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Microtubule-targeting agents and their impact on cancer treatment

Vladimír Čermák[a,b,1], Vojtěch Dostál[a,1], Michael Jelínek[c,1], Lenka Libusová[a], Jan Kovář[c], Daniel Rösel[a,b], Jan Brábek[a,b,*]

[a] Department of Cell Biology, Charles University, Viničná 7, 12843 Prague, Czech Republic
[b] Biotechnology and Biomedicine Centre of the Academy of Sciences and Charles University (BIOCEV), Průmyslová 595, 25242 Vestec u Prahy, Czech Republic
[c] Department of Biochemistry, Cell and Molecular Biology & Center for Research of Diabetes, Metabolism, and Nutrition, Third Faculty of Medicine, Charles University, Prague, Czech Republic

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ABSTRACT

Microtubule-targeting agents (MTAs) constitute a diverse group of chemical compounds that bind to microtubules and affect their properties and function. Disruption of microtubules induces various cellular responses often leading to cell cycle arrest or cell death, the most common effect of MTAs. MTAs have found a plethora of practical applications in weed control, as fungicides and antiparasitics, and particularly in cancer treatment. Here we summarize the current knowledge of MTAs, the mechanisms of action and their role in cancer treatment. We further outline the potential use of MTAs in anti-metastatic therapy based on inhibition of cancer cell migration and invasiveness. The two main problems associated with cancer therapy by MTAs are high systemic toxicity and development of resistance. Toxic side effects of MTAs can be, at least partly, eliminated by conjugation of the drugs with various carriers. Moreover, some of the novel MTAs overcome the resistance mediated by both multidrug resistance transporters as well as overexpression of specific β-tubulin types. In anti-metastatic therapy, MTAs should be combined with other drugs to target all modes of cancer cell invasion.

1. Introduction

The microtubular cytoskeleton controls many vital functions in eukaryotic cells ranging from cell division to cell movement and vesicular transport. The main structural component of microtubules is the protein tubulin. Given the importance of tubulin, it is not surprising that it has been successfully targeted by a plethora of natural and synthetic agents, some of which are now used in cancer treatment.

Tubulins are globular GTP-binding proteins, approximately 55 kDa in size, and found in all eukaryotic cells. There are 23 functional genes coding for tubulin in the human genome and they are classified into the α, β, γ, δ, and ε families (Findeisen et al., 2014). While tubulins γ, δ and ε are mostly present in the centrosome (Chang and Stearns, 2000), α- and β-tubulins are the main building blocks of microtubules. They first assemble into αβtubulin heterodimers and then, under favorable conditions, polymerize into microtubules, which are long hollow cylinders with a diameter of 24 nm. They usually consist of 13 protofilaments with a so-called microtubular "lumen" in the center. All αβ-tubulin subunits present in a protofilament are arranged head-to-tail and in such a way that the β-tubulins always point towards the so-called "plus end" of the microtubule and α-tubulins point towards the "minus end".

In the process of nucleation, new microtubules assemble from microtubule-organizing centers (MTOC) with the plus ends always pointing outwards. The most established MTOC in human cells is the centrosome but many cell types rely on non-centrosomal MTOC sites situated on the Golgi apparatus membrane or elsewhere (Toya and Takeichi, 2016). Microtubules grow by addition of new αβ-tubulin subunits to the plus ends of the microtubule. These newly incorporated subunits have two GTP molecules bound to them, one to the α-tubulin, the other to β-tubulin. However, only the latter is able to hydrolyze GTP to GDP, which happens shortly after incorporation into a microtubule (Mitchison, 1993). In effect, subunits with GTP attached to β-tubulin form a short-lived "cap" on the plus end of each growing microtubule. When this cap is lost, microtubules rapidly disassemble (shrink) until a new GTP cap is formed again and microtubule can grow. Periods of growth and shrinking alternate with periods of no apparent growth (the pause-state). This dynamic behavior termed dynamic instability is one of the trademark properties of microtubules (Wilson and Jordan, 1995).

Microtubules have several cellular functions, but their role in cell division is probably the best known. Microtubules of the mitotic spindle

Abbreviation: MTAs, microtubule-targeting agents

* Corresponding author at: Department of Cell Biology, Charles University, Viničná 7, 12843 Prague, Czech Republic.
E-mail address: brabek@natur.cuni.cz (J. Brábek).

[1] These authors contributed equally.

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attach to the kinetochores of separating chromosomes, ensuring equal distribution of genetic material to daughter cells (Helmke et al., 2013). However, microtubules play an important role in interphase cells as well. One such well-documented role is in vesicular trafficking. Microtubules serve as platforms for molecular motors, i.e., kinesins and dyneins. These protein complexes transport vesicles or other cargo over long distances toward the plus or minus end of the microtubule. Therefore, the function of various adhesive molecules, signaling receptors, and oncoproteins depend on the proper function of microtubules (Komlodi-Pasztor, 2011). All these functions of microtubules can be targeted by MTAs.

1.1. Microtubule-targeting agents

Microtubule-targeting agents (MTAs), also known as microtubule-binding agents, microtubule-interfering drugs, anti-microtubule drugs, or simply microtubule poisons, constitute a diverse group of chemical compounds that bind to microtubules and affect their properties. Far from being mere experimental tools for cell biologists, microtubule drugs have a myriad of practical applications in agricultural weed control (Anthony and Hussey, 1999), antiparasitic therapy (Fennell et al., 2008), and cancer treatment (chemotherapy). An overview of the chemical diversity of MTAs is presented in Table 1. Structures of the prototypical compounds representing individual structural categories are in Fig. 1. Structures of all compounds mentioned in the following text are in Supplementary Fig. 1.

One way to classify MTAs is based on the position of their binding sites on tubulin (Jordan and Wilson, 2004). The target of one group of compounds is known as the vinca domain, which is broadly localized in the interface between two longitudinally aligned αβtubulin dimers along one protofilament. These compounds include vincristine, vinblastine, vinorelbine, eribulin, and several others (Dabydeen et al., 2006; Gigant et al., 2005). Another group is named after its most prominent member, colchicine. These drugs occupy a space inside the αβtubulin dimer itself and predominantly bind to β-tubulin. Besides colchicine, this group includes combretastatins (e.g. combretastatin A4), benzimidazoles (e.g. nocodazole), and other compounds, none of which is currently in clinical use as an anticancer drug (Chatterji et al., 2011; Wang et al., 2016). The third well-established binding pocket is the taxane site, which is found on β-tubulin in the lumen of microtubules (Alushin et al., 2014). Notable representatives of this group include paclitaxel and epothilones. Interestingly, paclitaxel reaches its binding site by passing through molecular nanopores in the microtubule wall where it can also temporarily bind (Freedman et al., 2009). There are additional binding sites beyond the three classical ones, such as the maytansine site and the laulimalide/peloruside site, both on βtubulin (Prota et al., 2014a, 2014b). Although these are genuine binding sites, they can influence neighboring drug binding pockets, as is the case with the vinca domain and maytansine site (Prota et al., 2014a) or taxane site and the colchicine site (Gallego et al., 2017), see Fig. 2. Additionally, a unique binding site on α-tubulin is covalently bound by pironetin (Prota et al., 2016; Yang et al., 2016). A detailed review of various mechanisms and sites of binding was recently published (Steinmetz and Prota, 2018).

It should be noted that the precise interactions with amino acid residues of drug-binding pockets can vary even between compounds of the same group (Nettles et al., 2004; Prota et al., 2014b). Additional diversity is brought by differential binding along the microtubule. While some compounds preferentially target the GTP cap, others bind along the entire length of the microtubule. The latter is especially true for taxanes and epothilones (Nogales et al., 1995; Prota et al., 2013). Some MTAs can even bind free tubulin heterodimers (Field et al., 2012).

Clinical success of MTAs has been partially hampered by the emergence of drug resistance in certain cases (Fojo and Menefee, 2007). The most common mechanism of multidrug resistance is conferred by

Table 1
Microtubule-targeting agents with completed Phase II/III trials, or currently in use. Basic data concerning these agents including relevant citations are presented. Table is based on previously published data with several updates. A - approved.

Compound/Substance	Group	Binding site	Types of cancer tested or treated	Phase	Ref.
Vincristine	Vinca alkaloid	Vinca domain	breast cancer, lymphomas, sarcomas	A	Martino et al. (2018)
Vinblastine			breast cancer, lymphomas, sarcomas	A	
Vinorelbine			breast, lung cancer, sarcomas	A	
Vindesine			lung cancer	A	
Vinflunine			urothelial cancer	A	Bellmunt et al. (2009); Retz et al. (2015)
Vintafolide (vinflunine + folate)	Vinca alkaloidconjugate		lung, ovarian, endometrial cancer	II	Assaraf et al. (2014)
Eribulin	Macrolide		liposarcomas, metastatic breast, bladder cancer	A, III, II	Twelves et al. (2010), Kumar et al. (2017)
Dolastatin 10	Peptide		solid tumors	II	Kumar et al. (2017), Akaiwa et al. (2018)
Plinabulin	Heterocyclic nitrogen compound	Colchicine site	lung cancer	II	Gridelli et al. (2009)
Verubulin			glioblastoma	I	Grossmann et al. (2012)
ABT-751			lung cancer	II	Gridelli et al. (2009)
Ombrabulin	Combretastatin		ovarian cancer	II	Tae et al. (2007)
Fosbretabulin			thyroid cancer	II	Mooney et al. (2009)
Paclitaxel	Taxane	Taxane site	ovarian, breast cancer, many others	A	Choy (2001)
Docetaxel			breast, lung cancer, many others	A	Engels et al. (2005)
Cabazitaxel			hormone-resistant prostate cancer	A	Paller and Antonarakis (2011)
Larotaxel			non-small lung, breast, bladder cancer	I - III	Diéras et al. (2008), Sternberg et al. (2013)
Epothilone B	Epothilone		lung cancer	II	Larkin and Kaye (2007)
Ixabepilone			breast, endometrial cancer	III	Rugo et al. (2015); McMeekin et al. (2015)
TDM1 (Trastuzumab + mertansine)	Maytansine/auristatin conjugate	Maytansine domain	metastatic breast cancer	A	Geraud et al. (2017)
Brentuximab vedotin (Anti-CD30 antibody + monomethyl auristatin)			Hodgkin lymphoma	II	Moskowitz (2015)
SAR33419 (anti-CD19 antibody + maytansine)			large B-cell lymphoma	II	Kantarjian et al. (2016)

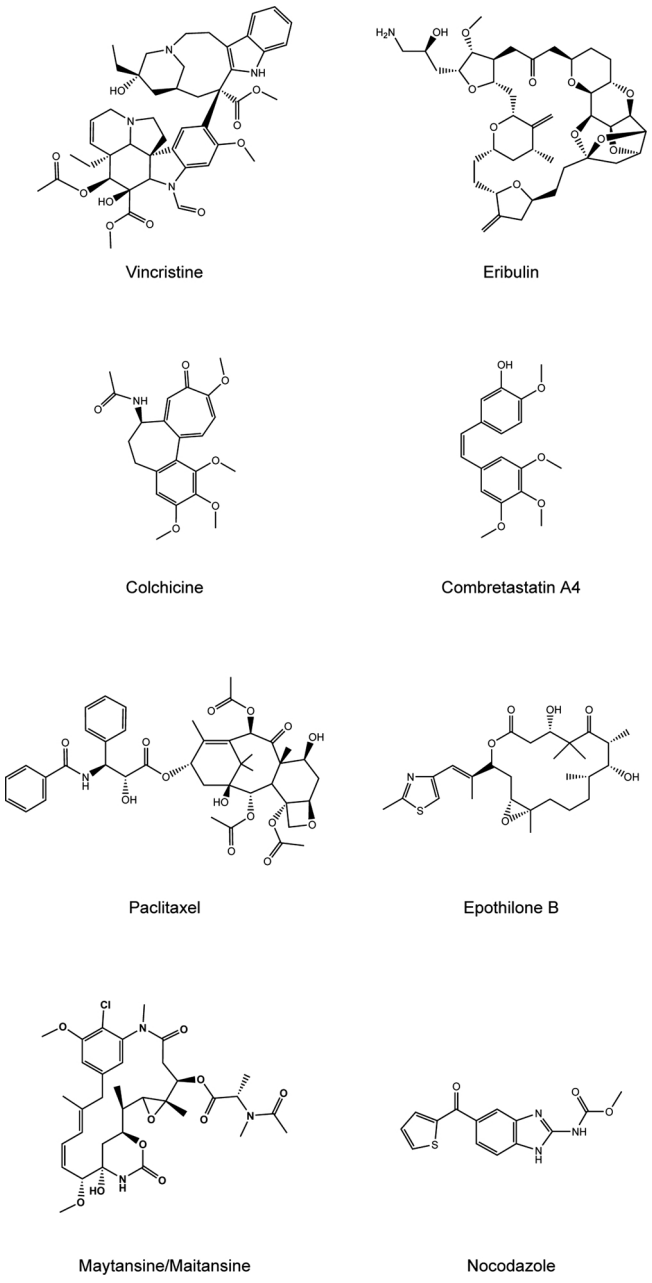

Fig. 1. Structures of prototypical microtubule-binding agents.

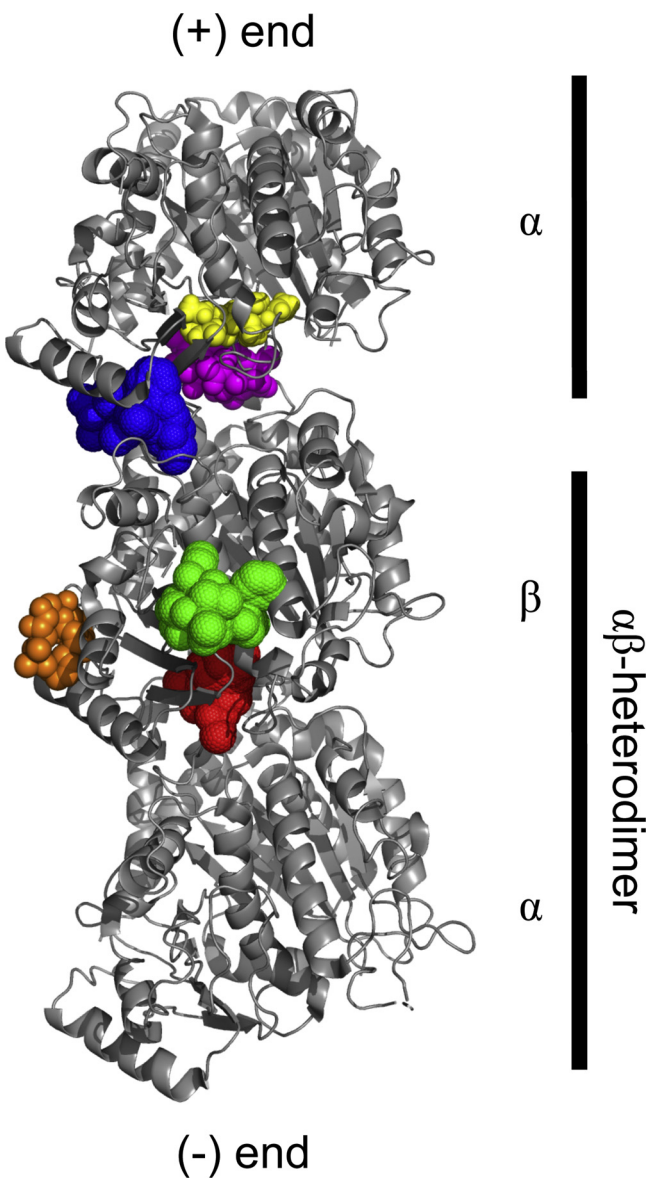

Fig. 2. Binding sites of six microtubule-binding agents situated on a fragment of a protofilament. View from the inside of the microtubule, showing colchicine (red), vinblastine (blue), paclitaxel (green), laulimalide (orange), maytansine (magenta) and pironetin (yellow). Schematic image using PDB files 1SA0 (Ravelli et al., 2004), 1Z2B (Gigant et al., 2005), 1JFF (Löwe et al., 2001), 4O4H (Prota et al., 2014a), 4TV8 (Prota et al., 2014b) and 5LA6 (Prota et al., 2016). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

the P-glycoprotein (Pgp) transporter, which can actively transport drug molecules out of cells. There is also evidence that expression of certain tubulin isotypes, such as class III β-tubulin, can desensitize cells to microtubule drugs (Parker et al., 2017; Roque et al., 2013).

1.2. Mechanism of action

Despite having different binding sites and strategies, most studied microtubule drugs elicit remarkably similar effects on a molecular level, especially at the lowest effective drug concentrations. Microtubules treated with these agents are thereafter less dynamic and often spend more time in the pause-state, neither growing or shrinking (Jordan et al., 1993, 1992). At the same time, MTAs can induce an increase or decrease in the total microtubular mass. This effect is especially pronounced at higher drug concentrations. Taxane site binding and laulimalide/peloruside site-binding compounds are "microtubule-stabilizing" (i.e., increasing the microtubular mass), while vinca site-binding agents are known as "microtubule-destabilizing" (Prota et al., 2014b; Smith et al., 2016), see Fig. 3. Other microtubule-destabilizing substances include colchicine, combretastatins, cryptophycins, maytansine and pironetin (Fanale et al., 2015; Prota et al., 2014a; Yang et al., 2016). The relative contribution of both effects to microtubular disruption is still a matter of scientific debate although a computational model has shown that both mechanisms may have a common denominator (Castle et al., 2017).

Disruption of microtubules induces various cellular responses, which can lead to cell death. The most obvious effect of these compounds is observed in cells undergoing mitosis. During metaphase, the ability of spindle microtubules to capture chromosomes is impaired by drugs that inhibit their dynamic behavior, leading to mitotic arrest and eventual checkpoint-induced cell death (Stanton et al., 2011). Some studies have found a poor correlation between levels of mitotic arrest

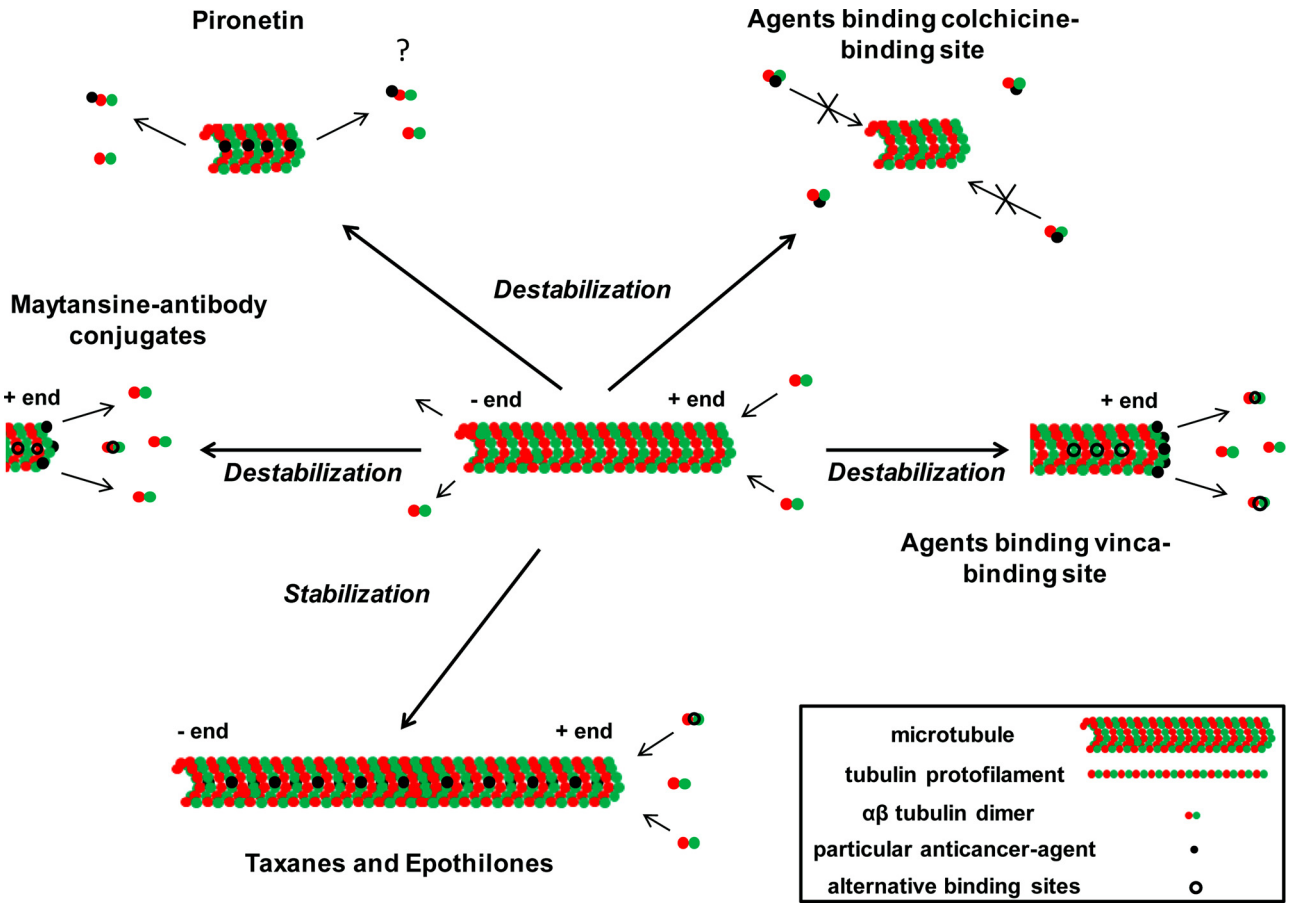

Fig. 3. Effect of MTAs on microtubule stability at high concentrations of the drugs. Taxanes and epothilones stabilize microtubules. Colchicine-site binding agents prevent microtubule polymerization. Vinca-site binding agents and maytansine conjugates destabilize microtubules by blocking of the plus end of a microtubule, as well as binding to an alternative site along the protofilament, however, the maytansine conjugates bind to a different site on the microtubule to the vinca site. Pironetin destabilizes microtubules by binding specifically to α-tubulin. A-Tubulin is in red and β-tubulin is in green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

and apoptosis (Milross et al., 1996; Shi et al., 2008) and there seem to be additional mechanisms leading to cell death after microtubule drug treatment. Some affected cells can slip through the first mitosis, become multinucleated or tetraploid and die in subsequent cell cycles (Gascoigne and Taylor, 2008; Orth et al., 2011; Zasadil et al., 2014). Alternatively, MTAs can also be lethal to cells that are not dividing by affecting mitosis-independent functions such as cell signaling, vesicular trafficking, or migration (Komlodi-Pasztor, 2011). Indeed, transport of several DNA repair proteins into the nucleus is perturbed by MTAs, thus prolonging the effect of DNA damage induced by radiation. This could explain why MTAs can act synergistically with DNA-damaging agents when used in cancer treatment (Poruchynsky et al., 2015).

For any microtubule-targeting drug to be suitable for cancer treatment, there must be a mechanism to selectively target cancer cells over normal healthy cells of the human body. This could be as simple as targeting rapidly dividing cells of the tumor by disrupting their mitotic spindle. However, only a minority of cancer cells in a typical human tumor are dividing at any given time, and the time window of typical cancer treatment is fairly short (Labi and Erlacher, 2015; Rohena and Mooberry, 2014). The observation that microtubule drugs can shrink even slow-growing tumors has been hailed as the "proliferation paradox". Several hypotheses explaining this have been proposed by various researchers. One theory suggests that cancer cells are very close to their apoptotic threshold and can easily slip into cell death. This may be contrary to common sense but, indeed, cancer cells constantly balance between proliferation on one hand and genomic instability, arrest, hypoxia, and growth factor withdrawal on the other (Brown and Wouters, 1999; Hahn, 2004; Mitchison, 2012; Ogden et al., 2015). In fact, these sensitized tumor cells could also die independently of any cell division by compromising their microtubule-dependent interphase functions, such as transport of signaling molecules (Darshan et al., 2011; Komlodi-Pasztor, 2011). Additionally, effects on tumor cells may be exacerbated by disruption of nearby non-cancer tissue, such as the vasculature that supplies the tumor with nutrients and oxygen (Shi and Mitchison, 2017). Compounds featuring these therapeutic properties are known as vascular disrupting agents and often bind to the colchicine site on tubulin. They preferentially target tumor vasculature due to its aberrant morphology characterized by a high proliferative index, defective cell junctions, and lack of certain cell types (Kanthou and Tozer, 2009; Porcù et al., 2014).

The number of MTAs is ever-growing, with new compounds discovered every year. The common themes described above should not obscure the fact that each of these compounds features unique molecular interactions with tubulin and elicits specific functional consequences leading to cell death. Ultimately, these properties not only determine the prognosis of cancer patients but also influence the discovery process for new compounds.

2. MTAs in cancer treatment

2.1. Taxanes and their significance for cancer treatment

The first taxane to be clinically used was paclitaxel (Taxol™). Paclitaxel has been used for the therapy of ovarian cancer since 1992

and for the therapy of breast cancer since 1994. The semi-synthetic taxane docetaxel (Taxotere™) is used for the treatment of breast and lung cancer (Engels et al., 2005). Paclitaxel and docetaxel are usually combined with radiotherapy and other chemotherapeutics such as cisplatin or trastuzumab (Choy, 2001; Cortes and Roché, 2012).

Because of cancer cell resistance, the low solubility, and cytotoxicity of classical taxanes, novel taxane derivatives have been synthesized. For instance, milataxel and ortataxel were partially effective in patients with various solid tumors (Flores and Saif, 2013). Although most of these novel derivatives did not pass their phase II trials, the novel derivative larotaxel (Ren et al., 2018) was assessed as a promising anticancer agent for non-small cell lung cancer, metastatic breast, and bladder cancer. It was mostly tested in combination with cisplatin or other taxanes (Diéras et al., 2008; Robert et al., 2010; Sternberg et al., 2013) (see Table 1).

Currently, the most promising novel derivative is cabazitaxel (Jevtana®), which has been approved for the therapy of hormone-resistant prostate cancer (Paller and Antonarakis, 2011).

Taxanes can be covalently bound to several types of nanoparticles to decrease their relatively high cytotoxicity. Taxane-containing nanoparticles can consist of fatty acids (Luo et al., 2010), albumin (Miele et al., 2009), poly-L-glutamate, and other substances (Singer, 2005). These nanoparticles are designed to preferentially target cancer cells. Albumin nanoparticles carrying paclitaxel (Abraxan®) have been approved for the therapy of pancreas and breast cancer (Miele et al., 2009) (see Table 1).

2.2. Cell death induction by taxanes

It is known that application of taxanes at high concentrations leads to the collapse of microtubule dynamics resulting in necrosis (Yeung et al., 1999). At lower concentrations, taxanes block the cell cycle in mitosis and usually induce caspase-dependent apoptosis.

Alternatively, taxane can induce a mitotic catastrophe (Morse, 2005). Additionally, programmed cell death dependent on cathepsins (Mediavilla-Varela et al., 2009), pyroptosis (Salinas et al., 2014), and autophagy (Huo et al., 2016) have been described as minor mechanisms of programmed cell death observed after taxane application in cancer cells.(Adams et al., 2016)

Taxane-mediated induction of apoptosis involves activation of initiator caspases (caspase-2, caspase-8 and caspase-9) and down-regulation of proteins of the Bcl-2 family. The role of caspase-8 seems controversial since activation of death receptors is not supposed to be a key step in taxane-induced apoptosis (Jelínek et al., 2015). However, activation of caspase-8 may possibly be mediated by FADD (Fas-associated protein with death domain) protein, or by other caspases, as previously described in lymphoma or breast cancer cells (Jelínek et al., 2015; Von Haefen et al., 2003). The formation of the apoptosome followed by activation of caspase-9 is crucial for apoptosis induction in many types of cancer cells (Fauzee et al., 2012; Janssen et al., 2007; Sharifi et al., 2014). Recently, apoptosis induction was observed to depend on caspase-2 activation in breast (Jelínek et al., 2013), melanoma (Mhaidat et al., 2007), and prostate (Luo et al., 2010) cancer cells. All three known executioner caspases, i.e., caspase-3, caspase-6 and caspase-7 seem to be involved in taxane-induced apoptosis execution.

Taxanes are able to bind antiapoptotic proteins of the Bcl-2 family and decrease their activity (Ferlini et al., 2009). Moreover, the levels of Bcl-2 and Bcl-xL are often seen to decrease as a result of inhibitory phosphorylation after taxane application (Sharifi et al., 2014; Yoshino et al., 2006; Zheng et al., 2017). Taxanes also release the Bak protein from the Bak/Bcl-xL complex (Flores et al., 2012). Such processes ultimately lead to the formation of Bax channels in mitochondria membranes and apoptosis induction. The BH3-only Bcl-2 proteins, i.e., the Bad (Craik et al., 2010; Fauzee et al., 2012), and Bim (Ajabnoor et al., 2012; Li et al., 2005; Savry et al., 2013) proteins, seem to be significantly involved in cell death induced by taxanes. However, elucidation of the precise mechanism of their effect needs further studies (Jelinek et al., 2017).

2.3. Resistance of cancer cells to taxanes

Long-term treatment and repeated application of taxanes may lead to the development of drug resistance in cancer cells, which represents a serious obstacle in taxane therapy. Developed taxane resistance can be based on the overexpression of transporters of the ABC family (Duran et al., 2015), tubulin mutations or production of a different tubulin class (McGrogan et al., 2008), increased taxane metabolism (Václavíková et al., 2006) or insufficient induction of programmed cell death, especially apoptosis (Jelínek et al., 2013).

ABC transporters translocate hydrophobic molecules across the plasma membrane in order to protect cancer cells against the effect of these molecules. The ABCB1 transporter (P-glycoprotein) is the most clinically important protein of this family. This transporter very effectively moves taxanes out of cancer cells, thus making taxane therapy ineffective (Aldonza et al., 2016; Hansen et al., 2015; Jelínek et al., 2018). Other members of the family, e. g. ABCC3, have also been described as taxane transporters (Němcová-Fürstová et al., 2016).

The resistance of cancer cells to taxanes can also be caused by mutations in the β-tubulin gene causing changes in the structure of important parts of the β-tubulin molecule, e.g. the taxane-binding site (Hari et al., 2006). These mutations can alter the affinity of taxanes towards microtubules or the ability of taxanes to block dynamics of microtubules. This type of resistance can be overcome by using different non-taxoid MTAs, some of which are discussed below. Some resistant cancer cell lines produce different classes of β-tubulin, most frequently βIII-tubulin (Kamath et al., 2005; McGrogan et al., 2008). This class of tubulin is not as readily polymerized by taxanes in vitro and in vivo (Mhaidat et al., 2008; Person et al., 2017; Sève et al., 2005). Indeed, some novel MTAs are designed specifically to block dynamics of the βIII-class tubulin as well (Matesanz et al., 2014; Pepe et al., 2009). Taxane resistance has been associated with microtubule-binding proteins, microtubule-regulating proteins, and mutations in α-tubulin (Martello et al., 2003; Singer et al., 2009; Smoter et al., 2011; Sun et al., 2015).

Resistance associated with insufficient induction of programmed cell death has been observed, for instance, in breast cancer cells where autophagy was induced and concurrently apoptosis was suppressed (Ajabnoor et al., 2012; Veldhoen et al., 2013). Taxane resistance is often a consequence of defective apoptosis induction. This is commonly the result of higher levels or higher activity of anti-apoptotic proteins of the Bcl-2 family. On the other hand, it can be the result of lower levels or lower activity of pro-apoptotic proteins of the Bcl-2 family (Fauzee et al., 2012; Mhaidat et al., 2007; Watanabe et al., 2013; Yoshino et al., 2006). Indeed, a deficiency in activation of initiator or executioner caspases has often been assessed as being responsible for cancer cell resistance (Ho et al., 2008; Jelínek et al., 2015; Mhaidat et al., 2007). A role of the BH3-only proteins of the Bcl-2 family remains questionable since resistant cancer cells have differing levels of these proteins (Craik et al., 2010; Fauzee et al., 2012; Jelinek et al., 2017; Miller et al., 2013).

2.4. Vinca alkaloids and their significance for cancer treatment

The vinca alkaloids used for cancer therapy are vincristine (VC), vinblastine (VBL), vindesine (VDS), vinorelbine, and vinflunine. VBL and VC are used for the therapy of breast cancer, lymphomas, and sarcomas. Further, they are components of several types of combination treatments. Vinorelbine was approved by the FDA in 1994 for treatment of breast cancer and non-small-cell lung cancer and sarcomas (Martino et al., 2018). Interestingly, vinorelbine at low concentrations suppressed angiogenesis in tumors (Biziota et al., 2016). The fluorine-containing vinca alkaloid vinflunine (Bellmunt et al., 2009) (Javlor™)

was approved in 2012 for the treatment of urothelial cancer (Retz et al., 2015).

Many other agents like eribulin and dolastatins 10 and 15 bind at the same β-tubulin site as vinca alkaloids. Eribulin was approved for relapsed metastatic breast cancer (Twelves et al., 2010) and liposarcomas (Schöffski et al., 2016), and tested in advanced breast cancer, triple negative breast cancer, bladder cancer, and salivary gland cancer (usually after anthracycline and taxane therapy) (Kumar et al., 2017). Furthermore, eribulin was able to remodel abnormal tumor vasculature in mice breast cancer xenograft models, a process expected to reduce tumor growth and aggressiveness (Funahashi et al., 2014). Dolastatin 10 and its analogs are currently being intensively tested in cancer cells (see Table 1) (Akaiwa et al., 2018).

According to recent studies, maytansinoids and auristatins occupy binding sites close to the vinca alkaloid binding site but they are more effective in depolymerization of microtubules, probably due to the much higher affinity of these drugs to microtubules (Lopus et al., 2010). Because they are themselves toxic, antibody-containing conjugates represent a very promising strategy. T-DM1, trastuzumab + emtansine (maytansinoid), was approved for metastatic breast cancer (Geraud et al., 2017). SAR3419, composed of anti-CD19 antibody and maytansine, reached phase II in diffuse large B-cell lymphoma (Kantarjian et al., 2016). Brentuximab vedotin, which consists of an anti-CD30 antibody linked to monomethyl auristatin E, was recently tested in Hodgkin lymphoma (see Table1) (Moskowitz, 2015).

2.5. Other MTAs and their significance for cancer treatment

Epothilones are agents that bind to the taxane-binding site. These drugs are effective in cell death induction, especially in paclitaxel-resistant cancer cells, generally because they are not bound so effectively by P-glycoprotein as classical taxanes. They are easier to administer than taxanes, having good water solubility, and can pass through the blood-brain barrier (Forli, 2014). Epothilone B has passed phase II in the treatment of lung cancer (Larkin and Kaye, 2007). Moreover, ixabepilone (Ixempra™) has been approved for the treatment of metastatic breast cancer and relapsed endometrial cancers (McMeekin et al., 2015; Rugo et al., 2015). Ixabepilone is now being tested on many types of cancers including colorectal, cervical, breast, renal, βIII-tubulin-positive lung, and triple negative breast cancer (Forli, 2014). PM060184 (plocabulin) tested in phase I in several advanced solid tumors (Elez et al., 2018) or pre-clinically tested zampanolide, that binds tubulin covalently in contrast to the other agents (Field et al., 2017), represent other promising agents that bind at the taxane site or close to it (see Table 1).

Marine sponge-derived agents peloruside A and laulimalide, which bind microtubules at a specific site different from the taxane site and stabilize them, are promising anticancer drugs (Johnson et al., 2007; Liu et al., 2007; Meyer et al., 2015). These agents induce death in cancer cells in vitro as well as in vivo, but their wider employment needs futher development to overcome their high systemic toxicity (Kumar et al., 2017; Liu et al., 2007).

One of the MTAs tested as an anticancer agent already decades ago is colchicine. Colchicine, a well-known microtubule-destabilizing drug, is not used in cancer therapy due to its high cytotoxicity (Kumar et al., 2016). However, other agents that bind to the colchicine-binding site seem to be more suitable. For example, plinabulin, verubulin (MPC-6827), BAL101553, and ABT-751 also bind to the colchicine-binding site. Plinabulin and AB-T-751 have been tested as anticancer regimens for non-small lung cancer (Gridelli et al., 2009) whereas verubulin in combination with carboplatin has passed phase I testing in glioblastoma (Grossmann et al., 2012). Interestingly, BAL101553 has recently entered phase IIa testing in ovarian cancer and glioblastoma patients (Joerger et al., 2019).

Combretastatins represent an important group of agents that bind to the colchicine-binding site. For example, combretastatin ombrabulin has been shown effective in ovarian cancer therapy (Tae et al., 2007). Fosbretabulin, another combretastatin, has been shown effective in combination with other agents in treating lung cancer and thyroid carcinoma (Garon et al., 2016; Mooney et al., 2009). It should be mentioned that although these agents induce cell death in cancer cells by themselves, more significant is their targeting of endothelial cells and hence suppression of tumor growth by blocking angiogenesis (see Table 1) (Micheletti et al., 2003).

2.6. Basic approaches for discovering novel MTAs

The goal of the design of novel MTAs is to prepare effective, resistance proof agents that will induce cell death in all cancer cells while sparing non-cancer cells. Additionally, the anticancer effect of the drugs should be prolonged, e.g. by inhibiting their own metabolism. This can be realized by insertion of various heteroatoms (e.g., fluorine or heavy metal atoms) into the MTA molecule (Jelinek et al., 2017).

2.6.1. Fighting resistance of cancer cells

Resistance of cancer cells to traditional anticancer MTAs is often determined by the expression of ABC transporters or specific tubulin classes. Novel MTAs should have structures that are not recognized and transported by P-glycoprotein and other ABC transporters (Duran et al., 2015; Oba et al., 2016). Furthermore, they should preferably bind to the classes of β-tubulin found in resistant cancer cells, namely βIII-tubulin (McGrogan et al., 2008; Mhaidat et al., 2008; Yeh et al., 2016).

Probably the most important approach is represented by the preparation of new molecules, usually derivatives of existing proved drugs. Concerning newly prepared taxane derivatives, these compounds usually have various functional substituents at positions C3´, C3´N, and C10 (Jelínek et al., 2018; Ojima et al., 1998, 1996). Recently, we have reported that phenyl groups at positions C3´ and C3´N could play an important role in taxane binding and transport by P-glycoprotein. Derivatives, such as SB-T-1216, with one or both phenyl groups replaced with non-aromatic substituents were not bound by P-glycoprotein so effectively and hence not transported from taxane-resistant cancer cells (Fig. 4) (Jelínek et al., 2018). Other chemical groups of the taxane molecule have also been reported to be important for binding into the pocket of P-glycoprotein (Alam et al., 2019). Thus it seems that there is certain variability in binding of taxanes to P-glycoprotein.

Beside taxane-like drugs, new derivatives of colchicine binding site-targeting drugs have also been reported. The most common modification is a change of the C ring of the colchicine molecule. Some of these new agents have shown promising results in various cancer cells (Kumar et al., 2016).

2.6.2. Sparing non-cancer cells

A very promising approach to avoid toxic side effects of drugs is based on chemically linking the drug to a carrier molecule to create a hybrid molecule (a conjugate) that preferentially targets cancer cells. Podophyllotoxin, combretastatins, noscapine, and vinca hybrids have been synthesized and tested with diverse results (Tangutur et al., 2017; Yurkovetskiy et al., 2015). For instance, vintafolide (a conjugate of vinflunine and folate) is effective in growth suppression of advanced ovarian and endometrial cancer and is a promising example of these types of molecules (Assaraf et al., 2014).

3. Potential use of MTAs as migrastatics

3.1. Cancer metastasis

In addition to cytotoxic activity, MTAs are now being considered for new approaches to cancer treatment that target the development of metastases. The ability to form metastases is the deadliest property cancer cells can acquire. Primary tumor cells can spread throughout the body and potentially form secondary tumors in a multistep process

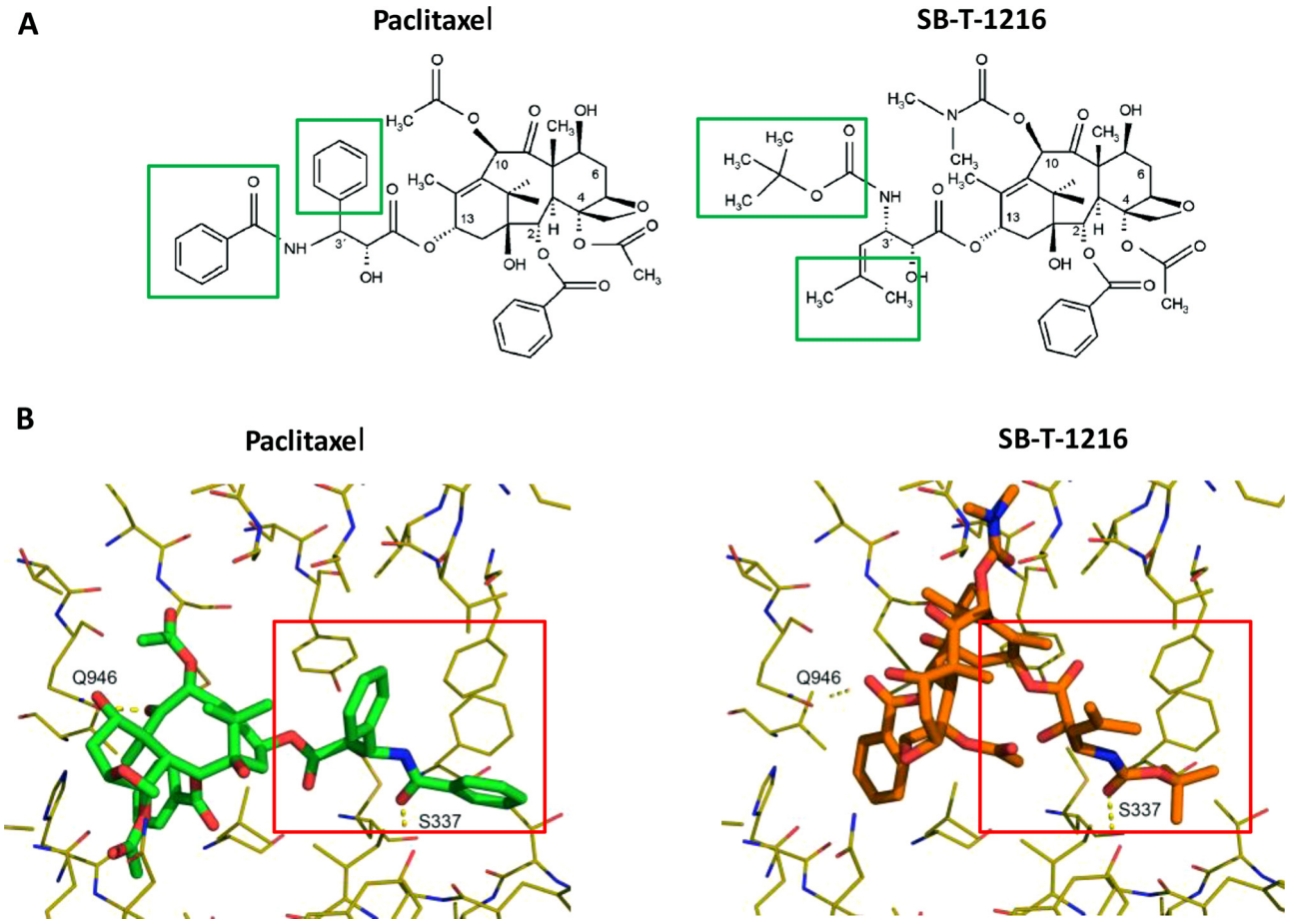

Fig. 4. Structure-function relationship of taxanes and the P-glycoprotein-binding site. (A) Structure of paclitaxel and SB-T-1216. Paclitaxel has two aromatic (phenyl) groups at C3´ and C3´N positions. The novel taxane derivative, SB-T-1216, has 2-methylpropyl at the C3´ position and *tert*-butoxycarbonyl at the C3´N position. The positions are highlighted with green frames. (B) Interaction of taxanes and the binding site of P-glycoprotein. Paclitaxel can readily bind to the taxane-binding site of P-glycoprotein by its R1 and R2 phenyl groups. The bond is significantly weaker for SB-T-1216 because of missing phenyl groups. Thus, paclitaxel can be transported out of the cells by P-glycoprotein more effectively than SB-T-1216 which can induce cell death in cancer cells that are resistant to paclitaxel due to P-glycoprotein overexpression. Interactions between paclitaxel and P-glycoprotein through paclitaxel's phenyl groups and absence of these groups in SB-T-1216 are highlighted with red frames. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

called the metastatic cascade (Riggi et al., 2018). Local invasion of tumor cells into the surrounding extracellular matrix or cell mass is the first step in the metastatic cascade. Cells can invade through tissues either collectively or individually. During a collective invasion, the intercellular adhesions remain preserved and the cells migrate as strands, tubes, sheets, or irregular masses (Friedl and Gilmour, 2009). Individual invasion is the penetration of single cells and can occur in the mesenchymal or amoeboid mode (Pandya et al., 2017; Panková et al., 2010; Te Boekhorst and Friedl, 2016). A mesenchymal, fibroblast-like invasion can be recognized by the typical elongated, spindle-like morphology of individually invading cancer cells and by their relatively unidirectional persistence. Mesenchymal migration depends on local degradation of the extracellular matrix (ECM) by proteolytic enzymes secreted preferentially from actin-rich adhesion structures called invadopodia (Linder et al., 2011; Tolde et al., 2010).

The morphology of amoeboid cells is typically round or ellipsoid in 3D conditions and their migration shows little directional persistence. Amoeboid cancer cell invasion is accompanied by contractions of cortical actin, which is regulated by the Rho-ROCK (rho-associated protein kinase) signaling pathway (Kosla et al., 2013), and by polarized membrane flow, which underlies cell translocation (O'Neill et al., 2018). Motile cancer cells can adapt their invasion mode to cope with different conditions, a phenomenon called invasion plasticity (Te Boekhorst and Friedl, 2016).

The development of metastases is determined by complex interactions among cancer cells and several types of host cells in the tumor microenvironment at both primary and secondary sites (Yang and Lin, 2017). Besides migration of cancer cells, the establishment of secondary tumors also depends on the migration of non-transformed cell types that contribute to the tumor microenvironment (cancer-associated fibroblasts, tumor-associated macrophages, endothelial cells, and other cell types). All these migratory processes, except amoeboid invasion of cancer cells, require microtubules and thus are potential targets of MTAs in preventing cancer progression to the metastatic stage.

3.2. Cell migration-related effects of MTAs

The effects of different classes of MTAs on cell migration have been studied in standard 2D conditions as well as in more sophisticated 3D cell culture conditions, with substantial discrepancies observed. Nocodazole, a synthetic drug binding to the colchicine site on β-tubulin, was found to robustly stabilize focal adhesions in cells spread on stiff 2D surfaces and to prevent migration by inhibiting focal adhesion turnover (Ezratty et al., 2005; Kadi et al., 1998). However, in 3D conditions, nocodazole induces cell rounding but does not decrease, and in some cases, even increases migration speed while reducing migration directionality (Makiyama et al., n.d.; Schweisguth et al., 1971). These effects correspond to the mesenchymal-amoeboid transition (MAT). In

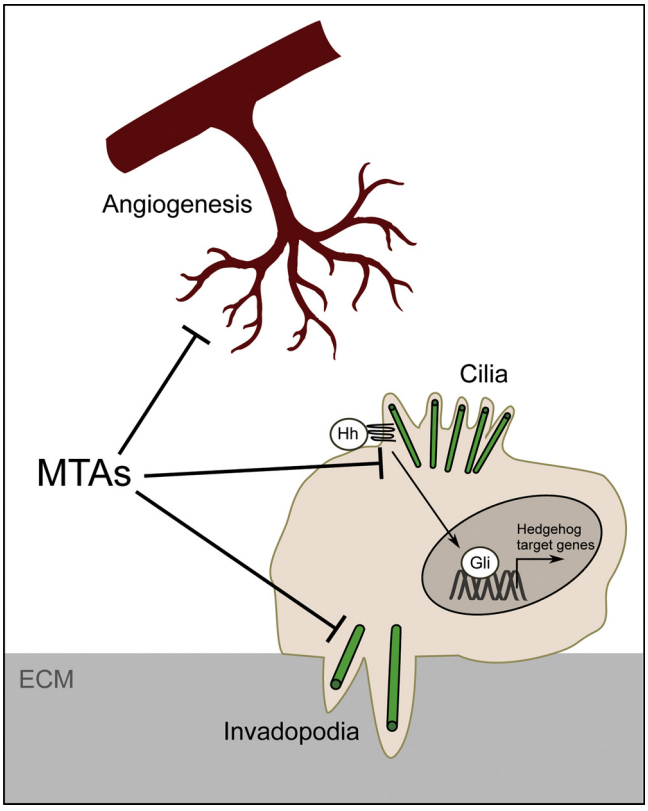

Fig. 5. Effects of low concentrations of MTAs on cancer progression. MTAs can target cancer progression at low concentrations through a few different mechanisms. Tumor angiogenesis is highly sensitive to MTAs. Hedgehog signaling is dependent on intact microtubules and can be effectively inhibited by MTAs. Formation and elongation of invadopodia are impaired by MTAs. Microtubules are depicted as green tubes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

another experimental situation, when cells are placed on the top of a layer of ECM material, nocodazole inhibited elongation of invadopodia, preventing mesenchymal invasion (Kikuchi and Takahashi, 2008; Schoumacher et al., 2010), Fig. 5. In addition, pseudopod-based mesenchymal migration within 3D matrices is uniquely dependent on intact microtubule dynamics as opposed to 2D conditions (Bouchet et al., 2016). Microtubule-stabilizing drugs inhibit cell migration as well (Field et al., 2017; Grigoriev et al., 1999). 3D mesenchymal migration was found to be 100-fold more sensitive to paclitaxel than 2D migration (Jayatilaka et al., 2018). For a detailed review of the role of microtubules in 3D migration see (Bouchet and Akhmanova, 2017). Importantly, the migration-inhibitory effects of MTAs have been observed at concentrations much lower than those required for cytostatic effects. For instance, it was demonstrated that sub-toxic concentrations of colcemid (a colchicine derivative) or vinblastine are sufficient to inhibit plus-end microtubule dynamic instability and cell migration without affecting cell division or microtubule assembly (Yang et al., 2010). Similarly, the microtubule stabilizing drug epothilone B inhibits migration of glioblastoma cells at non-cytotoxic concentrations by inducing microtubule catastrophes and affecting EB1 accumulation at the microtubule plus ends (Pagano et al., 2012).

3.3. Both established and newly forming tumor vasculature are highly vulnerable to MTAs

MTAs were originally thought to act mainly through mitotic spindle disruption and subsequent apoptosis induction. Hill et al. demonstrated that vinca alkaloids dramatically decrease blood flow through tumors followed by necrosis of tumor tissue (Hill et al., 1993). The underlying mechanism involves disruption of the tumor endothelial cell cytoskeleton and junctions between endothelial cells. This results in leaky vessels, congestion within the blood vessels, blocked blood flow, and ultimately tumor necrosis (Siemann et al., 2004; Tozer et al., 2005). The preferential targeting of tumor vasculature by MTAs, as opposed to that of normal vasculature, is due to the relative immaturity and instability of tumor vasculature (Siemann, 2011). In addition to vinca alkaloids, the vascular disruption effect of MTAs has also been demonstrated with other microtubule-depolymerizing agents (Kanthou and Tozer, 2007; Sherbet, 2017). Studies of the mechanistic details, using *in vitro* experiments, revealed that microtubules are required to stabilize endothelial cell protrusions in soft 3D conditions (Lyle et al., 2012) and microtubule depolymerization is particularly disruptive when endothelial cells interact with pliable 3D matrices (Martins and Kolega, 2012). Depending on the MTA concentration, tumor vasculature might not be disrupted, but the formation of new blood vessels might be prevented. This milder effect, i.e., inhibition of neo-angiogenesis at low, non-toxic concentrations has been demonstrated for several MTAs, for example, paclitaxel, docetaxel, vinblastine, and epothilone B (Bijman, 2006). This is especially important from the perspective of long-term anti-metastatic therapy.

3.4. Hedgehog signaling in cancer metastasis and its targeting by MTAs

An interesting target of MTAs in cancer therapy is the hedgehog (Hh) signaling pathway. Under physiological conditions, Hh signaling controls embryonic patterning, organ morphogenesis, tissue regeneration, and regulates self-renewal in stem cells. Aberrant activation of hedgehog signaling is responsible for the initiation of several cancers including glioblastoma, melanoma, medulloblastoma, rhabdomyosarcoma, basal cell carcinoma, and carcinomas of pancreas, lung, prostate, ovary, and breast. Its pharmacological inhibition has already been tested in cancer treatment with varied success (Armas-López et al., 2017; Pak and Segal, 2016). Hh signaling has been demonstrated to promote metastasis through activation of the epithelial-mesenchymal transition (EMT), increased expression of ECM degrading enzymes, and enhancing the stemness of cancer cells (Wang et al., 2018). Hh signaling is essential for metastasis of colon carcinoma (Varnat et al., 2009), while inhibition of Hh signaling inhibits pancreatic cancer invasion and metastases (Feldmann et al., 2007). The anti-metastatic effect of MTAs could be partly mediated by inhibition of the Hh pathway since its activation depends on intact microtubules (Khatra et al., 2018; Kim et al., 2010; Larsen et al., 2015), Fig. 5.

3.5. Anti-metastatic potential of MTAs

The aim of anti-metastatic therapy is to block any dissemination of the primary tumor, regardless of primary tumor mass shrinkage or growth prevention. However, the possibility of clinically testing drugs specifically for their anti-metastatic effects requires a radical paradigm shift in the thinking of clinical trial regulatory bodies and the pharmaceutical industry and is a matter for the distant future (Rösel et al., 2013). The anti-metastatic approach faces many procedural, regulatory, and economic challenges, but is at least starting to be seriously considered (Anderson et al., 2019). The use of anti-metastatic therapy would be most justified in following situations: First, an early diagnosis of a tumor with a well-known high propensity to metastasize, but still without detectable metastases (e.g., melanoma, glioblastoma, carcinoma of the esophagus); second, after removal of a primary tumor known to metastasize after a prolonged period of time (e.g., breast carcinoma); and third, as companion therapy to anti-angiogenic treatments that were, in some cases, shown to promote cancer metastasis due to hypoxia, necrosis, and inflammation (Ebos et al., 2009; Pàez-Ribes et al., 2009). In case of tumors that have already metastasized, the anti-metastatic treatment may still be beneficial, as additional metastases can originate from secondary sites, e. g. in lymph nodes, as

well (Brown et al., 2018; Pereira et al., 2018).

There is one great hypothetical advantage to the anti-metastatic approach: While cancers, through mutation and selection, develop mechanisms to sustain proliferation and will eventually overcome most if not all cytostatic therapies, targeting cancer cell migration with specific drugs, e.g., migrastatics, will likely not exert any selection pressure on the cancer cell population. Migrastatic-based anti-metastatic therapy thus could offer long-term control of a disease, if the primary tumor has been sufficiently managed with surgery or other means. The major expected weakness of the anti-metastatic approach is obviously the issue of timeliness, i.e., it needs to be used before the tumor has already spread. The ongoing improvement in early cancer diagnosis with novel imaging techniques and blood-based tests will expectedly ameliorate this problem (Schiffman et al., 2015).

In standard cytostatic therapy, short-term aggressive treatments, aimed at primary tumor shrinkage or precluding tumor relapse after surgery, are used despite severe side effects and high toxicity (maximum tolerable dose approach). Anti-metastatic therapy has almost the opposite requirements, i.e., toleration of long-term therapy by the patient is the most important concern. To be effective, anti-metastatic therapy would have to be started as soon as possible and continued for extended periods of time, maybe indefinitely. This would depend on how reliably and completely the primary tumor had been removed and on the long-term persistence of cancer cells released from a primary tumor in bone marrow or other sites (Fehm et al., 2008). Such approach is similar to metronomic chemotherapy where frequent application of low doses of cytostatic drugs sustains stable, but long-term tolerable blood levels of the drugs. Recent advance in preclinical models of metronomic chemotherapy brought promising results even in advanced metastatic disease (Kerbel and Shaked, 2017) and several tens of new clinical studies have been approved (see https://clinicaltrials.gov). Some of these studies even include MTAs (e.g. vinorelbine).

Cancer cell invasion can be targeted in many ways (Gandalovičová et al., 2017). However, not all molecular targets allow long-term interference with acceptable side-effects. MTAs with their potential to target molecular mechanisms essential for cancer cell invasion and formation of secondary tumors, at non-toxic concentrations, are very important migrastatics candidates.

In the migrastatic therapy regimen, the dosage of an MTA must not be cytostatic (i.e., targeting the mitotic spindle) but instead act via subtler mechanisms affecting only cancer cell invasion and migration, expectedly with concomitant inhibition of neo-angiogenesis. The conventional cytostatic MTAs from the taxane and vinca groups are conceivable migrastatics candidates, although finding long-term tolerable, non-toxic, but still effective dosages of these drugs might be more difficult than with some other types of MTAs. Moreover, paclitaxel was found to exacerbate metastasis in a mouse model of breast cancer, although this effect may be a non-specific consequence of any cytostatic chemotherapy as it was also observed with other cytostatic drugs (Chang et al., 2017; Karagiannis et al., 2017). Other types of MTAs might be preferable. There are a few well-tolerated MTAs currently in use for cancer-unrelated indications (e.g., the antihelmintics mebendazole and albendazole) that are still able to target microtubule-dependent processes at doses similar or only slightly higher than those used for their primary purpose (Ghasemi et al., 2017; Larsen et al., 2015; Pinto et al., 2015; Spagnuolo et al., 2010). Mebendazole is currently being tested in several clinical trials in different settings and phases for various types of cancer (source: https://clinicaltrials.gov). Another group of drugs deserving attention is the vascular disrupting agents. These drugs are being or have already been tested as components of chemotherapeutic regimens, for example, combretastatin A4 (Grisham et al., 2018; Sherbet, 2017). If effective at non-toxic concentrations these compounds could become useful migrastatics since a substantial amount of data about their safety and side effects will be available. There is an ongoing effort toward further improvement of these drugs. For instance, derivatives of combretastatin A4 with potent anti-invasion properties and decreased toxicity have been reported (Mahal et al., 2015).

In summary, of the drugs targeting microtubules, those with proven long-term safety and the potential to selectively target various microtubule-dependent processes through optimized dosing are promising candidates for future anti-metastatic therapy. Their therapeutic potential must be tested in suitable clinical studies, as part of the first-line and sustained therapy in patients with primary tumors expected to disseminate, but still without detectable metastasis.

4. Conclusion

MTAs are an important group of time-proven anticancer drugs, still holding a great potential for improvement in terms of increased efficacy and safety, and overcoming resistance. Beside classical taxanes (paclitaxel and docetaxel), novel derivatives (e.g. cabazitaxel) or novel formulations (e.g. Abraxan™ - paclitaxel loaded on albumin particles) have been approved for treatment of cancer and many other related drugs were or are being developed. Other classes of taxane site binding MTAs, epothilones (e.g. epothilone B and ixabepilone) and zampanolide have been extensively tested. Ixabepilone has already been approved for cancer treatment. Apart from the classical vinca alkaloids vincristine and vinblastine, novel vinca alkaloids vinflunine and the vinca site binding agent eribulin have been approved for cancer treatment. Other drugs binding the vinca site or close to it (dolastatin 10, dolastatin 15, conjugates of antibodies with maytansinoids or auristatins) are also very promising anticancer drugs. Finally, plinabulin, verubulin, and combretastatins, all binding to the colchicine site in tubulin, have attracted much interest and have been or are being tested clinically.

To overcome resistance of cancer cells, drugs with modified structure prolonging their effect or drugs not recognized by transporter proteins are being prepared and tested. To increase specificity towards cancer cells, conjugates of anticancer MTAs and targeting molecules have been synthesized.

In addition to improved cytostatic action of next generation MTAs and their advanced formulations, these drugs are also plausible candidates for specific anti-metastatic therapy. By targeting several processes required for cancer cell migration and colonization of distant sites at non-toxic concentrations, safe, long-term tolerated regimens could be developed to preclude metastatic spreading of cancers. However, a prerequisite for this approach is a radical progress in how the new therapeutic regimens are designed, tested and evaluated.

Declaration of Competing Interest

No competing financial interests exist.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejcb.2020.151075.

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