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Review

Future prospects for mitosis-targeted antitumor therapies

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ABSTRACT

Dysregulation of cell cycle progression is a hallmark of cancer cells. In recent years, efforts have been devoted to the development of new therapies that target proteins involved in cell cycle regulation and mitosis. Novel targeted antimitotic drugs include inhibitors of aurora kinase family, polo-like kinase 1, Mps1, Eg5, CENP-5 and the APC/cyclosome complex. While certain new inhibitors reached the clinical trial stage, most were discontinued due to negative results. However, these therapies should not be readily dismissed. Based on recent advances concerning their mechanisms of action, new strategies could be devised to increase their efficacy and promote further clinical trials. Here we discuss three main lines of action to empower these therapeutic approaches: increasing cell death signals during mitotic arrest, targeting senescent cells and facilitating antitumor immune response through immunogenic cell death (ICD).

1. Introduction

Cancer, the second leading cause of death worldwide with a yearly toll of 9.6 million lives, is a major global health problem. For almost a century, chemotherapy has been one of the front-line therapeutic approaches used to treat cancer. As cell cycle dysregulation is one of the hallmarks of cancer cells, they usually display an increased proliferative rate compared to normal cells. Targeting this process has been a long-standing anticancer strategy. Despite the clinical success of classic antimitotic agents, toxicity and drug resistance pose key issues [1–3]. Moreover, these mitosis-targeting agents often fail to achieve complete tumor elimination [4]. For that reason, the scientific community aimed its efforts at the search and development of novel, improved and more specific targeted inhibitors directed against the mitotic regulatory apparatus. These new targets include components of the mitotic machinery that are almost exclusively expressed during cell division and comprise different cellular components spanning from mitotic kinases to motor proteins as well as other protein complexes.

Although some of the new targeted chemotherapeutics have reached clinical evaluation, results have been discouraging as the agents have not reached expected endpoints. The more traditional antimitotic agents have been shown to be superior compared to the novel formulations. As suggested by some authors, it is possible that the attempts failed, among other hypotheses, due to the same reason they were chosen in the first place – their ability to induce mitotic perturbations that ultimately lead to cell death [5,6]. The mitotic aberrations generated could also favor a premature mitotic exit, allowing cells to escape, develop aneuploidy and genomic or chromosomal instability. These phenomena have the potential to promote carcinogenesis and enable cells to acquire adverse malignant characteristics, including resistance to therapy [7–9]. Thus, removing this unstable cell population is essential in preventing cancer growth and development [10]. Novel therapeutic approaches could be devised to circumvent the flaws exhibited by both the older and newer antimitotic agents.

The intense mechanistic research behind cell death, mitosis and cell fates that takes place upon mitotic arrest could all be harnessed to design more successful anticancer therapeutic protocols. For example, how the interplay between mitotic checkpoints and the Bcl-2 family of proteins regulates cell fate could be employed to tip the balance towards cell death during mitotic arrest. Similarly, targeting mitotic exit could also enhance mitotic cell death rates preventing cells from exiting mitosis and becoming increasingly malignant and tumorigenic. Another interesting option could be targeting cell senescence as it is one of the possible outcomes that cancer cells may develop when they escape abnormal mitosis. Finally, some antimitotic agents have been shown to induce immunogenic cell death (ICD) and polyploid cells could be recognized and eliminated by the immune system through engagement of danger signaling, contributing to tumor eradication. In this review,

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we have summarized the current knowledge regarding antimitotic therapies and corresponding clinical trials. We have also reviewed interesting therapeutic strategies to improve the effectiveness of these antimitotic approaches.

2. Targeting mitosis: An old, yet reliable, strategy to destroy tumor cells

Tumor growth takes place as a consequence of the imbalance between two key cellular processes: cell death and mitosis. In many cases, dysregulated cell proliferation drives cell accumulation and tumor development. Based on this premise, many traditional antitumor treatments were selected for their ability to prevent cell proliferation. Some of these first antitumor drugs were antimetabolites that interfered with DNA synthesis, halting the cell cycle at the S phase. Additionally, another subset of classic antitumor drugs targeted dividing cells by attacking the mitotic or M phase.

Mitosis consists of a complex sequence of molecular events, spatially and temporarily regulated to ensure the accurate segregation of genetic material during this last phase of the cell cycle. It is considered the most dynamic phase during cell division as a substantial number of events are executed within a relatively short period of time. Moreover, during mitosis, general protein translation is partially shut down and only certain transcripts, like those with internal ribosome entry site (IRES) motifs or those modulated by cytoplasmic polyadenylation can be translated [11]. In this situation, cells are left defenseless and cannot respond to or adapt against external insults like chemotherapeutic drugs. For these two reasons, cells undergoing mitosis are considered to be in a vulnerable state that facilitates tumor destruction [5]. Thus, antimitotic therapies are considered a good approach to treat cancer. In fact, microtubule-targeting agents (MTAs) have demonstrated considerable clinical efficacy for years. However, toxicity and resistance to therapy are still major issues with this approach.

Microtubule dynamics is an essential process required for the correct segregation of sister chromatids. Classic antimitotic drugs such as MTAs (also known as microtubule poisons) include natural or semisynthetic vinca alkaloids, taxanes and epothilones (Fig. 1). These types of drugs that have been used for decades to treat different cancers [12,13], bind to tubulin and alter microtubule dynamics by inhibiting polymerization (vinca alkaloids) or depolymerization (taxanes and epothilones) processes. As both processes are crucial for spindle assembly and proper chromosome segregation, disturbing cell microtubule dynamics can lead to prolonged mitotic arrest, mitotic catastrophe and cell death. However, the clinical success of MTAs likely goes far beyond its main effect on cell division. It is important to highlight that microtubules participate in several non-mitotic cellular processes such as directional trafficking, signaling and motility. Therefore, MTAs can also be toxic to cells in interphase [14], accounting for their neurotoxicity. Based on these findings, novel microtubule targeting agents have been developed, approved and entered into clinical trials [15]. Vintafolide, a conjugate between vinblastine and folic acid, reached phase III trials for platinum-resistant ovarian cancer. However, it did not show significant clinical

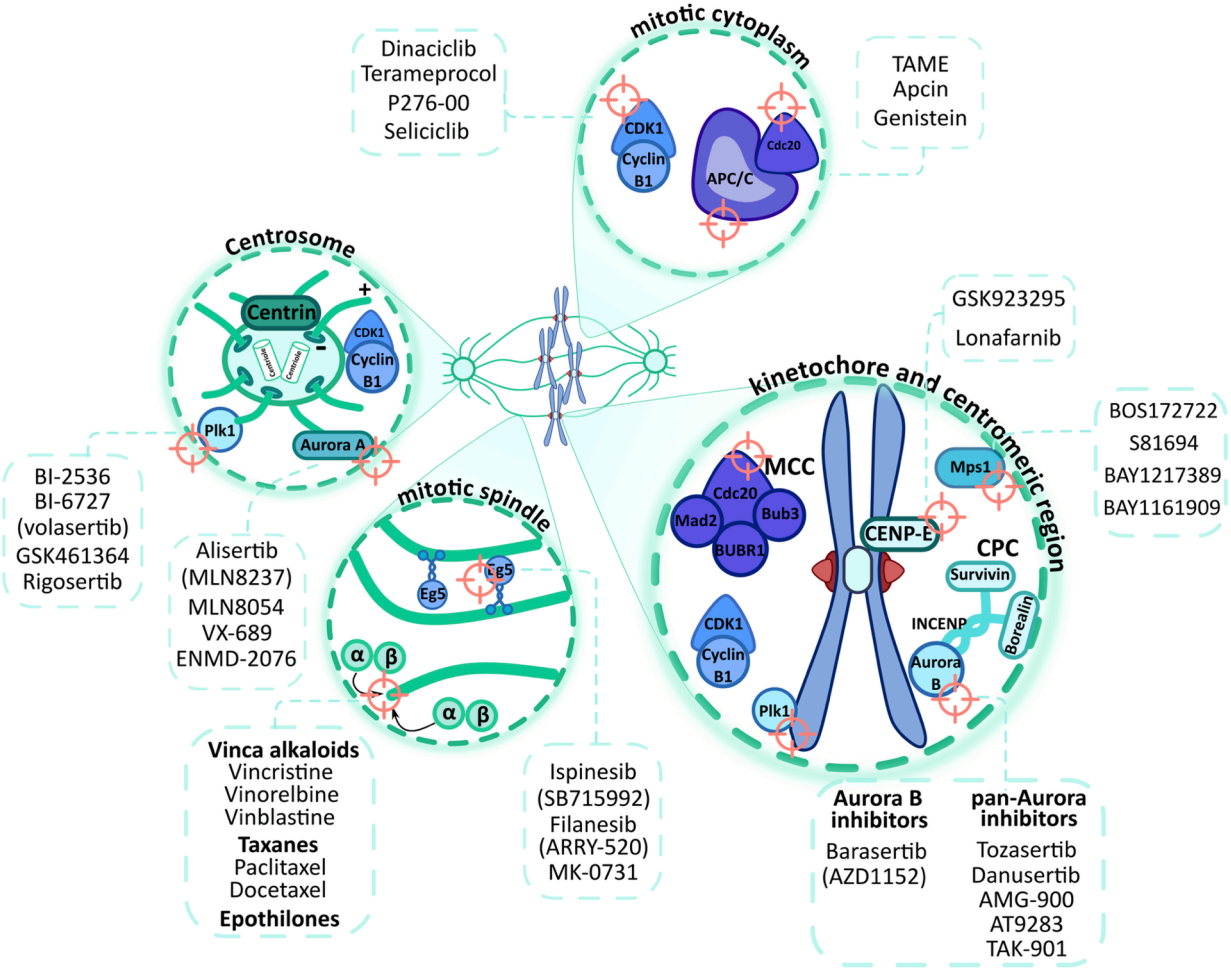

Fig. 1. Overview of current mitosis targeting therapies under development. Different molecular targets in the mitotic cytoplasm, mitotic spindle and the kinetochore/centromeric region are illustrated. Compounds that target them are indicated. Some of these chemotherapeutics are already approved and have long been used in the clinic (*eg.* vinca alkaloids and taxanes), while others are under preclinical or clinical development.

benefit [16,17].

Considering these and other obstacles, recent efforts have been directed (Figs. 2 and 3) towards seeking novel protein targets implicated in the control of cell cycle progression or mitosis. Among these new targets are kinases (Plk-1, Aurora kinase A, Aurora kinase B, CDK1, NDC80-NEK2 complex) and mitotic motor proteins (Eg5, CENP-E). Some of these proteins have been found to be upregulated in different types of tumors, making them attractive targets in cancer therapy [14]. In the following section, recent breakthroughs in the field of drug development regarding these mitotic proteins will be discussed.

3. Novel mitotic-specific targets to fight cancer

3.1. Aurora A/B

Aurora kinase inhibitors target the Aurora family of Ser/Thr kinases (Aurk). In mammals there are three members of the Aurora family: Aurora A, B and C (AurkA, AurkB and AurkC). Although they share similar substrate specificities, their distinct subcellular location enables them to perform different mitotic-specific tasks [18]. AurkA localizes preferentially to the centrosomes and spindle poles and participates in mitotic entry, centrosome maturation, duplication and mitotic spindle formation [19]. AurkA has been found to be overexpressed in several types of human tumors including breast, ovarian, colon, lung and pancreatic cancer. This amplification usually correlates with a poor clinical outcome [20]. AurkA has been shown to downregulate p53 stability via MDM2, further contributing to genomic instability and tumor formation [21].

Another member of the Aurora family is AurkB, which plays an important role in regulating proper chromosome segregation and spindle assembly checkpoint (SAC) signaling. AurkB is thought to operate as a tension sensor and is part of the error correction machinery, a mechanism in charge of dynamically stabilizing or destabilizing kinetochore-microtubule connections [18,22]. AurkB is also part of the multi-protein chromosome passenger complex (CPC) integrated by AurkB, INCENP, Borealin and Survivin. The CPC is divided into a catalytic module, formed by AurkB and the C-terminal region of INCENP, and a localization module constituted by the N-terminus of INCENP, Survivin and Borealin [18]. As part of the CPC, AurkB localizes at the kinetochores in early mitosis to regulate chromosome-spindle interactions, sister

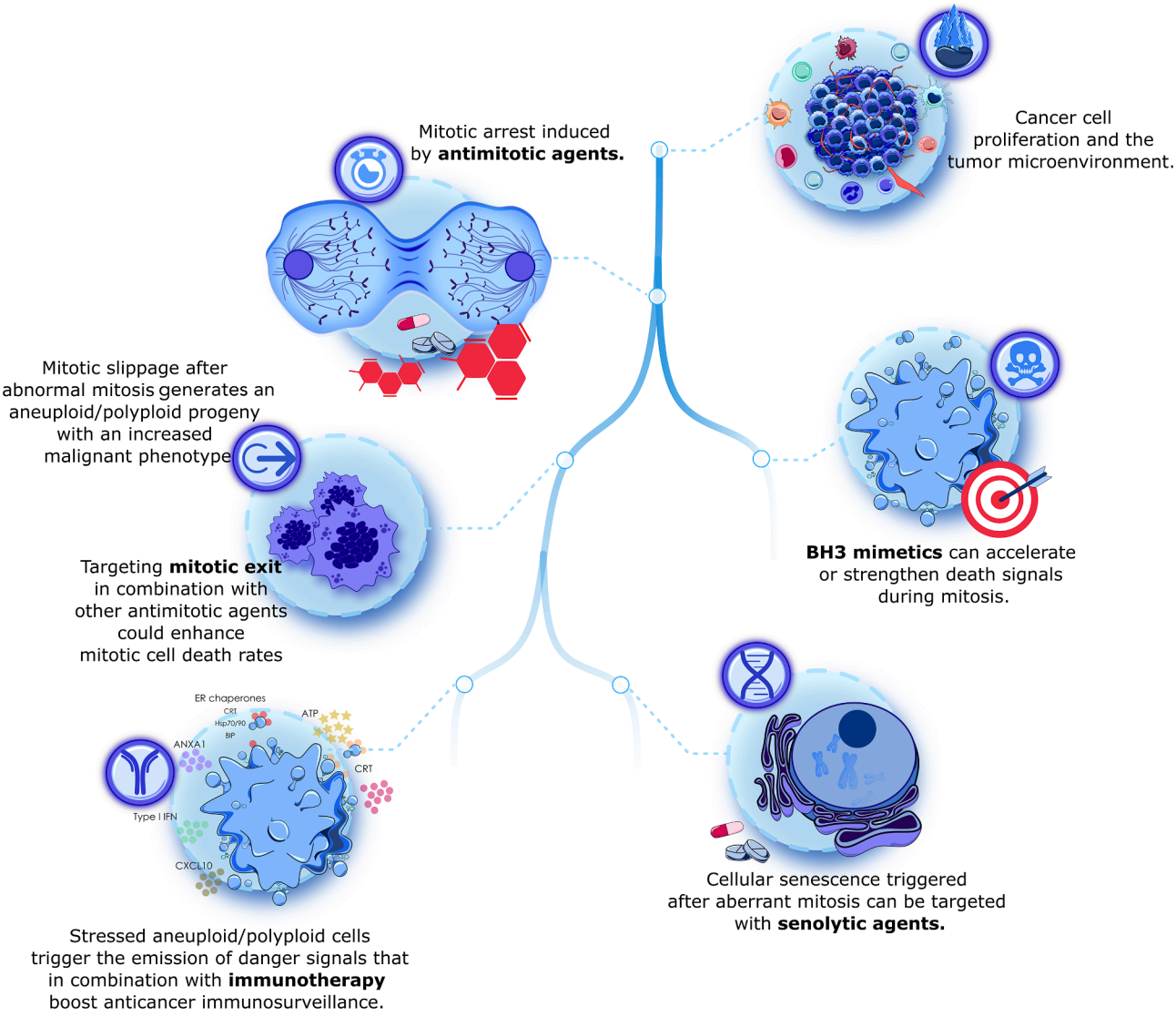

Fig. 2. Combinatory strategies for targeted antimitotic therapies. Antimitotic agents induce mitotic arrest of proliferating cells. Arrested cells can undergo cell death, escape to G1 phase generating an aneuploid/polyploid progeny or senescent cells. Cell death rates could be increased by combination with BH3 mimetics or other antimitotics. Combination with immunotherapies could help to eliminate aneuploid/polyploid cells that emit immunogenic signals. Senescent cells can be targeted by senolytic agents.

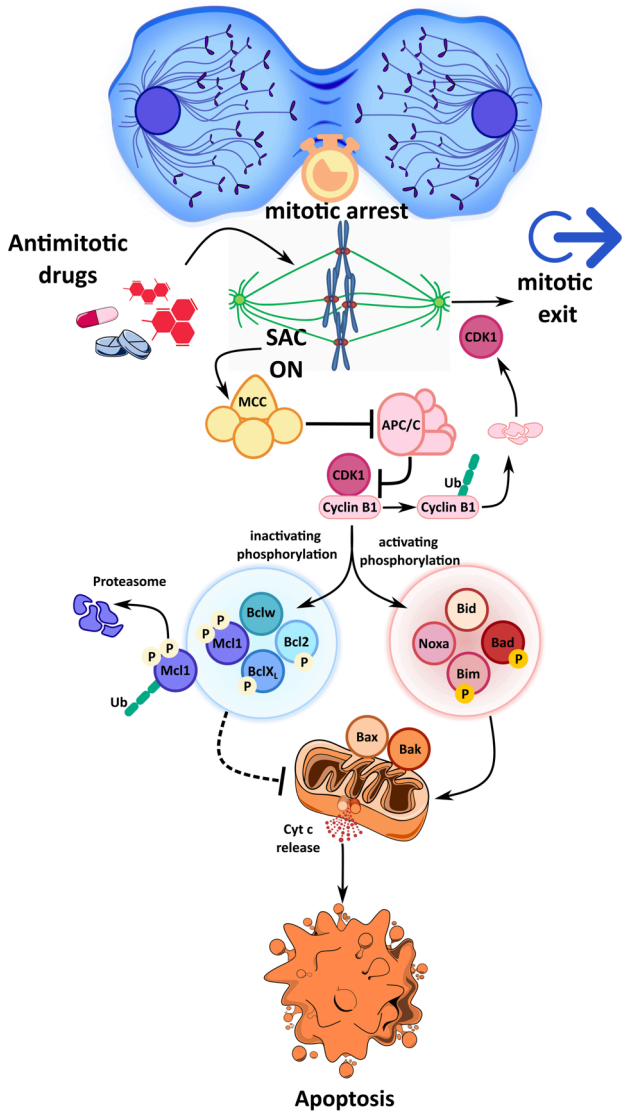

Fig. 3. Bcl-2 proteins and the control of mitotic cell death. Mitotic arrest upon exposure to antimitotic drugs depends on the efficient activation of the SAC. When the SAC is 'ON', the MCC inhibits APC/C, preventing the cell from entering anaphase. Thus, high cyclin B1/Cdk1 levels are kept during mitotic arrest. Cdk1 has been proposed to phosphorylate some members of the Bcl-2 family, affecting their pro- or anti-apoptotic activity.

chromatids cohesion and SAC signaling to ensure the proper segregation of chromosomes. The localization module of CPC drives the preferential localization of AurkB at erroneously attached kinetochores, where tension is low compared to properly bi-oriented kinetochores. Under these conditions, AurkB destabilizes and removes improper microtubule-kinetochore connections in order to allow the formation of correct bi-oriented attachments [22]. During anaphase, CPC is relocated to the mid-zone to regulate cytokinesis. Also, AurkB occupies an upstream position in the recruitment of SAC components [18]. In the presence of incorrect chromosome-microtubule attachments, SAC is activated to prevent premature mitotic exit and aberrant chromosome segregation.

A minimum of 15 Aurora kinase inhibitors have been developed in last years [23]. They are competitive inhibitors targeting the ATP-binding of aurora kinases [15]. Due to the high level of homology of the catalytic domains between family members, some of them are able to target more than one Aurora kinase (dual Aurk A/B or pan-aurora inhibitors). Moreover, many of these Aurk inhibitors have been shown to have off-target effects due to inhibition of non-mitotic kinases (Table 1) [23]. Aurk inhibitors are acknowledged as 'mitotic drivers', that is, molecules that provoke a premature mitotic exit with the ensuing generation of an offspring with aberrant aneuploid nuclei [24]. In certain instances, this aneuploid or polyploid daughter population can engage apoptotic pathways after escaping from mitotic arrest. However, an important fraction of cells manage to survive, endoreduplicate or become senescent, which can contribute to chemotherapy resistance and tumor progression [25,26].

Some non-specific Aurk inhibitors entered clinical trials but did not progress due to lack of activity, elevated toxicity or strategic reasons [27]. Tozasertib was the first pan-Aurk inhibitor to enter a clinical trial but was swiftly discontinued due to adverse cardiac events in a phase II trial [28]. More recently, results from two independent phase I clinical trials testing the pan-Aurk inhibitor AMG 900 have been published. In one study of acute myeloid leukemia (AML), 9% of the patients achieved a complete response (CR) with incomplete count recovery [29]. In the other study, safety and activity of AMG 900 was evaluated in ovarian, breast and prostate refractory tumors. A partial response was observed in approximately 10% of ovarian cancer patients, but not in triple negative breast cancer (TNBC) or cisplatin/etoposide resistant prostate tumors [30]. These results, although limited, suggest that AMG 900 could be clinically useful in certain types of cancer, possibly in combination with other drugs.

Several AurkA selective inhibitors have been developed in the last few years (Table 1). Inhibition of AurkA provokes aberrant mitotic spindles and chromosome missegregation [19], leading to cell death in a significant fraction of cells [31]. Alisertib (MLN8237) demonstrated antitumor activity in preclinical models, but lack of efficacy and intolerable toxicities in phase I/II trials have slowed its clinical development [15,32]. The majority of patients with solid tumors reached disease stabilization [15]. Meanwhile, in hematological malignancies such as non-Hodgkin lymphoma (NHL), multiple myeloma (MM) and chronic lymphocytic leukemia (B-CLL), slightly better responses were reported with up to 27% of patients exhibiting objective response in the best case scenario [15]. Despite these modest results, alisertib is still under clinical investigation both in solid and hematological malignancies [32]. Recent reports from phase II trials indicate that alisertib could be clinically useful for the treatment of high-risk AML patients [33] or some cases of prostate cancer [34]. Furthermore, the combination of alisertib with irinotecan and temozolomide has been reported to increase progression-free survival (PFS) rates in refractory neuroblastoma [35]. Promising responses were also evident in patients with aggressive B-cell non-Hodgkin lymphoma (B-NHL) when subjected to either alisertib/rituximab or alisertib/rituximab/vincristine combinations [36]. Compared to alisertib, other AurkA inhibitors have not advanced past the drug development stage into clinical trials (Table 1). For instance, MLN8054 was discontinued due to its severe toxicity to the central nervous system [28].

In regard to AurkB inhibitors, several agents have been developed and tested in the clinic: AZD1152 or barasertib, pan-Aurora inhibitors like ABT-348 or ilorasertib, TAK-901 and AT9283 among others (Table 1). Barasertib has demonstrated better efficacy in hematological malignancies than solid tumors [25]. However, response only reached 25% in AML patients [37,38], and was limited in diffuse large B-cell lymphoma (DLBCL) patients [39]. As seen in a subset of AurkA inhibitors, several AurkB specific inhibitors, such as PF-3814735 and BI811283, have been discontinued [40,41].

3.2. *Polo-like kinase 1*

Polo-like kinase 1 (PLK1) is a mitotic Ser/Thr kinase that plays a vital role in mitotic progression. It participates in centrosome maturation, bipolar spindle assembly, kinetochore-microtubule dynamics, chromosome segregation, cytokinesis and mitosis initiation by activating CDK1/cyclin B1 complex [25,42]. Like other mitotic kinases, PLK1 overexpression is a common feature of several human cancers [43].

Table 1
Inhibitors of mitotic proteins for cancer treatment. Small molecule inhibitors targeting different mitotic proteins have been developed as potential antitumor agents. Information about additional targets and clinical trials is included. The number of active or completed/terminated trials and the furthest phase reached is indicated.

Target	Inhibitors	Other targets	Clinical trials	
			Active	*Completed or terminated*
AurkA				
	Alisertib (MLN8237)		7, Phase III	47, Phase II [33–36,158–166]
	ENMD-981693/ ENMD-2076	VEGFR, FGFR, Flt3, RET		8, Phase II [167]
	Danusertib (PHA-739358)	AurkB/C, Abl, TrkA, RET		3, Phase II [168,169]
	MLN8054	AurkB		2, Phase I [170–172]
	MK-5108 (VX-689)	Aurk B/C, TrkA		1, Phase I [173]
	MK-8745			
AurkB				
	Barasertib (AZD1152-HQPA, AZD2811)	Lck	1, Phase I/II	9, Phase II [38,39]
	BI811283			2, Phase II
	GSK1070916	AurkC		1, Phase I
	PF-03814735	AurkA, Flt3, FAK, TrkA		1, Phase
	ZM-447439	AurkA, Lck, Src, MEK1		
Pan-Aurk				
	XL-228	Bcr-Abl, IGF-1R, Src, Lyn		2, Phase I
	Tozasertib(VX-680/MK-0457)	Bcr/Abl, Flt3		2, Phase II [174–176]
	CYC-116	VEGFR2, Src, Lck, FLT3		1, Phase I
	SNS-314	Trk A/B, Flt4, Fms, Axl, c-Raf, DDR2		1, Phase I
	AMG 900			2, Phase I [29]
	JNJ-7706621	pan-Cdk		
	Cenisertib (AS703569, MSC1992371A)	Abl1, Akt, STAT5, Flt3		3, Phase I [177–179]
	AT9283	Jak3, Jak2, Abl1		5, Phase II [180,181]
PLK1				
	Rigosertib (ON 01910)	PDGFR, Bcr/Abl, Flt1	6, Phase III	28, Phase III
	Volasertib (BI6727)		4, Phase III	16, Phase II
	Onvansertib (NMS-P937)		4, Phase I/II	
	BI2536	BRD4, Plk2/3		11 Phase II
	GSK461364			1, Phase I
	Tak9960			
	Poloxin-2			
Mps1				
	S81694 (NMS-P153)		1, Phase I/II	
	BOS172722		1, Phase I	1, Phase I
	Empesertib (BAY1161909)			1, Phase I
	BAY1217389			1, Phase I
	Mps1-IN-1	Alk, Ltk		
	Mps1-IN-2	Plk1		
	Mps1-IN-3			
	TC-Mps1-12			
	AZ3146			
	NMS-P715			
	MPI-0479605			
	CCT251455			
Eg5				
	Ispinesib (SB-715992)			16, Phase II
	Filanesib (ARRY-520)			8, Phase II
	SB-743921			2, Phase I/II
	AZD4877			6, Phase II
	Litronesib (LY2523355)			7, Phase II
	ARQ-621			1, Phase I
	MK-0731			1, Phase I
	EMD-534085			1, Phase I
	4SC-205			1, Phase I
CENP-E				
	PF-2771			
	GSK-923295			1, Phase I
	Compound-A			
	APC/C			
	Apcin			

Different small molecule PLK1 inhibitors have been developed including BI2536, BI6727 (volasertib) and GSK461364 (Table 1). They typically target either the kinase domain inhibiting the catalytic activity or the polo-box domain in charge of directing PLK1 to its correct substrates [15]. Inhibition of PLK1 activity results in monopolar spindle formation, growth arrest and cell death in preclinical models [44]. BI2536 was one of the first PLK1 inhibitors developed. Despite yielding promising results in phase I trials and moving to phase II, disappointing results were obtained in latter studies [15,43]. The chemical structure of BI2536 was improved and labeled BI2767 (volasertib). Although the clinical results rendered by volasertib were better than its predecessors, clinical responses in patients with advanced solid tumors were still limited [20,43]. More recently, volasertib, alone or in combination with the pan-PI3K inhibitor copanlisib, has shown antitumor activity in a patient-derived xenograft (PDX) model of mantle cell lymphoma (MCL) [45].

3.3. Monopolar spindle protein 1

Monopolar spindle protein 1 (Mps1) is a key component of SAC signaling [46]. This protein, in conjunction with MAD2, BUBR1 and BUB3, is recruited to the kinetochore when chromosomes are incorrectly attached to microtubules. In this situation, AurkB triggers Mps1 association to the kinetochore, initiating the SAC signaling cascade. Thereafter, Mps1 prompts kinetochore recruitment of BUB1 [18,47]. In turn, BUB1 in complex with BUB3 mediates recruitment of other SAC proteins to the kinetochore [47]. The SAC remains activated until the spindle is correctly assembled at the metaphase plate, halting the progression through anaphase and inducing mitotic arrest [48,49]. The SAC fulfils these tasks by inhibiting the activity of an E3 ubiquitin ligase, the anaphase promoting complex or cyclosome (APC/C) [5,10,50]. The mitotic checkpoint complex (MCC), composed of Cdc20, MAD2, BUBR1 and BUB3, operates as the main effector of the SAC. When activated and released from incorrectly attached kinetochores, it sequesters Cdc20, thereby inhibiting the APC/C complex [46]. When all the chromosomes are properly connected to the mitotic spindle, the SAC is turned off and Cdc20 is then able to activate the APC/C. Mps1 is a kinase that can phosphorylate several proteins involved in the release of the MCC and the correction of spindle assembly errors [46]. Once correct kinetochore attachments have been established, Mps1 is displaced, degraded and thereby SAC is switched off.

Its fundamental role in initiating SAC activation prompted the development of antimitotic drugs that target Mps1 activity. Several small molecules inhibiting Mps1 and exhibiting *in vitro* antitumor activity have been identified: Mps1-IN-3, Mps1-IN-1/2, TC-Mps1-12, AZ3146, BAY1217389, BAY1161909 (empesertib), BOS172722, NMS-P715, S81694 (NMS-P153), CCT251455 and MPI-0479605 (Table 1). Moreover, combinatorial drug schedules of BOS172722, S81694 and either BAY1217389 or BAY1161909, administered in combination with paclitaxel, have been or are currently being evaluated in phase I and II clinical trials in solid tumors. Results from these studies are not currently available.

3.4. Eg5

The kinesin motor protein Eg5 (also known as KIF11, KSP, kinesin-5), drives the formation of the bipolar spindle. It participates in the correct formation of the spindle by binding to opposite interpolar microtubules and moving towards the microtubule plus-end. An adequate number of Eg5 molecules, as well as a correct protein function are required for precise chromosome segregation. Eg5 overexpression has been detected in different types of tumors and is frequently related to a negative prognosis [51,52]. In contrast, Eg5 depletion or inhibition provokes mitotic defects such as monopolar spindles and mitotic arrest [53]. Several small molecule Eg5 inhibitors have been identified (Table 1) and their antitumor activity has been assessed in phase I/II clinical trials. Unfortunately, as evidenced by the limited number of published reports, the clinical efficacy of Eg5 inhibitors was shown to be modest [54–60] and no further trials are expected.

3.5. Centromere-associated protein-E

Centromere-associated protein-E (CENP-E, kinesin-7) is a large kinesin motor protein, essential for the alignment of chromosomes at the metaphase plate. This protein is preferentially expressed in mitotic cells and its function is regulated by several kinases, including mitotic kinases such as Cdk1, MPS1, AurkA and AurkB [61]. Despite the identification of several CENP-E small-molecule inhibitors, only GSK-923295 has undergone clinical evaluation. In a phase I clinical trial targeting solid tumors, 1 out of 39 patients showed a partial response [62]. Novel inhibitors have been developed and are detailed in Table 1. One of these inhibitors, Cmpd-A, exhibited *in vitro* antitumor activity against a wide panel of cell lines and inhibited growth of Colo205-derived xenografts *in vivo* [63].

3.6. Anaphase promoting complex/cyclosome

The Anaphase Promoting Complex/Cyclosome (APC/C) is a multiprotein E3-ubiquitin ligase with two important functions during mitosis: to trigger mitotic exit and to promote sister chromatid segregation. The activity of APC/C is regulated by its interaction with two co-activators, Cdc20 and Cdh1. These interactions result in the formation of two complementary ubiquitin ligase complexes - APC/C^{Cdc20} and APC/C^{Cdh1} - which target and bind to different substrates. The APC/C^{Cdc20} complex targets for degradation Cyclin B and securin, two proteins especially important for progression through the mitotic phase. Cyclin B degradation allows the cell to exit mitosis thanks to the inactivation of Cdk1-derived signals. The degradation of securin allows separase to start cleaving cohesins, the proteins that hold sister chromatids together [48,49]. Cdc20 overexpression has been reported in different tumor types, making this protein and the APC/C complex attractive targets for new cancer drugs [64]. Preclinical studies in DLBCL, MCL and MM have shown that ProTAME, a small molecule that inhibits protein interactions within the APC/C^{Cdc20} complex, is able to trigger cell death in tumor cells [65,66]. Apcin is another inhibitor of the APC/C, but its *in vitro* antitumor activity has been shown to be very limited [67].

4. Why have new antimitotic drugs failed?

As previously stated, most of the specific inhibitors of mitotic proteins have not shown significant antitumor activity in clinical trials, despite promising preclinical results. The reasons underlying this discrepancy are not explicitly known and could have several contributing factors. In the following section, we will focus on two possibilities: first, the connection between mitotic arrest and cell death; second, *in vivo* factors such as inter-individual response variations, pharmacological properties and primary tumor cell division rates.

4.1. Cell death mechanisms upon mitotic arrest

The characterization of the molecular pathways driving mitotic catastrophe has been a subject of interest over the last decade. The mechanisms and players that form and regulate the mitotic apparatus, as well as the molecular pathways involved in cell death and cell senescence programs have been further elucidated. However, connections between the mitotic perturbations and cell death remain obscure.

The accumulation of death signals and the duration of mitosis was originally proposed to explain cell fate after mitotic arrest [68,69]. The model consists of two competing independent cellular networks with each pathway working in opposite directions [68]. One pathway gradually accumulates pro-death signals. The other accounts for the slow and consistent degradation of Cyclin B1, even in the presence of persistent SAC activation, which ultimately drives mitotic slippage [68,70]. Cell fate is conditioned by which of the two molecular thresholds is breached first [71]. If death signals accumulate rapidly and reach sufficient strength to trigger cell death before CDK1-Cyclin B1 activity collapses, cells will die in mitosis. Conversely, if Cyclin B1 levels and CDK1 activity fall below the minimum level required to maintain the mitotic state before the death threshold is met, cells will exit mitosis, reaching the subsequent G1 phase in a tetraploid state. Several studies provide evidence supporting this binary model. For example, targeting mitotic exit can precipitate cell death in slippage-prone cells [72,73]. Similarly, if cell death is inhibited with pan-caspase inhibitors, an increased proportion of cells are able to slip out of mitosis (although with the same kinetics) when compared to cells undergoing nocodazole treatment (microtubule inhibitor) alone [74]. Furthermore, accelerating the timing of mitotic slippage favors survival of mitotic cells [68]. These studies also argue in favor of the independence of these competing networks [74,75].

Cell death during mitosis occurs through the intrinsic apoptotic pathway. Therefore, it is conceivable to think that the Bcl-2 family of proteins could be key determinants of cell fate during mitotic catastrophe. In particular, post-translational regulation of the Bcl-2 family has been shown to impact mitotic cell death. CDK1/Cyclin B1 mediates phosphorylation of anti-apoptotic members of the Bcl-2 family (Bcl-2, Bcl-X_L and Mcl-1) during prolonged mitotic arrest [76–78]. Phosphorylated forms of Bcl-2 and Bcl-X_L are considered to have lower affinity for the pro-apoptotic members Bak and Bax, hence promoting its oligomerization and MOMP [79,80]. Regarding Mcl-1, its phosphorylation by CDK1/Cyclin B1 during mitotic arrest fosters its proteolytic degradation via ubiquitination by the SCF/FBW7 or even APC/C^{Cdc20} E3 ubiquitin ligases [24]. When Mcl-1 levels and/or Bcl-2 and Bcl-X_L activity decline, Bax and Bak are free to oligomerize and initiate the mitochondrial apoptotic cascade.

According to this, in normal mitosis during the transient time that CDK1/Cyclin B1 is active, levels of anti-apoptotic members remain high to prevent cell death. On the contrary, under prolonged mitotic arrest, sustained activation of CDK1/Cyclin B1 allows for phosphorylation of anti-apoptotic Bcl-2 members, reducing its activity and triggering apoptotic cell death before mitotic slippage. Other members of the Bcl-2 family can also undergo post-translational phosphorylation by CDK1/CyclinB1 complex. Mac Fhearraigh and Mc Gee showed that the BH3-only protein Bim (specifically the Bim_{EL} and Bim_L isoforms) were hyperphosphorylated under sustained mitotic arrest [81]. The final cellular outcome of Bim phosphorylation and its implication in mitotic catastrophe-induced cell death is still a matter of debate and contradictory results have been reported [68,71]. The phosphorylated forms of Bim could show altered activity, either through increasing the interaction with Bcl-2 [82] or through stabilization/destabilization of certain isoforms [83,84]. The caspase family has also been shown to be a substrate of CDK1, particularly caspases 2, 8 and 9. Phosphorylation of these caspases reduces their apoptotic activity which is thought to be a cytoprotective measure during normal mitosis [71]. This complements the binary model, whereby the number of inhibited caspases declines with the reduction of CDK1/Cyclin B1 activity levels. Moreover, although cell death during mitotic catastrophe is mainly mediated by the caspase-dependent apoptotic pathway, other cell death scenarios governed by caspase-independent mechanisms have been reported [68,71].

4.2. Personalized medicine and treatment response in antimitotic approaches

It is well established that cancer is a heterogeneous and complex disease. Personalized cancer treatments would allow selection of the best therapies depending on patient characteristics. To date, few biomarkers with the ability to prospectively select patients that could benefit from antimitotic therapies have been clinically validated or implemented into clinical practice [85].

The use of targeted antimitotic agents according to the expression of mitotic kinases is a possible approach to a personalized treatment. As previously indicated, cancer cells can overexpress different mitotic kinases leading to a dysregulation of the cell cycle in a variety of cancers [86]. Moreover, overexpression of these proteins has been associated with a higher risk state and poor clinical outcomes. For example, PLK1 overexpression has been correlated with an increased aneuploid DNA content and a worse prognosis in gastric cancer [87]. Similarly, AurkB and PLK1 levels are elevated in prostate cancer and their expression is correlated with tumor grade and malignancy [88,89]. AurkB overexpression has also been linked with poor prognosis in colorectal [90], ovarian [91] and thyroid carcinoma [92]. Increased levels of AurkA expression have been associated with worse prognosis in different tumor types including bladder and colorectal cancers [90,93,94].

Identification of resistance mechanisms is of great interest as they are major obstacles in current cancer therapies. Precision medicines should be created to predict and overcome the development of possible drug resistances. The study targeting BCR-ABL in the treatment of chronic myeloid leukemia (CML) illustrated how resistance to targeted therapy may emerge and how rationalizing combinatorial approaches can lead to success [95–97]. AurkA mutants have shown resistance to some AurkA inhibitors [98]. A specific AurkA SNP at codon 57 predicted disease outcome and therapy response to alisertib in two phase 2 clinical trials [99]. Colorectal cancer patients with elevated expression of AurkB or patients harboring a specific AURKB allele had significantly reduced overall survival (OS) rates [100]. Similarly, p53 has been proposed as predictor of cell sensitivity to antimitotic agents such as Aurk inhibitors [101]. Among its tumor suppressor functions, p53 has the ability to activate a post-mitotic checkpoint to prevent the endoreplication of cells that escape the mitotic checkpoints after a defective mitosis. p53 mutations or overexpression in breast cancer cells has been shown to increase the sensitivity to an Aurk A inhibitor [102]. Resistance mechanisms have also been observed in regard to Mps1 targeted drugs. In particular, mutations in Mps1 kinase domain have been reported to confer resistance to specific Mps1 inhibitors [103].

Another factor that can determine the efficacy of antimitotic drugs is the proliferation rate of tumor cells. Cancers with shorter tumor-doubling times and increased propensity to rapidly divide could preferentially benefit from treatment with antimitotic agents. Clinical trials in hematological cancers have shown better responses to antimitotic agents, perhaps due to the fact that these cells typically have faster doubling times.

5. Is there still a chance for targeted antimitotic drugs? Strategies to boost their antitumor effectiveness

Despite the potential exhibited by the new generation of antimitotic agents in preclinical studies, promising outcomes have not been reflected in clinic [15]. Consequently, most of the antimitotic compounds that reached clinical phase development have been abandoned. Currently, only a few clinical trials assessing the efficacy of alisertib, barasertib and volasertib are active (Table 1). As discussed in previous sections, the mechanisms behind their lack of clinical efficacy are uncertain. Failure of antimitotic agents could be attributed to the erroneous idea that human cancer cells *in vivo* proliferate at the same rate as tumor cell lines *in vitro*. When compared, tumor-doubling rates are much higher in patients than in either preclinical models or cell line data. [4]. Moreover, the number of human cancer cells undergoing mitosis at any given time within the whole population (mitotic index) is estimated to be less than 1% [4,104]. These findings have led to the proposal of alternative mechanisms for the antitumor activity of MTAs including: drug retention time within the tumor, cytotoxicity of quiescent cells due to non-mitotic microtubule functions, targeting non-tumor cells in the microenvironment and alternative by-stander effects [105,106]. It is possible that the novel antimitotic agents developed do not currently fulfill these features and consequently lack the effectiveness of their predecessors. Nonetheless, it is undeniable that tumor cells divide and that the cell cycle and the mitotic phase are vital for cancer cells to thrive.

The pharmacodynamic properties and half-lives of antimitotic drugs are key aspects of efficacy given that the number of targeted mitotic cells at any given timepoint is limited. On the other hand, the effect on highly proliferative non-tumor tissues and off-target toxicities limits the dosage and frequency of use of antimitotic drugs, hampering the chances of achieving and maintaining a clinically effective dose over prolonged periods. However, antimitotic drugs have the advantage of producing targeted effects and influencing mitotic defects at a much lower concentration than is needed to trigger cytotoxic events. For this reason, combinatory approaches are suitable as they may allow for lower concentrations of antimitotic agents to be used without reducing mitotic targeting effects. Moreover, mitotic slippage and survival of aneuploid and polyploid cells could be overcome by using therapeutic combinations that specifically target escaped cells that survive after an aberrant

mitosis.

5.1. Exploiting cell death pathways during mitotic arrest

Although cell death either during mitotic arrest or after slippage in the next G1 phase is a possible and frequent outcome after exposure to MTAs or more novel antimitotic drugs, some cells experience different fates. As previously mentioned, mitotic slippage should be considered one of the resistance mechanisms cancer cells can harness to escape the actions of antimitotic agents [15]. Moreover, some targeted antimitotic drugs may favor this outcome as they do not induce a prolonged mitotic arrest. Instead, cells rapidly slip out of mitosis reaching the next cell cycle interphase generating an aneuploid or polyploid population [68]. In this circumstance, a significant proportion of these cells could eventually survive after slippage and continue dividing, building up the tumor mass, or acquire senescent features and contribute to cancer development in other ways.

At this point, the 'competing networks' model proposed by Gascoigne & Taylor could provide a framework to devise more efficient therapeutic approaches. As indicated before, this model states that cell fate in response to anomalous mitosis is determined by the finely-tuned balance between cell death signals and the molecular mechanisms that control mitotic exit [75]. Therefore, according to this model, resistance due to mitotic slippage could be resolved either by accelerating cell death during mitosis or by delaying mitotic exit. A good therapeutic strategy to tilt the cell fate balance in favor of cell death and upgrade the efficacy of antimitotic drugs would be accelerating or increasing the intensity of death signals during the vulnerable mitotic state. In this respect, the Bcl-2 family of proteins are key regulators of apoptotic cell death pathways and have been shown to be pivotal in cell fate decisions under prolonged mitotic arrest [107]. Importantly, the specific contribution of individual anti-apoptotic proteins in the regulation of cell death during mitosis may depend on the specific tumor type. Bcl-2 overexpression has different effects in solid tumors than in hematological malignancies. For example, elevated levels of Bcl-2 sensitize solid tumors to MTAs, whereas Bcl-2 overexpression in hematological cancer cells protects them from cell death induced by microtubule poisons [107]. In contrast, overexpression of Bcl-X_L or Mcl-1 has been found to be an important contributor to MTA drug resistance in several human cancers, both solid or hematological [107].

Pharmacological intervention to activate the intrinsic pathway of apoptosis is now possible thanks to the development of BH3-mimetics. These small molecules mimic the BH3 domain of pro-apoptotic proteins of the Bcl-2 family and bind to the hydrophobic groove of selected anti-apoptotic members. For that reason, BH3-mimetics are promising therapeutic candidates that should be combined with antimitotic agents to enhance the strength of death signals during mitotic arrest. In this way, by targeting anti-apoptotic proteins and neutralizing their pro-survival activity, BH3-mimetics may tip the balance towards cell death during protracted mitosis. The only BH3-mimetic approved in the clinic is the Bcl-2 inhibitor venetoclax (Venclexta), used for the treatment of B-cell chronic lymphocytic leukemia (B-CLL). Mechanistic studies suggest that Bcl-X_L [108,109] and Mcl-1 [110] are the main regulators of cell death during mitosis. While Mcl-1 inhibitors are in clinical development, Bcl-X_L inhibitors have been hindered by the occurrence of severe adverse thrombocytopenic events in patients subjected to navitoclax, a Bcl-2/Bcl-X_L/Bcl-W inhibitor. This adverse event was attributed solely to the inhibition of Bcl-X_L. Recently, a new dual Bcl-2/Bcl-X_L inhibitor APG-1252 (palcitoclax) with reduced platelet depleting effects has demonstrated promising antitumor activity in metastatic solid tumors [111]. It is currently in a phaseI/II clinical trial in combination with paclitaxel (NCT04210037).

The Bcl-2 inhibitor venetoclax and the Mcl-1 inhibitor S63845 have demonstrated synergic responses in combination with MTAs, both *in vitro* and in animal models [112,113]. Interestingly, venetoclax failed to enhance paclitaxel-induced cell death when Bcl-2 was phosphorylated by JNK. In fact, Bcl-2 phosphorylation by JNK has been proposed as a potential prognostic biomarker that would monitor patients' responses to venetoclax/paclitaxel combination [112]. Clinical trials are currently evaluating the administration of venetoclax along with other chemotherapeutic regimens that include antimitotic inhibitors such as vincristine in hematological cancers. In the Cavalli phase 1b trial, results indicated that adding venetoclax to R-CHOP (rituximab, cyclophosphamide, doxorubicin and vincristine) increased the percentage of CR in MYC+/Bcl-2 + DLBCL patients. The promising results led to a currently ongoing phase II trial [114].

Preclinical studies have also revealed potential synergy between targeted antimitotics and BH3-mimetics. Inhibition of Bcl-2/Bcl-X_L/Bcl-W with navitoclax, the orally available version of ABT-737, efficiently killed polyploid cancer cells generated after exposure to AurkB inhibitors in a diverse panel of tumors [115]. Navitoclax and ABT-737 also showed synergic responses with AurkA inhibitors in aggressive alveolar rhabdomyosarcoma [116] and with the Eg5 inhibitor ARRY-520/filanesib in AML [117]. Recently, combination of the PLK1 inhibitor volasertib and the Bcl-2 inhibitor venetoclax showed *in vivo* activity against double-hit lymphoma (DHL) in a PDX model [118]. This affirms the role of Bcl-2 protein in mitotic cell death in hematological neoplasms. However, blocking Bcl-X_L, but not Bcl-2, in pediatric glioblastoma and medulloblastoma enhanced the antitumor effect elicited by the AurkA inhibitor alisertib [119]. This is in accordance with the hypothesis that solid tumors are more reliant on the pro-survival activity of Bcl-X_L and/or Mcl-1 during prolonged mitotic arrest. Mcl-1 down-regulation has been proposed as a critical event that drives apoptotic induction after treatment of sarcoma cells with the PLK1 inhibitor Tak-960 [120]. To date, only a phase I clinical trial (NCT03217838) in AML combining barasertib nanoparticles, azacitidine and venetoclax has been launched. Further research in the mitotic cell death pathways is needed to attain optimal combinatory chemotherapeutic regimens that can be successfully translated into clinical practice.

5.2. Targeting mitotic exit

Cyclin B1 degradation is a key element controlling mitotic exit and dictating cell fate (slippage or apoptosis) upon protracted mitosis. Targeting cytokinesis is an alternative approach to prevent cancer cells from escaping terminal cell fates and gaining an increasingly malignant phenotype [5]. Moreover, this approach could be combined with antimitotic agents targeting other mitotic phases to achieve a synergistic antitumor response [86]. To ensure the proper exit from mitosis, the cell counts on a precise regulatory network that includes the APC/C ubiquitin ligase and cyclinB1, the regulation of mitotic kinase/phosphatase pathways and kinesins among other mitotic binding proteins [86].

Several APC/C inhibitors have been developed, such as TAME or apcin [121,122]. Combination of these inhibitors with paclitaxel or alisertib (AurkA inhibitor) efficiently exerted a potent antitumor effect [123]. Slow but continuous Cyclin B1 degradation is observed even in the presence of active SAC signaling occurring through unknown mechanisms. Other strategies should be utilized to prevent unwanted mitotic slippage and increase the cell's probability of undergoing mitotic cell death. Aurora kinases (PLK1 or kinesin superfamily proteins are examples of mitotic kinases involved in the regulation of cytokinesis [86]. Combination of small-molecule inhibitors against these mitotic proteins and other chemotherapeutics, including other antimitotic agents such as MTAs, have been shown to enhance tumor cell cytotoxicity rendering synergistic responses *in vitro* and *in vivo* [124–129]. Certain combinations showed antitumor efficacy in early phase clinical trials warranting future investigations [130,131]. In addition to the targets involved in mitotic exit, non-motor microtubule-binding proteins such as protein regulator of cytokinesis 1 (PRC1) have potential as anticancer targets. Simultaneously blocking mitosis at telophase by targeting PRC1 or KIF20B and metaphase with taxol has been found to exert potent antitumor effects in hepatocellular carcinoma (HCC) cell

lines and xenograft models [132,133]. In this scenario, those cells that manage to escape from the metaphase blockade have to pass through another obstacle before achieving mitosis exit, enhancing the probability that pro-apoptotic signals induced by MTAs or other chemotherapeutics accumulate within mitosis and eventually lead to cell death [86].

5.3. Targeting antimitotic-induced senescence

If cells do not succumb to intrinsic regulatory mechanisms and escape mitotic arrest, they can eventually give rise to an aneuploid/polyploid population. The new population has a high probability of exhibiting a malignant phenotype and being genetically unstable [134]. Some of the aforementioned targeted antimitotic inhibitors (like AurkB inhibitors, for instance) function as 'mitotic drivers'. They direct cells through a short mitotic arrest, allowing them to slip away from mitosis without experiencing cytokinesis, giving rise to the so-feared aneuploid progeny [135]. Cell senescence is a possible outcome when mitotic defects lead to a protracted M phase and cells survive after slippage. A wide variety of chemotherapeutics have been shown to primarily induce cell senescence [136,137]. Similar to replicative and oncogene-induced senescence, chemotherapy-induced senescence is another form of cellular senescence likely caused as part of stress-induced premature senescence (SISP) [138]. Classically, genotoxic and cytotoxic agents that induce a DNA damage response eventually initiate a cellular senescence response. Examples include bleomycin, camptothecin, cisplatin, doxorubicin and etoposide [138,139]. Different antimitotic agents have also been reported to induce cell senescence as a predominant outcome or in a significant portion of the target cell population. Small-molecule inhibitors targeting PLK1 (MLN0905, BI2536) have been shown to induce cell senescence in cell lines [36]. Other antimitotic agents like MTAs (discodermolide, docetaxel, vincristine, paclitaxel) have also been reported to induce varying degrees of cell senescence in different tumor cell lines [139,140]. Alisertib and barasertib, two small-molecules inhibitors targeting AurkA and AurkB respectively, are also able to trigger cell senescence [141,142].

Senescence has long been defined as a state of permanent growth arrest, being considered a *bona fide* oncosuppressive mechanism that limits tumor growth [143]. However, the irreversibility of senescent growth arrest has been called into question. Several studies have shown that senescent cancer cells may have the ability to escape and resume proliferation. In particular, when senescence induction is associated with mitotic defects and polyploidization, cancer cells that subsequently undergo a depolyploidization process can recover the ability to proliferate [144]. For these reasons, eliminating senescent cells has emerged as a promising therapeutic strategy in cancer.

Considerable efforts have been directed towards developing senolytic agents for cancer and age-related disorders. Interestingly, combination of senescence-inducing antimitotics and senolytics could be a profitable strategy in anticancer therapy. The previously mentioned BH3-mimetic navitoclax has senolytic properties and has been shown to induce apoptosis of senescent cancer cells generated after incubation with palbociclib, a Cdk4/6 inhibitor [145]. Also, Shahbandi *et al.* demonstrated that navitoclax, alone or combined with a Mcl-1 inhibitor, selectively induced apoptosis in the emerging senescent cells that resulted from previous treatment with doxorubicin, irradiation or paclitaxel [146]. Besides BH3-mimetics, other molecules can operate as senolytic agents including Hsp90 inhibitors (e.g. geldanamycin, 17-AAG/tanespimycin and 17-DMAG) and cardiac glycosides (e.g. digoxin, digitonin and ouabain) [147]. Nonetheless, in a phase 1 trial, the combination of 17-AAG/tanespimycin and paclitaxel showed no activity against advanced solid tumors [148]. Since paclitaxel is a 'mitotic blocker', it is possible that senescence was not induced as efficiently as with other types of antimitotics. Perhaps the combination of senolytics with mitotic drivers like AurkB inhibitors could produce better results.

These studies highlight the importance of therapy-induced cellular senescence as a target to prevent progression of senescent cells into newly aggressive cancer cells [139].

5.4. Immunogenic cell death

The immune system has been recognized as a decisive ally in cancer therapy. Important advances in the field of oncoimmunology have enabled the introduction of promising therapeutic approaches such as immune checkpoint inhibitors and CAR-T cells. In parallel, immunostimulatory modalities of cell death (immunogenic cell death, ICD) have also been identified. ICD differs from the immunologically silent apoptosis in its ability to elicit antigen-specific adaptive immune responses [149]. This is achieved through the exposure or emission of endogenous molecules that act as danger signals known as damage-associated molecular patterns (DAMPs). These molecules interact with their cognate receptors (pattern recognition receptors, PRRs) expressed by innate immune cells such as monocytes, macrophages and dendritic cells (DCs). This is followed by the activation and maturation of immune cells carrying cancer-derived antigens towards draining lymph nodes. Cancer material is presented to T cells ($CD4^+$ and $CD8^+$ T lymphocytes) triggering potent anticancer adaptive immune responses [150]. ICD could contribute to the success of chemotherapy. Multiple screening studies have unveiled the immunogenic potential of anticancer agents: anthracyclines, oxaliplatin, bortezomib and MTAs like vincristine and docetaxel [151]. It has been proposed that the immunogenicity of cancer cells treated with antimitotic drugs is related to the generation of micronuclei, activation of the cGAS-STING pathway or release of HMGB1 [152]. According to this model, proposed by Mitchison *et al.*, proinflammatory signals emitted by cells with micronuclei would be able to trigger immune responses in taxane treated patients, critically contributing to tumor elimination. Early data indicate that targeted antimitotics generally do not provoke an extensive degree of micronucleation. This could be the underlying reason for their limited clinical activity as compared to MTAs like taxanes. Still, the available mechanistic data for antimitotic molecules are scarce. It cannot be ruled out that some of these compounds may have the ability to induce inflammatory micronucleation in certain tumor types.

It is well established that senescent cells acquire a characteristic secretory phenotype called SASP (senescence-associated secretory phenotype) whereby they secrete mitogenic and immunomodulatory factors that can be pro-inflammatory. Harnessing the ability of antimitotic agents to produce senescent cells may help produce an effective immune response. Elicitation of anticancer immune responses *in vivo* are heavily influenced by the host and the microenvironment. Conventional chemotherapeutics can have deleterious effects on the immune system. However, some of the effects driven by chemotherapeutics, including antimitotics, can assist in creating a more favorable immune environment for the success of antitumor immune responses. For instance, taxanes have been reported to deplete immunosuppressive cells like Tregs in non-small cell lung cancer (NSLC) patients [153] and suppress induction of M2 macrophages [154] and myeloid-derived suppressor cells (MDSCs) [155] in various cancers. Combining taxane-based therapies with immune checkpoint inhibitors could improve clinical results. There are several clinical trials testing this strategy (mainly in lung cancer; clinicaltrials.gov). Recent reports indicate that certain antimitotic drugs could reshape the immune microenvironment and elicit active antitumor responses. Alisertib was shown to model the tumor microenvironment in breast cancer models [156] by promoting either $CD8^+$ T cell tumor infiltration or up-regulation of IL-10Ra transcription [157]. Moreover, Yin *et al.* [156] demonstrated that alisertib also synergizes with anti-PD-L1 checkpoint blockade therapy, opening the door for new clinical trials.

6. Concluding remarks and future directions

Antimitotic agents have been used in cancer treatments for decades and have demonstrated important clinical success. Scientific efforts have been directed towards developing a new set of mitotic inhibitors that target different players in the mitotic apparatus, each with increased specificity. To date, results from clinical studies have been disappointing as the new compounds have not surpassed the effectiveness of traditional antimitotic agents. New and improved therapeutic strategies should be designed based on the mechanistic insights gathered from different cellular processes. Mitosis, cell death and the different possible cellular cell fates, as well as the interplay between these networks are important aspects around which to design treatment plans. The therapeutic schemes reviewed in this manuscript hold promise as they may prevent the generation and/or help in the elimination of the genetically unstable aneuploid population. This cell population hides a great potential to become more tumorigenic, more resistant to therapy and hence more likely to develop high-risk states of the disease [104]. Moreover, as aneuploidy and genomic instability are distinctive features of cancer cells, therapies targeted towards these aspects of the cell will spare non-malignant cells, yielding better outcomes. Strategies that target the uncontrolled proliferative capacity of tumor cells and that either accelerate or strengthen death signals, when used to target senescent or chromosomally aberrant stressed cells, may increase the success of antimitotic therapies in clinic. Combinatorial approaches to antimitotic regimens, while promising, need further study. Characterizing the molecular networks governing these complex processes is the next step towards optimized antimitotic cancer therapies.

CRediT authorship contribution statement

Alfonso Serrano-del Valle: Writing - original draft. **Chantal Reina-Ortiz:** Writing - review & editing. **Andrea Benedi:** Writing - review & editing. **Alberto Anel:** Writing - review & editing. **Javier Naval:** Writing - review & editing. **Isabel Marzo:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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