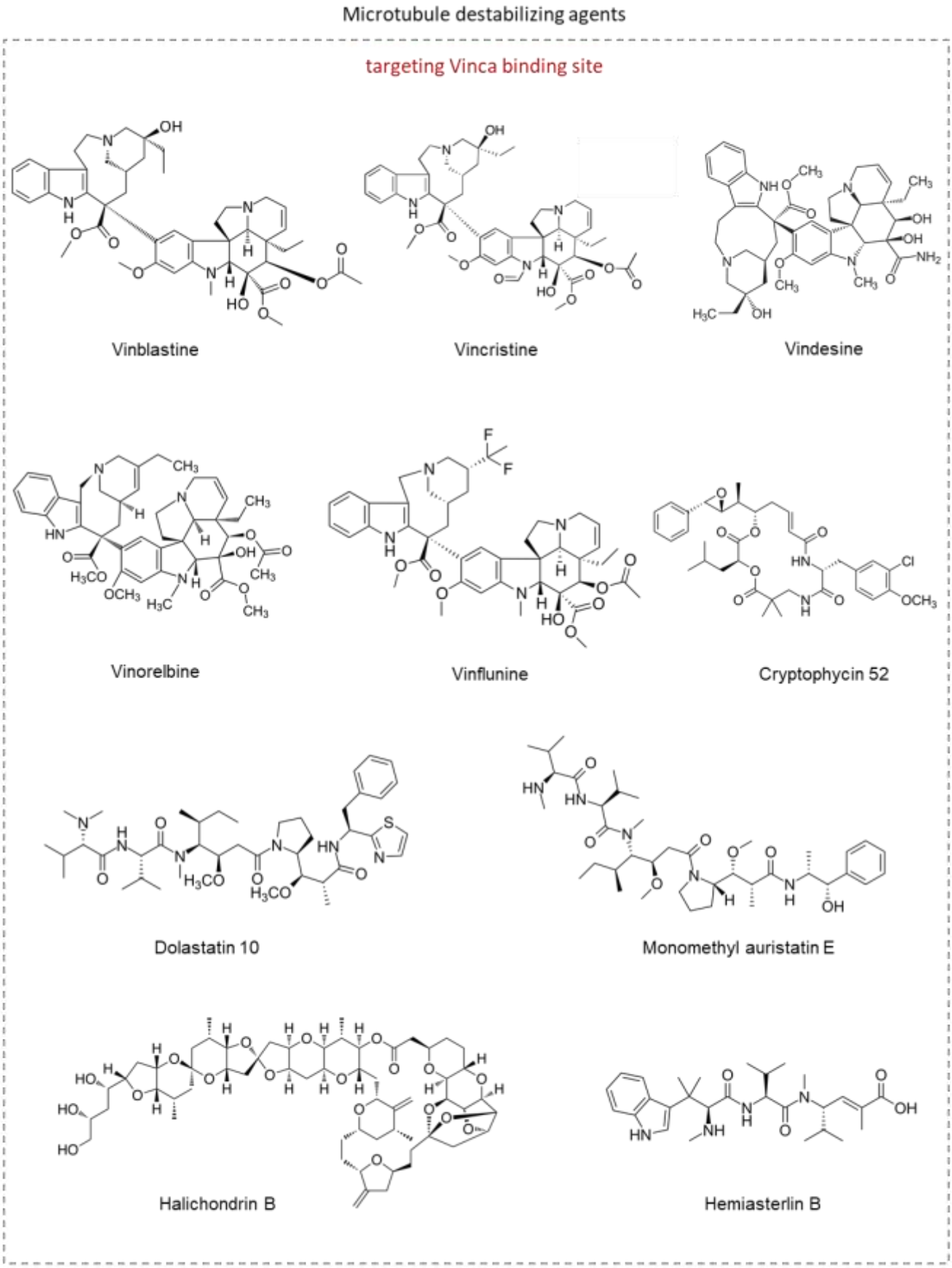

Fig. 3 – Chemical structures of MDAs targeting colchicine binding site.

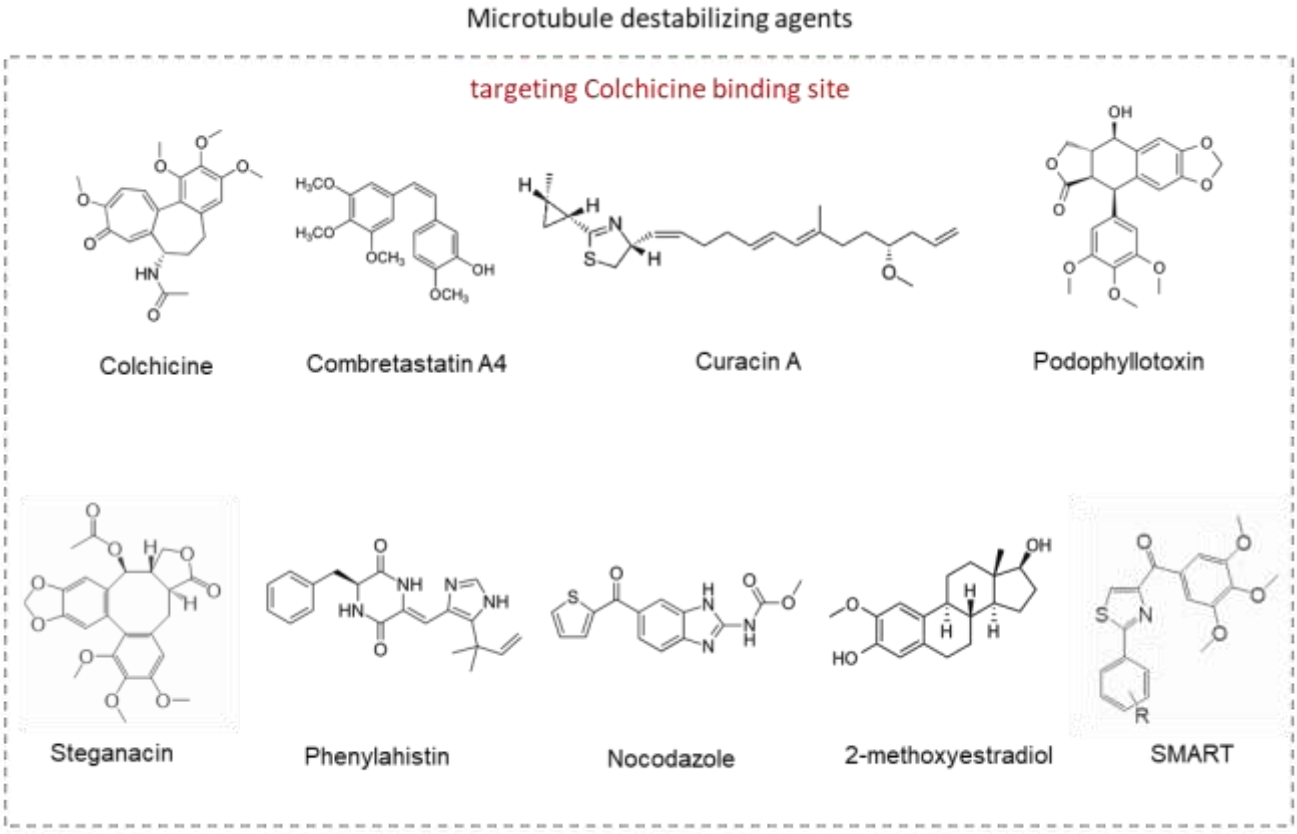

Fig. 4 – Chemical structures of MSAs targeting taxane binding site.

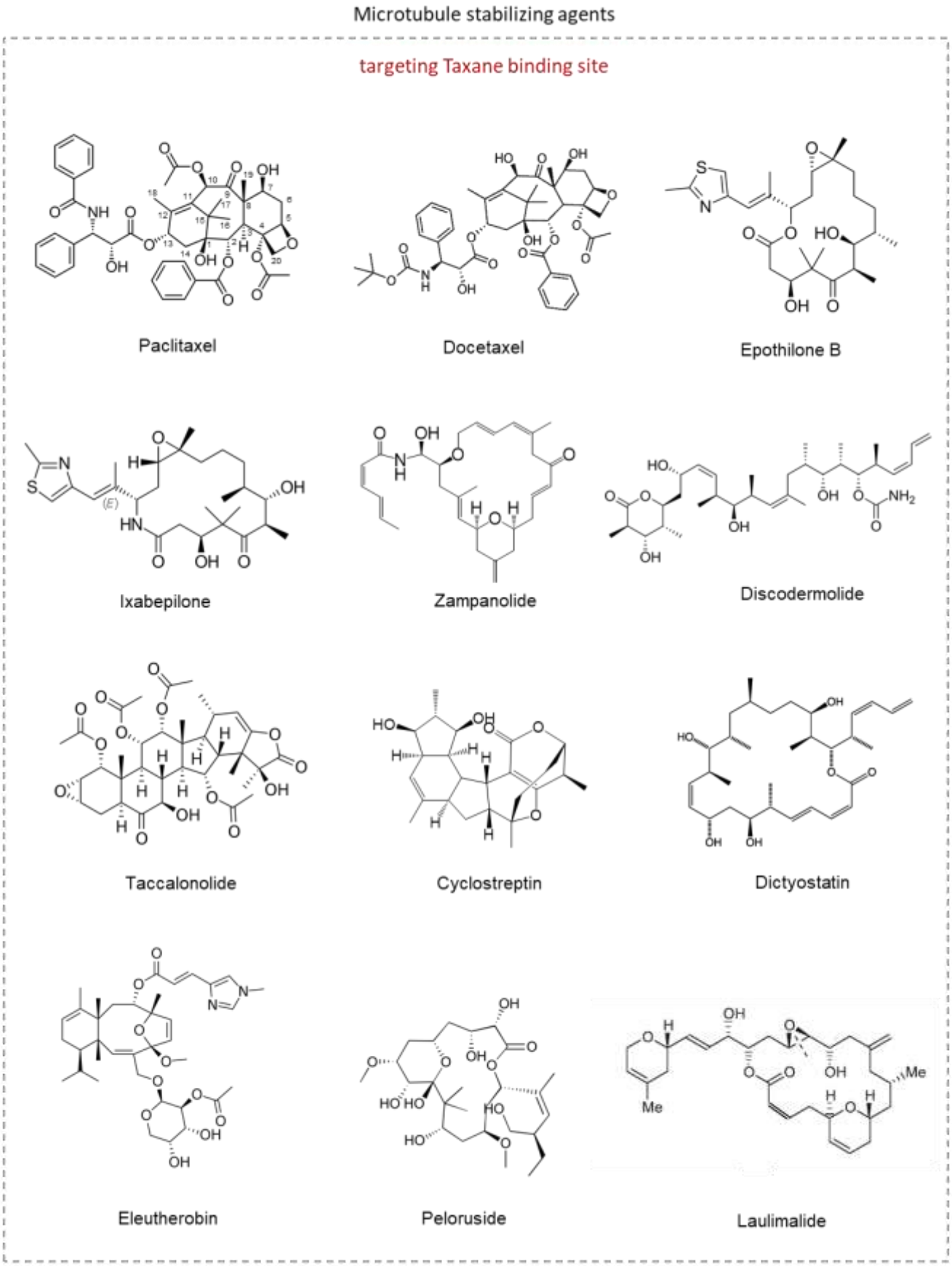

Table 1. Microtubule agents used as payloads in antibody-drug conjugates for lymphoma patients.

Payload	Target	ADC	Linker
Monomethylauristatin E (MMAE)	CD30	Brentuximab vedotin	valine-citrulline
Monomethylauristatin E (MMAE)	CD22	Pinatuzumab vedotin (DCDT2980S, RG-7593)	valine-citrulline
Monomethylauristatin E (MMAE)	CD79B	Polatuzumab vedotin (DCDS4501A, RG7596)	valine-citrulline
Monomethylauristatin F (MMAF)	CD70	SGN-75	aline-citrulline
Monomethylauristatin F (MMAF)	CD70	SGN-CD70A	maleimidocaproyl
Monomethylauristatin F (MMAF)	CD19	SGN-CD19A	aleimidocaproyl
Maytansinoid DM1	CD56	Lorvotuzumab mertansine (hu901DM1)	N-succinimidyl 4-(2 pyridyldithio) pentanoate (SPP)
Maytansinoid DM4	CD37	naratuximab emtansine (IMGN529/Debio1562)	N-succinimidyl 4-(2 pyridyldithio) butyrate (SPDB)
Maytansinoid DM4	CD19	Coltuximab Ravtansine (SAR3419)	N-succinimidyl 4-(2-pyridyldithio) butyrate (SPDB)
Maytansinoid DM4	CD205	MEN1309/OBT076	N-succinimidyl-4-(2-pyridyldithio) butanoate